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Information for Authors:

Purpose

The mission of the *University of Virginia Journal of Medicine* is to provide residents, fellows, and faculty members the opportunity to publish original materials generated from their experiences in patient care or patient care related research. Broadly, each edition will include 5-10 case reports, 3-4 clinical reviews and updates on recent advances, and 1-2 clinical commentaries. **The journal will give UVA housestaff the opportunity to work with the faculty in writing medical case reports, thus providing a forum for learning about the process of journal article submission and revision.** In addition, the journal offers referring physicians in the state of Virginia, alumni of the medicine training programs, and healthcare providers associated with the University the opportunity to learn from the breadth of clinically based educational experiences generated from patient care at the University of Virginia.

Article Submission

Only original, unpublished materials will be considered for publication. Inclusion of housestaff on all articles is strongly recommended. Submissions should be made electronically to Cathy Keefe-Jankowski (ck8h@virginia.edu). Any images or figures accompanying the article should be emailed as separate .jpg files. When submitting a manuscript, authors should provide full disclosure of any duplicate publication of any content of the paper in a cover letter to the Editor.

Manuscript Format

- Authors are encouraged to follow the AMA writing style as outlined in *Writing and Publishing in Medicine*, 3rd Edition, Edward J. Huth, MD. Accepted manuscripts are edited in accordance with the *American Medical Association Manual of Style: A Guide for Authors and Editors*, 9th edition. All measurements should be expressed in SI units. Abbreviations that are nonstandard should be avoided; other abbreviations must be defined on first use. Generic drug names are preferred. The manuscripts must be free of any identifying patient information in order to respect confidentiality.

Images

- Any supporting images for an article must be submitted as .jpg files of at least 360 dpi. Files should be sent as separate attachments, and not imbedded within the article text. A placeholder such as <<image 1>> should be used within the text. Please take into consideration that all images will be converted to black and white for printing.

References

- All information not considered statements of common knowledge must be supported by citation of published articles in the medical scientific literature.

- Literature sources must be cited according to AMA guidelines.

  Examples of Reference Style:
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  1. Spock MR, McCoy D. Extraterrestrial transfusion methods. *J Interplanetary Med.* 2800;13:53-65.

  Book
  1. West H. *Reanimation in Theory and Practice*. Arkham, MA: Miskatonic University Press; 1923.

Guidelines for Article Review Process

- Manuscripts will be blindly reviewed by two members of the review board. Decisions regarding acceptance for publication will be based on the strength of the paper compared with other papers in the literature, the need for the *University of Virginia Journal of Medicine* to represent a balanced picture of important advances in internal medicine, and the number of accepted papers in the paper's category and topic area. In addition, reviewers will score submissions based on the following criteria.
  i. Originality of case presentation
  ii. Clarity of teaching points
  iii. Balanced and evidence-based representation of recommendations
  iv. Quality of the writing

UVa Journal Article Categories:

Clinical Vignettes: *length - 800-1600 words*

- Clinical vignettes describe patients with classic presentations of rare diseases or common diseases with unusual or interesting aspects. Authors are encouraged to present a brief review of pertinent literature and discuss salient parts of the patient diagnosis. Clinical Vignettes are coauthored by the resident or fellow and the attending physician who supervised the care of the patient and focus on one or two teaching points related to diagnosis, management, or treatment.

UVa Images in Medicine: *length - maximum 250 words*

- Presentation of a radiographic image or digital photograph of an intriguing patient case accompanied by a brief case report. Authors should focus on the diagnosis and management of underlying pathophysiology related to the presented image and associated medical condition.

Invited Articles

Medical Grand Rounds: *suggested length - 1600-3200 words*

- A review article written by an attending physician who recently presented during Medical Grand Rounds at the University of Virginia. Specifically, this article should provide readers a thorough overview of recent scientific and technologic advances, discussed during the Grand Rounds and developed at the University of Virginia, which have contributed to the overall understanding and management of specific conditions.

Clinical Review Article: *length - 1600-3200 words*

- A comprehensive review article written by an attending physician based on a thorough assessment of the literature with the goal of outlining the current understanding of the pathophysiology and up-to-date practice guidelines for specific clinical topics.

Clinical Commentary: *length - 1600-3200 words*

- The Clinical Commentary offers attending or resident physicians an opportunity to provide a unique clinical perspective on a component of patient care, education, or medical advancements. The scope of this submission is quite broad and may incorporate discussion of controversial issues in the practice of medicine, topics related to or examples of patient care that have affected the author's personal or professional outlook, and/or commentaries about health care policy or public health.

The Academic Hospitalist Corner: *length - 1600-3200 words*

- This section is dedicated to the emerging field of inpatient hospitalist medicine. Article submissions may be case reports, clinical reviews, perspective pieces, and/or commentaries on medical education and training as related to hospitalist medicine.

Chief Resident Clinical Medicine Conference: *length - 1600-3200 words*

- A report that describes a rare or unusual case, with an emphasis on processes of differential diagnosis, work-up, and management that are also applicable to commonly encountered medical conditions. The article should include a thorough discussion of several diagnostic dilemmas with the goal of addressing both the management of complex pathophysiology and the process of systematically arriving at difficult diagnoses.

Tutorials in Medicine: *length - 1600-3200 words*

- A classic presentation of a disease process with board-style questions about the case. This is followed by a discussion of one or more of the following: differential diagnosis, pathophysiology, management, or treatment. These should be authored by an attending physician with resident or fellow physician collaboration.

Streptococcus intermedius *in a Patient with Femur Osteomyelitis and a Surrounding Abscess*

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Streptococcus intermedius, a viridans group Streptococcus, is a commensal organism of the oropharynx that produces enzymes that may lead to pyogenic infections. *S. intermedius* typically causes deep tissue infections of the neck that are usually associated with periodontal disease or dental procedures, but several reports describe infections at more distant sites disseminated through hematogenous spread. The most commonly reported distant infections have been abscesses of the liver and brain, and rare cases of muscle abscesses and osteomyelitis have also been reported.[1] We present a case of S. *intermedius* osteomyelitis of the right femur, with a surrounding abscess.

CASE DESCRIPTION

A 42-year-old man presented to the emergency room complaining of pain and swelling in his right thigh. The patient, a dry-wall installer, reported that 3 weeks earlier he felt pain in his right thigh while lifting heavy materials at his job. He was able to continue work that day. By the day of admission the pain and swelling had progressed, and the patient was unable to work because he suffered significant pain with any weight-bearing activity. He described the pain as a burning pain radiating from the middle of his right thigh to his knee. The patient denied associated constitutional symptoms such as fevers, chills, or weight loss and further denied nausea/vomiting, shortness of breath, and chest pain.

The patient had no chronic illnesses and had never been hospitalized or had any previous surgery. The only medications he was taking were over-the-counter acetaminophen, naproxen, and ibuprofen, which he had been using as needed for pain. The patient had a history of alcohol abuse but had not used alcohol for more than a year prior to admission. He also reported smoking approximately 1 pack of cigarettes a day for the past 30 years, as well as a remote history of intravenous drug use 20 years prior to admission. He denied injection of illicit drugs, steroids, or any other substance into his leg.

Vital signs were completely normal, and the patient was afebrile. Physical examination was notable for poor dentition with multiple dental caries and a warm, edematous right thigh significantly tender to palpation. No swelling or calf tenderness was present below the knee, and sensation, movement, and distal pulses were all normal. No heart murmurs were detected, and abdominal examination findings were normal. Laboratory test results were notable for a white blood cell count of 19,800/mcL with 85% neutrophils, 11% lymphocytes, 2% monocytes, 1% eosinophils, and 1% bands.

DIAGNOSIS

X-rays of the pelvis and femur showed a cortical irregularity of the femur with periosteal reaction extending into the medullary bone (Figure 1). This image suggested the possible presence of cancer such as lymphoma, or a solid tumor that had metastasized to this site. A skeletal survey showed no other lytic lesions. Results of a lower extremity ultrasound were negative for any deep-vein

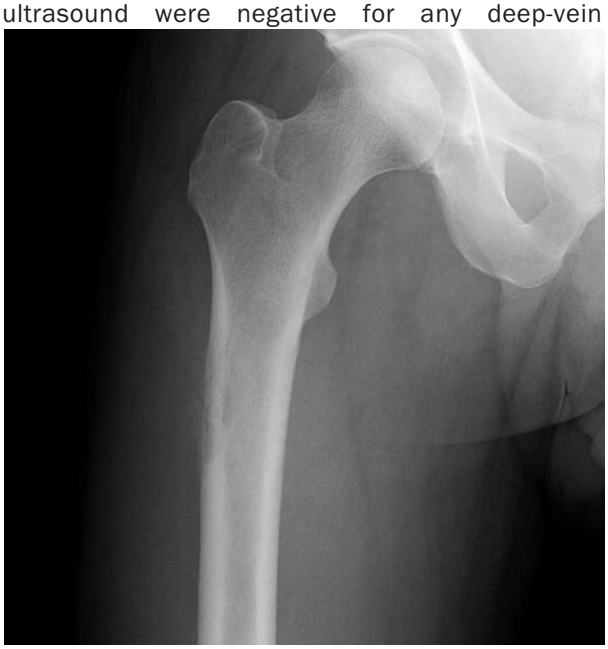

Figure 1. X-ray of the right femur demonstrating cortical irregularity with periosteal reaction extending into medullary bone.

thrombosis. Magnetic resononance imaging (MRI) of the femur for further characterization of the lesion found on x-ray showed osteomyelitis of the proximal femur with intra- and extraosseous involvement. A collection of fluid (8.5 cm (6.5 cm (10 cm) was noted within the vastus lateralis muscle adjacent to the proximal femoral diaphysis in the region of the cortical abnormalities. The MRI also revealed multiple smaller fluid pockets, suspected to be abscesses, within the vastus lateralis, vastus intermedius, adductor longus, and abductor brevis muscles. No mass or evidence of malignancy was found. The study also showed a right knee effusion (Figure 2). The orthopedic service was consulted and recommended a computed tomography (CT)-guided aspiration of the fluid and a bone biopsy. The procedure was performed successfully, and an aspirated sample of pus was sent for culture along with peripheral blood cultures.

MANAGEMENT

The day following the CT-guided biopsy and aspiration, orthopedic surgeons performed a debridement and irrigation of the thigh. Joint aspiration of the knee was also performed because the effusion on MRI suggested a possible septic joint. The patient was initially started on vancomycin and piperacillin/tazobactam. When the preliminary culture reports from the CT-guided aspiration and biopsy revealed gram-positive cocci, the piperacillin/tazobactam was stopped and the patient was continued on vancomycin. An echocardiogram was performed to evaluate for endocarditis, which revealed no valvular vegetations. The gram-positive cocci were eventually identified as *S. intermedius*, which was sensitive to penicillin G (minimum inhibitory concentration 0.032 (g/mL). *S. intermedius* was found in all cultures from the original debridement and from a repeat debridement, but cultures of blood and synovial fluid remained negative. The patient was switched to penicillin G with a continuous infusion of 20 million units/day to complete a 6-week course, and he was discharged from the hospital. Two weeks after discharge, the patient returned for treatment of a pathologic fracture. This complication led to a 6-week admission during which he had an open reduction and internal fixation, with placement of an extramedullary rod encased in antibiotic cement followed by multiple further debridements. After final debridement, the patient was discharged from the hospital and then completed a 6-week course of intravenous penicillin. After completion of the intravenous antibiotics, his medication regimen was changed to oral amoxicillin 875 mg twice a day. The patient slowly improved with physical and occupational therapy and was able to return to work months later.

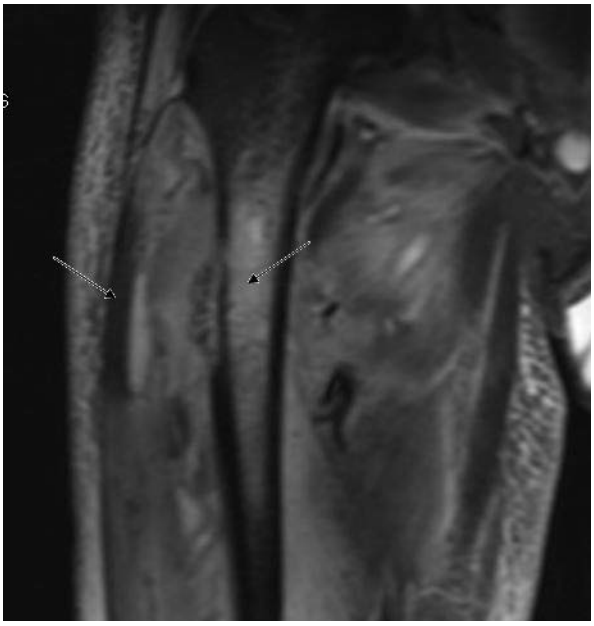

Figure 2. Magnetic resonance imaging cross section of the right femur showing osteomyelitis with intra- and extraosseous involvement and surrounding soft tissue abscess.

DISCUSSION

Osteomyelitis caused by hematogenous spread of *S. intermedius* is rare, with only a small number of case reports in the literature. Because *S. intermedius* is a commensal organism of the oropharynx, the most likely source of infection in the case we report was hematogenous spread as a result of the patient's poor dentition. In another reported case, liver and brain abscess in an otherwise healthy 39-year-old patient was attributed to severe periodontal disease.[2] These abscesses can also occur within muscle tissue, and have been found in conjunction with other mouth flora. A case report from China describes a thigh abscess without osteomyelitis occurring in an otherwise healthy 35-year-old woman. This infection was caused by *S. intermedius* and *Eikenella corrodens,* and although the patient did not have oral disease, an oral source was suspected owing to the presence of 2 endogenous mouth flora organisms.[3] One case of iliac osteomyelitis with an associated gluteal abscess caused by *S. intermedius* was also reported in an immunocompetent 30-year-old patient

with a much more acute disease course than our patient.[1]

Our patient was not immunocompromised but did have a history of alcohol abuse. In a Japanese study comparing mouth flora in alcoholics and nonalcoholics to examine the relationship between *Streptococcus anginosus* and esophageal cancer, levels of *S. intermedius* were twice as high in alcoholics. This finding was postulated to be related to poorer nutrition and oral hygiene among alcoholics.[4] Our patient also smoked tobacco, but a study in Saudi Arabia comparing oral flora of smokers to nonsmokers showed very little difference in the prevalence of *S. intermedius*.[5]

The Streptococcus milleri group consists of 3 distinct species: *S. intermedius, S. anginosus,* and *Streptococcus constellatus. S. intermedius* is the most prevalent cause of abscesses,[1,6,7] probably because it produces 2 virulence factors, hyaluronidase and sialidase. These factors destroy host tissues and convert them to nutrients for the pathogen. *S. constellatus* produces only hyaluronidase but not sialidase, and *S. anginosus* produces neither.[7] In a study of antibiotic susceptibility of Streptococcus milleri group isolates, all 44 isolates, 12 of which were *S. intermedius,* were sensitive to penicillin as well as ampicillin and ceftriaxone. Of the 3 species, *S. intermedius* was found to have the lowest geometric mean\minimum inhibitory concentration (MIC),, with a mean MIC of 0.037 (g/mL; *S. constellatus* and *S. anginosus* had mean MICs of 0.089 and 0.049 (g/mL, respectively.[8]

SUMMARY

We describe a case of a right thigh abscess and osteomyelitis caused by *S. intermedius* in an adult male patient who had dental caries and a history of alcohol abuse, but otherwise had previously been healthy. Prompt diagnosis allowed proper treatment with multiple surgical debridements and a prolonged course of antibiotics. Although such infections are rare, it is important to recognize this pathogen as a potential cause of abscesses and osteomyelitis in immunocompetent hosts. The ultimate need for hardware placement and therefore ongoing antibiotic therapy of indefinite duration further add to the unique nature of this case.

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"Double-Positive" Rapidly Progressive Glomerulonephritis

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Rapidly progressive glomerulonephritis (RPGN), which accounts for 2%-4% of all cases of glomerulonephritis, presents with an abrupt decline in renal function that may lead to end-stage renal disease (ESRD) within weeks. Thus rapid diagnosis and treatment are essential for maximizing outcomes in patients with RPGN.

CASE DESCRIPTION

The case patient was a 76-year-old woman who was referred to our medical center for treatment of RPGN diagnosed at another facility. The patient had initially presented with an asymptomatic increase in creatinine from her baseline of 1.1 mg/dL to 2.4 mg/dL (normal value <1.2 mg/dL). This finding was followed by a 1-week period of deteriorating kidney function during which her creatinine increased to 3.5 mg/dL, and she was admitted to an outside hospital for further work-up. The patient had no recent exposure to known nephrotoxins, a chest radiograph was unremarkable, and a renal ultrasound showed kidneys of normal size and echogenicity with no evidence of hydronephrosis. A complete blood count and metabolic panel showed slightly elevated potassium. Her medical history was significant for chronic obstructive pulmonary disease, hyperlipidemia, osteopenia, hypertension, and hypothyroidism, and she reported a 75 pack-year smoking history (quit in 2000). She had no family history of renal disease. A review of systems was negative for gross hematuria, oliguria, hemoptysis, or recent upper respiratory tract infections. On physical exam, the patient was afebrile with a blood pressure of 135/64 mm Hg, a heart rate of 64, and an oxygen saturation of 93% on room air. Her heart rate was regular and she did not have any extra heart sounds, but lung auscultation revealed a few scattered wheezes. Examination of the extremities revealed no edema, rashes, or synovitis.

After her rapid deterioration in kidney function the patient underwent a number of studies (summarized in Table 1). Notable findings were increased concentrations of antinuclear antibody (ANA), anti-glomerular basement membrane (anti-GBM) antibody, and antineutrophil cytoplasmic antibody (ANCA).

Light microscopic analysis of a renal biopsy specimen revealed cellular crescent formation in 1 of 2 glomeruli, minimal interstitial edema and fibrosis, and scattered interstitial mononuclear cell infiltrates. Immunofluorescence microscopy showed no deposition of antibody or complement, and electron microscopy revealed no immune complex deposits. Although observed on a marginal sample, these findings were suggestive of a pauci-immune glomerulonephritis due to small-vessel vasculitis.

After being transferred to the University of Virginia Health Sciences Center, the patient was treated with prednisone 60 mg daily, cyclophosphamide 100 mg

Table 1. Diagnostic Studies on Admission

	Patient	**Normal**
Urine Studies		
Appearance	**Bloody**	**Clear**
Specific Gravity	1.010	1.005-1.030
pH	5.0	5.0-8.0
Ketones	Trace	Negative
Glucose	Negative	Negative
Nitrite	Negative	Negative
Leukocyte Esterase	Trace	Negative
Heme	**Large**	**Negative**
Bilirubin	**Large**	**Negative**
Protein	**3+**	**0**
Microscopy	**Dysmorphic RBCs, rare RBC casts**	**No Casts**
Fractional Excretion of Sodium	**4.25%**	**1-2%**
UPEP	No monoclonal proteins	No monoclonal proteins
Serum Studies		
ANA	**1:320, speckled**	**Negative**
Double-Stranded DNA Antibody	Negative	Negative
C3	**37**	**83-156**
C4	12	10-38
CH50	130	101-300
Anti-GBM Antibody	**125 units**	**<20**
ANCA	**>1:640, perinuclear**	**Negative**
Anti-streptolysin O Antibody	<60	<60
HCV Antibody	Negative	Negative
HBV core Antibody	Negative	Negative
SPEP	No monoclonal proteins	No monoclonal proteins

daily, and 7 sessions of plasmapheresis, which were initiated 10 days after her initial presentation with asymptomatic elevated creatinine. Her serum creatinine decreased to 2.5 mg/dL, and she was discharged with no need for hemodialysis. Unfortunately, several weeks later she relapsed. Her creatinine was 3.5 mg/dL (see Figure 1), and hemodialysis was initiated for metabolic complications. The patient continued to be dialysis dependent 6 months after her initial presentation.

DISCUSSION

Glomerulonephritis, defined as intraglomerular inflammation associated with hematuria and proteinuria, is the most common cause of ESRD in the world, accounting for just over 50% of treated cases.[1] There are generally 5 different clinical presentations of glomerulonephritis: asymptomatic hematuria, with normal renal function; acute glomerulonephritis, with abrupt onset of decreased renal function in association with hypertension and edema; chronic glomerulonephritis, with a slowly progressive decline in renal function; nephrotic syndrome, with proteinuria in excess of 3 g/day leading to hypoalbuminemia and edema; and RPGN, with an abrupt decline in renal function that may lead to ESRD within weeks.[1]

RPGN, also known as crescentic glomerulonephritis (CGN), accounts for 2%-4% of all cases of glomerulonephritis and contains the pathologic feature of cellular crescents within the Bowman space of most glomeruli.[1] CGN is further subclassified into 3 histologic categories (Table 2): linear immunoglobulin deposition (type I CGN), as seen in anti-GBM disease, accounting for 20% of cases; granular immune complex deposition (type II CGN), as seen in lupus nephritis, accounting for 30% of cases; and the relative absence of immune deposition (type III CGN), as seen in small-vessel vasculitides, accounting for 50% of cases.[2] Type I CGN is invariably associated with anti-GBM antibodies and is referred to as Goodpasture syndrome when accompanied by pulmonary hemorrhage (50% of cases).[2] Type III CGN, also known as pauci-immune glomerulonephritis, is associated with ANCA in 80% of cases and is either associated with a systemic disease (75% of cases) or limited to the kidneys.[2] ANCA exist in 2 unique patterns: perinuclear ANCA (pANCA) directed against myeloperoxidase, and cytoplasmic ANCA (cANCA) directed against proteinase-3.[3]

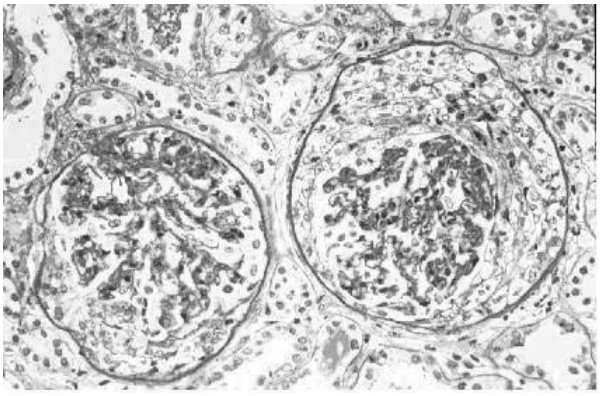

Figure 1.

The treatment for RPGN includes a prolonged course of high-dose steroids combined with a cytotoxic agent, typically cyclophosphamide. Although plasma exchange has traditionally been reserved for cases involving anti-GBM antibodies, recent evidence suggests improved renal outcomes in patients with purely ANCA-associated RPGN and severely reduced kidney function.[4,5] Therapy induces remission in 90% of type-III CGN cases, but up to one third of these patients experiences a recurrence within several years.[2] This pattern differs significantly from that seen in patients with type I CGN, up to 60% of whom are dialysis dependent at 1 year after disease presentation.[1]

In a minority of patients with either type I or type III CGN, serological analysis results are "double positive," meaning they contain anti-GBM antibodies as well as ANCA. Published data regarding this unique

Table 2. Classification Scheme of Crescentic Glomerulonephritis (RPGN)

Type	Incidence	Serology	Pathology	Associated Disease
I	20%	Anti-GBM Antibody	Linear immunoglobulin deposition	Anti-GBM Disease, Goodpasture's Syndrome
II	30%	ANA, ASO, or none	Granular immune complex deposition	Lupus, Post-infectious, Henoch Schonlein purpura
III	50%	pANCA, cANCA	Absence of immune deposition	Wegener's granulomatosis, Microscopic polyangiitis, Churg-Strauss syndrome

pattern are limited to a handful of case series reports. One series of 122 patients with type I or III CGN found the frequencies of ANCA, anti-GBM, and double-positive cases to be 80%, 12%, and 8%, respectively.[3] It is estimated that positivity for anti-GBM antibodies occurs in approximately 5% of type III CGN cases, and increased ANCA levels occur in 32% of type I CGN cases.[2,6,7] pANCA occur in almost all double-positive cases, whereas cANCA seem to be isolated to cases in which anti-GBM antibodies are directed against GBM antigens other than the typical alpha 3 chain of type IV collagen.[6] Compared to patients with isolated anti-GBM disease, patients with double-positive disease are more likely to be older (average age 59 vs 33) and present with extrarenal manifestations.[7] Slightly more than half of these patients present with pulmonary disease, and slightly less than half present with other organ involvement, most commonly rash, arthralgias, sinusitis, scleritis, neuropathy, and constitutional symptoms.[6-8] In one series, patients who presented with pulmonary manifestations were more likely to be elderly females who had never smoked, a finding that contrasts greatly with the classic association of pulmonary manifestations in Goodpasture syndrome with young male smokers.[9]

Although renal prognosis in types I and III CGN has been shown to be fairly consistent, the outcome in double-positive cases is difficult to assess because most case reports in the literature do not give a pathologic diagnosis but rather define such cases as a distinct entity. In one series comparing pANCA, anti-GBM, and double-positive cases, patients with double-positive disease (n = 10) had courses paralleling those of patients with anti-GBM disease.[3] These double-positive patients were more likely to present with oliguria/anuria and higher creatinine concentrations and subsequently had a worse 1-year renal survival rate: 64%, 15%, and 10% for pANCA, anti-GBM, and double-positive cases, respectively.[3] In another series (n = 27), the outcomes of double-positive patients were correlated with the degree of renal failure at presentation; no double-positive patients who had creatinine concentrations greater than 5.66 mg/dL or who were dialysis dependent at presentation recovered renal function. For patients with lower creatinine or without dialysis dependence, the 1-year renal survival rate was 71%.[6] In another series of 6 double-positive patients, no patients recovered renal function. These patients seemed to have quite severe disease; the lowest presenting creatinine was 6.8 mg/dL, and the anti-GBM titers were all markedly elevated.[9] Another series (n = 8) revealed a 50% renal recovery rate and linked outcome with the anti-GBM:ANCA ratio; there was a much better outcome in cases with the lowest anti-GBM antibody titer and the highest ANCA titer.[7]

Owing to the varying courses of this disease, there has been much interest in the temporal relationship between the development of ANCA and anti-GBM antibodies in the serum of double-positive patients. It has been hypothesized that an initial antibody may induce the formation of a second antibody by damaging the GBM and exposing underlying immunogenic antigens.[3,6,10] In all the case series we reviewed, we found only 1 report of a double-positive patient who tested positive for ANA.[8] The significance of these "triple-positive" cases, as occurred in our case patient, is unknown, but according to the above theory this scenario could result in the development of multiple autoimmune phenomena.

Our case patient presented with several features favoring a good prognosis. These findings included a serum creatinine <5.66 mg/dL, dialysis independency, no extrarenal involvement, and a pathologic diagnosis of type I rather than type III CGN. Despite receiving the recommended aggressive therapy, however, she became dialysis dependent. The renal biopsy sample was noted to have few glomeruli, and it is possible that a sampling error concealed the true extent of her pathology. Because the patient was asymptomatic at presentation, a delay in diagnosis and subsequent treatment may have been a factor in her poor outcome, and the importance of her elevated ANA titer also remains in question. Alternatively, the presence of high-titer anti-GBM antibodies may be an independent predictor of a poor prognosis in patients who otherwise have signs of the more indolent ANCA-associated RPGN.

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Lactic Acidosis and Malignancy: A Case Series and Review

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Lactic acidosis, a rare complication of advanced malignancy, is usually associated with hematologic malignancies with large tumor burdens or solid tumors accompanied by hepatic metastases.[1-8] Lactic acidosis in this setting occurs without typical precipitating factors such as sepsis, hypoxia, or tissue hypoperfusion[9-12] and is attributable to excessive lactic acid production by neoplastic cells and impaired lactate uptake.[9,11,12] Lactic acidosis was first described by Huckabee in 1961.[13] Cohen and Woods first made the distinction between type A and B lactic acidosis.[14] Type A lactic acidosis is caused by tissue hypoperfusion or acute severe hypoxemia. Type B lactic acidosis, which may be caused by drugs, toxins, and common diseases such as alcoholism, liver disease, diabetes, and malignancy, occurs in 3 different subtypes differentiated on the basis of underlying etiology (Table 1). Type B was originally described as occurring in the absence of poor tissue perfusion or oxygenation; however, in many cases occult tissue hypoperfusion accompanies the underlying primary etiology. Luft et al defined it with the criteria of pH ≤ 7.35 and serum lactate concentration >5 mEq/L.[15]

Patients suffering from lactic acidosis may present with hyperventilation, hypotension, nonspecific tachycardia, weakness, or stupor.[16] Laboratory study findings typically include anion-gap metabolic acidosis and elevated serum lactate concentration. Treatment measures include basic resuscitation, fluid repletion if there are signs of tissue hypoperfusion, and identification of the underlying illness with directed treatment. This treatment may include antibiotic administration, surgical drainage or debridement, cessation of contributing medications, chemotherapy for malignancy, and dietary modification for inborn errors of metabolism.

Field et al first described lactic acidosis from a neoplastic cause in patients with acute leukemia.[17] In total, approximately 74 cases of type B lactic acidosis in patients with leukemia or lymphoma have been reported in the medical literature.[4,18-22] We present 2 cases of lactic acidosis due to malignancy that occurred in the past year at our institution.

CASE 1

A 45-year-old Haitian man with a history of human immunodeficiency virus (HIV) and hepatitis B virus infection and hypertension presented with a 6-month history of diffuse lymphadenopathy. He also complained of fever, malaise, diaphoresis, and a 30-lb weight loss over this time. Of note, the patient had started highly active retroviral therapy (HAART) for treatment of HIV approximately 3 months prior to presentation.

On initial examination, the patient's vital signs included a temperature of 36.3° C, heart rate 109 bpm, blood pressure 115/81 mm Hg, respiratory rate 22/min, and oxygen saturation 98% on room air. Examination was notable for palpable lymphadenopathy of the cervical, axillary, and inguinal regions, with axillary lymph nodes measuring approximately 3-4 cm in diameter. Results of the patient's initial laboratory work (Table 2) revealed increased concentrations of lactic acid and lactate dehydrogenase, acute renal failure, and transaminitis. Computed tomographic scans of the brain, chest, abdomen, and pelvis showed extensive thoracic, abdominal, and pelvic adenopathy, multiple hypodense lesions within the liver, and a mottled appearance of the spleen (Figure 1). Fine-needle aspiration biopsy of a cervical lymph node was performed, and immunohistochemical stains of the biopsy specimen were consistent with diffuse large B-cell lymphoma (Figure 2).

Table 1: Lactic Acidosis Classification

	Definition/Mechanism	Examples
Type A	Poor tissue perfusion or oxygenation	Shock, cardiac arrest, acute pulmonary edema, severe exercise
Type B:	pH<7.35 & serum lactate>5 mEq/L	
B1	Systemic disease	Renal failure, hepatic failure, malignancy, diabetes, HIV
B2	Drugs & Toxins	Biguanides, alcohols, iron, isoniazid, salicylates, antiretrovirals
B3	Inborn errors of metabolism	Enzymatic defects in glycogenolysis or gluconeogenesis (glucose-6-phosphatase deficiency, pyruvate dehydrogenase deficiency, oxidative phosphorylation deficiency)

The patient was treated with intravenous fluids with bicarbonate to correct the lactic acidosis and aid in volume resuscitation. Treatment with HAART was not considered to be a cause of the patient's elevated lipase or lactic acidosis, because he had previously been on these medications without adverse effects. On day 3 of hospitalization, the patient demonstrated worsening somnolence, tachypnea, and tachycardia with onset of fever. In the setting of lactic acidosis, it was unclear if the patient's deterioration was attributable to the progression of malignancy or sepsis. Repeat arterial blood gas (ABG) analysis showed a pH of 7.17, pCO2 16.5, and pO2 121. Lactic acid levels escalated to 20 mmol/L. Blood and urine cultures were performed, and results remained negative. Chest imaging did not show evidence of infection.

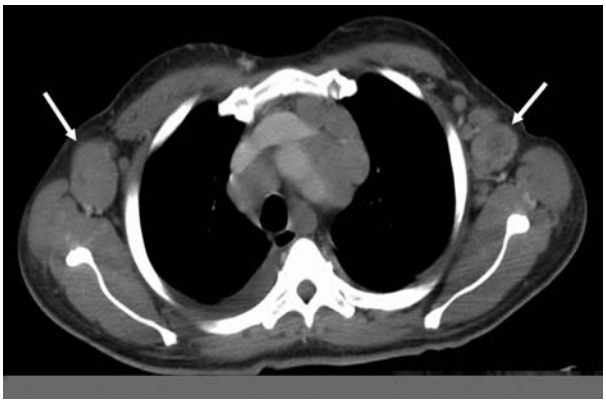

Figure 1. Chest computed tomographic scan of the case 1 patient demonstrates bulky axillary lymphadenopathy.

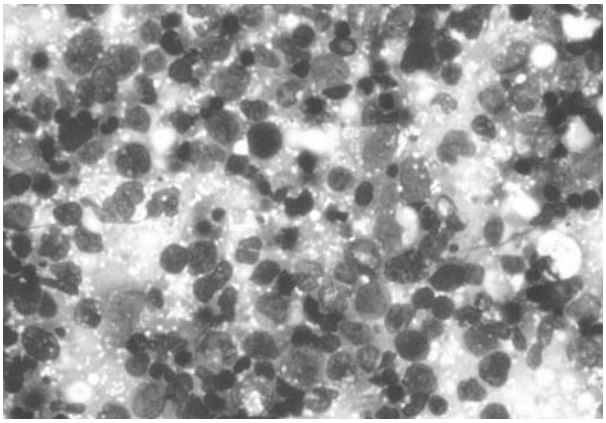

Figure 2.. Photomicrograph of a fine-needle aspiration biopsy specimen from the case 1 patient. Cervical lymph node aspirate shows a noncohesive population of large atypical cells consistent with high-grade lymphoma. On excisional biopsy, the lymph node demonstrated an immunohistochemical profile consistent with a high-grade B-cell lymphoma.

Table 2: Laboratory Values on Admission for Case 1

	Results	Reference Range
WBC	17.2 k/uL	4-11
Hematocrit	31.30%	40-52
Platelets	137 k/uL	150-450
Sodium	134 mmol/L	136-145
Bicarbonate	17 mmol/L	22-29
BUN	35 mg/dL	8.9-20.6
Creatinine	1.4 mg/dL	0.7-1.3
Anion gap	14	
AST	857 U/L	<35
ALT	173 U/L	<55
Alkaline phosphatase	187 U/L	40-150
Lactic acid	8.2 mmol/L	0.5-2.2
Lactate dehydrogenase	6040 U/L	180-360
CD4	210 /uL	
HIV viral load	176 copies/mL	
Hepatitis B viral load	>17 million IU/mL	
Hepatitis A	negative	
Hepatitis C	negative	
ABG on room air:		
pH	7.51	
pCO2	22.7	
pO2	69	

The patient was intubated for airway protection. He became hypotensive and was treated with aggressive fluid resuscitation, vasopressors for blood pressure support, and empiric antibiotic coverage. He was also started on continuous veno-venous hemofiltration for refractory lactic acidosis. Chemotherapy was initiated to treat both the malignancy and acidosis. Despite aggressive treatment, the patient died on day 5 of hospitalization.

CASE 2

A 21-year-old white man with a history of hepatitis C and stage-IIIB anaplastic large cell lymphoma who had recently been treated with 3 cycles of chemotherapy presented with a 3-day history of fever and arthralgias of the elbows and knees.

On initial examination, the patient's vital signs were temperature 38.6° C, heart rate 118 bpm, blood pressure 110/70 mm Hg, respiratory rate 24/min, and oxygen saturation 98% on room air. Physical exam revealed diffuse cervical, axillary, and inguinal lymphadenopathy. Laboratory values on admission (Table 3) demonstrated mild metabolic acidosis, transaminitis, and acute renal failure.
The patient was treated empirically with antibiotics as well as chemotherapy with methylprednisolone. A computed tomographic scan demonstrated diffuse pathologic adenopathy and an enlarged spleen with a

heterogeneous appearance thought to reflect a combination of lymphomatous infiltrate and evolving infarction. Despite volume resuscitation with normal saline and treatment with antibiotics and chemotherapy, the patient was persistently febrile and tachycardic.

Table 3: Laboratory Values on Admission for Case 2

	Results	Reference Range
WBC	4.1 k/uL	4-11
Hematocrit	26.40%	40-52
Platelets	61 k/uL	150-450
Sodium	131 mmol/L	136-145
Bicarbonate	23 mmol/L	22-29
BUN	29 mg/dL	8.9-20.6
Creatinine	1.7 mg/dL	0.7-1.3
Anion gap	12	
Alkaline phosphatase	467 U/L	40-150
AST	64 U/L	<35
ALT	30 U/L	<55
Hepatitis C viral load	undetectable	
ABG on room air:		
pH	7.37	
pCO2	33.5	
pO2	68	

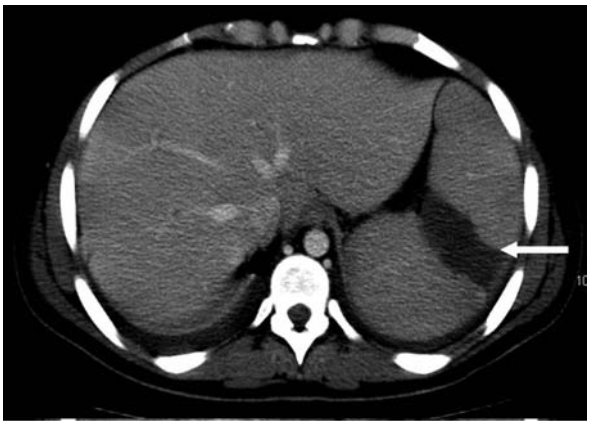

Figure 3. Abdominal computed tomographic scan of the case 2 patient demonstrates a splenic infarct.

The patient's respiratory status worsened, and a repeat ABG showed pH of 7.39, pCO2 23.9, and pO2 79.7 on a 4-L nasal cannula. Bronchoalveolar lavage was performed, and the lavage fluid was negative for infectious etiologies. A repeat computed tomographic scan of the chest and abdomen showed worsening splenic involvement with interval progression of splenic infarcts and new regions of infarction (Figure 3). In addition to worsening respiratory status, the patient developed disseminated intravascular coagulation and lactic acidosis, with a lactic acid of 11.2 mmol/L. The patient was intubated to relieve increased work of breathing and treated with supportive care for disseminated intravascular coagulation. He subsequently had worsening lactic acidosis and developed hypotension and was treated with intravenous vasopressive agents as well as a intravenous bicarbonate infusion, without improvement. Because of the patient's poor prognosis, dialysis treatment was not pursued. Laboratory results confirmed the patient's worsening condition, showing that lactic acid had increased to 21.9 mmol/L, and an ABG on 60% FiO2 showed pH 6.87, pCO2 61, and pO2 71. After discussions with the patient's family, we discontinued vasopressor medications, and the patient died. No infectious cause was identified as an etiology of the lactic acidosis.

DISCUSSION

In the setting of impaired oxygen delivery, pyruvate metabolism proceeds mostly through the production of lactate via anaerobic glycolysis (Figure 4) as a means to produce adenosine triphosphate for energy.[23] Excess lactate production causes metabolic acidosis because of the subsequent hydrogen ion production.[24] Lactic acidosis occurs when lactate production exceeds lactate utilization, a process that occurs predominately in the liver. Most causes of lactic acidosis are due to overproduction of lactic acid, but impairment in lactate utilization, such as in hepatic dysfunction, can increase the severity of

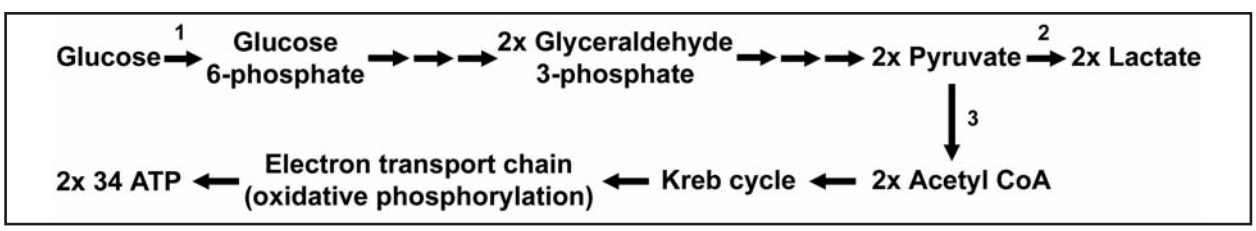

Figure 4. Diagram of lactate metabolism. Enzymes reported to contribute to lactic acidosis in malignancy are numbered: hexokinase (1), lactate dehydrogenase (2) and pyruvate dehydrogenase with thiamine as a cofactor (3).

lactic acidosis. The liver has a large capacity to eliminate lactate via gluconeogenesis and oxidation.[25] Lactic acidosis is not common in liver diseases, possibly because the kidneys also metabolize lactate and excrete it if serum levels are higher than 6-10 mmol/L.[26,27] In healthy patients, 10%-20% of lactate is renally cleared, but as much as one third can be cleared by the kidneys in patients with poor liver clearance.[28] However, patients with both liver and kidney dysfunction do not consistently develop lactic acidosis, suggesting a more complicated mechanism.[22]

Cancer cells have a higher rate of anaerobic glycolysis than normal cells, thus producing more lactate than normal cells.[29] Fast tumor-cell proliferation and poor hepatic utilization of lactic acid due to metastases have been thought to promote lactic acidosis in malignancy.[1,7,9,11,12,30] Overproduction of lactate occurs from accelerated[29,31-36] or altered[37,38] metabolism by cancer cells in a hypoxic setting.[30,32,36] Hepatic infiltration can compromise lactic acid metabolism and affect the elimination of lactate.[7-9,11,15,17,39-41] Low cardiac output causes decreased hepatic and renal blood flow and hypotension, which further contribute to lactic acidosis progression.[23] When ischemia is present, the remaining normal hepatic parenchyma may not be able to use increased quantities of lactate. Interestingly, some oncology patients present with lactic acidosis without liver metastasis, suggesting that impaired lactate elimination alone is not sufficient to explain lactic acidosis.[6,25,42,43] Patients with chronic liver disease generally do not have significant lactic acidosis unless it is associated with an acute complication such as sepsis or shock.[44-47]

Some studies have suggested that particular enzymes and binding proteins related to the glycolytic pathway may contribute to the pathophysiology of lactic acidosis in the setting of malignancy. Insulin regulates type II hexokinase, the first rate-limiting step in glycolysis.[48-50] Because cancer cells can overexpress insulin-like growth factors and their receptors and mimic insulin activity,[21] type II hexokinase may be overexpressed in malignancy. This type II hexokinase overexpression allows rapid proliferation of tumor cells and extended periods of tumor cell survival.[49] Sillos et al found that in the setting of malignancy insulin growth factor (IGF)-1, IGF-2, and IGF-binding protein (IGFBP)-3 concentrations were low and IGFBP-1 and IGFBP-2 concentrations were high.[21] These abnormalities were proportional to the degree of disease activity. Other studies had similar findings, with the exception of increased IGFBP-1 concentrations found in patients with leukemia and lymphoma (plasma lactate concentrations were not reported).[51-53] One supposition is that in malignant cells IGF and IGFBP play roles in signaling to induce overexpression of enzymes of the glycolytic pathway.[21]

A review of reported data suggests that thiamine or riboflavin deficiency associated with malignancy may also play a key role in the development of type B lactic acidosis.[22] In the pyruvate dehydrogenase complex, thiamine is a cofactor that converts pyruvate into acetyl coenzyme A; thiamine deficiency thus promotes anaerobic metabolism by conversion of pyruvate into lactate.[54,55] Thiamine deficiency occurs in cancer patients receiving total parenteral nutrition without vitamin supplementation, and lactic acidosis has been reported as a complication in these patients.[54-56]

Occurrence of lactic acidosis is a strong marker for poor prognosis.[21] We found 73 cases of lactic acidosis from leukemia or lymphoma whose outcomes are reported in the literature. Of these patients, 66 died from related complications. The 2 patients in our series failed to respond to alkalinization or dialysis to correct their underlying acidosis. No initial causes other than malignancy were noted for the lactic acidoses in these patients; only later did other potentiating causes such as hypoxia and hypoperfusion occur and likely contribute to worsening lactic acidosis. HIV in our first case and hepatitis in both cases were possible additional contributing factors. Although acidosis can respond rapidly to chemotherapy,[21,57] neither of our patients improved with chemotherapy.

Sodium bicarbonate infusion can compensate for, but not reverse, lactic acidosis.[48] Alkalinization may potentiate lactate production in patients who have lactic acidosis from malignancy.[33,58] To prevent adverse cardiovascular effects of elevated lactate concentration and acidosis, alkalinization may be necessary.[21] Hemodynamic function can be compromised and catecholamine response impaired when the pH is less than 7.2.[21] pH correction may need to be attempted to maintain tissue oxygen delivery until chemotherapy can be administered.[21] Severe lactic acidosis not associated with malignancy can be successfully treated with hemodialysis and

hemofiltration with a bicarbonate-based replacement fluid.[59] Another ongoing hypothesis is that repletion of B vitamins could be a simple, safe method to help reverse type B lactic acidosis.[22] Effective treatment of the underlying malignancy can promote resolution of the lactic acidosis.[1,6] Without effective therapy, however, lactic acidosis due to malignancy has a poor prognosis.[1] Fatal metabolic complications from lactic acidosis due to malignancy can be avoided by the rapid institution of cytoreductive agents; patients who do not respond die quickly.[1,30]

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ABC's of a Bronchioloalveolar Carcinoma-Like Malignancy

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In the United States, lung cancer is the leading cause of cancer mortality in individuals of both sexes. In 2001, 169,500 deaths, more than one-fourth of all cancer deaths in this country, occurred as a direct result of lung cancer.[1] Pathologically, lung cancer is categorized into small cell and non-small cell lung cancer (NSCLC) types. NSCLC is further subcategorized into an acinar, papillary, mucinous, and bronchoalveolar carcinoma (BAC). Among the subgroups of NSCLC, BAC and the related lung adenocarcinomas with BAC-like features are called "great imitators in medicine" or "mystery tumors" because radiographic and clinical features of BAC mimic many other pulmonary diseases.[2,3] However, because of the increasing prevalence of NSCLC, particularly BAC, more is being learned about these disease entities. We report a case of invasive mucinous adenocarcinoma with BAC-like spread. Despite initial diagnostic difficulties, this great imitator was uncovered.

CASE PRESENTATION

A 59-year-old white male patient presented to the emergency department after having a 14-mm reaction to a purified protein derivative (PPD) skin test for tuberculosis and an abnormal chest x-ray. The patient reported feeling well aside from dyspnea on exertion and a steady cough productive of mucoid sputum, both of which had been ongoing for several months. He denied fevers, chills, night sweats, and weight loss.

The patient's occupational history included work with prisoners. Travel history was significant for a vacation to Mexico in 1995. He had a 40 pack-year smoking history. Medical history was significant for diabetes and 3 bouts of complicated pneumonia within the past 2 years. At least 1 of the episodes required a left pleural decortication.

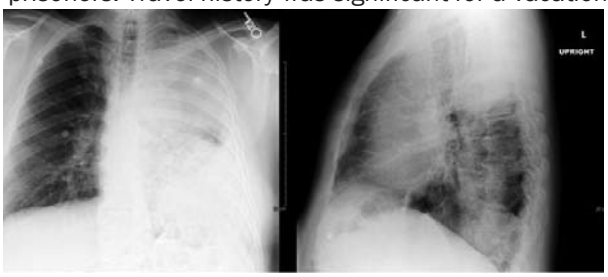

Figure 1. A chest x-ray shows left lower lobe infiltrate and loculated effusion within the left upper lobe.

Physical exam revealed an afebrile patient with normal vital signs. Auscultation of the upper lung fields revealed bronchial breath sounds anteriorly and posteriorly. Egophony and tactile fremitus were also found at those sites. Rhonchi were noted at the left base. The patient's comprehensive metabolic panel and complete blood count were normal; an enzyme-linked immunosorbent assay for the human immunodeficiency virus was negative. Analysis of arterial blood gas on room air revealed a pH of 7.43, pCO2 of 39 mm Hg, and pO2 of 66 mm Hg. The A-a gradient was 35 mm Hg, compared with an age-matched normal value of 17 mm Hg.

A chest x-ray obtained in the emergency department (Figure 1) showed a left lower lobe infiltrate and loculated effusion within the left upper lobe. In light of the recent 14-mm PPD, the patient was admitted and isolated in a negative-pressure room for possible active tuberculosis.

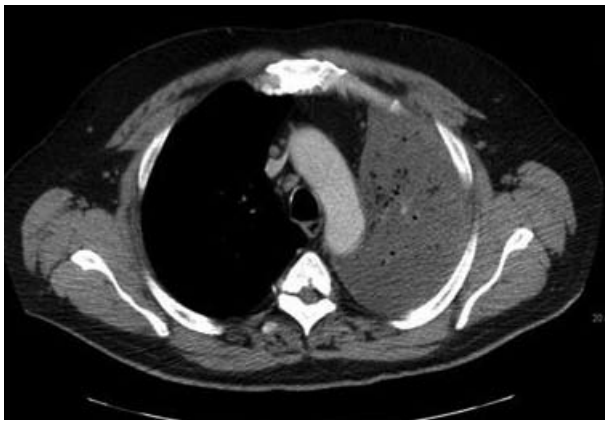

Figure 2. Computed tomographic scan of the chest with contrast shows necrotizing lobar pneumonia involving the left upper lobe and left lower lobe. Fine needle aspiration biopsy results revealed bronchoalveolar carcinoma.

DIAGNOSIS

To further evaluate the patient, a computed tomographic scan of the chest with contrast was performed (Figure 2), which revealed necrotizing lobar pneumonia involving the left upper and lower lobes. Because of this finding, a diagnosis of primary tuberculosis could not be excluded. However, sputum sample tests for acid-fast bacilli, gram stain, and culture were negative. Additionally, lack of systemic symptoms argued against a pulmonary infective process. Diagnostic bronchoscopy with brochoalveolar lavage of the left upper lobe demonstrated atypical cells, suspicious for adenocarcinoma, but did not yield a definitive diagnosis. Subsequently, an ultrasound-guided fine-needle aspiration biopsy of the left upper lobe was performed, and based on analysis of the biopsy sample an initial diagnosis of mucinous BAC was made.

MANAGEMENT

The patient was referred to medical oncology, where his work-up for BAC was continued. A computed tomographic scan of the chest, abdomen, and pelvis, as well as magnetic resonance imaging of the brain, demonstrated limited-stage disease. The patient then underwent a left pneumonectomy. Pathological analysis of the left lung revealed multifocal invasive mucinous adenocarcinoma, with extensive bronchioloalveolar-type spread. No evidence of malignancy was seen in excised lymph nodes. The patient's disease was initially classified as stage IIIB (T4N0M0).

The patient completed 4 cycles of adjuvant chemotherapy with cisplatin and vinorelbine in anticipation of postoperative radiation therapy (for a close diaphragmatic margin at the time of surgery). However, a computed tomographic scan of the chest revealed new pulmonary nodules in the right lung, consistent with metastatic disease. At the time of this report, the patient had been started on second-line chemotherapy with docetaxel and bevacizumab.

DISCUSSION

BAC is an indolent malignancy that develops from the epithelia of terminal bronchioles and alveoli. It can spread in a lepidic or aerogenous fashion. There is typically no invasion of the stroma, pleural cavity, or vascular system.[4] Consequently, when Liebow originally coined the term "bronchioloalveolar carcinoma," he was describing a peripheral, well-differentiated malignancy that does not deform the pulmonary interstitium.[5]

The pure form of BAC comprises only 2% to 5% of lung carcinomas.[4] In 1999 and 2004 the World Heath Organization and the International Association for the Study of Lung Cancer revised the diagnostic criteria for BAC. Depending on the definition used (pure BAC, BAC with focal invasion, and/or adenocarcinoma with BAC-like features), the prevalence of BAC changes greatly.[4-6]

As in the case presented here, many pulmonary adenocarcinomas contain BAC-like pathologic features and may behave more like BAC than adenocarcinoma. Clinically, patients with BAC are often asymptomatic. In some studies, up to 60% of BAC cases were first found when chest x-rays were performed for other indications. Symptoms may occur, however, and can include cough, dyspnea, weight loss, and hemoptysis.[5] Specifically, a small proportion (<10%) of those afflicted with BAC may present with large-volume bronchorrhea. This complication is typically found in patients with advanced mucinous BAC. Additionally, those with mucinous BAC may develop intrapulmonary shunting as a result of alveoli filled with malignant cells and mucous. Subsequently, V-Q mismatch occurs, resulting in an increased A-a gradient.[5]

The radiographic findings of BAC are diverse. In most cases (43%) BAC presents as a nodule or mass. It is usually found in the upper lobes and may have a "ground-glass" appearance on CT. In other cases (30%), BAC can present as a regional pneumonia-like consolidation. Slightly less frequent (27%) is diffuse dissemination of BAC.[4] Nonetheless, air-space disease with air bronchograms is typical and reflective of BAC, as tumor and mucinous debris fill alveoli while surrounding bronchi remain aerated and preserved.[7]

Prevalence of BAC is evenly distributed in men and women. Although smoking can play a role, nearly one-third of BAC cases are diagnosed in nonsmokers.[5] Such epidemiological observations are likely explained by epidermal growth factor receptor (EGFR) mutations, which are more common in patients with BAC than other histological varieties of lung cancer. Studies have found that women, nonsmokers, and Asians have an increased incidence of the EGFR mutation.[8]

The best treatment for BAC, as with other NSCLC, is surgical resection. Patients with incomplete resection live less than 5 years. Given the common pulmonary-only spread and infrequent finding of nodal metastases, consideration has been given to lung transplantation, especially in those patients with recurrence of BAC.[4]

Because of the relatively small number of patients with pure BAC, no prospective trials have been performed, but the BAC component (BAC pattern and pathological stage) may be useful in predicting outcomes for patients with lung adenocarcinoma.[9] Additionally, because most cases of adenocarcinoma with BAC-like features are classified as adenocarcinoma, it is difficult to determine a true response rate of chemotherapy treatment of BAC.[8] BAC patients seem to have a poorer chemotherapy response rate (5%) compared to that of other lung cancer patients (25%). A 96-hour infusion of paclitaxel induced a 14% response rate and median survival of 1 year, results similar to those of other lung cancer types.[10]

Fortunately there is increasing evidence of sensitivity of BAC to the EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib. Because EGFR mutations occur in 58% of tumors with BAC histology, these chemotherapeutic agents show promise. Some studies, however, show no EGFR mutations in mucinous BAC variants. Furthermore, there is still insufficient evidence to support use of these agents as first-line therapy.[8]

CONCLUSIONS

Our case demonstrates the incidental finding of adenocarcinoma with BAC-like spread after a 14-mm PPD triggered further evaluation with a chest x-ray. Relevant symptoms included mucoid sputum, tobacco history, and an indolent course marked by 3 episodes of pneumonia. A review of the literature detailed the evolving classification of BAC cases-pure, those with focal invasion, and adenocarcinoma with BAC-like features. Our patient suffered the latter. As such, his treatment options included excision and adjuvant chemotherapy.

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Pelger-Huët Pseudobandemia

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A 30-year-old woman who recently started oral contraceptives presented to the emergency department with acute unilateral ear pain and was found to have dural sinus thrombosis. The patient's neurological examination results were normal, and she showed no signs of infection. Laboratory result on admission included a platelet count of 264,000 platelets/μL and a white blood cell count of 7090 cells/μL; no differential count was performed at the time. On hospital day 4, the patient developed daily fevers and a maculopapular rash on her right arm at the site of heparin infusion. Clinical and laboratory evaluations for infection were unrevealing except for a white blood cell count of 3730 cells/μL, of which 54% were segmented neutrophils and 15.6% were band forms. Her rash and fevers resolved after heparin was discontinued; the patient remained without signs of infection, but the bandemia persisted. Because a diagnosis of septic thrombophlebitis was unlikely, we further evaluated the bandemia on a peripheral blood smear. The smear showed granulocytes with bilobed nuclei connected by a thin bridge of nuclear material and no toxic granulation, findings consistent with the Pelger-Huët anomaly (Figure 1A). Nuclei of Pelger-Huët cells are characterized as having a "pince-nez" appearance, named after the style of spectacles that lack ear stems (Figure 1B). The presence of giant platelets (Figure 1C) suggested acquired disease, or pseudo-Pelger-Huët, rather than the autosomal dominant congenital form. Acquired disease is frequently associated with myelodysplastic disorders and myeloid leukemia. It has also been associated with medications (mycophenolate mofetil, tacrolimus, valproic acid, colchicine, sulfonamides, ibuprofen, taxoids) and infections such as tuberculosis and mycoplasma. The patient's platelet count did not change significantly during her hospitalization. Ultimately, her fever was ascribed to the heparin. She was discharged with outpatient follow-up to evaluate for an underlying hematologic disease.

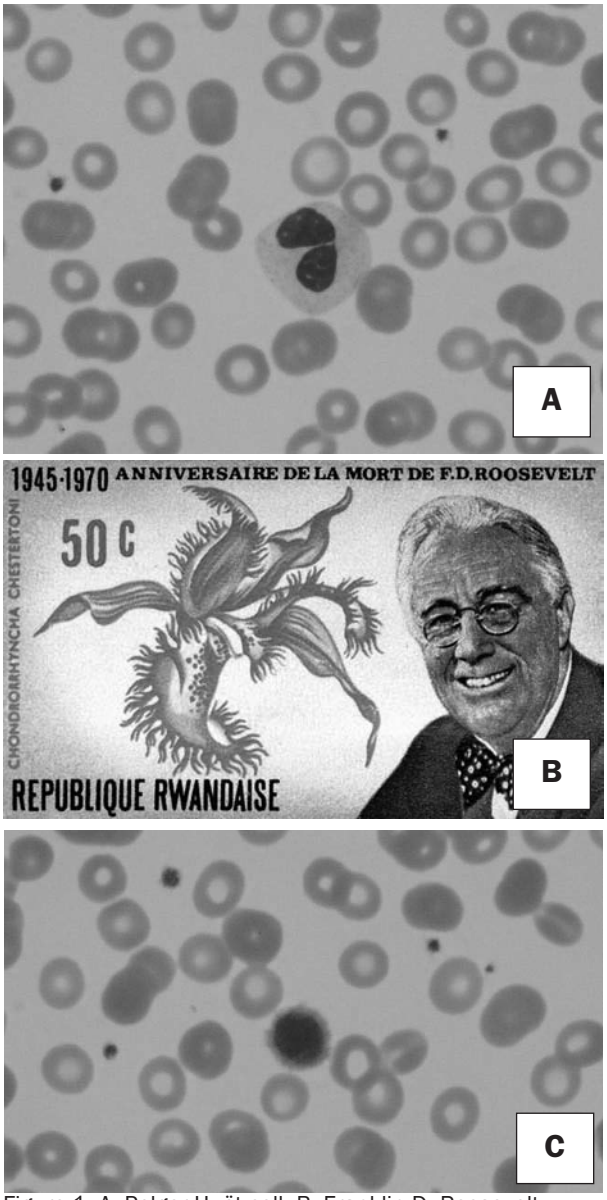

Figure 1. A. Pelger-Huët cell. B. Franklin D. Roosevelt wearing pince-nez spectacles. C. Giant platelets, which suggest acquired rather than congenital disease.

Cardiac Magnetic Resonance Imaging of Acute Myocarditis

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Cardiac Magnetic Resonance Imaging (CMR) has high sensitivity and specificity for detecting myocardial edema and myocyte damage and is often helpful in making a diagnosis in cases of myocarditis, such as the one we report.

CASE DESCRIPTION

A 35-year-old man presented with new-onset "aching" chest pressure radiating to the upper back, neck, and mouth that lasted for hours at a time, waxing and waning. These symptoms were not associated with exertion, had no exacerbating factors, were slightly alleviated by leaning forward, and were only partially relieved with aspirin, nitroglycerine, ß-blocker, and morphine. Associated symptoms included palpitations, malaise, myalgias, and nausea. The patient reported a recent history of upper respiratory symptoms 3 weeks prior to admission. Otherwise, the review of systems was negative. The patient reported exercising on a regular basis, including jogging several miles each day. He denied tobacco, alcohol, and drug use and high-risk sexual activities. He also denied use of medications or herbal products. The patient had no significant medical history, but his grandfather died of myocardial infarction (MI) at age 65.

Physical exam results were unremarkable except for bradycardia and a soft systolic flow murmur. In addition, the patient appeared anxious. Laboratory results were significant for a C-reactive protein of 14.8 mg/L and troponin-I of 6.7 ng/mL. Test results for D-dimer, human immunodeficiency virus, and hepatitis C virus were negative. Electrocardiogram showed sinus bradycardia (56 beats per minute) with J-point elevations in V2, V3, and V4; T- wave inversions in III, aVF, V5, and V6; and a right bundle-branch block. Telemetry revealed several episodes of 6-9-beat runs of asymptomatic nonsustained ventricular tachycardia. Coronary angiography results were normal.

CMR imaging (Figure 1) showed normal left ventricular size and systolic function. Triple short inversion time inversion recovery (STIR) images (precontrast) of the apex and lateral wall demonstrated a patchy high signal consistent with myocardial edema (Figure 1A). Short-axis (Figure 1B) and long-axis (Figure 1C) inversion recovery images obtained 10 minutes after gadolinium infusion demonstrated subepicardial and midmyocardial late gadolinium enhancement involving the left ventricular apex and the anterior, lateral, and inferior walls, findings consistent with myocarditis.

Myocarditis is characterized by focal patchy or diffuse inflammatory infiltrate with adjacent myocyte injury.[1-5] The inflammation is not always limited to the myocardium and may involve the adjacent endocardium, pericardium, and valvular structures. A detailed history and physical examination, including a

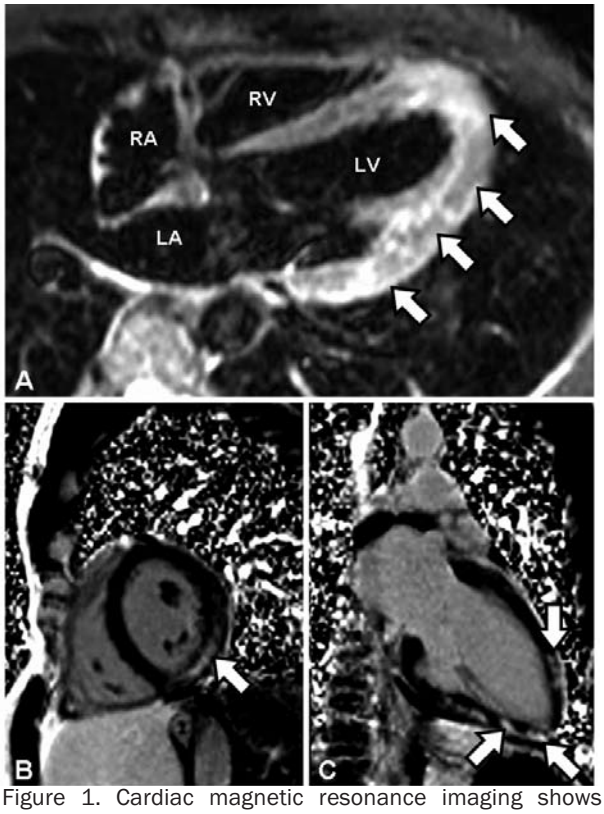

Figure 1. Cardiac magnetic resonance imaging shows normal left ventricular (LV) size and systolic function. Triple short inversion time inversion recovery inversion recovery (STIR) images (precontrast) of the apex and lateral wall demonstrate a patchy high signal consistent with myocardial edema (A). Short-axis (B) and long-axis (C) inversion recovery images obtained 10 minutes after gadolinium infusion demonstrate subepicardial and midmyocardial late gadolinium enhancement involving the LV apex, and the anterior, lateral, and inferior walls, findings consistent with myocarditis. RA indicates right atrium; RV, right ventricle; LA, left atrium.

stress test, transthoracic echocardiography, and coronary angiography may be useful for distinguishing myocarditis from coronary artery disease, valvular heart disease, cardiomyopathies, or other less common variants of cardiac problems. The diagnosis may be unclear, however, in a subgroup of patients with impaired cardiac function that cannot be explained by coronary artery disease or abnormal preload. In these patients, CMR is often helpful in making a diagnosis.

CMR has high sensitivity and specificity for detecting myocardial edema and myocyte damage.[6] In particular, the STIR sequences are useful for detection of edema/inflammation (sensitivity>80%), and late gadolinium enhancement identifies myocardial scarring (specificity, 100%), which appears white, whereas normal myocardium appears black. Myocarditis shows a characteristic pattern of contrast enhancement, originating from the epicardium and sparing the subendocardium. In contrast, MI typically shows early subendocardial perfusion defects and subendocardial or transmural delayed segmental enhancement in a vascular distribution (Figure 2). The degree of enhancement correlates with clinical status and cardiac function. Interestingly, in patients who eventually develop dilated cardiomyopathy after an episode of acute myocarditis, the enhancement pattern may change over time, so that eventually a repeat CMR study may show the characteristic midwall enhancement of nonischemic dilated cardiomyopathy. Although the location of the late enhancement in the midwall and subepicardium increases the likelihood for diagnosing acute myocarditis, other inflammatory cardiomyopathies such as sarcoidosis may also show patchy enhancement.

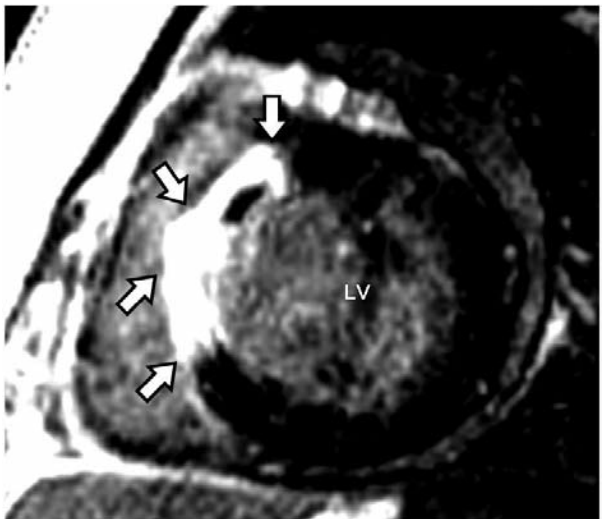

Figure 2. Typical cardiac magnetic resonance imaging findings for myocardial infarction show early subendocardial perfusion defects and subendocardial or transmural delayed segmental enhancement in a vascular distribution.

Several features of this patient's CMR study are typical of acute myocarditis, including the patchy edema on the STIR images, the subepicardial late gadolinium enhancement, and the primarily anterolateral location of the abnormalities. The CMR study with late gadolinium enhancement also confirmed that this patient did not have an acute MI. Normal coronary angiography does not necessarily rule out MI, because it is possible that the patient could have had an embolic occlusion of a coronary artery that subsequently resolved, leaving the artery patent. If a patient like this truly had an embolic event causing arterial occlusion and MI, we would have expected echocardiographic or MR functional images to show a wall-motion abnormality in a vascular distribution (as described above) and to demonstrate late gadolinium enhancement in the subendocardium rather than the midwall and subepicardium.

Of note, gadolinium is still safe in most patients but has been associated with instances of nephrogenic systemic fibrosis in patients with severe renal insufficiency requiring hemodialysis or peritoneal dialysis.[7-9] Thus, CMR protocols attempt to minimize the contrast volume for specific clinical indications, especially in patients with moderate to severe renal failure.

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Some Things I Taught You about Infectious Diseases 30 Years Ago that Were Wrong

Condensed from the 30th C. Richard Bowman Memorial Lecture, Department of Medicine Grand Rounds, October 23, 2007

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On the 30th anniversary of the Bowman Lecture, one is tempted to look back and consider how things have changed over the past 30 years. Unfortunately, many of the things I then taught have now been proven wrong, and I will provide just a few examples.

There are some things unique to infectious diseases that have gotten us into particular trouble. First of all, ours is the only field in which there is feedback from the individual to the environment. Were I taking an antimicrobial, I would be transferring to the environment organisms resistant to that agent. One must temper one's use of antibiotics with the knowledge that such use will always have an effect on flora and has, therefore, an effect on which antibiotics may still be of use in the future. Infectious disease treatment is the only clinical area in which there is actual loss of drugs. Thiazides do what they always did, but penicillin no longer cures some infections for which it was once effective. Also, we have new diseases. Toxic shock syndrome, human immunodeficiency virus/acquired immune deficiency syndrome, Legionnaires disease, and West Nile virus infection are just a few examples of diseases that did not exist, or at least were not recognized, 30 years ago.

The loss of antibiotics has caused major changes in our approach to treatment. In 1969, my resident confidently told me "this new drug, Keflin(r), is just like penicillin, but it cures everything." Thirty years ago, we thought that we had lots of excellent new antibiotics, new classes of antibiotics were being developed all the time, and we were probably staying ahead of the bacteria. Unfortunately, bacteria developed a whole range of resistance mechanisms, including decreased permeability, efflux pumps, (-lactamases, and changes in target proteins. At the same time, the number of new antimicrobials decreased dramatically.[1-4] Whereas between 1983 and 1987, 16 new antimicrobial agents were approved, this number dropped in almost linear fashion until between 1998 and 2002 only 7 new antimicrobials were approved, and in 2002, of 89 drugs approved, none was an antimicrobial. This argument is the first of several that I will make for the careful stewardship of our use of antimicrobials.

For example, 30 years ago, we told you that nafcillin cured infection with *Staphylococcus aureus.* I taught that one should never administer more than 9 g of nafcillin intravenously over a 24-hour period, because using more than 9 g increased the risk of interstitial nephritis, hepatitis, and possibly maturation-arrest bone marrow suppression. When challenged recently on this contention, I could find no support in the literature. Indeed, a total daily dose of 12 g of nafcillin is actually cheaper than 9 g, because the drug is purchased in 2-g packets. If one prescribes 2 g given intravenously every 4 hours, individual packets can be administered. If, however, one prescribes 1.5 g every 4 hours, the smaller dose must be made up in the pharmacy, and the cost of administration goes up considerably.

The effectiveness of the antistaphylococcal penicillins has decreased dramatically. Methicillin-resistant *Staphylococcus aureus* is, as you well know, prevalent in both the hospital and the community.[5] Indeed, serious staphylococcal infections, wherever acquired, must now be treated initially with vancomycin because of the relatively high likelihood that the etiology is, indeed, methicillin-resistant *S. aureus*. If the causative organism is subsequently identified as methicillin-sensitive, then a ß-lactam can be substituted for the vancomycin. Fortunately, vancomycin is actually considerably less toxic than we thought 30 years ago. It used to be brown, but it is now colorless, and improvements in the manufacturing process seem to have eliminated contaminants and reduced toxicity. Furthermore, we can now obtain serum levels of the drug, and so overdosage is largely a thing of the past. Thirty years ago, we taught you that all gram-positive pathogens, with the exception of such way-out bacteria as

Leuconostoc spp. and *Pediacoccus spp.*, were susceptible to vancomycin. Alas, the microorganisms have again proven this incorrect, and we now frequently deal with vancomycin-resistant enterococci. Indeed, relative resistance to vancomycin predicts treatment failure for some infections. One becomes very uncomfortable treating a serious infection by *S. aureus* that has a minimum inhibitory concentration (MIC) for vancomycin of 2 µg/mL or greater.[6-8]

In our state of antibiotic bliss of 30 years ago, we were delighted by the arrival of the antipseudomonal aminoglycosides, such as gentamicin. Actually, we were probably overly optimistic even 30 years ago, because organisms with decreased sensitivity to gentamicin had already been reported from intensive care units. Still, I happily taught you, "we won't have to use colistin anymore." My limited experience with colistin 30 years ago convinced me that it was usually ineffective and was, at the same time, highly toxic. Now, as we shall see, we return to the use of colistin as a drug of last resort,[9-11] but people with current experience have suggested that, like vancomycin, colistin is less toxic than we originally felt.

I would like to mention something that we actually failed to tell you 30 years ago, and that omission was wrong. Thirty years ago, we never even mentioned *Acinetobacter baumannii*.[12-18] Thirty years ago, this organism was felt to be an infrequent cause of nosocomial pneumonia, and isolation from sputum was far more likely to reflect colonization than true infection. Bacteremia caused by this organism was rare, and was usually associated with intravenous catheters and occasionally caused wound and skin infections. Once again, even 30 years ago, this organism was showing initial signs of resistance to the standard antibiotics. *A. baumannii* organisms from several geographical areas are already showing high levels of resistance to many antimicrobials, and unfortunately colistin is once again needed.
Risk factors for acquiring *A. baumannii* include being a patient in an intensive care unit, where environmental survival of the pathogen has been well documented[19]; carrying of one of the enterobacteriaceae or *Pseudomonas aeruginosa* capable of elaborating an inducible extended-spectrum ß-lactamase (ESBL); the use of prior antimicrobials; or serving in Afghanistan or in the Iraq/Kuwait region.[20] Because of this pathogen, we now require colistin-based regimens for many of our patients. Surprisingly, ampicillin/sulbactam is often effective against this organism. Indeed, the sulbactam moiety actually provides the antimicrobial activity.

At least as important is prevention of the spread of the organism by employing excellent antibiotic stewardship (Table 1) and infection control. We must; I repeat, *must* reduce the unnecessary use of broad-spectrum antimicrobials. We must carefully differentiate colonization from infection. Before treating for an organism isolated from sputum, one should have some clinical evidence of pneumonia, such as new infiltrate, new fever, change in the quantity or character of sputum, sputum gram stain, which now reveals the appropriate morphotype, or new requirement for respiratory support. As one would expect, initiating antimicrobial therapy to treat colonization does not benefit the patient, yet it dramatically increases selective pressure for resistant organisms. One must be rigorous about obtaining appropriate specimens for specific etiological diagnosis, even when this process involves invasive procedures, such as broncroscopy, biopsy, or incision. To hold that such procedures are unnecessary because we can provide broad-spectrum antimicrobial coverage is, even in the short run, self-defeating.

Thirty years ago, we were convinced that the klebsiellae were uniformly sensitive to the first-generation cephalosporins, although the enterobacters were not. This distinction was considered so reliable that it was actually used for

Table 1. Principles of Antibiotic Stewardship

Reduce the unnecessary use of antibiotics
Do not use newer antibiotics in patients at low risk for infection with resistant organisms
Do not use more (duration or number) antimicrobials than are required
Carefully differentiate colonization from true infection
Carefully differentiate contamination from true infection
Obtain appropriate specimens for specific, etiological diagnosis
De-escalate antibiotic spectrum when etiology is defined

initial differentiation of the 2 genera. I taught that this difference in sensitivity was easy to remember because the first-generation cephalosporins, including Keflex®, Keflin®, and Kefzol®, like *Klebesiella*, all began with *K*. Unfortunately, the *Klebesiella spp.* became resistant to many antimicrobial agents and became notorious for being able to develop ESBLs. We responded to this challenge by treating such infections with other antimicrobial agents, including the newly developed carbapenems, such as imipenem/cilastatin, meropenem, ertapenem, and doripenem. These newer agents are relatively resistant to many of the most common ESBLs. It is inappropriate to adopt the practice of not bothering to make a specific etiologic diagnosis given that carbapenems have such broad spectra that a cure is still reasonably assured. So, we have been using a lot of carbapenems, particularly in intensive care settings, where one is most likely to run into an organism capable of producing an ESBL. Organisms have responded, and we now face infection with members of the genus *Klebesiella* that produce enzymes capable of inactivating the carbapenems.[21] These *Klebesiella producers of carbapenemases* (KPC) have caused recent outbreaks in New York, New Jersey, and Philadelphia. The major risk factor for infection with these agents is prior extensive exposure to antibiotics, not necessarily including the carbapenems. Recent data from an outbreak in New York City[22,23] involving 99 patients reveals that 69% had received a carbapenem within the previous 2 weeks. A statically significant fraction of these patients were solid organ transplant recipients, and the mortality was 48%, versus 20% in patients who were not infected with these agents. This resistance is plasmid mediated, so it is likely to be transferred to other genera. Indeed, this pattern of resistance, genetically identified, has been seen in: *Citrobacter freundii, Klebsiella oxytoca, Enterobacter spp., Escherichia coli, Salmonella spp.,* and *Serratia spp*. We have isolated KPCs from several patients at the University of Virginia Health Sciences Center, and as a result have become suspicious of organisms that are resistant to the extended-spectrum ß-lactams, such as ceftriaxone and cefepime, because it is in this setting that the KPCs are likely to arise.

Most importantly in the long run, we must reduce the inappropriate use of carbapenems. One unnecessary use of carbapenem antibiotics is as preoperative prophylaxis. The use in this setting is supported by flawed data, because the study purporting to show an advantage over traditional approaches was based on a study of patients who were undergoing bowel surgery but in whom a preoperative bowel preparation was specifically excluded.[24] The postoperative infection rates were therefore considerably higher than we see here. It is our practice at the University of Virginia Health Sciences Center to encourage the use of alternative perioperative regimens, such as a combination of a first-generation cephalosporin and metronidazole, as equally effective perioperative prophylaxis.

A little over 30 years ago, I taught that penicillin cured gonorrhea. Approximately 30 years ago, however, a new organism made its appearance, penicillinase-producing *Neisseria gonorrhoeae*. But, I taught, we still have tetracycline, which, by the way, would cure coincident chlamydial infection. Recognized shortly thereafter was a self-transferable plasmid that contained a mutation rendering gonococci absolutely resistant to achievable levels of tetracycline. Having been forced to give up on penicillin and tetracycline, we turned for the treatment of uncomplicated gonorrhea to the cephalosporins and then to the fluoroquinolones, including ciprofloxacin, which could be given as a single pill, and which was far more economical and patient-acceptable than the parenteral cephalosporins. It did not take long for *N. gonorrhoeae* to develop chromosomal mutations that altered the target proteins for the fluoroquinolones and conferred relative resistance to the agent. Indeed, a gonococcal MIC of 4 µg/mL of ciprofloxacin conferred a 50% failure rate with standard antigonococcal treatments. Fluoroquinolone-resistant *N. gonorrhoeae* originated in the Pacific Rim. The organism was soon thereafter isolated in Hawaii and then from the West Coast of the United States, and the specific travel history for patients and their partners therefore became important for management. In 2003, however, a relatively high prevalence of fluoroquinolone-resistant gonococci was noted among men who have sex with men. The original reports came from Massachusetts and New York City. As of April 13, 2007, the US Centers for Disease Control and Prevention (CDCP) no longer recommend the use of fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) for gonorrhea and associated conditions.[25,26]

How should one treat uncomplicated gonorrhea in 2008? The CDCP has long recommended a single-

dose treatment with cefixime 400 mg. This regimen has produced a cure rate of 97.4%. Unfortunately, at present, cefixime is available only as a powder, which is reconstituted to a liquid form. If one is not treating lots of gonorrhea, the limited shelf life of the remaining liquid will dramatically increase the cost of individual treatments. Spectinomycin, recommended by the CDCP, is not available in the United States. One might consider using cefpodoxime proxetil 400 mg, as a single oral dose. A 200-mg single oral dose was approved by the US Food and Drug Administration, but not by the CDCP. The reason for this difference is that, based on the data available when the new drug application was submitted, the 95% confidence limits on the cure rate ranged from 94.8% to 99.8%. The CDCP prefers to recommend regimens for which the lower bound of the 95% confidence limit on cure is at least 95%. Studies of a 400-mg regimen are currently underway.

Thirty years ago, I paid little attention to coagulase-negative staphylococcus (CoNS) and considered that it was not much of a pathogen (except for some mild urinary tract infections); now I know better. Currently, we put far more foreign material in our patients and for longer periods of time than we did 30 years ago. Furthermore, we deal with more patients who are severely immunocompromised and who, therefore, are at increased risk of serious infection with organisms of limited intrinsic virulence. Finally, like almost all other groups of microorganisms, CoNS exhibit detrimental changes in antimicrobial sensitivity. We now recognize that CoNS are important causes of bacteremia in the patients who are immunocompromised and those suffering osteomyelitis, particularly in sternal wounds; postoperative endophthalmitis; native valve endocarditis; and, of course, infection of foreign bodies.

The foreign bodies that are well-recognized sites of infection with CoNS include intravenous catheters, hemodialysis shunts and grafts, cerebrospinal fluid shunts, pacemaker wires, prosthetic joints, prosthetic cardiac valves, breast implants, and penile prostheses. Other CoNS species have been implicated as infectious organisms . *Staphylococcus lugdunensis* causes native valve endocarditis of high virulence. *Staphylococcus haemolyticus* is resistant to multiple antibiotics, including vancomycin. *Staphylococcus schleiferi* has been reported to cause prosthetic valve endocarditis. Like *S. lugdunensis, S. schleiferi* possesses a clumping factor and so may be found to have higher virulence than some of its cousins.

Additionally, CoNS have become resistant to standard antimicrobial agents. Thirty years ago, many remained susceptible to the penicillinase-resistant penicillins, such as methicillin. Rapidly thereafter, they became resistant to methicillin, but they remained susceptible to the first-generation cephalosporins. Currently, 80% of *Staphylococcus epidermidis* and *S. haemolyticus* are resistant to methicillin.[27] Thus we have changed our practice and use first-generation cephalosporins for preoperative prophylaxis for surgery involving implantation of foreign bodies. Many of the CoNS now contain the *MecA* gene, which alters penicillin-binding protein 2 and confers resistance to all ß-lactams.[28]

Resistance among the CoNS is heterotypic. In a culture of any given isolate, many of the individual cells will be sensitive. This characteristic is treacherous because it may make the in vitro MIC look favorable, but we must beware.[29] The reason that single doses of the first-generation cephalosporins probably work as perioperative prophylaxis is that this regimen seeks only to kill the very small number of bacteria introduced at the time of surgery, and heterotypy insures that cephalosporin resistance will be rare. In established infection, however, one confronts large numbers of organisms. Treatment with first-generation cephalosporins will select for the few cells that are resistant. In fact, we do see failures in animal models of infection with “sensitive” CoNS, when these infections are treated with ß-lactams or related antibiotics.[30] Therefore it is probably better to use vancomycin as empirical therapy when infection with CoNS is suspected.

We must remember, however that CoNS is still frequently a contaminant. Overall, 1%-3% of positive blood cultures are contaminated, and 25%-74% of CoNS isolated in blood cultures are felt to be contaminants.[31] To differentiate true bacteremia from contamination, *one must always draw 2 sets of blood cultures from different venipuncture sites! Always!* Finding these organisms in one but not both of these blood cultures supports the idea that one is dealing with contamination.

Thirty years ago I considered infection with human papillomavirus (HPV) a trivial sexually transmitted

disease. That was wrong. Epidemiologically cancer of the cervix is a sexually transmitted disease. HPV mRNA is found in most lesions of cervical carcinoma.[32] Prospective studies of HPV infection confirm an increased risk of premalignant and malignant change, indicating that the presence of HPV precedes such changes.[33] Perhaps most telling, however, is that vaccination against oncogenic HPV types reduces the rate of malignancy.[34,35]

The mechanism of malignant transformation by HPV has been partially defined.[36] In benign genital warts, the HPV DNA resides in the nucleus of the host cell but remains distinct from the host DNA. It is considered an "intranuclear episome," which reproduces along with the nucleus. In cancer, however, the viral DNA has been inserted into the host DNA. Such integration occurs in about 80% of cancers, but it is observed in about three-fourths of infections with HPV type 16 and in essentially 100% of infections with HPV type 18. Integration does not occur with types 6 or 11, the causes of benign genital warts. Insertion into the host DNA occurs at the codon for HPV protein E2. There is disruption of its open reading frame, and there is resulting loss of suppression of proteins E6 and E7. These proteins are then produced in larger amounts and are thought to combine with cellular oncogene suppressors, with loss of this suppressive activity and a resulting increase in mammalian oncogenic activity. There is increasing recognition of the association of HPV with other forms of genital cancer including anal, vulvar, vaginal, and penile malignancies. The organism is also associated with oropharyngeal cancer.

Might the HPV vaccine be used in women already infected?[37] Thirty years ago, I frequently and gleefully cited a small series of patients afflicted with intractable genital warts. Some of those warts were excised and treated with phenol, and the patients were then injected with an autologous preparation, which reportedly resulted in "healing."[38] Unfortunately, immunity to HPV is rather complex, and it seemed unlikely that the available vaccines would be effective in decreasing the duration of infection. It is clear that type-specific antibody, as elicited by the vaccines, protects against initial infection. We actually already suspected this, because reinfection from sexual partners is uncommon with HPV, as opposed to such bacterial diseases as gonorrhea and chlamydial infection. On the other hand, it appears that cell-mediated immunity is required for clearance of established infection. The available vaccines are made from and produce an antibody response to protein L1. This is a late protein. L1 is not expressed in epithelial basal cells, where the infection begins and resides, and clearance of infection probably requires an immune response to other or multiple proteins. It is thus unlikely that vaccination of already infected individuals would be curative. Recent data support this contention. In the initial studies of the bivalent (type 16 and 18) HPV vaccine, some women were already infected with one of the viruses at the time of vaccination. Some of these infected women had received the vaccine, and others received an ineffective control. Clearance of HPV types 16 and 18 was almost exactly the same in both groups. There may still be value in vaccinating infected women. Many women with HPV subsequently acquire other types,[39] and the vaccine might well be protective in this setting.

Thirty years ago, I taught you that there were no firm human data supporting antimicrobial prophylaxis for bacterial endocarditis but you should do it anyway. We suggested that prophylaxis should be given in the settings in which bacteremia was anticipated if the patient had one of the following: prosthetic heart valves, previous bacterial endocarditis, congenital heart disease, rheumatic valve dysfunction, hypertrophic cardiomyopathy, or mitral valve prolapse with valvular regurgitation.

We now recognize that only an extremely small number of cases of infective endocarditis are prevented by prophylaxis, and we limit the recommendations for such prophylaxis to several specific conditions.[40] Antibiotic prophylaxis is considered reasonable only for patients with those underlying cardiac conditions that are associated with the highest risk of adverse outcome from infective endocarditis. It is now suggested that prophylaxis for dental procedures be given only when there is a prosthetic cardiac valve or prosthetic material used for a cardiac valve repair, previous infective endocarditis, or some congenital heart diseases. It should be given to patients who have undergone cardiac transplantation and who then developed valvulopathy; obviously not something we would have discussed 30 years ago. The greatest difference in recommendations is that prophylaxis should not be given solely to prevent infective endocarditis in the setting of genitourinary or gastrointestinal tract procedures.

Thirty years ago we were quite certain that 95% of orolabial herpetic infection was caused by herpes

simplex virus (HSV) type 1 (HSV-1), and 95% of genital herpes was caused by HSV type 2 (HSV-2). Although most HSV-2 remains localized to the genital tract, the percentage of genital infections caused by HSV-1 has undergone a dramatic increase. Studies suggest that the fraction of newly acquired genital herpetic infection due to HSV-1 now approaches 75%.[41,42] Possible reasons for the relative increase in genital HSV-1 include an increase in orogenital contact. It is perhaps possible that a decreased rate of nonvenereal acquisition of HSV-1 in childhood has left people susceptible to genital infection as they become adults. Also, we have done a fairly good job in convincing people to use condoms for penile-vaginal intercourse, which might therefore decrease the rate of genital-genital transmission of HSV-2. Condom use during orogenital contact remains extremely limited.[43]

There are several consequences of this change in epidemiology. First of all it is no longer appropriate to use the terms HSV-1 and HSV-2 respectively when referring to anatomic sites. It is also clear that we should be advising our patients that orogenital sex is not safe sex. HSV-2-specific antibody screening has become less useful; people who are HSV-2 negative but HSV-1 positive cannot be reassured that they are free of genital infection with HSV-1. HSV-2-specific serologic screening underestimates the prevalence of genital infection.[44]

So, finally, I apologize to my students for teaching them things that were wrong. In the meantime, never stop learning. As Thomas Jefferson said in 1807, "[the medical student's] mind must be strong indeed, if, rising above juvenile credulity, it can maintain a wise infidelity against the authority of his [or her] instructors and the bewitching delusions of their theories."[45] Please rise above such credulity and maintain a wise infidelity.

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Disseminated Histoplasmosis in a Patient on Methotrexate: A Case Report and Review of the Literature

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With the growing use of immunosuppressive medications, physicians should be aware of the increased likelihood of opportunistic infections, including the endemic mycoses. The most common endemic mycosis requiring hospitalization is histoplasmosis.[1] Histoplasmosis may become disseminated in the immunocompromised patient,[2-4] and thus requires prompt diagnosis and treatment.

CASE DESCRIPTION

A 57-year-old man presented to an outside hospital with a 2-week history of fever, chills, night sweats, malaise, cough, and a 27-lb weight loss. A chest x-ray revealed findings suggesting pneumonia, and the patient was found to be newly pancytopenic. He was started on broad-spectrum antibiotics and transferred to the University of Virginia Health Sciences Center (UVA) for further evaluation.

The patient's medical history was significant for rheumatoid arthritis, type 2 diabetes mellitus, gastric bypass, and vitamin B12 deficiency. He had been on multiple immunosuppressant medications for rheumatoid arthritis, including infliximab, etanercept, adalimumab, and azathioprine. At the time of admission, he was taking methotrexate, hydroxychloroquine, and prednisone 10 mg daily. All immunosuppressants were discontinued prior to his transfer to UVA.

During his physical examination on admission to UVA, the patient appeared to be in no acute distress. Temperature was 36.1oC, blood pressure 84/53 mm Hg, pulse 103, respiratory rate 18, and oxygen saturation 92% on room air. Bitemporal wasting was evident. Heart rate was regular, without murmurs. Bibasilar crackles were present, without rhonchi or wheezes. No cervical, axillary, or inguinal lymphadenopathy was present. The remainder of the exam was unremarkable.

Initial lab values at UVA were notable for a white blood cell count of 2.4 k/μL (reference interval 4.0-11.0 k/μL) with a normal differential, hematocrit 21.7% (reference values 40%-52%; normocytic) and platelets 42,000 k/uL (reference interval 150-450 k/uL). The absolute reticulocyte count was 90 k/μL (reference interval 30-100 k/μL), ferritin 1435 ng/mL (reference interval 20-275 ng/mL), and haptoglobin/lactate dehydrogenase and vitamin B12/folate were normal. Additional laboratory results included erythrocyte sedimentation rate 54 mm/h (reference interval 0-15 mm/h), C-reactive protein 96.5 mg/L (reference interval 1.0-3.0 mg/L), creatinine 1.2 mg/dL (reference interval 0.7-1.3 mg/dL), albumin 1.8 g/dL (reference interval 3.5-5.7 g/dL), negative urine protein, international normalized ratio 2.0 (reference interval 0.9-1.2), and partial thromboplastin time 64.3 sec (reference interval 24.1-35.8 sec).

A chest x-ray performed at UVA revealed bilateral fine reticulonodular versus ground-glass opacities). A computed tomographic scan of the chest, abdomen, and pelvis showed interstitial thickening and multiple noncalcified pulmonary nodules with upper and midlung predominance, hepatos-plenomegaly, and periaortal and periportal lymphadenopathy, with normal adrenals.

The patient was admitted to the general medicine service. The initial differential diagnosis was broad and included malignancy, infection, medication side effects, and vasculitis. Because blood cultures were negative and pulmonary findings were not consistent with bacterial pneumonia, antibiotics were discontinued.

We obtained consultations from hematology and pulmonary medicine. A bone marrow biopsy was performed and revealed scattered small granulomata and increased histiocytes containing yeast forms consistent with histoplasmosis (Figures 1 and 2). A subsequent urinary histoplasmosis antigen test was positive. The bone marrow biopsy, computed tomographic scan, and laboratory values noted above indicated disseminated histoplasmosis, with involvement of the bone marrow, lungs, and liver.
The patient was started on amphotericin B. Soon after

the initial dose, he suffered hypotension that was refractory to 5 L of normal saline. He was transferred to the medical intensive care unit, and vasopressors were initiated. A transthoracic echocardiogram was normal. After failing results were obtained with a cosyntropin stimulation test, treatment with stress-dose steroids was begun. Five days later the patient was weaned from pressors and transferred from the intensive care unit back to the general treatment floor. After developing acute kidney injury, he was switched to liposomal amphotericin and completed a 14-day course. His treatment was then changed to oral itraconazole. On the morning of his discharge from the hospital, 20 days after he was admitted, he was afebrile and his white blood cell count, hematocrit, and platelet values were 6.5 k/μL, 30.7%, and 83,000 k/μL, respectively.

After his hospital discharge the patient was seen for follow-up at the infectious disease clinic, where his urinary histoplasma antigen was monitored for disease resolution. Given the patient's continued need for immunosuppressive therapy for rheumatoid arthritis, he was considered to be at high risk for relapse, so itraconazole therapy was continued indefinitely.

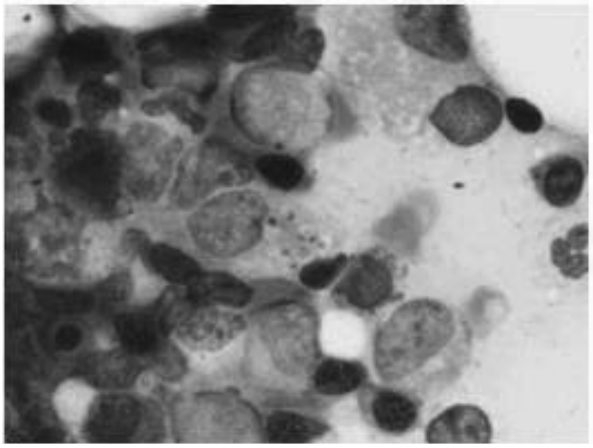

Figure 1. Roughly normocellular marrow with scattered small epithelioid granulomas.

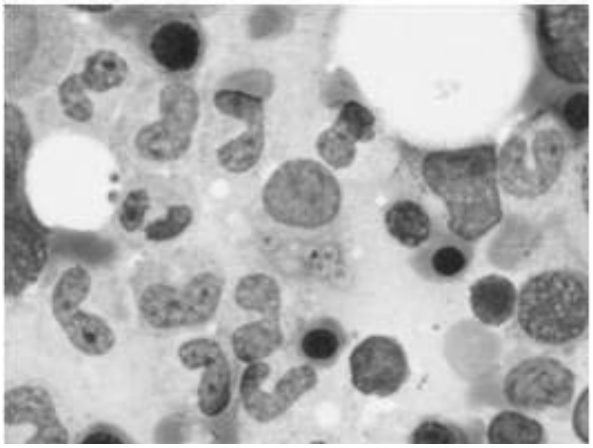

Figure 2. Yeast forms were identified on both PAS and silver stain. AFB stain is negative. CD 68 stain reveals increases in histiocytes, which are occasionally phagocytizing hematopoietic elements.

Of note, it was discovered during the hospitalization that the patient's family had recently removed 230 bats from their attic shortly before the patient became sick. The family was advised to have the bat droppings removed before the patient returned home.

DISCUSSION

Given the growing use of disease-modifying antirheumatic drugs (DMARDs), physicians should be aware of the associated risk for opportunistic infections. A reported metaanalysis of randomized controlled trials of infliximab and adalimumab revealed a pooled odds ratio of 2.0 for serious infection among patients treated with these tumor necrosis factor (TNF)-*a* inhibitors.[5] A German registry reported an adjusted relative risks of 2.3 and 3.0, respectively for moderate or severe infection with etanercept and infliximab compared to conventional DMARDs.[6] In addition, TNF-*a* inhibitors, particularly infliximab, have been implicated in the reactivation of histoplasmosis.[7]

Methotrexate, which works by inhibiting folic acid metabolism and increasing extracellular adenosine concentrations,[8] increases the risk for a variety of opportunistic infections.[9-15]. Pneumocystis is the most commonly reported opportunistic lung infection associated with methotrexate,[10-12] but patients are also at increased risk for a variety of other infections, including histoplasmosis.[12-15.]

Histoplasmosis is a dimorphic fungus with a saprophytic phase dependent on high nitrogen content. Thus, environments with a high density of roosting birds and bats, such as caves, barns, and attics, are commonly associated with transmission.[16-18] Among infections with endemic mycoses, histoplasmosis infection most commonly leads to hospitalization.[1] In heavily endemic areas, which include the Midwestern United States, the entire population may become infected and be subjected to multiple reinfections over time.[2] Most histoplasmosis infections are asymptomatic and self limited,[19] but in

patients with an acquired immunodeficiency, approximately 1 in 2000 acute histoplasmosis infections become disseminated.[2-4]

In 50% to 70% of patients with histoplasmosis, chest x-ray findings are abnormal, commonly showing diffuse interstitial or reticulonodular infiltrates, with mediastinal adenopathy occurring in about 20% of patients[3,4,20]. Infections usually begin in the lung,[15] because aerosolized microconidia are inhaled and phagocytized by neutrophils and macrophages. At body temperature the organisms transform into a yeast phase, replicate within macrophages, and spread to regional lymph nodes and subsequently throughout the reticuloendothelial system.[21]

In immunocompromised patients presenting with evidence of systemic infection, prompt diagnosis is essential. Because laboratory test results and radiologic studies can be nonspecific or slow to return, tissue diagnosis is often necessary. Given our patient's respiratory compromise and coagulopathy, we felt that a bone marrow biopsy would be the safest and most expeditious means of reaching a unifying diagnosis.

Bone marrow cultures are positive in more than 75% of cases of disseminated histoplasmosis.[3,4] Serum antibody testing, on the other hand, is inadequate because of the high prevalence of exposure in endemic areas.[22] Histoplasma antigen, however, can be detected in the urine in 92% and serum in 85% of patients with histoplasmosis.[23] False positives can occur, however, and are usually attributable to cross-reactivity with other endemic mycoses[24] or, in organ transplantation patients, with rabbit antithymocyte globulin.[25] Although false negative results may occur early in the illness,[26] urinary antigen testing remains the most common method of initial diagnosis.[23]

Untreated disseminated histoplasmosis is nearly universally fatal, but the mortality rate can be reduced to less than 25% with antifungal therapy.[3,27-29] Choices for initial therapy include amphotericin B, liposomal amphotericin, or itraconazole.[30] The choice between these drugs depends on disease severity.

In patients who are sufficiently ill to require hospitalization, induction therapy with amphotericin is recommended for 1-2 weeks followed by oral itraconazole.[30] Liposomal formulations offer favorable side-effect profiles but high cost may prohibit initial use.[30,31]

Itraconazole should not be used as an initial treatment of severe histoplasmosis, because it does not eradicate fungemia as rapidly as amphotericin.[32] Itraconazole may be used in mild cases and for continued therapy in patients with severe histoplasmosis who have already completed treatment with amphotericin B. In noncomparative trials, itraconazole was more successful[33,34] than ketoconazole[35,36] and fluconazole.[37,38] The echinocandins do not appear to be effective in treating histoplasmosis.[30,39] Regular monitoring of serum itraconzole levels may be necessary to ensure adequate treatment.[30] If adequate levels are not present, a trial of itraconazole solution could be considered, because it is associated with a higher serum concentration and thus clearance of fungal burden.[40] Clinicians should also be aware that many drugs interact with itraconazole.

Our patient experienced profound hypotension after his first dose of amphotericin. Anaphylactoid reactions due to induced prostaglandin synthesis and reversible dilated cardiomyopathies have been associated with amphotericin use.[41-44] Although computed tomographic scan of the adrenals appeared normal, our patient's inadequate response to cosyntropin indicated adrenal insufficiency, to which histoplasmosis, cessation of long-standing steroids, and sepsis all could have contributed. Without a biopsy we cannot definitively know the contribution of histoplasmosis to this complication.

Patients with histoplasmosis infection require follow-up to ensure response to treatment. Antigen concentration in the urine and serum decreases with effective therapy,[45-47] and an absence of response after 3 months suggests treatment is not effective.[48] Patients who have responded to therapy should be monitored at 3- and 6-month intervals to monitor resolution.[50]

In chronically immunosuppressed patients, maintenance therapy is necessary. Itraconazole, at doses of 200 mg once[47] or twice[48] daily have been shown to be effective in at least 90% of patients. Amphotericin B is an equally effective maintenance therapy but is not well tolerated and requires intravenous access.[4,50]

CONCLUSION

We present a case of disseminated histoplasmosis associated with acquired immunodeficiency secondary to methotrexate. This case illustrates the growing need to consider opportunistic infections in patients on immunomodulators. Histoplasmosis should be suspected in all endemic areas, and prompt diagnosis, via histopathology or antigen detection, should lead to treatment with amphotericin in severe cases. If treated patients continue to remain immunosuppressed, secondary prophylaxis with itraconazole is recommended.

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The Free Clinics of Virgnia: Coming Of Age as a Core Member of the Health Care Safety Net

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ABSTRACT

Context: Core members of the health care safety net for the uninsured include federally qualified community health centers (CHCs), academic medical centers (AMCs), public hospitals, local health departments, and private physicians. Little has been written about free clinics, another safety-net provider network that has been growing rapidly in Virginia.

Hypothesis: Relative to more traditional providers in the health care safety net, free clinics are playing a largely unrecognized and substantially growing role in the care for the uninsured.

Design: Survey of Virginia free clinic directors in 1998, 2001, and 2004; CHC data collected from the Federal Bureau of Primary Health Care Uniform Data System; AMC data collected from the research database of the University of Virginia Health System.

Results: The number of free clinics increased from 32 in 1998 to 47 in 2004; unique patients from 37,760 to 63,625; and patient visits from 103,245 to 186,742. Three clinics provided only dental care and 2 only mental health services; the remainder focused on primary care services. During the study period, the number of uninsured patients seen by free clinics and CHCs increased steadily, with free clinics surpassing CHCs in 2004. The number of uninsured patients seen by the academic medical center was less and did not increase substantially.

Conclusions: Free clinics have dramatically increased in number and services, with the number of uninsured patients seen surpassing that seen by CHCs in 2004. Thus free clinics have earned full status as core members of the health care safety net. Free clinics need continued financial and political support to sustain their successful expansion and to address the increasing need for chronic illness management.

INTRODUCTION

In the United States, people without health insurance suffer. The uninsured receive fewer therapeutic and preventive health services,[1,2] and these individuals usually seek treatment when their disease is at a more advanced stage than that of insured patients, resulting in higher mortality and more disability.[1] The number of uninsured persons in the United States is growing, increasing from 30 to 47 million people during the past 15 years.[3] For at least part of the fiscal year 2002-2003, approximately 82 million people-1 in 3 under the age of 65 years-were without health insurance, and in Virginia in 2005, more than one million citizens, 14% of the population,[5] were uninsured. The sharpest spike in numbers of uninsured people is among those 18 to 65 years old,[6] most of whom are employed. Unfortunately, employment-based health insurance, the foundation of the US health insurance system, continues to erode. In 2005, for the fifth year in a row, the percentage of persons with employment-based health insurance fell; now it is just 59%.[7]

The health care safety net for the uninsured has been defined as the providers who arrange and deliver a significant level of health care to uninsured individuals, Medicaid recipients, and other vulnerable populations.[8] Core members of the safety net have included federally qualified community health centers (CHCs), academic medical centers (AMCs), public hospitals, local health departments, and private physicians. To our knowledge, only one previously reported investigation has specifically addressed safety-net providers in comparative fashion.[9] In that study, national databases were searched for number and characteristics of visits to private offices, hospital

outpatient departments, and CHCs. Free clinics were not included. Very little has been written about the free-clinic network, a safety-net provider that specifically targets the uninsured.[10]

Currently more than 600 free clinics are registered in the United States.[11] Free clinics are community based, nonprofit organizations that rely heavily on volunteer professional and ancillary staff. They offer services that reflect the specific needs and available resources of their respective communities, including medical, dental, pharmaceutical, and subspecialty care at low or no charge.[10] When free clinics were first established more than 40 years ago, they were primarily a source of episodic care for acute illnesses in otherwise healthy adults. In recent years, free clinics have been seeing steadily increasing numbers of patients requiring care for chronic illnesses, including hypertension, depression, and diabetes.[12,13]

Free clinics in Virginia have a rich history dating back to 1970, but free clinic expansion in Virginia has been particularly dramatic during the past decade. In this report we document the expansion of Virginia free clinics and their services during a 6-year period and compare the Virginia free-clinic contribution to the health care safety net to that of 2 more traditional health care safety-net providers. This information is important to health care providers, who all have patients who are or who become uninsured, and to those in involved in free-clinic management and health policy.

METHODS

The Virginia Association of Free Clinics (VAFC) surveyed all free clinics operating in Virginia in 1998, 2001, and 2004, using questionnaires sent to clinic directors. Information obtained included numbers of unique patients seen; visits for primary, specialty, dental, and mental health care; and prescriptions dispensed, as well as annual operating costs. The 2-page survey was mailed each year in January and requested clinic data from the preceding calendar year. The survey was purposefully kept brief. To facilitate a high return rate, multiple methods for responding were allowed, and phone call reminders from the director of the VAFC were made.

Through the Uniform Data System, the Health Resources and Services Administration collects data from each CHC funded by Bureau of Primary Care grants.[14] Demographic details, including the insurance status of each patient, are reported. We retrieved archival, state-specific data on the number of uninsured served collectively by Virginia's CHCs in the years 1998, 2001, and 2004 via the website[14] and direct communication with the Bureau's public health analyst (personal communication. Anne Pope. Public Health Analyst, Office of Policy and Program Support, HHS/HHSA/BPHC. May 18, 2006).

For AMC data, we searched the research database of the University of Virginia Health System for the numbers of uninsured patients seen in outpatient clinics. To identify uninsured patients similar to those served by free clinics and CHCs, we queried the database for the number of patients seen in general medicine, family practice, obstetrics/gynecology, dental, mental health, and pediatric clinics throughout the system and then narrowed our search to include only those patients reporting no health insurance. Data for years 1998, 2001, and 2004 were retrieved. Similar data were requested from the other large AMC in Virginia, but our request was declined.

RESULTS

Each year 100% of the free-clinic surveys were returned. Table 1 presents the number of free clinics in Virginia and the volume and type of services according to year. The number of clinics increased from 32 in 1998 to 47 in 2004. The number of unique patients seen annually increased by 68% from 1998 to 2004. Of this increase in patients, 50% was attributable to new clinics established after 1998, and the rest to expansion of preexisting clinics. The total number of patient visits annually increased by 81% from 1998 to 2004. Mean visits per clinic increased by 31%, almost entirely owing to more specialty, dental, and mental health visits.

Services varied from clinic to clinic. Three clinics provided dental care exclusively, and 2 provided only mental health services. The remainder focused on delivery of primary medical care, with or without other services. Mean numbers of patients per clinic, prescriptions, and annual operating costs steadily increased over the study period. The number of prescriptions dispensed per patient visit increased from 2.7 in 1998 to 3.0 in 2004.

A comparison of the number of unique patients seen in Virginia's free clinics with the number of uninsured patients seen by CHCs and in the outpatient clinics of the AMC is shown in Figure 1. The number of uninsured

patients cared for by CHCs in Virginia also greatly increased, although not as rapidly as patients seen in free clinics. In 2004, free clinics actually surpassed CHCs in number of uninsured patients seen. Whereas the number of patients seen by free clinics and CHCs steadily increased, the number seen by the AMC grew initially, then decreased slightly.

DISCUSSION

Since 1998, free clinics in Virginia have dramatically increased both in number and in their contribution to the health care of the uninsured. The increases in measured clinical services provided, including the numbers of unique patients, patient visits, and prescriptions dispensed, and expansion of free-clinic operating budgets support this conclusion. Free clinics provide mostly primary care, although selected clinics provide a greater range of services or focus on a specific area such as dentistry or mental health. A variety of factors have influenced the changes in the relative contributions of safety-net providers in Virginia in recent years:

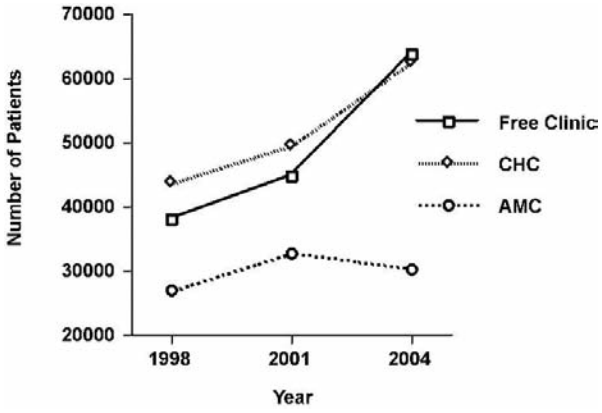

Figure 1. Total number of unique uninsured patients served according to safety net provider. CHC, community health centers; AMC, academic medical center.

Free Clinics. The first free clinic was established in Richmond, Virginia, in 1970, but only 9 additional clinics were started over the next 20 years. Beginning in the early 1990s, 4 key developments spurred the creation of new clinics: *(a)* the largest private health insurance company in Virginia, Anthem Blue Cross and Blue Shield, began funding free clinics, initially at the fiscal level of $25,000 per clinic per year (currently $10,000 per clinic per year), providing more than nine million dollars in support since 1992 (personal communication. Joy Bechtold, Community Relations Coordinator, Anthem Blue Cross and Blue Shield. February 13, 2008); *(b)* the VAFC was established, providing member clinics with personnel training and technical and managerial support; *(c)* the Virginia General Assembly passed legislation extending charitable immunity status to free-clinic health care providers; and *(d)* the Virginia Joint Commission on Health Care created the Virginia Health Care Foundation (VHCF) with the mandate to promote public-private partnerships specifically to increase health care access for the underserved. The VHCF, funded by the state of Virginia, grants, and donations, has provided nearly 6 million dollars of funding to Virginia free clinics and 12 million dollars to CHCs (personal communication. Deborah Oswalt. Executive director, Virginia Health Care Foundation. February 12, 2008).

Community Health Centers. CHCs, initiated by Lyndon Johnson in 1964 as part of his larger War on Poverty, have often been viewed as the largest provider of safety-net services. Located primarily in underserved areas and supported in part by federal grant money, CHCs provide subsidized primary health care services to low-income Americans. In 2001, President George W. Bush introduced the Presidential Five-Year Initiative to Expand Health Centers.[18] With a proposed budget of 2.2 billion dollars, 1200 new or expanded CHCs were

Table 1. Number of Virginia Free Clinics, Services Provided, and Costs According to Year

Year	1998	2001	2004
No. of Clinics	32	37	47
Total unique patients	37,760	44,720	63,625
Total patient visits	103,245	119,614	186,742
Unique patients/clinic, mean (range)	1242 (205-4728)	1209 (48-5500)	1317 (30-5856)
Patient visits/clinic, mean (range)	3032 (449-13,570)	3231 (318-16,215)	3974 (97-19,638)
Primary care visits/clinic, mean (range)	2564 (396-10,065)	2476 (0-14,033)	2582 (0-17,568)
Specialty visits/clinic, mean (range)	234 (9-2644)	489 (0-2402)	772 (0-6650)
Dental visits/clinic, mean (range)	234 (13-1506)	228 (0-1804)	458 (0-2389)
Mental health visits/clinic, mean (range)	Not available	38 (0-312)	162 (0-1910)
Prescriptions/clinic, mean (range)	8213 (162-32,550)	10,757 (529-37,112)	12,070 (23-41,064)
Annual operating costs/clinic, mean (range)	$179,990 ($15,960-$616,552)	$257,652 ($8,137-$988,000)	$334,052 ($25,775-$1,585,412)

to be funded nationally. As a result, 19 grants were awarded for new or expanded sites in Virginia (personal communication. Anne Pope. Public Health Analyst, Office of Policy and Program Support, HHS/HHSA/BPHC. May 18, 2006). Although these measures have sparked growth in the CHC network, only 1 in 10 qualified proposals was approved nationally in 2004. Unfortunately, the original budget is facing cutbacks, and in contrast to the increase in federal funding, there has been a sharp decrease in state funding of CHCs.[15] Thus, although new sites are opening, existing CHCs are struggling to balance fixed costs with further budget cuts while seeing increased numbers of uninsured patients.

Academic Medical Centers. Two AMCs in Virginia, the University of Virginia and Virginia Commonwealth University, although they compromise just 2% of hospitals in Virginia, provide nearly half the cost of all charity care services (inpatient and outpatient) for the state.[16] Funding for indigent care at AMCs relies heavily on the federally mandated Medicaid Disproportionate Share Hospital (DSH) program, which supports hospitals that provide a substantial amount of indigent care relative to other hospitals. However, in the 1990s, federal legislation limited funding for the DSH program.[16] This funding cut, combined with declining reimbursement from private insurance, changes in Medicare reimbursement, higher managed-care penetration, and increasing numbers of uninsured has threatened the financial viability of AMCs,[17] an important source of inpatient and outpatient specialty care for the underserved.

Private Sector. It has been reported that 82% of outpatient visits for the uninsured are provided by the private sector.[18] Once a doctor-patient relationship is established, many physicians reportedly reduce fees when a patient's insurance lapses. However, given the current market pressures from insurance companies, rising malpractice premiums, and dwindling government-based payments, fewer physicians have been willing or able to continue this practice. The percentage of doctors providing free care has declined from 76% in 1996-1997 to 68% in 2004-2005.[19]

A strength of our study is the 100% response rate from the free clinics. The VAFC has affiliate clinics throughout Virginia and strongly supports the creation of new clinics. We believe that it is unlikely that there were clinics unknown to the VAHC network that escaped survey. Our findings are limited by several factors. Because the survey did not ask for data on clinical diagnoses, we are not able to comment on changes in the spectrum of clinical conditions treated or severity of illness. We obtained data from only 1 of the 2 AMCs in Virginia, limiting our findings concerning the total contribution of Virginia's AMCs to the care of the uninsured. We were unable to determine the number of visits of uninsured patients to CHCs, so we used only totals of unique patients to compare the relative contributions of the safety-net providers. It is possible that patients were cared for by more than 1 provider in a given year and that the volume and intensity of services per patient varied among providers. For example, the AMC might reasonably be expected to have treated uninsured patients with more severe health problems than those seen in free clinics or CHCs and to have provided a greater intensity of services.

Our data show that the free clinics of Virginia have come of age, providing care to as many or more patients than CHCs, and have earned a place as a core member of the Virginia health care safety net. This status carries obligations. Episodic care for acute illnesses is not the only health care need of adults of working age. More than one third of the uninsured population who are of working age have 1 or more chronic conditions,[20,21] and free clinics report providing increasing amounts of chronic illness care.[12,13] Comprehensive care of chronic illnesses, such as hypertension, diabetes, emphysema, and psychiatric disorders, requires regular office visits, continuous medication, and periodic testing, as well as occasional specialty consultation. Preventive services, including colon and breast cancer screening, which can be costly, must be offered as well.[22]

Are free clinics now in a position to assume comprehensive care for a substantial proportion of our nation's uninsured patients? There are many barriers to success. Free-clinic health care providers typically volunteer once or twice a month, making it challenging to arrange for a patient to see the same provider at follow-up visits. Frequent patient relocations, lack of transportation, limited availability of appointments and translators, and the use by patients of other providers, including emergency rooms, contribute to a lack of continuity in this population. Eligibility for free-clinic care may change repeatedly as patients gain or lose health insurance, exacerbating access problems. Finally, the cost of chronic illness care, including medications, laboratory tests, clinical procedures, and consultations, may strain the budgets of clinics that are largely funded by private donations.

In Virginia, with the encouragement of community support and successful public-private partnerships, free clinics are now a major part of the health care safety net for the uninsured. To meet the treatment needs of uninsured patients with chronic health problems, free clinics will need to address continuity of care issues, find ways to provide preventive care, and develop methods to evaluate outcomes and quality of care. Free clinics will need continued financial and political support to sustain their successful expansion, because it is predicted that the number of uninsured Americans will grow to 56 million by 2013.[23]

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Inpatient Glycemic Control: More than Just Sliding Scale

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Diabetes mellitus is a frequent comorbid illness in hospitalized general medical and surgical patients, complicating 12% to 38% of all cases.[1,2] The importance of inpatient glycemic control in acute-care patients has historically been overlooked because most physicians placed more importance on avoiding inpatient hypoglycemia and extreme hyperglycemia rather than on achieving glycemic control, to an extent that that mirrors ambulatory targets. Growing amounts of reported data, however, have provided important evidence that tighter glycemic control improves patient outcomes. In recent years, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) issued recommendations for glucose concentrations of less than 180 mg/dL in non-intensive care unit (ICU) patients, and preprandial goals of less than 110 mg/dL (per the AACE) or less than 130 mg/dL (per the ADA).[3] The ADA has also recommended that physicians begin discontinuing the use of sliding-scale insulin regimens and has formally encouraged incorporation of scheduled long-acting insulin to cover basal insulin requirements and scheduled mealtime, or prandial, boluses of rapid-acting insulin with supplemental correctional dosing. Focused on non-ICU inpatient settings, this report summarizes recent evidence, critiques the longstanding pattern of sliding-scale insulin monotherapy, reviews recent literature describing inpatient glycemic control, and recommends a more physiologic strategy of treating hyperglycemia, using a basal-bolus regimen.

Evidence for Inpatient Glycemic Control

In general medical and surgical patients, tighter blood glucose control is correlated with improved outcomes, although this has been demonstrated in only a limited number of observational studies. A statistically significant increase in postoperative infection rates was seen in surgery patients with a single blood glucose level greater than 220 mg/dL.[4] Additionally, Umpierrez et al found that for patients with a new diagnosis of hyperglycemia, as well as for those with established diabetes, there was increased inpatient mortality, hospital length of stay, ICU admission, and need for nursing facility care after discharge.[2] Improvement in outcomes related to glycemic control in patients with community-acquired pneumonia or with exacerbations of acute chronic obstructive pulmonary disease have also been observed.[5-7] Multiple studies have shown associations between hyperglycemia and increased mortality in acute myocardial infarction as well as increased severity and mortality in acute stroke.[8-10]

Beyond the acute-care patient populations that are the focus of this report, studies have demonstrated improved outcomes with tighter glycemic control in cardiothoracic surgery patients and a mixed medical-surgical ICU population.[11-14] Taken together, these studies led to the aforementioned expert recommendations for improvements in blood glucose control in both acute care and ICU settings. In a strictly medical ICU population, Van den Berghe et al found that mortality benefits of tighter glycemic control were seen in a subgroup with an ICU length of stay greater than 3 days, and that episodes of hypoglycemia were associated with worse outcomes.[15] In contrast, a recent study by Brunkhorst et al showed no mortality benefit among ICU patients with severe sepsis who received intensive insulin therapy; this study and the Van den Berghe et al medical ICU study showed higher rates of hypoglycemia than seen in earlier ICU-based studies.[16] Of note, these ICU-based studies had more aggressive, (ie, lower) blood glucose targets (average blood glucose of 80-110 mg/dL) than those recommended for the acute care patient population (<180 random and <110 or <130 mg/dL preprandial), and thus further investigation is needed with regard to the ICU setting.

Sliding-Scale Insulin Alone: An Unfortunate Status Quo

The increasing focus on inpatient hyperglycemia highlights the inadequacies of the conventional method of managing hyperglycemia in the acute-care patient. Thirteen years after the discovery of insulin by Banting and Best in 1921, Joslin first introduced the concept of a sliding scale for insulin to treat hyperglycemia based on the estimated level of glycosuria.[17] During the first 50 years that insulin therapy was used, the sliding-scale method became the preferred method of insulin administration for hospitalized patients with decompensated diabetes or

diabetic ketoacidosis.[18,19] Following the introduction of capillary blood-glucose monitoring in the 1970s, urine glucose algorithms were modified to blood glucose targets that were widely accepted by general practitioners as part of the insulin treatment of diabetic patients.[20]

Despite more than 40 years of editorials and original reports discouraging the use of sliding-scale insulin monotherapy, and no studies showing any benefit on glycemic control or clinical outcomes, the use of this method remains entrenched in the management protocols for hyperglycemia in the hospitalized patient.[21] It is difficult to understand how this entrenchment of sliding-scale insulin for treating inpatient diabetes came about, given the tremendous advances in oral diabetic medicine and insulin therapy. The reality is that the practice of reflex-ordering of various insulin sliding scales was routinely passed from attending physicians to residents to medical students despite a lack of scientific evidence supporting its routine use.[21]

The perceived advantages of sliding-scale insulin included its easy implementation in general surgical and medicine wards and independence from the need for physician input regarding each insulin dose. The fundamental disadvantage of using a sliding scale is that it is a reactive approach to hyperglycemia instead of a proactive intervention that simulates the body's natural insulin physiology (Figure 1).[22] Regular insulin, most commonly used in sliding-scale regimens, is typically scheduled to be given just before meals. These insulin doses are reactive in that they are intended to cover only the hyperglycemia detected before meals, thus ignoring the insulin requirement for the upcoming meal. Furthermore, if regular insulin were intended to cover meal-time carbohydrate intake, it would have to be given 30 minutes prior to that meal. The scheduling of regular insulin before meals, based on premeal blood glucose, perpetuates a cycle of treating hyperglycemia after it has occurred and does not also cover the anticipated additional hyperglycemia induced by the upcoming meal. Thus, it makes sense that blood glucoses will remain elevated in a hyperglycemic patient who is eating and whose blood glucose is managed only with sliding-scale regular insulin.

The type of insulin used on a sliding-scale basis and the timing of its administration also contribute to the dysfunction of this treatment method. Focusing on the type of insulin used in sliding scales is important when the duration of action is considered. Figure 2 demonstrates how regular insulin's duration of action (4 to 6 hours) lasts beyond the time interval between meals, a characteristic that can lead to the phenomenon of insulin stacking (Figure 3), in which the effect of the prior dose of regular insulin has not worn off before another dose is administered.[23-25] When meals are frequently skipped for various reasons, this additive effect sometimes leads to dangerous hypoglycemic episodes.

In general, a sliding-scale regimen is not coordinated with patient physiology and treats hyperglycemia *after* it has already occurred. In contrast, a basal-bolus regimen more closely mimics the body's natural response to glucose (Figures 1 and 2) and, when titrated appropriately, more effectively prevents hyperglycemia.[22-24] The more rapid onset of insulins such as lispro, aspart, or glulisine allows them to be administered while the patient is eating or within 20 minutes after a meal is consumed. Their duration of action lasts 3 to 4 hours and wears off prior to a subsequent mealtime dose, and thus their use entails less risk of insulin stacking. Similarly, as seen in Figures 1 and 2, regular insulin has a peak effect that makes it poorly suited to provide ideal coverage of basal insulin needs for most patients who are eating. The effects of administering NPH insulin twice daily can be unpredictable if used to cover basal insulin needs. Ideal basal coverage is provided by insulin glargine, which is relatively peakless. Detemir insulin requires more study before we know how well it will perform in this respect in the inpatient setting.

The effects of a reactive approach to inpatient hyperglycemia include a higher mean blood glucose

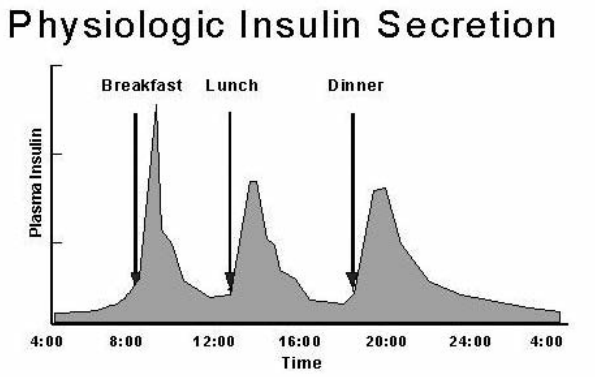

Figure 1. Physiologic insulin secretion. The fundamental disadvantage of using a sliding scale is that it is a reactive approach to hyperglycemia instead of a proactive intervention that simulates the body's natural insulin physiology. In contrast, a basal-bolus regimen more closely mimics the body's natural response to glucose and, when titrated appropriately, more effectively prevents hyperglycemia.[22]

(>200 mg/dL) with static insulin regimens, despite persistent hyperglycemia (above ADA guidelines), and hypoglycemic episodes due to poor coordination between nutritional support and insulin administration (insulin stacking).[20,21] In the face of a wealth of studies discrediting it use, sliding scale insulin remains the default regimen for treating inpatient hyperglycemia in most institutions across the country.[26-29]

Basal-Bolus Insulin Strategy

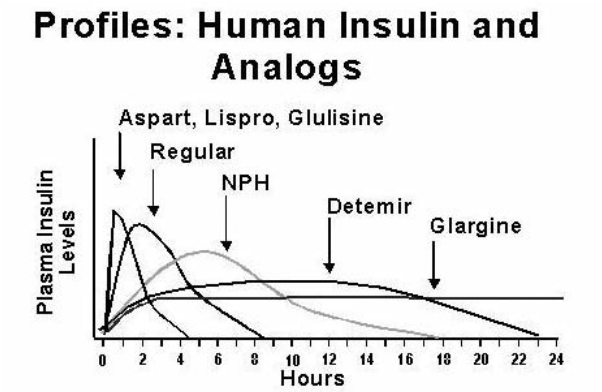

Figure 2. Peak plasma insulin levels in response to available types of insulin, demonstrating how regular insulin's duration of action (4 to 6 hours) lasts beyond the time interval between meals. The more rapid-onset of insulins such as lispro, aspart, or glulisine allows them to be administered while the patient is eating or within 20 minutes after a meal is consumed. Their duration of action lasts 3 to 4 hours and wears off prior to a subsequent mealtime dose, and thus their use entails less risk of insulin stacking.. Ideal basal coverage is provided by insulin glargine, which is relatively peakless.[23,24]

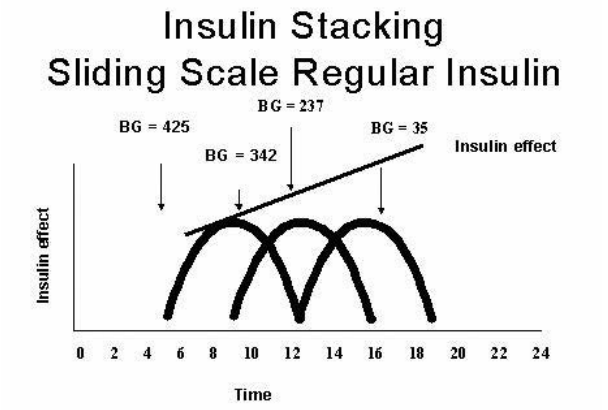

Figure 3. Insulin-stacking effect resulting from administration of sliding-scale regular insulin. The effect of the prior dose of regular insulin has not worn off before another dose is administered. When meals are frequently skipped for various reasons, this additive effect sometimes leads to dangerous hypoglycemic episodes. BG indicates blood glucose.[25]

The RABBIT 2 trial (RAndomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes) was the first prospective, randomized clinical trial comparing the efficacy and safety of basal-bolus insulin with that of sliding-scale only treatment of noncritically ill patients with type 2 diabetes mellitus.[30] Study participants were 130 nonsurgical, insulin-naive, acute-care patients with a known history of diabetes for at least 3 months and hyperglycemia on admission. Patients were excluded who were nondiabetic, undergoing corticosteroid treatment, preoperative, pregnant, or not competent to grant informed consent or who had hepatic disease or serum creatinine values above 3.0 mg/dL.

All oral diabetic medicines were held on admission, and patients were randomly assigned to a sliding-scale protocol alone (n = 65) or basal-bolus regimens (n = 65). Patients randomized to the basal-bolus protocol were given a weight-based total daily dose of insulin divided between 0.4 units/kg for admission blood glucose of 140-200 mg/dL or 0.5 units/kg if admission blood glucose was 201-400 mg/dL. One half of the total daily dose was given as basal insulin (glargine) once daily and the other half was divided into 3 equal prandial insulin doses (glulisine). Patients who were unable to eat received only their basal insulin each day to avoid episodes of hypoglycemia. For premeal blood glucose values above 140 mg/dL, supplemental glulisine was added to prandial insulin doses per a preset sliding scale based on the patient's assessed level of insulin resistance (Tables 1 and 2). Throughout the hospital stay, in patients with preprandial or fasting AM blood glucose above 140 mg/dL or below 70 mg/dL, the basal insulin dose was increased or decreased by 20%, respectively.

For blood glucose values above 140 mg/dL, patients randomized to sliding-scale insulin treatment received regular insulin before each meal and at bedtime according to a "usual" sliding scale if they were able to eat. Those unable to eat received regular insulin every 6 hours for blood glucose values above 140 mg/dL, but according to an insulin-sensitive sliding scale (see Table 2 for dose examples). If fasting and/or premeal blood glucose levels remained above 140 mg/dL, the sliding-scale insulin doses were increased from the "insulin sensitive" to the "usual" or from the "usual" to the "insulin resistant" range. Patients were moved to the basal-bolus arm of the study if blood glucose values remained above 240 mg/dL for 3 consecutive measurements (n = 9).

Fasting or preprandial blood glucose levels were targeted to stay below 140 mg/dL while avoiding hypoglycemia (< 60 mg/dL). There were no significant differences in mean length of stay or episodes of hypoglycemia (n = 2). Patients treated with basal-bolus insulin administration had significantly lower mean glucose values than patients treated with sliding-scale insulin (166 ± 32 vs. 193 ± 54 mg/dL, P <.001). The percentage of patients whose mean glucose was within the target (<140 mg/dL) was 66% in the basal-bolus group versus 38% in the sliding-scale group. Of the 9 patients in the sliding-scale group who had to be moved to the basal-bolus group, blood glucose control rapidly improved once the patients were switched to the basal-bolus regimen.

Limitations of this study were its relatively small sample size, its exclusion of patients with hepatic and renal disease, and its inclusion of only patients who were known to have diabetes but had not previously been treated with insulin. The latter point may, however, underestimate the beneficial effect of a more aggressive insulin regimen, because previous evidence shows greater mortality in hospitalized general medical patients with new hyperglycemia.[2] Another study limitation was that less total insulin was used in the sliding-scale arm of the study than the basal-bolus arm; thus it is unclear whether the observed differences were attributable more to the regimen of insulin employed or to the total dosing.[31] The effect on blood glucose control was encouraging, but the results certainly suggest the need for further evidence comparing different methods of inpatient glycemic control.

System Barriers to Inpatient Glycemic Control

Recent descriptive studies further illustrate shortcomings with current practices of inpatient glycemic control. A frequent system failure is the aforementioned lack of titration of insulin doses in response to hyperglycemia; despite persistent hyperglycemia, patients are often left on a static sliding-scale-only regimen without having basal insulin added. Schnipper et al looked at the patterns of inpatient glycemic control in more than 100 consecutive patients with diabetes or hyperglycemia managed by housestaff general medicine teams at Brigham and Women's Hospital.[32] These investigators described the status quo practices of glycemic control in patients with at least 5 days of hospitalization. Interestingly, they observed no statistically significant improvement in glycemic control during 5 days of hospitalization. Little was done to modify patients' home insulin regimens despite poor glycemic control, with 76% of patients experiencing hyperglycemia at some point in hospitalization.[32] This pattern is an

Table 1. Typical Initial Basal-Bolus Strategy

Basal insulin dose (based on weight and assessed insulin sensitivity)

- *Usual:* 0.3-0.4 units/kg of glargine, subcutaneously, once daily
- *Insulin sensitive* (renal or liver failure, advanced age, altered mental status, active coronary ischemia): decrease to 0.2 units/kg glargine, once daily
- *Insulin resistant* (severe obesity, admission blood glucose > 200 mg/dL): increase to 0.5-0.6 units/kg glargine, once daily

Bolus or prandial insulin (scheduled at meals)

- 0.1 units/ kg of Humalog (lispro), subcutaneously, given *with* each meal or up to 15 minutes after meal
- This is a rapid acting insulin, onset within 15 minutes
- Do not administer before arrival of food tray

Correctional insulin (used as a supplement to scheduled basal and bolus insulin)

- *Added* to prandial insulin doses when ordered separately

Table 2. Example of Low, Medium, and High-Dose Correctional Dose Algorithms based on Expected Insulin Sensitivity*

Blood Glucose, mg/dL	Insulin Sensitive	Usual	Insulin Resistant
>151-200	1 unit	1 unit	2 units
201-250	2 units	3 units	4 units
251-300	3 units	5 units	7 units
301-350	4 units	7 units	10 units
≥351	5 units	8 units	12 units

* Algorithms used at the University of Virginia Health Science Center; dosing algorithms tend to be institution dependent.

example of a phenomenon some have referred to as clinical inertia.[26] Only 12% of patients in the study had a basal-insulin treatment regimen newly initiated to treat persistent hyperglycemia, and less than 4% of patients received scheduled nutritional insulin.[32] Overall, only 35% of patients with either hyperglycemia or hypoglycemia had any change made to their insulin regimen, even though 76% of patients were hyperglycemic and 11% of patients were hypoglycemic at some point.[32]

In a similar descriptive study by Knecht et al at the Mayo Clinic, Scottsdale, AZ, only 35% of patients on insulin were receiving any basal insulin whereas 65% of insulin-receiving patients were on sliding-scale insulin alone.[27] This lack of basal-insulin utilization occurred even though 33% of patients had admission blood glucose levels greater than 200 mg/dL, and 29% had persistent hyperglycemia throughout admission. Changes in insulin regimens occurred in 34% of all patients, and only 50% of patients with blood glucose concentrations greater than 200 mg/dL had any change made to their prescribed insulin regimen.

In a follow-up study at the Mayo Clinic that included 2916 patients with diagnoses of diabetes or hyperglycemia, Cook et al tracked blood glucose control and stratified patients into 3 tertiles based on mean blood glucose during their hospitalization.[33] These investigators observed that 42% of all study patients were on a basal-bolus regimen, and the percentage of patients receiving this regimen increased from 34% of patients in the first tertile (with the best glycemic control) to 54% of patients in the third tertile (with the worst glycemic control), indicating some intensification of therapy. Nevertheless, almost half of patients in this third tertile did not have their regimen changed to a basal-bolus strategy. Among this group with the worst inpatient glycemic control, 31% actually experienced a *decrease* in their total daily dose of insulin during the course of hospitalization. Notably, this decrease did not occur in response to a higher rate of hypoglycemia seen in this group.

Another frequent system problem is overreaction to episodes of hypoglycemia with insulin dose reduction in the face of continued overall hyperglycemia. In the study by Knecht et al, 11% of patients experienced hypoglycemia, and of these patients 89% had a change in insulin regimen.[27] However, as mentioned above, a much lower percentage of hyperglycemic patients received changes in their insulin regimen. This finding suggests greater concern and a greater likelihood of treatment regimen changes in response to episodes of hypoglycemia than to episodic or persistent hyperglycemia.

In the study by Schnipper et al, 2 interesting variables emerged in association with glycemic control.[32] Use of sliding-scale insulin alone was independently associated with higher glucose levels. There was also statistically significant variation between patients with different medical teams and hospital floor locations, indicating that some physicians and some nursing floors were able to achieve better glycemic control. This finding suggests that the particular decisions of individual physicians and the integrated health care system greatly affect glycemic control, and that more effective education and coordination of all components of the health care system are necessary. For example, a hypoglycemic episode could be triggered more by poor timing of nutritional support and/or insulin administration than by the dose of insulin itself.

SUMMARY

Although hyperglycemia is often not the primary medical problem in the inpatient setting, increasing evidence and expert opinion suggest that tighter glycemic control results in improved clinical outcomes. Years of study have shown that reliance on sliding-scale insulin is an ineffective means for controlling blood glucose and does not substantially reduce the incidence of hypoglycemia. Emulating normal physiology with an insulin regimen that relies on 2 components-a scheduled basal (or long-acting) insulin as well as scheduled prandial boluses of rapid-acting insulin that match the timing of caloric intake-is more likely to reach goals for glycemic control than a sliding-scale-only regimen. Basal-bolus regimens have not been shown to cause more episodes of hypoglycemia when administered correctly. Improvements in systems of care can further help achieve these goals without sacrificing patient safety. Further evidence would help to more clearly define the extent of benefit and ideal targets of glycemic control in both acute care and ICU settings.

ACKNOWLEDGMENTS

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A Young Adult Presenting with Wide Complex Tachycardia

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A 27 year-old man without significant medical history presented to the emergency department with right-sided pleuritic chest pain accompanied by dyspnea, palpitations, nausea, diaphoresis, and lightheadedness. These symptoms were sudden in onset and occurred while he was sitting at work.

The patient's medical history was significant only for a "heart murmur" noted in childhood, which had resolved and never required therapy. The patient was not taking any medications. He worked as a carpenter, and reported that he used tobacco and minimal alcohol but no illicit drugs. His family history was significant for myocardial infarction in his father at age 60 years.

Examination revealed the patient to be alert, oriented, and fully conversant. He showed a moderate degree of distress and was diaphoretic. Vital signs were blood pressure 108/70 mm Hg, pulse 259 bpm, respirations 18/min, temperature 36.8˚C, and oxygen saturation of 98% on room air. The electrocardiographic monitor demonstrated an irregular wide complex tachycardia at a rate of approximately 230 bpm.

Cardiac examination demonstrated a tachycardic, irregularly irregular rhythm with a rate of approximately 240 bpm; no additional heart sounds were noted. The lungs were clear to auscultation with normal aeration in all fields. Distal pulses were intact and strong, with capillary refill of less than 2 seconds in all 4 extremities.

The electrocardiographic monitor (Figure 1) demonstrated an irregular wide QRS complex tachycardia with a very rapid ventricular rate. The 12-lead electrocardiogram (ECG) (Figure 2A) demonstrated a similar irregular, wide, complex tachycardia with marked beat-to-beat variation in the QRS complex morphologies; in addition, an initial slurring of the QRS complex was noted in several complexes. The chest x-ray was normal. The serum laboratory tests demonstrated a creatinine of 1.5 mg/dL and a troponin I of 0.06 mg/dL; all other laboratory test results were within normal limits.

Question 1 (Answers can be found at the end of the Conclusion)
In this patient, the most likely electrocardiographic rhythm diagnosis is:

A. atrial fibrillation with bundle branch block
B. monomorphic ventricular tachycardia
C. pre-excitation syndrome with atrial fibrillation
D. wide complex tachycardia due to sodium channel poisoning
E. paroxysmal supraventricular tachycardia

Question 2
Electrocardiographic clues to the appropriate rhythm diagnosis include all of the following except:

A. very rapid ventricular response
B. bizarre QRS complex configurations
C. beat-to-beat variations in QRS complex configuration
D. marked irregularity
E. delta wave

Question 3
The most appropriate initial therapy for the patient's dysrhythmia is:

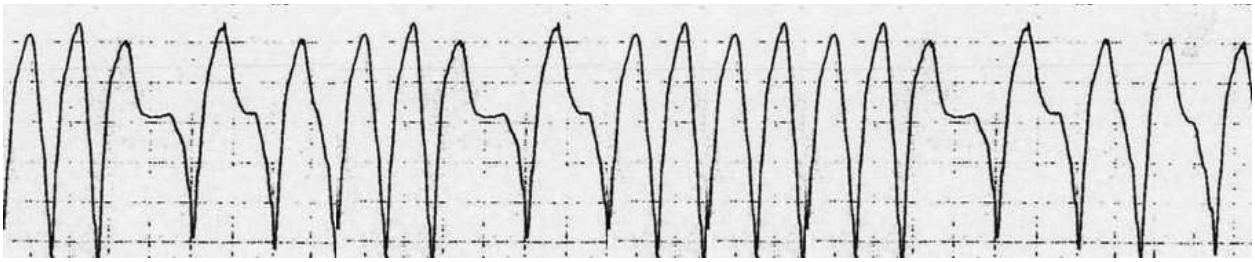

Figure 1. Electrocardiographic monitor of the case patient revealed irregular, wide QRS complex tachycardia.

A. intravenous diltiazem
B. intravenous procainamide
C. electrical defibrillation
D. intravenous esmolol
E. intravenous amiodarone

The patient was considered hemodynamically stable on presentation. His high ventricular rate warranted close observation while therapy was instituted, however, so he was placed on a cardiac monitor with supplemental oxygen administration, and 2 large-bore intravenous lines were placed, with ongoing infusion of normal saline. The patient's ECG suggested a diagnosis of preexcited atrial fibrillation (i.e., atrial fibrillation in the setting of the WPW syndrome), and intravenous procainamide was started with close monitoring. Despite a 1-gm loading dose administered over a 40- minute period, the patient's dysrhythmia did not resolve (Figure 2B).

The patient was then sedated with intravenous etomidate and cardioverted at 100 joules. He converted to a sinus tachycardia with ventricular rate of 125 bpm. Immediately after the cardioversion, the patient experienced a brief period of myoclonic

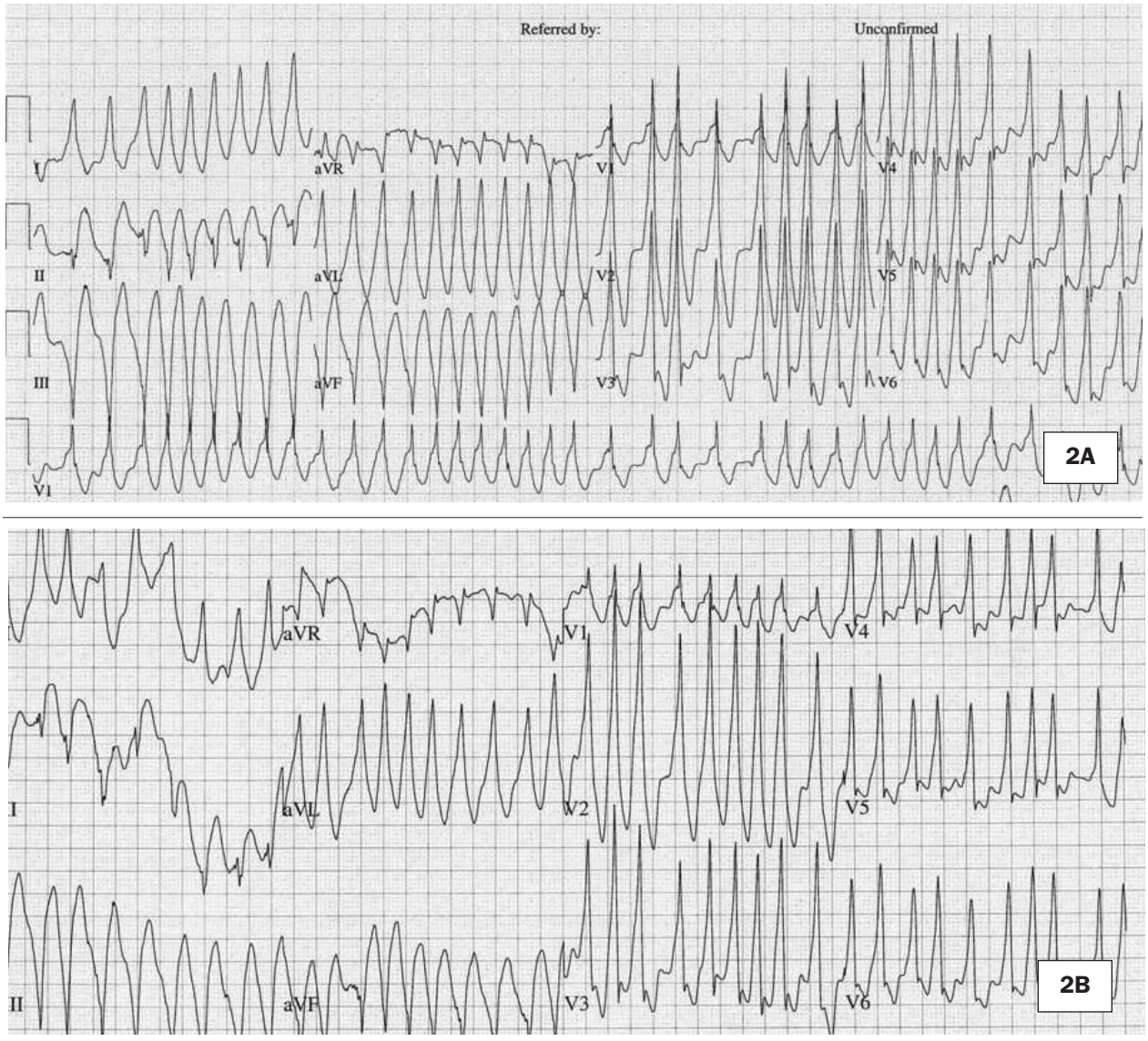

Figure 2. A 12-lead electrocardiogram demonstrating the irregular, wide QRS complex tachycardia (A). Note subtle beat-to-beat variations in the QRS complexes in any single lead and the initial slurring of the QRS complex seen in various complexes. B. Continued irregular, wide QRS complex tachycardia despite a full procainamide load.

jerking in all 4 extremities. Subsequent vitals signs demonstrated normal blood pressure and respiratory rates; the pulse remained minimally elevated. The subsequent 12-lead ECG (Figure 3) demonstrated sinus rhythm with evidence of WPW with shortened PR interval, delta wave, and minimally widened QRS complex.

DISCUSSION

Approximately 80 years ago, Wolff, Parkinson, and White described the ventricular pre-excitation syndrome that came to be known as the WPW syndrome, a combination of bundle-branch block, shortened PR interval, and recurrent episodes of tachycardia occurring in young, healthy patients with structurally normal hearts.[1] In WPW, an accessory pathway-or aberrant link-connects the atrial tissue to the ventricular myocardium; this connection bypasses the atrioventricular (AV) node, creating a direct electrical connection between the atria and ventricles. Patients with WPW may experience a range of supraventricular tachydysrhythmias, which can lead to unpleasant, disabling symptoms and, in the extreme, sudden cardiac death.

In sinus rhythm in the normal heart, electrical impulses originate in the sinus node and spread throughout atrial tissue via intraatrial conduction pathways, ultimately arriving at the AV node. Physiological slowing of the impulse within the AV node occurs, protecting the ventricle from excessive rates. The impulse is then conducted through the His-bundle and bundle branches to the ventricular muscle. In the patient with WPW, atrial impulses bypass the AV node and His-Purkinje system, instead traveling via an accessory pathway, activating the ventricular myocardium directly and earlier than a normal signal.[2] The resultant ventricular depolarization is due to a combination of impulses traveling through both the AV node and the accessory pathway.

In the adult patient in sinus rhythm, the electrocardiographic definition of WPW includes the following characteristics (Figure 4): a PR interval less than 0.12 seconds; initial slurring of the QRS complex, known as a delta wave; a widened QRS complex with a duration greater than 0.12 seconds; and secondary repolarization changes involving the ST segment and T wave.[2]

The PR interval is shortened because the impulse progressing down the accessory pathway is not subjected to the physiological slowing that occurs in the AV node. Thus, the ventricular myocardium is activated by 2 separate pathways, resulting in a fused, or widened, QRS complex. The initial part of the QRS complex, the delta wave, represents aberrant activation through the accessory pathway; and the terminal portion of the QRS complex represents activation of the remaining ventricular myocardium, via both the accessory pathway and the His-Purkinje system.[2]

Diagnosis of the WPW syndrome is based on the electrocardiographic findings in sinus rhythm noted above as well as presentation with symptomatic tachydysrhythmia. These tachydysrhythmias include paroxysmal supraventricular tachycardia (70%), atrial fibrillation (20%), and atrial flutter (5%); rarely, ventricular fibrillation occurs, but this dysrhythmia most often results from therapeutic error.[2]

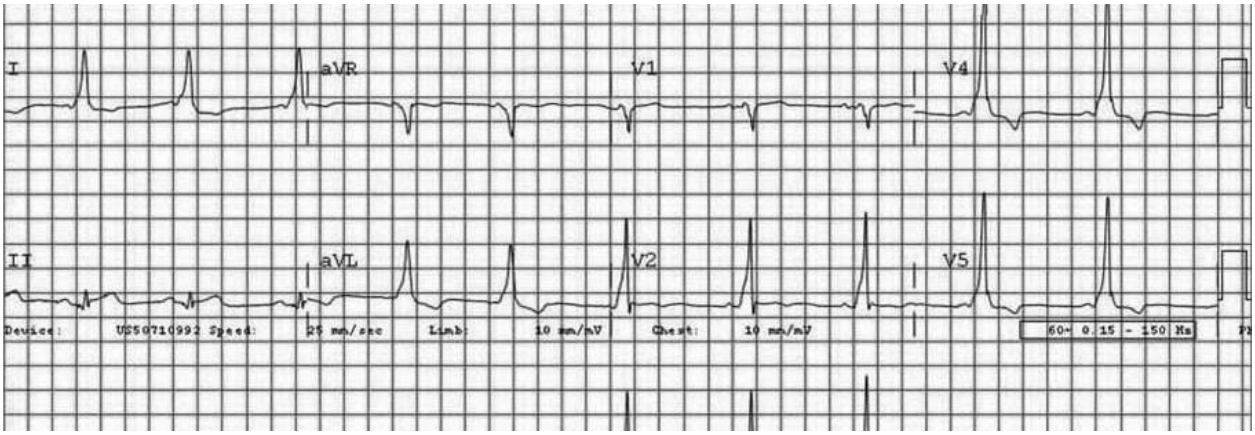

Figure 3. After electrical cardioversion, the patient converted to normal sinus rhythm with Wolff-Parkinson-White syndrome (shortened PR interval with delta wave and minimally widened QRS complex).

Several functional properties of the accessory pathway are involved in tachydysrhythmia. The accessory pathway is characterized by rapid, nondecremental conduction occurring in either an anterograde or retrograde fashion. The term "nondecremental" indicates that the accessory pathway does not allow reduction or control of the number of impulses transmitted onto the ventricles per unit time, thus differing markedly from the AV node, which conducts only a fixed number of electrical discharges to the ventricles during a given time period. Because of this property of the accessory pathway, the ventricle is no longer protected from excessive rates by the AV node. The terms antegrade and retrograde refer to the directions of the electrical impulse as it travels across the accessory pathway.

Atrial fibrillation, the second most frequent dysrhythmia in the WPW patient, is found in up to 20% of patients with the syndrome.[3] The multiple foci in the atrial tissues generate impulses that are conducted to the ventricular myocardium via both the AV node and the accessory pathway. The AV node controls the rate of impulse transmission to the ventricle; the accessory pathway, however, transmits any and all impulses. Thus, the accessory pathway is unable to control the ventricular response; in fact, the pathway can conduct atrial impulses at extremely rapid rates, approaching 300 beats per minute. With increasingly higher ventricular rates, the risk of ventricular fibrillation also increases.[4] The resultant ventricular depolarization is attributable to a combination, or fusion, of the 2 separate electrical impulses that arrive via the AV node and accessory pathway.

The ECG demonstrates several unique features of WPW-related atrial fibrillation (Figure 5). Electrocardiographically, atrial fibrillation in the WPW patient is characterized by very rapid, irregular tachycardia with wide, bizarre QRS complexes; within any single lead, beat-to-beat variation is observed in the QRS complex morphology. The important electrocardiographic clues for pre-excited atrial fibrillation are the irregularity of the rhythm, the rapid ventricular response (much too rapid for conduction down the AV node), and the wide, bizarre QRS

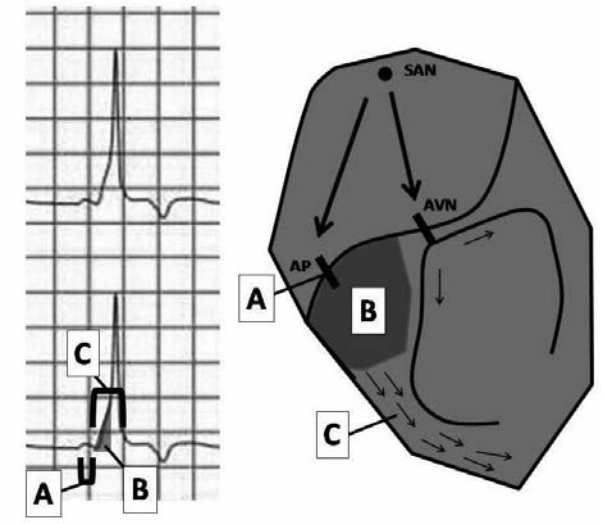

Figure 4. Normal sinus rhythm in Wolff-Parkinson-White syndrome. Note the shortened PR interval resulting from a sooner than expected arrival of the impulse at the ventricular myocardium (A). Also note the segment of the ventricular myocardium that depolarizes earlier than anticipated, the delta wave (B). The QRS complex is widened minimally owing to the partial spread of the depolarization wave via myocyte-myocyte transmission (indicated by C), rather than the intraventricular conduction system.

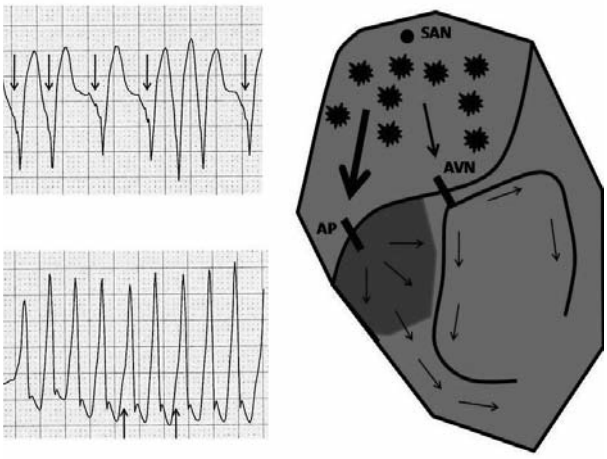

Figure 5. Wolff-Parkinson-White atrial fibrillation with multiple atrial foci. The impulse is transmitted to the ventricular myocardium via both the accessory pathway and the atrioventricular node. The ventricular myocardium is depolarized from both impulse sources. The delta wave on the electrocardiogram results from earlier-than-expected depolarization of the ventricular myocardium. The QRS complex is widened because of the inefficient spread of the depolarization wave from myocyte to myocyte rather than via the ventricular conduction system. The QRS complexes vary in morphology from one beat to the next owing to the differing contributions of the impulse from both the accessory pathway and the atrioventricular node.

complex, signifying conduction down the aberrant pathway. A delta wave is seen in this form of atrial fibrillation, depolarization of the ventricular myocardium that occurs earlier than normal owing to signals that arrive via the accessory pathway.

The management of WPW-related atrial fibrillation must be approached with consideration of the hemodynamic status of the patient. In the hemodynamically unstable patient, electrical cardioversion with sedation is the treatment of choice. In the stable patient, initial medication administration is reasonable, but electrical therapy and other resuscitation interventions should be immediately available. Procainamide is the primary agent for this rhythm presentation, because it prolongs the effective refractory period of atrial, ventricular, and accessory pathway tissues and also slows antegrade and retrograde conduction in the accessory pathway. The loading dose for procainamide is 20 to 30 mg/min until the dysrhythmias terminate or one of the following occurs: hypotension with a systolic blood pressure less than 90 mmHg, prolongation of the QRS complex duration by 50% from its original width, acceleration of tachycardia, or completed administration of the full loading dose (i.e. 1 g). Unfortunately, this dosing protocol requires an average of 40 to 50 minutes for the complete dosing. An alternative approach, necessitating close hemodynamic monitoring, requires a mere 10 minutes for a maximum dose of 10 mg/kg (700 mg in the typical adult).[5] Using this protocol in stable patients with ventricular tachycardia, Gorgels and colleagues infused procainamide at a markedly higher rate of 100 mg/min until a maximum of 10 mg/kg was reached or one of the above-mentioned criteria occurred. This higher rate of infusion entails a higher risk for adverse cardiovascular effects, so close monitoring of the patient is strongly advised, and an intravenous line with normal saline infusion is a wise precaution. Furthermore, regardless of the administration strategy, procainamide has a relatively slow onset of action, not reaching therapeutic blood levels for 40 to 60 minutes.

Early work on ibutilide suggests that it may be an acceptable alternative to procainamide in the patient with WPW atrial fibrillation. Ibutilide prolongs the refractory period of the accessory pathway and also decreases the ventricular response in WPW atrial fibrillation patients.[6] Evidence from case reports suggests that ibutilide should be considered in such patients.[7,8] Ibutilide is administered intravenously over a10-minute period at a dose of 1 mg in adults weighing more than 60-70 kg and 0.01 mg/kg in smaller adults. The primary concern with ibutilide use is the development of torsade de pointes due to prolongation of the QT interval; this significant adverse effect is less likely in the typically younger WPW patient plagued with atrial fibrillation.

Amiodarone, administered as an intravenous 150-mg dose over a 10-minute period, is considered an acceptable agent in this setting. In fact, the American Heart Association Guidelines of 2005 noted that amiodarone is the antiarrhythmic of choice in the WPW atrial fibrillation patient.[9] Nevertheless, caution should be exercised with the use of amiodarone in this type of rhythm presentation. Because the diverse electrophysiologic actions of this drug affect _-adrenergic, calcium channel, and fast sodium-channel mechanisms, with their acute impact on the accessory pathway, rapid intravenous administration of amiodarone may cause acceleration of the ventricular rate accompanied by cardiovascular collapse and/or ventricular fibrillation.[10-12]

AV nodal-blocking agents are contraindicated in WPW patients with atrial fibrillation. Calcium channel antagonists, ß-adrenergic blocking agents, and digoxin are contraindicated in this setting because they enhance conduction via the accessory pathway, subjecting the ventricle to excess rates, malignant ventricular dysrhythmia, cardiovascular collapse, and death.[4,13] Adenosine is clearly contraindicated in this setting, not only for the reason cited above but also because it acts primarily on the AV node and thus provides no benefit to the patient with WPW atrial fibrillation.

CASE CONCLUSION

After the patient underwent successful cardioversion in the emergency department, he was admitted to the coronary care unit for observation and continued procainamide infusion. The patient underwent successful radiofrequency ablation of a left posterolateral accessory pathway found on electrophysiologic testing. A subsequent echocardiogram revealed normal heart function without evidence of a dilated atrium or ventricle. Review of the results from the inpatient workup led to the determination that the patient's dysrhythmia was lone atrial fibrillation. The patient was observed for a total of 2 days and then discharged from the hospital

on aspirin without anticoagulation therapy because of his low CHADS (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke history) score. At a 2-month follow-up with the cardiologist, the patient had been asymptomatic and without complaints.

CONCLUSION

Atrial fibrillation occurring in the setting of the WPW syndrome should be in the differential diagnosis for patients presenting with wide-complex tachycardias. Clinical clues to the diagnosis include a young patient with previous episodes of palpitations and/or syncope. ECG features suggestive of atrial fibrillation in the WPW syndrome include rhythm irregularity, rapid ventricular response, presence of the delta wave, and a wide, bizarre QRS complex with beat-to-beat variation. If unstable, these patients should undergo electrical cardioversion. In stable patients, an attempt at chemical conversion can be attempted with procainamide or ibutilide; amiodarone should be used with caution.

Answers

1. In this patient, the electrocardiographic rhythm diagnosis is most likely [C] pre-excitation syndrome with atrial fibrillation. The other answers are incorrect as follows: [A] atrial fibrillation with bundle branch block-very rapid rate with bizarre QRS complex that varies subtly from beat to beat; [B] monomorphic ventricular tachycardia-very rapid rate with irregularity and polymorphic QRS complexes; [D] wide complex tachycardia due to sodium channel poisoning-possible yet unlikely owing to the very rapid rate with irregularity and variations in the QRS complex morphology; and [E] paroxysmal supraventricular tachycardia-usually a narrow QRS complex that appears normal, with significant regularity.

2. Electrocardiographic clues to the appropriate rhythm diagnosis include all of the following except [D] marked irregularity. All other answers: [A] very rapid ventricular response, [B] bizarre QRS complex configurations, [C] beat-to-beat variations in QRS complex configuration, and [E] delta wave are suggestive of WPW atrial fibrillation. Of course, any single feature of the 12-lead electrocardiogram is not diagnostic of WPW atrial fibrillation by itself; rather, a combination of these findings in the appropriate patient are suggestive of the diagnosis.

3. The most appropriate initial therapy for the patient's dysrhythmia is [B] intravenous procainamide. The other answers are incorrect as follows: [A] intravenous diltiazem is an atrioventricular nodal-blocking agent and thus is contraindicated in this rhythm scenario; [C] electrical defibrillation is a reasonable therapy, but medication use is probably a better choice in a stable patient; [D] intravenous esmolol is also an atrioventricular nodal-blocking agent and thus is contraindicated in this rhythm scenario; and [E] intravenous amiodarone is likely not the most appropriate antiarrhythmic agent with other, more acceptable alternatives available.

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ABSTRACTS SELECTED FOR PRESENTATION AT

ASSOCIATES' DAY

VIRGINIA CHAPTER
AMERICAN COLLEGE OF PHYSICIANS

JANUARY 19, 2008
RICHMOND, VIRGINIA

A SALTY SAILOR TALE: A CASE OF CEREBRAL SALT WASTING IN AN INDIAN NAVY SAILOR

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Cerebral salt wasting (CSW) is a rare disease that is usually found in neurosurgical patients. The exact pathophysiology of this entity is unclear, however it is believed that an inciting event, most commonly intra-cranial disease, causes the inappropriate loss of sodium in the urine and accompanying osmotic diuresis. This naturesis and osmotic diuresis propagates severe intra-vascular volume depletion, thereby causing the release of anti-diuretic hormone (ADH) and subsequent hyponatremia.

We present a case of a 23 year-old male in the Indian Navy who developed hypovolemic hyponatremia in the setting of hydrocephalus secondary to an infectious meningoencephalitis, presumably Mycobacterium tuberculosis. On initial presentation, his serum sodium was 131 mmol/Liter and urine output up to 1 Liter per hour. CSW, the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) and Diabetes Insipidus (DI) were all considered. Since volume restriction resulted in persistent elevated urine output, worsening hyponatremia and hypotension, the diagnosis of CSW was definitively made. Administration of large volumes of intravenous 0.9% normal saline solution (200 - 350 mL/hour) resulted in the correction of the hyponatremia and hyoptension. Attempted down-titration of IV fluids was met with worsening hyponatremia and increased urine output. 3% normal saline solution was considered as a replacement fluid, but was not instituted. CSW spontaneously resolved approximately 4 weeks into his hospital course. This is the first case of CSW, presumably due to M. tuberculosis meningoencephalitis in the United States that has been reported, and as such is worthy of review.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

IT'S NOT A TUMOR: ULCERATIVE COLITIS ASSOCIATED CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND PRIMARY SCLEROSING CHOLANGITIS

Rashad C. Wilkerson, D.O., Naval Medical Center, Portsmouth

Introduction: Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an autoinflammatory rarely report in the adult literature. There is a rare association with Inflammatory Bowel Disease (IBD). We present a case of an adult female with Ulcerative Colitis (UC) associated CRMO and Primary Sclerosing Cholangitis (PSC).

Case: A 24 y/o African American female with a history of UC and PSC presented to the emergency room with progressive pain and right sternoclavicular chest mass enlargement over a 9 month period. Seven months prior to presentation, biopsy of the mass revealed evidence of acute and chronic inflammation. No cultures were taken. She was empirically treated with 6 weeks of antibiotics without resolution of symptoms or regression of the mass. Repeat biopsy revealed lymphocytic infiltrates with scattered neutrophils and occasional microabscesses within fibrotic tissue. Stains for fungi, bacteria and acid fast bacilli were unremarkable. Routine bacterial cultures were negative. The patient was diagnosed with CRMO and started on NSAIDS. Four months after hospital discharge she developed right knee and ankle pain. X-ray and MRI of the right leg were consistent with CRMO.

During her treatment for CRMO, Infliximab and steroids therapy were initiated for PSC and UC exacerbation.. Seven months after presentation, her chest mass regressed with resolution of pain without physical limitations. She is currently awaiting liver transplant.

Conclusion: CRMO is a poorly understood inflammatory process. Therapy with NSAIDS and/or immunosuppressant agents are supported by case reports. Chronic Recurrent Multifocal Osteomyelitis may represent a marker of severity of IBD. Lastly, CRMO is possibly under diagnosed in adult patients with IBD. It should be included in the differential diagnosis of patients with IBD and boney complaints.

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A CASE OF AUTOIMMUNE NEUTROPENIA IN ASSOCIATION WITH AUTOIMMUNE HEPATITIS

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Autoimmune neutropenia (AIN) may occur as an isolated entity, but in adults is more commonly associated with other conditions such as collagen vascular disorders, viral infections, drug ingestions, neurological diseases, organ transplantation and malignancies. SLE and RA were the most commonly implicated of the identified autoimmune disorders associated with AIN.

We present a 32 year-old multiparous female who presented with severe autoimmune neutropenia and hepatitis. She had a history of autoimmune hepatitis diagnosed by liver biopsy 10 years prior. Since then she had been was otherwise healthy. She presented with 4 days of low grade fevers, sore throat and left-sided facial and neck pain and mild generalized abdominal pain. She denied any history of new medications, illicit drug use, HIV or recent alcohol intake. Physical exam was remarkable for an initial self limiting delirium. She had stable vitals and was afebrile with exquisitely tender left subman-dibular lymphadenopathy, jaundice and diffuse abdominal tenderness.

Initial labs revealed a hemoglobin of 12.4g/dl, platelets of 118K/uL and leukoctye count of 1.2K/uL, with 3% segs, 1% bands and an absolute neutrophil count of 48/mm3. Total bilirubin was 8.1mg/dl, INR 1.7, AST 583IU/L, ALT 514 IU/L, ALP 93 IU/L and LDH 159 IU/L. Liver function tests and leukocyte counts were normal in 2004 and her leuckocyte count had never been low. Serologies for hepatitis A, B and C, cytomegalovirus, West Nile virus, EBV, RMSF, toxoplasmosis, HIV and HSV were all negative. ANA, AMA, anticentromere, cANCA, alpha-1-antitrypsin, ferritin, cryoglobulins and ceruloplasmin were all unremarkable. Rheumatoid factor was elevated at 230 and antismooth muscle antibody at 104. Globulins rose to 7.3g/dl. Her peripheral blood smear showed leukopenia with severe lack of neutrophils, but normal morphology along with a normocytic normochromic anemia and borderline thrombocytopenia. Bone marrow biopsy similarly showed paucity of the entire myeloid series and its precursor blasts without evidence of malignant infiltrate or dysplasia. The patient declined a repeat liver biopsy. As she failed to respond to several days of granulocyte colony stimulating factor an autoimmune cause for the neutropenia was suspected and relevant tests done. She was found to have significant titres for antineutrophil antibodies to HLA class I and II specificity. High dose corticosteroids were initiated and led to resolution of both the neutropenia and hepatitis without complication.

Our patient's findings support the presence of antibody directed neutropenia in association with active autoimmune hepatitis. Several antigenic targets for antineutrophil antibodies have been described including FcγRIII, thyrotropin-like receptor and actin-like molecules. Antibodies to actin have been implicated in patients with AIN, having the greatest specificity in chronic active hepatitis. There have been no prior reports of autoimmune hepatitis and autoimmune neutropenia occurring simultaneously. This may well represent another but rare association between two autoimmune syndromes.

A 60-YEAR OLD WOMAN WITH AGITATION AND PSYCHOSIS FOLLOWING INGESTION OF DEXTROMETHORPHAN AND OPIOID ANALGESICS

Suzanna Jamison MD, Carilion

The patient was a 60-year-old Caucasian woman with no prior psychiatric illness or hospitalization who was brought to the Emergency Department due to "bizarre behavior," including backing her car into a police cruiser while trying to rid the vehicle of demons.

A few days before admission, the patient had taken a new job and moved into a new apartment, shortly after which she experienced auditory hallucinations and stopped trusting her pastor and church members. She felt fearful because Satan-worshippers were after other residents of her apartment complex, so she called 911. She called her landlord in the middle of the night to report a strange smell. Regular medications prior to admission included propoxyphene and hydroco- done-acetaminophen, but she had also been taking more than the maximum daily recommended dose of a dextromethorphan-containing over-the-counter cold preparation. The patient's temperature was 99.3; otherwise, vital signs were unremarkable. She had clear, syntactically correct speech but bizarre answers. HEENT, neck, cranial nerve, cardiac, lung, abdominal and extremity exam were normal. Total white blood cell count was 13,600/μL. The following tests were negative/normal: WBC differential, red blood cell indices, antitreponemal antibodies, basic metabolic panel, liver and thyroid function, B12, folate, electrocardiogram, non-contrast computerized tomography of the head, and cerebrospinal fluid analysis. Erythrocyte sedimen-tation rate was 51 mm/hr. Urine drug screen was positive for opiates. Urinalysis showed positive leukocyte esterase, positive nitrite, and many bacteria. The patient's delirium improved with olanzapine. Her urinary tract infection (UTI) resolved with treatment. Antipsychotic medication was cross-titrated to aripiprazole due to metabolic concerns. The patient received psychoeduca-tion about taking over-the-counter preparations without physician consultation. She was dis- charged in stable condition with outpatient psychiatric follow-up.

Dextromethorphan has serotonergic and sigma-1 opioidergic properties. It is metabolized by liver cytochrome P4502D6. Dextromethorphan's toxidrome is that of the serotonin selective reuptake inhibitors and propoxyphene, as well as psychosis and dissociation. The sigma-1 opioid receptors likely modulate opioid analgesic drugs; agonism of the sigma-1 opioid receptor diminishes opioid analgesia. Haloperidol antagonizes this receptor, thus potentiating the effect of narcotic analgesia. Clozapine has an antinociceptive effect that suggested a similar mechanism in an animal model, and olanzapine decreased opioid analgesia requirements in a series of cancer patients. Cytochrome P4502D6 metabolizes propoxyphene and hydrocodone, two of the patient's regular medications. The combination of dextromethorphan with opioids, previously unreported in the literature, had adverse outcomes via several possible mechanisms. The liberal ingestion of dextromethorphan may have caused a decreased effect of propoxyphene and hydrocodone via sigma-1 agonism. Propoxyphene and dextromethorphan both cause agita-tion via serotonergic mechanisms. Furthermore, dextromethorphan could slow the metabolism of the patient's analgesia, leading to an accumulation of delirium-producing metabolites. In light of the frequency with which SSRI's and opioid analgesics are prescribed, the availability of dextro- methorphan, and the scant history that an intoxicated patient provides, it behooves both the psychiatrist and hospitalist to be aware of this clinical presentation.

VARIANT ANGINA REFRACTORY TO TREATMENT - A RARE OCCURRENCE

Christopher Gelwix, M.D., MSc., Virginia Commonwealth University

A 52 year-old African American male, former smoker, with controlled diabetes and hypertension presented to the emergency department complaining of sudden onset chest pain, shortness of breath and diaphoresis that woke him from sleep. He characterized his chest pain as "tightness" rated as an 8/10 in intensity and radiating into the neck. He denied any dyspnea on exertion, paroxysmal nocturnal dyspnea, lightheadedness or palpitations. His symptoms were partially relieved by sublingual nitroglycerin. ECG showed ST-segment elevations in the anterior precordial leads associated with mild isolated troponin-I elevation. He was admitted to the ICU and treated for acute coronary syndrome. Coronary angiography revealed 60% occlusion of the mid left anterior descending artery and a 90% ostial lesion of the first diagonal artery that was not amenable to intervention. Despite optimal medical management for coronary artery disease, the patient continued to have intermittent episodes of chest pain associated with transient ST segment elevation that were relieved by nitrates and morphine. Cardiac markers remained negative. Repeat catheterization on hospital day 7 showed no new disease. A nitroglycerin drip and calcium channel blockers were begun for presumed coronary artery vasospasm; aspirin and beta-blockers were discontinued. Over the next three days, the distribution of ST-segment elevation associated with chest pain progressed in a stepwise fashion to include anterior, inferior, and lateral leads. By hospital day 10, intravenous nitrates had been replaced by oral nitrates, and the patient had been pain free for over 24 hours. While awaiting transfer out of the ICU, diffuse ST elevations again appeared on telemetry, followed by pulseless electrical activity and ventricular tachycardia. The patient was resuscitated with defibrillation and amiodarone. Emergent cardiac catheterization revealed severe multi-vessel spasm that resolved with intra-coronary diltiazem and nitroglycerin. In the cath lab, he again developed pulseless electrical activity. He was resuscitated but continued to have vasospasm refractory to medical therapy. Coronary artery bypass grafting was performed, but the patient expired on hospital day 15. Variant angina (VA) is characterized by angina attacks associated with transient ST segment elevation that is caused by episodic vasospasm of an epicardial coronary artery. In the era of calcium channel blockers and nitrates, VA without significant coronary obstruction has an excellent prognosis. VA that is refractory to medical therapy is rarely reported and carries a poor prognosis. The presence of multi-vessel coronary spasm is an independent predictor of adverse cardiac outcome. Recognizing the characteristics of refractory VA may be crucial to guiding early aggressive management to prevent acute myocardial infarction, life threatening arrhythmias and sudden death.

FAT THAT LEAVES YOU BREATHLESS

Dana F. Davis, M.D., Eastern Virginia Medical School

The prevalence of obesity has increased sharply for adults. It is well known that being obese increases the risk of many diseases and health conditions. Some conditions do not come to mind readily. We report a patient presenting with one of those rarely seen conditions. A 63 year-old male presented to the ED with progressive symptoms of dypsnea, cough, and chest discomfort. PMH was significant for Type II diabetes, OSA, dyslipidemia and 2-vessel CAD. Vital signs showed T- 98.6, BP - 108/45, HR - 97 and RR - 20. Pulse-oximetry on room air was 91%. The patient was an alert, morbidly obese male in no distress. Cardiac exam was unremarkable. Pulmonary wise he exhibited non-labored breathing and symmetrical chest rise. Breath sounds were reduced bibasilar and diffuse expiratory wheezing appreciated. CBC, cardiac enzymes, BNP were normal. Chest x-ray showed pleural thickening bilaterally with right base lung encasement suspicious for mesothelioma. A right-sided pleural effusion was also in the differential. Although the decubitus film showed no free flowing fluid, ultrasound guided thoracentesis and pleural biopsy were performed on hospital day 2, yielding 1cc of pleural fluid. Follow up CT scan of the chest showed small bilateral pleural effusions, extensive mediastinal lipomatosis and bilateral pleural rinds of lipomatous tissue encasing the lower lung on the right. Pleural biopsy confirmed lipomatous tissue. Random serum cortisol and 24 hour urinary cortisol were both normal and serum cortisol suppressed appropriately with dexamethasone. The patient was treated with oxygen, bronchodilators and an aggressive weight loss regimen. Despite losing over 50 pounds, his symptoms have persisted and follow up radiographic studies of the chest showed little improvement. Thoracic lipomatosis is a rare clinical entity that involves abnormal > accumulation of adipose tissue in the paraspinous, mediastinal and pleural spaces. It is most often associated with iatrogenic steroid administration or Cushing's syndrome, neither of which was present in our patient. His risk factor appears to be morbid obesity with a BMI of 44. Thoracic lipomatosis may be mistaken for intrathoracic neoplasm or pleural effusion on plain films. The classic appearance seen on chest radiograph is a smooth widening of the anterior and superior mediastinum without any deformity of the trachea. CT and biopsy will usually confirm that the abnormal tissue is lipomatous. Thoracic lipomatosis may cause restrictive lung disease as in our patient. The diagnosis of thoracic lipomatosis should be considered in patients with mediastinal and pleural masses discovered in the setting of exogenous corticosteroids, Cushing's syndrome, or morbid obesity.

WORDS FAIL ME: EXPRESSIVE APHASIA AFTER MALARIA

Lauren C. Fiske, M.D., Virginia Commonwealth University

Malaria has become an increasingly common infection in North America as travel to endemic areas becomes more frequent. While neurological signs and symptoms are common during a malaria infection, a transient post-infection neurological syndrome is rarely recognized.

A 42 year-old Caucasian male presented to an urgent care facility with a two day history of headache, fevers to 101.8o F, chills, and malaise 12 days after returning from the Dominican Republic. The patient was diagnosed with a viral infection. Two days later, he was admitted to an outside hospital after a blood smear showed 23% parasitemia with P. falciparum. His cerebrospinal fluid (CSF) showed no evidence of infection or inflammation. The patient received a dose of mefloquine at the outside hospital and was transferred to this facility for treatment with quinidine due to the severity of his infection. By the fourth hospital day, his blood smear showed less than 0.1% parisitemia. He was switched to atovaquone/proguanil and doxycycline, and he received active treatment for 12 days. The patient was discharged home with close follow-up in the Infectious Disease Clinic. 17 days after discharge from the hospital, the patient returned to the emergency room with headache localized to both temples, dizziness, and word-finding difficulty. He denied any changes in vision and had no bowel or bladder incontinence. His neurologic exam was remarkable for an expressive aphasia and perseveration but was otherwise normal. A lumbar puncture showed a glucose of 60 mg/dL, protein of 92 mg/dL, 19-20 white blood cells/mL (100% lymphocytes). The CSF was negative for bacteria, viruses, Cryptococcus, and malaria. An MRI of the brain showed no hemorrhages or masses and no evidence of acute ischemic injury. The patient was started on prednisone with gradual improvement in his aphasia and was subsequently discharged home on a prednisone taper.

Post-malaria neurologic syndrome (PMNS) is a rare complication of malaria (only one reported case in the United States) characterized by the onset of neurological symptoms (confusion, convulsions, tremor, dizziness, headache) within two months after recovery from a severe malarial infection. CSF studies show a lymphocytic pleocytosis and imaging of the brain is unremarkable. The syndrome is usually self-limited but its duration may be reduced by the use of steroids. While acute bacterial or viral meningitis must always be included in the differential diagnosis of headache and confusion, post-malaria neurologic syndrome should also be considered in a patient with recent malaria infection.

RHABDOMYOLYSIS ASSOCIATED WITH DIABETIC MUSCLE INFARCTION: A NEW MANIFESTATION OF A RARE DISEASE

Clay A. Cauthen, M.D., University of Virginia

Introduction: Spontaneous Diabetic Muscle Infarction (DMI) is a rare clinical sequelae of longstanding poorly controlled diabetes mellitus. We present a classic presentation of DMI that, to our knowledge, is the first case associated with rhabdomyolysis.

Case Description: Mr. M is 67 year-old male with poorly controlled type-2 diabetes complicated by nephropathy, retinopathy and peripheral neuropathy who presented complaining of sudden onset of bilateral proximal lower extremity edema, weakness and pain. Past medical history was significant for ischemic cardiomyopathy, heart failure, hyperlipidemia, hypertension, peripheral vascular disease, chronic kidney disease, and diabetes. For the past 2 years, Mr. M had been on a stable medical regimen of insulin, gemfibrozil, asprin, metoprolol, lisinopril, -pravastatin, furosemide, pantoprazole and nortriptyline. Review of systems was positive for dark urine. The patient denied any recent trauma or intense physical exertion.

Physical examination revealed an obese, elderly male who appeared his stated age. His vital signs were stable with a blood pressure of 123/73, pulse of 68, oxygen saturation of 98% on room air, and temperature of 36 degrees Celsius. Physical exam was positive for bilateral isolated decreased strength with adduction, hip flexion and leg extension as well as bilateral tenderness and swelling of the adductor and medial flexor muscles of the thigh. There were no obvious signs of muscular atrophy or wasting. Joint examination demonstrated no

effusions, erythema or point tenderness. Skin exam revealed no signs of trauma or new rashes. The remainder of his exam was unremarkable.

Abnormal laboratory analysis included serum glucose of 270 mg/dL, glycosylated hemoglobin of 10.3%, blood urea nitrogen of 40 mg/dL, serum creatine of 2.0 mg/dL, HDL of 30, aspartate aminotransferase of 1021 U/liter, and creatine kinase 73860 U/liter. Urinalysis was remarkable for myoglobinuria, large hematuria, trace glucosuria and > 2+ proteinuria. MRI-STIR of his lower extremities demonstrated symmetric intramuscular edema, most prominent in the adductors and flexors bilaterally. Nerve conduction velocity and electromyography studies were consistent with an acute myopathic pathology. Muscle biopsy of the anterior thigh muscles demonstrated multifocal myonecrosis with macrophage infiltration without evidence of myositis. Stains and cultures were negative for bacteria, fungi or acid-fast bacilli. After short period of supportive care, hydration and bed rest, the patient fully recovered without any residual muscle weakness or disability.

Discussion: As the differential is broad in this clinical presentation, the diagnosis of DMI was based on clinical presentation, radiographic imaging and confirmed by tissue biopsy. Treatment is supportive followed by aggressive glucose control and physical therapy. To our knowledge this is the first reported case of DMI complicated by rhabdomyolysis.

BEWARE OF THE SILO

Michelle Loch, M.D., University of Virginia

Silo filler's disease is an occupational lung injury occurring after exposure to irritant gases formed in recently filled silos. It is a rare and preventable with proper work safety measures.

A 41year-old male without any past medical history was helping his cousin with work in a recently filled corn silo in early September. He and his cousin were in the silo, and noted a fan blowing dust around for approximately 20 minutes. Several hours later he began to feel fatigued, feverish, nauseated with retching, and severe dyspnea. His dyspnea was associated with sharp centrally located chest pain with chest tightness, non-radiating, worse with deep inspiration and accompanied by a dry cough. His symptoms were worse with exertion and improved with rest. His cousin was experiencing similar symptoms. He sought medical attention on that evening. He was febrile on presentation, and O2 saturations were 92% on room air. A CTPA was obtained to rule out PE, as his dyspnea and pleuritic chest pain were acute in onset. There was no evidence of PE, however the scan did show evidence of bilateral lower lobe atelectasis and patchy ground glass opacities without septal thickening or nodules. He was admitted to our service due to his persistent shortness of breath, and after pulmonary embolism was ruled out, it was felt his symptoms were most consistent with silo fillers disease. He was started on Prednisone 60mg daily and monitored in the hospital for progression to pulmonary edema. He did well during hospitalization, and 24 hours after receiving steroids, had marked improvement in his symptoms, and resolution of his oxygen requirement. He was released several days later with close follow up. One week after discharge, he followed up with the pulmonary clinic and had near resolution of symptoms with very mild chest tightness on rigorous exertion.

This case is an example of a rarely seen entity described in silo workers. There are few case reports in the literature either because patients do not seek medical attention, or safety measures instituted have minimized this hazard. Its broad range of presentations varies from immediately fatal, to bronchiolitis obliterans weeks after exposure. Early recognition and close monitoring initially are important, and the patient should seek follow up evaluation for long-term complications. Most importantly, workers should be aware of the dangers and should remove themselves from the environment if symptoms should develop.

PARANEOPLASTIC PEMPHIGUS WITHOUT UNDERLYING MALIGNANCY

Raj Majithia, M.D., Eastern Virginia Medical School

Introduction: Paraneoplastic Pemphigus (PNP), is a rare autoimmune disease usually initiated by an underlying lymphoproliferative disorder. There have been less than a handful of cases in which an underlying malignancy could not be identified.

Case Description: A 45 yo AAM was admitted to a tertiary care center for odynophagia caused by mucous secreting oral ulcerations. The patient was then transferred to our hospital for care of his weight loss and failure to thrive. The patient's past medical history is significant for nephrotic syndrome secondary to membranous glomerulonephritis, hypertension, ascites, pancytopenia and oral ulcerations. The ulcerations were noted as painful erythematous papules with dusky centers. The patient was also noted to have a 3-cm by 4-cm erythematous, flat lesion with irregular borders on his left palm. The patient did not have lymphadenopathy. Dermatology biopsy of the lesions found it to be consistent with PNP. The report showed Desmoglein Antibodies 1 and 3 to be positive and indirect immunoflourescense showed IgG antibodies staining the basement membrane zone of mouse bladder and monkey esophagus epithelium, consistent with PNP. Heme/Onc was consulted for thrombocytopenia and workup which included CT of the neck, abdomen and pelvis, along with bone marrow biopsy. CT showed 2 1-cm lesions in the thyroid and lung apex. Both lesions, after biopsy, were proven to be non-malignant with inflammatory changes. PET scan was performed which was negative for malignancy. The bone marrow biopsy showed no evidence of fibrosis, granulomatous inflammation, lymphoma, leukemia, or cells extrinsic to the marrow. The patient's oral ulcerations, thought to be related to pemphigus were well controlled on 10 mg Prednisone. The patient's condition improved without resolution of his PNP and no evidence of underlying malignancy.

Case Discussion: This case illustrates a rare dermatologic finding. PNP has five diagnostic criteria including, and most commonly, painful stomatitis, histologic acantholysis, direct immunoflourescence demonstrating epidermal IgG deposition, and serum autoantibodies that identify desmogleins 1 and 3. Most commonly, PNP is associated with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's tumor, sarcoma and thymoma (J of Inv Derm. 9, 29-33, 2004). Although the dermatologic lesions were clearly diagnosed as PNP, an underlying malignancy could not be identified.

PARANEOPLASTIC LIMBIC ENCEPHALITIS

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Paraneoplastic Limbic Encephalitis is a syndrome characterized by mood and behavioral changes, memory dysfunction, complex-partial seizures and cognitive dysfunction. It is most commonly associated with small cell lung cancer.

A 62 year old male presented to his local emergency room with intermittent episodes of right sided numbness. Laboratory studies, computed tomography (CT) scan of the brain and electroencephalogram was normal. A clinical diagnosis of transient ischemic attack versus partial seizures was made and he was discharged on phenytoin. Two weeks later he represented with the same problem. Laboratory and imaging studies where again normal and he was discharged on carbamazepine. He was subsequently witnessed to have tonic-clonic seizures and admitted to his local hospital. CT scan, magnetic resonance imaging (MRI) and magnetic resonance angiography revealed only evidence of old periventricular white matter disease. Cerebrospinal fluid (CSF) analysis showed 11 white blood cells with lymphocyte predominance, normal protein and glucose. The patient continued to suffer from multiple seizures and developed a significant delirium. The patient was transferred to our facility where a CT and MRI again revealed only evidence of periventricular white matter disease. CSF analysis revealed 24 white blood cells with a lymphocyte predominance and a normal glucose and protein level. CSF analysis for herpes simplex, mycobacterium tuberculosis, Cryptococcus, Toxoplasmosis, Creutzfeldt-Jakob syndrome and serum HIV tests were all normal. Electroencephalogram showed severe slow wave activity consistent with a diffuse cerebral disturbance but no epileptiform potentials were noted. His seizures were controlled with phenytoin and valproic acid. He remained agitated, confused, and delirious. Two weeks later a MRI of his brain revealed five enhancing lesions within the frontal, parietal and temporal lobes the largest of which measured 0.9cm. Note was also made of increased abnormal signal intensity within both hippocampi and medial aspects of both temporal lobes suggestive of an encephalitis versus vasculitis. A vasculitic work up was negative. CT scan of his chest revealed hilar and mediastinal lymphadenopathy but no focal parenchymal lesion. A brain biopsy subsequently revealed evidence of metastatic small cell carcinoma. Anti Hu, Ri and Yo antibodies where all negative. The patient later died.

Paraneoplastic limbic encephalitis should always be considered in patients who present with rapidly progressive memory deficits and seizures. The diagnosis often precedes that of their primary cancer which is most often small cell lung cancer or testicular cancer. Typical MRI findings include unilateral or bilateral mesial temporal lobe abnormalities. Certain antibody assays, as highlighted above, are proving to be of benefit in the diagnosis. Once diagnosed a search for the underlying cancer should be sought. Treatment is supportive and that of the underlying cancer.

GLOMERULAR DISEASE: NOT JUST KID STUFF

Rabih Halabi, M.D., Virginia Commonwealth University

A 46-year-old African-American male with a prior medical history of hypertension and cocaine abuse presented with one day of bilateral leg edema and dyspnea on exertion. On the day of admission, the edema appeared around his ankles on waking and progressed up to his knees. He also complained of rhinorrhea, sneezing, and cough productive of clear, thick sputum for the past 6-8 weeks. He denied sore throat. He admitted to tobacco, alcohol, and cocaine use. His blood pressure was 182/84 mmHg, his heart rate was 84 bpm, his respiratory rate was 18, and his temperature was 96.9 degrees Fahrenheit. The remainder of the physical examination was significant for a normal cardiac examination without gallops or murmurs, no JVD, and moderate hepatomegaly. The extremities revealed 2+ pitting edema bilaterally from the ankles to the knees without other skin changes, warmth, or tenderness of the extremities. Laboratory data showed a serum creatinine level of 2.0 mg/dL, which was increased from a baseline value of 0.9 mg/dL. Urinalysis revealed >300mg/dL protein and 10-20 RBC's. Spot urine protein/creatinine ratio was 21.2. Antibodies to hepatitis C were positive, but cryoglobulins were negative. Complement levels showed a reduced C3 and a normal C4. An ASO titer was 400 IU/mL. A renal biopsy was performed, which showed tram-tracking of the glomerular basement membrane on the silver stain, consistent with a hepatitis-induced secondary membranoproliferative glomerulonephropathy (MPGN). However, when the pathology team was alerted about the positive ASO titer, the specimen was examined by electron micrograph, which revealed large, subepithelial electron-dense deposits with a "towering hump" morphology, consistent with postinfectious glomerulonephritis. His renal function stabilized, and he was discharged on diuretics.

This case highlights the utility of clinical information in guiding further pathologic studies. The severe proteinuria and hepatitis C infection made MPGN, usually a nephrotic syndrome, a likely
> diagnosis. However, his recent upper respiratory infection, hematuria, and elevated ASO titer pointed to a posinfectious glomerulonephritis (PIGN), which is usually a nephritic syndrome. Both MPGN and PIGN can present as both nephritic and nephrotic. In addition, both pathologies are highly proliferative with large numbers of leukocytes and thickening and swelling the glomerular basement membrane (GBM). Likewise, "tram-tracking", which describes the double contour appearance of the glomerular basement membrane (GBM), is usually associated with subendothelial or intramembranous deposits, most commonly seen in MPGN but possible in PIGN as well. Only by electron microscopy could the discrete electron-dense subepithelial humps of PIGN be seen. Because the prognosis for renal function improvement with PIGN is much better than with MPGN, the patient was counseled that his nephritis and edema would most likely resolve spontaneously without hemodialysis.

VENTING THE SPLEEN: SPLENOSIS PRESENTING AS A SOLITARY PULMONARY NODULE

Cynthia Miranda-Gonzalez, D.O., Eastern Virginia Medical School

Splenosis is the auto-transplantation of normal splenic tissue that occurs after splenic trauma and disruption. This ectopic splenic tissue is typically found in the abdomen, but may rarely be found intrathoracically, especially in cases where a diaphragmatic tear accompanied the splenic injury. We report a case of a patient with a solitary pulmonary nodule, which ultimately proved to be due to splenosis. A 49-year-old female complained of an approximate five-month history of asthenia, dyspnea with minimal exertion, dry paroxysmal cough and chest tightness. Past medical history was notable for asthma, multiple skin cancers, depression and traumatic splenectomy secondary to self-inflicted gunshot wound to the abdomen and chest. Physical exam was remarkable only for an obese and slightly anxious female with post-surgical scars from her splenectomy and trace lower extremity edema. Initial chest radiograph revealed a remarkably well-demarcated solitary lung nodule, measuring 2.0 cm x 2.0 cm, in the left lower lobe. Computed tomography of the chest showed evidence of prior splenectomy and multiple upper abdominal nodules suggestive of splenules. In addition to the 2 cm x 2 cm nodule in the left lower lobe,

the CT scan identified numerous other small nodules near the cardiac border. The thoracic and abdominal nodules were all similar in appearance and Hounsfield density, suggesting splenic origin. A technetium-99 red blood cell scan with SPECT imaging identified multiple areas of accumulation corresponding to the nodules noted on CT of the chest and abdomen, confirming the diagnosis of splenosis non-invasively. Thoracic splenosis is a rare entity with approximately 30 cases reported to date. It is not typically included in the differential diagnosis of a solitary pulmonary nodule, but should be considered in cases when there has been thoracoabdominal trauma and injury or surgery of the spleen. To definitively diagnose splenosis, tissue biopsy or radioisotope scanning can be used with the latter being done in this case. Since splenosis can mimic malignancy in appearance on radiographic imaging, it is important to include this in the differential diagnosis for those patients who have had splenic surgery or trauma. Having a high index of suspicion for splenosis in the appropriate setting can prompt the clinician to use radionuclide studies for diagnosis thus eliminating the need for tissue biopsy. Nuclear imaging is the preferred diagnostic approach for splenosis to avoid bleeding complications, preserve functional splenic tissue, and also to avoid generating additional splenic implants. Ectopic splenic nodules are benign and therapy is generally not recommended unless the patient is symptomatic.

MEMOIRS OF THE INVISIBLE SUBAORTIC STENOSIS

Nehemiah Thrash, M.D., Eastern Virginia Medical School

Introduction: Subaortic Stenosis is the second most common form of aortic stenosis; which encompasses a variety of lesions including a thin membrane which is the most common type of lesion. The typical diagnostic approaches of a patient with clinical evidence of subaortic stenosis include transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and cardiac catheterization. With the development of new forms of cardiac imaging, different modalities can be considered for diagnosis of a clinically evident lesion not demonstrated on tradition imaging.

Case presentation: The patient is a 54-year-old Caucasian female with history of rheumatic fever with mild aortic valve sclerosis and associated II/VI systolic murmur over the aortic valve region; presented to her cardiologist for routine follow up and annual assessment of her valvular function. According to the patient's previous TTE one year prior, she had evidence of mild aortic valve insufficiency (AI) with an outflow gradient between 20 and 40 mmHg and normal ejection fraction. During this visit, it was discovered that the patient had developed a new I-II/VI diastolic murmur. Another TTE was performed which showed a stable outflow gradient but progression of AI now being described as moderate. Based on the worsening of AI, it was determined that the patient needed further evaluation of her valve function and assessment of her cardiac anatomy to rule out a subaortic membrane. A TEE with color Doppler was performed which showed aortic outflow gradient which peaked at 46 mmHg and outflow turbulence proximal to aortic valve suggestive of subaortic membrane but no obvious visualization of the lesion. Next, gated 64-slice CT angiography was used to attempt to visualize a lesion but the results did not show definite evidence of subaortic membrane. The patient was then admitted to a hospital for cardiac catheterization to try to demonstrate the gradient beneath the aortic valve and to visualize the subaortic membrane with intracardiac echocardiography (ICE). The study demonstrated a subaortic membrane with clear-cut turbulence below the aortic valve starting at the site of the lesion. Cardiothoracic surgery was consulted and a transaortic resection of subaortic fibromuscular ridge was performed to prevent progression of AI.

Discussion: This case illustrates two major teaching points. First, this case demonstrates the usage of different forms of cardiac imaging to evaluate and support what was discovered on physical exam. Second, this presentation supports ICE as adjunct modality in evaluating intracardiac structures.

CUTANEOUS CROHN'S DISEASE IN THE SETTING OF PROLONGED INTESTINAL CROHN'S

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Cutaneous Crohn's disease is a rare manifestation of Crohn's, with less than 100 cases reported in the literature. It is widely variable in appearance and should be suspected with the appearance of any new skin lesion in a patient with known Crohn's.

A 30 year old male with a presumed history of Crohn's disease presented to his physician with complaints of worsening pustular lesions on his chest. He was initially diagnosed with inflammatory bowel disease felt to be ulcerative colitis at age 9 and underwent a procto-colectomy with continent ileostomy at age 13. His course continued to be complicated by perianal disease and fistula formation. He underwent multiple surgical procedures as well as systemic treatment with azathioprine for presumed Crohn's. Systemic treatment had little effect on his symptoms, so he discontinued azathioprine and was lost to follow-up for approximately 2 years prior to this presentation. He reported a history of intermittent skin lesions during these two years, which he described as acne-like. These lesions had become more numerous and inflamed over the past 4-6 months, prompting his presentation for care. He denied any luminal symptoms of Crohn's, but endorsed worsening perianal pain and drainage over the past year. He denied fevers, chills, and ocular or oral symptoms but did endorse mild intermittent arthralgias, primarily in his knees.

Physical examination revealed multiple erythematous lesions, some nodular and some pustular, on the anterior chest wall. In addition, there were numerous perianal sinus tracks with scant drainage and areas of painful induration and erythema on bilateral buttocks. A 15mm x 20mm erythematous nodule on the mid-chest was biopsied and pathology review revealed fibrosis extending into the septum of the subcutaneous tissue and granulomatous inflammation consistent with a diagnosis of cutaneous Crohn's disease. Given his cutaneous manifestions and severity of his disease, he was started on a month-long course of ciprofloxacin and metronidazole. After appropriate laboratory studies were obtained, he was also started on adalimumab. Eight weeks following initiation of adalimumab therapy, he reported marked improvement in his perianal pain and drainage and a mild improvement in his chest wall cutaneous disease.

Cutaneous Crohn's disease (also known as metastatic Crohn's disease) is a rare manifestation of Crohn's in which there is prominent granulomatous inflammation involving skin areas distant from the affected gastrointestinal tract. It can occur in patients with or without a known diagnosis of intestinal Crohn's and its course can vary independent of gastrointestinal symptoms. There is no standard treatment regimen for cutaneous Crohn's, although steroids, methotrexate, mycophenylate, azathioprine and infliximab have all been used with some efficacy.

THE WOMAN WITH PERSISTENT RENAL FUNGAL BALLS

Henry C. Ho, M.D., University of Virginia

Cholesterol-dependent Candida glabrata may not be detected in specimens set up on standard primary plating media, and this variant may be subsequently difficult to eradicate with antifungal agents directed against ergosterol and its synthetic pathway.

A 61 year-old female with a history of chronic urinary fungal infection presented to the Emergency Department with complaints of persistent nausea, vomiting, and suprapubic pain consistent with her prior episodes of fungal urinary tract infections (UTI). Her past medical history was notable for insulin-dependent diabetes mellitus and chronic kidney disease, stage III. Initial laboratory studies demonstrated a mildly elevated creatinine from baseline, normal white blood cell count, and a urinalysis showing small blood, moderate leukocyte esterase, and few bacteria. There were 29 red cells and 214 white cells per high-power field. A renal ultrasound showed bilateral, enlarged, echogenic kidneys without evidence of obstruction or stones. The patient was therefore admitted to the hospital on the general medicine service with symptoms referable to cystitis. The patient had had numerous urine cultures in the past that were negative for fungus; although her outpatient infectious disease physician reported isolation of C. glabrata years ago. The patient had allegedly undergone multiple, prolonged inpatient treatments with amphotericin. Urology was consulted and a cystoscopy and retrograde pyelograms were performed. It was noted that a significant amount of debris was returned from the right kidney on cannulation of the right ureter. This was gram stained and showed 3+ yeast. The pyelogram was grossly normal. The patient underwent MRI scanning to evaluate for anatomic abnormalities. This showed marked cortical thinning of the right renal cortex with expansion of the renal pelvis and filling with renal fat. These findings were consistent with renal lipomatosis due to chronic inflammatory changes. There was also noted significant debris without gross hydronephrosis. Infectious Disease was then consulted. Given the complicated fungal genitourinary history, the patient's most recent urine specimen was plated with bile and quickly grew out C. glabrata. It was therefore felt that the patient was colonized with Candida that required bile as a growth co-factor and had therefore been resistant to prior treatments with azoles and amphotericin. The patient was discharged with a plan for long-term anidulofungin therapy and follow-up with urology and infectious disease.

C. glabrata has become a more frequent agent of UTI; however, detection may not occur secondary to bile-dependence in certain variants on standard primary culture media. The diagnosis can therefore frequently be missed and inadequately treated.

SUSAC'S SYNDROME: A MULTIPLE SCLEROSIS MIMICKER

Jonathan D. McDivitt, M.D., Naval Medical Center, Portsmouth

Case: A 36 year-old woman with a history of migraine headaches and the diagnosis of multiple sclerosis (MS) previously made via MRI criteria was admitted with acute onset hearing loss and visual disturbances. Her symptoms were thought to be due to an exacerbation of her MS so she was treated with steroids, showed improvement and was discharged from the hospital. A week later, she was readmitted with mental status changes and confusion with EEG demonstrating slowing consistent with encephalopathy. A repeat MRI showed extensive white matter disease, worsened from previous studies and audiometry revealed bilateral sensorineural hearing loss. An ophthalmologic examination showed evidence of branched retinal artery occlusion (BRAO) and "box caring" in both eyes, with no evidence of optic neuritis. After ruling out infectious, metabolic and embolic sources of her symptoms, the diagnosis of Susac's syndrome was made and the patient was started on steroids and IVIG. After completion of treatment, her mental status and hearing had improved and repeat eye exam demonstrated resolution of the BRAO. A repeat Brain MRI a few months later also showed marked improvement of her white matter disease.

Discussion: Susac's syndrome is a rare entity that is defined by the clinical triad of encephalopathy, BRAO and hearing loss and is often mistaken for MS due to similarities on MRI. Pathogenesis is of an autoimmune microangiopathy that affects primarily the microvasculature of the brain, retina and inner ear. Female to male ratio is 3:1, commonly presenting between the ages of 20 and 40. Headaches are almost always associated with the encephalopathy and may be severe and migrainous in nature. Multifocal neurologic symptoms, psychiatric disturbances, cognitive changes, memory loss and confusion may rapidly progress to irreversible dementia. Treatment is via immunosuppression and is important to start early to prevent the severe sequela of this disease.

OSTEOMYELITIS WITH INTRAOSSEOUS GAS IN A PATIENT WITH SICKLE CELL DISEASE

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A 38 year-old woman with sickle cell disease presented through the ER with a six week history of lower extremity pain and swelling along with fluctuating mild confusion. The history began six weeks prior while hospitalized with acute chest syndrome for which she was treated with antibiotics and had a right femoral catheter inserted for exchange transfusion. Prior to discharge, left lower extremity swelling was noted with venous dopplers showing no evidence of thrombosis. Because of progressive pain and swelling, Doppler examination was repeated as an outpatient the day before this admission, again showing no evidence of thrombosis. With increased opioid use, the family's note of mild intermittent confusion was attributed to the medications. No fevers had been noted during this time. On admission, the patient was afebrile with normal vitals. Exam was notable for an unchanged grade II/VI systolic murmur, non-tender abdomen, and no lymphadenopathy. The right leg had mild pitting edema to the knee while the left was massively swollen to the upper thigh associated with warmth and a darkened skin appearance. There was no skin breakdown, wounds, rash, or crepitus. Laboratories were most notable for the Hgb 4.4, platelets >1million, and WBC 18.8 and corrected calcium of ~11.5. X-ray of the left leg/knee revealed evidence of gas in the bone and surrounding soft tissue. CT scan of the left lower extremity confirmed evidence of extensive osteomyelitis with intramedullary gas in the distal third of the femur along with extensive surrounding myositis. The patient subsequently became febrile to 39.5 C. Additional imaging revealed osteomyelitis involving both femoral heads. Echocardiogram found no evidence of endocarditis. Extensive surgical debridement of the muscle and bone was performed, yet ultimately the patient required an above knee amputation. Blood cultures, joint aspirate, and tissue cultures grew multiple organisms. She was discharged with a prolonged course of IV antibiotics in stable condition.

Osteomyelitis, a bone infection, may result from hematogenous spread, direct inoculation via trauma, or by extension from a contiguous soft tissue infection. Intraosseous gas formation as a manifestation of osteomyelitis has been reported in the literature rarely with one only one reported case associated with sickle cell disease. The mechanism is likely hematogenous with multiple areas of involvement; however, the exact source of this polymicrobial infection remains uncertain. Despite the extensive bone and soft-tissue involvement, our patient

presented with a subacute clinical course of pain and swelling without fever or crepitus. Patients with sickle cell disease have an increased susceptibility to osteomyelitis which can clinically be mistaken for the more common vaso-occlusive pain crises. This serious infection must, therefore, be kept in the differential of bony pain in this population.

PROTEASE INHIBITOR-INDUCED CUSHING'S SYNDROME AND SECONDARY ADRENAL INSUFFICIENCY

LT Kristina J. St.Clair, M.D., Naval Medical Center, Portsmouth

A 52 year old man treated with ritonavir, atazanavir and efavirenz for Human Immunodeficiency Virus (HIV) infection and both inhaled and nasal fluticasone for chronic bronchitis and allergic rhinitis, presented with complaints of mouth sores, dysphagia and hoarseness 10 weeks after commencing fluticasone. Physical exam revealed oral candidiasis and his CD4 count was 323/L. He was treated with fluconazole and told to discontinue the fluticasone. His thrush resolved, but 2 weeks later, he complained of severe fatigue, malaise and lower extremity edema. Laboratory testing revealed an AM cortisol level of 1.7 mcg/dL, and a follow-up cosyntropin stimulation test demonstrated a blunted response of 9.6 mcg/dL and 12.8 mcg/dL at 30 and 60 minutes, respectively. The patient's adrenocorticotrophic hormone (ACTH) level was also low at 5 pg/mL several weeks after discontinuing the fluticasone. The patient responded well to hydrocortisone replacement. Concomitant use of ritonavir with inhaled glucocorticoids has recently been described in association with Cushing's Syndrome and secondary adrenal insufficiency, resulting in significant morbidity. Protease inhibitors interact with numerous drugs through inhibition to the CYP3A4 isoenzyme, the mechanism by which fluticasone is metabolized. This case raises awareness of this potential adverse interaction and emphasizes the importance of weighing the risks and benefits of non-systemic glucocorticoid use in HIV patients taking ritonavir. When combination therapy is medically necessary, patients should be monitored closely to ensure early recognition and intervention of medication-induced Cushing's Syndrome and secondary adrenal insufficiency.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

HYPERHEMOLYTIC SYNDROME: A SERIOUS COMPLICATION OF TRANSFUSIONS RESULTING WITH THE PATIENT MORE ANEMIC THAN BEFORE

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A 29 year old woman with sickle cell disease presented with bony crises pain, hypoxemia, and a infiltrate on CXR concerning for pneumonia. She was treated with oxygen and antibiotics. She was transfused on admission prior to which new alloantibodies where detected. Six days into the admission, with increased fever and worsening infiltrate on CXR, the antibiotics were broadened and PRBC were administered for treatment of acute chest syndrome. With no improvement in the hemoglobin, additional units of PBRC were given. Within hours, the patient developed tachypnea, dyspnea and sinus tachycardia progressing to altered mental status and seizure activity. She was transferred to the ICU minimally responsive and intubated. Neurologic status normalized with treatment of a low glucose, 27, with exam otherwise notable for profound jaundice, clear breath sounds, and non-painful hepatomegaly. Labs revealed potassium of 5.3, markedly worsened transaminases (AST 861; ALT 247) and bilirubin (8.9 direct; 1.3 indirect), INR 1.5, and a PTT 51. The hemoglobin was reported as "invalid" with a hematocrit of 8.0% compared with 6.6 and 18.8% before the last transfusion, respectively. The post-transfusion repeat crossmatch revealed a +DAT with a negative eluate and no detectable incompatibility between the patient and administered blood products. The haptoglobin was <20, and free plasma hemoglobin was elevated at 58. Post-transfusion hemoglobin electrophoresis had 57% HgbA and 41% HgbS. The patient was diagnosed with a hyperhemolytic reaction for which she was infused with IVIG (1 g/kg/day) and methylprednisolone (1 g/day) each for three days. Signs of tissue hypoxia developed with increased cardiac enzymes, increased creatinine (2.2) and hepatocellular injury (AST 3489; ALT 1116). Subsequent transfusions with "least incompatible" PRBC were administered emergently treating the lowest hematocrit of 4%, with gradual improvement. She was extubated 5 days after the arrival to the ICU, and by discharge, her creatinine and transaminases approached baseline. The hemoglobin was 14.

The hyperhemolytic syndrome is a potentially underreported and thus overlooked adverse transfusion reaction. This alloimmune-mediated reaction results in a worsening of the anemia due to hemolysis of the transfused cells possibly compounded by transfusion-related suppression of marrow production. This syndrome may be complicated by additional transfusions without appropriate medical therapy. It is, therefore, important for the physician to be aware of this entity for early recognition.

CONTRAST-INDUCED NEPHROPATHY IS A STRONG PREDICTOR OF DEATH AFTER DRUG-ELUTING STENT IMPLANTATION

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Background: Contrast-induced nephropathy (CIN) is an independent risk factor for adverse outcomes following percutaneous coronary intervention (PCI). The predictive value of CIN in patients with left ventricular dysfunction (LVD) undergoing coronary stenting in the drug-eluting stent (DES) era is unknown. The aim of this study was to assess mortality in high-risk patients with LVD undergoing DES placement.

Methods: We performed a retrospective analysis of patients with LVD (defined as LVEF <45%) who underwent PCI with placement of at least one DES between April 2003 and December 2005. Patients with previous CABG and those on hemodialysis were excluded. Values for creatinine were collected at baseline and 48hrs following PCI. CIN was defined as >25% rise in creatinine or a rise of ≥0.5mg/dL. Mortality data was collected from the Social Security Death Index and a Kaplan Meier survival curve was created.

Results: We analyzed data from 93 patients with a mean LVEF of 36+/-8%. Twenty two (24%) had pre-existing CKD (GFR<60ml/min/1.73m2). Thirteen patients (14%) developed CIN. The incidence of CIN was 13% in those with moderate-severe CKD and 18% in patients with preserved renal function. All patients were on clopidogrel at discharge, 98% were on aspirin, 95% were on statins, and >80% were on beta-blockers and ACE inhibitors. The mean duration follow-up was 27+/-11 months, and there were 13 deaths (14%). Mortality was higher in those who developed CIN compared with patients who did not (32% and 9% respectively, P=0.0059), independently of baseline GFR. A similar trend for mortality was noticed even restricting the analysis to patients with normal baseline GFR (5% vs 35% for

without and with CIN, respectively, P=0.0003), whereas the mortality was higher in patients with pre-existing CKD independently of the development of CIN (P=0.954).

Conclusion: In the DES era, CIN remains a strong predictor of mid- to long-term mortality in patients with impaired cardiac function undergoing coronary stenting despite the optimal use of clopidogrel, statins, and ACE-inhibitors. In patients with preserved baseline renal function the development of CIN confers an increase in mortality risk comparable to pre-existing CKD.

HEPATITIS C TREATMENT BY AN INTERNIST IN AN UNDERSERVED AREA - A NOVEL CONCEPT

Sajid Melvin George, M.D., Carilion Health System

Introduction: In the United States, Chronic Hepatitis C Virus Infection (CHCVI) is a major public health problem (2.5million patients) and is a leading cause of chronic liver disease and death from liver disease. Most HCV exposure leads to chronic infection. In CHCVI patients, up to 33% develop cirrhosis over 30 years, and roughly 5% develop End Stage Liver Disease and/or hepatocellular carcinoma. Gastroenterologists typically treat these patients, yet access to and provision of treatment are often difficult. In 2004, one of our Faculty Internists started a CHCVI clinic in his primary care office located in a federally underserved urban area. He performs evaluation (including liver biopsies) and treatment (with pegylated interferon and ribavarin) for both his own and referral patients.

Methods: We performed a retrospective analysis of the 84 patients in our CHCVI clinic. We examined demographic data and rates for End of Treatment Response (ETR = no virus detectable at completion of treatment) and Sustained Virologic Response (SVR = cure) as well as relapse and non responder rates.

Results: Eighty four patients were evaluated. 31(37%) patients were uninsured with another 10(12%) on Medicaid. Approximately 25% were African American. Treatment was offered to 31 (37%) patients; 53 (63%) patients have not yet been offered treatment. Reasons included: ongoing alcohol and/or drug abuse in 33 %, psychiatric disease in 6%, and old age and/or co-morbidities in 17%. Twenty patients (65% of those offered treatment) have been treated with pegylated interferon and ribavarin. Uninsured status was not a factor limiting treatment. Seven patients completed the treatment (all with ETR); another 4 patients are currently on therapy. Four were lost on follow up after treatment was started. One stopped due to side effects. Three were primary non-responders. There was one relapse during treatment. SVR was obtained in 4 (with another one pending follow-up viral load assays). There were two recurrences after ETR (one GT1, one GT3). ETR based on patient's genotype (GT) was as follows: GT1 = 4, GT2 =1, and GT3 = 2 patients. SVR genotype breakdown was: GT1 = 2 (with one result pending), G2 = 1, and GT3 = 1 patients.

Conclusion: This ongoing innovative approach demonstrates that trained Internists can treat CHCVI in their offices with good efficacy. This is a novel concept and can provide cost-effective access to care for HCV infected patients as access to specialists is difficult in many areas. By increasing access to effective treatment, it is likely that benefits would include reduction of both cirrhosis-related complications for patients and costs for the U.S. health system.

NOVEL PRECIPITANTS OF APICAL BALLOONING SYNDROME

David E. Winchester, M.D., University of Virginia

Introduction: Apical Ballooning Syndrome (ABS, also known as Takotsubo Cardiomyopathy) is an uncommon condition characterized by sudden onset of left ventricular dysfunction that is not due to ischemia or infection. First described in 1991 in Japanese patients, symptoms include sudden onset of chest pain, diaphoresis, and/or dyspnea. Recovery is prompt, and prevalence is highest in elderly women. ABS is typically, but not universally, precipitated by a socially, emotionally, or clinically stressful event. Classic examples include the death of a loved one or an exacerbation of COPD. Our research has identified several stressors not previously described.

Methods: We conducted a retrospective review of the coronary catheterization database, clinical data repository, and medical records of the University of Virginia Health System. Patients were identified using ICD9 codes and coronary catheterization images. Both authors reviewed all the pertinent data and identified 31 cases of ABS, making this one of the largest case series in patients from the US. Data was collected on patient demographics, clinical history, physical examination, laboratory values, electrocardiogram findings, invasive and noninvasive imaging, and follow-up imaging and clinical condition when available. Results: Our patient population showed a marked predominance for women (90.3%) with a median age of 65 years. Abnormal electrocardiograms were present in 93.5% of patients with the most common abnormalities being ST elevation (38.7%) and T-wave inversions (71%). Social and emotional stressors preceded ABS in 32.3% of cases while stressful clinical events were noted in 35.5%. No precipitating event could be identified in 32.3% of patients. Several unique stressors were noted including: electroconvulsive therapy for depression, first-time use of sumatriptan for treatment of migraine, intolerance of bowel preparation for colonoscopy, post-coiling of a cerebral aneurysm, and post-kyphoplasty.

Discussion: We report the findings of our case series of apical ballooning syndrome, one of the largest conducted in the US. Many of the associations noted in our results, such as the female predominance, the median age, the electrocardiographic and cardiac biomarker patterns, are similar to those reported by other investigators. The pathophysiology of this condition is not fully known, but there have been several proposed mechanisms. The patients in our series demonstrate several novel precipitants of ABS and highlight the heterogeneity of the condition. In patients thought to have an acute coronary syndrome, prevalence of ABS is roughly 2%. This makes it a diagnosis that all clinicians should be aware of.

THE BCL-2 FAMILY PROTEINS INHIBITOR ABT-737 AND THE SELECTIVE TYROSINE KINASE INHIBITOR IMATINIB INHIBIT SMALL CELL LUNG CANCER GROWTH SYNERGISTICALLY

Bo H. Chao, M.D., Virginia Commonwealth University

Introduction: There will be an estimated 28,000 new cases of small cell lung cancer (SCLC) in the United States in 2007. Despite a high response rate to chemotherapy, greater than 90 percent of patients will die of their disease. Targeting anti-apoptotic pathways is a promising novel therapeutic strategy. Over-expression of Bcl-2 is a potent anti-apoptotic stimulus for SCLC cells. ABT-737, an inhibitor of the anti-apoptotic function of Bcl-2 family proteins has been shown in preclinical development to induce apoptosis across SCLC cell lines, albeit with some outliers showing resistance. The majority of SCLC cells express the Kit receptor tyrosine kinase and its ligand, stem cell factor (SCF). Imatinib, a drug originally designed as a Bcr-Abl tyrosine kinase inhibitor, has efficacy against SCF-mediated Kit activation in vitro, leading to growth inhibition followed by apoptosis. This study aims to determine whether the selective tyrosine kinase inhibitor imatinib can enhance apoptosis of SCLC cells induced by ABT-737.

Methods: This study utilized four SCLC cell lines incubated in complete medium: H69, H209, H526, and WBA. SCLC cell growth in vitro at 72 hours was quantified using a MTT assay following exposure to various concentrations of ABT-737 and imatinib. The combined effects of these two drugs were analyzed using the Chou and Talalay multiple drug effect equation.

Results: Cell growth decreased with increasing ABT-737 concentrations in all four SCLC cell lines ($P = 0.0002$). Similarly, cell growth decreased with increasing imatinib concentrations in the H69, H209, and WBA cell lines ($P = 0.009$), while imatinib had no significant effect on the H526 cell line ($P > 0.05$). Chou and Talalay model revealed significant synergy between the combined effects of ABT-737 and imatinib in the H69, H209, and WBA cell lines (combination index values <0.7).

Conclusions: Significant synergy between the combined effects of ABT-737 and imatinib was found in three out of four SCLC cell lines examined in this study. The combination of Bcl-2 inhibition by ABT-737 and Kit inhibition by imatinib may potentially be a novel therapeutic approach for the treatment of SCLC.

IDENTIFYING SUB-CLINICAL INNER EAR BAROTRAUMA (IEBT), A POTENTIAL RISK FACTOR FOR SENSORINEURAL, HEARING LOSS (SNHL) IN DIVERS VIA OTOACOUSTIC EMISSION (OAE)TESTING

Christopher Duplessis, M.D., Naval Medical Center, Portsmouth

Introduction: Divers may sustain sub-clinical IEBT not apparent on contemporary pure-tone audiometry (PTA), which may be an important contributor to SNHL, which they experience exceeding matched controls. Otoacoustic emissions (OAEs) are sounds made by healthy inner-ears to noise stimulation, sensitive measures of inner-ear health. OAE testing identifies transient emission shifts (TES), analogous to transient threshold shifts (TTS) identified in PTA both well correlated. OAE testing may be a more sensitive measure than PTA in assessing noise induced inner-ear injury identifying significant TES in advance of TTS. These observations are significant as hearing loss and tinnitus induced by noise exposure may be mitigated with prophylactic corticosteroid administration. In 2003, there were 30,000 new Veterans Administration hearing loss claims at a cost of $548 million. Recognizing the potential efficacy in mitigating the incidence and severity of SSHL in divers with earlier detection, we performed a pilot study investigating the potential of OAEs to identify subclinical barotraumas (TES without identifiable TTS) in divers subject to a provocative repetitive diving protocol.

Methods: 8 U.S. Navy trained male divers participated in a provocative repetitive diving protocol. OAE testing was performed on both ears prior to, and after each dive. All subjects received an Otoscopic exam, and tympanometry prior to and immediately after each dive. Audiometry was evaluated prior to and after each week of repetitive diving.

Results: There were 316 potential comparisons of OAEs acquired before and after a repetitive dive. 35 data pairs were withdrawn due to high noise floors, and 104 pairs were discarded due to middle ear pressures out of range, leaving 212 data pairs for comparison. The average group wideband TEOAE shift was -1.24 dB. Additionally, using the criterion of 1.58 dB for a significant wideband TEOAE shift, we found that 86 out of the 212 manifested significant shifts. There were no significant TTS identified.

Conclusions: OAE testing identified significant TES in a provocative repetitive diving protocol in advance of TTS acquired via PTA supporting the assertion that sub-clinical barotraumas may contribute to SSHL in divers. Exploiting this technology may identify those at risk for subsequent IEBT and hearing loss, facilitating opportunities for interventions to mitigate/circumvent it. Internists are often the first physician seeing patients presenting with the chief complaint of hearing loss, or tinnitus. We provide data supporting the assertion that we need to remain vigilant to the risk of hearing loss invoked by barotraumas in the absence of significant noise exposure. OAEs may offer a potential expedited modality to identify those at risk for inner ear injury who may benefit from prophylactic interventions, or expedited consultation to ENT.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

KINETIC MEASUREMENTS AT 37°C ARE NECESSARY TO UNDERSTAND THE DYNAMIC MOLECULAR NATURE OF LIGAND-RECEPTOR INTERACTIONS

Deeptankar Demazumder, M.D., University of Virginia

BACKGROUND: Detailed information about the ligand binding site of receptors (e.g., on ligand-gated ion channels) has emerged from structural and mutagenesis experiments. However, these approaches provide only static images of ligand-receptor interactions. Equilibrium measurements of protein function provide little insight into physiological processes because the free ligand, ligand-receptor bound and free receptor states are not at equilibrium in vivo. Kinetic measurements of changes in protein function are needed to develop a more dynamic

picture. Moreover, little is known about the temperature dependence of ligand-gated ion channel function. Human and animal studies suggest selective and variable sensitivity to temperature. In vivo studies are difficult to interpret, however, because temperature affects many physiological processes. No prior in vitro study has reported the kinetics of competitive antagonism at 37°C for any ligand-gated ion channel.
METHODS: Previously, we used a novel electrophysiological assay to measure association and dissociation rate constants for competitive inhibition of current at 25°C through the nicotinic acetylcholine receptor (nAChR), the prototypical ligand-gated ion channel. Here, we performed measurements at 37°C and used thermodynamics to estimate the energetics of competitive antagonism. We used rapid solution exchange protocols to determine equilibrium and kinetics of inhibition of acetylcholine-activated currents in outside-out patches by (+)-tubocurarine (the prototypical competitive antagonist) and by other clinically used antagonists, such as pancuronium and cisatracurium.

RESULTS: Kinetic rates as high as 600/second were resolved. Binding was primarily enthalpy and not entropy driven. The 12°C increase in temperature decreased Equilibrium antagonist binding by 1.7- to 1.9-fold. In contrast, association and dissociation rate constants increased 1.9- to 6.0-fold. Activation energies for dissociation were 90±6, 106±8 and 116±10 kJ/mol for cisatracurium, (+)-tubocurarine and pancuronium, respectively. The corresponding apparent activation energies for association were 38±6, 85±6 and 107±13 kJ/mol.

CONCLUSIONS: The higher activation energy for association of (+)-tubocurarine and pancuronium compared with cisatracurium is notable. This may arise from either a more superficial binding site for the large antagonist cisatracurium compared to the other ligands, or from a change in receptor conformation upon binding of (+)-tubocurarine and pancuronium but not cisatracurium. Our results demonstrate that the combination of kinetic and thermodynamic measurements on the nAChR reveals dynamic and energetic information that cannot be deduced from Equilibrium measurements. The temperature-dependence of equilibrium inhibition alone obscures the dramatic changes in the underlying rate constants and the fundamental differences among the antagonists. Although electrophysiological measurements at elevated temperatures may be technically difficult, they are necessary for realistic modeling of physiological processes.

A MARKOV MODEL ASSESSING THE EFFECTIVENESS AND COST-EFFECTIVENESS OF FOLFOX COMPARED WITH FOLFIRI FOR THE INITIAL TREATMENT OF METASTATIC COLORECTAL CANCER

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Purpose: To analyze the efficacy and cost-effectiveness of FOLFOX compared with FOLFIRI for patients with metastatic colorectal cancer.

Methods: FOLFOX provides a non-irinotecan based regimen that reduces the risk of diarrhea and neutropenia, but is associated with a greater risk of neuropathy. We developed a Markov decision model using a hypothetical cohort of patients with metastatic colorectal cancer beginning chemotherapy to compare FOLFOX and FOLFIRI. Probabilities of toxicities, including neutropenia, diarrhea, and neuropathy, were based on published literature for FOLFOX and FOLFIRI. Costs were estimated using Centers for Medicare & Medicaid Services reimbursement data to calculate costs for physician and hospital services unadjusted for geographic location. Drug costs were estimated using Medicare B reimbursement and the Federal Supply Schedule. Health outcomes were measured in quality adjusted life years (QALYs). Univariate and probabilistic sensitivity analyses were performed to address uncertainty in the model parameters.

Results: The FOLFOX strategy provided 1.003 QALYs and cost $29,895, whereas FOLFIRI provided 0.921 QALYs at a cost of $24,551. The incremental cost-effectiveness ratio for FOLFOX treatment was $65,534/QALY. In 10,000 probabilistic Monte Carlo simulations, the FOLFOX treatment was cost-effective in 48.59% of trials using a $50,000/QALY threshold. The most influential variables in the univariate sensitivity analysis were the expected years of survival associated with each chemotherapy regimen.

Conclusions: FOLFOX therapy does not appear to be cost-effective when using the $50,000/QALY threshold but is clearly within the range of a $100,000/QALY limit, a commonly accepted threshold in oncology.

DOES ETIOLOGY OF ANEMIA PREDICT OUTCOME IN PATIENTS UNDERGOING CORONARY STENTING?

Amit Varma, M.D., Virginia Commonwealth University

INTRODUCTION Anemia is a known unfavorable prognostic factor in patients undergoing percutaneous coronary intervention (PCI). Whether different types of anemia may be associated with differences in cardiac and non-cardiac mortality is currently unknown. The aim of this study was to assess mortality in patients receiving optimal medical management that have a reduced ejection fraction (EF<45%) and a hemoglobin (Hb)<12g/dL undergoing coronary stenting and whether the etiology of anemia itself was a predictor of outcome.
METHODS One hundred twenty patients undergoing PCI between April 2003 and December 2005 were enrolled and prospective data was collected from the time of PCI for a median follow-up period of 30 months. Patients were divided into 2 groups, anemic (Hb<12 g/dL, 29 pts, 24%) and non-anemic. Patients with anemia were then divided into 3 subgroups according to etiology of anemia: 9 patients (31%) had iron-deficiency anemia (IDA), 7 patients (24%) had a malignancy-associated anemia, and 13 patients (45%) had anemia of chronic disease (including chronic kidney disease). Mortality rates and cause of death were retrieved using both the Social Security database and hospital records. Kaplan-Meyer survival curves were used to compare time-dependent variable. P values ≤0.05 were considered statistically significant.

RESULTS Overall mortality was 12% with 3% cardiac, 7% cancer-related, and 2% undetermined and no deaths were directly attributable to bleeding complications. All-cause and cardiac mortality were significantly higher in anemic vs. non-anemic patients, (31% vs. 6%, P<0.001, and 10% vs. 1%, P=0.016, respectively). There was a significant trend for higher morality with lower hemoglobin levels as mortality was highest in anemic patients with Hb<10 (44%) vs. anemic patients with Hb 10.1-12 (24%) or non-anemic patients (6%, P for trend<0.001). However, different etiologies of anemia had different predictive values. IDA strongly predicted cardiac mortality (33% vs. 1% in non-anemic patients, P<0.001), while malignancy-associated anemia was the strongest predictor of non-cardiac death (57% vs. 4% in non-anemic patients, P<0.001) but not cardiac death. Anemia of chronic disease neither predicted cardiac nor non-cardiac death. The difference in outcome between anemia types remained statistically significant even after correction for differences in Hb levels as a possible confounder (P=0.030).

CONCLUSION Anemia is a frequent condition in cardiac patients and it remains an important predictor of mortality in patients undergoing PCI despite optimal medical management. To our knowledge, this is the first study to show that IDA is a strong predictor of cardiac death when compared to patients with other types of anemia or to non-anemic patients. A better understanding of the association between anemia and adverse outcomes may lead to targeted interventions in the hypothesis that identifying and correcting anemia will lead to prevention of long term morbidity and mortality in high patients undergoing PCI.

EFFECT OF CLOPIDOGREL ON ENDOTHELIAL FUNCTION IN PATIENTS WITH TYPE II DIABETES

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Introduction: Platelet activation, present in type II diabetes (DM2), can lead to endothelial cell activation and inflammatory cytokine production, important in atherogenesis. Stimulation of the platelet P2Y12 receptor is one pathway through which platelets are activated. Clopidogrel, an antagonist to the P2Y12 receptor, has been shown to decrease platelet activation.

Objective: Given the above, we hypothesized that clopidogrel administration to patients with DM2 would cause a reduction in platelet activation resulting in a decrease in vascular inflammation and enhanced endothelial nitric oxide availability.

Methods: To test this hypothesis, we administered clopidogrel for one month to eleven patients, mean age 52.9 (10.9) (SD) years, with DM2 without documented cardiovascular (CV) disease. Aspirin was stopped for this time period if initially taken. End points for the study were brachial artery endothelial-dependent vasomotor responses (FMD) measured by vascular ultrasound and markers of vascular inflammation, including sCD40 ligand, sP-selectin, hsCRP and leukocyte adhesion molecules. These were measured pre and post clopidogrel treatment with differences determined by paired t-test.

Results: Baseline BP [Mean(SD)] 147(14)/81(11) mmHg, and HbA1C 7.0(1.1)% did not change after clopidogrel. FMD pre 4.1 (3.2) % improved slightly compared with post 5.1 (2.4) %, but was not significant (P=0.35). Vascular inflammatory markers also exhibited no significant change after clopidogrel.

Conclusions: These data suggest that in a cohort of patients with DM2 without documented cardiovascular disease, not on aspirin, that clopidogrel resulted in no improvement in endothelial function. The cohort we studied was similar to the primary prevention cohort in CHARISMA. Our results suggest that the increased death rate observed from CV causes in that trial did not occur from deterioration in vascular function due to clopidogrel.

ESTABLISHING THE RELATIONSHIP BETWEEN THE CLASSIC ETIOLOGICAL CATEGORIZATION FOR AKI WITH THE NOVEL RIFLE CRITERION AND COMPARING OUTCOMES IN TERMS OF MORTALITY AND PROGRESSION TO ESRD

Alan Brijbassie, M.D., Carilion Health System

Background and Rationale Acute Kidney Injury (AKI) is a condition in hospitalized patients which can be classified according to its underlying etiology or to its severity (RIFLE classification). It is unclear what the relationship between the novel RIFLE classification and the classical etiological categorization of AKI is, and it is unknown which classification is better at predicting outcomes in patients with AKI.

Methods: We examined 707 male US veterans hospitalized with AKI at a single medical center. AKI was classified based on etiology (pre-renal, intrinsic or post renal) and severity, based on the RIFLE criteria using the change from baseline serum creatinine. Outcomes (all-cause mortality and end stage renal disease (ESRD) associated with the different etiologic and RIFLE categories were examined using the Kaplan-Meir method and the log rank test. The effects of confounding variables were examined in multivariable Cox models.

Results: 502 patients (71 %) had a pre renal cause of AKI and 86% of these fell into the Risk (R) category of the RIFLE classification. AKI from intrinsic causes (149, 21%) was more likely associated with the Injury (I) and Failure (F) categories (20% and 54% respectively). Of the 56 patients (0.08%) with AKI from a post-renal cause, 23 (41%) and 20 (35%) fell into categories (R) and (F) respectively. 409 patients died and 49 patients reached ESRD. Intrinsic etiology of AKI was associated with higher mortality compared to pre-renal and post renal etiologies: multivariable adjusted hazard ratios (HR) (95% confidence interval [CI]) for intrinsic and post renal categories compared to the pre-renal category were 1.66 (1.31-2.13) and 0.95 (0.64-1.42) respectively. RIFLE categories showed a less, consistent association with mortality: HR (95%CI) for I and F compared to the R category were 1.32 (1.02-1.71) and 1.14 (0.87-1.49) respectively. RIFLE categories were associated with the risk of ESRD: HR (95% CI) for I and F compared to the R category were 2.30 (0.72-7.40) and 10.25 (3.91-26.87) respectively. Intrinsic etiology of AKI was also associated with a higher risk of ESRD compared to pre-renal and post-renal etiologies: 6.30 (3.14-12.64).

Conclusion: The novel RIFLE criteria correlated closely with the classical etiological classes. RIFLE classes are easier determined than etiologic categories and are strongly associated with the risk of ESRD. Etiologic classification shows a stronger association with mortality.

TWO "HITS" TO CUSHING'S SYNDROME: CARNEY COMPLEX AND ACTH RECEPTOR MUTATIONS IN THE SAME INDIVIDUAL

Bradley Javorsky, M.D., University of Virginia

Introduction: The pathophysiology of the hypothalamic-pituitary-adrenal axis is complex making diagnostic investigation of hypercortisolemia challenging. Here we present a patient with ACTH-independent Cushing's syndrome who was found to have mutations in both the protein kinase A regulatory subunit 1A (PRKAR1A) and ACTH receptor genes (MC2R).

Case Description: A 16 year-old female presented with features of Cushing's syndrome including central obesity and violaceous striae. No other features of Carney complex were present. Serum cortisol at 8 AM following 1 mg dexamethasone at 11 PM was 32.7 mcg/dl. Imaging

of the pituitary was normal; an adrenal CT scan showed slightly enlarged adrenals without definite masses. She received 45 Gy of radiation to the region of the sella turcica for presumed pituitary Cushing's disease. Over the next 22 years she continued to have episodic hypercortisolism with undetectable ACTH levels. The normal diurnal variation of serum cortisol was absent and urinary cortisol excretion increased paradoxically in response to dexamethasone. During these 22 years, urinary cortisol excretion ranged from <10 mcg/d to 200 mcg/d (normal <50 mcg/d). DNA studies showed the patient was homozygous for an activating MC2R mutation and heterozygous for a PRKAR1A mutation. At age 41, the patient underwent bilateral adrenalectomy. Pathology showed findings of primary pigmented nodular adrenocortical disease characteristic of Carney complex. The patient's son was found to be heterozygous for both the MC2R and PRKR1A mutations with less severe clinical signs of Cushing's syndrome, consistent with a gene-dose effect. The patient's mother was heterozygous for the MC2R mutation, but was without Cushingoid features.

Discussion: This case illuminates the complex pathophysiology underlying hypothalamic-pituitary-adrenal axis disorders and the challenge of evaluating hypercortisolism. Though rare, Carney complex and/or activating ACTH receptor mutations should be considered during challenging cases of hypercortisolism. A better understanding of these disease processes may improve our understanding of basic adrenal physiology and the relationship between genotype and phenotype.

GENITAL SWELLING IN AN ALCOHOLIC

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Case: AB is a 41 year old African American gentleman with a history of alcohol abuse recently discharged after alcohol detoxification who re-presented with worsening penile, scrotal and lower extremity edema. The patient reported a three day history of dramatic worsening of this swelling in addition to dyspnea on exertion, paroxysmal nocturnal dyspnea, mild orthopnea and a dry cough. Past medical history was revealing only for a history of alcohol withdrawal seizures and an abdominal stab wound in the distant past. Social history confirmed that the patient continued to drink significantly as well as smoke one pack of cigarettes daily. The only prescription medications the patient reported were magnesium and lorazepam which he took as needed for anxiety. Review of systems was significant for orthostatic dizziness, but otherwise negative.

Physical exam: On admission, the patient was breathing comfortably with an oxygen saturation of 97% on room air and a heart rate of 107. Other vital signs were within normal limits. He had jugular venous distension to the level of the jaw. Cardiac exam showed regular rate and rhythm with an S3 but without murmurs or rubs. Pulmonary exam showed soft crackles at the bilateral lung bases. Bilateral lower extremities showed 2+ edema to the waist. The patient also exhibited scrotal and penile edema.

Labs and Radiology: Albumin 3.3, Magnesium 1.2, BNP 1250, urinanalysis within normal limits. Lower extremity ultrasound was negative for deep venous thrombosis bilaterally. Transthoracic echocardiogram showed normal left ventricular chamber size, low normal left ventricular function, mildly reduced right ventricular global systolic function and evidence of severe pulmonary hypertension. CT of the pulmonary arteries showed multiple small pulmonary emboli predominantly involving segmental and sub-segmental branches of the lower lobes bilaterally.

Hospital Course: The patient was treated with intravenous loop diuretics with resolution of his lower extremity and genital edema. He was treated with low molecular weight heparin for pulmonary emboli. He underwent inferior vena cava filter placement during his admission as there was concern for the patient's ability to follow up with outpatient appointments as well as concern in continuing oral anticoagulation in this patient who would likely resume alcohol use after discharge.

Discussion: AB's symptoms are consistent with bilateral pulmonary emboli causing pulmonary hypertension and right heart failure. Pulmonary embolism is a common diagnosis recognized for its ability to masquerade as other illnesses. This case reinforces the need for clinicians to remain vigilant in evaluating for pulmonary embolism. In addition, this case reflects the importance of treating medical conditions within the context of the patient's biopsychosocial sphere.

AUTOIMMUNE PANCREATITIS WITH NORMAL SERUM IgG4 LEVELS

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Autoimmune pancreatitis (AIP) is an unusual cause of pancreatic inflammation secondary to an autoimmune mediated process that is responsive to corticosteroids. AIP generally presents in older patients with a radiographic appearance ranging from diffuse pancreatic enlargement to a mass causing biliary obstruction and mimicking malignancy. Serum IgG4 levels are typically elevated and suggestive of the diagnosis and help in guiding treatment.

We present the case of a 22 year old Caucasian male with a one month history of progressive weight loss, fatigue, abdominal pain, and jaundice. Clinical and lab findings revealed scleral icterus, hepatomegaly, elevated transaminases, alkaline phosphatase and a total bilirubin of 11.2 mg/dL. Total IGG: 967 mg/dl, IGG4: 75 mg/dl. Patient had a normal CA 19-9 and ANA levels.

A CT scan showed prominence of the pancreatic head associated with intrahepatic and extrahepatic biliary ductal dilatation. ERCP demonstrated a 2 cm distal common bile duct stricture which was stented and had a negative brush cytology for malignancy. Endoscopic ultrasound revealed an irregular hypoechoic, heterogeneous mass in the pancreatic head with enlarged peripancreatic lymphadenopathy. Fine needle aspiration during EUS of the mass and lymph nodes were also negative for malignancy. A high clinical suspicion for malignancy prompted a Whipple resection of the lesion. Pathology demonstrated an intense lymphoplasmacytic infiltration of the pancreas and biliary system. These findings are consistent with the diagnosis of AIP.

This case demonstrates that elevated serum IgG4 levels, while characteristic of AIP, are not a diagnostic necessity. In the appropriate clinical setting, a normal IgG4 level does not exclude the diagnosis of AIP and it must remain in the differential diagnosis of focal pancreatic masses.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

SCROFULA IN A YOUNG INDIAN MALE

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Tuberculous cervical lymphadenitis (scrofula) is a common presentation of extrapulmonary tuberculosis worldwide, but accounts for <10% of extrapulmonary cases in the United States. We describe a 22 year old Indian Navy sailor who presented to his ship's physician with complaints of swollen right neck masses 6 months into an 8 month deployment to Norfolk Virginia for the refitting of the former USS Trenton (LPD-14) as the INS Jalashva. He was otherwise symptomatic and reported no chronic illness or known tuberculous contacts. He was treated for presumed lymphadenitis with a 2 week empiric course of amoxicillin-clavulanate followed by ciprofloxacin with some subjective improvement. After a discrete area of fluctuance developed, he underwent incision and drainage and received an empiric course of doxycycline. Over the next month, his neck swelling increased, and his physician noted an increase in size and number of involved posterior cervical lymph nodes. Upon referral to Infectious Diseases, scrofula was suspected. Excisional biopsy revealed caseating granulomas with multi-nucleated giant cells and rare acid fast bacilli on Fite stain. This case illustrates the importance of considering scrofula in patients with lymphadenitis from endemic areas as well as those with a history suggesting higher risk for tuberculosis. Risk factors in adults and children, causative mycobacteria, clinical presentation, appropriate diagnostic tools and therapeutic options in deferent settings are reviewed.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

KIKUCHI-FUJIMOTO DISEASE WITH PAROTID GLAND INVOLVEMENT

Alan Brijbassie, M.D., Carilion Health System

Background: The Kikuchi- Fujimoto disease is an esoteric self-limiting condition of unknown etiology. It is predominantly found in young Asian women where its most common clinical manifestation is localized cervical adenopathy. Parotid gland involvement is rare, with only 3 cases thus far being cited in the literature. We now present the case of a young Caucasian female with histologically proven Kikuchi-Fujimoto disease with parotid gland involvement.

Case: A 24 year old Caucasian female college student presented with a 6 month history of right sided parotid gland enlargement with an associated 2 week history of fever and diaphoresis. History was negative for weight loss, exposure to sick contacts or foreign travel. Physical examination further revealed bilateral axillary and cervical adenopathy. Laboratory evaluation was significant for previous Epstein Barr Virus (EBV) infection; serology for HIV, CMV and antinuclear antibody titers were all negative. Salivary ultrasound and sialogram studies were all negative; MRI of the neck was inconclusive. Excisional lymph node biopsy was then performed which revealed patchy necrotizing lesions consisting of eosinophilic fibrinoid material with striking degrees of karyorrhexis. A diagnosis of Kikuchi- Fujimoto disease was made. The patient recovered without treatment in less than 2 months.

Discussion: Kikuchi- Fujimoto disease was first described 1972, and though initially thought to be confined to Asian countries, cases have been reported in Germany, Italy, Spain and the United States. It predominantly affects females (4:1) and carries a pathogenesis that still remains elusive. Explanations ranging from an idiopathic pattern of nodal involvement secondary to viral infection (EBV, CMV and human herpes virus 6 and 8 most commonly implicated) to an autoimmune contribution due to an observation that the condition may precede or occur in association with systemic lupus erythematosus (SLE) have all been postulated, but conclusive evidence still remains lacking. Cervical adenopathy favoring the posterior cervical triangle and jugular carotid chain is the most common presenting feature; parotid gland involvement is rare. Constitutional symptoms, hepatosplenomegaly, myocarditis, ataxia, arthralgias, polymyositis or aseptic meningitis have all been reported and may complicate the clinical picture. Definite diagnosis relies on an excisional lymph node biopsy illustrating the characteristic necrotizing pattern with three histologic patterns being described- proliferative, necrotizing and xanthomatous. Treatment remains observational although some patients benefit from steroids. The prognosis is good with full resolution expected within 6 months, though fatal cases have been reported. The possible association with SLE is well known, and it is recommended that these patients be followed for this condition. Early diagnosis via biopsy is necessary in order to minimize unnecessary examinations or even harmful treatment.

PULMONARY EMBOLISM, VENTRICULAR THROMBUS, AND MYOCARDIAL INFARCTION: THE TRIPLE THREAT OF PERIPARTUM CARDIOMYOPATHY

Raquel Villavicencio, M.D., Virginia Commonwealth University

Introduction: Peripartum cardiomyopathy (PPCM) occurs in 1:15,000 deliveries in the United States; however its complications, mainly related to persistent left ventricular (LV) dysfunction, thrombus formation, and thromboembolism, can be devastating and may create a prognostic challenge to the clinician.

Case Presentation: A 19-year-old G1P1 mixed African-American/Caucasian female, status post cesarean section at 39+6 weeks for failure to progress complicated by gestational hypertension and chorioamionitis treated with IV antibiotics x forty-eight hours, presented to the Emergency Department nine days post-op with orthopnea, hemoptysis, fatigue, and increased lower extremity edema. She had no personal or family history of cardiac problems, pre-eclampsia, or clotting disorders. Physical exam revealed BP 150/100, HR 141, RR 24, temperature 100.9 F, room air oxygen saturation 86%, jugular venous distention to 10 cm, bilateral crackles bottom third of lung fields, abdominal incision which was clean, without erythema or exudate, and 3+ bilateral pitting edema to her knees. Initial laboratory studies were remarkable for white blood cell count of 25.7, ABG of pH 7.37, pCO2 44, pO2 44, HCO3 25.4, O2 saturation 74%, BNP of 1799, CKMB of 12.8 (which later peaked at 17.8), and troponin-I of 1.79 (peaking at 3.17). EKG showed sinus tachycardia with T-wave inversions in anterolateral leads. Chest x-ray demonstrated enlarged cardiac silhouette, interstitial edema and bilateral pleural effusions. Transthoracic echocardiogram showed an ejection fraction of 20% and a mural thrombus extending from the mid-lateral wall into the apex of the LV measuring 1.8 x 3.8 cm. Lower extremity dopplers were negative for deep vein thrombus, however CT scan revealed a pulmonary embolus in the right lower lung lobe. Despite these tragic complications, the patient did quite well and by discharge repeat echocardiography showed recovery of LV function at rest with an ejection fraction of 55-60%.

Discussion: To my knowledge this is the first report of pulmonary embolus, ventricular thrombus, and myocardial infarction occurring simultaneously as a consequence of PPCM. Elevations in cardiac enzymes were thought to be secondary to microemboli from the left ventricular thrombus migrating into the coronary arteries. This case illustrates that patients with PPCM are at significant increased risk for complications of CHF and thromboembolic disease. Advising patients regarding risk of subsequent pregnancies can be a challenge to the clinician, especially in the case of recovered LV function. Despite normal resting echos, it is thought these patients may have impaired contractile reserve leading to a higher risk of maternal and fetal complications. Dobutamine stress echos may play an important role in determining prognosis, as noted by Lampert et al., and in counseling these women on risks of future pregnancies.

THROMBOPHILIA PRESENTING AS MYOCARDIAL INFARCTION IN AN ADOLESCENT MALE

Christopher P. Gregory, M.D., Eastern Virginia Medical School

Thrombophilia has been well described as a risk factor for venous and to a lesser degree arterial thromboses in older adults, however, its role in adolescent vascular disease is uncommon. A 15 year old white male with no past medical history presented to the emergency department complaining of sudden onset of severe chest pain while playing basketball. That evening, he had eaten multiple slices of pizza and drunk a caffeinated energy drink. He described the pain as radiating from one axilla to the other and initially 10/10 in severity which had subsided to 4/10 upon presentation. Family history was negative for clotting disorders or cardiovascular disease except for hypertension in the patient's grandparents. Social history was negative for tobacco or illicit drug use. Physical exam revealed a well developed adolescent male in no distress, ashen in appearance, without marfanoid habitus or obesity, and otherwise without abnormalities. Electrocardiogram revealed 0.5mm ST elevation in the inferior leads suggesting early repolarization. Upon arrival in the ER, I-stat troponin was elevated at 3.0 and urine drug screen was negative. Immediate CT angiogram of the chest was obtained to rule out aortic dissection with the possibility of right coronary artery involvement, which was negative. Stat bedside echocardiogram, however, showed regional wall motion abnormalities in the basal inferior wall and basal septum. Serum troponin returned elevated at 9.25, and the patient was sent for emergent cardiac catheterization which showed a short 100% occlusion in a distal branch of the posterior descending artery with collateral filling. Consequently, medical management was implemented and the patient did well over the next two days, remaining symptom free, and was discharged. A hypercoagulable workup was ordered prior to discharge which showed a heterozygous prothrombin G20210A gene mutation and was otherwise negative. This case presents a rare finding of coronary arterial thrombosis resulting in a myocardial infarction in an adolescent with previously unknown thrombophilia. Prothrombin gene mutations are autosomal dominant and have been estimated to be present in 2% of the population. They have been associated with venous thromboemboli in patients with other risk factors but have also been described in a few case reports of arterial thrombi, especially of the cerebral circulation. Other environmental factors are generally required to cause clinical thrombi formation and it is interesting in this case that the patient had eaten a high fat meal and drunk a large caffeine load just prior to the onset of his symptoms. In patients without other risk factors, especially the young, it is imperative to search for thrombophilia as a cause of pathology.

USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN POLYCYTHEMIA

Rashad Wilkerson, D.O., Naval Medical Center, Portsmouth

Introduction: Secondary Polycythemia (SP) is an increase in red blood cell mass without a concomitant increase in plasma volume. Management consists of treating the primary etiology, symptomatic treatment, and phlebotomy. Angiotensin Converting Enzyme Inhibitors (ACE-I) have rarely been described in the literature for treatment of this disorder. We present a case of Secondary Polycythemia, with clinical features of Polycythemia Vera, effectively treated with low dose Lisinopril. Case: A 28 year old female, with a past medical history of resolved Idiopathic Thrombocytopenia Purpura and recurrent migraine headaches, was referred to Hematology Oncology for evaluation of persistently elevated hemoglobin and symptoms concerning for a Myeloproliferative Disorder. Presenting symptoms were persistent headaches, erythralgias, pruritis and fatigue. Laboratory evaluation of red blood cell mass, bone marrow biopsy, cytogenetics, erythropoietin levels, ferritin, iron, JAK-2, CFU-E, bone biopsy and renal ultrasound were normal.

Her symptoms ameliorated with multiple phlebotomies. It was hypothesized her symptoms were related to a hypervolemic state. It was noted that ACE-I were used in symptomatic hypervolemic kidney transplant patients. She was placed on five milligrams of Lisinopril, resulting in marked symptomatic improvement and normalization of hemoglobin levels. The dose was increased to 20 mg with further improvement in symptoms and stable hemoglobin levels requiring no further phlebotomy. Conclusion: The effective treatment of SP with Polycythemia Vera traits with ACE-I is rarely noted in medical literature. Treatment efficacy is attributed to ACE-I renin-angiotensin-aldosterone system inhibition, vasodilatation and the proposed apoptosis affect ACE-I cause in erythroid progenitor cells. This may prove to be an alternative treatment modality of Secondary Polycythemia.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

MOLLARET'S MENINGITIS

Danielle Culbert, M.D., MS , Virginia Commonwealth University

Aseptic meningitis is a fairly common syndrome, with 25,000 to 50,000 cases diagnosed annually. However, benign recurrent aseptic meningitis, otherwise known as Mollaret's meningitis, is an extremely rare variant, and left untreated it can cause prolonged and unnecessary suffering for patients.

A 45 year-old African American female with a history of migraine headaches and 6 prior episodes of proven herpes simplex virus (HSV) meningitis presented with one day of diffuse headache, neck and back pain, generalized weakness, photo- and phonophobia and fever. She > denied any active skin lesions, nor did she have any recollection of genital infections. Her neurologic exam was remarkable for markedly positive Kernig and Brudzinski sings. Lumbar puncture revealed 565 white blood cells/mL, initially concerning for bacterial meningitis. White blood cell differential was 3% neutrophils, 85% lymphocytes and 12% monocytes. She was placed on droplet precautions and initially treated with dexamethasone, ceftriaxone, vancomycin, ampicillin, and acyclovir. Cerebrospinal fluid (CSF) culture did not grow bacteria, but her CSF was positive for the presence of HSV type 1 and/or 2 (detected by polymerase chain reaction (PCR) assay). The dexamethasone and the antibiotics were stopped. The patient's headache initially required intravenous opiates for adequate relief but improved dramatically after 2 days of intravenous acyclovir, and she was quickly tapered off of opiates. The patient received intravenous acyclovir for 14 days, and she was subsequently started on life-long suppressive therapy with oral acyclovir (400mg twice daily).

First described in 1944, fewer than 60 cases of Mollaret's meningitis have been reported. The typical course includes brief episodes of acute aseptic meningitis alternating with symptom-free periods over the course of many years. Most cases of Mollaret's meninigitis have been found to be the result of reactivation of HSV, typically type 2. The CSF usually reveals a lymphocytic pleocytosis with large mononuclear cells (Mollaret cells). The majority of patients have no active skin lesions at the time of presentation, and many have no history of genital lesions. The trigger for reactivation is unknown in these patients. Acyclovir works well when used as a suppressive medication to prevent further episodes of meningitis. Because an effective suppressive medication exists, pursuit of a microbiologic diagnosis in episodes of recurrent aseptic meningitis should be strongly considered. The recognition and treatment of Mollaret's meningitis can prevent significant morbidity in patients.

HOSPITAL-ACQUIRED ENDOCARDITIS

Jared Shipley, M.D., Virginia Commonwealth University

An 81-year-old Caucasian man with a history of extensive atherosclerotic disease, including mitral valve thickening with severe mitral regurgitation, presented with syncope. On admission, he had a large melanic bowel movement as well as orthostatic hypotension. Cardiac exam revealed a II/VI systolic murmur, loudest at the apex. Labs revealed a serum hemoglobin of 7.3 g/dL (baseline 10-12 g/dL). For standard gastrointestinal bleeding treatment, two peripheral intravenous catheters were inserted, and the patient was stabilized with fluid resuscitation and blood transfusion. On hospital day 3, the patient underwent upper endoscopy without any antibiotic prophylaxis. Two days post-endoscopy, the patient developed a fever of 102 degrees Fahrenheit. Mild erythema and swelling were noted around the site of one of his peripheral intravenous catheters. He was started on vancomycin and ceftriaxone. The next day, his speech became garbled with word salad. His systolic murmur was harsher and had increased in volume. Skin exam revealed new non-blanching, nontender petechiae on three fingertips, two toes, and one heel. Two sets of blood cultures revealed methicillin-sensitive Staphylococcus aureus (MSSA) in both aerobic and anaerobic bottles. A transthoracic echocardiogram showed small mobile echodensities on the posterior leaflet of the mitral valve, suspicious for endocarditis. Magnetic resonance imaging scan of the brain showed acute ischemia in several noncontiguous areas, consistent with an embolic etiology. The patient was treated with four weeks of nafcillin and made a full recovery.

Onset of infective endocarditis (IE) during hospitalization is rare. In this patient, the most likely sources for IE are transient bacteremia during endoscopy or an infected intravenous catheter. The rate of bacteremia during endoscopy has been reported to be as high as 2-5%, yet the rate of associated IE is exceedingly rare. However, the morbidity and costs of IE are great, while the adverse effects of a single dose of an antibiotic are minimal. For this reason, peri-procedural ampicillin had been recommended for higher-risk patients, including those with mitral valve prolapse with regurgitation or valve thickening. In April of 2007, the American Heart Association updated its guideline for prevention of IE and retracted the original recommendation to give prophylaxis to patients undergoing gastrointestinal procedures for two reasons: 1) the rarity of IE even with documented peri-procedural bacteremia and 2) an increase in highly-resistant strains of enterococcus. In this patient's case, prophylaxis with ampicillin would not have prevented the development of MSSA IE. Although this dramatic presentation of IE was temporally related to the endoscopy, the identification of the offending organism as MSSA makes it more likely that an infected peripheral intravenous catheter was the cause. This highlights the importance of checking intravenous catheters daily for signs of infection and reducing the number of catheters to the minimum necessary.

In Memoriam
Brandon F. Falk, MD

It is with great sadness that we mourn the loss of one of our colleagues, Brandon Falk, who passed away on April 11, 2008. Brandon came to the University of Virginia in 2003 for his Internal Medicine Residency. During his residency, he was highly regarded by his resident colleagues, being described as clearly one of the brightest in his class. In fact, he was often found to be buried in textbooks as he strived to learn as much as he could to better care for his patients. His attendings often commented on his attentiveness to detail and his priority to patient care. One quote, in particular, summarizes Brandon's time here- "it is a comfort when he is on call knowing that the patients are well taken care of."

In his spare time, Brandon was an accomplished musician. He played lead guitar in several bands, including one during his tenure in Charlottesville. A friend, colleague, and band member remembers his joy and passion for music, much the same way he approached the practice of medicine.

Upon graduation, he took a hospitalist position in Maryland. Even though he had moved on from the University of Virginia, like all our residents, he was still considered part of our extended family and will be sorely missed.

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