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A Note from the Editor

The 2006-2007 academic year marks the 100th anniversary of the Department of Medicine at the University of Virginia. Excellence in clinical care, research, and education, the cornerstones of the Department, has been embodied in the activities of the housestaff and faculty for a century, and we hope this excellence will now be reflected in the *University of Virginia Journal of Medicine*. The vision for the Journal came from the 10th Chairman of the Department, Dr. Robert Strieter, who came to Charlottesville in July, 2006. Dr. Strieter viewed the creation of the Journal as a means of furthering and communicating the Department's tradition of outstanding medical pursuits.

Issues of the Journal will feature clinical vignettes of patients cared for at the University of Virginia Health System, which were prepared for publication in a joint effort by resident and attending physicians. In addition, you will also find updates of translational research and technological advances developed within the Department, as well as reviews of important clinical concepts, written by faculty members and coauthored by residents and fellows.

The *University of Virginia Journal of Medicine* allows alumni, who have played such a central role within the Department during their time here, and the medical community within the Commonwealth the opportunity to learn from the breadth of clinically based educational experiences generated from patient care at the University of Virginia. It is an honor to have been asked to be the first chief editors and contribute to this new and exciting endeavor of a Department that has meant so much to many of us.

Sincerely,

Gerald Donowitz, MD & John Densmore, MD

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. Submissions should be made electronically to Cathy Keefe-Jankowski (ck8h@virginia.edu). 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.

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:

Journal Article:

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

Book:

1. **West H.** *Reanimation in Theory and Practice.* Providence, RI: Miskatonic Universtiy Press; 1923.

Guidelines for Article Review Process

Manuscripts will be blindly reviewed by two members of the editorial 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:

Case Reports/Clinical Vignettes: *suggested length - 800-1600 words*

Case Reports describe case patients with 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 case reports 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: *suggested length - 800-1600 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.

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

A comprehensive review article 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.

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 Commentary: *suggested 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: *suggested 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: *suggested 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.

The Serotonin Syndrome: a Spectrum of Serotonin Excess

Brian W Hanrahan, MD, Postgraduate Year 3, Internal Medicine
Mark E Williams, MD, Professor of Medicine, Division of General Medicine, Geriatrics and Palliative Care

Physicians have a number of tools to help patients with various mood disorders, such as depression, bipolar illness, and dementia, with associated behavioral disturbances. The number of medications used both alone and in combination to treat these disorders has expanded rapidly. Although the benefits of pharmacological therapy are significant, associated risks can be substantial. We present a case of the serotonin syndrome produced by a combination of psychoactive medications and discuss the diagnosis and treatment of the disorder.

CASE DESCRIPTION

A 57-year-old woman presented to the emergency department of a university teaching hospital with a 2-day history of restlessness, insomnia, jerking movements, and general malaise. She had a past medical history of hypertension, depression, and significant alcohol abuse. The patient had been drinking a bottle of wine daily for several days prior to the day of admission, but denied using any illicit drugs. Her depressive symptoms had been worsening over the month preceding her admission. Her depression was being treated with 100 mg of trazodone and 150 mg of extended-release venlafaxine daily. The patient continued to have significant symptoms, and without seeking medical attention, increased the venlafaxine to 600 mg daily (maximum recommended dose 225 mg daily). She presented to the emergency department approximately 72 hours after beginning this increased dose of venlafaxine.

Physical examination revealed an ill-appearing woman with significant akathesia. Her oral temperature was 37.7°C, blood pressure was 183/102, and pulse was 120. She had dilated pupils bilaterally that were equal and briskly responsive to light. Cardiac examination showed a regular tachycardia with no extra heart sounds. Neurological evaluation revealed hypertonia in all tested muscle groups and hyperreflexia with clonus in all 4 extremities, greater in her lower extremities bilaterally than in her upper extremities. Babinski and Hoffman signs were present bilaterally.

The patient's initial electrocardiogram showed a sinus tachycardia with biphasic t-waves in leads V2-V5 and QRS and QTc durations within normal limits. Serum cardiac troponin I was <0.02 ng/mL (normal <0.02 ng/mL). Serum creatine kinase was 3714 U/L (normal 30-170 ng/mL). Serum creatinine was 1.1 mg/dL (normal 0.6-1.1 mg/dL). Urinalysis showed moderate blood on dipstick, but no red blood cells on microscopy. Urine myoglobin was positive.

The patient was admitted to the general medicine service for management of apparent serotonin syndrome, although ethanol withdrawal and cocaine intoxication remained in the differential diagnosis. The patient's constellation of signs and symptoms was considered to be most consistent with the serotonin syndrome with some superimposed ethanol withdrawal. Cocaine intoxication was thought to be less likely, but a drug screen to rule it out was never performed. Adminstration of all serotonergic agents was discontinued. The patient was given intravenous normal saline at 200 mlL/hour through the first 48-hours of admission and was treated with both scheduled and symptom triggered lorazepam, which is usuallyeffective in treating symptoms

associated with the serotonin syndrome, ethanol withdrawal, and cocaine intoxication. The patient continued to receive hydrochlorothiazide and amlodipine, the antihypertensive agents she had been taking prior to admission, and was also given a low dose of metoprolol to help control the tachycardia. Despite this initial therapy, the patient became febrile, with a temperature ≤40°C, was persistently tachycardic, and showed worsening hyperreflexia and clonus. On hospital day 2 the patient was started on oral cyproheptadine. A repeat electrocardiogram showed new deep t-wave inversions in the precordial leads. The patient was not experiencing chest pain, cardiac troponins were negative, and a transthoracic echocardiogram showed no changes consistent with ischemia. Thus the electrocardiographic changes were attributable to excessive autonomic output. With continued intravenous hydration at 150-200 mL/hour, the patient's serum creatine kinase decreased and her renal function remained stable. By hospital day 3, the patient's vitals signs normalized and her neurological symptoms began to resolve. Her symptoms had entirely resolved by the morning of the day of discharge, 4 days after admission.

DISCUSSION

The serotonin syndrome is an adverse drug reaction or interaction that results in excessive serotonin levels. This syndrome can occur with both normal and toxic levels of medications known to increase serotonin. Excessive serotonin can produce a variety of clinical effects, ranging from mild to life-threatening, comprising mental-status changes, neuromuscular hyperactivity, and autonomic excess. The spectrum of clinical manifestations of the serotonin syndrome is broad (Table 1). Mild cases may present with delirium, restlessness, and tremor. Severe cases can result in muscular rigidity, clonus, and life-threatening hyperthermia, mimicking the malignant neuroleptic syndrome (1,2).

Table 1. Manifestations Associated with Serotonin Excess*

Autonomic
Tachycardia
Diaphoresis
Mydriasis
Diarrhea
Neuromuscular
Tremor
Hyperreflexia
Hypertonia
Inducible clonus
Spontaneous clonus
Ocular clonus
Mental Status
Agitation
Hypervigilance
Pressured speech
Delirium
Other
Rhabdomyolysis
Acute renal failure
Metabolic acidosis
Disseminated intravascular coagulopathy
Seizures
Hyperthermia (mostly secondary to muscle hyperactivity)

*Adapted from Boyer and Shannon.[1]

Table 2. Hunter Serotonin Toxicity Criteria*

1. Patient must have taken serotonergic agent within the prior 5-weeks
2. Tremor AND hyperreflexia
3. Spontaneous clonus
4. Muscular rigidity with temperature > 38°C AND EITHER ocular OR inducible clonus
5. Ocular clonus AND EITHER agitation OR diaphoresis
6. Inducible clonus AND EITHER agitation OR diaphoresis

*Diagnosis requires 1 and ≥1 of 2-6. Adapted from Gillman.[8]

Serotonin is produced by decarboxylation and hydroxylation of L-tryptophan. It then interacts with a family of receptors, the 5-hydroxytryptamine (5-HT) receptors. There are 7 types of 5-HT receptors, several of which have multiple subtypes. The 5-HT receptors are found throughout the central and peripheral nervous system, with each type of receptor leading to a different physiologic effect. Although several of the 5-HT receptors seem to contribute to the development of the serotonin syndrome, the 5-HT_{2A} receptors appear to lead to the hyperthermia and hypertonicity found in cases of severe serotonin syndrome (1,10).

The true incidence of the serotonin syndrome is difficult to know, because many physicians are unaware of the syndrome or of how to accurately diagnose it. The incidence is likely to rise as the number of serotonergic agents being prescribed increases.

Diagnosis of the serotonin syndrome remains clinical, with no laboratory tests that can reliably diagnose the disorder. Proper identification of the syndrome depends on physician recognition of the characteristic findings of the syndrome combined with a high index of suspicion. The patient history should include all medications, both new and old, and use of illicit drugs, herbal products, and over-the-counter medications. In addition to a full, careful physical examination, focus should be placed on the nervous and neuromuscular systems. The Hunter Serotonin Toxicity Criteria (Table 2) has a sensitivity of 84% and specificity of 97% for the diagnosis of the serotonin syndrome (3).

Many classes of prescription medications, over-the-counter medications, herbal therapies, and illicit drugs have been associated with the serotonin syndrome. Selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, antiemetics, antibiotics, dietary supplements, and illicit drugs such as 3,4-methylenedioxy-N-methylamphetamine (ecstasy) and lysergic acid diethylamide-25 are the most common offenders. In addition, drugs with no known serotonergic properties have clear effects on the metabolism and clearance of serotonergic drugs, and underlying medical issues such as renal or liver failure can affect the clearance of serotonergic agents. Physicians often prescribe serotonergic drugs to geriatric patients, who for several reasons are at much higher risk of developing the

Table 3. Medications Associated with Serotonin Syndrome*

Selective serotonin-reuptake inhibitors:	sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs:	trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors:	phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants:	valproate
Analgesics:	meperidine, fentanyl, tramadol, and pentazocine
Antiemetics:	ondansetron, granisetron, and metoclopramide
Antimigraine agents:	sumatriptan
Bariatric medications:	sibutramine
Antibiotics:	linezolid and ritonavir
Over-the-counter cold remedies:	dextromethorphan
Drugs of abuse:	MDMA (ecstasy), LSD, 5-methoxydiisopropyltryptamine, and Syrian rue
Herbal products:	tryptophan, St. John's wort, and ginseng
Other:	lithium

*Adapted from Boyer and Shannon.[1]

syndrome. Geriatric patients often take multiple medications, a situation in which the chances of significant drug interactions are quite high. In addition, the volume of distribution, and thus drug concentrations and drug elimination rates differ in geriatric patients.[1,4-6]

Treating the serotonin syndrome involves withdrawing the offending agent, providing hemodynamic support, correcting autonomic hyperactivity, managing agitation and hyperthermia, and administering serotonin antagonists. Supportive care involves intravenous fluid hydration and benzodiazepine therapy. Most mild cases of the syndrome should resolve with the withdrawal of the agent and supportive therapy. More severe cases may require administration of serotonergic antagonists. Oral cyproheptidine is the antiserotonergic agent of choice, but chlorpromazine can be used if parenteral administration is required. Cyproheptadine is a 5-HT_{2A} antagonist that is given as an initial dose of 12 mg orally, followed by a maintenance dose of 8 mg every 6 hours until symptoms resolve. Side effects of cyproheptadine include central nervous system depression, gastrointestinal distress, and rarely liver toxicity. Chlorpromazine may be used as an antiseritonergic agent, but this drug may exacerbate hyperthermia in patients with neuroleptic malignant syndrome misdiagnosed as serotonin syndrome. β-Blockade may be used to treat tachycardia and hypertension associated with the syndrome, but because tachycardia is a measure used to determine length of treatment, abolishing tachycardia may lead to prolonged therapy. In addition, unopposed α-stimulation in the setting of cocaine intoxication could lead to worsened clinical outcomes. Dantrolene and bromocriptine are not recommended for the treatment of the serotonin syndrome. For life-threatening symptoms, especially severe hyperthermia, endotracheal intubation and neuromuscular paralysis should be considered.[1,7-9]

In summary, the serotonin syndrome is a potentially life-threatening entity associated with many drugs. This syndrome may occur at any dose of offending agents, even a single dose. The diagnosis of serotonin syndrome must be made clinically, and physicians should be quick to recognize the associated constellation of signs and symptoms and initiate prompt therapy. Paramount in the treatment of the syndrome is the removal of the serotonergic agent and administration of supportive therapy. Severe cases may require administration of serotonergic antagonists and even intubation and induced paralysis for life-threatening hyperthermia.

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Etiology of Deep Vein Thrombosis: A 2-Hit Hypothesis

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The development of recurrent venous thromboemboli (VTE) in an adult should prompt investigation into predisposing causes including hematologic disorders and mechanical risk factors. Both inherited and acquired conditions should be considered because most, if not all, episodes of VTE are caused by a combination of these factors.[1]

CASE DESCRIPTION

A 42-year-old woman presented with a complaint of left lower extremity swelling and tenderness. During the previous 20 years, she had developed a total of 5 left lower extremity deep vein thromboses (DVT). The first DVT occurred after the birth of her first child; however, all of her pregnancies were otherwise uncomplicated. The patient denied recent immobilization, surgery, trauma, or pregnancy. Neither her past medical history nor her medication list revealed a risk factor for thrombus formation, but her family history was significant because her mother suffered chronic thromboses. Results of the patient's previous workup included normal factor V Leiden, anticoagulant proteins C and S, antithrombin, and lupus anticoagulant studies.

A left lower extremity ultrasound showed an acute or chronic thrombosis extending from the left common femoral vein to the deep veins of the distal calf. Additional hypercoagulable workup revealed that the patient was heterozygous for the prothrombin gene mutation. The predilection for VTE in the left lower extremity raised the suspicion of an anatomic condition contributing to thrombus formation. Magnetic resonance imaging angiography of the left lower extremity showed compression of the left common iliac vein by the crossing right common femoral artery; consistent with May-Thurner syndrome. Standard anticoagulation therapy was initiated and lifelong treatment recommended. On therapy, the left lower extremity swelling and pain resolved.

CASE DISCUSSION

Hypercoagulable Workup

The hypercoagulable evaluation to determine the etiology of VTE is complex; however, with aggressive investigation the cause is identified in 50% of cases.[1] Both acquired and inherited risk factors must be considered. The patient's history is especially useful when attempting to identify acquired risk factors.[2] Predisposing conditions such as recent travel, immobilization, trauma, surgery, or increased estrogen states such as pregnancy can be identified. Comorbid conditions contributing to thrombotic risk, such as vasculitis, inflammatory bowel disease, or hematologic disorders are also identified. A history of multiple abortions should raise the suspicion of antiphospholipid syndrome or possibly an inherited predisposition to thrombosis. The medication list is reviewed, with particular attention to contraceptive use and other hormonal therapies. The patient should be questioned about previous malignancy, and all age- and risk-factor appropriate cancer screenings performed. Both a family history of VTE and a young age of first thrombus suggest an inherited etiology.

For each patient, the clinician must determine which tests are needed and when they should be performed. This task has become more cumbersome because the number of identified causes of a VTE has grown significantly in recent years. Furthermore, there are no consensus statements to guide the workup, and studies to

determine the significance of many disorders, such as homocysteinemia, are ongoing. A practical approach that takes into consideration the patient's personal or family history of VTE as well as the severity and location of the thrombus is provided in the Table.

The timing of studies is critical for the workup of antithrombin, protein C, and protein S deficiencies as well as for antiphospholipid syndrome. Treatment with heparin reduces the plasma levels of antithrombin, and warfarin lowers the activity levels of proteins C and S.[3] In addition, the acute thrombus can transiently decrease the plasma levels of all 3 factors. As a result, these deficiencies should be investigated at least 2 weeks after treatment has been completed. If normal results are obtained from study samples drawn in the acute setting, these conditions can be excluded. The workup for antiphospholipid syndrome should be initiated in the acute setting, but the assays must be repeated 12 weeks later to confirm the diagnosis.[4]

If the etiology of a VTE is still uncertain despite this initial workup, there are further hematological studies that may be performed. However, consultation with a hematologist is advised because of the ever-changing data about the significance of suspected risk factors.

Prothrombin Mutation

The prothrombin gene is located on chromosome 11, where a transition mutation of guanine to adenine at nucleotide 20210 has been associated with significantly higher serum prothrombin levels and higher incidence of thrombus.[5] The mechanism by which the G20210A mutation increases prothrombin levels is unclear. Multiple studies have concluded that G20210A is a functional mutation.[6,7] Various authors have postulated that the mutation alters prothrombin mRNA by increasing the processing efficiency, decreasing the decay rate, or increasing the accumulation of prothrombin mRNA.[7-9]

The prothrombin mutation is more prevalent in causcasians, and has been reported in 2% to 5% of the general population and in 7% to 18% of patients with spontaneous DVT.[10,11] Heterozygotes are approximately 3 times more likely to develop a thrombus than the general population.[5]

Some authors question the likelihood that the prothrombin mutation alone can lead to VTE formation. One study found that the risk of thrombus associated with this mutation was significant only in the subset of patients with additional risk factors.[12]

May-Thurner Syndrome

May-Thurner syndrome is an acquired stenosis of the left common iliac vein that causes pain, edema, and eventually DVT.[13] Compression of the left iliac vein by the right iliac artery is an anatomic variant that has been described for many years.[14] In 1851, Virchow observed that a DVT was 5 times more likely to occur in the left leg.[15] In 1956, May and Thurner found that the left common iliac vein was compressed by the right common iliac artery, and that the compression led to the formation of a spur in the vein. They concluded that these anatomic changes were responsible for the higher incidence of left lower extremity DVT.[16]

The incidence of May-Thurner syndrome is uncertain. It is more common in women, and usually presents in the 3rd to 5th decade of life.[17] It has been estimated that 2% to 5% of patients with lower extremity venous disorders have May-Thurner syndrome.[18] Magnetic resonance venography showed that 37% of patients with isolated left lower extremity edema had compression of the left iliac vein.[19]

The significance of May-Thurner syndrome as a sole contributor to the development of thrombus has been questioned. May and Thurner's early autopsy studies found the spur-like change of the iliac vein in 22% of cases.[16] A recent compute tomographic

imaging study of an asymptomatic population found that approximately one fourth of the participants had >50% compression of the left iliac vein and that two thirds had >25% compression.[14] These authors have concluded that the anatomic changes associated with the syndrome may represent a normal variant that may lead to thrombus formation only when it occurs in concert with other hypercoagulable risk factors.

CONCLUSION

The development of VTE, particularly when it is recurrent, should prompt a patient-specific hypercoagulable evaluation that investigates both inherited and acquired causes. The importance of this strategy has been highlighted in recent years with the realization that the etiology of most VTE is multifactorial. In fact, many authors suggest that acquired and inherited factors work dynamically to produce a thrombus.[20] In the case we report, the patient's family history of thrombus increased the probability of an inherited risk such as the prothrombin mutation. The case patient also had recurrent thrombi in a single location, prompting evaluation for an anatomic cause and the discovery of May-Thurner syndrome. Alone, neither the prothrombin mutation nor May-Thurner syndrome are high-risk conditions for thrombus.[12,14] In combination, however, these 2 conditions cause vessel-wall disorder, venous stasis, and increased coagulability, the Virchow triad of conditions associated with thrombogenesis. Therefore, this case illustrates the concept of multifactorial etiology for VTE formation and reinforces the need for a thorough hypercoagulable workup.

VTE Workup for the Case Patient

Factors	Negative Family or Personal History	Negative Family or Personal History w/Severe Clot or Unusual Location	Positive Family or Personal History
Lupus anticoagulant	X	X	X
IgG and IgM Anticardiolipin or 2 glycoprotein-1 antibody	X	X	X
Homocysteine level	X	X	X
Factor V Leiden		X	X
Prothrombin mutation		X	X
Factor VIII level		X	X
Fibrinogen studies		X	X
Protein C			X
Protein S			X
Antithrombin			X

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Secondary Cutaneous Cryptococcosis in a Lung Transplant Recipient

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CASE DESCRIPTION

A 64-year-old man presented to the emergency department with a 3 to 4 week history of malaise, fevers, chills, and some mental confusion. The patient's past medical history was significant for left lung transplantion secondary to chronic obstructive pulmonary disease in December 2005, hypertension, hyperlipidemia, and type 2 diabetes mellitus. His current medications included tacrolimus, mycophenolate mofetil, prednisone, acyclovir, and trimethoprim sulfamethoxazole DS 3 times weekly.

Physical examination revealed that the patient had a temperature of 39.6˚C, blood pressure of 86/65 mm Hg, a heart rate of 67 beats/min, a respiratory rate of 16 breaths/min, and an oxygen saturation of 98% on 2 L nasal cannula. He was fully alert and oriented and had no focal neurologic deficits. A thorough ophthalmologic examination showed no papilledema, hemorrhage, or retinitis. Examination of the patient's skin revealed a 2 X 1 cm ulcerated lesion with raised borders on the lateral aspect of his neck. Also, noted were multiple raised flesh-colored umbilicated papules on his left shoulder, gluteus, and forehead. The patient stated that he first noticed these lesions approximately 2 weeks prior to the onset of his other symptoms. Initial laboratory values were notable for blood urea nitrogen 34 mg/dL, creatinine 2.4 mg/dL (baseline 1.5 mg/dL), white-cell count 10.8 k/µL, and an erythrocyte sedimentation rate of 102 mm/h.

The patient was admitted to the general medicine service. Chest x-ray on admission showed no acute cardiopulmonary process. A noncontrast head computed tomography (CT) scan was unremarkable. A lumbar puncture was performed, and the opening pressure was elevated at 37 cm of water; cerebrospinal fluid (CSF) analysis revealed a white-cell count of 2/mm^3, a protein level of 85 mg/dL (normal range 15-25 mg/dL), glucose level of 78 mg/dL (normal range 40-70 mg/dL). Viral cultures and herpes simplex virus polymerase chain reaction were negative. The CSF cryptococcal antigen assay was positive at a dilution of 1:64. India ink preparation of the CSF revealed numerous round, budding, encapsulated yeasts characteristic of cryptococcus. Peripheral blood cultures drawn on admission also were subsequently positive for cryptococcus, indicating disseminated infection. CT scan of the chest revealed an 11 mm left upper lobe pulmonary nodule.

Infectious disease and dermatology consultations were obtained, and a lesion on the patient's shoulder was biopsied. Histologic examination of the skin biopsy revealed numerous small, round, gray-staining organisms within the dermis, surrounded by clear capsules consistent with *Cryptococcus neoformans*. The patient was started on liposomal amphotericin B 400 mg daily. Serial lumbar punctures were also performed, on hospital days 3 and 6, with opening pressures of 18 cm of water and 20 cm of water, respectively. The patient's initial hospital course was notable for intermittent fever and periodic disorientation. After 7 days of liposomal amphotericin treatment, however, the patient was afebrile with complete normalization of mental status, and was felt to be stable for discharge. Repeat blood cultures were negative. The patient was discharged to home and there completed a 4-week course of intravenous liposomal amphotericin B followed by a 10-week course of oral fluconazole 400 mg daily, and then chronic suppressive therapy with oral fluconazole 200 mg daily for at least 1 year.

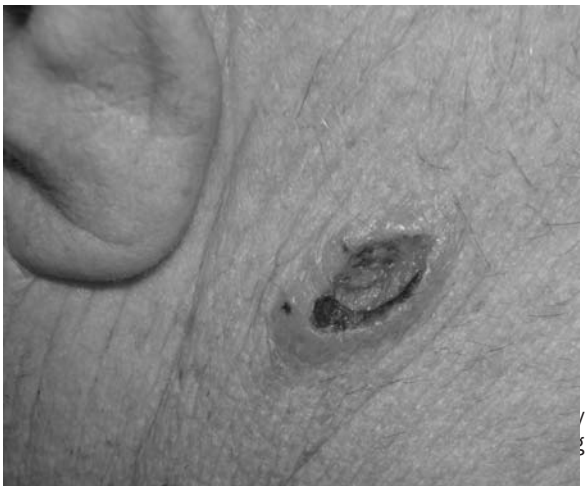
CASE DISCUSSION

The incidence of cryptococcal infections has increased in recent years and immunocompromised individuals constitute the majority of patients diagnosed.[1] A number of factors have contributed to this increase, including: the AIDS epidemic, the use of corticosteroids in autoimmune diseases, chemotherapy, and the use of immunosuppressants after organ transplantation.[2,3] The widespread availability of testing for human immunodeficiency virus infection combined with antiretroviral therapy has markedly decreased the frequency of cryptococcal infection in persons with AIDS in the US.[4] At the same time, however, there has been a sharp rise in organ transplantation, making this the most common risk factor for acquiring the infection.[5] A recent review of the incidence of *C. neoformans* in transplant recipients found the mean incidence of infection was 2.8 per 100 transplant recipients, with a case fatality rate of 42% (72/172).[6]

The portal of entry of *Cryptococcus* is primarily through direct inhalation of the fungus from the environment. Direct inoculation into tissue from trauma and transplantation of infected tissue can be the portal of entry in occasional cases.[7] After the fungus enters the human body, it can produce latent infection or acute disease. Cell-mediated immunity is the most important arm of host defenses against *C. neoformans,* and a strong cell-mediated immune response is crucial for containing cryptococcal infection.[8] The organisms can remain dormant for years in hilar lymph nodes or pulmonary foci of asymptomatic individuals. When an individual's cellular immunity is suppressed, the organisms may grow and disseminate outside these host immune complexes.[9]

Although cutaneous cryptococcal infection is unusual, the skin is the third most common clinical site of cryptococcosis[10], the most common being the central nervous system (CNS) and lung, and skin lesions are found in approximately 5% of patients with cryptococcal meningitis.[7] Cutaneous cryptococcosis can manifest as many types of skin lesions including molluscum contagiosum-like lesions; ulcers; pustules; acneiform, nodular, or herpetiform lesions; abscesses; or cellulitis.[10-13] Cutaneous cryptococcosis can occur from local inoculation, although it most often occurs through hematogenous dissemination. Because many skin manifestations of cryptococcosis may mimic other infections, biopsy of the skin lesion with culture and histopathology is essential for definitive diagnosis, especially in immunocompromised patients, who may have multiple coexistent dermatologic disease processes.[14] Patients with a diagnosis of cryptococcosis from a skin biopsy or culture should undergo evaluation to exclude disseminated disease, and if there is no obvious underlying immunodeficiency state, an evaluation of cell-mediated immunity. Our patient's skin lesions on presentation included both molluscum-like lesions and the large ulcerated lesion depicted in Figure 1.

The CNS and respiratory tract are the most common sites involved in cryptococcal infections; however, every organ in the body may be infected.[1] Patients with CNS involvement can present with acute, subacute or chronic meningitis or



meningoencephalitis. Signs and symptoms are usually present for several weeks and include headache, fever, cranial neuropathy, altered consciousness, lethargy, memory loss, meningeal irritation signs, and coma.[1] Patients can present with acute or intermittent headaches or with altered mental status without signs of meningeal irritation, even though the burden of fungal organisms in the CNS is high.[10] Our patient's presentation with subacute mild confusion as the only neurologic symptom was typical of cryptococcal meningoencephalitis.

The presentation of pulmonary cryptococcosis can range from asymptomatic nodular disease to severe acute respiratory distress syndrome. Classic symptoms of pneumonitis, including cough, fever, and sputum production, may be present, or pleural symptoms may predominate.[15] In our patient's case, the only pulmonary manifestation was the left upper lobe nodule noted on chest CT scan.

Several laboratory methods for diagnosing cryptococcosis have been established, including direct examination of the fungus in body fluids, cytologic or histopathologic analysis of infected tissues, serologic studies, or culture. A rapid and inexpensive diagnostic test for cryptococcal meningitis is direct microscopic examination for the presence of encapsulated yeasts using an India ink preparation of CSF.[16] This simple technique is 30% to 50% sensitive in cases of non-AIDS cryptococcal meningitis and up to 80% sensitive in AIDS-related cryptococcal meningitis.[10] Histologic stains of tissues from lungs, skin, bone marrow, brain, or other organs can also be used to identify cryptococci with their prominent capsule.[17,18.] Detection of cryptococcal capsular polysaccharide antigen via latex agglutination tests in serum or CSF can also used as a screening test in immunocompromised patients who have some mild symptoms referable to the CNS; the serum cryptococcal antigen can be used to establish the diagnosis when it is felt that a lumbar puncture is not indicated. Overall sensitivities and specificities of the latex agglutination tests were found to be 93% to 100% and 93% to 98%, respectively.[19]

The choice of treatment for disease caused by *Cryptococcus* depends on both the extent of the disease and the host's immune status. In cryptococcal meningitis and disseminated cryptococcosis, recommended treatment is amphotericin B (0.7 to 1 mg/kg per day) plus flucytosine for 2 weeks, followed by 8 to 10 weeks of fluconazole (400 to 800 mg/day).20,21. Then long-term suppressive/maintenance therapy with lower dose fluconazole (200 to 400mg/day) for at least 12 months is recommended 20.

CONCLUSION

The majority of cryptococcal infections occur in immunocompromised individuals; thus clinicians must have a high index of suspicion in such patients because of the often insidious onset of symptoms. The disease should be suspected in any immunocompromised patient with fever, headache, and signs and symptoms referable to the CNS. Moreover, because CNS symptoms and signs are often nonfocal and pulmonary symptoms absent, the dermatologic manifestations may be the key clue to establishing the diagnosis. Because many skin manifestations of cryptococcosis are nonpathognomonic, biopsy of the skin lesion with culture and histopathologic analysis is necessary to confirm the diagnosis in immunocompromised patients. Because patients with a diagnosis of cryptococcosis from a skin biopsy or culture usually have concomitant systemic or CNS involvement, they should undergo a full clinical examination, chest x-ray, and lumbar puncture. CSF and blood should be assayed for the presence of fungal elements, and the cryptococcal antigen test, which provides a sensitive and rapid means of diagnosis, should be performed on serum and CSF.

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Takotsubo Cardiomyopathy in an Elderly Man

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Takotsubo cardiomyopathy, also referred to as transient left ventricular apical ballooning syndrome, broken heart syndrome, and stress-induced cardiomyopathy, is a poorly understood clinical entity. It is characterized by transient wall-motion abnormalities involving primarily the left ventricular apex and mid-ventricle in the absence of obstructive coronary disease.[1] Because of recent recognition this unusual syndrome, which is much more common in women than men, is being diagnosed with increasing frequency.[1]

CASE DESCRIPTION

A 78-year-old man with no known history of coronary artery disease presented to the emergency department with acute onset of chest pressure, lightheadedness, nausea, diaphoresis, and shortness of breath while driving to work. He had been in his usual state of health, routinely walking while playing golf without limitations due to chest pain or shortness of breath. The electrocardiogram at presentation showed a prolonged corrected QT interval of 550 msec with diffuse T wave inversions in leads I, II, and V2-V6 (Figure 1). The initial troponin I was elevated at 0.13 ng/mL.

Approximately 4 hours after presentation the patient developed tachycardia, worsening shortness of breath, and hypotension. A chest x-ray demonstrated pulmonary edema, and a bedside echocardiogram revealed a large anteroseptal wall motion abnormality. By this time the troponin I was 3.5 ng/mL. The patient was transferred to the cardiac care unit, where his disease course was complicated by a transient third-degree heart block, which resolved spontaneously. He was referred emergently for cardiac catheterization.

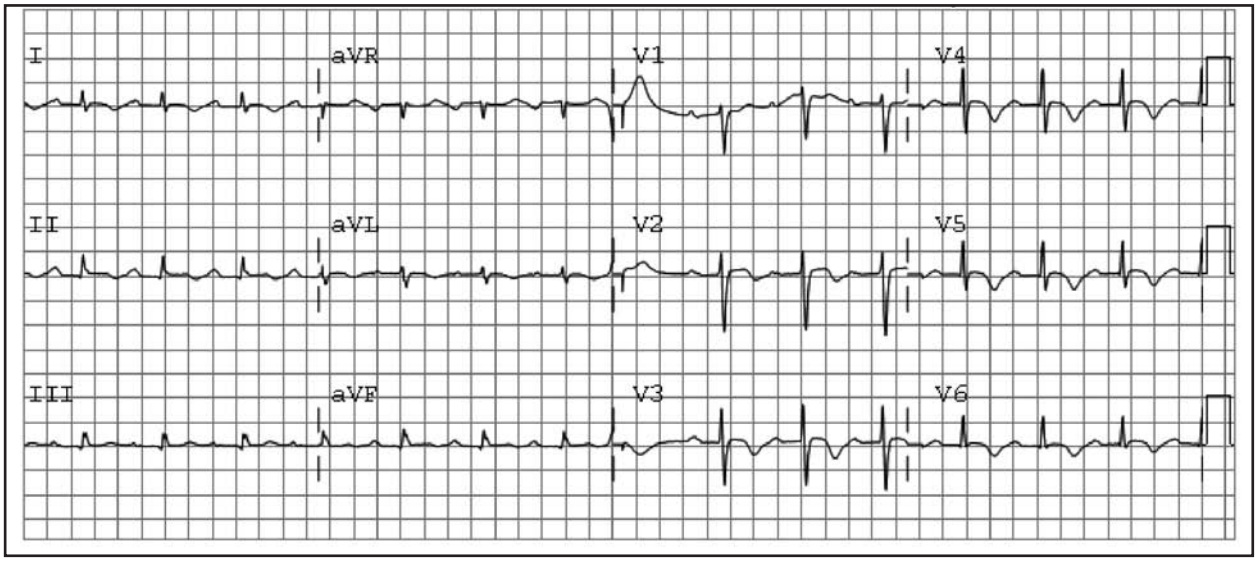


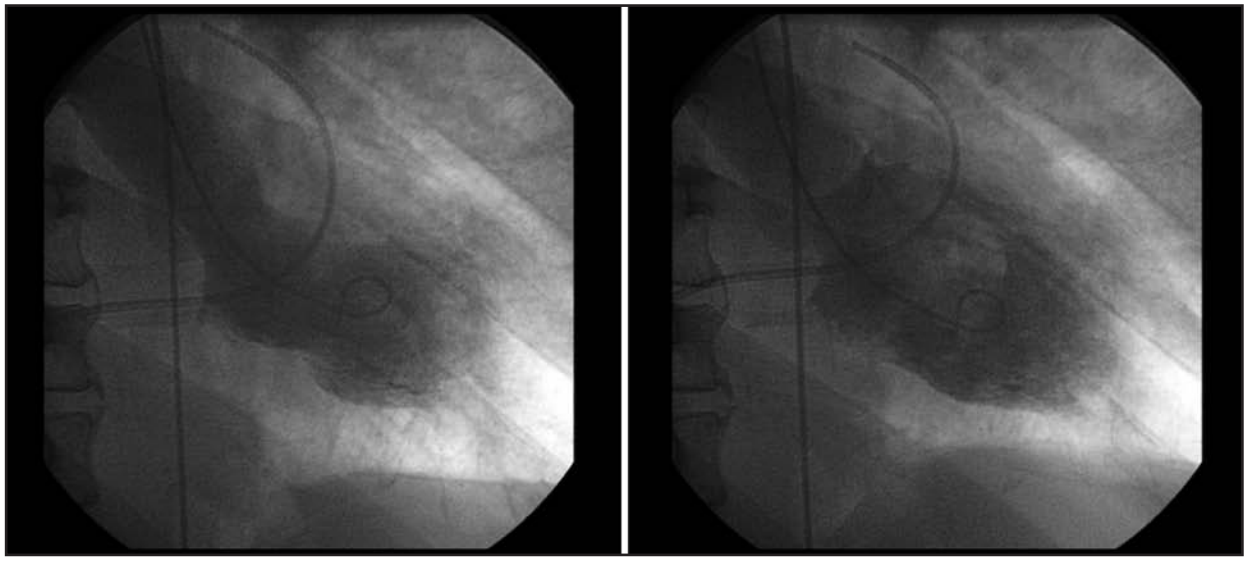
Figure 1. Twelve-lead electrocardiogram demonstrating diffuse deep T-wave inversions in leads I, II, and V2-V6 and marked prolongation of the QT interval, all characteristic of takotsubo cardiomyopathy.

Coronary angiography showed mild luminal irregularities but no significant stenoses. Left ventriculogram (Figure 2) demonstrated an ejection fraction of 30%-35% with extensive anteroapical, lower septal, inferoapical akinesis and relatively intact basal motion. Right heart catheterization revealed elevated filling pressures with a pulmonary capillary wedge pressure of 28 mm Hg and a cardiac index of 1.17 L/min, all consistent with cardiogenic shock. There was no pressure gradient between the left ventricle and aortic outflow tract. Additional history provided by family revealed that the week prior to this event the patient's best friend and golfing partner died unexpectedly of a myocardial infarction and the patient was devastated by this news, becoming increasingly emotionally labile and withdrawn.

The patient was treated with inotropes, pressors, and diuresis, and his condition improved. On the third hospital day he was extubated and in stable condition. He was transferred to a monitored unit and began treatment with aspirin, a statin, an angiotensin-converting enzyme inhibitor, and a β-blocker. Two months later the patient was seen in follow-up and denied any further chest pain or shortness of breath. Repeat echocardiogram at that time demonstrated improvement of left ventricular function, with an ejection fraction of 45%-50% with only mild apical hypokinesis. Given his clinical course, this patient's nonischemic cardiomyopathy was attributed to takotsubo or stress-related cardiomyopathy.

DISCUSSION

Takotsuboor stress-induced cardiomyopathy is an increasingly recognized clinical syndrome often mistaken for myocardial infarction or an acute coronary syndrome. In 1990, Satoh et al were the first to describe this syndrome in Japan, naming for the resemblance of the left ventriculogram to a Japanese pot (takotsubo) used as an octopus trap.[2] Initial reports were predominantly from Japan; however, recent cases have been documented in non-Asian races throughout the world, including the United States.[3] A review of 7 case series demonstrated that takotsubo cardiomyopathy is more common in women, with postmenopausal females accounting for 82% of cases, with a mean age at occurrence of 62-75 years.[1] Although estimation



of disease prevalence is difficult, 1% of admissions for acute myocardial infarction in Japan were later classified as takotsubo cardiomyopathy.[4]

The pathogenesis of takotsubo cardiomyopathy is unknown; however, the inciting event usually involves psychological or physical stress that leads to an overwhelming emotional response, causing myocardial stunning.[2,5] Recognized triggers include domestic abuse, news about a catastrophic medical diagnosis, devastating business or gambling losses, and grief over loss of a loved one.[2] Several mechanisms have been proposed, including catecholamine-induced myocardial stunning and microvascular coronary spasm or dysfunction.[1] Wittstein et al compared plasma catecholamine levels in 13 patients with stress-induced cardiomyopathy to 7 patients with Killip class III myocardial infarctions. Those with takotsubo cardiomyopathy had elevated levels of plasma catecholamines and stress-related neuropeptides, several times greater than those with myocardial infarction.[5] Five patients with stress-induced cardiomyopathy underwent endomyocardial biopsy; 4 had interstitial infiltrates consisting primarily of mononuclear lymphocytes and macrophages with contraction bands without myocyte necrosis. These findings are histologically consistent with clinical syndromes of catecholamine excess such as pheochromocytoma.[5]

Takotsubo cardiomyopathy can create confusion for the clinician, often presenting as an acute myocardial infarction. Chest pain at rest is the most common presenting symptom, affecting 33%-71% of case series patients; dyspnea and syncope are also commonly reported.[1] Pooled case series data indicated that antecedent acute emotional or physiologic stress was noted in up to 77% of patients.[1] The initial electrocardiogram commonly demonstrates ST-segment elevation, with almost all patients developing T-wave inversions in most leads.[1] In addition, the QT interval is often markedly prolonged in the early phase of initial presentation.[6] In an attempt to differentiate takotsubo cardiomyopathy from acute anterior myocardial infarction (AMI), Inoue et al compared 18 patients with takotsubo cardiomyopathy to 85 with acute AMI. The takotsubo cardiomyopathy patients had less reciprocal ST segment depression in the inferior leads than did patients with a coronary lesion proximal to the first septal and diagonal branch of the left anterior descending artery.[6] Laboratory analysis of takotsubo cardiomyopathy patients reveals modest elevation of cardiac markers, including troponin. Given the increasing recognition of this clinical syndrome, the Mayo group has proposed a diagnostic algorithm with 4 criteria, all of which must be met (Table).[1]

Proposed Mayo Criteria for the Clinical Diagnosis of the Transient Left Ventricular Apical Ballooning Syndrome (Takotsubo Cardiomyopathy)*

1.	Transient akinesis or dyskinesis of the left ventricular apical and midventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution.
2.	Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3.	New electrocardiographic abnormalities (either ST segment elevation or T wave inversion).
4.	Absence of: Recent head trauma Intracranial bleeding Pheochromocytoma Obstructive epicardial coronary artery disease Myocarditis Hypertrophic cardiomyopathy

*Adapted from Bybee KA et al.[1]

Given the rarity of takotsubo cardiomyopathy and the absence of definitive pathophysiological features, no general consensus statements are available on the optimal treatment. Most therapy is supportive and includes treatment of hypotension, pulmonary edema, and left ventricular dysfunction. A recognized complication of takotsubo cardiomyopathy is outflow tract obstruction attributable to the hypercontractile bases and systolic anterior motion of the mitral valve.[7] In the presence of obstruction (detected by echocardiography or left ventricular pressure measurement), inotropes will worsen the obstruction and must be avoided. Volume expansion and cautious use of β-blockers to increase diastolic filling time and increase left ventricular end-diastolic volume will help to minimize the degree of obstruction.[8] Strategy for long-term therapy is unclear, but commonly considered options are angiotensin converting enzyme inhibitor therapy and β-blockers similar to those used for other causes of reduced left ventricular function.

The prognosis for patients with takotsubo cardiomyopathy is generally favorable for those who survive the initial episode. The reported in-hospital mortality has ranged from 0% to 8%, with the largest case series from Japan, involving 88 patients, reporting a mortality rate of 1%.[1,4] Complications include cardiogenic shock, outflow tract obstruction, pulmonary edema, and ventricular arrhythmias.[1] Most patients will recover left ventricular function. Wittstein et al demonstrated a median increase of left ventricular ejection fraction 2 to 4 weeks after presentation.[5]

CONCLUSION

We present a case of an elderly man presenting with chest pain at rest and a rapid hemodynamic decline with severe left ventricular dysfunction and no angiographic evidence of coronary obstruction, an event precipitated by severe emotional stress. This case illustrates a rare but increasingly recognized clinical entity in the differential diagnosis for acute myocardial infarction. Although more common in postmenopausal women, takotsubo cardiomyopathy should be considered in any patient presenting with an acute coronary syndrome with evidence of severe left ventricular dysfunction but lacking angiographic evidence of obstructive coronary lesions. This case also demonstrates the importance of a thorough history, because the syndrome is usually triggered by intense emotional or physical stress. Treatment is generally supportive for the acute period, and management of the hypotensive patient often requires knowledge of the presence of possible left ventricular outflow obstruction. Further study is warranted to evaluate the pathogenesis and need for long-term therapy for this condition.

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A 95-year-old Woman with Bruising and Hematoma

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Bleeding disorders due to acquired inhibition to factors within the clotting cascade can be potentially life threatening, especially in elderly patients. In such cases typical treatments such as pressure and prothrombogenic agents are often not effective in controlling bleeding. We present a case of acquired factor VIII inhibitor in an elderly woman with new onset bleeding.

CASE DESCRIPTION

A 95-year-old white woman presented with a chief complaint of an enlarging "purple knot" on her left hand and easy bruising. Her past medical history was significant for hospitalization secondary to pneumonia 3 weeks prior to admission, during which she received intravenous medications and fluids in the affected hand as well as oral amoxicillin. In addition, the live-in caretaker reported that the patient had an enlarging hematoma on her sacrum that began as an area of small ecchymosis 2 weeks earlier. The patient denied any previous episodes of bleeding or easy bruising and had no family history of bleeding diathesis. She reported no recent heparin use.

Physical examination revealed a thin white elderly woman with appropriate mental status. Blood pressure was 130/70 mm Hg, pulse 105, temp 36.1ºC, respiration 24, and oxygen saturation at baseline 98% on 3 L. Skin examination revealed multiple areas of ecchymosis on the arms, legs, and back as well as a 3.5 x 3 cm circumscribed nodule consistent with subcutaneous hematoma on the dorsum of the left hand. The remainder of the exam was unremarkable.

Laboratory results for blood samples were within reference intervals except for a lactase dehydrogenase value of 855 IU/L. Complete blood count results were remarkable for a macrocytic anemia with normal platelets. Peripheral smear demonstrated no schistocytes or spherocytes, and a Coombs test was negative. Coagulation study data are presented in Table 1.

Factor VIII inhibitor was diagnosed based on the laboratory values and the clinical presentation. Differential diagnoses for the etiology of this inhibitor included the patient's recent treatment with a penicillin antibiotic as well as the possibility of myelodysplastic syndrome. Given the patient's continual bleeding and high Bethesda titer of 171.5 Bethesda units (BU)/mL, the patient was treated with factor VIIa at a dosage of 90 µg/kg every 6 hours for 4 doses titrated to the same amount every 12 hours and

Table 1. Case Patient Coagulation Study Data

Study	Value	Reference Interval*
PT/INR, s	14.3/1.2	12.5-15.2/0.9-1.2
aPTT, s	93	23.5-34.8
aPTT mixing study immediate/1 h, s	53/77	27.8/28.6 Control
Factor VIII level, %	11	61-187
Bethesda titer, BU/mL	171.5	

*Reference interval used at the University of Virginia Health Sciences Center.

then every 24 hours after clearance of potential thrombotic contraindications. The patient was also given a 3-week course of prednisone at 1 mg/kg per day divided into 2 doses per day. When the patient did not respond to these therapies, she was given rituximab, 4 doses of 375 mg/m^2.

CASE DISCUSSION

Factor VIII inhibitor, an extremely rare disease, occurs annually in approximately 1.5 people per million in the nonhemophilic population, although the incidence in the general population may be increasing.[1] Most affected patients tend to be older than 50 years, with major identifiable causes listed in Table 2. Classic hemophilia A is caused by a decrease in production of factor VIII secondary to a mutation in the factor VIII gene, whereas acquired factor VIII inhibitor is attributable to an IgG antibody directed against epitopes on the factor VIII molecule.

Patients with factor VIII inhibitor usually present with large hematomas or deep tissue bleeds in the absence of trauma, extensive ecchymoses, severe mucosal bleeding such as epistaxis, gastrointestinal bleeding, hematuria, and delayed extensive postsurgical bleeding that cannot controlled with traditional hemostasis methods.

Table 2. Major Identifiable Causes of Factor VIII Inhibitor*

Cause of Factor VIII Inhibitor	Cases
Autoimmune disease	12%
Malignancy (particularly lymphoproliferative disorders)	15%
Pregnancy/postpartum	10%
Medications	6%
Dermatologic conditions	5%
Unknown etiology	50%

*Constructed from Data and Reports by Bossi et al.

In contrast to classic hemophilia A, factor VIII inhibitor does not commonly include hemathroses in the initial presentation.

LABORATORY STUDIES

Initial laboratory analyses for patients with factor VIII inhibitor reveal an abnormally increased activated partial thromboplastin time (aPTT) with normal prothrombin time. Other differential diagnoses that should be considered with this coagulation pattern include both inherited deficiencies and acquired conditions (Table 3).

To determine inhibitor presence, a mixing test should be performed in which sample plasma from the patient is mixed with normal pooled plasma and the aPTT is measured. Typically, a test is considered positive for inhibitor with no correction of the aPTT either immediately or after 1 to 2 hours incubation. Immediate correction usually suggests a factor deficiency. Factor VIII inhibitor is unique, however, in that there can be an immediate correction of the aPTT but a lack of correction after sample incubation at 37˚C for 1 to 2 hours. Factor VIII levels can be assayed and, if low, confirmatory Bethesda titers can be obtained to help measure the relative activity of

Table 3. Differential Diagnoses Associated with Factor VIII Inhibitor

Inherited	Acquired
Deficiency of factors VIII, IX, XI	Heparin administration
Deficiency of factor XII, prekallikrien, or high molecular weight kininogen (no bleeding diathesis)	Lupus anticoagulant
Von Willebrand disease	Inhibitor of factors VIII, IX, XI, or XII
	Acquired von Willebrand disease

factor VIII in the coagulation cascade. A Bethesda titer assay is performed when serial dilutions are made of patient plasma with saline, then mixed with normal plasma containing close to 100% factor VIII activity and incubated for 1 hour. An aPTT-based factor VIII assay using factor VIII-depleted plasma substrate is then performed on these incubated mixtures. Results are compared to those of incubated normal plasma. One BU is defined as the amount of factor VIII inhibitor that neutralized 0.5 IU of factor VIII in this system. The number of serial dilutions tested is based on the anticipated level of the inhibitor.[2]

Once the diagnosis of factor VIII inhibitor is made, a thorough workup of the underlying cause should be a priority. As with many acquired disease processes secondary to an underlying primary pathology, therapy directed at the underlying process is usually necessary to achieve resolution of the inhibitor.

THERAPY

The immediate focus of treatment should be control of acute bleeding. As previously mentioned, traditional hemostasis methods are often ineffective in controlling acute bleeding in these patients. Because of the propensity for continual bleeding, only an experienced phlebotomist should attempt venipuncture in a patient with factor VIII inhibitor. If central access is required, the potential exists for catastrophic bleeding during catheter placement, and therefore ultrasound or computed tomographic guidance should be used.

Strategies for pharmacologic therapy for acute bleeding are based largely on the Bethesda titer value. Most patients with Bethesda titers <5 BU/mL can be treated with factor VIII concentrates that act to overwhelm the amount of inhibitor present in the plasma. However, patients with high Bethesda titers will likely need an alternative means of therapy such as an activated prothrombin complex or recombinant human factor VIIa as a means of controlling acute bleeding.[3] Factor VIIa directly activates factor X, effectively bypassing the affected intrinsic coagulation pathway and thereby controlling bleeding. If the above measures are not adequate, extracorporeal plasmapharesis may be used as an immediate means of absorbing the autoantibody, but only if access can be obtained in a safe manner.[4]

Long-term therapy should focus on the elimination of the inhibitor itself. Therapeutic efforts should concentrate on reversal of the underlying cause, whether it is an autoimmune phenomenon, malignancy, or other etiology as mentioned in Table 2.

Well-documented strategies for long-term control of factor VIII inhibitor levels are steroid administration (prednisone 1 mg/kg for 3 weeks) and cyclophosphamide therapy. Iintravenous Ig (1g/kg for 2 days or 400 mg/kg for 5 days) can be considered a second-line therapy in these patients according to a recent prospective study that demonstrated response in days to months.[5]

Rituximab, the chemotherapeutic agent used in this case patient, is gaining acceptance for use in long-term therapy of factor VIII inhibitor. Recent review articles by Stachnik and Franchini et al highlight the use of rituximab as an effective option for treatment of acquired factor VIII inhibitor after other modalities of therapy have failed.[6,7]

A recent report by Wiestner et al. described 4 patients with high factor VIII levels who obtained sustained remission of bleeding diathesis with the use of rituximab and high-dose prednisone.[8] In a 2004 study, patients were given weekly intravenous rituximab at a dose of 375 mg/m^2 for 4 consecutive weeks. Chemotherapy response

was assessed based largely on the level of Bethesda titer in individual patients. Eight patients with a titer <100 BU/mL achieved complete remission. Three patients who had remission after the first cycle of rituximab achieved sustained response after undergoing a second cycle at the same dosage. Two patients with inhibitor titers >100 BU/mL showed only partial response of the inhibitor after rituximab dosing but did experience complete remission with rituximab plus IV cyclophosphamide.[9]

Although factor VIII inhibitor is an extremely rare disease, it is associated with a number of disease processes and should always be considered on the differential for an elderly patient who presents with multiple hematomas or ecchymosis in the absence of a prediagnosed bleeding diathesis or trauma. If discovered early with an appropriate history and physical exam and proper laboratory workup, this potentially fatal disease can be successfully treated.

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Relapsing Polychondritis: Case Report and Diagnostic Considerations

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Relapsing polychondritis (RPC) is a rare rheumatologic disorder characterized by inflammation of cartilaginous structures, with the cartilage of the ear, nose, peripheral joints, and tracheobronchial tree most commonly affected.[1] Although the disorder was initially described in 1923[2], the term polychondritis was first used in 1960.[3] Pulmonary involvement in RPC is a major cause of morbidity. Pulmonary complications, which affect 48% to 67% of patients with RPC at some time during the course of the disease, portend a poor prognosis.[1,4] These complications generally manifest as hoarseness, cough, dyspnea, wheezing, and choking.[1,4,5]

We present a case of dynamic tracheal collapse associated with RPC. The case illustrates the signs and symptoms of this ominous event and demonstrates the utility of dynamic expiratory computed tomography (CT) in its diagnosis.

CASE DESCRIPTION

A 44 year-old woman with a 6-month history of progressive dyspnea, cough, and hoarseness was referred to our pulmonary clinic. Her illness had been diagnosed as RPC approximately 5 years earlier, after recurrent episodes of steroid-responsive ear pain and swelling. At that time the evaluation of her symptoms led to a diagnostic auricular cartilage biopsy. Treatment with prednisone and antiinflammatory agents resulted in a generally good response, with reduction of auricular, nasal, and arthritic symptoms.

The patient stated that approximately 6 months prior to her visit to the pulmonary clinic she began experiencing dyspnea on exertion as well as a nonproductive cough that was initially worse in the morning but had become persistent, occurring throughout the day. Her progressive dyspnea now occurred with any activity and was associated with orthopnea and paroxysmal nocturnal dyspnea. The patient also reported persistent heartburn and waterbrash but denied fevers, chills, chest pain, hemoptysis, colored sputum, sinus fullness, postnasal drip, and wheezing. Prior evaluation included a chest x-ray and CT scan of the chest, both of which were unremarkable. The patient showed no improvement with empiric treatment for allergies, asthma, and gastroesophageal reflux disease.

The patient's past medical history was also significant for 2 episodes of community-acquired pneumonia within the previous 2 years; antibiotic treatment was effective in both cases. The patient reported a 45 pack year smoking history but had quit smoking 10 months prior to presentation. Current medications included fluticasone/salmeterol inhaler, albuterol inhaler, montelukast, fexofenadine, cetirizine, prednisone, colchicine, diclofenac, bufexamac, acetaminophen with codeine, metoclopramide, esomeprazole, lansoprazole, pantoprazole, and an estradiol/norethindrone oral contraceptive.

On examination the patient was afebrile with normal vital signs, including an oxygen saturation of 99% on room air. Head examination was notable for early cauliflower ear deformation, slight tenderness to palpation in the cartilaginous areas of both ears, and a marked saddle-nose deformity. There was no evidence of rhinitis or oropharyngeal cobblestoning. Lung exam revealed coarse breath sounds with transmitted upper airway sounds throughout bilateral lung fields and an extremely prolonged

expiratory phase. The onset with vocalization of stridor and mild respiratory distress was apparent. No clubbing of the digits was noted, and the remainder of the exam was unremarkable.

Chest x-ray showed no acute cardiopulmonary process. Pulmonary function tests revealed severe obstruction, airtrapping, and a flow-volume loop (FVL) pattern consistent with variable intrathoracic airway obstruction (Table 1, Figure 1). The patient showed no improvement after bronchodilator administration.

Given the concern for airway obstruction, a high-resolution CT scan of the chest with inspiratory and end-expiratory views was performed and revealed moderate airway obstruction, mainly in the left mainstem bronchus. On further consultation with the radiologists, we sought to detect tracheomalacia by use of repeat imaging with the recently validated dynamic expiratory CT. The resulting images revealed previously unidentified tracheal collapse; the end-inspiratory distal tracheal diameter of 9 mm x 13 mm decreased during active exhalation to 3 mm x 3 mm (Figure 2). These findings indicated tracheomalacia and dynamic airway collapse and were consistent with the intrathoracic location suggested by the FVL.

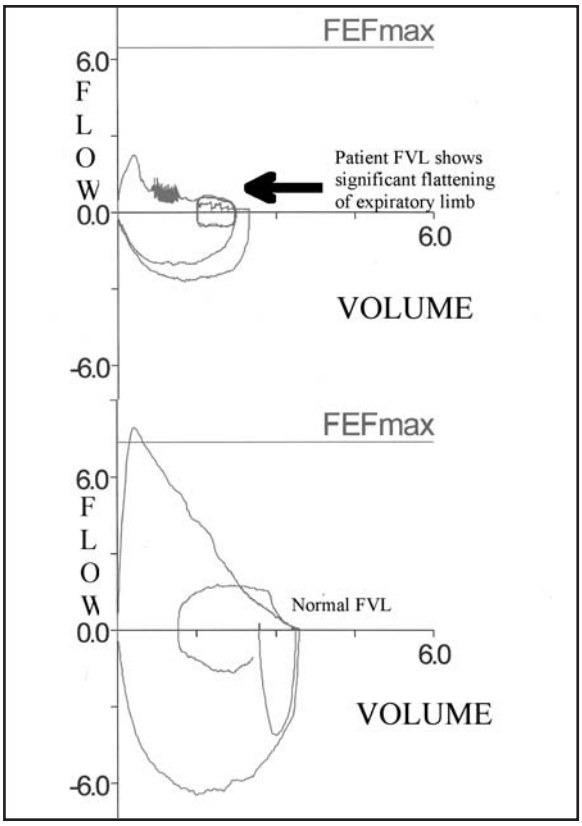

Figure 1. The patient flow-volume loop (FVL) compared with a normal FVL. The patient FVL illustrates characteristic findings during expiration that are consistent with variable intrathoracic airway obstruction. In the patient FVL, the reduction in maximal flow rates on both inspiration and expiration and the shape of the expiratory limb are indicators of intrathoracic pathology. FEF indicates maximum forced expiratory flow rate.

Table 1. Results of Pulmonary Function Tests*

Index	Value	Percentage of Predicted
FEV_1, L	1.06	40
FVC, L	2.49 L	57
FEV_1/FVC	0.45	
Total lung capacity, L	4.55 L	102
Residual volume, L	2.68 L	178
Diffusion capacity, mL/mm Hg/min	21.38	92
Airways resistance, cm water/L/s	10.93†	

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity.
†Normal range, 0.2-2.50 cm water/L/s.

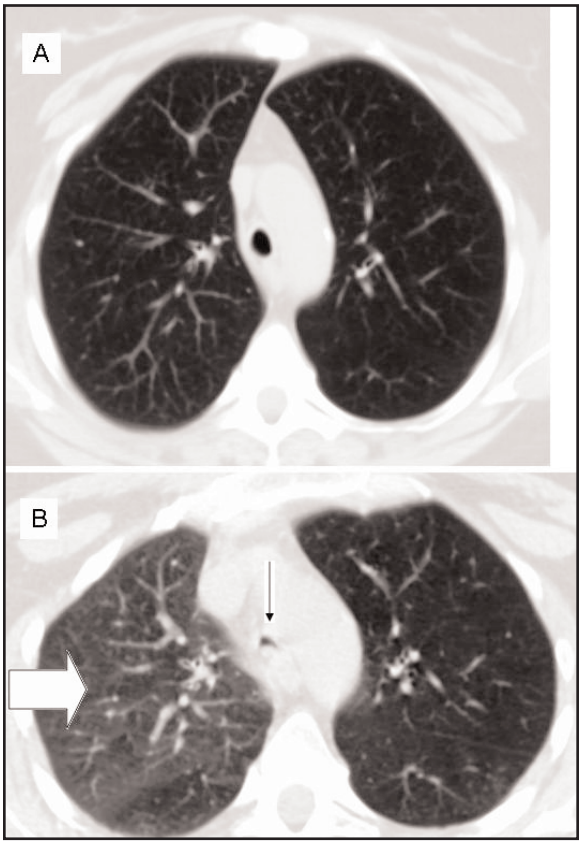

Figure 2. Transverse (A) end-inspiration and (B) dynamic expiratory computed tomographic scans at the level of the distal trachea. The scans reveal both visible airway collapse (thin arrow) and normal expiratory changes in airways (thick white arrow) with increased opacification in the right lung. The darker (unemptied) left lung shows evidence of airtrapping.

On the basis of the findings of tracheal pathology and the patient's progressive respiratory symptoms, her initial medical management consisting of noninvasive ventilation and intensified corticosteroid therapy was abandoned and she underwent successful bronchoscopic placement of a Y-stent that spanned the trachea and right and left mainstem bronchi. This procedure resulted in complete resolution of her presenting symptoms.

DISCUSSION

Relapsing polychondritis is a rare disorder with an estimated incidence of 3.5 per million.[5] Diagnostic criteria (Table 2) were first established by McAdam et al in 1976.[1] In 1979, Damiani and Levine revised these criteria to include histologic findings and response to therapy (Table 2).[6] The histologic findings include loss of basophilic staining of cartilage matrix, pleomorphic white cell infiltration, and loss of cartilaginous integrity, with eventual fibrotic replacement.[1]

Trentham and Le[4] evaluated 3 large case series to better define the epidemiology and natural history of the disease. These series showed a male-to-female ratio ranging from 1:1 to 1:3, with a mean age at diagnosis of 47. The most

Table 2. Diagnostic Criteria for Relapsing Polychondritis

Initial criteria (3 or more of the following):

(1) Bilateral auricular chondritis
(2) Nonerosive seronegative inflammatory polyarthritis
(3) Nasal chondritis
(4) Ocular inflammation
(5) Respiratory tract chondritis
(6) Audiovestibular damage

Revised criteria:

(a) 3 or more initial criteria without histology
(b) 1 or more intial criteria with confirmatory histology
(c) Involvement in 2 or more locations, with response to either corticosteroids or dapsone or both

common symptom at the time of diagnosis was auricular chondritis (43%), with arthritis being present in 32% of patients and nasal chondritis in 21%. Respiratory symptoms were present in 23% at the time of diagnosis, with 55% of patients developing these symptoms at some point during the course of their disease. Women appear to be more prone to respiratory pathology.

Evaluation for respiratory involvement includes pulmonary function tests, which should be done in any patient with RPC and respiratory complaints. Progressive degeneration of cartilaginous structures over time can result in dynamic airway collapse. Dynamic collapse is a result of decreased intraairway pressure in accordance with the Bernoulli principle, and FVLs in this setting can show variable airway obstruction. Alternatively, fixed airway obstruction can occur as a result of fibrosis and contraction as a consequence of recurrent bouts of inflammation. In fixed airway obstruction, airflow limitation evidenced on FVL would occur both on inspiration and expiration.[7]

Radiographic investigation in the setting of respiratory symptoms has generally involved chest CT, although recent data suggest that standard CT may be insufficient to detect dynamic airway obstruction.[8,9] Lee et al[8] reviewed conventional end-inspiratory CT and dynamic expiratory phase CT in 18 patients with RPC referred for airway imaging. Dynamic imaging involved acquisition of images of the central airways in rapid succession during active exhalation. Behar et al[9] found that compared to previously reported findings based on static end-expiratory views, dynamic expiratory imaging revealed a higher incidence of tracheomalacia in RPC patients, with airway narrowing on end-inspiratory CT occurring in 5 of 18 patients (28%) and evidence of tracheomalacia and airway collapse in 13 of 18 patients (73%). These results led Behar et al to recommend that dynamic expiratory CT be performed to diagnose respiratory tract involvement in RPC patients. Congenital defects, end-stage chronic obstructive pulmonary disease, infection, sequelae of intubation, radiation therapy, and extrinsic compression can also be causes of tracheomalacia and should be considered as possible etiologies when airway collapse is seen on dynamic expiratory imaging.

The prognosis of RPC is largely determined by the presence of extra-articular involvement. In one case series, multivariate analysis revealed the 3 variables that predicted mortality were anemia, age at diagnosis, and laryngeotracheal stricture.[10] The overall survival rates in RPC seem to have increased with improved medical management and surgical treatment of complications; 10-year survival in a 1986 case series was 55%[10], whereas a series reported in 1998 showed an 8-year survival of 94%[4].

Respiratory involvement in RPC is especially concerning because it can lead to chronic infections, need for tracheostomy, and sudden death.[11] Respiratory complications are cited as the cause of death in 10% to 59% of patients.[1,10] Treatment is multidisciplinary, with medical management consisting of intensified antiinflammatory and corticosteroid therapy. Evidence exists that indicates early diagnosis and treatment can improve objective measures of airway disease[12], but to our knowledge, no long-term follow-up to evaluate the importance of early diagnosis and treatment has been conducted. Corticosteroids have been shown to decrease frequency and severity of disease flares, but do not slow progression.[1] Antiinflammatory agents are commonly used, and immunomodulators such as methotrexate and cyclosporine have shown efficacy in some series.[1,4] Interventional therapies have included tracheostomy, external airway splinting, and tracheobronchial stenting.[11,13] Data are scant on the efficacy of

these interventions, and further work in stent therapy is ongoing.[13] Continuous positive airway pressure has been used in some cases as a functional airway splinting mechanism to prevent airway collapse.[14]

SUMMARY

RPC is a rare clinical entity that must be considered in patients with complaints of ear pain, nasal deformity, and/or arthralgias. RPC is a rare cause of chronic cough, but cough in the setting of a known diagnosis of RPC or occurring with symptoms suggesting autoimmune disease mandates further evaluation. As our case patient illustrates, dynamic expiratory CT may be a better method for detection of respiratory involvement than conventional CT techniques, including end-expiratory high-resolution views. Therapy in the setting of respiratory involvement generally involves an intensified medical regimen, with interventional therapy a viable option in severe cases.

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Sinuorbital Zygomycosis Complicated by Diabetic Ketoacidosis

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The reported incidence of zygomycosis has increased over the past several decades, owing to an increased prevalence of patients who are immunocompromised from diabetes mellitus, organ transplantion, and treatment with corticosteroids.[1] Periorbital swelling in a patient with diabetes (types 1 and 2), and in particular in patients with diabetic ketoacidosis, should warrant an evaluation for zygomycetes infection. Prompt initiation of antifungal therapy and early surgical evaluation are critical components of therapy and can decrease mortality.

CASE DESCRIPTION

A 20 year old woman presented to her primary care physician complaining of 4 days of right eye pain, right periorbital swelling, and overlying erythema. Her past medical history was notable for poorly controlled type I diabetes mellitus with a hemoglobin A1C of 12.4 and multiple previous admissions to outside facilities for diabetic ketoacidosis (DKA). The patient reported that her blood glucose had been poorly controlled the week prior to admission, with several readings in the 400s.

A presumptive diagnosis of preseptal cellulites was made, and the patient was treated with ceftriaxone with plans for close daily follow-up as an outpatient. Despite 3 days of antibiotic therapy, the patient's eye swelling worsened, and results of a basic metabolic panel suggested DKA. She was therefore admitted to an outside hospital for aggressive management of her diabetes and additional work-up of the periorbital swelling and erythema.

Physical exam on admission was notable for tachypnea with Kussmal respirations and increasing lethargy. Other vital signs were stable, but the patient did have gross right facial swelling, especially of the right periorbital area, decreased sensation along the second division of cranial nerve V, and an asymmetric smile. Given the extensive swelling, it was unclear if the deficits noted on neurological exam were secondary effects of her facial swelling or if they represented cranial nerve deficits. Careful ophthalmologic examination, however, revealed right-sided proptosis and decreased right eye visual acuity. The remainder of the physical exam was unremarkable.

Initial laboratory test results demonstrated a severe metabolic acidosis with a pH of 6.82, pO2 of 121 mm Hg, pCO2 of 9 mm Hg, and serum bicarbonate of 1 mmol/L. Given the pateint's altered mental status and respiratory distress, she was intubated and admitted to the intensive care unit, where she received broad-spectrum antibiotics and aggressive fluid resuscitation and was started on an insulin infusion. During the next 2 days the patient's blood glucose levels were brought under control and her respiratory status improved to the point where she was successfully extubated. She remained intermittently febrile, however, and in addition to persistent right facial swelling, developed a 3-cm black eschar over the medial canthus and inferior eyelid. Given the clinical presentation and antibiotic failure, a computed tomographic scan of the head was ordered. Evidence of right ethmoid sinusitis with lesser involvement of the right frontal and sphenoid sinus and soft tissue swelling at the medial aspect of the right orbit were noted. A biopsy specimen of the eschar was sent to the microbiology laboratory for culture and fungal staining, and the patient was started on amphotericin B deoxycholate (1 mg/kg per day).

Unfortunately the patient developed acute renal failure coincident with the start of amphotericin, and given the probable need for surgical intervention was transferred to the University of Virginia Health Sciences Center. On arrival, she was noted to be stable with adequately treated blood glucose and a normal anion gap. Review of the microbiology and imaging studies from the outside hospital were consistent with invasive mucormycosis. The patient was started on liposomal amphotericin (3 mg/kg per day) and was taken to the operating room to undergo urgent surgical treatment that included debridement of the necrotic tissue and a right ethmoidectomy. Intraoperatively, a significant amount of purulent fluid and necrotic tissue was noted, mandating excision of the medial canthus and the medial portions of the upper and lower eyelids. A photograph of the tissue sample taken at that time is shown in Figure 1. After successful debridement and several days of well-controlled blood glucose, the patient was discharged with plans for prolonged therapy.

Six weeks after discharge the patient continued to do well on combination posaconazole and liposomal amphotericin therapy, with close follow-up in the infectious disease clinic. At the time of this report she had brought her blood glucose levels under control and expressed her awareness of the importance this plays in her prognosis. The planned length of treatment was 3-6 months, with the final duration to be determined by symptomatic improvement and radiographic, laboratory, and clinical confirmation of the absence of ongoing disease.

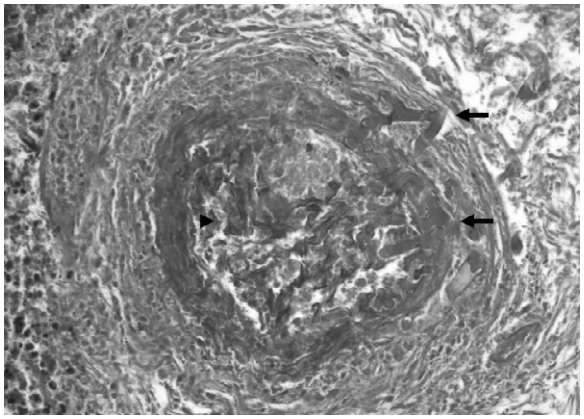

Figure 1. Zygomycosis in biopsy tissue from the case patient. Broad, irregularly branching, virtually aseptate fungal hyphae exhibit striking angiocentricity (arrows). Another characteristic feature, thin hyphal walls, predisposes to the formation of the collapsed, distorted forms seen here intraluminally (arrowhead) (Hematoxylin and eosin, original magnification x 200).

DISCUSSION

Natural History of Zygomycosis

Recognition of zygmomycetous fungal infections has become increasingly important over the past several decades as the population of immunocomprised patients has grown. Zygomycosis (also referred to as mucormycosis) involves infection by one of any of the members of the order Mucorales, including Rhizopus, Absidia, Cunninghamella, Rhizomucor, Mucor, Apophysomyces, Saksenaea, Syncephalastrum, and Cokeromyces.[1] These fungi are ubiquitous in the environment and are naturally found in the soil and on decaying matter.

Infection can involve one or multiple organ systems. Documented cases of infection have involved the sinuses, orbit, lungs, skin, brain, intestine, kidney, and rarely of bone and bladder. During the 1990s the overall mortality for zygomycosis involving any site was 47%, but mortality correlates strongly with the site of infection and the etiology of immunocompromise.[2] According to a literature review zygomycosis diagnosed in 929 from 1940 to 2000, the mortality rate in patients with diabetes was 36% and in patients with underlying malignancy was 66%.[2] Moreover, patients with infections confined to the sinuses had a mortality of 16%, whereas patients with pulmonary, gastrointestinal, and disseminated infections had mortality rates of 76%, 85%, and 96%, respectively.[2] These outcomes have remained

largely unchanged since the introduction of amphotericin B deoxycholate in the 1960s.

Diabetes Mellitus and Zygomycosis

Risk factors for zygomycosis are listed in Table 1.[2,7] In addition to causing severe opportunistic infections in immunodeficient patients, zygomycetes often affect patients with conditions involving less severe immunocompromise, such as diabetes (type 1 or 2), injection drug use, and treatment with desfuroxamine. Diabetes mellitus is the most common predisposing condition, accounting for 36% to 88% of reported zygomycosis cases.[3] Although zygomycosis has been documented in patients with well-controlled diabetes, patients with poorly controlled blood glucose, in particular those with DKA, are at the highest risk.[3] In this patient group, rhinocerebral disease is the most common presentation, followed by pulmonary and sinuorbital disease.[2] Because zygomycetes are ubiquitous in the environment, it is not surprising that the initial seeding is typically from inhalation, with traumatic implantation or ingestion as less frequent causes.[5] Zygomycetes have a preference for vascular structures and quickly spread to nearby locations, spreading infectious hyphae and necrotic tissue (Figure 1).

In rhinocerebral disease, the initial presentation includes typical symptoms of sinusitis including congestion, sinus pain, purulent discharge, and possibly fever. Within a few days the infection can spread to nearby structures, including the brain, orbit, and palate. Although not seen in all patients, a black eschar may form as a result of necrosis secondary to fungal vascular invasion of the nasal mucosa or palate. Periorbital edema, proptosis, and visual defects may indicate involvement of the orbit, and facial numbness suggests infarction of sensory nerves. Finally, cranial nerve palsies and stroke should prompt immediate investigation for cavernous sinus or cerebral involvement.[6]

Table 1. Risk Factors associated with Zygomycosis

Underlying Condition	Treatment/Toxicity
Diabetes mellitus	Immunosuppressive meds •Corticosteroids, Chemotherapy
Hematologic malignancy	Desfuroxamine therapy •Treatment for iron overload
Renal Failure	Aluminum Toxicity
Organ transplant	Penetrating Trauma
HIV Infection	Surgery
Malnutrition	Injection drug use (IDU)
Inherited Immunodeficiency	Burn wounds

The pathophysiology behind the association of DKA with increased risk of zygomycosis is not fully understood, but may be partially due to an increase in free iron, which the fungus can then more easily scavenge from the patient, as well as from phagocytic defects associated with hyperglycemia and acidosis.[4] Effective treatment of the fungal infection requires aggressive management of DKA and well controlled blood glucose throughout the treatment course. Our patient was maintained on an insulin infusion during surgery and the first postoperatve day in an effort to ensure adequate blood glucose control. Careful steps were then taken to make certain that she was discharged on an effective insulin regimen and that she received adequate diabetes education.

MANAGEMENT

Early recognition of disease coupled with prompt initiation of antifungal therapy and timely surgical evaluation are cornerstones of zygomycosis treatment. The introduction of amphotericin b deoxycholate in the 1960s offered a new medical treatment to a historically very morbid disease. Newer liposomal preparations of amphotericin are as effective and offer reduced nephrotoxicity, an important consideration in the management of our patient. Even with appropriate medical therapy, however, multiple studies have shown decreased mortality when patients are treated with a

combined surgical and medical approach.[2,3] The need for early surgical evaluation is a reflection of the aggressive nature of this infection, as clearly illustrated by our patient who, over the course of 2 weeks, progressed from baseline to an invasive, necrotic infection requiring disfiguring surgical debridement. This case underscores the critical importance of early imaging by computed tomography or magnetic resonance imaging to define the extent of fungal invasion and the potential need for surgical intervention. Cultures from superficial swabs or discharge samples are not diagnostically useful because these fungi are ubiquitous in the environment. Colonization of the respiratory and gastrointestinal tracts without the striking morbidity and mortality associated with invasive zygomycosis has been reported in transplantation patients.[8] Ultimately, the diagnosis of zygomycosis must be made by visualization of the broad based ribbon-like fungi with irregular wide-angle branches invading the tissue[3] (see Figure 1, tissue from our patient).

FUTURE CONSIDERATIONS

Zygomycetes are typically resistant to voriconazole, fluconazole, ketoconazole, flucytosine, and the echinocandins.[3] The new azole antifungal, posaconazole, however, offers a novel addition to the medical armamentarium. Initial in vitro data for posaconazole have been promising, and a recent retrospective study supports its use as a salvage therapy for patients who fail to improve on amphotericin. In that study, patients intolerant of or with disease refractory to amphotericin at 12 weeks were switched to posaconazole. Subsequently 60% of patients had a complete or partial response with their new regimen.[9] Posaconazole has not been adequately studied for use as a single-drug first-line regimen, and a recent animal study showed lack of activity of posaconazole in *Rhizopus oryzae* infections, the leading cause of zygomycosis in humans. Amphotericin was an effective treatment in that trial.[10] Posaconazole to date appears to be a relatively safe drug, with nausea and headache as the most common side effects. Also reassuring, animal studies have not shown antagonism between posaconazole and amphotericin in studies of several fungal organisms.[11] Given the marked mortality in zygomycosis even on liposomal amphotericin, we elected to treat our patient with both liposomal amphotericin and posaconazole. Future studies may find an advantage to combination antifungal therapy. To date, effective therapy with posaconazole has been demonstrated in 2 reported cases, but there have been no clinical trials.[12]

Zygomycosis is a rare disease, and data to support a particular length of treatment are scarce. We opted to treat our patient for 3 to 6 months with close monitoring for either progression of disease or adverse drug effects. In the absence of clear therapeutic guidelines patients must be closely followed and their predisposing condition resolved.

CONCLUSIONS

Patients who present with sinuorbital infections and who may be immunocompromised because of an underlying condition such as poorly controlled diabetes should be promptly evaluated for zygomycosis. The importance of early detection cannot be overstated, because swift, aggressive medical and surgical management of this disease clearly decrease mortality. In this case, the patient ultimately had a good outcome, but the use of antifungal treatment and diagnostic imaging earlier in the disease course may have decreased the need for invasive surgery. The key points demonstrated in this case include the need for rapid diagnosis, the fundamental principles of medical and surgical treatment, and the importance of aggressive management of hyperglycemia and DKA to effectively treat the fungal infection.

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Possible Bupropion-Induced Clopidogrel Intolerance

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We present a case of serum sickness-like reaction (SSLR) to clopidogrel, possibly induced by bupropion. Given the incidence of patients who may attempt smoking cessation after a coronary event, the possibility of interaction between bupropion (Zyban) and clopidogrel (Plavix) has significant clinical relevance.

CASE DESCRIPTION

A 38-year-old man presented with acute coronary syndrome, and subsequent cardiac catheterization revealed a single lesion, amenable to angioplasty. After insertion of a paclitaxel-eluting coronary stent, the patient was given a loading dose of 600 mg clopidogrel and started on a regimen of 75 mg daily thereafter. His medications at the time of discharge were lisinopril 10 mg daily, clopidogrel 75 mg daily, aspirin 325 mg daily, niacin 500 mg nightly, and simvastatin/ezetimibe 40/10 mg nightly.

Three weeks after discharge the patient was seen in follow-up at an outpatient clinic, where he was started on bupropion 150 mg twice daily for smoking cessation. Three days after starting bupropion, the patient complained of itching, rash, fever, and joint pain. Despite progressive development of urticaria, he had no respiratory symptoms and no oropharyngeal, epiglottic, or facial edema. The appearance of urticaria was preceded by intense pruritus, although itching did not bring on urticaria. Individual hives were apparent for 15-30 minutes before resolving. Each flare of urticaria was followed by intense joint pains occurring primarily in his hands, shoulders, knees, and hips. The arthralgias were asymmetric, not associated with myalgias, and lasted 1-2 hours per episode. Although each affected joint was rendered relatively immobile during an episode, full range of motion returned in each instance. The patient could identify no clear precipitant except to note that the symptoms occurred more frequently in the morning. He did, however, have episodes throughout the day and night, averaging 6 episodes/24 hours. Ultimately, both the arthralgias and urticaria were self-limited.

Given the concern regarding a possible medication reaction, bupropion and lisinopril were discontinued, and the patient was given 20 mg of prednisone twice daily for 1 day, started on cetirizine 10 mg daily, diphenhydramine 25 mg 4 times daily, and famotidine 20 mg twice daily. Despite these adjustments, the patient continued to have episodes of arthralgia preceded by urticaria multiple times daily. The patient was subsequently admitted for the symptoms and underwent a laboratory work-up, the results of which were unrevealing and included normal or negative rheumatoid factor, antinuclear antibody test, sedimentation rate, and creatine kinase and complement levels. A Lyme titer was negative, and urinalysis showed no blood or protein. The patient's symptoms were found to worsen after the morning dose of clopidogrel, and finally resolved when clopidogrel was discontinued. The patient was discharged on a combination of aspirin 325 mg daily, cilostazol 100 mg twice daily, and warfarin (goal INR 2-3) to decrease the risk of in-stent thrombosis, a regimen based on that reported by Garg et al.[1] Additionally, the patient was prescribed 60 mg daily of prednisone with the dosage tapering over 14 days. He had a mild recurrence of his symptoms while undergoing corticosteroid treatment; however, these symptoms fully resolved after an additional week of treatment.

DISCUSSION

Serum sickness and SSLR are characterized by the occurrence of fever, urticaria, polyarthralgias, and lymphadenopathy 7-10 days after primary exposure to a heterologous protein (classic serum sickness) or a nonprotein drug such as penicillin or sulfa (SSLR).[2] Both conditions are immune complex-induced hypersensitivity reactions (type III hypersensitivity reaction). Type III reactions are characterized by the massive formation of circulating immune complexes, which exceed the clearance capacity of the phagocytic system and lead to deposition of those complexes in tissues, thereby triggering inflammatory reactions. Type III hypersensitivity reactions are most frequently seen as a complication of passive immunotherapy with heterologous antisera (eg snake venom antisera or mouse monoclonal antibodies used in cancer immunotherapy).[3] The initial event is a humoral immune response, accounting for the lag period of 7-10 days between administration of protein (or drug) and the beginning of clinical symptoms. Mechanistically, this scenario also explains why the lag period is shorter and the reaction more severe if the humoral response has been presensitized to the antigen in question.

Our case patient suffered an acute SSLR to clopidogrel that appeared to be primed by bupropion. Because we did not rechallenge the patient with either medication we did not prove causation, ,but the constellation of fever, arthritis, and rash in temporal sequence and the clinical outcome support the relationship. Specifically, the patient had completed 3 weeks of clopidogrel therapy without adverse events until the addition of bupropion. He had no prior exposure to bupropion and took this medication for only 3 days, a much shorter period than the 7-10 days required for a humoral response to bupropion alone. Given the shared structural features of bupropion and clopidogrel, we believe that bupropion primed the immune response to clopidogrel, causing a hypersensitivity reaction to the putative reactive metabolite of clopidogrel.[1,4,6] Interestingly, an interaction between clopidogrel and bupropion has been postulated but to our knowledge never reported.[4] Clopidogrel shares structural homology with another thienopyridine, ticlopidine (Ticlid), and there are reports of arthritis, rash, and/or pruritus associated with both medications.[1,4,5] The case reported by Phillips et al describes a 51-year-old man who developed fever, arthralgias, and rash 10 days after starting on clopidogrel.[4] Similarly, the description from Garg et al details a patient who developed severe, acute polyarticular joint pain after beginning clopidogrel.[1] In each report, the symptoms were self limited, responded to corticosteroids, and did not recur once the clopidogrel or ticlopidine was discontinued.[1,4,5] For these reasons, we label this case as SSLR and make the argument that earlier reports of cases labeled as hypersensitivity vasculitis[5] and arthritis[1] are actually more consistent with SSLR.

CONCLUSION

Although bupropion and clopidogrel have SSLR reported and share structural features, the causative metabolite is unknown.[6,7] In addition to the immunological characteristics of the patient, these metabolites are postulated to be critical for the development of SSLR.[6] The current patient case report is an example of a type III hypersensitivity reaction to clopidogrel, an uncommon and potentially underreported adverse event. Patients such as our case patient, who take bupropion in an attempt to quit smoking after a recent myocardial infarction, are frequently treated with clopidogrel to decrease in-stent thrombosis. Clinicians should therefore be aware of the risk for SSLR in response to bupropion and clopidogrel, alone and in combination.

Teaching Points

- Humoral immunity is the mechanism that leads to type III hypersensitivity reactions.
- Clopidogrel is associated with an uncommon but important SSLR, a form of type III hypersensitivity.
- Clinicians should be aware of the potential for a significant reaction between clopidogrel and bupropion and may elect to use an alternate medication for smoking cessation in patients taking clopidogrel.

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Dyspnea in an Elderly Woman with a Clotting Disorder

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Vena caval filters are devices used to prevent pulmonary embolic complications of deep venous thrombosis. Although fatal complications of permanent vena cava filters are rare (0.16%),[1] it is estimated that approximately one third (29%) of patients with vena cava filters experience some complication. These include venous stasis changes (27%), lower extremity edema (25%-43%), improper placement (7%), migration (2%-3%), vessel stenosis (2%-3%) or occlusion (2%), vessel rupture (1%), and air embolus (1%).[2-4] Ensnarement of guidewires during placement of central venous catheters has been reported. Migration of vena cava filters into the heart has been described before for both permanent and retrievable vena cava filters.[5,6] We report a case of a patient who suffered filter migration from the inferior vena cava to the right ventricle.

CASE DESCRIPTION

This 77-year-old woman presented to a community hospital with shortness of breath of 24 to 48 hours duration. Her medical history was significant for obesity-hypoventilation syndrome requiring tracheostomy, pulmonary and systemic hypertension, tachycardia-bradycardia syndrome, status-post dual-chamber pacemaker placement, and pulmonary emboli (PE) being treated with oral anticoagulation therapy. Two weeks prior to the onset of symptoms, the patient had developed a serious rectus sheath hemorrhage. At that time, oral anticoagulation therapy was discontinued and a retrievable inferior vena cava filter was placed (OptEase, Cordis).

A chest radiograph (Figure 1) and computed tomographic pulmonary angiogram (not shown) performed at the outside facility showed the presence of the vena cava filter in the apex of the right ventricle just below the pacemaker lead and additional pulmonary emboli (PE). After an unsuccessful attempt by interventional radiologists at the outside institution to retrieve the filter, the patient was promptly transferred to the University of Virginia Health System for further therapy and management.

DIAGNOSIS

Chest radiograph from the transferring hospital showed the presence of the vena cava filter in the apex of the right ventricle just below the pacemaker lead, confirming filter migration from the inferior vena cava to the right ventricle (Figure 1). The combination of the vena cava filter in the patient's heart and new PE was the cause of the patient's dyspnea.

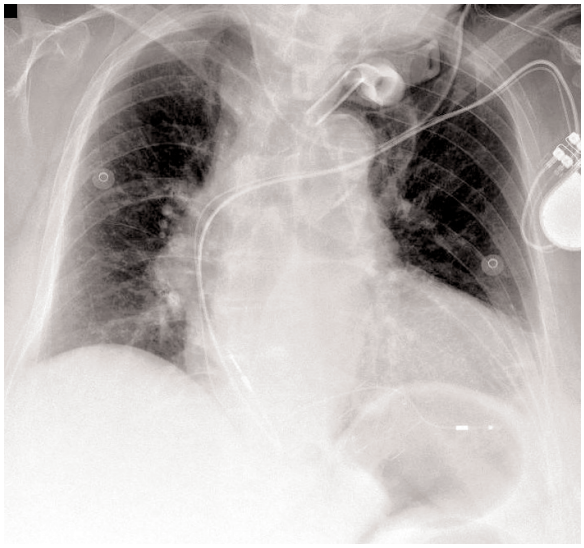

Figure 1. Radiographic image showing filter migration from the inferior vena cava to the right ventricle.

MANAGEMENT

Interventional radiologists at the University of Virginia made another attempt to retrieve the filter, which was also unsuccessful because the device was entangled in the chordae tendinae of the tricuspid valve (Figure 2). Although the device was captured at 2 sites, it was not possible to remove the filter from the tricuspid valve.

Cardiothoracic surgeons were consulted and open-heart surgery was offered to the patient and her family for retrieval of the device. The patient's family declined and instituted a "Do Not Resuscitate" order. The patient died later that day from dysrhythmia-induced cardiac arrest.

DISCUSSION

We could not locate any prior reports in the medical literature of migration of an OptEase filter such as occurred in this case. The federal government

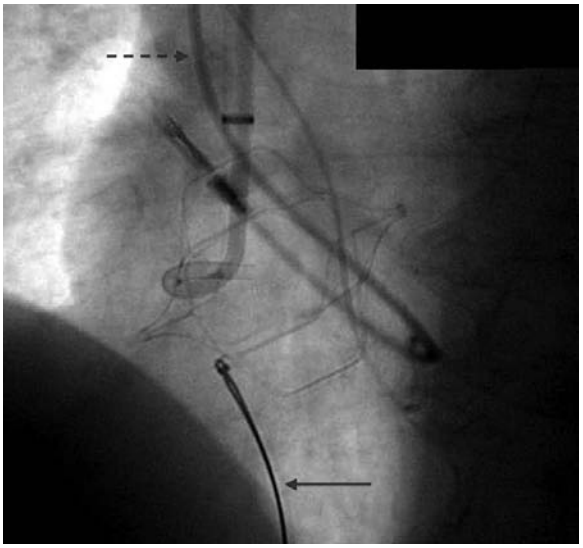

Figure 2. Oblique fluoroscopic view of the heart. The right heart border and right hemidiaphragm are readily identifiable. The filter can be clearly seen and the superior portion of the filter is captured with a tip-deflecting sheath introduced from a right jugular venous access point (dashed arrow). Also visible is a loop-snare device that was introduced through the femoral vein and captured the filter device through the filter struts (solid arrow).

maintains a database of voluntarily reported adverse events involving medical devices (Manufacturer and User Facility Device Experience Database, MAUDE). This database is not intended for evaluation of rates of adverse events; however, a search of reports filed from 2004-2006 yielded 37 reports of events leading to OptEase filter failure (such as fracture, failure to remove, and migration), 4 of which described migration of the device into the heart.[7] Both surgical and percutaneous transvenous removal of vena cava filters from the right side of the heart have been documented.[8] Migration may also occur during removal.

The maximal safe implantation time of vena cava filters is not clear. Small studies have shown successful retrieval rates of 78% to 100%.[9-11] Duration of implantation in these studies ranged from 9 to 150 days. In one series of 40 patients who underwent placement and transvenous retrieval of an OptEase filter, neither migration nor significant bleeding was noted at the time of removal. Duration of filter retention ranged from 3 to 48 days.[11]

The use of vena cava filters is becoming more commonplace, a situation attributable in part to the advent of retrievable filters. In 1979, 2000 of these devices were inserted. By 1999, that number had grown to 49,000.[4] The American College of Chest Physicians (ACCP) has developed guidelines for the use of vena cava filters. Clinicians considering using these devices in managing their patients should be aware of the appropriate indications and contraindications. For initial treatment of deep vein thromboses, the ACCP recommends against routine use of vena caval filters, except in patients with contraindication for or complication of anticoagulation therapy.[12] Most of the recommendations in these guidelines are based on observational studies. Several prophylactic roles for vena cava filters have been proposed, including prevention of PE in high-risk trauma and orthopaedic patients, during

thrombolytic therapy, and in patients with minimal pulmonary reserve at risk for PE.[1,10] Further study of potential indications is needed.

CONCLUSIONS

We present a report of a rare but catastrophic complication of vena cava filter therapy. To our knowledge, this is the first published report associated with the OptEase filter. When choosing to insert a vena caval filter (permanent or retrievable), clinicians must balance the ratio of benefit to risk and include the risk of filter migration in this equation.

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Hospitalists as Teachers: It's About Time

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The hospitalist movement is now officially 10 years old, the term having been coined in 1996 by Wachter and Goldman at the University of California, San Francisco (UCSF).[1] Although this movement was named by academicians, much of the early growth of hospitalist programs occurred in community hospitals. According to the Society of Hospital Medicine (SHM), approximately 800 physicians identified themselves as hospitalists in 1996. By 2005, this number had swelled to 15,000, and SHM projects that the movement will be 30,000 physicians strong by 2010. This explosive growth has largely been fueled by the ability of hospitalists to shorten lengths of stay, decrease costs, and provide quality care to the growing number of "unassigned patients."

More recently, academic medical centers have also embraced the hospitalist concept. Currently, hospital medicine programs exist in at least 55 university-affiliated medical centers and more than 250 teaching hospitals nationwide (SHM, unpublished data). The University of Virginia became one of the newest members of this group in July 2006, when the 5-physician Section of Hospital Medicine was formed within the Division of General Internal Medicine, Geriatrics and Palliative Care. The forces behind the development of hospitalist programs at academic medical centers are varied. Certainly university hospitals cannot escape the financial pressures of managed care, declining reimbursement from Medicare/Medicaid, and the burgeoning problem of uninsured patients, so they too are interested in reducing costs. In addition, the duty hour regulations set forth by the Accreditation Council for Graduate Medical Education in 2003 decreased the number of patients trainees can manage. In some academic institutions this reduced capacity resulted in the need for some patients to go "uncovered" by housestaff. Such patients are usually cared for by hospitalists. Lastly, many academic centers, including the University of Virginia, have recognized the potential educational benefits a hospitalist program can bring to their Internal Medicine Residency Program and have thus used hospitalists as medical educators.

The use of hospitalists as teachers initially met with significant skepticism, particularly in major academic centers. To this point, hospitalists have typically been younger physicians with less postgraduate experience than traditional ward attending physicians, and they may not have the academic credentials of their subspecialty counterparts.[2,3] In 1999, Goldman suggested that hospitalists may be less likely to request consultations from subspecialists and thus negatively affect their clinical revenue.[4] He also suggested that the increased physical presence of an attending on the wards might threaten resident autonomy. Although these concerns merit consideration, hospital medicine programs continue to grow and play an increasing role in training the internists of the future.

REVIEW OF PUBLISHED STUDIES

What evidence do we have that hospitalists are effective teachers? Data are limited, but 4 published studies address this issue specifically as it applies to internal medicine training.[2,3,5,6] All are retrospective, and 3 of the 4 are limited to a single institution. In the first study, Chung et al surveyed internal medicine residents at the University of Chicago Pritzer School of Medicine

during the 1997-2000 academic years.[5] The General Internal Medicine section began using hospitalists as attending physicians on 1 of 4 inpatient teams in 1997. At the end of each month and the end of the year, trainees completed a questionnaire on attending physician performance. The overall response rate was 75%, with 86 residents participating. In the year-end survey; 76% of hospitalist service residents were very satisfied with the overall inpatient rotation compared to 48% of traditional service residents ($P = .05$). Trainees on the hospitalist service were more likely to be very satisfied with the emphasis placed on learning by the attending (80% vs 44%, $P < .01$) and the quality of attending rounds (72% vs. 44%, $P = .02$). When asked which service they would chose given the opportunity, 72% selected the hospitalist service. Written comments from the residents cited the hospitalists' lack of other clinical or administrative duties as a reason for the superior performance. The survey also addressed resident attitudes about loss of autonomy due to the presence of a hospitalist service. Whereas 28% of those who had never worked with the hospitalists expressed such concerns, only 8% of those who had ever rotated on the hospitalist service agreed that this was an issue. Additionally, housestaff noted no difference between the 2 groups in the propensity to obtain appropriate consultations.

In a much larger study from the Emory University School of Medicine, Kripalani et al used a previously validated survey tool, the McGill Clinical Tutor Evaluation, to document the perceptions of 423 residents and medical students regarding 63 faculty members.[2] Hospitalists were compared to general medicine and subspecialty attending physicians covering the teaching services at Grady Memorial Hospital during the 1998-1999 academic year. Emory instituted an Academic Hospitalist Program in July 1998, which provided teaching on 6 of the 12 ward teams. Overall, hospitalists and general medicine attendings were rated significantly higher than subspecialists, with composite scores of 134.5, 135.0, and 126.3, respectively, on a 150-point scale. Specific cited attributes that accounted for the higher ratings of these groups included being readily available, providing the opportunity for discussion, and providing feedback and direction. Written comments from trainees described the hospitalists as enthusiastic teachers who respected team members' time and other obligations. Residents also appreciated the greater presence of hospitalists on the wards and their increased involvement in patient care.

Hauer et al, from the UCSF hospital medicine program headed by Wachter, analyzed end-of-rotation evaluations from trainees at 2 hospitals within the UCSF system during the 1999-2001 academic years.[3] Overall, 1587 resident and student evaluations of 69 faculty members were reviewed. The survey completion rate was 91%. The UCSF hospitalist program was created 4 years prior to the study period and had grown to cover 55% of all inpatient ward months by the start of the study period. Trainees reported significantly higher overall satisfaction with hospitalists compared to traditional attending physicians (8.3 vs 8.0 of 9, $P < .001$), and rated the overall teaching effectiveness of hospitalists as superior (4.8 vs 4.5 of 5, $P < .001$). Hospitalists received statistically higher ratings than their traditional colleagues in knowledge of the subject matter (8.4 vs 7.9), provision of feedback (7.9 vs 7.1), and serving as role models (8.4 vs 8.0). The authors suggest that the advantages in teaching effectiveness demonstrated by hospitalists were attributable to the increased time they spent on the inpatient wards and the specific skill set they acquired as a result of this experience, rather than a greater commitment toward or enjoyment of teaching. This theory is based partially on the fact that as the hospitalist group assumed a larger teaching

presence the comparison group of traditional attending physicians was reduced substantially, and those who continued to teach did so because of their own interest and previously demonstrated skill in teaching.

The final study considered in this review, by Hunter et al at the Oregon Health and Science University School of Medicine (OHSU), is a retrospective look at end-of-rotation evaluations from the 1998-2000 academic years.[6] This small study was limited to medical students and included only 99 total evaluations, with a survey response rate of 72%. During the study period, hospitalists covered about 75% of all ward services. The authors note the reason OHSU created a hospitalist program:

> *In 1995, our Department of Medicine and residency program recognized a progressive decline in medical student and housestaff satisfaction with the educational experiences on the university hospital inpatient rotation. To a large extent, this was attributed to reductions in faculty availability due to increasing clinical and research demands. In response, the Department of Medicine established a hospitalist program.*[6]

In addition, the traditional attending physician roster was trimmed from 51 to 22 based on resident evaluations. Despite this preselected comparison group, the hospitalists received a higher overall rating for teaching (8.56 vs 8.22 of 9, $P < .001$). The hospitalists received higher numerical scores for all attending physician characteristics, although the results were statistically significant only for communication of goals (8.52 vs 8.02) and effectiveness as a clinical teacher (8.66 vs 8.32). The authors speculate that a key reason for the increased student satisfaction was enhanced availability of attending physicians, particularly in the afternoon.

AT HOME ON THE WARDS

Taken together these 4 studies paint a very favorable picture of hospitalists as medical educators. It must be noted, however, that all 4 studies were performed by members of the hospitalist group at the study institutions, raising the possibility of bias in data interpretation. Furthermore, particularly in the UCSF and OHSU surveys, both hospitalist and nonhospitalist attendings received high ratings on all survey questions and the differences between groups, even when statistically significant, were small. Despite these criticisms, I believe the data presented demonstrate that hospitalists can be at least as effective on inpatient ward rotations as traditional attendings and perhaps can provide an even more satisfying educational environment for both residents and medical students.

How do hospitalists create such an effective environment for education? The answer is simple: time and expertise. Hospitalists have time to teach on the inpatient wards because that is where they work. In successful academic hospitalist programs, a hospitalist serving as a ward attending has few, if any, conflicting responsibilities and thus can dedicate his or her full energy to supporting and teaching the resident team. Physicians in this position can stimulate discussion and learning during attending rounds because they are not rushing simply to "get all the patients seen". Patients not discussed during morning rounds can be evaluated in the afternoon as a team or by the hospitalist alone, if necessary. Changes in patient status can be discussed in real time. Radiology and laboratory studies can be reviewed and interpreted together. And for trainee performance evaluations, providing meaningful feedback is much easier for teachers who have actually have time to observe residents and students completing a history and physical,

inserting a central venous catheter, running a code, or discussing end-of-life issues with a patient and family.

Hospitalists also bring expertise to the management of medically complex inpatients. This is what we do! We are not organ system-based experts like cardiologists or nephrologists but rather site-of-care-based experts like emergency medicine physicians and intensivists. We dedicate our professional lives to understanding our hospital and local medical system and helping patients safely navigate what can be a dangerous and frightening place. By concentrating on inpatients, we become adept at diagnosing and managing complex conditions such as pneumonia, exacerbations of chronic obstructive pulmonary disease, venous thromboembolism, congestive heart failure, and diabetic ketoacidosis. Hospitalists often serve as consultants in perioperative medicine, champions of quality improvement initiatives, and liaisons to hospital administrators. These skills are crucial to the practice of internal medicine and exactly what residents want to learn on inpatient ward rotations. Hospitalists should play a prominent role in teaching these competencies just as outpatient internists should provide training in their specialties, such as preventative healthcare and chronic disease management.

The hospitalist model is now firmly entrenched and will be a key component of the healthcare delivery system of the future. Demand for hospitalists is growing rapidly and trainees are taking note. Data on career plans collected during the Internal Medicine In-Training Examination in 2005 showed that 6.5% of residents planned on working as hospitalists, and the numbers are steadily rising (Academic Alliance for Internal Medicine). In comparison, 15.8% anticipated a career in general internal medicine, a number that continues to decline. If hospital medicine was a recognized subspecialty it would be the fourth most common choice of trainees, trailing only cardiology (12.9%), gastroenterology (8.5%), and hematology/oncology (7.5%). Given the increasing interest among housestaff and the growing demand from the healthcare system, training in the skills necessary to become a competent hospitalist should be offered by internal medicine residency programs. Furthermore, hospital medicine faculty and residency program directors at academic medical centers should take the lead in defining the role of hospitalists in medical education.

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Cardiovascular MR and CT: The Future is Now

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Recent advances in cardiovascular imaging have had a major impact on the care and evaluation of cardiac patients. The most dramatic technologic improvements have occurred with cardiac magnetic resonance (CMR) and cardiac computed tomography (CCT). CMR has developed into a highly versatile tool that enables comprehensive cardiac examination. Its excellent tissue and temporal resolution make it a powerful tool for evaluation of cardiac structure and function, determination of myocardial perfusion and viability, and differentiation of various cardiomyopathies. For CCT, the combination of increased gantry rotation speed and the addition of more rows of detectors have resulted in the temporal, spatial, and contrast resolution needed for accurate and noninvasive evaluation of coronary artery disease (CAD). Furthermore, both CMR and CCT have a large field of view, which allows for a more confident evaluation of complex congenital heart disease, cardiac masses, and the right ventricle.

LEFT VENTRICULAR STRUCTURE AND FUNCTION

The majority of cardiovascular disorders result in distortion of the left ventricular (LV) structure and function. Prognosis is related to the extent of pathological impact on LV mass, end-diastolic volume, end-systolic volume, and ejection fraction. The accurate measurement of these parameters requires a 3-dimensional volumetric data set to minimize any geometric assumptions, excellent endocardial definition to clearly differentiate the myocardium from the blood pool, and high temporal resolution to ensure that the true end-diastolic and end-systolic frames are captured. Both CMR and CCT are well adapted to acquire a volumetric data set that minimizes geometric assumptions. The long axis of the LV is used to create a series of sequential short-axis slices from the base to the apex. The volume of the LV cavity and the mass of the myocardium within each slice can be readily measured by drawing a region of interest around the epicardium and the endocardium and then summing the volume measurements of each slice. The use of steady-state free precession enables easy differentiation of the myocardium and blood pool; the myocardium appears dark and the blood pool appears white.[1] CMR has become the gold standard for measuring LV mass[2-4], volume, and ejection fraction.[5-7] Although CCT measurements of LV volumes and ejection fraction correlate well with CMR, the lower temporal resolution of CT leads to systematic overestimation of these values[8], although improvements in temporal resolution are on the horizon. One limitation of both CMR and CCT for the assessment of ventricular volumes is that electrocardiographic gating is required to synthesize a single image from data acquired during multiple cardiac cycles. This form of image acquisition is particularly problematic in patients with significant arrhythmias or an inability to hold their breath for an adequate period of time. Recent advances in real-time imaging with CMR have begun to address this problem but at the expense of spatial and temporal resolution.[9-12] In addition, new CMR techniques such as parallel imaging have significantly shortened the required breath-hold time without sacrificing spatial or temporal resolution.[13]

The assessment of the LV always includes evaluation of regional wall motion. Although some reports[14,15] suggest that CCT may be used for this purpose, its role has not been fully evaluated. CMR, on the other hand, is an excellent tool for the

evaluation of wall motion abnormalities. Holman et al demonstrated that wall motion abnormalities as evidenced by cine MR imaging (MRI) correlate well with infarct size.[16] MRI tagging is a technique for measurement of deformation within the myocardium that improves detection of wall motion abnormalities.[17-19] Further improvements in spatial resolution and ease of analysis are forthcoming with the development of 3-dimensional cine displacement encoding with stimulated echoes (DENSE).[20] The ability to accurately assess intramyocardial function has led to improved understanding of the effects of myocardial infarction on the LV. Additionally, the presence of regional wall motion abnormalities suggests the presence of significant CAD.[21]

CORONARY ARTERY DISEASE

CAD is the leading cause of morbidity and mortality in the industrialized world, making noninvasive evaluation of CAD an important goal. CAD symptoms typically occur only when there is significant limitation of coronary blood flow, so the disease usually is fairly advanced by the time of clinical manifestation. Furthermore, the Glagov hypothesis suggests that most atherosclerotic growth occurs through extraluminal or outward expansion. Calcium is particularly easy to detect with CT (Figure 1) and is strongly correlated with atherosclerotic burden.[23,24] Detection of presence of calcium and its location does not, however, enable identification of specific flow-limiting stenoses.[23] Nevertheless, the likelihood of an adverse cardiovascular event is directly related to the coronary artery calcium score[25-27], although the absolute event rate remains low.

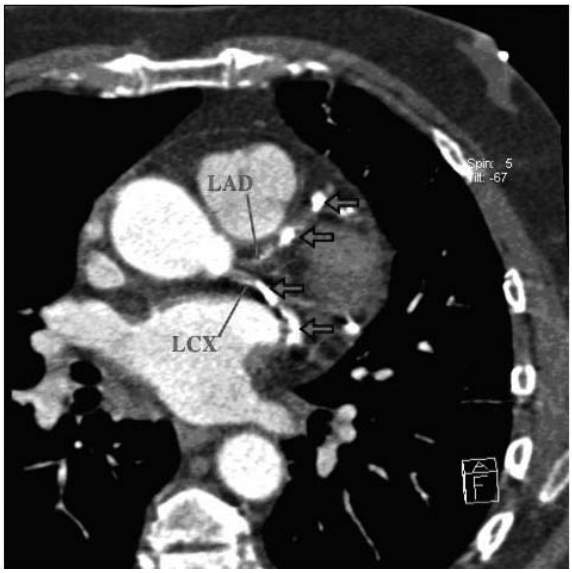

Figure 1. A computed tomographic image at the level of the base of the heart. Coronary calcium (arrows) is present on both the left anterior descending artery (LAD) and the left cirumflex artery (LCX).

Improved multidetector CT (MDCT) technologies, such as CMR and CCT, have made noninvasive coronary angiography feasible. Both 16- and 64-slice MDCT can be used for the evaluation of CAD. The major benefit of 64-slice MDCT is a shorter scan time; a complete coronary angiogram can be completed in less than 10 seconds. The primary strength of CCT is that it enables physicians to rule out CAD. Most studies evaluating the ability of CCT to detect significant CAD have shown that the negative predictive value is approximately 95% to 100%.[28-32] Although CCT has an excellent negative predictive value, its positive predictive value is limited by the presence of artifacts resulting from calcium and cardiac motion.[33,34] The use of (-blockers for strict heart rate control (<60 to 70 beats per minute) and careful patient selection can decrease the influence of calcium and motion artifacts. The image in Figure 2, obtained in a patient in whom the extent of the left main lesion was unclear on cardiac catheterization, reveals a significant lesion in the left main coronary artery. CCT may be particularly valuable for the evaluation of CAD in certain patients such as those in need of a preoperative evaluation for CAD prior to undergoing valvular surgery.[35,36] Other cases in which CCT may be useful include left bundle branch block[37], cardiac transplantation[38], and coronary artery bypass graft.[39] CCT is a reference standard technique for the evaluation of anomalous coronary arteries.[40,41] Figure 3 clearly demonstrates a right

coronary artery originating from the left coronary sinus and traveling directly between the aorta and pulmonary artery.

Although CMR has also been used for the anatomical evaluation of native coronary arteries, coronary artery bypass grafts, and anomalous coronary arteries, its more limited and anisotropic spatial resolution currently make it inferior to CCT. Recent advances such as whole heart coronary imaging and spiral coronary imaging are potential steps forward, but further improvements are still needed.[42,43]

In contrast, CMR has significant advantages over CCT for the physiologic evaluation of ischemia and viability. The ischemic burden of CAD is an important determinant of future cardiovascular events.[44,45] CMR enables evaluation of this parameter by use of either vasodilator perfusion stress testing with adenosine or inotropic functional stress testing with dobutamine. With vasodilator stress testing, first-pass myocardial perfusion with gadolinium is evaluated both with adenosine and at rest. Regions of myocardium that are supplied by a coronary artery that is significantly stenosed will have visibly reduced perfusion seen as hypoenhancement in the subendocardium. A large perfusion defect that is present in the stress images but absent in the rest images is shown in Figure 4. When coronary angiography was used as the gold standard, vasodilator CMR was shown to have sensitivity and specificity similar to those of nuclear stress testing.[46-50] Furthermore, a negative vasodilator CMR stress test can identify patients who have a low likelihood of future cardiovascular events.[51]

Alternatively, stress testing with CMR can be performed with dobutamine. At higher doses of dobutamine, regions of myocardium supplied by a significantly stenosed coronary artery develop a wall motion abnormality indicative of ischemia. In clinical trials, dobutamine CMR has been

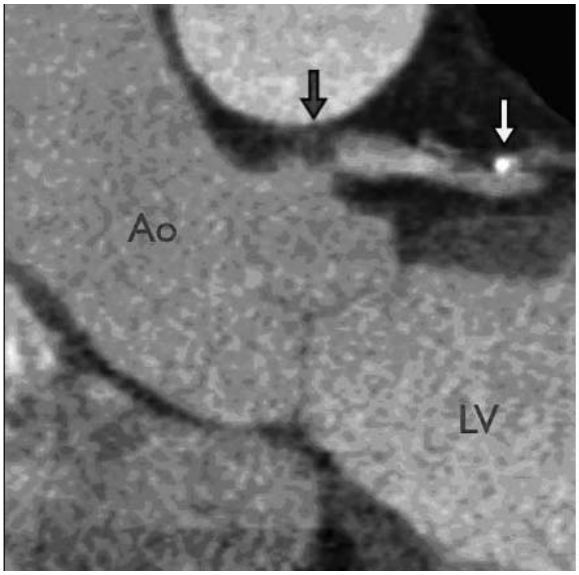

Figure 2. In this computed tomographic multiplanar reconstruction, a severe lesion in seen in the ostium of the left main coronary artery (red arrow). A second calcified atherosclerotic plaque (yellow arrow) is noted in the proximal left anterior descending artery. Ao indicates aorta; LV, left ventricle.

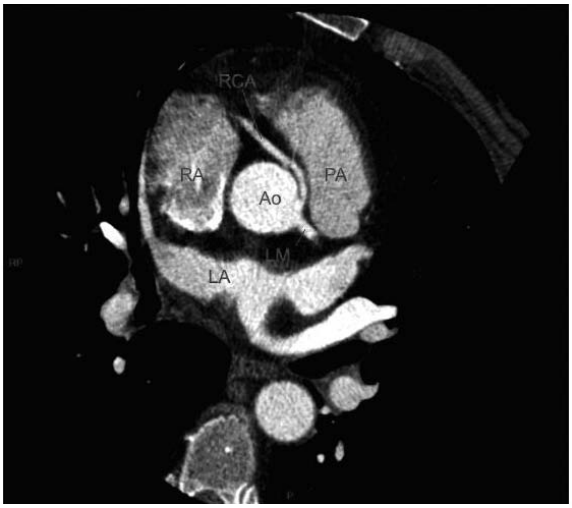

Figure 3. This multiplanar reconstruction was created using 16-slice multidetector computed tomography. The right coronary artery (RCA) originates from the left coronary sinus next to the left main (LM) coronary artery. The RCA clearly travels between the aorta (Ao) and pulmonary artery (PA). This anatomy may be associated with an increased risk of sudden cardiac death in younger patients.

performed safely[52] and has a similar or better sensitivity and specificity for the detection of significant CAD than do nuclear and echocardiographic stress testing.[53-57] Patients with a normal dobutamine CMR have a favorable prognosis.[58]

In addition to its usefulness in diagnosing CAD and its ischemic burden, CMR can be used to determine whether myocardium is dead or alive. The excellent endocardial definition offered by CMR enables assessment of improved myocardial thickening with low-dose dobutamine infusion. Presence of significant contractile reserve has been shown to correlate well with viability as determined by positron emission tomography (PET).[59] In chronically dysfunctional regions with significant contractile reserve, revascularization can improve ejection fraction and myocardial.[60,61] In addition to contractile reserve evaluation, CMR can be used to determine the transmurality of scar tissue with a technique called delayed hyperenhancement (DHE). Areas of myocardium that are inflamed or infarcted have an increased volume of distribution for gadolinium, and in these regions gadolinium washes out more slowly. These areas will thus appear bright on CMR images obtained at least 10 minutes after infusion (Figure 5). The transmural extent of scar that is present is predictive of whether the region is likely to recover function after revascularization.[62,63] Viability as determined by DHE correlates strongly with PET analyses.[64,65] Regions of myocardium with no evidence of DHE have more than 80% likelihood of improved contractility after revascularization; whereas regions of more than 75% scar are extremely unlikely to improve after revascularization.[66] Segments with scar involving 1% to 75% of the wall thickness have an intermediate likelihood of functional improvement with revascularization. Performing a low-dose dobutamine study for evaluation of contractile reserve can help further differentiate between viable and nonviable myocardium.[67,68] Early studies suggest that the burden of scar can also be evaluated with CCT, but a second dose of radiation is required.[69]

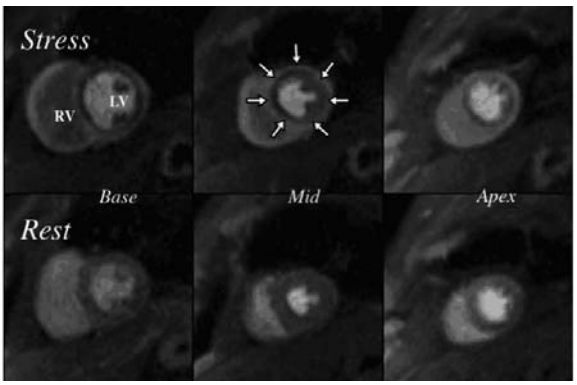

Figure 4. Adenosine stress test magnetic resonance images. Images obtained during stress are on top and those from rest are on bottom. A large perfusion defect with low signal relative to the remainder of the myocardium (arrows) is present in the subendocardium at 3 different slices of the left ventricle (LV) during adenosine perfusion but not during rest perfusion.Coronary angiography revealed that this perfusion defect was a result of severe left main stenosis. RV indicates right ventricle.

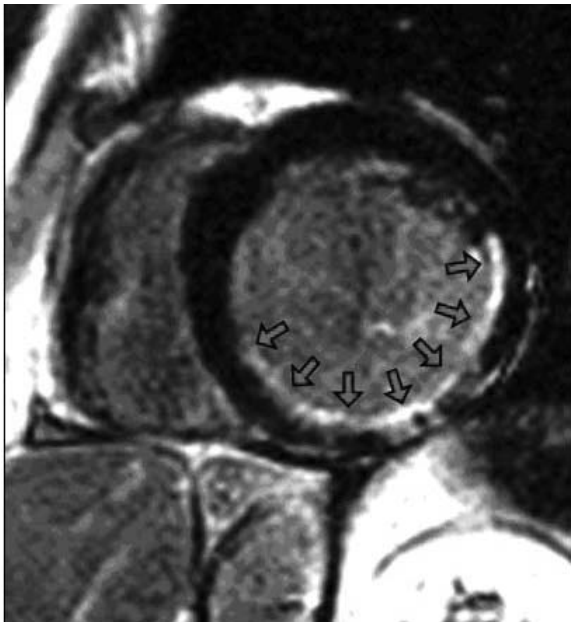

Figure 5: A short axis view of the left ventricle obtained with a delayed hyperenhancement technique. The arrows show a large scar involving the endocardial aspect of the inferoseptum and the inferolateral wall.

CARDIOMYOPATHY

Determinations of LV ejection fraction and volumes are extremely important in the evaluation of cardiomyopathy. Of equal importance is the etiology of the LV dysfunction. In the industrialized world, most cardiomyopathy is a result of complicated CAD. As discussed above, areas of myocardium that are scarred or inflamed retain gadolinium on DHE imaging. The pattern of DHE can be used to differentiate ischemic from nonischemic cardiomyopathy.[70,71] Specifically, the classic pattern for myocardial infarction is DHE extending from the endocardium toward the epicardium in the perfusion distribution of a coronary artery. Furthermore, the scar burden as determined by DHE imaging correlates with prognosis.[72] Although many patients with dilated cardiomyopathy do not have any evidence of DHE, some patients have a distinct pattern of DHE located in the midwall of the myocardium. The presence of midwall myocardial DHE is an indicator of poor prognosis[73] and may predict risk for ventricular tachycardia.[74] Another distinct pattern of DHE is seen in cardiomyopathies resulting from myocarditis. Mahrholdt et al demonstrated that the DHE was often localized to the epicardial border of the myocardium and correlated to areas of active myocarditis, as determined by histology.[75]

The high quality of tissue characterization by CMR gives it a unique role in the evaluation of other cardiomyopathies. Moon and colleagues have demonstrated that the presence of DHE in hypertrophic cardiomyopathy, generally in the right ventricular insertion points of the septum, corresponds to regions infiltrated with greater than 15% collagen.[76] Furthermore, greater DHE involvement is seen in patients with more risk factors for sudden cardiac death.[77] DHE is also seen in some patients with amyloidosis, an infiltrative cardiomyopathy in which large diffuse areas of subendocardial DHE are often found. Amyloid deposits may lead to more "extraction" of gadolinium from the blood pool, thus effectively reducing the difference in signal intensity between the myocardium and the blood pool.[78] Another pattern of DHE can be seen in sarcoidosis patients, in whom large patchy areas in a nonvascular pattern are often present.[79] DHE may also be useful for diagnosing myocarditis. In this condition, the inflammatory process is typically limited to the epicardial portion of the myocardium. Another cardiomyopathy well suited for evaluation with CMR is hemochromatosis. In this disorder the extensive infiltration with iron leads to local distortion of the magnetic field and ultimately decreases the signal intensity of the myocardium.[80] CMR has also been used in the diagnosis of Chagas myocarditis[81] and Anderson-Fabry disease.[82]

LIMITATIONS

Although both CMR and CCT are extremely powerful tools for the evaluation of cardiovascular diseases, they each have limitations. The potential radiation burden of CCT is a significant limitation. A typical CCT examination may result in greater than 10 mSv of exposure to the patient. This radiation dose is 2-3 times higher than that typically used during a diagnostic cardiac catheterization.[83] Furthermore, CCT uses iodinated contrast material, which may be nepthrotoxic. Limitations of CMR include difficulties with patients who suffer claustrophobia or have cardiac devices such as pacemakers and defibrillators that may not be safely imaged. Furthermore, stress CMR cannot be readily combined with exercise. Another potential limitation of CCT and CMR is the inadvertent discovery of noncardiac findings with unclear clinical significance.[84] Despite these potential limitations, both emerging technologies will continue to have a positive impact on the advancement of cardiovascular imaging.

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Can We Prevent Osmotic Demyelination Syndrome? The Role of Reintroduction of Hyponatremia

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A 38 year-old man with a history of schizophrenia and depression was admitted to the University of Virginia Health System with progressive worsening of his mental status and abdominal pain. Initial laboratory work revealed a serum sodium of 98 mmol/L with a urine osmolality of 118 mOsm/kg and a urine sodium of 18 mmol/L. Therapy with 3% sodium chloride and furosemide led to a rapid rise in serum sodium concentration, which was managed by reintroduction of hyponatremia and a subsequent slower correction of serum sodium. Despite this, the patient suffered osmotic demyelination involving the basal ganglia and pons. This report discusses osmotic demyelination syndrome, including preventative measures.

CASE DESCRIPTION

A 38 year-old man with a history of schizophrenia and depression was brought to the emergency department by his care-givers with a chief complaint of worsening confusion and abdominal pain. The patient had been residing in a state mental institution. On arrival to the emergency department, the patient was alert and noted to be moderately confused (oriented to place and person but not time) with a blood pressure of 138/89 mm Hg, pulse of 87 beats/min, respiratory rate of 12 breaths/min, and a temperature of 36.9˚C. Oxygen saturation was 100% on room air. No jugular venous distention was noted. Chest auscultation was clear. Abdominal examination revealed diffuse tenderness without rebound, hypoactive bowel sounds, and no guarding. There was no peripheral edema. Neurological examination revealed no cranial nerve abnormalities, 5/5 strength in all muscle groups, and normal sensory examination. Mini-Mental Status examination revealed a score of 23/30. The patient's medications included: risperidone, paroxetine, and omeprazole. Of note, he reported drinking between 7 to 10 L of water per day.

Table 1 shows the results of initial laboratory evaluation. A computed tomographic (CT) scan of the head without contrast was within normal limits (not shown) and a CT of the abdomen with contrast was notable only for some cholelithiasis without biliary ductal dilatation (not shown). Chest x-ray showed no pulmonary edema.

The patient initially received 1 L of normal saline infused over 1 hour. This was followed by 10 mg of intravenous furosemide and initiation of 3% saline at 35 mL/hour along with fluid restriction to 1000 mL/day. Five hours after presentation, his serum sodium was noted to be 111 mmol/L and the 3% saline infusion was discontinued. Over the first 6 hours, the patient's urine output was 5 L with an average osmolality of 105

Table 1. Initial Laboratory Values

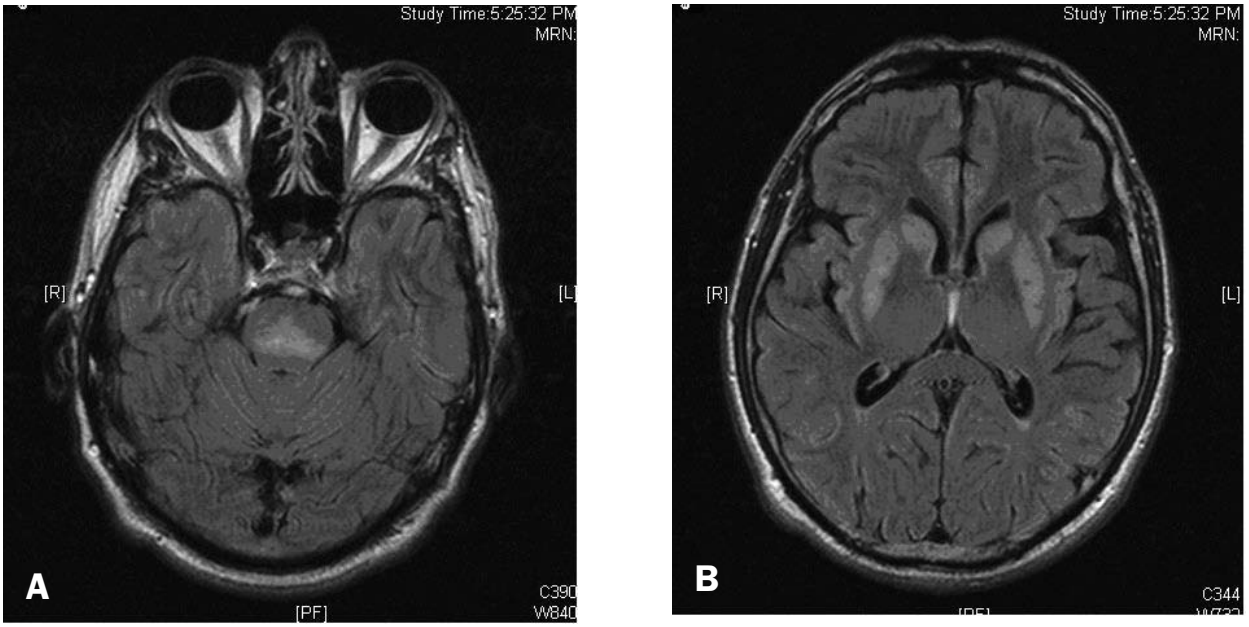
Serum:	
Sodium, mmol/L	98
Potassium, mmol/L	3.1
Bicarbonate, mmol/L	22
Chloride, mmol/L	66
Creatinine, mg/dL	0.6
Blood urea nitrogen, mg/dL	10
Osmolality, mOsm/kg	207
Urine:	
Sodium, mmol/L	18
Potassium, mmol/L	10
Osmolality, mOsm/kg	118

mOsm/kg. At 16 hours after presentation, his serum sodium was 120 mmol/kg. Nursing staff at this time noted some slight improvement in his mental status. Given concern over the rapidity at which the serum sodium was increasing, an infusion of 5% dextrose in water at 100 mL/hour was begun with the goal of decreasing the serum sodium to approximately 110 mmol/L (reintroduction of hyponatremia) to potentially lessen the risk of neurological complications. Twenty-five hours after presentation, the patient's serum sodium was 112 mmol/L, and from that point onward, slow correction of his serum sodium at a rate <0.5 meq/hour was initiated. The patient was discharged on hospital day 4 with serum sodium of 135 mmol/L. At that time, neurological examination results were normal.

Six days after hospital discharge, the patient was noted to have difficulty speaking and swallowing, an unsteady, shuffling gait, and a prominent resting tremor. Magnetic resonance imaging of the brain (Figure) demonstrated prominent demyelinating lesions in the pons and basal ganglia consistent with osmotic demyelination. The patient's serum sodium at this time was 134 mmol/L. He was treated supportively and with physical therapy as well as dopaminergic medications for his movement disorder. His neurological symptoms improved (especially his movement disorder) but did not completely resolve.

CASE DISCUSSION

This patient presented with severe dilutional hyponatremia associated with relatively mild neurological symptoms indicative of a chronic condition. In general, patients presenting with a serum sodium <105 mmol/L must have undergone some neurological adaptation, because the brain cannot tolerate such rapid lowering of the serum sodium without an increase in volume >10% (a level that would lead to herniation and death).[1] The etiology was likely due in part to water intake that exceeded the excretory capacity of the kidneys (pychogenic polydipsia). This theory was validated by the



Magnetic resonance images of the brain of the case patient. (A) A predominant high-intensity signal (T2-weighted) in the pons is consistent with a demyelinating process. (B) A predominant high-intensity signal (T2-weighted) in the basal ganglia consistent with a demyelinating process.

finding of markedly dilute urine (urine osmolality near 100 mOsm/kg) at the time of presentation. Also likely was the presence of inappropriate arginine vasopressin release (syndrome of inappropriate antidiuretic hormone secretion), particularly considering the apparent chronicity of this patient's condition. Furthermore, the patient's urine osmolality was slightly >100 mOsm/kg, a level exceeding that seen with psychogenic polydipsia alone.

In the therapy of this patient's hyponatremia, the rise in serum sodium was rapid and not anticipated by the patient's physicians, who did not account for the excretion of a large volume of dilute urine (large free water clearance). On the basis of prior case reports, reintroduction of hyponatremia followed by more gradual correction was attempted to lessen the risk of neurological complications. Despite this attempt, the patient developed neurological symptoms and demyelinating lesions. This case raises important questions regarding the pathophysiology of osmotic demyelination and action that can be taken to prevent this condition.

Differentiation between acute (<48 hours duration) and chronic (> 48 hours duration) hyponatremia is important because treatment varies for these disorders. Acute hyponatremia is often associated with neurological symptoms that can range in severity from headache and lethargy to seizures, neurologically mediated pulmonary edema, and death.[2] These acute symptoms result from the development of cerebral edema and the inability of homeostatic mechanisms to rapidly buffer changes in cell volume. Over time, however, cellular mechanisms allow adaptation to chronic hyponatremia. Through extrusion from the cell of intracellular sodium, potassium, organic solutes (myoinositol, taurine, glutamine, glutamate, aspartate and glycine), and water, cellular edema is minimized and as a result patients may remain asymptomatic.[1] This adaptive mechanism, while minimizing symptoms, increases the risk for the development of osmotic demyelination syndrome (ODS) when hyponatremia is corrected.

ODS can occur as the serum sodium is rapidly corrected. The initial descriptions of this condition in 1959 by Adams and colleagues focused on demyelinating lesions in the pons (central pontine myelinolysis) that affected alcoholics and malnourished individuals.[3] Subsequently, lesions outside the pons were identified, and in 1976 a link between these demyelinating lesions and rapid correction of serum sodium in hyponatremic patients was noted.[4,5] The link between rapid correction of hyponatremia and osmotic demyelination has been conclusively confirmed in animal studies.[6] Although this condition was initially termed central pontine myelinolysis, the finding of lesions in other parts of the brain prompted the adoption of the broader term ODS. In the largest pathological series investigating ODS, it was shown that demyelinating lesions can occur throughout the brain (Table 2).[4] In this series of 58 cases, isolated pontine lesions were seen in 50% of cases, pontine and extra-pontine lesions

Table 2: Locations of Central Nervous System Lesion in Osmotic Demyelination Syndrome*

- Pons
- Cerebellum
- Lateral geniculate body
- External capsule
- Internal capsule
- Hippocampus
- Putamen
- Cerebral cortex/subcortex
- Thalamus
- Caudate nucleus

*Listed in descending order of frequency. Adapted from Wright DG et al.[4]

in 30%, and isolated extra-pontine lesions in 20%. The reasons for the specific localization of the demyelinating lesions are not clear but may relate to different rates of reaccumulation of organic osmolytes in different brain regions.[1] Pathologically, there is degeneration and loss of oligodendrocytes with axonal preservation.[7]

Depending on the location of the lesion, patients with ODS may exhibit a variety of neurological symptoms including dysarthria, dysphagia, encephalopathy, mutism, Parkinsonism, dystonia, and flaccid quadriparsis.[7] The time course for the development of these symptoms can vary from a few days or more after the initial insult. The prognosis for ODS has been considered poor, with mortality rates as high as 50% to 90% and surviving patients at high risk for devastating neurological deficits. This grim prognosis has been called into question, however, by recent studies in which some patients showed considerable clinical improvement or even complete recovery.[8]

Although the precise pathogenesis of osmotic demyelination is unclear, disruption of the blood-brain barrier may occur as the serum sodium rises rapidly.[6,9] A rapid rise in extracellular tonicity does not allow cells to re-accumulate the osmotic particles that they had previously lost, a situation that can result in dehydration of brain vascular endothelial cells and disruption of intercellular tight junctions. These changes allow circulating proteins such as cytokines, complement proteins, and vasoactive amines to gain access to the central nervous system, where they can lead to oligodendrocyte injury and demyelination.[6,9,10] Alternatively, there may also be injury to axons caused by shrinkage of the brain as cellular water rapidly moves out of the central nervous system.[11] Oligodendrocytes may be particulary prone to this type of shear injury, which may activate apoptotic pathways.[6] Interestingly, some of the associated risk factors for the development of osmotic demyelination can be explained by their effects on cellular metabolism. For example, hypoxia and malnutrition may prevent the re-accumulation in cells of osmolytes that are critical to volume regulation.[1]

The diagnosis of ODS is made when the patient experiences new-onset neurological symptoms in the context of a rapid correction of hyponatremia. The diagnostic modality of choice is magnetic resonance imaging.[12] Patients demonstrate hypo- to isointense lesions on T1-weighted images and hyperintense lesions on T2-weighted, proton density-weighted, and fluid-attenuated inversion-recovery images.

ODS occurs in only a small proportion of patients with hyponatremia who have their serum sodium rapidly corrected.[1,6] Furthermore, studies have indicated that overly slow correction of serum sodium is also associated with adverse outcomes in patients with severe hyponatremia.[13] Thus, clinicians must carefully balance the risks of ODS versus the risks of overly slow correction of serum sodium in their treatment decisions. Patients at highest risk of ODS, such as those with malnutrition, chronic alcoholism, hypoxia, and hypokalemia, should have their serum sodium slowly corrected (no more than 8 mmol/L in 24 hours).[1,13] Although ODS has been rarely reported in patients with acute hyponatremia, the majority of these patients can have their serum sodium safely corrected at faster rates (or to levels at which neurological symptoms improve).[13] For those patients with chronic hyponatremia and serious neurological symptoms, a 5% acute increase in serum sodium levels will usually suffice, followed by more gradual correction over the next few days.[1,13] Clearly, slow correction of hyponatremia is the most important factor in preventing ODS.

Despite best efforts, serum sodium occasionally

rises faster than anticipated. What should be done under these circumstances, in which the risk for ODS is substantially increased? In a rat model of ODS, Soupart et al demonstrated that reintroduction of hyponatremia improved survival and outcomes in animals who developed myelinolysis-related neurological symptoms.[14] Subsequently, several case reports have been published where therapeutic re-lowering of serum sodium followed by slow correction in patients who have developed neurological symptoms has proved beneficial.[15,16] However, the role of reintroduction of hyponatremia in patients who have had over rapid correction but no immediate neurological symptoms has not been reported. In this current case, despite reintroduction of hyponatremia, ODS still occurred. Thus, the role of therapeutic relowering of serum sodium in these patients remains unclear. Furthermore, the risks associated with relowering of the serum sodium have not been explored.

Many other therapies have been attempted to improve the outcome of patients with ODS. Most, however, have been reported only in case-report formats and thus are subject to reporting bias. Plasmapheresis has been shown to be beneficial in 4 patients with ODS, perhaps due to the modulation of inflammatory and toxic soluble mediators.[17] Corticosteroids have been shown to beneficial in both animal studies and case reports, perhaps to due to beneficial effects on the blood brain barrier.[6] Dopaminergic medications often demonstrate benefit in ameliorating symptoms (as in this patient).[7] Silver et al recently reported data that systemic administration of myoinositol (the most abundant of the organic intracellular osmoles in the brain) improved the survival of rats with chronic hyponatremia who underwent rapid correction of their sodium.[18] This exciting development may hold promise for the prevention of ODS.

CONCLUSION

Overly rapid correction of chronic hyponatremia can have severe and irreversible neurological consequences. The best method for prevention is careful diagnosis of patients at risk and very slow correction of serum sodium. In patients who have more rapid, inadvertent correction of hyponatremia, the best course of action is not clear. Reintroduction of hyponatremia has shown anecdotal benefit in patients who develop neurological symptoms, but as this case demonstrates, this treatment is not uniformly beneficial. In the absence of new therapies (corticosteroids, myoinositol), prevention and vigilance remain the best approaches for these patients.

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