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Information for Authors

Purpose

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

Article Submission

Only original, unpublished materials will be considered for publication. Inclusion of housestaff on all articles is strongly recommended. Submissions should be made electronically to Cathy Keefe-Jankowski (ck8h@virginia.edu). 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*. Arkham, MA: Miskatonic University 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:

Clinical Vignettes: *length - 800-1600 words*

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

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

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

Invited Articles

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

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

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

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

Clinical Commentary: *length - 1600-3200 words*

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

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

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

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

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

Rhabdomyolysis Associated with Diabetic Muscle Infarction: A New Manifestation of a Rare Disease

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Spontaneous diabetic muscle infarction (DMI) is a rare clinical sequela of longstanding poorly controlled diabetes mellitus. This entity was first described in 1965 by Angervall and Stener,[1] and 166 cases have subsequently been reported. The diagnosis is often difficult to establish, however, and requires the combination of clinical presentation, radiographic imaging, and high clinical suspicion. Thus, as recent literature suggests, DMI is underdiagnosed in diabetic populations.[2-5] We describe a classic presentation of DMI with a previously unreported complication, rhabdomyolysis.

CASE DESCRIPTION

A 67-year-old man with poorly controlled type 2 diabetes complicated by nephropathy, retinopathy, and peripheral neuropathy presented to the emergency department with the complaints of sudden onset of bilateral proximal lower extremity edema, weakness, and pain and cola-colored urine. The patient indicated that 2 days prior to presentation he experienced abrupt proximal lower extremity pain and weakness, followed by profound thigh swelling on the day of admission. The patient also noted that his urine color had darkened to a cola color on the morning of admission. In addition to the patient's long-standing diabetes, his medical history was significant for ischemic cardiomyopathy after 3-vessel coronary artery bypass graft surgery in 1996, congestive heart failure, poorly controlled hyperlipidemia, hypertension, peripheral vascular disease, gastroesophageal reflux, and stage 3 chronic kidney disease. For the past 2 years, the patient had been maintained on a stable medical regimen of NPH insulin 80 units in the morning and 60 units in the evening, sliding scale regular insulin, gemfibrozil, baby asprin, metoprolol, lisinopril, pravastatin, furosemide, and pantoprazole as well as nortriptyline for peripheral neuropathy.

The patient reported that before onset of his current symptoms he had been in his normal state of health, performing his normal daily activities. The patient denied recent trauma, injection of insulin into the affected muscle groups, prolonged immobility, symptoms of decompensated heart failure, fevers, chills, and weight loss.

Physical examination revealed an obese, elderly man who appeared his stated age. His vital signs were stable with a blood pressure of 123/73 mm Hg, temperature 36˚C, pulse 68 beats/min, respirations 18/min, and oxygen saturation of 98% on room air. Neck exam demonstrated no thyromegaly, cervical lymphadenopathy, or increased jugular venous pressures. Cardiac rate and rhythm were regular, and the patient had a soft murmur consistent with mitral regurgitation, no atrial or ventricular gallops, and warm extremities with equal pulses bilaterally in the upper and lower extremities. Lower extremity exam findings included bilateral tenderness and swelling of the abductor and thigh flexor muscles groups. The patient demonstrated decreased strength isolated to adduction, hip flexion, and leg extension. There were no obvious signs of muscular atrophy or wasting. Joint examination results were negative for effusions, erythema, and point tenderness. Skin exam revealed no signs of trauma or new rashes. The remainder of the patient's exam findings were unremarkable.

Laboratory analysis results for samples drawn at the time of admission showed normal complete blood count, electrolytes, and thyroid studies. The patient's glucose was increased (270 mg/dL), and his glycosylated hemoglobin was 10.3%. Initial blood urea nitrogen and serum creatinine were elevated (40 mg/dL and 2.0 mg/dL, respectively), with an estimated glomerular filtration rate of 36. A lipid panel demonstrated

mild dyslipidemia with a total cholesterol of 140 mg/dL, triglycerides of 76 mg/dL, high-density lipoprotein of 30 mg/dL, and low-density lipoprotein of 97 mg/dL. Aspartate aminotransferase, alanine aminotransferase, and creatine kinase were elevated, at 1021 U/L, 230 U/L, and 73,860 U/L, respectively. Urinalysis was remarkable for myoglobinuria, large hematuria, trace glucosuria, and 2+ proteinuria. Other laboratory analysis results, including rheumatologic indices and C-reactive protein, were unremarkable. Chest radiograph demonstrated cardiomegaly without signs of acute cardiopulmonary disease. Magnetic resonance imaging (MRI) of the patient's lower extremities, acquiring short T1 inversion recovery images, demonstrated symmetric intramuscular edema, most prominent in the abductors and thigh flexors bilaterally (Figure 1). Nerve conduction velocity and electromyography study results were consistent with an acute myopathic pathology. Muscle biopsy of the anterior thigh muscles demonstrated multifocal myonecrosis with macrophage infiltration and without evidence of myositis. Stains and cultures were negative for bacteria, fungi, and acid-fast bacilli.

The combined findings of clinical presentation, laboratory data, radiographic imaging, nerve conduction studies, and muscle biopsy confirmed the diagnosis of bilateral DMI complicated by rhabdomyolysis.

DISCUSSION

DMI, or diabetic myonecrosis, is a rare and serious complication of poorly controlled diabetes mellitus. According to a systematic review of DMI by Trujillo-Santos,[2] the clinical presentation is relatively consistent, with abrupt, atraumatic swelling (76%) and exquisite tenderness (80%) of the affected muscle. A palpable mass is noted in 33% of cases. Patients are typically in their mid-40s (range 19-81 years) and female (61%) and have had type I diabetes for more than 14 years (59%). Manifestations of diabetic complications such as nephropathy (71%), retinopathy (57%), and neuropathy (55%) are commonplace. The muscles involved are typically in the thigh (84%), and involvement is usually unilateral (91%). Recurrence is high, with a predilection for new muscle groups.[2] Peripheral vascular disease has occurred in up to 45% of patients with DMI.[6]

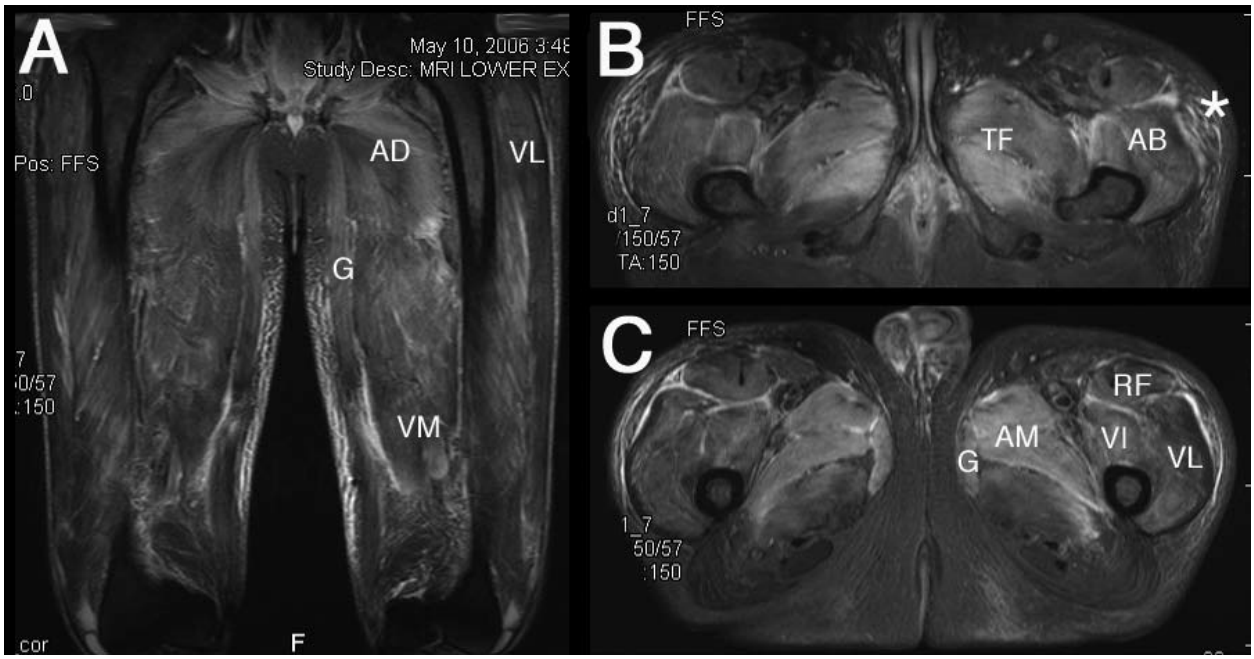

Figure 1. Magnetic resonance image of the patient's lower extremities. Coronal and axial short T1 inversion recovery images of the lower extremities demonstrate symmetric intramuscular edema predominantly of the thigh flexor (TF) and abductor (AB) muscles. Coronal sections (A) demonstrate symmetric hypointensity of the gracilis (G), adductor muscle group (AD), vastus medialis (VM), and vastus lateralis (VL) muscles. Axial sections (B and C) further demonstrate involvement of the gracilis (G), adductor magnus (AM), vastus intermedius (VI), rectus femoris (RF), and vastus lateralis (VL) muscles. Subcutaneous fat stranding (*) is also visible anteriorly.

Patients may also present with fever (11%-50%). Diagnosis is usually delayed, with an average time of 4 weeks (range, 1 day to 40 weeks) from onset of symptoms to diagnosis.

The differential diagnosis is extensive (Table 1), but can be narrowed to muscular complications, rheumatologic diseases, infection, tumors, and vascular complications. In evaluating a patient with suspected DMI, life-threatening illnesses, such as deep vein thrombosis and necrotizing fasciitis, must be ruled out.

The diagnosis of DMI relies on clinical presentation, laboratory analysis, and radiographic imaging. Laboratory analysis is important in ruling out other possible diagnoses. Most patients with DMI present with evidence of poorly controlled diabetes (elevated hemoglobin A1c) and microvascular end-organ damage, most commonly with a decreased estimated glomerular filtration rate. Less than 10% of cases present with leukocytosis. Creatinine kinase levels are elevated in only half of reported cases.[2,6] In our patient, urine analysis and creatinine kinase levels confirmed the diagnosis of rhabdomyolysis, which has not been previously been associated with DMI.

Imaging studies are essential to DMI diagnosis. Lower extremity ultrasound and computed tomography play important roles in the exclusion of deep vein thrombosis and discrete masses, respectively. Although computed tomography has been useful in demonstrating edema of isolated muscle groups, a feature typical of DMI,[7,8] most authors agree that MRI is the preferred imaging modality to support a diagnosis of DMI. Typical MRI findings are acute edema, inflammation, and infarction of isolated muscle groups. Acute edema and inflammation are best visualized with T2-weighted images, inversion recovery, and gadolinium enhanced MR. Compared to unaffected muscle, infarcted muscle appears as hypo- or isointense on T1-weighted images and hyperintense on T2-weighted images.[9,10] Postinfarct hemorrhagic conversion has been demonstrated with an increase in T1-weighted signal.[11]

Tissue biopsy is considered the gold standard for DMI diagnosis, but this invasive procedure should be reserved for cases involving diagnostic uncertainty, atypical presentations, and treatment failure.[12] Initial biopsy findings show necrosis of the muscle fibers, edema, and inflammatory infiltration.[6] Later findings demonstrate regenerative myofibrils and mononuclear cell infiltration.[7]

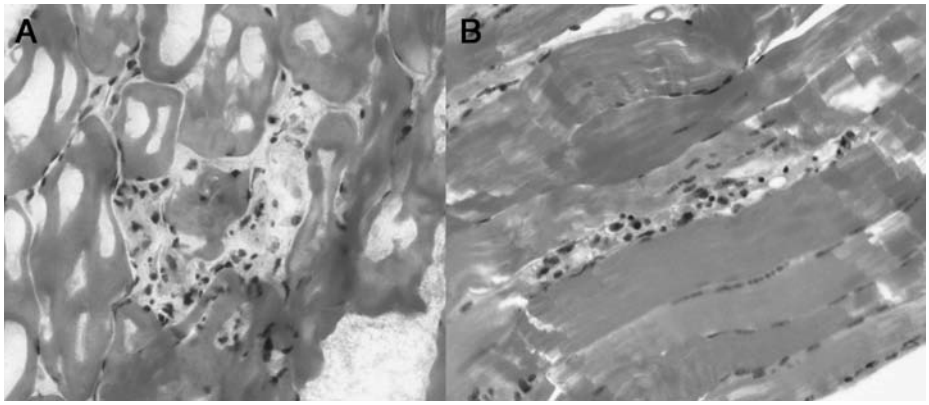

Figure 2. Tissue biopsy results. Hematoxylin and eosin stains of skeletal muscle tissue from the patient's left thigh demonstrate diffuse myonecrosis accompanied by macrophage infiltration. A. "Ghost cell" pattern, which represents the shells of formerly healthy tissue. B. Moderate variation of muscle fiber shape and size, which is typical with acute damage.

Table 1. Differential Diagnosis of Abrupt Onset of Lower Extremity Pain and Edema

Muscle	Rheumatologic	Infection	Oncology	Vasculature	Other
Trauma	Pyomyositis	Abscess	Benign Tumor	Deep Vein Thrombosis	Baker's Cyst Rupture
Exertional Muscle Rupture	Proliferative, Nodular or Focal Myositis	Osteomyelitis	Sarcoma	DMI	
Diabetic amyotrophy	Dermatomyositis		Necrotizing faciitis	Lymphoma	

Treatment of patients with DMI is supportive, and symptoms typically resolve spontaneously over several weeks. Most authors agree that bed rest is warranted initially owing to exquisite pain with mobility. When tolerable, a physical therapy evaluation should be performed. Opioid analgesics are commonly used to treat refractory pain. Long-term treatment must include aggressive glycemic control. Early case descriptions report treatment with surgical exploration and excision,[1] but the mainstay of current treatment involves pain management, early immobilization, tight glycemic control, and time-appropriate physical therapy. After diagnosis, the patient we describe was treated with supportive care, pain management, and early immobilization. Because this case was complicated by rhabdomyolysis, the patient also received aggressive intravenous hydration.

The pathogenesis of DMI is still unclear. Three separate etiologies have been reported: macrovascular and atheroembolic disease, microvascular disease, and acquired hypercoaguable states associated with endothelial dysfunction. Chester and Banker[12] proposed that focal muscle infarction in diabetic patients is due to occlusive, nonembolic disease of large and medium arteries, causing hypoxia-reperfusion injury resulting in arteriosclerosis obliterans. In this scenario, anoxic injury due to macrovascular hypoperfusion leads to mild compartment syndrome, thus worsening ischemia and generating myonecrosis. Macrovascular disease is not the only type of vascular injury noted in patients with DMI. Silberstein et al[13] reported further evidence of hypoxia-reperfusion injury, but also demonstrated by Tc-sestamibi scans and biopsy that microvascular damage, precipitated by microvascular thomboembolic events or local trauma by injections, produced a focal compartment syndrome as seen in DMI.[14] These data support Barohn and Kissel's conjecture[15] that diabetic microvascular disease involved in diabetic nephropathy and retinopathy may also predispose individuals to DMI. Another theory is that DMI is associated with hypercoagulable states occurring in diabetic microvascular disease. Abnormalities in fibrinolysis and coagulation[16] as well as the presence of antiphospholipid antibodies have been demonstrated.[17,18] The difficulty in elucidating the pathogenesis of DMI suggests a multifactorial etiology that includes arteriosclerotic processes and diabetic microvascular disease.[19]

In the 166 reported DMI cases, diagnosis was typically delayed because of initial failure to recognize DMI as a diabetic complication. Frequently, DMI is misdiagnosed as an abscess, neoplasm, or myositis.[20] In addition, the clinical significance of DMI has been misunderstood and underestimated. Results of 2 small case series[21,22] indicate that DMI is catastrophic, with short-term mortality equal to that of myocardial infarction in diabetic patients.[23,24] Most DMI patients demonstrate manifestations of diabetic end-organ damage and are at higher risk for further complications such as infection, cardiovascular disease, and life-threatening diabetic emergencies. Thus DMI is a serious diabetic complication that mandates closer attention for risk reduction and aggressive management for tighter glycemic control.

CONCLUSION

The case we describe exemplifies a classic presentation of an uncommon disease and is the first reported case of DMI complicated by rhabdomyolysis. DMI should be considered in patients with poorly controlled diabetes complicated by more typical manifestations of microvascular disease, such as nephropathy, retinopathy, and neuropathy, who present with acute nontraumatic swollen muscular pain. Diagnosis is based on clinical presentation and radiographic imaging, with MRI as the most reliable modality. Tissue biopsy should be reserved for diagnostic uncertainty or atypical presentations. Treatment is mainly supportive, with immobilization and adequate analgesia as the initial mainstay followed by aggressive glucose control, risk reduction, and appropriate physical therapy.

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Acute Lymphoblastic Leukemia Presenting with Chest Pain and Normal White Blood Cell Count

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We describe a case of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in a 70-year-old man with a chief complaint of chest pain. Pain as the presenting symptom in ALL is unusual, and has been previously reported almost exclusively in pediatric patients. We also discuss recent advances in the treatment of ALL.

CASE PRESENTATION

A 70-year-old man presented to the University of Virginia (UVA) emergency department, stating that he had band-like pain and tightness around his diaphragm, "as if someone had tied a belt around [his] chest." The pain, which had awakened him the previous night, was 8/10 in severity and radiated to his back but not the neck or jaw. The patient stated that he had eaten a large meal with wine the night before and initially thought the pain was caused by gastrointestinal distress. Antacids taken at home had no effect on the pain, but a gastrointestinal "cocktail" (magnesium hydroxide, aluminum hydroxide, simethicone, lidocaine, and donnatal) administered in the emergency department reduced it to 4/10. The patient denied fatigue, dizziness, dyspnea, loss of consciousness, epistaxis, and bleeding gums. He also denied having experienced similar symptoms in the past. The patient's medical history was significant for a coronary artery bypass graft, bilateral carotid endarterectomy, aortic stenosis with porcine valve replacement, hyperlipidemia, gastroesophageal reflux, and colorectal cancer with history of hemicolectomy 13 years previously. The remainder of his review of systems was unremarkable. The patient's mother had a history of congestive heart failure. Social history was significant for exposure to solvents, including toluene and methyl ethyl ketone, during his long-time hobbies of sculpting and boat construction. The patient reported occasional use of alcohol and denied use of tobacco or recreational drugs.

Physical examination revealed the patient to be afebrile, normotensive, alert, and oriented. A left carotid bruit was audible. Deep inspiration caused pain in the same diaphragmatic distribution as the pain that was his chief complaint. The patient denied shortness of breath, and his lungs were bilaterally clear to auscultation and normal to percussion. Cardiac exam revealed regular rate and rhythm with normal S1 and S2. A II/VI systolic murmur was detectable and was loudest at the right upper sternal border. Abdominal exam revealed a functioning ostomy bag, normal bowel sounds, and no hepatosplenomegaly. Lower extremities showed rare, nonblanching petechiae and no clubbing or edema.

Initial laboratory values showed that troponin, basic metabolic panel, and hepatic panel were all within normal limits. A complete blood count was notable only for a platelet count of 16,000/μL. Repeat platelet count showed 13,000/μL. An electrocardiogram was unchanged from baseline, and a chest x-ray was unremarkable.

The patient was admitted to the general medicine service. Computed tomographic pulmonary angiogram showed no pulmonary embolus, dissection of the aorta, osseous lesions, or other findings that would explain the patient's chest pain. A transthoracic echocardiogram showed a normally functioning aortic valve and normal ventricular function.

The patient's white blood cell (WBC) count was normal, but a differential count showed 52% blasts. Peripheral blood smear revealed atypical lymphocytes (Figure 1) consistent with this finding. Flow cytometry of the peripheral blood

showed that the blasts were positive for CD34, CD10, and CD19, consistent with a diagnosis of ALL.

The patient was transferred to the hematology/oncology service for initiation of chemotherapy. Cytogenetic studies were performed and the patient was noted to have the translocation (9;22), indicative of Ph+ ALL. Initial induction therapy for ALL was imatinib for 1 month, and intrathecal methotrexate was given as prophylaxis against central nervous system (CNS) disease.

The patient continued to experience pain in his chest. Moderate control was achieved with intravenous opiates. Magnetic resonance imaging of the thoracic spine and chest was obtained and showed diffuse marrow abnormalities in the patient's ribs suggesting diffuse marrow replacement consistent with the diagnosis of ALL.

DISCUSSION

The overall incidence of ALL in the United States is 1.5/100,000 in whites and 0.8/100,000 in African-Americans, with a slight male predominance. More commonly diagnosed in children younger than 5 years (5.3/100,000), ALL becomes gradually more common at age 35 and reaches a second, minor peak in the age group of 80 to 84 years (2.3/100,000).[1] Although incidence rates have remained largely unchanged worldwide for decades, a small and unexplained increase in ALL cases has been observed recently.[2] People exposed to radiation, including radiotherapy,[3] are at increased risk of developing leukemia, and exposure to chemicals such as benzene may also increase risk. Benzene, however, is more strongly associated with acute myelogenous leukemia.[4] Our patient's history was significant for exposure to toluene and methyl ethyl ketones.

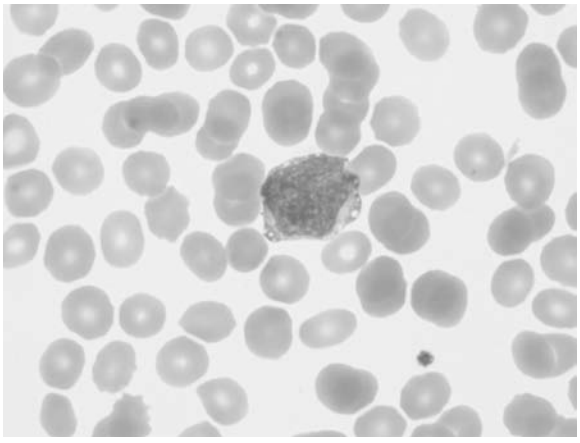

Figure 1. Hemotoxylin and eosin stain of a sample of the patient's blood shows red blood cells of normal morphology and precursor (blast) white blood cells with fine chromatin and prominent nucleoli. Auer rods are absent and there is no granulation. This cell is consistent with acute leukemia but is not diagnostic of acute myelogenous leukemia or acute lymphoblastic leukemia.

Perhaps the most unusual feature in our patient's case was his presenting symptom of chest pain and his isolated thrombocytopenia. Pain as the presenting symptom in ALL has been reported previously, although almost exclusively in pediatric patients. The pain is then often localized to joints and/or extremities.[5] Search of the medical literature yielded only 2 previous cases of ALL preceded by chest pain, and one of them was attributed to the development of pleuropericarditis.[6,7] According to 2 consecutive German multicenter trials, adults with ALL are more likely to present with clinical signs of infection/fever or hemorrhage, 36% and 33%, respectively. Physical examination revealed lymphadenopathy in 57% of cases, splenomegaly in 56%, and hepatomegaly in 47%. If our patient's "band-like, diaphragmatic" pain was due to inferior rib pain, it would be consistent with the 1.2% of patients who experienced bone pain as part of their clinical course.[8]

Hematological abnormalities are also common in ALL, but thrombocytopenia in the setting of an otherwise normal complete blood count results is rare. Normal platelet count (150,000-450,000/μL [UVA reference value]) occurs in only 15% of patients, a platelet count below 25,000/μL occurs in 30% of patients,[8] normocytic anemia is almost universal,[9] and aberrant WBCs are extremely common (86%). More than half of patients have a leukocytosis greater than 15,000/μL. In 97% of patients further diagnostic workup reveals greater than 50% leukemic blast infiltration into the marrow.[8] In our patient the presence of circulating blasts allowed for flow cytometry to be performed on a

blood sample, and thus bone marrow biopsy could be deferred.

An immediate concern in a patient with a new diagnosis of ALL is the possibility of CNS involvement. In adult ALL patients, 7% to 10% have active CNS disease at the time of diagnosis, and it is frequently asymptomatic. If not adequately treated, many patients will eventually develop CNS disease, so routine CNS prophylaxis is an important part of the standard of care.[10]

Treatment for Ph+ leukemias has changed dramatically since the introduction of imatinib, a specific inhibitor targeting the BCR-ABL tyrosine kinase responsible for Ph+ leukemic transformation.[11,12] Originally indicated for chronic myelogenous leukemia, imatinib has been investigated for use as induction therapy in ALL and has proven capable of eradicating more than 99% of the initial leukemia burden and restoring normal hematopoiesis.[13] Complete remission rates approach 97% in patients induced with imatinib 600 mg/day, compared to 50% in patients undergoing induction with multiagent chemotherapy. In addition to this direct improvement in the efficacy of induction therapy, severe adverse reactions (including neutropenic fever, septicemia, nausea, vomiting, and diarrhea) were markedly reduced with imatinib, occurring in 39% of patients compared to 86% receiving standard chemotherapy. Estimated median remission duration was not significantly affected by treatment regimen.[12]

This advancement in the treatment of Ph+ ALL is particularly exciting because presence of the Philadelphia chromosome has historically been one of the poorest prognostic factors in ALL. Complete remission is less frequent in Ph+ than Ph- patients (68% vs 84%) and less frequently maintained (17% vs 50%). Median survival duration is also shorter in Ph+ than Ph- ALL patients (330 days vs 900 days).[14] High WBC count, age above 50 years, and time to achievement of complete remission are established as other poor prognostic factors.[15] Patients with the BCR-ABL rearrangement have the poorest prognosis.[14] In multivariate analysis, however, these factors lost their relevance, indicating they may have been influenced in earlier trials by their correlation to the Ph translocation.[15] Studies have suggested that one reason that ALL prognosis is poorer in adults than children is that ALL is positive for BCR-ABL in 37% of cases in adults compared to 3% in children.[14]

CONCLUSION

This case underscores the necessity of thorough evaluation of patient complaints when initial treatment attempts do not cause symptoms to abate, especially in light of this patient's atypical presentation of a relatively common disease. Recent advances in the treatment of ALL are promising, particularly in Ph+ disease. Imatinib has been widely used in the management of this and other diseases that are positive for the (9;22) translocation, and research continues on other potential applications. At the time of this report, the patient was undergoing treatment with the Linker regimen for ALL. He had been recently hospitalized for neutropenic fever, and was recovering his WBC as an outpatient.

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A 73-Year-Old Woman with CLL and Recurrent Blistering on Her Extremities

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Skin vesicles and bulla, commonly termed blisters, are fluid-filled, raised areas. Blisters are 5 mm or less in diameter and bulla are greater than 5 mm.[1] Vesicles and bulla have many causes and are best understood by separating them into 2 categories, those that arise from primary cutaneous diseases and those that are outward manifestations of systemic diseases. Primary cutaneous diseases are further categorized into primary (autoimmune) blistering diseases (pemphigus vulgaris, bullous phemphigoid, herpes gestationis, linear IgA disease, epidermolysis bullosa acquisita), secondary blistering diseases (contact dermatitis, erythema multiforme, toxic epidermal necrolysis), and infections (varicell/zoster, herpes simplex, staph-scalded skin syndrome, bullous impetigo). The systemic diseases are further classified as autoimmune (paraneoplastic pemphigus), infections (cutaneous emboli), metabolic (diabetic bullae, porphyria cutean tarda and varigeta, pseudoporphyria, bullous dermatosis of hemodialysis), and ischemic (coma bullae).[2] A formal diagnosis is typically based on the histopathologic description from a punch biopsy of affected skin.

CASE DESCRIPTION

A 73-year-old white female with chronic lymphocytic leukemia (CLL) diagnosed in 2006 presented with blistering of her anterior, right lower leg associated with redness and swelling. The patient had undergone chemotherapy and was receiving monthly granulocyte colony-stimulating factor (G-CSF) for persistent neutropenia. The blistering had started 1 week prior to presentation and developed underneath a compression stocking worn for venous stasis. The patient had recently been admitted to the hospital for "blistering cellulitis" of the left hand, which improved after prolonged intravenous and oral antibiotics.

The patient's primary care physician had initiated moxifloxacin for the right leg blistering, but after 4 days the patient noted only "mild" improvement. One the day of admission, her primary care physician sent the patient for Doppler ultrasound of her lower extremities, which revealed a nonocclusive right greater saphenous vein thrombosis from knee to midcalf. She was then admitted to our hospital for management of skin blistering associated with superficial venous thrombosis.

On admission, the patient denied possible contact with poison ivy or previously known contact allergens. A review of her history revealed that she had been seen at the dermatology clinic the previous year for similar symptoms on the same leg, which were thought to indicate contact dermatitis and were treated symptomatically. She described the current lesions as being preceded by itching followed by redness and edema, and then the development of multiple small vesicles that coalesced into larger bulla, which were not easily ruptured. The patient denied fever, chills, chest pain, shortness of breath, and recent illness.

Physical exam was notable for the absence of fever, normal vital signs, and oxygen saturation of 96% on room air. The patient had two 1-cm immobile, nontender right inguinal lymph nodes (unchanged since previously noted in the patient's medical record). There were no oral mucosal lesions. Right lower extremity exam revealed a well-healed 2-cm scar just above the ankle line, 2 large (3 x 3 cm) bullae, and 2 smaller (1 x 2 cm) bullae filled with transparent fluid, with surrounding erythema. The surrounding skin was tender to palpation, faintly nodular, edematous (2+), and erythematous from the midcalf to the ankle but without red-streaks or crusted areas (Figure 1).

Initially, the differential diagnosis included cellulitis, contact dermatitis, bullous pemphigoid, and Trousseau syndrome. Treatment with intravenous clindamycin was started, and the erythema, edema, and bullae showed only mild improvement. Of note, the patient refused biopsy of the skin at the time due to her fear of poor wound healing due to her venous stasis. Heparin treatment for the superficial nonocclusive thrombus was started after 24 hours of antibiotics. She was discharged with oral clindamycin, and lovenox was continued at the request of her primary oncologist.

Five days after discharge, the patient returned to the dermatology clinic with improved right lower leg symptoms but return of left hand blistering, swelling, and redness, despite oral clindamycin and resumption of moxifloxacin treatment initiated by her primary care physician. Also noted was a new purple nodule on the patient's left hand. Daily infusions of vancomycin were begun, again with only mild improvement in her hand symptoms. The continued symptoms convinced the patient to consent for a punch biopsy of the left hand.

Punch biopsy revealed marked papillary dermal edema extending deep into the dermis, with an interstitial and perivascular infiltrate consisting predominantly of neutrophils. Gomori methenamine silver, acid fast, and gram stains were all negative for organisms. Tissue biopsy results were consistent with neutrophilic dermatitis (Sweet syndrome). At the time of diagnosis the patient had completed antibiotic therapy and started on ibuprofen and a prednisone taper. Her left hand symptoms rapidly resolved.

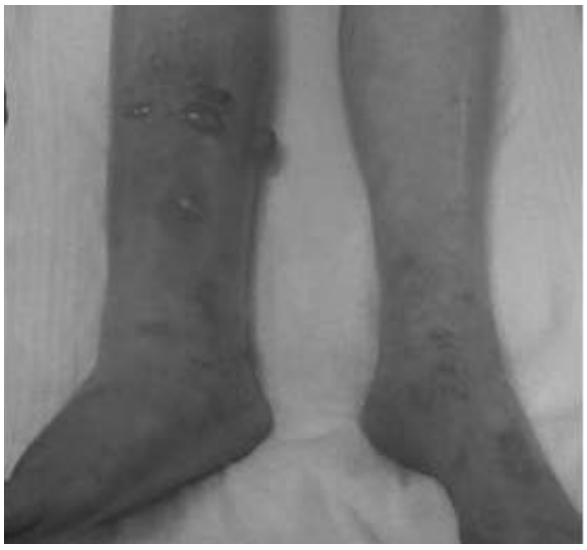

Figure 1. Patient's lower extremities at the time of admission

DISCUSSION

Skin lesions in cancer patients are common and can herald the diagnosis of malignancy, signal a local or systemic infection (especially in neutropenic patients), or occur as a side effect of chemotherapy or in association with certain existing malignancies.

Sweet syndrome was first described in 1964 and is usually seen in patients with neutropenic cancer (20%-25%), most often in association with acute leukemia but also with a variety of other malignancies.[3] The age of onset is usually between 30 and 60 years, with a 4:1 female predominance.[3,4] Other conditions associated with Sweet syndrome include bacterial infection (streptococcus, mycobacterium, yersinia, typhus, salmonella), viral infections (cytomegalovirus, chronic active hepatitis, HIV), vaccinations, drug usage (lithium, furosemide, hydralazine, oral contraceptives, trimethorprim-sulfamethoxazole), autoimmune and collagen vascular disorders, inflammatory bowel diseases, and pregnancy.5

The exact pathogenesis of Sweet syndrome is unknown. In the past it has been reported to be a direct response to mechanical and chemical irritants, an infectious disease, or a disorder of neutrophilic chemotaxis and/or phagocytosis, but most often it has been described as a hypersensitivity reaction. Each of these theories can account for particular symptoms, but none reconciles the dominating clinical and laboratory features of the disease.6 Current research is focusing on cytokine dysregulation. The cytokines in question are interleukin (IL)-1, IL-3, IL-6, IL-8, G-CSF, granulocyte-macrophage CSF, and interferon gamma.4,6 For example, serum levels of IL-6 and G-CSF showed isolated increases that paralleled the acute phase and resolution of skin lesions in patients with Sweet syndrome.6 Furthermore, this syndrome has also been described as a

complication of exogenous G-CSF therapy, which the patient we describe received monthly for recurrent neutropenia.[7,8]

Histologically, the diagnostic features are infiltration of mature neutrophils throughout the dermis with perivascular neutrophilic infiltrates but without evidence for leukocytoclastic vasculitis. Neutrophils can migrate through the epidermis and create subcorneal pustules and spongiosis of the epidermis. In edematous lesions, reticular degeneration and vesiculation may occur. Typical clinical features are fever (40%-80%), leukocytosis, and red tender papules, which enlarge to plaques that usually occur on the face, neck, upper trunk, and limbs, but often spare the mucosa. With severe dermal edema, true pustulation and blistering can occur. Diagnostic criteria were described in 2002, and both major criteria and 2 of 4 minor criteria must be met to confirm the diagnosis (Table 1).[9]

No controlled trials have been performed to evaluate and direct current treatment of Sweet syndrome. The standard therapy is short tapered administration of prednisone. A standard recommended steroid taper is 1 week of 40 mg per day of oral prednisone, followed by 30 mg daily for 1 week, then 20 mg daily for week 3, and finally 1 to 2 weeks of 10 mg/day. Recurrence occurs in 20%-30% of patients treated with steroids, typically toward the end of the taper. Alternatives for relapsing symptoms include nonsteroidal antiinflammatory drugs (ibuprofen 400 mg every 8 hours or indomethacin 150 m daily for 1 week then 100 mg daily for 2 weeks), dapsone, potassium iodide, colchicines, doxycycline, and clofazimine.[10,11]

Our patient had recurrent episodes of abrupt onset of red, swollen areas on her extremities, which developed small vesicles and eventually large bullae. Her underlying CLL and concurrent treatment with G-CSF, along with the biopsy showing dense perivascular and interstitial infiltrate of neutrophils, confirmed the diagnosis of Sweet syndrome. The patient's reluctance to consent for biopsy and the appearance of blisters, a rare manifestation of Sweet syndrome, instead of discrete plaques and nodules, made the diagnosis elusive and led to treatment with prolonged courses of antibiotics and topical treatment. An oral prednisone taper (as above) produced improvement, with relapse occurring at the end of the steroid taper, but her symptoms rapidly resolved with ibuprofen 400 mg 3 times a day.

Table 1. Diagnostic Criteria of Sweet Syndrome

Major criteria
Abrupt onset of erythematous plaques and nodules
Dense neutrophilic infiltrate on biopsy
Minor criteria
Fever with temperature >38(C
Association with an underlying hematological malignancy, inflam-matory disease, or pregnancy, or preceded by an upper-respiratory or gastrointestinal tract infection
Response to treatment with systemic corticosteroids
Abnormal laboratory values at presentation (3 of 4):
1. Erythrocyte sedimentation rate >20 mm/h
2. Positive C-reactive protein
3. Leukocyte count >10 x 103/mL;
4. Neutrophils >70%

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Late Outcome of Extensive Drug-Eluting Stenting ("Full Metal Jacket") for Spontaneous Coronary Artery Dissection of the Left Anterior Descending Artery

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Spontaneous coronary artery dissection (SCAD), defined as a coronary artery dissection in the absence of an aortic dissection or trauma from coronary angiography or intervention, was originally described in a 42-year old woman in 1931.[1] SCAD is rare and may present as a chest pain syndrome, acute coronary syndrome, ST-segment elevation acute myocardial infarction, or sudden cardiac death. Although the optimal treatment of SCAD is unclear, successful strategies have included conservative medical therapy,[2-4] surgical revascularization,[5] and coronary artery stenting.[6-8] Data are scarce regarding the long-term outcome of stenting for SCAD. When a percutaneous approach is taken, adequate treatment may require extensive coronary artery stenting to ensure an acceptable angiographic outcome. In this report, we present the case of a spontaneous coronary dissection involving the left anterior descending coronary artery (LAD) treated successfully with multiple drug-eluting stents, with follow-up angiography performed 18 months later.

CASE REPORT

A 44-year-old African-American woman with no prior cardiovascular diagnosis presented to a referral hospital with the acute onset of chest discomfort, nausea, diaphoresis, and left arm pain that occurred while she was at rest watching television. The initial electrocardiogram showed anterior ST-segment elevation. Her chest pain resolved after administration of sublingual nitroglycerin, intravenous metoprolol, aspirin, intravenous heparin, and oxygen. Her electrocardiogram returned to normal. Initial troponin I results were negative for myonecrosis (0.02 ng/dL), but concentrations subsequently increased to 3.48 ng/dL at 4 hours and 15.5 ng/dL at 6 hours. The patient was transferred to the University of Virginia Health System for further management and was pain free on arrival.

The patient's medical history was significant for a panic disorder, 2 previous full-term pregnancies, and bilateral tubal ligation. She had not smoked for 7 years (4 pack-year history), denied a history of alcohol or illicit substance use, and had no family history of premature coronary disease. She was not prescribed any regular medications and only occasionally used over-the-counter analgesics for headaches. She denied any symptoms or signs of connective tissue disorders. On physical examination, she appeared comfortable, with a heart rate of 72 beats/min and blood pressure of 98/60 mm Hg. The remainder of her exam was normal, with no murmurs or rubs on cardiac auscultation, and her lungs were clear to auscultation.

The patient developed recurrent chest discomfort and ST-segment elevation the following day (Figure 1) and was taken emergently to the catheterization lab for coronary angiography. A

Figure 1. Electrocardiogram with Recurrent Chest Pain Episode

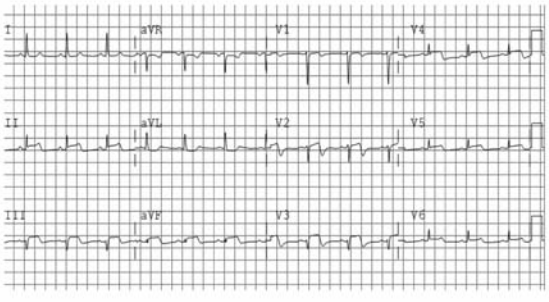

Figure 1. Electrocardiogram shows anterior, lateral, and inferior ST-segment elevation suggestive of an extensive, acute anterior myocardial infarction.

severe stenosis of the middistal segment of the LAD was apparent as well as a prominent distal dissection flap with limited flow (Figure 2). There was no evidence of coronary atherosclerosis in the right or circumflex coronary arteries. Left ventriculography confirmed an ejection fraction of 40% and a large anterior wall motion abnormality. A heparin bolus of 3500 units was administered intravenously, followed by eptifibatide (double bolus plus infusion). A Pilot 50 0.014-in floppy guidewire (Guidant, Santa Clara, CA, USA) was passed to the distal portion of the artery. A

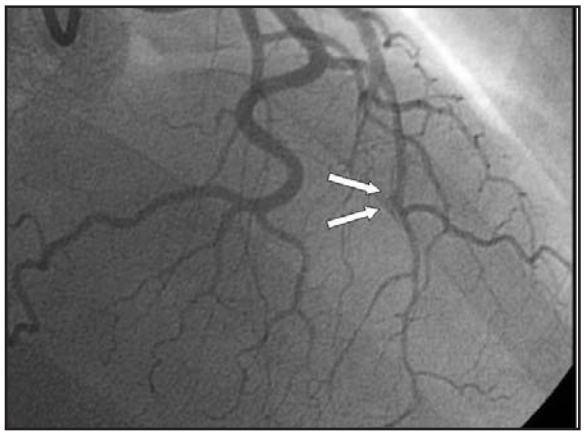

Figure 2. Right anterior oblique projection of the left coronary artery demonstrating a double lumen (arrows) consistent with coronary dissection. There was diminished flow distally.

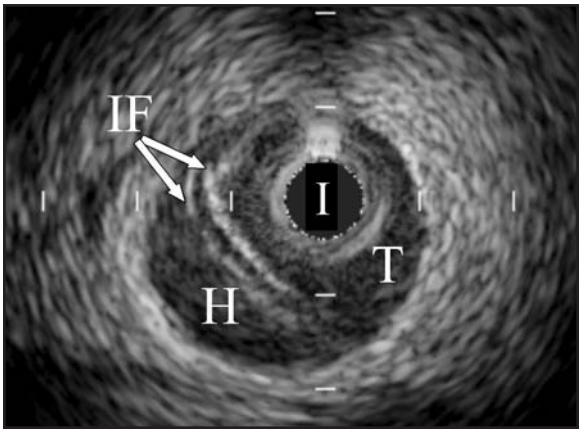

Figure 3. Intravascular ultrasound of the mid segment of the left anterior descending artery demonstrates a coronary dissection with intimal flaps (IF), an intramural hematoma in the false lumen (H), and a diminished true lumen (T).

Voyager™ Rx 2.0 x 15 mm balloon (Abbott Laboratories, Abbott Park, IL, USA) was used for balloon angioplasty and was inflated 3 times at 6 atm. Intracoronary nitroglycerin (200 µg) was administered prior to angiography in an effort to reduce coronary vasospasm. There was only limited improvement in the stenosis, but flow appeared to improve, and the chest pain and electrocardiogram changes resolved. Due to the complexity of the dissection and the concern about the extent of stenting necessary to correct the injury, a conservative treatment strategy was used, with aspirin, beta blocker, and an angiotensin-converting enzyme inhibitor. No further antithrombotic agents were used because of the risk of extending the dissection.

Two days later, the patient's chest pain and anterior ST-segment elevation recurred, and she was taken emergently back to the catheterization lab. She was immediately given a heparin bolus and infusion as well as a nitroglycerin infusion. Angiography revealed 60% stenosis of the previously normal proximal LAD, with occlusion of the mid-LAD. Intravascular ultrasound (Atlantis 40 MHz, Boston Scientific/Scimed, Maple Grove, MN, USA) revealed no significant coronary atherosclerosis, but there was a prominent dissection of the mid-LAD (Figure 3) with an intramural hematoma causing luminal compromise in the proximal segment to the origin of the vessel. After placement of an Asahi Prowater 0.014-in guidewire (Abbott Laboratories), 2 balloon dilatations were performed using a Voyager™ Rx 2.5 x 15 mm balloon at 6 atm for a total of 90 s, restoring patency to the artery. Four sirolimus-eluting stents (Cypher® , Cordis Corporation, Miami Lakes, FL, USA) were deployed in succession, totaling 117 mm (from proximal to distal: 3.5 mm x 28 mm to 16 atm, 3.0 mm x 33 mm to 16 atm, 2.5 mm x 28 mm to 14 atm, and 2.5 mm x 28 mm to 12 atm). A total of 800 (g of intracoronary adenosine was used, and thrombolysis in myocardial infarction 3 flow was achieved. The patient was treated with a 600-mg loading dose of clopidogrel. The remainder of her hospitalization was uncomplicated, with no further chest pain. She was discharged and prescribed aspirin plus clopidogrel 75mg daily for an indefinite period.

Eighteen months later, the patient presented with a chest pain syndrome occurring at rest but different in quality than her initial presentation. Clopidogrel had been discontinued several months earlier by her primary care physician for unclear reasons. Admission electrocardiogram showed anterior T-wave abnormalities unchanged from prior electrocardiograms, and serum biomarkers were negative for myonecrosis. Repeat coronary angiography showed angiographically normal right and circumflex coronary arteries and a widely patent LAD with no evidence of restenosis (Figure 4). The distal LAD had the appearance of a double lumen suggestive of a healed dissection. The pain was considered noncardiac, and the patient was discharged and treated with aspirin and clopidogrel.

DISCUSSION

SCAD is a rarely observed cause of acute myocardial infarction. The incidence of SCAD in the general population is thought to be around 0.1% based on clinical series, but the diagnosis is made only at autopsy in up to 75% of SCAD cases.[2,5,9] SCAD cases can be divided into 3 major categories: peripartum, atherosclerotic, and idiopathic. Most reported cases have occurred in young women who were either pregnant or in the peripartum period,[5] but several other conditions have been associated with SCAD including intense physical exertion,[10] oral contraceptive medications,[11] fibromuscular dysplasia,[12] and rheumatologic or collagen vascular diseases.[13] Women are affected twice as often as men, with the majority of cases in women occurring in the peripartum period.[2,5] The left coronary artery is thought to be the most susceptible to spontaneous dissection, with the LAD involved in up to 66% of women.[14] Up to 50% of all spontaneous dissections in men involve the right coronary artery.[14] Multivessel SCAD has also been reported, with a higher incidence in females with connective tissue diseases.[14,15]

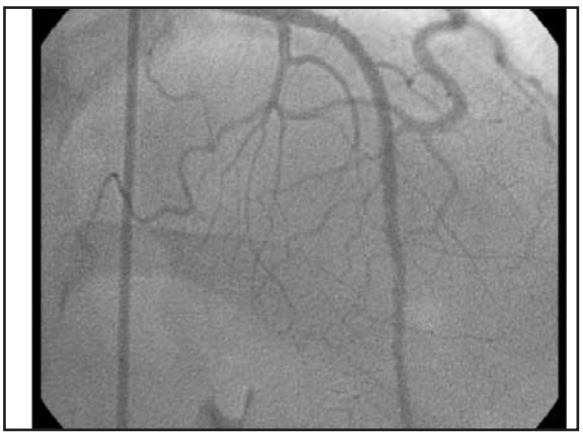

Figure 4. Angiogram in the right anterior oblique projection showing wide patency of the left anterior descending artery 18-months after surgery.

The pathophysiology of SCAD is unclear but generally occurs in the outer third of the artery's media or between the media and adventitia. The 2 most commonly cited causes of SCAD are intimal tear with medial dissection and intramural hemorrhage into the media without a tear. Intramural hemorrhage is thought to be the predominant pathological mechanism.[16]

SCAD should be suspected in young patients with few coronary risk factors and symptoms suggestive of stable or unstable angina, myocardial infarction, arrhythmias, or sudden cardiac death. Coronary angiography has traditionally served as the gold standard diagnostic tool for suspected SCAD. In cases in which the intimal flap is absent or unrecognizable, intravascular ultrasound can distinguish spontaneous dissection from atherosclerosis.[16] Computed tomographic angiography and cardiac magnetic resonance imaging may develop into helpful diagnostic tools for SCAD. The prognosis of SCAD depends on the etiology and the possibility for treatment. In one case series in which the patients were predominantly women, patients who survived the initial event had a long-term survival (mean follow-up of 38 months) of 82%.[9]

In the absence of acute ischemia from threatened or abrupt vessel closure, medical therapy may be successful with healing of the dissection over time. Unstable patients, however, may require a more aggressive approach with either surgery or percutaneous treatment. Surgical management, usually consisting of bypass surgery, may be difficult or impossible in the presence of an extensive dissection similar to that observed in this case. Percutaneous treatment of SCAD with

coronary stents is an attractive strategy but may be challenging. Defining the extent of the dissection, negotiating a guidewire through the serpiginous path of the true lumen, and maintaining side-branch patency can prove very difficult. Compromise of the lumen may be due to the dissection flap as well as an associated intramural hematoma. Importantly, as observed in this case, multiple stents over a long arterial segment are often required to adequately repair the dissection and restore luminal patency. The need for stents is a major concern to the clinician, because bare-metal stents used in patients with coronary artery disease without dissection, long lesion length, and multiple overlapping stents, have been associated with unfavorable outcomes, including stent thrombosis and diffuse in-stent restenosis.[17,18]

In-stent restenosis is less likely with drug-eluting stents, but the pivotal studies demonstrating their efficacy compared to bare-metal stents did not involve patients with SCAD or who required stenting of an extensive length of artery.[19-21] Several studies describe the use of multiple drug-eluting stents to treat diffuse disease and other processes in single and multiple coronary arteries,[22-25] but we are not aware of any reports describing the outcome of extensive stenting for SCAD with drug-eluting stents.

Extensive coronary artery stenting, or the "full metal jacket" approach, has been described as a treatment for diffuse coronary atherosclerosis of single and multiple coronary arteries (Table 1). In aggregate, these studies show rates of restenosis of 3.8% to 15%.[22-24] Although these rates are higher than those typically attributed to drug-eluting stents, they appear much lower than the historical rates of long stent length associated with bare-metal stents.[17,26]

In summary, we report the acute and 18-month angiographic follow-up of an unusual case of SCAD successfully treated with multiple drug-eluting stents in a full metal jacket approach.

Table 1. Studies Using Drug-Eluting Stents in the "Full Metal Jacket" Approach*

Reference	No. of Patients	No. of Stents†	Stent Length, mm†	Angiographic Success	Follow-up, months	TVR	MACE
Tsagalou et al[22]	66	2.8 ± 0.7	80 ±20	95%	6	15%	18%
Mishra et al[23]	99	2.6 ± 0.9	63 ± 13	100%	6	4.5%	5.7%
Aoki et al[24]	122	3.3 ± 1.1	79 (Median)	NR	12	7.5%	18%
Lee et al[25]	347	2.5 ± 0.7	72 ± 14	97.7%	17 ± 7	3.8%	8.7%

*TVR indicates target vessel revascularization; MACE, major adverse cardiac events, NR, not reported.
†Results are presented as mean ± SD unless otherwise indicated.

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Yokenella regensburgei *as a Cause of Sepsis in an Immunocompromised Patient*

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Yokenella regensburgei, a member of the *Enterobacteraceae* family, is rarely isolated from humans and its clinical importance is not yet defined. This organism was originally distinguished from its closest enteric relative, *Hafnia alvei*, in 1z985 by the National Institute of Health in Japan, who proposed the name *Y. regensburgei* after the Japanese abbreviation "Yoken" for the NIH in Tokyo.[1] Near-contemporaneous identification of the organism by the US Centers for Disease Control and Prevention under the proposed name Koserella trabulsii, in recognition of the American bacteriologist Stuart A. Koser,[2] led to the dual use of the 2 names until 1991, when the US Centers for Disease Control and Prevention acknowledged that *Y. regensburgei* had priority on the basis of earlier publication.[3] Of the original 23 isolates of the organism, 16 were from human sources including wounds, stool, sputum, an abscess, and a knee-joint fluid specimen, but no information was available as to the clinical significance of the organism's recovery from human sources.[1,2] In 1994, Abbot and Janada reported the isolation of *Y. regensburgei* from the synovial fluid of a patient with a suspected joint infection and from the blood of a patient with transient bacteremia but no overt signs of septicemia.[4] We describe a case of *Y. regensburgei* as a cause of sepsis.

CASE PRESENTATION

A 57-year-old man with a history of diabetes mellitus type I complicated by renal failure and 2 heterotopic renal transplants, most recently 5 years ago, presented to the emergency department with a 3-day history of back pain, nausea, vomiting, low-grade fevers, and night sweats. The patient's medical history was also significant for *Streptococcus mutans* bacteremia and a previous urinary tract infection with *Enterococcus faecalis.* The patient's outpatient medications included mycophenolate mofetil, sirolimus, prednisone 5 mg, metoprolol, and furosemide. On physical examination, he was afebrile, with a pulse of 75 beats/min, blood pressure of 139/69 mm Hg, respiratory rate of 24, and O_2 saturation of 99% on room air. The remainder of the physical examination was unremarkable, and laboratory results were notable for a white blood cell (WBC) count of 11,900 cells/mm^3, with 17% bands; a creatinine level of 3.0 mg/dL (baseline 2.5 mg/dL); normal liver function tests; and urinalysis with 3+ protein, 3+ glucose, large ketones, large blood, negative nitrite, and trace leukocyte esterase. Microscopic examination demonstrated 16 red blood cells, 35 WBCs, 6 casts, few bacteria, and 4 epithelial cells. Chest x-ray was notable only for a small linear opacity, consistent with atelectasis.

The patient was admitted to the general medicine service, where blood and urine specimens were collected for culture, his immunosuppressant regimen was continued, and he was started on piperacillin/tazobactam for empiric treatment of a suspected complicated urinary tract infection due to immunosuppression. On hospital day 2, the patient developed a fever of 39.8˚C with a WBC count of 12,000 cells/mm^3. A renal ultrasound demonstrated a normal left renal transplant with no evidence of hydronephrosis or perinephric fluid, atrophic native kidneys, and right renal transplant unchanged from prior examinations. A repeat chest x-ray did not reveal a focal infiltrate. The patient's renal function continued to decline, and urine electrolytes were obtained to evaluate the etiology of his renal failure. Because the patient's condition met sepsis criteria and his urine electrolytes were consistent with prerenal physiology, he was aggressively volume resuscitated. On hospital day 4, urine and blood cultures were positive for gram-negative rods identified by the VITEK system (Ilex Medical) as *Y.*

regensburgei. Based on in vitro susceptibilities for *Y. regensburgei* reported in the literature and the patient's overall clinical improvement, piperacillin/tazobactam was continued. On day 5, disk diffusion studies demonstrated susceptibility of the organism to ciprofloxacin, and the patient was switched to oral ciprofloxacin 250 mg every 12 hours for 14 days. On hospital day 6, the patient had been afebrile for 72 hours, his WBC count and renal function had improved, and he was discharged. He has remained well during a 3-month period of follow-up.

DISCUSSION

The role of *Y. regensburgei* as a pathogen in humans is poorly defined. Reported studies have isolated *Y. regensburgei* from wounds and septic joints, and in one reported case *Y. regensburgei* caused transient bacteremia. To our knowledge, however, this case is the first reported for which *Y. regensburgei* was a cause of sepsis. The clinical issues raised by this case include the delineation of risk factors that may contribute to infection with this uncommon organism and the question of appropriate antibiotic therapy once the pathogen is identified.

Of the reports of extraintestinal isolations of *Y. regensburgei* from humans, only 2 include significant clinical data. In both of these cases the patients were immunocompromised from alcohol abuse and suspected liver disease.[4] That the recovery of *Y. regensburgei* in the case we describe occurred in a patient with altered underlying anatomy who was receiving immunosuppressive medications supports the potential characterization of *Y. regensburgei* as an opportunistic pathogen. Whether the bacteria had been previously a part of the patient's normal gastrointestinal flora or was acquired from an environmental source at the time of infection remains unclear. Because of the patient's history of previous infections with commensal flora, there was initial concern that the pathogen may have been introduced into the bloodstream as the result of an underlying gastrointestinal malignancy. This scenario was considered unlikely, however, because the patient had recently had colonoscopy with normal findings. The role of the patient's native kidneys and right renal transplant as possible sources of infection was also evaluated but was not confirmed by renal ultrasound, for which findings were unremarkable. The fact that cultures from both blood and urine were positive for *Y. regensburgei* indicated that the urinary tract and possibly the left renal transplant were the most likely source of infection.

Despite the rarity of this organism, the antimicrobial susceptibility patterns of *Y. regensburgei* have been relatively well characterized. The 12 isolates originally described by Hickman-Brenner et al[2] and the 10 strains tested by Stock et al[5] demonstrated susceptibility to a wide range of *B*-lactam and non-*B*-lactam antibiotics but diminished susceptibility to ampicillin and amoxicillin. The results of disk diffusion analysis of the *Y. regensburgei* isolate in this case confirm both the broad antimicrobial susceptibility and the relative resistance to aminopenicillins (Table 1). This reduced susceptibility to aminopenicillins is consistent with the demonstration in *Yokenella* of homology of the *ampC* gene responsible for the strongly inducible *B*-lactamases found in many members of the *Enterobacteriaceae* family. The *ampC* gene encodes a *B*-lactamase that has been show in other species to provide resistance to ampicillin and amoxicillin, reduce the efficacy of

Table 1. Comparison of Antimicrobial Susceptibilities of *Yokenella regensburgei**

	Hickman-Brenner et al[2] 12 Strains	Stock et al[5] 10 strains	Current case 1 strain
Penicillin G	R	R	
Ampicillin	I	R	I
Piperacillin-tazobactam		S	
Cefazolin		R	S
Cefuroxime		S	S
Cefotaxime		S	S
Cefepime		S	S
Imipenem		S	S
Aztreonam		S	S
Ciprofloxacin		S	S
TMP/SMZ		S	S
Gentamicin	S	S	S
Streptomycin	I	S	
Kanamycin	S	S	
Tetracycline	I	S	S
Chloramphenicol	S	S	
Nitrofurantoin		S	S

*S indicates susceptible;
I, intermediate susceptibility; R, resistant.

clavulanic acid, and cause resistance to cephalosporins.[5] On exposure to a *B*-lactam antibiotic, *ampC* expression is up-regulated, increasing *B*-lactamase production and providing resistance to antibiotics to which the organism was originally susceptible.

The decision in this case to continue the piperacillin-tazobactam while awaiting susceptibility data was based on the patient's clinical improvement and the in vitro susceptibility of *Yokenella* strains reported in previously published studies. No information is currently available regarding recommended treatment duration, necessary follow-up, need to rule out endocarditis, or initial in vivo antibiotic choice. The demonstration of inducible *B*-lactamase activity in *Yokenella* species in vivo suggests a treatment strategy of avoiding aminopenicillins and choosing a non-*B*-lactam antibiotic as initial therapy. Because the patient in this case improved rapidly on a broad-spectrum *B*-lactam, however, the clinical relevance of the *ampC* expression in *Y. regensburgei* remains unclear.

CONCLUSION

Y. regensburgei remains an infrequently encountered organism whose clinical significance is largely undefined. This case is significant because it establishes *Y. regensburgei* as a potential cause of sepsis and supports the characterization of the organism as an opportunistic pathogen. The susceptibilities of the isolate in this case continue to suggest avoidance of treatment with aminopenicillins, and the patient's response to piperacillin/tazobactam provides an example of successful treatment with a *B*-lactam antibiotic. Continued research is needed to determine the significance of the *ampC* gene in initial antimicrobial choice, to further describe the role of the *Y. regensburgei* as a human pathogen, and to establish an approach to treatment of the rare patient infected with *Y. regensburgei.*

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Takayasu Arteritis in a 42-Year-Old Woman with Subclavian Steal Syndrome and Mesenteric Ischemia

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Takayasu arteritis (TA) is a rare, chronic inflammatory disease of the aorta and its major branches resulting in progressive stenosis, occlusion, and aneurysm formation. The diagnostic classification of TA, published by the America College of Rheumatology, lists 6 criteria; at least 3 must be met to establish a diagnosis of TA.[1] The manifestations of disease can be variable with regard to age and clinical symptoms, however, and thus diagnosis can be delayed months to years after symptoms first develop. We describe a 42-year-old woman in whom TA was diagnosed after more than 2 decades of disease.

CASE DESCRIPTION

The patient was a 42 year-old white woman who had suffered several days of dizziness and near syncope associated with assuming an upright position. She reported a 6-month history of postprandial nausea, abdominal pain, and a 20-lb weight loss. The abdominal complaints had prompted a cholecystectomy a few months earlier, but her symptoms persisted. The patient also reported that her left arm had been considerably smaller than her right arm for more than 20 years, and she regularly experienced left arm numbness and weakness with minimal exertion. For the last several years blood pressure measurements could not be obtained from the left arm. Prior to admission, computed tomographic angiography of the abdomen revealed narrowing of the celiac and superior mesenteric arteries, and she was admitted for further evaluation.

The patient's medical history was notable for hypertension, type II diabetes mellitus, hypothyroidism, and hyperlipidemia. She was a nonsmoker. Family history was negative for vasculitis.

On physical examination, the patient was alert and in no apparent distress. Her blood pressure was 120/38 mm Hg in the right arm and 58/33 mm Hg in the left, obtained after 5 attempts. Cardiovascular exam revealed bilateral carotids bruits, a III/VI systolic crescendo murmur at the right second intercostal space, bilateral subclavian bruits, a midabdominal bruit, nonpalpable left brachial and radial pulses, and 2+ pulses in the right upper extremity and bilateral lower extremities. The entire left upper extremity was markedly atrophic compared with the right (Figure 1). The remaining physical exam findings were normal.

Laboratory test results were notable for a hemotocrit of 33.3%, an erythrocyte sedimentation rate of 40 mm/h, and a C-reactive protein of 2.6 mg/dL. Serum electrolytes, renal function test results, C3, C4, and CH50 were normal. Tests for rheumatoid factor, antinuclear

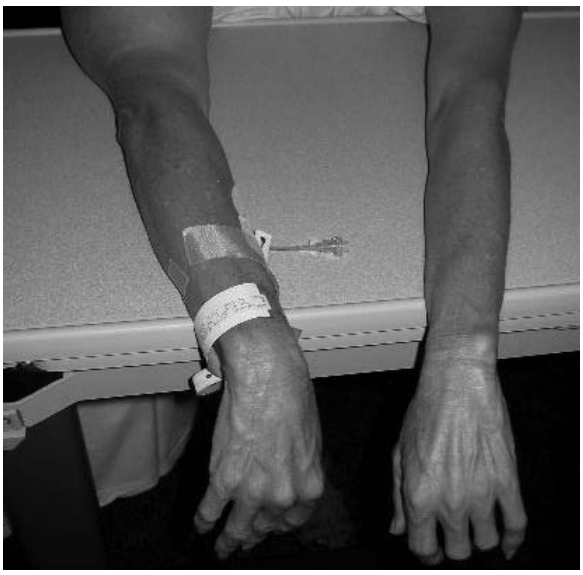

Figure 1. Photograph demonstrating marked atrophy of the patient's proximal left arm.

antibody, anti-double-stranded DNA antibody, and antineutrophil cytoplasmic antibody were negative.

Imaging studies included computed tomographic angiography of the abdomen and pelvis and conventional contrast arteriography of the aorta and large vessels (Figure 2). Collectively these images showed long segmental occlusion of the left subclavian artery at its origin, with reconstitution via retrograde blood flow from the left vertebral artery, diffuse narrowing of the common carotid arteries bilaterally, mild proximal and moderate distal narrowing of the right subclavian artery, diffuse narrowing of the infrarenal abdominal aorta, 50% stenosis of the celiac artery, and 80% stenosis of the superior mesenteric artery. Positron emission tomography (PET) failed to demonstrate any abnormal uptake. Echocardiography demonstrated mild mitral, mild aortic, and trace tricuspid regurgitation and a left ventricular ejection fraction of 60%-65%.

The clinical, laboratory, and radiographic findings indicated the presence of mesenteric ischemia, subclavian steal syndrome, and left upper extremity claudication due to advanced TA. With the confirmation of a consulting rheumatologist, a PET scan was performed to evaluate for active disease, and the patient started treatment with prednisone 60 mg/day. In addition, outpatient revascularization was planned on the basis of a vascular surgery consultation. The patient was discharged and approximately 1 month later underwent superior mesenteric and celiac artery stenting performed by the interventional radiology team. With this treatment the patient's intestinal angina essentially resolved and she regained some weight. She continued to have left extremity claudication, however, and underwent surgical exploration for a potential bypass. Unfortunately the patient had an atretic subclavian artery that was inadequate for a procedure. Therefore no surgical intervention was undertaken.

DISCUSSION

TA is a rare idiopathic chronic inflammatory disease involving the large vessels, including the aortic arch and its branches. Although first described by Yamamoto in 1830,[2] the disease was formally termed TA in 1942[3] in recognition of the Japanese ophthalmologist who in 1905 described a case of a young woman with a retinal arteriovenous fistula and absence of a radial pulse.[2] TA has also been called pulseless disease, occlusive thromboaortopathy, aortoarteritis, and Martorell syndrome.[2]

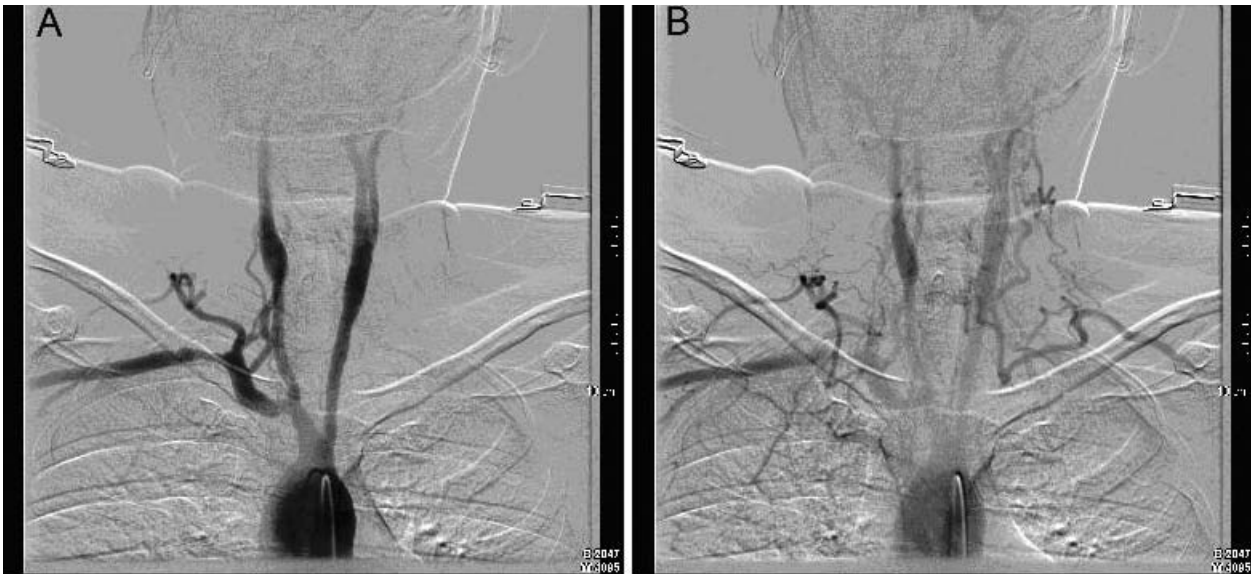

Figure 2. Arteriogram of aortic arch. A. Complete occlusion of the left subclavian artery (a), narrowing of the common carotid arteries (b), and narrowing of the right subclavian artery (c). B. Retrograde blood flow from the left vertebral artery to a branch of the thyrocervical trunk (a).

The prototypical patient with TA is an Asian woman in her second or third decade of life, although the disease occurs in men and women and in multiple racial and ethnic groups worldwide.[2] The incidence of TA is highest in Japan, Southeast Asia, India, and Mexico. In North America, the annual incidence is estimated to be 2.6 per million people.[2] Interestingly, the predominance of TA in females is geographically dependent, with female:male ratios ranging from 29:1 in the United States and 9:1 in Japan to 1.2:1 in Israel.[4]

Classically, patients manifest disease in 3 phases. The acute phase is characterized by vague symptoms, including fever, arthralgias, headaches, malaise, or weight loss; some patients may be completely asymptomatic. Because of the protean and nonspecific nature of these symptoms, delays in diagnosis are common. A cohort study of 107 patients found that the time from onset of symptoms to diagnosis ranged from 2 to 11 years.[2]

The acute phase of TA is followed by the vascular inflammatory phase, which is characterized by months to years of inflammation of the aorta and its major branches, including the subclavian, common carotid, coronary, pulmonary, and renal arteries. Chronic, progressive large-vessel panarteritis progresses until the disease reaches the occlusive phase, in which stenosis, vascular occlusion, and aneurysm formation predominate. Patients in this phase can present with absent or diminished peripheral pulses, often associated with limb claudication and/or marked blood pressure differences. Vascular bruits are often heard, particularly over the subclavian, carotid, and abdominal vessels. Late manifestations can also include hypertension, often as a result of renal artery stenosis, Takayasu retinopathy, aortic regurgitation, congestive heart failure, myocardial ischemia, and pulmonary artery involvement.[2]

The pathophysiology of TA remains unclear. Multiple studies have failed to demonstrate a link between TA and autoimmune processes, infectious etiologies, or genetic abnormalities. At the microscopic level, chronic inflammation of the vessels leads to thickening and fibrosis of all 3 layers of the vessel wall. In the acute phase, there is inflammation of the adventitial vasa vasorum. In the adventitia, the inflammatory infiltrate is composed mainly of T cells and dendritic cells, whereas in the media the infiltrate is composed of mainly lymphocytes and occasional giant cells with neovascularization. Mucopolysaccharides, smooth muscle cells, and fibroblasts invade the intima, leading to excessive ground substance and thickening. In the chronic phase, fibrosis predominates, with breakdown of the collagen and elastin layers similar to findings seen in giant-cell arteritis.

Laboratory evaluation often reveals an elevated erythrocyte sedimentation rate (usually >20 mm/h) and increased C-reactive protein concentrations, but these inflammatory markers correlate poorly with disease activity. Other serological tests, including tissue factor, von Willebrand factor, soluble adhesion molecules (sICAM-1, sVCAM-1), and soluble E-selectin have been studied, but none have been shown to reliably distinguish TA patients from healthy volunteers.[3] Antiendothelial antibodies may be present at high titers, but this finding is nonspecific and may occur in other vascular inflammatory conditions. A recent small study showed that matrix metalloproteinase (MMP)-2 was elevated in TA patients, and MMP-3 and MMP-9 were elevated only in patients with active disease. Moreover, MMP-3 and MMP-9 levels fell with corticosteroid treatment.[2]

The most widely used diagnostic criteria for TA are the 6 clinical and radiographical features outlined by the American College of Rheumatology in 1990 (Table 1).[1] At least 3 criteria must be met to confirm the diagnosis, yielding a sensitivity of 90.5% and specificity of 97.8%.[1] These criteria primarily reflect clinical findings or outcomes that arise from hemodynamically-compromising stenoses. Therefore, they are not useful in the diagnosis of patients with early disease before significant occlusions develop.[5] Unlike giant-cell arteritis diagnosis, for which biopsies are integral, TA diagnosis seldom involves the use of biopsies.

Angiography has been the gold standard for diagnosis of TA for many years because it provides direct visualization of the arterial lumen,

including localized stenoses and luminal irregularities. The presence of "skip" lesions, in which segments of arterial narrowing are flanked by areas of normal vessel anatomy, is a characteristic finding of TA.[2] Angiography provides visualization only of the lumen, however, and thus changes within the arterial wall may go undetected, especially in patients in the early acute phase of disease. Magnetic resonance angiography (MRA) is gaining popularity for the evaluation of suspected TA, with recent studies reporting a diagnostic accuracy equivalent to angiography.[2,6] Furthermore, MRA may allow the detection of more subtle changes within the vessel wall, including wall thickening and edema.[6] Another radiological technology that may be useful for TA is PET imaging, which uses ^{18}F-flurodeoxyglucose to identify areas of increased metabolic activity. Commonly used in clinical oncology to identify metastases, PET can also identify areas of inflammation and thus may be useful for evaluating affected large-vessel walls in TA.[5] PET can also detect prestenotic disease and may be useful in the assessment of response to therapy. Currently, however, no large studies are validating the use of PET in TA disease management, and further evaluation is necessary.

Medical management of TA is primarily based on immunosuppression with corticosteroids or other immunomodulators. Few controlled trials have been performed, but it has been reported that approximately half of patients treated with corticosteroids will have a response of some kind.[2] Corticosteroid therapy typically consists of prednisone at 1 mg/kg per day for 1 month, a dosage that is slowly tapered after resolution of symptoms and normalization of acute-phase reactants.[4] Unfortunately, disease relapses in approximately 50% of patients during tapering.7 In patients who suffer relapse, are unresponsive to corticosteroids, or have intolerable side effects, other immunosuppressive drugs are often used. Methotrexate is the most widely used agent, in part because of practitioner familiarity and evidence from several small open-label studies. Methotrexate may induce remission in early disease and improve remission rates in steroid-resistant TA.[2] No data, however, confirm that steroids or any other immunosuppressive agents alter the course of disease.

Only a minority of TA patients require revascularization with either surgery or percutaneous transluminal angioplasty.[8] Because all 3 vessel layers are often involved in TA, the surgical procedure of choice is bypass rather than endarterectomy. Surgery should be considered for stenotic lesions or aneurysmal dilatations that

Table 1. 1990 American College of Rheumatology Criteria for Classification of Takayasu Arteritis*

Criteria	Definition
Age at disease onset <40 years	Development of symptoms or findings related to Takayasu arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of 1 or more extremities while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mm Hg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia or similar causes; changes usually focal or segmental

*For purposes of classification, a patient is considered to have Takayasu arteritis if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%. Adapted from (1).

lead to hemodynamic compromise. Other indications for surgery include cerebrovascular disease due to severe carotid disease, severe aortic regurgitation, severe coarctation of the aorta, hypertension resulting from renovascular involvement, coronary artery disease, limb claudication, and progressive aneurysm enlargement with risk of rupture or dissection. To avoid complications such as anastomotic aneurysms and strictures, surgery is generally recommended after remission is achieved with immunosuppressive therapy. With appropriate patient selection and an experienced vascular surgery team, the results of surgical bypass procedures are generally very good, with low morbidity and survival rates reported to be 80%-97% at 10 years.[8,9]

SUMMARY

TA is a rare, chronic inflammatory disease of the aorta and large vessels, with unclear etiology. Diagnosis of TA is often delayed, as in this case patient who had TA for more than 20 years prior to diagnosis. Although initial symptoms can be vague, TA should be suspected in patients with unilateral upper extremity claudication, pulselessness, or a marked blood pressure discrepancy. Although the American College of Rheumatology criteria for the classification of TA are useful for stenotic disease, most patients in the early phase of illness will not fulfill diagnostic criteria. Angiography remains the gold standard for radiological diagnosis but cannot reveal disease activity. Advances in imaging technology, including MRA and PET, hold promise for both the diagnosis and management of TA but require further study. Current treatment consists of steroids, immunosuppressive agents, and in select patients, revascularization.

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Thromboangiitis Obliterans with Cerebrovascular Involvement

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We present a case of cerebral infarction occurring in a young man whose only identifiable risk factor was a history of thromboangiitis obliterans with continued smoking. We also discuss cerebral involvement in thromboangiitis obliterans, which is predominantly a disease of the distal extremities but may affect multiple organ systems.

CASE REPORT

A 40-year-old left-handed white man was transported by rescue squad to our university hospital after awakening in the morning with right-arm weakness and confusion. The patient had a history of hepatitis C infection, cluster headaches, and thromboangiitis obliterans (Buerger disease), which was diagnosed 5 years prior to the current presentation. After the diagnosis of thromboangiitis obliterans, the patient continued to smoke 1 pack per day and suffered progressive claudication leading to toe amputations and sequential below-knee amputations. The patient had no known history of cerebrovascular disease, coronary artery disease, hypertension, or diabetes. He also had demonstrated no systemic symptoms of hepatitis C or evidence of cryoglobulinemia.

The patient reported that on the night prior to admission he had consumed 2 to 4 alcoholic beverages and 2 to 4 20-mg tablets of his scheduled methadone (prescribed for chronic pain control). When he awoke the morning of admission the patient had difficulty moving his right arm. He also reported confusion and feeling "not himself." He was found by rescue squad personnel to be awake, alert, and oriented, but with mental status somewhat altered from his baseline. There was no history of loss of consciousness. The patient reported subjective fevers on the day before admission but denied any symptoms of focal infection and otherwise was reportedly in his usual state of health. On arrival to the emergency department, the patient was found to be hypotensive (blood pressure 70/40 mm Hg). Hypotension responded well to fluid resuscitation without the need for vasoactive agents. Physical exam findings included right upper extremity monoplegia and hyperreflexia. Upper extremities were well perfused bilaterally. Other findings included rhabdomyolysis (creatinine kinase 5093 mU/mL) with leukocytosis and acute kidney injury. Noncontrasted computed tomography of the head showed a left frontoparietal infarction without evidence of hemorrhage. This infarction appeared acute in nature. The patient maintained adequate blood pressure after admission and his leukocytosis, acute kidney injury, and rhabdomyolysis quickly resolved. A transthoracic echocardiogram with agitated saline contrast demonstrated no source of embolus. Magnetic resonance imaging of the head showed multiple foci of restricted diffusion consistent with acute infarcts involving primarily the left frontal and parietal lobes but also involving both cerebral hemispheres, with additional punctate foci in both occipital lobes and cerebellum. These infarcts corresponded to a watershed territory. Magnetic resonance angiography showed no significant intra- or extracranial stenosis. Radiologic images did not show evidence of inflammatory or vasculitic involvement. Laboratory data are provided in Table 1. The patient was able to work with physical and occupational therapy and was discharged to a rehabilitation center approximately 1 week after admission.

DISCUSSION

Thromboangiitis obliterans is an inflammatory disease that affects mainly the small- to medium-sized veins and arteries of the extremities.[1,2] It

most commonly involves the distal vessels initially and moves proximally as the disease progresses. Early in the disease process, biopsy may demonstrate inflammatory thrombi of vessels. In chronic thromboangiitis obliterans, however, biopsy generally shows only organized thrombus and fibrosis.[3-5] This vasculopathy is most commonly seen in males around the age of 40 and is almost universally associated with a history of smoking.[6,7] Patients typically present with distal extremity claudication with ischemic ulceration, often in more than one limb.[8] With continued smoking, the disease process progresses proximally and often requires amputation, as in this case. Diagnosis is based largely on clinical presentation and exclusion of other disease processes (Table 2).[9]

Although thromboangiitis obliterans is a disease of the distal extremities, scattered case reports demonstrate involvement of multiple organ systems including bowel, myocardium, spleen, and cerebrum.[10-12] In 1939, Lindenberg and Spatz[13] described 2 types of cerebrovascular disease associated with thromboangiitis obliterans, type 1 affecting large vessels and type 2 affecting distal small vessels of the brain. Type 1 disease may predispose patients to ischemic stroke, and type 2 has been associated with vascular dementia.[14] Cerebral blood flow may be reduced in patients with thromboangiitis obliterans.[15] In our patient, imaging demonstrated watershed infarcts, and after ruling out other vasculitides or source of emboli, we concluded that his infarcts were secondary to cerebral involvement of his thromboangiitis obliterans without large-vessel involvement. Unfortunately, the patient was rehospitalized 6 months after discharge, with another ischemic stroke thought to be related to his thromboangiitis obliterans.

Table 1. Patient Laboratory Data

Routine Labs	
Total Cholesterol	106 mg/dL
Low-density lipoprotein	68 mg/dL
High-density lipoprotein	16 mg/dL
International normalized ratio	1.5
Partial thromboplastin time	54 s
Whit blood cell count	34,000/mm3
Hematocrit	43 g/dL
Platelets	331,000/mm3
Hypercoagulable workup	
Protein C	Normal
Protein S	Normal
Antithrombin III	Borderline low
Lupus anticoagulant	Normal
Anticardiolipin antibody	Normal
Factor II	Normal
Factor V Leiden	Normal
Homocysteine	Normal
Rheumatologic Workup	
Antinuclear antibody	Negative
Antineutrophilic cytoplasmic antibodies	Negative
Complement	Normal
Rheumatoid factor	Negative
Anticentromere antibody	Negative
Anti-SCL70	Negative
Cryoglobulin	Negative

CONCLUSION

Thromboangiitis obliterans generally affects the small vessels of distal extremities but can also act systemically, affecting other organ systems. It may predispose patients to stroke and should be considered a risk factor in young patients who otherwise demonstrate no evidence of autoimmune or hypercoagulable states. Patients with thromboangiitis obliterans should be aware that continued smoking may lead to cerebrovascular injury as well as extremity amputation.

Table 2. Diagnostic Criteria for Thromboangiitis Obliterans*

1. Age of onset <45 years
2. Current or recent tobacco use
3. Claudication or ulceration of distal extremities

* All of these criteria must be met to establish the diagnosis of thromboangiitis obliterans. Exclusion of diabetes, autoimmune disease, source of emboli, or hypercoagulable state should be sought to rule out other disease processes. Arteriographic images may demonstrate characteristic changes and can be helpful in ruling out other etiologies.

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Falsely Increased Cardiac Troponin Concentrations and Their Influence on Clinical Management of Chest Pain

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Cardiac troponin T and cardiac troponin I (cTnI), specific markers used in the diagnosis of acute myocardial injury and cardiac risk stratification, have become the preferred biomarkers in the diagnosis of myocardial infarction. Clinicians should be aware, however, that troponin values may be spuriously elevated. We report 3 closely-spaced cases of falsely increased troponin assay results in patients presenting to the emergency department.

CASE DESCRIPTIONS

A 43-year-old man presented to the University of Virginia (UVA) Emergency Department (ED) after suffering 3 episodes of substernal chest pain during the previous 2 days. The pain was sharp, radiated to his right jaw and right arm, and was associated with transient dyspnea. Each episode lasted for 10-15 min and occurred during rest. The patient had no associated diaphoresis, nausea, or vomiting. Risk factors included obesity and a history of smoking 1 pack per day for 25 years. One year ago, the patient underwent a sestamibi stress test because of exertional chest pain. The test showed an exaggerated increase in systolic blood pressure, supporting the diagnosis of myocardial hypertrophy, with a normal left ventricular ejection fraction and no focal perfusion defects. The only abnormal findings on physical exam were a blood pressure of 149/95, weight of 239 lb, and mild tenderness on palpation in the right upper quadrant. Electrocardiograms with and without pain showed no dynamic ST-T changes. Plain films of the chest were unrevealing, and a right upper quadrant ultrasound was within normal limits. Laboratory studies revealed a normal lipase, total cholesterol 243 mg/dL, triglycerides 540 mg/dL and high-density lipoprotein 20 mg/dL. The patient's cTnI was initially <0.02 ng/mL, below the level of detection. A result of 0.10 ng/mL on a subsequent sample prompted the patient's admission to the acute cardiology service (normal reference value for cTnI is <0.02 ng/mL). On the night after admission, the patient had 2 more episodes of atypical chest pain radiating to the right side. Two subsequent cTnI values were <0.02 ng/mL. Because of ongoing chest pain and a single elevated cTnI result, the patient underwent cardiac catheterization, which demonstrated normal coronary arteries, no regional wall motion abnormalities and a normal ejection fraction.

Later the same night, a 42-year-old white woman came to the ED with a 3-day history of worsening shortness of breath and atypical right sided chest pain. Her medical history was noteworthy for a congenital hypoplastic right lung, chronic obstructive pulmonary disease treated with home O2 therapy, and depression. When the patient's initial cTnI was found to be elevated at 0.11 ng/mL, she was admitted to the acute cardiology service. There her electrocardiogram results were found to be unchanged from those previously recorded, showing only right ventricular hypertrophy. Subsequent cTnI values were <0.02 ng/mL. To investigate a possible noncardiac etiology for her symptoms, a noninvasive transthoracic echocardiogram was performed, and did not reveal any major wall motion abnormalities.

A third patient presented to the ED on the same night with atypical chest pain. The patient, a 45-year-old man, complained of both sharp and dull chest pain, neither associated with exertion. He had walked 1 mile 2 days earlier without any chest pain. Three serial cTnI measurement obtained overnight were <0.02 ng/mL. The patient was subsequently sent home from the ED and scheduled for an outpatient stress test the next day, which he missed. The patient then

returned to the ED the next evening, and a second set of serial cTnI values were obtained, with results of 0.02, <0.02, and 0.11 ng/mL. A new sample collected within 1 hour of the third had a value of <0.02 ng/mL. The patient remained in the hospital over the weekend for observation and underwent an exercise nuclear stress test, which showed a normal left ventricular ejection fraction and no evidence of inducible ischemia.

In light of unexpectedly high cTnI values and initial workups that failed to yield evidence of acute cardiac ischemia in these patients with no prior cardiac history, laboratory personnel investigated what appeared to be closely-spaced false elevations of troponin. Repeat testing of the samples that had cTnI of 0.1-0.11 ng/mL, revealed that all had cTnI concentrations below the level of detection (<0.02 ng/mL).

DISCUSSION

Cardiac troponin T and cTnI have been defined by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) as diagnostic markers for acute myocardial injury and cardiac risk stratification1 and have become the preferred biomarkers in the diagnosis of myocardial infarction. In 2000, the ESC/ACC redefined acute myocardial infarction as an increased serum troponin (above the value at the 99th percentile of a healthy reference population) with clinical or electrocardiographic signs of cardiac ischemia[1] Increased troponin concentrations are also useful short- and long-term prognostic indicators in patients with a variety of illnesses.[2,3]

Troponin complexes, consisting of troponins I, T, and C,4 regulate the movement of calcium between actin and myosin. These complexes are located on the thin filaments of striated and cardiac muscles. Cardiac troponin T and cTnI are unique forms of troponins T and I that are found only in myocardial tissue. Both are released into serum after myocardial necrosis. Until recently, assays were insufficiently sensitive to detect cardiac troponins I or T in the circulation of most healthy people. Increases of cardiac troponins also can be seen in nonischemic disease and have been reported in pulmonary embolism, myocarditis, pericarditis, coronary vasospasm, renal insufficiency, congestive heart failure, and other conditions that affect the heart.[4]

In addition to these noncoronary conditions that increase cardiac troponins, nonpathological factors can interfere with assays for cardiac troponins, leading to falsely increased results (Table 1). These factors include heterophile antibodies, particularly human anti-mouse-immunoglobulin antibodies (HAMA), which are present in up to 1% of the population.[5,6] The increased use of monoclonal mouse antibodies in cancer treatment has increased the chances a person will develop heterophilic antibodies directed against mouse immunoglobulins and have false-positive results. At UVA, however, the cTnI assay reagents contain proteins to bind HAMAs. In addition, the patients we describe in this report had not been treated with mouse antibodies.

Rheumatoid factor, present in up to 5% of the population, can also interfere with immunoassays and has increased measured cTnI in some assays.[7] To our knowledge, however, this interference has not been reported for the cTnI assay used at UVA.

Two other sources of error are recognized, neither of which could be ruled out immediately in this case: If the specimen is centrifuged before a clot is completely formed, the remaining fibrin can nonspecifically bind the antibody.[8] The finding of normal cTnI on repeat analysis was consistent with this possibility, but not diagnostic. A second reported cause is malfunction of the analyzer itself, which may lead to sporadic false elevations in cTnI results. One study described the misalignment of a bulk solution dispenser as the likely source of falsely increased cTnI results that

Table 1. Causes of Falsely Increased Troponin Concentrations

Assay interference
Heterophile antibody
Rheumatoid factor
Excess fibrin
Analyzer malfunction

occurred without signals of an error from the instrument.[9]

We addressed the problem in the laboratory by immediately initiating duplicate testing for troponin, a process considered appropriate for sporadic analytical errors. Duplicate results that did not agree within 0.05 ng/mL in the lowest part of the range (0.02 to 0.4 ng/mL) were automatically repeated, again in duplicate. From May 3 to May 28, 2007, 8 of 503 samples tested had differences of >0.05 ng/mL on duplicate testing, more commonly with 1 of the 2 analyzers used for cTnI testing than with the other. Both machines were ARCHITECT ci8200 analyzers from Abbott Diagnostics. This finding represented a strikingly high rate of potentially clinically important error of 1.6% (which was avoided by the testing protocol).

The analyzers were examined by maintenance personnel from the manufacturer, but after attempted repairs spuriously high results were still observed (Figure 1). Implementation of a new reagent lot number resulted in improved results. The laboratory has continued to perform testing in duplicate to avoid reporting of falsely elevated cTnI results. Abbott Diagnostics is in the process of reformulating the cTnI assay reagents to reduce assay imprecision at low concentrations, and has recently released the reformulated reagent.

After analyzer repair and initiation of a new reagent lot, approximately 3 important cTnI duplicate discrepancies have been noted per week, an error rate of about 0.5%, with discrepancies that had the potential to affect clinical decision-making. To avoid reporting of erroneously high results, all such samples are now retested (also in duplicate) before results are reported.

At the time that the clinical false positives described in this report were discovered at UVA, other laboratories were also experiencing increased cTnI assay imprecision in the low concentration range, and Abbott Diagnostics issued a customer notification letter warning of increased assay imprecision.[10] At the request of the US Food and Drug Administration, Abbott also issued a revised letter describing increased imprecision at low assay concentrations (<0.1 ng/mL), warning laboratories and clinicians to be aware that the increased imprecision could lead to false positives or false negatives at these low concentrations with the use of the specific test diagnostic threshold of <0.1 ng/mL.[11]

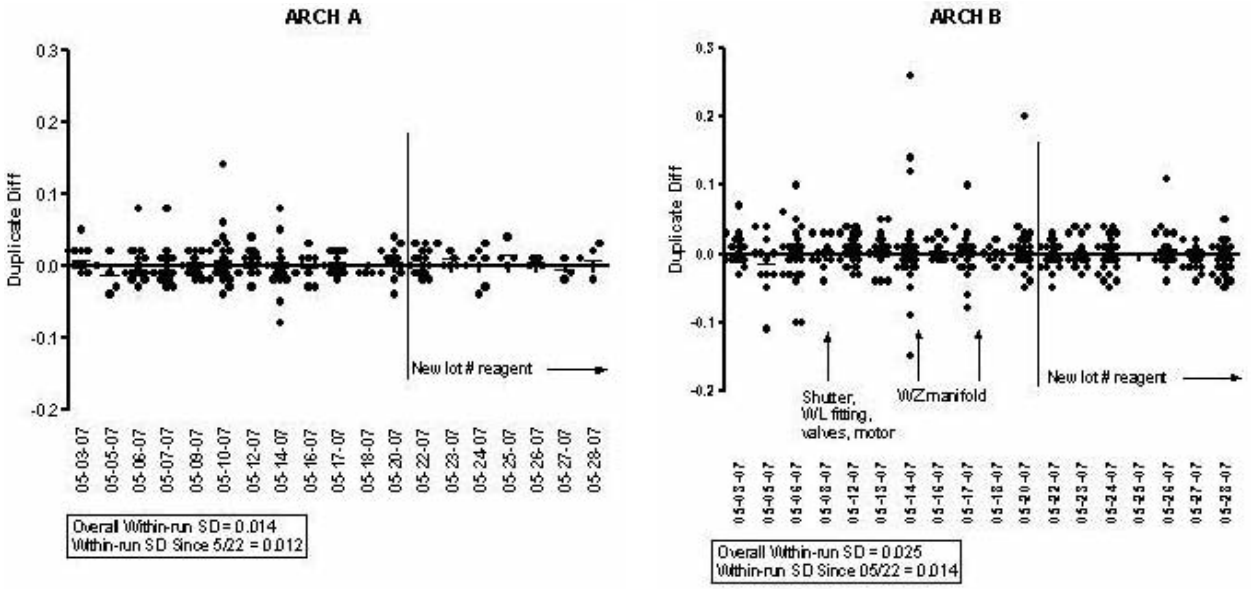

Figure 1. Observed differences between duplicate measurements of cTnI by date on Architect analyzers A (panel a) and B (panel b). With institution of a new reagent lot number, the frequency of spuriously large differences decreased.

CLINICAL IMPLICATIONS

Serial measurement of cardiac troponin has become an important tool for the diagnosis of acute myocardial ischemia. Spuriously increased results of assays for either of the cardiac troponins (I or T), however, can adversely influence triage and management decisions. These false-positive results often occur at the lower concentrations, near the limit of the assay's range, where it is difficult to differentiate between clinically important indications of myocardial damage and falsely elevated results. For patients with results in this range, it is particularly important for clinicians to exercise sound clinical judgment to avoid unnecessary invasive diagnostic testing.

CONCLUSION

These 3 cases of falsely elevated troponin assay results highlight the importance of clinician awareness of the possibility of spuriously elevated troponin values, particularly in the absence of other confirmatory signs of acute cardiac ischemia. At our institution the subsequent contact between the medical service and the pathology department identified analytical error in the low concentration range as the cause of the falsely-elevated cTnI results, and cTnI testing in duplicate by the laboratory was initiated to avoid further reporting of such false elevations. Clinicians should be aware of the possibility of spuriously elevated troponin values and be cognizant of the possibility of inaccurate results in the absence of other confirmatory signs of acute cardiac ischemia. In the cases presented here, when we felt the test results did not correspond with the clinical picture, we considered the possibility of false-positive results. An unnecessary cardiac catheterization in one of our patients would have been avoided if the false-positive result had not occurred.

There are many qualitative and quantitative components in the evaluation of a patient. Medical practitioners should avoid giving too much deference to clinical evaluations that yield quantitative results at the expense of accurate diagnosis. Our experience with false-positive troponin results are a reminder that there is no substitute for sound, integrated clinical judgment.

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Meralgia Paresthetica: One Construction Worker's Story

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Leg pain is a common symptom in both the inpatient and outpatient settings. The differential diagnosis for this particular complaint is quite broad and can include conditions ranging from malignancy to a simple case of bursitis. The astute physician can occasionally narrow the differential diagnosis based on history and physical examination alone. Although meralgia paresthetica has been widely recognized as a cause of lateral leg pain, its diagnosis is often delayed by lengthy workups for other conditions that mimic its symptoms. We describe a patient with meralgia paresthetica that was diagnosed early based on the history and physical and discuss treatment modalities that can be employed for this disease.

CASE PRESENTATION

A 39-year-old man with a history of right-sided nephrolithiasis 1 year previously and a remote history of surgical decompression of right testicular torsion presented to the emergency department at a university hospital with a 24-hour history of left flank pain and chills. The pain started when the patient bent down to pick up a shovel the day prior to admission and was described as sharp and burning in quality. The pain was constant and radiated down through the left groin. The pain varied in intensity, was worsened by ambulation and urination, and improved with lying still. The patient also noted that the outside of his left thigh was numb. The patient denied fever, nausea, vomiting, abdominal pain, changes in urination or bowel habits, leg weakness, point tenderness, or a history of back pain, diabetes, or thyroid dysfunction. The patient's family history was noncontributory. The patient denied any known drug allergies and was taking cyclobenzaprine and diclofenac as needed for pain. The patient was employed as a foreman of a construction crew and reported that on most days he wore a 50-lb carpenter's belt slung low across his lower abdomen.

On physical exam, the patient was afebrile at 36.8˚C, pulse was 59 beats/min and regular, blood pressure was 131/97 mm Hg sitting, respirations were 20/min and unlabored, with 100% oxygen saturation on room air. In general, the patient was a well-appearing, athletic male in moderate distress. Findings of head and neck, respiratory, and cardiac exams were all within normal limits. The abdominal exam was pertinent for pain in response to testing for left costovertebral angle tenderness. The patient also reported tenderness to palpation along the left lateral iliac crest at the beltline. The neurological examination showed preserved deep tendon reflexes, normal muscle tone, and 5/5 strength in both lower extremities. The left thigh was about 1 inch larger in diameter that the right thigh (measured 15 cm from the patella). A urine analysis with reflex culture was negative for infection.

Based on the history and physical examination findings, we made a presumptive diagnosis of meralgia paresthetica attributable to the chronic use of a heavy tool belt and exacerbated by hamstring swelling secondary to muscular injury. Abdominal computed tomographic scan with and without contrast showed a complex right renal cyst but was negative for calculi or acute processes. Lumbar and pelvic magnetic resonance imaging showed mild diffuse disc bulging at the vertebral levels of lumbar (L)3-L4, L4-L5, and L5-sacral 1, with no signs of vertebral canal compromise. The rest of the patient's laboratory study results, including a comprehensive metabolic panel, complete blood count, lipase, uric acid, erythrocyte sedimentation rate, antinuclear antibody, and prostate-specific antigen were notable only for a slightly elevated

creatinine at 1.4 mg/dL (baseline 1.3 mg/dL) with a fractional excretion of sodium of 0.54% on admission.

Neurology consultation results noted the same history and physical exam findings as mentioned above but also documented decreased sensation to fine touch, pin prick, and temperature on the left lateral thigh from the level of the inguinal ligament extending down to about 2 inches above the patella.

The patient's pain was eventually controlled on oral medications, and he was sent home on gabapentin, tizanidine, and naproxen, with follow-up appointments with both the neurology and acute pain services.

DISCUSSION

The lateral femoral cutaneous nerve is a pure sensory nerve that originates from a variable combination of the dorsal nerve roots of L1-L3 in the lumbosacral plexus.[1] Normally, the nerve runs through the abdominal cavity, under the inguinal ligament, superior to the sartorius muscle, and into the subcutaneous tissue of the lateral thigh, where it divides into anterior and posterior branches that extend to the knee (Figure 1). A small percentage of anatomic variants will enter the thigh lateral to the anterior superior iliac spine or medial to the insertion of the inguinal ligament on the pubis.[2] Meralgia paresthetica is the clinical syndrome that results from impingement of the lateral femoral cutaneous nerve.[3]

The most common cause of meralgia paresthetica is mechanical compression of the nerve as it traverses the inguinal ligament. Frequent precipitating factors include constrictive clothing along the waistline, carpenter's belts, diabetic neuropathy, a sagging pannus from obesity, scar tissue around the inguinal ligament, seat-belt injuries, pelvic fractures, injuries during spinal surgery, pregnancy, scleroderma, and idiopathic causes. Cases of meralgia paresthetica due to long distance cycling, as a consequence of local ischemia from repetitive muscle contractions, have also been reported. Bilateral meralgia paresthetica has been associated with pelvic inflammatory disease, and a rare autosomal dominant familial syndrome has also been described.[4-10]

Patients usually present with paresthesias, hypesthesia, dysesthesia, and/or anesthesia confined to the upper anterolateral portion of the thigh and radiating down to the knee; this pattern coincides with the sensory distribution of the lateral femoral cutaneous nerve. These symptoms are not exacerbated by direct pressure over the affected area or by hip or lower back movement, and the patient's ambulation is usually minimally affected.[2] Symptoms become much more pronounced, however, when the patient engages in activities that exacerbate impingement on the nerve, such as wearing a particular pair of pants, pantyhose, or tool belt; bending over; or progression of a pregnancy.

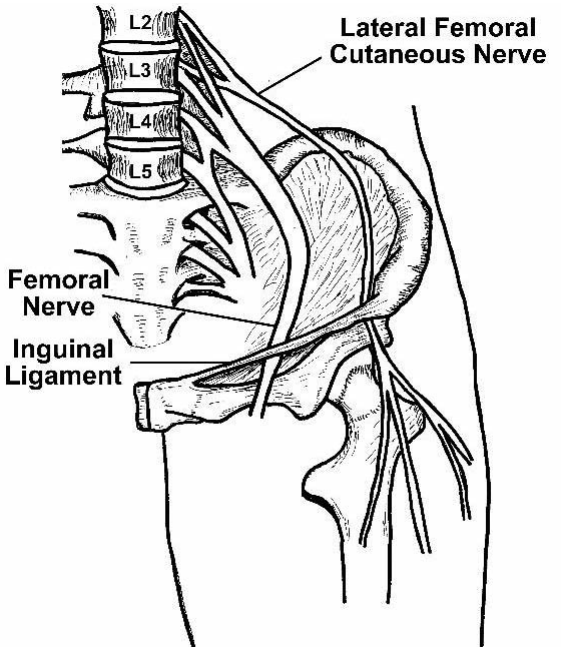

Figure 1. The lateral femoral cutaneous nerve is a pure sensory nerve that originates from a variable combination of the dorsal nerve roots of level 1 to level 3 in the lumbosacral plexus. Normally, the nerve runs through the abdominal cavity, under the inguinal ligament, superior to the sartorius muscle, and into the subcutaneous tissue of the lateral thigh where it divides into anterior and posterior branches that extend to the knee

Symptoms can also be aggravated by valsalva maneuvers because of increased intraabdominal pressure and resulting impingement on the nerve as it traverses the abdominal cavity superior to the inguinal ligament. In more advanced cases, the sensory losses can become fixed.

The diagnosis of meralgia paresthetica is clinically based on the above symptoms in the unique distribution supplied by the lateral femoral cutaneous nerve. Diagnosis can be confirmed by findings of decreased sensation to light touch, pin prick, and deep pain in the affected dermatome.[2] No motor deficits should occur in the affected limb, however, because the nerve is purely sensory in origin; consequently, a complete neurological exam of both lower extremities should be performed to rule out other conditions. Plain x-rays of the hip and pelvis are not usually indicated. Nerve conduction studies can be performed if confirmation of the diagnosis is necessary; but responses are often exceedingly variable.[11]

The differential diagnosis for lateral leg numbness includes lumbar radiculopathy of L4-L5 and trochanteric bursitis. Radiculopathy, however, often extends over a much wider area, radiates down the leg and into the foot, can involve motor deficits, and is often associated with lower back pain. With meralgia paresthetica, deep tendon reflexes and motor strength will both be preserved, and the straight leg sign will be negative. Trochanteric bursitis usually presents with point tenderness over the bursa, and inflammation and pain commonly limit hip movement on the affected side. If the history is suggestive but the physical examination is nonspecific, a local anesthetic block of the lateral femoral cutaneous nerve can be a helpful diagnostic tool. A 1.5-inch, 22-gauge needle is inserted perpendicular to the skin 1 inch medial and 1 inch inferior to the anterior superior iliac spine. Symptom resolution after the block confirms the diagnosis of meralgia paresthetica.[11]

Meralgia paresthetica is a self-limited process in most individuals. The major goals of treatment are to limit the exacerbating activity and implement lifestyle modifications to reduce pressure over the lateral groin area. Patients should be told to avoid wearing tight garments and to lose weight if appropriate. Nonsteroidal antiinflammatory drugs are often helpful for pain relief.[4] More than 90% of patients will respond to these conservative measures alone.[1] Recurrent symptoms are common, however, and local corticosteroid injections,[12] lidocaine patches, and gabapentin[13] can be used for refractory symptoms. In rare cases surgical decompression is employed in patients with chronic symptoms refractory to other treatment modalities. This procedure can involve releasing the lateral attachment of the inguinal ligament in the hope of preserving sensory function, or sectioning the nerve itself, which results in permanent anesthesia of the affected area.[14]

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Fever in a Traveling University Student

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With increasing numbers of people traveling to nonindustrialized countries each year, fever in a returning traveler has become an increasingly prevalent chief complaint reported to health care providers. Although most illnesses reported by travelers are mild, 1% to 5% of travelers become ill enough to seek medical attention.[1] Malaria is the most important cause of fever among persons who have recently traveled. Specifically, malaria caused by *Plasmodium falciparum* can be rapidly fatal and must be immediately ruled out in all febrile persons who have recently visited a malaria endemic area. We report a case of a febrile returning traveler who met several criteria for severe malaria from *P. falciparum.*

CASE DESCRIPTION

A 23-year-old man presented to the University of Virginia Emergency Department with a chief complaint of fever. Thirteen days prior to presentation, he had returned from a semester-long program in Ghana. Before the patient embarked on his trip, his primary care physician prescribed doxycycline for malaria prophylaxis. The patient reported that he had been noncompliant with this medication while overseas and was treated empirically for malaria 3 times with an artemisinin derivative but never completed a full course of this treatment. On returning home, the patient developed fevers to 40.7˚C that occurred almost daily. He was seen by his primary care physician, who began empiric treatment with atovaquone-proguanil (Malarone) for presumed malaria. The following day, the patient developed severe nausea and vomiting and was unable to tolerate his oral antibiotic regimen.

Physical examination revealed a young adult male in mild distress who was lethargic but lucid, with fluent, coherent speech. He was febrile to 40.˚C and tachycardic, with a heart rate of 103 beats/min. Blood pressure was 106/60 mm Hg, and oxygen saturation was 98% on room air. Sclerae were anicteric. Neck was supple with negative Kernig and Brudzinski signs. Lungs were clear to auscultation. Abdomen was soft and nontender, with normal, active bowel sounds and without hepatosplenomegaly. Skin showed no evidence of petechiae or purpura. Neurologic exam was nonfocal.

Laboratory studies in the emergency department were significant for a hematocrit of 24.2%, a platelet count of 57,000/µL, a total bilirubin of 2.3 mg/dL, and a haptoglobin of <8 mg/dL. All other liver function tests were within the normal limits. The patient's basic metabolic panel was significant for sodium of 130 mmol/L, magnesium of 1.3 mg/dL, and phosphorus of 1.1 mg/dL. His international normalized ratio was 1.0. The patient was admitted to the general medicine service for further management.

DIAGNOSIS

Peripheral blood thick and thin smears demonstrated developing trophozoite forms within numerous red blood cells (RBCs) and with features suggestive of P. falciparum (Figure 1). These findings confirmed the diagnosis of malaria, and the parasite burden was determined to be 5.4%.

MANAGEMENT

The patient met several criteria for severe malaria, including a parasite burden greater than 5%, severe anemia, and thrombocytopenia, indicating early disseminated intravascular coagulation. Given these findings, the patient was transferred to the medical intensive care unit for

treatment with parenteral quinidine gluconate in combination with doxycycline. He had further evidence of hemolysis during additional checks of his hematocrit, with a nadir of 18.6%. The patient received 2 units of packed red blood cells, which he tolerated uneventfully. While on quinidine gluconate, the patient did have asymptomatic prolongation of his QTc interval to 580 ms and elevation of his alanine and aspartate aminotransferases to 101 U/L and 174 U/L, respectively. After 4 days of parenteral therapy, the patient's hematocrit stabilized, and his QTc interval and transaminases normalized. He was able to tolerate a regular diet, so his antimalarial medication was changed to oral atovaquone-proguanil. On hospital day 7, he was afebrile and stable and was discharged to complete a 7-day course of atovaquone-proguanil at home.

DISCUSSION

In 2004, more than 1,300 documented cases of malaria resulting in 4 deaths occurred in the US. Almost all of these cases were in patients who had recently traveled to a malaria endemic region.[2] Of the 4 malaria species that cause disease in humans, *P. falciparum* is most likely to cause severe illness or death and is responsible for almost all cases of severe malaria.[3] Because of malaria's potential for deadly sequelae, this illness should be diagnosed and treated promptly. Despite the recent US Food and Drug Administration clearance of a rapid diagnostic test for malaria,[4] microscopic examination of thick and thin blood smears remains an important tool in malaria diagnosis. Thick smears concentrate RBCs on the slide, and the staining process lyses them, releasing extracellular merozoites that can be seen under the microscope. This method allows for more effective screening because detectable parasitemia often lags behind symptom onset. Giemsa-stained thin smears are prepared from a much smaller amount of blood and are useful for determining *Plasmodium* species. *P. falciparum* has several distinguishing features on thin smear. The young trophozoites ("signet ring" forms) of *P. falciparum* are usually smaller than those of other *Plasmodium* species, comprising only one-fifth or one-sixth the diameter of the cell. Double chromatin dots and multiple infections of single cells are more frequently found in this species than in the others. During the sexual stage, characteristic crescentic (or "banana-shaped") mature gametocytes are often seen on blood smear, and they appear in pulses rather than simultaneously with asexual forms, as may be seen in other *Plasmodium* species. Another distinguishing feature of *P. falciparum* is an absence of mature trophozoites and schizonts (appearing as RBCs filled with merozoites), presumably owing to the tendency of this species to complete its growth and development in the microvasculature of internal organs.[5]

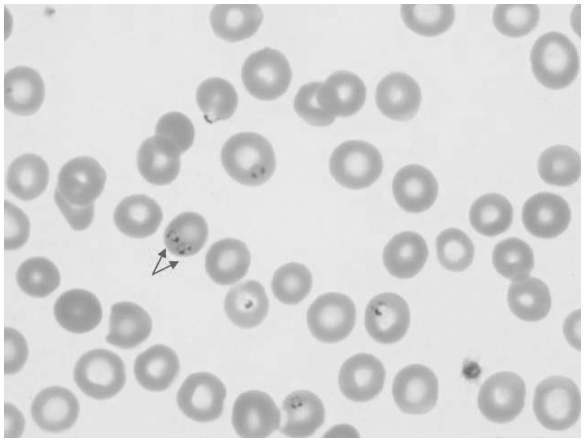

Figure 1. Thin peripheral blood smear showing multiple immature trophozoites within red blood cells. Arrows indicate a red cell infected with multiple trophozoites.

The clinical diagnosis of malaria is most often suggested by febrile illness after recent travel to an endemic region, but there are other associated symptoms. In a series of 160 German nationals or residents who presented with malaria at a travel clinic, symptoms included fever (100%), headache (100%), weakness (94%), night sweats (91%), insomnia (69%), arthralgias (59%), myalgias (56%), diarrhea (13%), and abdominal cramps (8%).[6] Findings on physical exam can include hepatosplenomegaly and pallor, and laboratory findings can include anemia, thrombocytopenia, and hypoglycemia. In a recent case-control study of 336 returning travelers with fever, the posttest probability of correct malaria diagnosis in a patient with both splenomegaly and thrombocytopenia was 98%.[7] All travelers who have returned from an endemic area within 3

months before onset of fever or who have other suggestive symptoms should be considered to have malaria until proven otherwise.[8]

Severe malaria is diagnosed by the presence of *P. falciparum* malaria in the setting of any of the findings listed in Table 1, which are based on the WHO criteria for severe malaria.[9] Severe malaria should be treated as a medical emergency, because death or debilitating effects can occur within a very short time. Most deaths due to severe malaria occur within the first 24 to 48 hours of therapy, so parenteral treatment and careful monitoring should be initiated immediately.[3] Because hypoglycemia can be a dangerous manifestation of severe malaria, serum glucose levels should also be monitored in these patients.

Until recently, quinine or quinidine gluconate plus doxycycline were the drugs of choice for malaria and, indeed, the only options available in the US for parenteral treatment of severe malaria. Quinidine's limited availability, however, and its potential adverse side effects, such as cardiac toxicity and hypoglycemia, make it difficult to use in patients who are already seriously ill. Fortunately, intravenous artesunate, which has become an important component of severe malaria treatment worldwide, is now available for the treatment of severe malaria in the US under a recently FDA-cleared investigational new drug protocol.[10] Artesunate has been shown to produce a greater decrease in mortality, have fewer adverse effects, and to be better tolerated than quinine for severe malaria.[11] Like quinidine, artesunate can be obtained through the US Center for Disease Control and Prevention malaria hotline if not readily available at your institution.

Table 1. Features Suggestive of Severe Malaria*

Cerebral malaria (impaired consciousness, convulsions)
Respiratory distress
Pulmonary edema
Abnormal bleeding
Jaundice
Hemoglobinuria
Severe anemia
High parasite burden
Hypoglycemia
Evidence of vital organ dysfunction
Inability to swallow

*Based on World Health Organization criteria.[8]

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The Renin-Angiotensin System: New Discoveries and Their Clinical Implications

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The renin-angiotensin system (RAS) is a major hormonal regulator of blood pressure, hypertension, and tissue damage.[1] RAS contributes to acute changes in extracellular fluid volume and blood pressure homeostasis primarily by regulating renin concentrations in the circulation. Angiotensin (Ang) II, the major effector peptide of the RAS, binds to 2 major receptors, Ang type-1 (AT1) and AT2, which generally oppose each other. The RAS blockade has been central to our treatment of hypertension and its complications, such as heart failure, atrial fibrillation, coronary artery disease, and progression to renal failure. During the past 5 years, several new RAS pathways have been discovered, including a (pro)renin receptor, and/or clarified, such as the functional significance of the AT2 receptor, angiotensinogen (Agt)-converting enzyme (ACE)-2, and Ang (1-7). This review discusses the actions and clinical implications of these components and pathways.

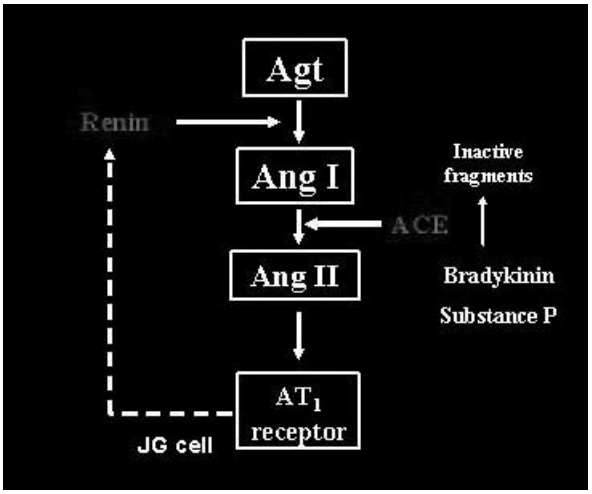

Figure 1. Schematic depiction of the classical renin-angiotensin system. Agt indicates angiotensinogen; Ang, angiotensin; ACE, angiotensin-converting enzyme; JG, juxtaglomerular.

Renin

According to classical understanding, the RAS (Figure 1) begins with biosynthesis of the glycoprotein hormone renin by the juxtaglomerular (JG) cells of the renal afferent arteriole (Figure 2). Renin is encoded by a single gene, and renin mRNA is translated into preprorenin, which contains 401 amino acids.[2] In the JG cell endoplasmic reticulum a 20-amino-acid signal peptide is severed from preprorenin, leaving prorenin. Prorenin is packaged into secretory granules in the Golgi apparatus, where it is further processed into active renin by cleavage of a 46-amino-acid peptide from the N-terminal region of the molecule. Mature, active renin is a glycosylated carboxypeptidase with a molecular weight of approximately 44 kDa. Active renin is released from the JG cell by an exocytotic process involving stimulus-secretion coupling. Inactive prorenin is released constitutively across the cell membrane and is converted to active renin by a trypsin-like activation step.[3]

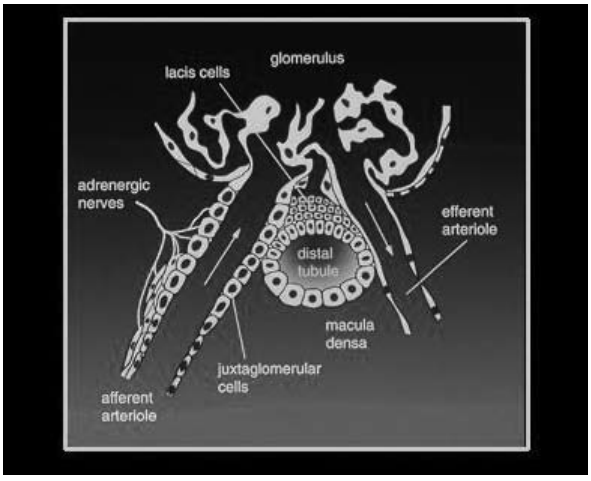

Figure 2. Schematic representation of the renal juxtaglomerular apparatus showing the various components.

In the past, renin was thought to have no intrinsic biological activity, serving solely as an enzyme cleaving Agt, the only known precursor of Ang peptides, to form the decapeptide Ang I (Figure 1). Liver-derived Agt provides the majority of systemic circulating Ang peptides, but Agt is also synthesized and constitutively released in other tissues, including heart, vasculature, kidney, and adipose tissue. Agt-converting enzyme (ACE), a glycoprotein (molecular weight180 kDa) with 2 active carboxy-terminal enzymatic sites, hydrolyzes the inactive Ang I into biologically active Ang II (Figure 1).[4] ACE has been found to exist in 2 molecular forms, soluble and particulate. ACE is localized on the plasma membranes of various cell types such as vascular endothelial cells and on the brush border (microvilli) of epithelial cells (eg. renal proximal tubule cells) and neuroepithelial cells. In addition to cleaving Ang I to Ang II, ACE metabolizes bradykinin (BK), an active vasodilator and natriuretic autacoid, to BK (1-7), an inactive metabolite (Figure 1),[5] thus increasing production of the potent vasoconstrictor Ang II while simultaneously degrading the vasodilator BK.

Angiotensin II

Unlike renin and Agt, which have relatively long plasma half-lives, Ang II is degraded within seconds at different amino-acid sites by peptidases, collectively termed angiotensinases, a process that leads to formation of fragments, mainly des-aspartyl1-Ang II (Ang III), Ang (1-7), and Ang (3-8) (Ang IV). Ang II is converted to Ang III by aminopeptidase A, and Ang III is converted to Ang IV by aminopeptidase N.[1]

The majority of cardiovascular, renal, and adrenal actions of Ang II are mediated by the AT1 receptor, which is widely distributed in these tissues. The AT1 receptor, a 7-transmembrane G-protein-coupled receptor, is coupled positively to protein kinase C and negatively to adenylyl cyclase.[6] AT1 receptors mediate vascular smooth muscle cell contraction, aldosterone secretion, thirst, sympathetic nervous system stimulation, renal tubular Na+ reabsorption, and cardiac ionotropic and chronotropic responses (Figure 3). Ang II also binds to another cloned receptor, the AT2 receptor, whose cell-signaling mechanisms and functions were unknown until recently.[6]

RAS Mechanisms

Biochemically, renin is the rate-limiting step in the RAS.[3] After bilateral nephrectomy renin quantitatively disappears from the circulation, indicating that renal JG cells are the only source of circulating rennin.[7] On the other hand, nephrectomy does not alter circulating prorenin concentrations, indicating that nonrenal tissues not only produce prorenin but also secrete it into the circulation. In addition, many organs, such as the heart, can take up renin from the circulation by mechanisms that remain to be elucidated.[8]

The primary contribution of the RAS to acute changes in extracellular fluid volume and blood pressure homeostasis is the adjustment of circulating renin concentrations. This process is mediated by active renin release from the secretory granules of JG cells. A primary mechanism of renin release is the afferent arteriolar baroreceptor, which increases renin release when arterial (and renal) perfusion

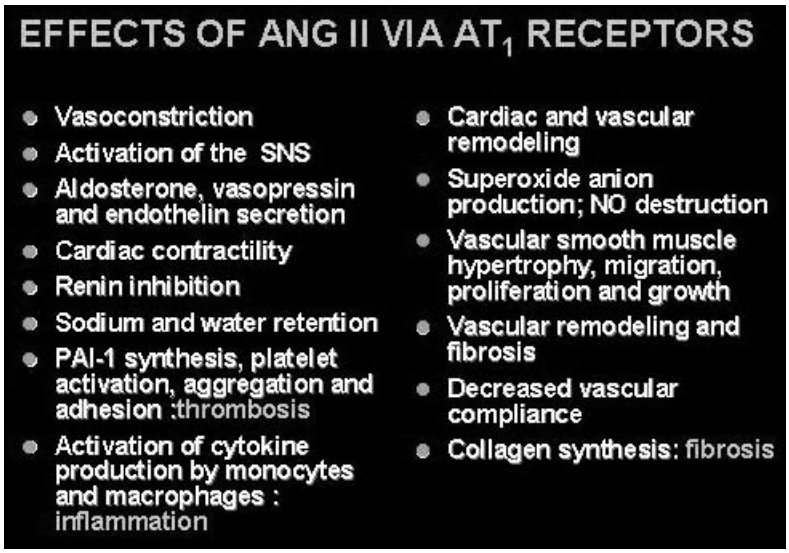

Figure 3. Effects of angiotensin (Ang) II via Ang type-1 (AT1) receptors. SNS indicates sympathetic nervous system; PAI-1, plasminogen activator inhibitor 1; NO, nitric oxide.

pressure decreases and vice-versa. In addition, JG cells are innervated by sympathetic neurons, the activation of which stimulates norepinephrine release and subsequent stimulation of ß1-adrenergic receptors, triggering renin release. Thus suppression of renin release by the ß1-adrenergic receptor blockade occurs directly at the JG cells (Figure 4). JG cells also express both AT1 and AT2 receptors, and circulating Ang II participates in a short-loop negative-feedback mechanism to inhibit renin release by binding to these 2 receptors, as shown recently by our laboratory.[9] Conversely, blockade of the RAS increases renin release and circulating renin concentrations (see Figure 5 for ACE inhibitors and Figure 6 for AT1 receptor blockers). Indeed, chronic RAS blockade by AT1 receptor antagonists or ACE inhibitors induces the recruitment of new renin-secreting cells in renal microvessels, further augmenting renin secretion, as shown by our group.[10] Another renin secretory control mechanism resides in the macula densa segment of the early distal tubule, which relays a signal to the JG cell to increase renin release when a decrease in Na+ and Cl- in the distal tubule is detected.

Renin had been considered to be the enzyme that cleaves the decapeptide Ang I from substrate Agt but to have no direct biological actions. Recent in vitro studies, however, demonstrated renin binding to human glomerular mesangial cells, leading to cell hypertrophy and increased concentrations of plasminogen-activator inhibitor.[11] The bound renin was not internalized or degraded. A renin receptor has now been cloned from mesangial cells, and its functional significance has been partially clarified.[12] The receptor is a 350-amino-acid protein with a single transmembrane domain that specifically binds both renin and prorenin (Figure 7).[12] This binding induces the activation of the extracellular signal-related mitogen-activated protein kinases (ERK 1 and ERK 2) associated with

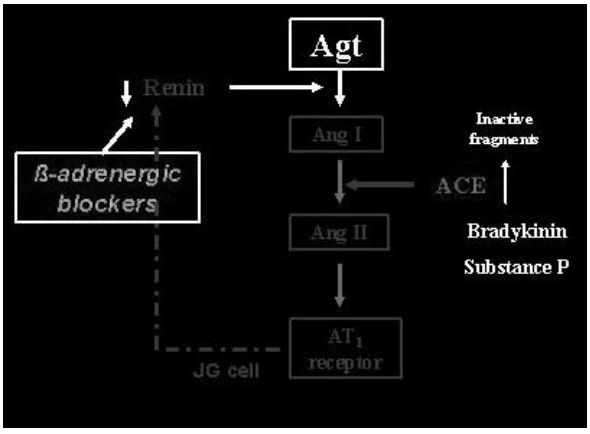

Figure 4. Schematic representation of changes in the renin-angiotensin system in response to ß-adrenergic blocker therapy. Renin secretion and Ang peptide production are uniformly suppressed.

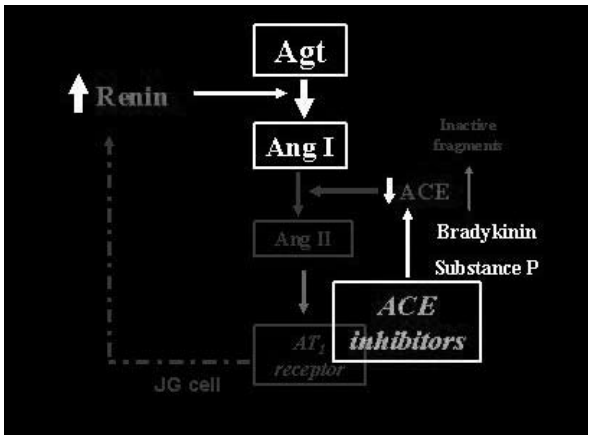

Figure 5. Schematic representation of changes in the renin-angiotensin system in response to ACE inhibition. Ang II formation and bradykinin and substance P degradation are simultaneously reduced while renin biosynthesis and secretion are markedly increased due to inhibition of Ang II interaction with the AT1 receptor on JG cells (short-loop negative feedback).

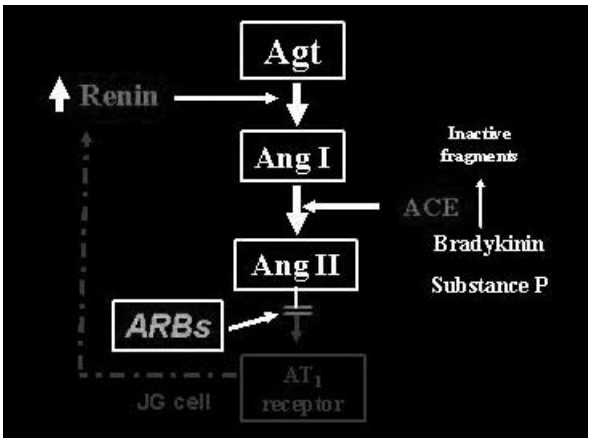

Figure 6. Schematic representation of changes in the renin-angiotensin system in response to angiotensin AT1 receptor blockers (ARBs). Renin biosynthesis and secretion are driven to high levels by interruption of short-loop negative feedback, leading to markedly increased Ang II levels.

serine and tyrosine phosphorylation and a 4-fold increase in the catalytic conversion of Agt to Ang I (Figure 8). This renin receptor has been found to be localized in renal mesangial cells and the subendothelial layer of both coronary and renal arteries, associated with vascular smooth muscle cells, and colocalized with rennin.[12] Recent data support the possibility of a direct functional role of renin and prorenin via the renin/prorenin receptor, and the importance of this receptor in the biology of the RAS awaits further investigation.

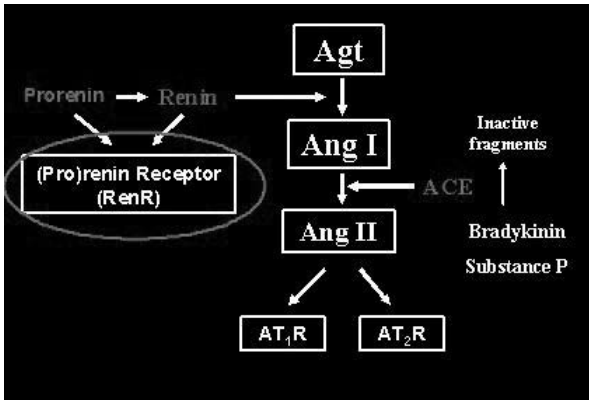

Figure 7. Schematic representation of the renin-angiotensin system depicting the interaction of prorenin and renin with a newly discovered and cloned (pro)renin receptor.

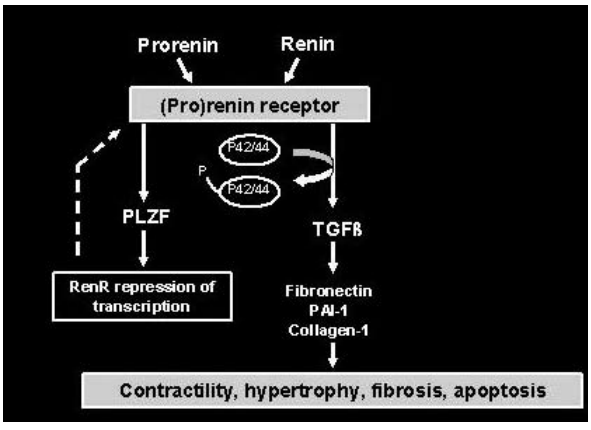

Figure 8. Schematic representation of potential Ang II-independent direct effects of renin and prorenin mediated by the recently discovered prorenin receptor. Receptor activation results in phosphorylation of MAP kinases (P42/44), which mediate increased production of transforming growth factor-_ (TGF_), resulting in fibronectin, PAI-1, and collagen-1 formation in renal mesangial cells. These changes lead to increased contractility, hypertrophy, fibrosis, and apoptosis.

Agt-Converting Enzyme

ACE inactivates 2 vasodilator peptides, BK and kallidin. BK is both a direct and an indirect vasodilator via stimulation of NO and cGMP and also by release of the vasodilator prostaglandins, PGE2 and prostacyclin.[13] Thus, when an ACE inhibitor is employed (Figure 5), not only is the synthesis of Ang II inhibited but also the formation of BK, NO, and prostaglandins is facilitated. ACE inhibition induces cross-talk between the BK B2 receptor and ACE on the plasma membrane, abrogating B2 receptor desensitization and potentiating both the levels of BK and the vasodilator action of BK at its B2 receptor.[14]

Another ACE has recently been discovered (Figure 9). ACE-2 is a zinc metalloproteinase consisting of 805 amino acids with significant sequence homology to ACE.[15] Unlike ACE, however, ACE-2 functions as a carboxypeptidase rather than a dipeptidyl-carboxypeptidase. In contrast to ACE, ACE-2 hydrolyzes Ang I to Ang (1-9), but the major pathway is in the conversion of Ang II to Ang (1-7) (Figure 9). ACE-2 also degrades BK to [des-Arg9]-BK, an inactive metabolite. In marked contrast to ACE, ACE-2 does not convert Ang I to Ang II, and its enzyme activity is not blocked with ACE inhibitors. Thus, ACE-2 acts as an inhibitor of Ang II formation by stimulating alternate pathways for Ang I and Ang II degradation. ACE-2 has been localized to the cell membranes of cardiac myocytes, renal endothelial

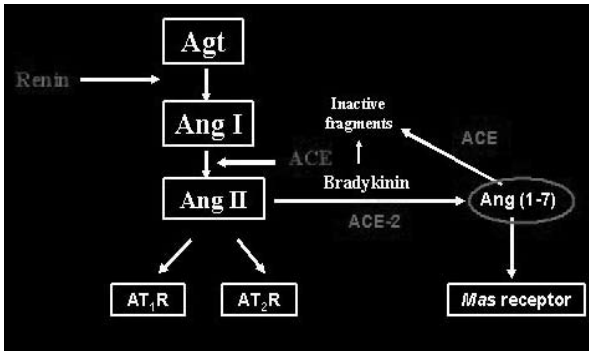

Figure 9. Schematic representation of the renin-angiotensin system depicting Ang II binding to both AT1 and AT2 receptors and the newly discovered ACE-2 pathway for conversion of Ang II directly to Ang (1-7), which interacts with the mas receptor to inhibit cell growth and stimulate vasodilation and natriuresis via prostglandins and NO. Because Ang (1-7) is metabolized to inactive fragments by ACE, ACE inhibitors result in markedly increased Ang (1-7) levels.

and tubule cells, and the testis. ACE-2 gene ablation does not alter blood pressure but impairs cardiac contractility and induces increased Ang II levels, suggesting that ACE-2 may at least partially nullify the physiological actions of ACE.[16]

Ang II and Ang (1-7)

The heptapeptide fragment of Ang II, Ang (1-7) (Figure 9) has been discovered to have biological activity.[17] Ang (1-7) can be formed directly from Ang I by a 2-step process involving conversion to Ang (1-9) by ACE-2 followed by conversion to Ang (1-7) by endopeptidases. However, as stated above, the major pathway for Ang (1-7) formation is directly from Ang II by the action of ACE-2 (Figure 9). Interestingly, the major catabolic pathway for inactivation of Ang (1-7) is by ACE (Figure 9). Thus, ACE inhibitor administration markedly increases the level of Ang (1-7).[18] The kidney is a major target organ for Ang (1-7). The peptide is formed in the kidney, where it has specific actions via a non-AT1 or -AT2 receptor. These actions include increased glomerular filtration rate, inhibition of Na /K/ATPase, vasorelaxation, and down-regulation of AT1 receptors, all of which are blocked by the specific Ang (1-7) antagonist (D-Ala7)-Ang (1-7) and are mediated at least in part by NO and prostacyclin.[19] Most of these effects of Ang (1-7) oppose those of Ang II via the AT1 receptor. Although a specific Ang (1-7) receptor has not been cloned, the peptide is an endogenous ligand for the mas oncogene, which mediates many of its actions (Figure 9).[20]

AT1 and AT2 Receptors

Ang II, the major effector peptide of the RAS, binds to AT1 and AT2, 2 major receptors that generally oppose each other.[6] The AT1 receptor is widely distributed in the vasculature, heart, and kidney.[21] Actions of Ang II mediated by the AT1 receptor include vasoconstriction; sympathetic nervous system activation; aldosterone, vasopressin and endothelin secretion; plasminogen activator inhibitor biosynthesis; platelet aggregation; thrombosis; cardiac contractility; superoxide formation; vascular smooth muscle growth; and collagen formation (Figure 3). These actions are conducted by both G protein-coupled and -independent pathways and involve phospholipases C, A2, and D activation; increased intracellular Ca++ and inositol 1,4,5- trisphosphate; activation of MAP kinases, ERKs, and the JAK/STAT pathway; enhanced protein phosphorylation; and stimulation of early growth-response genes.6 Tyrosine phosphorylation and inhibition of MAP kinase phosphorylation are the major intracellular signaling pathways for the AT1 receptor.[22]

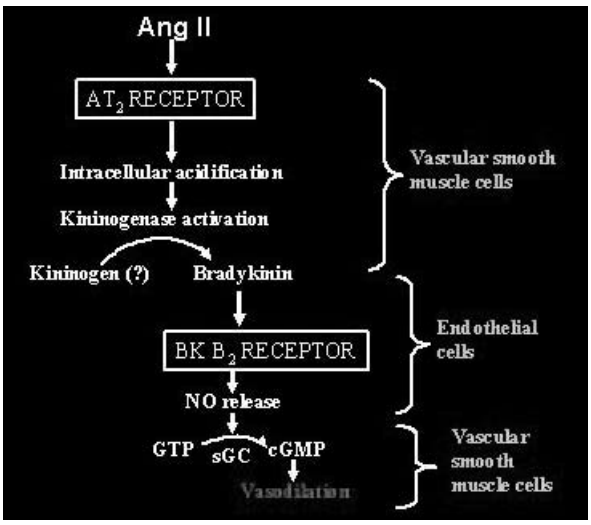

Figure 10. Schematic depiction of the paracrine vasodilator cascade elicited by activation of AT2 receptors by Ang II. AT2 receptor activation can stimulate NO production directly or can do so via increased levels of bradykinin (BK) via its B2 receptor.

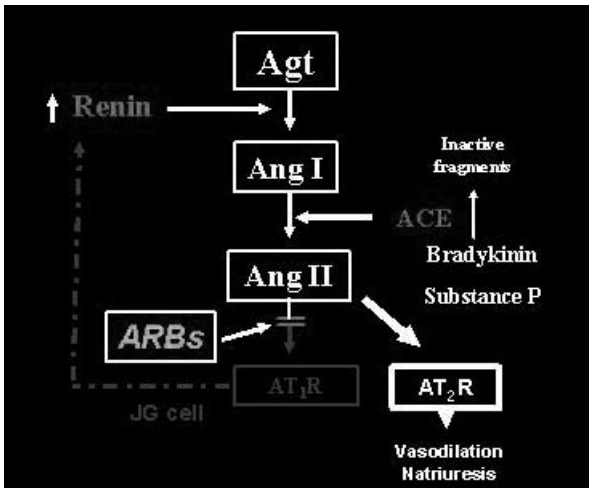

Figure 11. Schematic representation of changes in the renin-angiotensin system induced by AT1 receptor blockade (ARBs). Ang II levels are increased by interruption of short-loop negative feedback on renin secretion. Ang II is free to activate unblocked AT2 receptors inducing vasodilation and natriuresis.

The AT2 receptor is highly expressed in fetal tissues but regresses substantially in the postnatal period.[23] However, the AT2 receptor is still expressed at low copy numbers in the adult vasculature, especially in the endothelium and renal vasculature, JG cells, glomeruli, and tubules.[24] The AT2 receptor acts via the third intracellular loop by a Gi protein-mediated process involving stimulation of protein tyrosine phosphatases and reduction of ERK activity.[25] The AT2 receptor also induces sphingolipid and ceremide accumulation.[25] A major mechanism of action of AT2 receptors, discovered by our laboratory, is BK release (probably via kininogen activation through cellular acidification), with consequent NO and cGMP generation (Figure 10).[26,27] AT2 receptors also can stimulate NO directly without BK as an intermediate. As shown by our laboratory, the AT2 receptor mediates vasodilation, natriuresis, and inhibition of cell growth.[28] When the AT1 receptor is blocked, augmentation of renin release by inhibition of short-loop negative feedback leads to increased Ang II formation (Figure 11). Increased levels of Ang II, while inhibited from binding to the AT1 receptor, are free to activate the unblocked AT2 receptor, potentially leading to vasodilation and/or natriuresis (Figure 11). Acute studies in experimental animals from our laboratory have demonstrated that these beneficial effects of AT1 receptor blockers are mediated, at least acutely, by activation of AT2 receptors.

Some of the actions of Ang II may be related to heterodimerization. If AT1 and AT2 receptors are expressed in the same cell, the physical association of these receptors on the cell membrane may inhibit the action of AT1 receptors in a ligand-independent manner.[29] Similarly, there is evidence for AT1 receptor and BK-B2 receptor heterodimerization resulting in increased AT1 receptor effects via G-protein activation and, as shown by our laboratory, AT2-B2 receptor heterodimerization resulting in increased cGMP formation.[30,31]

Clinical Implications

From the preceding discussion, it is apparent that the RAS is a highly complex hormonal cascade with multiple interacting, redundant pathways and several newly discovered protein/peptide agonists and receptors. In addition, it is now clear that the RAS is not only a systemic hormonal system but also functions independently of systemic influence as a localized hormonal system in several tissues. Our laboratory was the first to show that the intrarenal RAS exerts a powerful influence on renal function, independent of circulating renin and Ang peptides.[32,33] There is also considerable evidence that local tissue RASs are present in the brain, heart, and vasculature and even in adipocytes. The precise role of cell-to-cell (paracrine), cell-to-same-cell (autocrine) and even intracellular (intracrine) RAS activity and function await future investigation.

From the clinical standpoint, there is no question that the major effector mechanism of the RAS is Ang II action via the AT1 receptor, which is highly expressed in most tissues. Ang II by this mechanism engenders antinatriuresis directly at the renal tubule,[34] aldosterone secretion, sympathetic nervous system stimulation, vasoconstriction, and tissue damage via cell growth and proliferation, inflammation, thrombosis, and fibrosis leading to vascular and cardiac remodeling and renal disease. Virtually all of the pharmaceutical effort thus far has justifiably been placed in developing blockers of the RAS. ACE inhibitors and AT1 receptor antagonists have had a major clinical impact to improve/prevent progression of cardiovascular and renal disease. As shown in Figure 12, clinical trials have demonstrated the efficacy of RAS blockade in

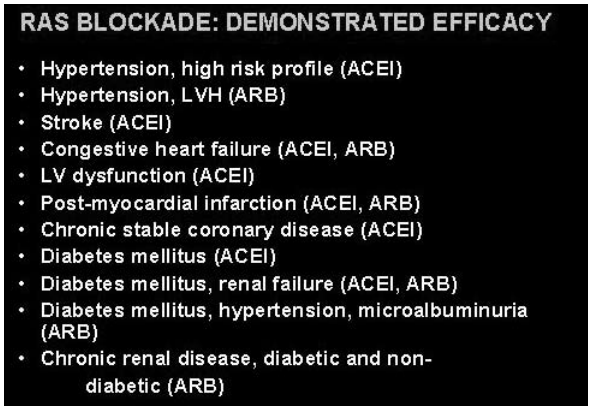

Figure 12. List of clinical conditions proven to be benefited by renin-angiotensin system blockade with ACE inhibitor (ACEI) and/or AT1 receptor blocker (ARB) therapy. Studies were randomized, double-blinded, placebo-controlled trials.

hypertension, stroke, congestive heart failure, chronic stable coronary disease, prevention of cardiac remodeling after myocardial infarction, diabetes mellitus with and without hypertension and/or renal failure, and even in nondiabetic renal disease. Although the available clinical trials have been performed with either ACE inhibitor or Ang II receptor blocker, very few reported studies have comparing responses to these 2 methods of RAS inhibition. The available studies generally demonstrate the equivalence of each approach. Several studies have documented long-term escape of Ang II and aldosterone suppression with ACE inhibitors, and several studies in progress are evaluating the efficacy of combination therapy with both ACE inhibitor and AT1 receptor blocker.

A novel approach to RAS blockade has been introduced this year in the form of the first clinically available inhibitor of the enzymatic action of renin (Figure 13). Aliskiren is a new orally active renin inhibitor that when given alone has antihypertensive efficacy similar to hydrochlorothiazide.[35] Interestingly, however, the antihypertensive actions of aliskiren are additive with those of hydrochlorothiazide and also with those of ACE inhibitors and AT1 receptor blockers. As shown in Figure 13, renin inhibitors block the catalytic action of renin to cleave the decapeptide Ang I from Agt. Under some circumstances, renin inhibition could theoretically be circumvented at least in part by enzymes such as cathepsin D or tonins. Renin inhibitors block the RAS at the highest point achieved so far in the hormonal cascade, resulting in reductions in both Ang I and Ang II. Importantly, plasma renin activity is suppressed by renin inhibitors, providing a useful laboratory marker of clinical efficacy. However, renin inhibitors do not block the biosynthesis or secretion of renin, which is augmented by inhibition of the short-loop negative feedback loop of Ang II via JG-cell AT1 receptors. If the activation of the (pro)renin receptor is proven to induce tissue damage, this mechanism may limit cardiovascular and renal effectiveness of all RAS blockers, including renin inhibitors.

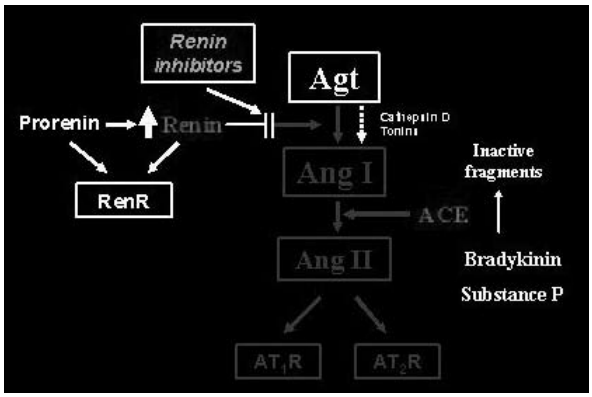

Figure 13. Schematic depiction of changes in the renin-angiotensin system in response to renin inhibitor therapy. Renin inhibitors result in blockade of the catalytic conversion of Agt to decapeptide Ang I. The entire Ang cascade is suppressed, but increased renin biosynthesis and secretion still occur via interruption of short-loop negative feedback at JG cells. Renin and prorenin may be free to act at (pro)renin receptors (RenR).

CONCLUSION

In summary, the RAS is a hormonal cascade of major importance in the regulation of blood pressure and cardiovascular and renal function. Within the past decade, several new components and pathways have been discovered, including the AT2 receptor, ACE-2, Ang (1-7), the mas receptor, and the (pro)renin receptor. Although Ang II activation of the AT1 receptor remains the most important pathway leading to cardiovascular and renal damage, several counter-regulatory pathways, including the AT2 receptor and the ACE-2-Ang (1-7)-mas receptor pathways, may limit the damaging tissue actions of Ang II. These pathways appear to have a potential beneficial role, especially in the presence of AT1 receptor blocker therapy. The recent discovery that prorenin and renin act directly at their specific receptor, leading to cell signaling mechanisms that may be detrimental, opens the door for an additional therapeutic target. The role of renin inhibitors in the armamentarium of RAS blockers also requires further investigation. In particular, we need to answer the questions “Does a rennin inhibitor prevent tissue damage?”; “When should a renin inhibitor be employed?”; and “Should a renin inhibitor be used in combination with other RAS blockers?”

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Clinical Commentary

Osteoporosis in 2008

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Osteoporosis is a significant health problem in an aging population. World Health Organization (WHO) criteria were originally developed to describe fracture risk in white, postmenopausal women, but osteroporosis affects both women and men. The presence of low-trauma fractures is the clinical hallmark of osteoporosis, but earlier diagnosis and fracture prevention in high-risk individuals should be the standard of care.

DEFINITION AND EPIDEMIOLOGY

Osteoporosis is defined as a skeletal disorder characterized by low bone density and poor bone quality that lead to an increased risk of fragility fractures. Primary or involutional osteoporosis refers to the normal bone loss that occurs with aging. This classification can be further subdivided into type I or II osteoporosis syndromes.[1] Type I is characterized by the rapid bone loss observed in the first 15-20 years after menopause, with a disproportionate trabecular over cortical bone loss. During this accelerated rate of bone loss, women may lose as much as 20%-30% of trabecular bone and 5%-10% of cortical bone and are at increased risk of Colles fractures and vertebral compression fractures. Type II or senile involutional osteoporosis entails a slow phase of age-related bone loss and leads to equal losses of cortical and trabecular bone. This second type of osteoporosis affects the entire population and it is progressive throughout aging, resulting in increased in fracture risk in people at the lower end of the age-specific distribution for bone mineral density (BMD). Clinically, this type of osteoporosis presents with predominantly proximal femur and vertebral fractures, but fractures at other sites with a combination of cortical and trabecular bone can also be seen.

A primary and widely recognized contributor to type I osteoporosis is low estrogen concentration during menopause. Estrogen deficiency also leads to increases in certain cytokines such as interleukin-6 and tumor necrosis factor as well as in urinary calcium excretion. Genetically determined susceptibility to these effects in the bone and kidney likely determine, to a great extent, the degree of observed bone loss. On the other hand, type II osteoporosis seems to be the result of a combination of secondary hyperparathyroidism and decreased bone formation rates, both processes that are a consequence of lower estrogen concentration in aging women and men.

The presence of low-trauma fractures is the clinical hallmark of osteoporosis, but earlier diagnosis enables identification of individuals who may be at high risk for fracture, in whom

Table 1. Defining Osteoporosis by BMD Based on the WHO Criteria*

Category	Definition by BMD	T-score
Normal	BMD within 1 SD of a young normal adult	≥-1.0
Osteopenia	BMD 1-2.5 SD below a young normal adult	-1 to -2.5)
Osteoporosis	BMD ≥2.5 SD below a young normal adult	≤-2.5
Severe osteoporosis	BMD >2.5 SD below a young normal adult in the (established) presence of 1 fragility fractures	

*Adapted from the World Health Organization (WHO) definition 1994.34 BMD indicates bone marrow density..

fracture prevention should be the standard of care. Thus, in 1994, the World Health Organization (WHO) offered a definition of osteoporosis based on bone density measurements and history of fracture (Table 1). These criteria designate osteoporosis as a bone mineral density equal to or less than 2.5 SD below a mean value for young adults. Based on the WHO criteria, 20%-30% of postmenopausal women in the United States have osteoporosis, and 1.3 million fractures a year are attributable to the disease. The WHO criteria were originally developed to describe fracture risk in white, postmenopausal women. Whether these same criteria can be applied to other populations, particularly men, is an area of much controversy. Nonetheless, in recent years, the International Society for Clinical Densitometry, in association with an expert panel determined that it is appropriate to apply these same criteria to men while using a sex-specific database for BMD. On the basis of these established cut-offs, it is estimated that 1-2 million men have osteoporosis and 8-13 million have osteopenia. The respective age-adjusted prevalence figures are 6% and 47%. If fracture is used as a clear end-point, then estimated lifetime risk is 13%-25%. Either estimation indicates that osteoporosis is a significant health problem for both aging women and men.

The morbidity and mortality following a vertebral or hip fracture is high. Vertebral fractures lead to progressive decrease in physical activity, kyphotic deformity, height loss, and chronic back pain all, of which, in turn, cause increasing social isolation, depression, and low self-esteem. The 5-year age-matched survival after a vertebral fracture is 72% for men and 84% for women. Similarly, hip fracture leads to significant disability. One year after hip fracture, 40% of patients are unable to walk independently and 60% require assistance with activities of daily living. Hip fracture mortality is higher for men than women. About 8% of men and 3% of women >50 years of age die during their initial hospitalization for hip fracture. One year after a hip fracture, mortality is 36% for men and 21% for women. Thus, the challenge is to recognize individuals who are at high risk for osteoporotic fractures before the first fracture occurs. Although it is recognized that for every 1 SD decrease in BMD there is an associated 2- to 3-fold increase in fracture risk, 50% of patients who suffer a fragility fracture have a BMD above the osteoporosis threshold as defined by the WHO criteria. Case-finding strategies should therefore incorporate known risk factors for fracture, and treatment decisions should be based not only on BMD scores but also on risk factor assessment.

EVALUATION AND DIAGNOSIS

The first step in assessing fracture risk is a thorough assessment of clinical risk factors (Table 2). The most important, readily recognized factors are probably age and female sex. It is well known that for any given BMD, fracture risk increases with aging. For example, the risk of hip fracture increases 30-fold between the ages of 50 and 80 years, whereas a 4-fold increase would be predicted based solely on average BMD. Other significant risk factors for fracture that capture aspects of risk beyond those assessed by BMD include previous fragility fracture, glucocorticoid therapy, family history of fragility fracture, and low body weight. Thus risk factor assessment can be use to identify a subgroup of patients for whom the risk of a future fracture is high enough to warrant therapy regardless of baseline BMD. In these patients, BMD may still be used to monitor

Table 2. Risk Factors for Osteoporotic Fractures

Major risk factors in white women
Personal history of fracture as an adult
History of fragility fracture in a first-degree relative
Low body weight (<127 lb)
Current smoking
Use of oral corticosteroid therapy for >3 months
Additional Risk Factors
Premature menopause (<45 y)
Primary or secondary amenorrhea
Primary and secondary hypogonadism in men
Impaired vision
Prolonged immobilization
Dementia
Excessive alcohol consumption (>2 drinks per day)
Low calcium intake
Recent falls
Poor health/frailty

response to therapy. On the other hand, individuals with a paucity of risk factors may not warrant BMD testing, because their fracture risk is low regardless of bone density measurements. Thus, the National Osteoporosis Foundation has provided a set of guidelines to aid practitioners in identifying patients for whom BMD testing is appropriate (Table 3). These and similar guidelines issued by Medicare and the International Society for Clinical Densitometry are not all-encompassing and therefore should be used in the context of a patient's particular situation.

BMD testing remains a cornerstone of osteoporosis diagnosis and assessment of response to treatment. Central dual x-ray absorptiometry (DXA) is the standard for BMD testing. Central DXA has been used extensively in epidemiologic studies and therefore, its relationship to fracture risk has been best characterized. Fracture prediction at a specific site is most accurate for BMD measurements at that particular site. For instance, BMD at the hip correlates best with hip fracture risk, although a general fracture risk assessment can be estimated from measurement at any site. Quantitative computed tomography (QCT) of the spine is another central modality for bone density measurement. The greatest advantage of this technology is that it provides a true volumetric assessment of bone density, whereas DXA provides only an areal density value. QCT requires specific software and it has not been traditionally used in epidemiologic studies or longitudinal studies of treatment effect. Furthermore, QCT results in a high radiation exposure far in excess to that observed with DXA. This technology may best be used in patients at the extremes of size or weight.

Peripheral technologies such as pQCT, pDXA, and quantitative ultrasound (QUS) are increasingly being used for screening purposes. The WHO criteria should not be applied to these measurements, and thus it is recommended that anyone with a positive study undergo central DXA measurement. Furthermore, sites traditionally measured by these methods respond poorly to osteoporosis treatment, and it is recommended that central sites be used to assess response to therapy. On the other hand, peripheral BMD does provide an assessment of global fracture risk, as recently demonstrated in 2 large prospective studies, and may therefore serve as a cost-effective initial screening tool.

Although osteoporosis has few diagnostic signs apparent on physical exam, a number of findings can alert the practitioner to the possibility of disease and/or an increased fracture risk. Poor visual acuity and depth perception, decreased proprioception, decreased proximal muscle strength, and an impaired "get up and go test" are all risk factors for fall and fracture and can be easily assessed in the clinic. Furthermore, kyphotic deformity of the spine is a late sequela of vertebral fractures and should prompt the physician to pursue further diagnosis and treatment.

Table 3. Criteria for Osteoporosis Testing

National Osteoporosis Foundation
1. All women age 65 and older regardless of risk factors
2. Younger postmenopausal women with 1 or more risk factors (other than being white, postmenopausal, and female)
3. Postmenopausal women who are considering therapy if BMD testing would facilitate the decision
4. Postmenopausal women who present with fractures (to confirm the diagnosis and determine disease severity)
Medicare Coverage for BMD in individuals age 65 and older-Bone Mass Act
1. Estrogen-deficient women at clinical risk for osteoporosis
2. Individuals with vertebral abnormalities
3. Individuals receiving or planning to receive long-term glucocorticoid (steroid) therapy
4. Individuals with primary hyperparathyroidism
5. Individuals being monitored to assess the response or efficacy of an approved osteoporosis drug therapy

We recommend that all patients with a diagnosis of osteoporosis undergo basic laboratory testing for secondary causes of osteoporosis. These tests should include, at a minimum, measurement of calcium, phosphorus, magnesium, creatinine, parathyroid hormone (PTH) and 25 (OH) vitamin D levels. The prevalence of vitamin D deficiency in the elderly population is estimated to be between 25% and 54%. This number is probably even higher for institutionalized or debilitated individuals. Vitamin D deficiency may, in turn, lead to secondary hyperparathyroidism and its associated adverse effects on bone. Thus, vitamin D deficiency should be routinely screened for and aggressively treated. All men should have a serum testosterone measurement because treatment of hypogonadism may result in increased bone mass. In addition, other tests such as serum and urine protein electrophoresis, and screening tests for hypercortisolism or malabsorptive syndromes should be obtained in selected patients.

The use of measurement of 24-hour urine excretion for calcium is controversial. There is high variability in calcium urine excretion from day to day, related at least partly to dietary variability. This measurement may be useful when calcium malabsorption is a significant issue and may result in a therapeutic change. There are also a significant number of individuals in this patient population with idiopathic hypercalciuria, which has been associated with secondary hyperparathyroidism and low bone mineral density. Such patients may benefit from treatment with thiazide diuretics to reduce renal calcium excretion.

As previously outlined, treatment decisions should be based on a combination of clinical risk factor assessment and BMD measurement. The National Osteoporosis Foundation recommends that treatment should be considered in postmenopausal women with a T-score of <-2.0 or in women with a T-score of <-1.5 but with other risk factors. These criteria have also been extrapolated to men. In the absence of other risk factors, treatment on the basis of BMD alone should be reserved for men older than 65-70 years of age, because this is when fracture risk increases in this population (Figure 1).

MANAGEMENT

The management of osteoporosis is multifactorial and includes a combination of lifestyle modifications, nutritional counseling, and pharmacologic interventions. As described above,

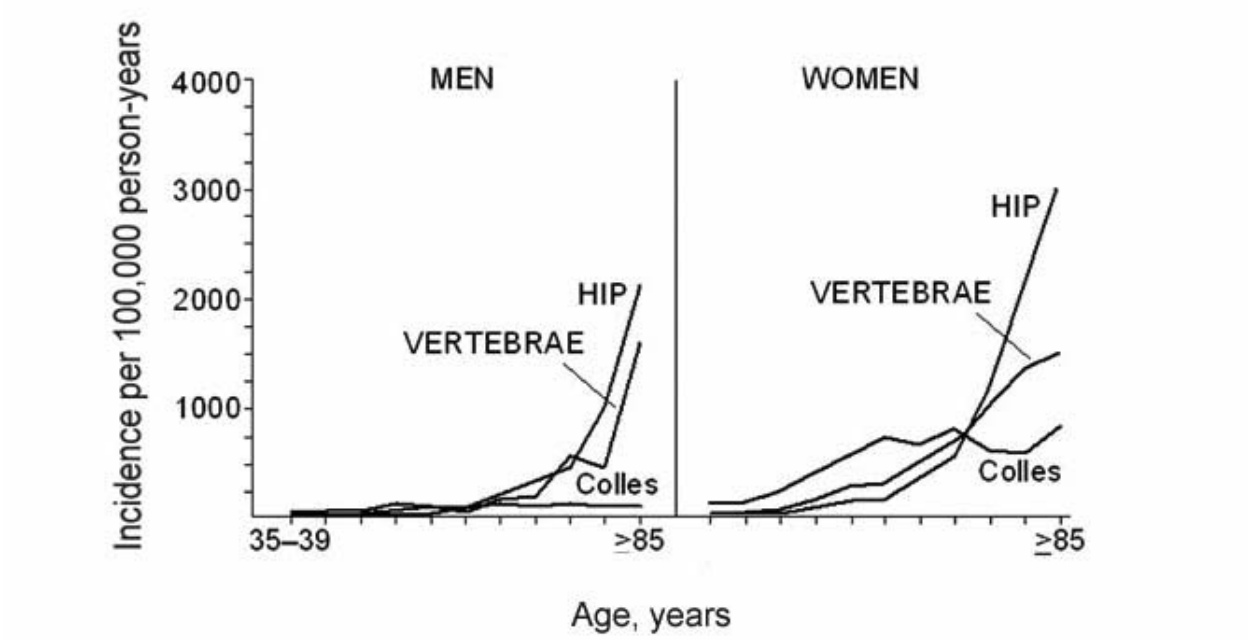

Figure 1. Age-related increase in fracture risk in men and women. Adapted from Cooper et al.[33]

the first step in osteoporosis management entails screening for secondary causes of osteoporosis and their correction as indicated.

Lifestyle interventions are crucial in the treatment of osteoporosis but, perhaps more importantly, in fracture prevention. All patients should be advised to pursue a combination of weight-bearing exercises and strength training. Exercise serves to decrease osteoporosis and fracture risk in several important ways. Low impact to bone stimulates bone remodeling with uptake of old, possibly fragile bone, and deposition of new, stronger bone. In addition, exercise increases balance and muscle strength and thus decreases the risk of falls. Patients with severe mobility impairment should be referred to physical therapy for instruction on appropriate exercises and balance training. All patients should be advised to pursue fall prevention measures at home including: (a) proper lighting in all rooms, (b) removal of area rugs and floor clutter, (c) use of walking devices as deemed appropriate, and (d) avoidance of uneven walking surfaces. In addition, patients should be advised against smoking and excessive alcohol use, because both of these have been shown to have detrimental effects on bone metabolism.

Nutritional counseling plays a central role in the treatment of osteoporosis. The vast majority of adult Americans do not consume the currently recommended daily allowances of calcium and vitamin D. It is estimated that fewer than 1 in 100 women older than 70 years and fewer than 25% of men in any age group meet the daily dietary calcium requirements. The numbers for vitamin D consumption are similar. In the clinic, we encounter a large number of patients with superimposed osteomalacia due to vitamin D deficiency and consequent bone mineralization defects. Vitamin D in its active form [$1,25(OH)_2D_3$] is crucial for normal calcium and phosphorus absorption from the gastrointestinal tract. Inadequate vitamin D concentration leads to a decrease in serum calcium levels and a resultant increase in parathyroid secretion. This secondary hyperparathyroidism acts to increase calcium and phosphorus mobilization from bone through octeoclast activation and bone resorption. In addition, PTH acts in the kidney to increase calcium retention and increase phosphorus excretion. The decrease in phosphorus absorption from the gut, in addition to the increase renal phosphorus excretion, leads to low serum phosphorus levels. Although low vitamin D levels probably have a direct effect on bone, the majority of the osseous consequences of vitamin D deficiency are probably mediated through the low calcium and phosphorus levels and the effects of PTH on bone.

The goal in all osteoporosis patients is to maintain a 25 (OH) vitamin D concentration of 30 ng/mL or greater. Patients with vitamin D deficiency should be treated with ergocalciferol (vitamin D_2) 50,000 units once or twice weekly until the vitamin D concentration returns to normal. The normal range for vitamin D is quite broad, but studies have shown that a 25 (OH) D concentration of 30 ng/mL or higher is necessary for skeletal health. Once a goal of 30 ng/mL or higher has been reached, patients should continue to be treated with 800-1000 units of vitamin D daily. Patients with intestinal malabsorption may require higher doses, sometimes as high as 10,000-50,000 units a day, to maintain normal levels. In addition, although the recommended daily intake for calcium in adults varies greatly worldwide, the current consensus is that all patients with a diagnosis of osteoporosis should be advised to take 1500 mg of calcium daily. These daily requirements should be met by a combination of foods high in these nutrients and dietary supplements. In general, calcium is poorly absorbed in the gut. It is thus important to recognize that not all dietary supplements have been tested for absorption efficiency.[2] Calcium carbonate, the most commonly used supplement, is best absorbed with food. Because the calcium-absorbing capacity of the gastrointestinal tract is limited, no more than 500 mg of calcium should be ingested at one time. It is best to spread calcium and vitamin D supplementation throughout the day. In patients with underlying achlorohydria either from chronic use of H_2 blockers or proton-pump inhibitors or secondary to gastrectomy, vagal surgery, or autoimmune disease, calcium malabsorption may be of particular concern.[3] Acidity in the gut is required for dissolution of calcium from supplements and

food. Therefore, in patients with low acid levels in the gut, the use of calcium citrate, with a higher dissolution, may be indicated. Studies of calcium and vitamin D supplementation have shown a reduction of fractures at all sites, including the hip.[4,5] In addition, other minerals are known to have both direct and indirect effects on bone. Magnesium deficiency is also a common problem in the United States population. Magnesium is important in the regulation of PTH secretion, and thus a goal of treatment should be to maintain normal magnesium levels.

Pharmacologic therapy remains the mainstay of therapy for osteoporosis. There are several general classes of medications available for both osteoporosis prevention and treatment. These include: hormone therapy (HT), selective estrogen receptor modulators (SERMs), calcitonin, bisphosphonates, and recombinant human PTH.

Hormone therapy. HT has been shown to be efficacious in trials of both osteoporosis prevention and treatment, which demonstrated measured increases in BMD at the spine, hip and forearm. Analyses of these trials by estrogen dose have shown persistent increases in BMD with the use of low-dose estrogen (equivalent to Premarin 0.3 mg), albeit more modest than those observed with high dose therapy.[6] The results of the Women Health Initiative showed a 23% reduction of all fractures and 34% reduction in hip and vertebral fracture after an average of 5.2 years of HT.[7] Thus, HT is currently recommended for osteoporosis prevention in high-risk women who have no known contraindications to HT use. However, given the increasing number of alternative therapies for osteoporosis and the potential side effects of long-term HT, the use of these agents should be approached cautiously with a plan for short-term use only in postmenopausal women.

SERMs. These compounds bind with high affinity to the estrogen receptor and may act as an estrogen agonist or antagonist, depending on the specific type of estrogen responsive tissue. Tamoxifen has been used for many years for the treatment of estrogen-receptor positive breast cancer. In trials of breast cancer treatment and prevention, tamoxifen was shown to act as an estrogen agonist at the level of the bone, with observed increases in bone density. Raloxifene, as tamoxifen, has been shown to act as an estrogen agonist in bone. Raloxifene has been approved for the treatment and prevention of postmenopausal osteoporosis. The currently approved daily dose of 60 mg a day has been shown to increase bone mineral density at the spine, hip, and total body after 2 years of treatment.[8] Also observed was an associated decrease in bone turnover markers, with restoration to premenopausal levels. Most importantly, in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a large placebo-controlled trial including 7705 postmenopausal women, raloxifene was shown to decrease clinical vertebral fractures by 62% after 1 year of treatment.[9] On the other hand, there was no significant decrease in the rate of nonvertebral fractures after the original 36-month study or after the 1-year extension. The safety profile of raloxifene is quite favorable. Patients in the MORE trial, however, had an increased risk of thromboembolic disease similar to that observed with HT. On the other hand, given the low incidence of this complication, the attributable risk is still very low.

Calcitonin. Calcitonin acts as a hypocalcemic factor via its inhibitory effect on osteoclast resorption. This 32 amino acid peptide is secreted by the C-cells of the thyroid, but its exact physiologic role in calcium homeostasis is still unknown. Salmon calcitonin is available in a parenteral and a nasal spray formulation for the treatment of women with osteoporosis who are more than 5 years postmenopause. Although only very modest increases in BMD of 1%-2% at the lumbar spine have been shown with the use of nasal calcitonin in postmenopausal women, the PROOF (Prevent Recurrence of Osteoporotic Fractures) trial in women with osteopenia (T <-2.0) of the spine showed a 33% reduction in vertebral risk in the treatment compared to the placebo group.[10] This effect was observed only with a dose of 200 IU a day but not with the 100 or 400 IU doses. No increases in BMD or decreases in fracture of the hip or other sites have been demonstrated with the use of any calcitonin preparation. Calcitonin is probably unique among osteoporosis treatments in that it

has an analgesic effect on bone pain after an acute vertebral fracture and is thus sometimes used for this indication. The most common side effect with the use of nasal calcitonin is a higher incidence of rhinitis and/or epistaxis. Injectable calcitonin may cause flushing, nausea, and vomiting. In clinical practice, the use of calcitonin has been reserved for the treatment of patients with acute bone pain or who are intolerant to other approved osteoporosis therapies.

Bisphosphonates. These compounds bind with high affinity to hydroxyapatite crystals in the bone surfaces, particularly those of active bone, leading to osteoclastic apoptosis and thus to a decrease in bone resorption with a subsequent increase in BMD. Four bisphosphonates, alendronate, risedronate, ibandronate, and zoledronic acid, are approved in the United States for the treatment and prevention of osteoporosis. These are all nitrogen-containing compounds. The bioavailability of all oral bisphosphonates is poor, and they should therefore be taken on an empty stomach with a large glass of water, and the patient should wait at least 30 min before eating. Alendronate, the first bisphosphonate approved in the United States for the treatment of osteoporosis, is approved for the prevention and treatment of postmenopausal osteoporosis. It is also approved for treatment of glucocorticoid-induced osteoporosis and for the treatment of osteoporosis in men. BMD has been shown to increase by 9% in the lumbar spine and by 6% in the hip after 3years of treatment with alendronate.[11] BMD continues to increase after 10 years of therapy, albeit at a slower rate.[12] In addition, BMD gains are maintained for at least 2 years after cessation of therapy, with a concomitant decrease in bone turnover markers of 50%-70%. These BMD increases translate to a 55% reduction in vertebral fractures and a 51% reduction in hip fractures.[13] Furthermore, in recently menopausal women, a 5 mg daily dose of alendronate was shown to prevent bone loss at the spine and hip during 5 years of treatment. Alendronate is formulated in a 5-mg daily and 35-mg weekly tablet for osteoporosis prevention and a 10-mg daily and 70-mg weekly tablet for osteoporosis treatment.

Risedronate has been FDA approved for the prevention and treatment of postmenopausal osteoporosis and for the prevention and treatment of glucocorticoid-induced osteoporosis. This agent increases BMD at the spine by 5% and in the hip by 3% within 3 years. These increases are associated with decreases in bone turnover markers of 40%-60%. Risedronate has been shown to decrease vertebral fractures by 41% and novertebral fractures by 39% compared to placebo during 3 years of treatment.[14] In the Hip Intervention Program, which enrolled almost 9500 women, there was a significant 30% decrease in overall hip fracture risk after 3 years of therapy.[15] Interestingly, in a subset of elderly women who were enrolled on the basis of clinical risk factors but not low BMD, there was no observed decrease in hip fracture risk, a finding that highlights the importance of a comprehensive approach to fracture prevention. Risedronate has also been shown to either maintain or increase BMD at the lumbar spine, femoral neck, trochanter, and distal radius in men and women on glucocorticoid therapy.[16] Furthermore, after 1 year of therapy with risedronate in these patients, there was a significant 70% reduction in vertebral fracture compared to the placebo-treated group. Risedronate is available in a 5-mg daily and 35-mg weekly tablet for both osteoporosis treatment and prevention.

Most recently, a head to head trial comparing once weekly 70 mg alendronate vs once weekly 35 mg risedronate for 1 year showed greater increases in BMD at 6 and 12 months for the alendronate group at the hip trochanter with greater increases for the alendronate group at all measured sites (lumbar spine, total hip, and femoral neck) after 12 months of treatment.[17] In addition, a greater decrease in bone turnover markers occurred in the alendronate group at 3 months. No differences in adverse events were observed between the 2 groups. This study was not powered to detect differences in fracture rates between groups. Therefore, the clinical importance of the observed BMD differences remains unclear.

Ibandronate was also recently approved for the treatment and prevention of postmenopausal osteoporosis. Ibandronate is available as a 2.5-

mg daily tablet, a 150-mg once monthly formulation, and a 3-mg intravenous formulation administered at 3 month intervals. The majority of the available ibandronate data were obtained with ibandronate 2.5 mg daily. A subsequent study showed noninferiority in BMD increases with ibandronate 150 mg monthly compared to the more extensively studied 2.5 mg daily administration. In a 3-year study of postmenopausal women with osteoporosis.[18] BMD at the lumbar spine increased by 6.4% and at the total hip by 3.1% by the end of the 3-year period. Also after 3 years, there was a relative risk reduction of 52% in new vertebral fractures. On the other hand, there was no significant difference in the number of nonvertebral fractures, including femur, hip, and pelvis, in the ibandronate treated group compared to placebo. Ibandronate is also approved to be given intravenously as a 3-mg dose every 3 months. A trial comparing intravenous ibandronate with oral ibandronate (2.5 mg daily) showed equivalent gains in BMD.[19] No trials, however, have show fracture reduction with the approved intravenous schedule. In addition, an earlier study of lower-dose intravenous ibandronate (1 mg every 3 months) did not show any fracture efficacy at this lower dose.[20]

Zoledronic acid, a potent bisphosphonate, has recently been approved for the treatment of osteoporosis in postmenopausal women. In a 3-year study women received either zoledronic acid 5 mg yearly or placebo yearly.[21] This study demonstrated an increase in BMD at the lumbar spine of 6.71%, at the total hip of 6.02%, and at the femoral neck of 5.06%. In addition, treatment with zoledronic acid decreased the risk of morphometric vertebral fracture by 70% compared to placebo during the 3-year study and reduced the risk of hip fracture by 41%. Adverse events, including changes in renal function, were similar in the 2 study groups. However, atrial fibrillation occurred more frequently in the zoledronic acid group (50 vs 20 patients, $P < .001$).

Although combination therapy with 2 antiresorptive agents has been shown to lead to greater increases in BMD, no studies have demonstrated greater fracture reduction with this therapy. As a result, the simultaneous use of 2 antiresorptive agents is generally not recommended.

The safety profile with all bisphosphonates is quite favorable. With daily alendronate and ibandronate therapy, there appears to be an increased incidence of upper gastrointestinal side effects, including heartburn and dysphagia; however, this increased incidence has not been observed with weekly or monthly dosing schedules. There is concern that long-term therapy with potent bisphosphonates such as alendronate and risedronate may lead to adynamic bone disease or “frozen” bone, but long-term biopsy data have not confirmed this possibility. In addition, intravenous formulations of ibandronate and zoledronic acid have been associated with the occurrence of flu-like symptoms for the first 24-48 hours after medication administration. No long-term side-effects have been documented.

Beginning in 2003, case reports have described a possible link between the use of bisphosphonates, predominantly nitrogen-containing intravenous preparations, and osteonecrosis of the jaw (ONJ).[22] Prospective data regarding this condition are scarce, however. The proposed working definition of ONJ refers to exposed bone in either the mandible or the maxilla, which may be asymptomatic or result in pain and infection. The lesion typically heals poorly or heals slowly over a period of 6 to 8 weeks. Most case reports are in patients with multiple myeloma or metastatic cancer, particularly breast cancer, being treated with intravenous bisphosphonates. The type of bisphosphonate used and the duration of exposure may both contribute to ONJ risk. In addition, more than 60% of patients with ONJ have a history of dental problems or invasive dental procedures. One prospective study of patients on intravenous bisphosphonate therapy for bone metastases identified 17 cases of ONJ over a 32-month period, with an estimated incidence of 6.7%.[23] Isolated cases of ONJ have been reported in patients treated with oral bisphosphonates for osteoporosis. The incidence of ONJ in this setting is unknown and has been estimated to be very low (0.7 cases per 100,000 person-years exposure).[24]

Several societies have convened expert panels and issued position papers regarding ONJ, including the American Academy of Oral and Maxillofacial Pathology,[25] the American Society of Bone and Mineral Research,[26] and the American Dental Association.[24] In the absence of information regarding the pathophysiology and risk factors for ONJ, it is recommended that patients being treated with intravenous bisphosphonates undergo a dental exam and that invasive dental procedures be postponed or completed prior to initiation of therapy. It is hoped that increased awareness and attention to oral hygiene may prevent complications associated with this condition.

Teriparatide. This drug is the only anabolic agent currently approved for the treatment of osteoporosis, including glucocorticoid-induced osteoporosis, in men and women. The approved dose of teriparatide is 20 (μg subcutaneously once daily for 2 years. This agent is composed of the amino terminal portion of the human PTH molecule [hPTH(1-34)]. This fragment of the intact molecule binds to the PTH1 receptor and, when given as intermittent daily injections, results in recruitment of quiescent bone-forming osteoblast cells. In addition, teriparatide also prevents apoptosis of osteoblast cells, prolonging their bone-forming potential. These combined effects of teriparatide result in net bone formation. A study of 1637 postmenopausal women receiving teriparatide 20 μg or 40 μg or placebo showed increases in BMD with teriparatide of 9%-13% for the lumbar spine and 2%-4% for the total hip after 21 months of treatment.[27] In contrast, BMD at the shaft of the radius decreased by 2%-3%, a decrease that reached statistical significance only for the higher dose tested (40 μg). The risk of vertebral fracture for both teriparatide-treated patient groups was decreased by 65%-69% and that of nonvertebral fractures by 35%-40%. Studies of teriparatide in men with idiopathic osteoporosis and in men and women with glucocorticoid-induced osteoporosis have shown a similar response to therapy.

Whether teripararatide should be used in combination with an antiresorptive drug is an area of much controversy and is being further explored by ongoing studies. A study on the effects of teriparatide alone or in combination with alendronate in men with osteoporosis showed that increases in BMD at the lumbar spine and the femoral neck were greatest for men treated with teriparatide alone compared to alendronate alone or the combination of alendronate and teriparatide.[28] The diminished effect on bone density acquisition observed with combination therapy may be the result of blunting of teriparatide-induced bone formation by a potent antiresorptive. In contrast, postmenopausal women treated with combination estrogen and teriparatide had increases in BMD similar to those observed with teriparatide alone. Thus, whether concomitant treatment with teriparatide and a weaker antiresorptive agent is of clinical benefit remains unknown. Substantial data do, however, suggest a rapid decline in BMD after teriparatide is discontinue, an effect that can be abrogated by follow-up treatment with an antiresorptive agent.[29]

At the lower approved dose of teriparatide, there appear to be few clinically significant side-effects. Transient mild hypercalcemia and increased uric acid levels were noted during the study of postmenopausal women. Neither of these changes in chemical values had any apparent clinical sequelae. A higher incidence of dizziness and leg cramps has been reported with the use of teriparatide compared to placebo. In addition, initial clinical studies of teriparatide were terminated early because of concerns raised by results in Fisher rat studies showing a higher incidence of osteosarcoma with high-dose drug administration to growing rats. In more than 2000 study patients treated with teriparatide, there have been no reported cases of osteosarcoma. Nonetheless, use of this agent is limited by the FDA to no more than 2 years, and it is not approved for use in children or adolescents or in patients with Paget disease of the bone, hyperparathyroidism, or a history of bone cancer.

FUTURE THERAPIES

In the last few years the mechanisms responsible for osteoclast activation and survival have been better elucidated.[30,31] It is now clear that PTH, vitamin D, and other hormones, and factors that stimulate osteoclastic bone resorption work

through the receptor activator of nuclear factor (NF)-kappa(((RANK)/RANK ligand (RANKL) system in bone. RANKL and its 2 known receptors RANK and osteoprotegerin (OPG) are the key regulators of osteoclastic bone resorption in vivo and in vitro. Hormones and factors that stimulate bone resorption in vivo increase RANKL expression in osteogenic stromal cells. RANKL expression by osteoblasts coordinate bone remodeling by binding to its receptor RANK and stimulating bone resoprtion by local osteoclasts. OPG acts as a decoy receptor by blocking RANKL binding to RANK and thus preventing osteoclastic bone resorption.

New therapeutic modalities are looking to exploit our current knowledge of the RANK/RANKL pathway. Denosumab, a fully human monoclonal antibody (formerly known as AMG 162), binds RANKL with high affinity and specificity and thus inhibits RANKL action. In postmenopausal women with low bone density, denosumab treatment for 12 months increased BMD at the lumbar spine by 3.0% to 6.7% compared to an increase of 4.6% with alendronate and a loss of 0.8% with placebo.[32] Similarly, at the total hip, treatment with denosumab resulted in a 1.9%-3.6% increase in BMD at the lumbar spine compared to a 2.1% increase with alendronate and loss of 0.6% with placebo. There are ongoing studies using this agent for the treatment of osteoporosis as well as the treatment of rheumatic diseases and bone metastasis.

SUMMARY

Osteoporosis is a silent disease that results in great morbidity and mortality in our aging population. The expectation is that as our population ages, this disease will become increasingly prevalent, resulting in enormous health care costs. Practitioners have the ability to diagnose this disease early, but a high index of suspicion is required. There are efficacious therapies available for the treatment of osteoporosis in both women and men, with observed decreases in fracture risk. Newer therapies offer even more choices in terms of ease of administration with very few side effects. Organizations such as the WHO, National Osteoporosis Foundation, and International Society for Clinical Densitometry have continued their efforts to educate the public and their physicians about this common and highly treatable disease.

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