Nontuberculous mycobacterial musculoskeletal infections: Recognizable, when suspected

Dactylitis from *M intracellulare* infection

Which ICU patients need stress ulcer prophylaxis?

Painful swelling of the right hand: Unraveling a challenging diagnosis

Mondor disease of the breast

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A 59-year-old inpatient with acute anxiety and tachycardia

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Nontuberculous mycobacterial musculoskeletal infections: Recognizable, when suspected

In this issue of the Journal, we have 2 Clinical Picture articles\textsuperscript{1,2} portray and emphasize a shared clinical theme. Both depict patients with peripheral musculoskeletal infections with nontuberculous mycobacteria. One was an infection with *Mycobacterium intracellulare* and the other with *Mycobacterium marinum*. These papers were independently submitted in the same time frame from medical centers half a world apart. Serendipitously, the second crossed my desk while I was coordinating a repeat surgical intervention on a patient of mine with recurrent *M intracellulare* infection of a finger proximal interphalangeal joint and flexor tendon. I’ll say a bit more about that patient below.

These stories of patients with nontuberculous mycobacterial (NTM) infections share distinctive historical and physical examination components. The stories and pictures offer important diagnostic caveats, especially for those who don’t frequently consider such infections in the diagnosis of patients with swollen, indurated peripheral soft-tissue structures. (And that would be most of us.)

NTM musculoskeletal infections are not common and tend to be indolent. As a result, the diagnosis is often delayed\textsuperscript{3} for many months, as in the patients pictured in this issue. Multiple species of these bacteria are ubiquitous in the environment, and the source of infection often cannot be identified. Many species exist in soil. *M marinum* is considered to be a waterborne infection (in the wild as well as in home aquariums). It is important to recognize when *M marinum* may be the infectious agent so as to notify the microbiology laboratory not only to set up protracted routine mycobacterial cultures at 37°C but also to incubate parallel cultures at cooler temperatures to facilitate *M marinum* growth.

Cost-conscious care dictates that it is not necessary or reasonable to send fluid from all potential musculoskeletal infections for mycobacterial or fungal cultures at initial evaluation. NTM joint infections tend to have an insidious onset and can be confused with more typical bacterial infections, which should be excluded. No growth on routine cultures and the lack of a clinical response to empiric antibiotics should raise a red flag when there is concern for a possible infected joint.

The diagnosis of NTM infection is reasonable to consider in patients who present with chronic, unexplained, indurated peripheral tendon sheaths. Particularly challenging can be the management of patients described in this issue,\textsuperscript{1,2} who have an underlying rheumatic condition or are receiving immunosuppressive therapy. Suspicion of NTM infection should increase if a patient being treated for a systemic inflammatory arthritis responds in most involved areas but is not responding as expected in adjacent anatomic areas, or if there are anatomic quirks on examination. In the patient pictured by Shimizu et al,\textsuperscript{1} a clinical clue to NTM infection was dactylitis of a single finger in a patient with rheumatoid arthritis. Rheumatoid arthritis is not expected to elicit dactylitis! Also, the presence of chronic distended hand or foot tenosynovitis resistant to anti-inflammatory therapy should raise concern for NTM infection, even in the absence of any known immunodeficiency. These infections tend to not be dramatically painful but can cause significant functional limitations or even nerve compression (eg, carpal tunnel syndrome). The markedly chronic nature of these infections is highlighted by the frequent presence of chunks of infarcted synovium and
cellular debris, so-called “rice bodies,” which used to be characteristic of chronic severe undertreated rheumatoid arthritis but now are found more frequently in the setting of chronic infection. While NTM infections may also be limited to the lungs, they can be systemic, particularly in markedly immunodeficient patients such as those with undertreated HIV/AIDS. Musculoskeletal infections often remain limited to local areas of bone (vertebral osteomyelitis) or joint (usually monoarticular or oligoarticular), and especially tendon sheaths and surrounding tissue. Patients with musculoskeletal infections may not have a fever and may have normal acute-phase reactants. Often, the patient provides a history of injury, surgical intervention, or prior inflammation of an affected joint. I have cared for a patient with rheumatoid arthritis and isolated M intracellulare infection in a prosthetic hip joint. My recent patient with palmar flexor tendon sheath infection with M intracellulare manifested many of the above demographic characteristics. He is a renal transplant recipient, who had been doing well on mycophenolate and cyclosporin immunosuppression. He developed crystal-proven gout in multiple areas including metacarpal phalangeal (MCP) joints, with uric acid deposits documented by ultrasonography. He was treated with a several-month course of pegloticase to dissolve the deposits, and his hand function improved. But after switching back to traditional oral urate-lowering therapy, the third MCP and flexor tendons started to enlarge, despite maintaining a serum urate level below saturation (6.8 mg/dL). It was felt to be unlikely for gout inflammatory symptoms to return after the (presumed) dissolution of the uric acid deposits with persistent low serum urate. A biopsy was done and the infection was documented. He was treated successfully, or so it seemed, with “radical tenosynovectomy” and sensitivity-directed multidrug therapy for more than 6 months. More than a year after the antibiotics were stopped, doughy swelling of the palmar tendons and MCP joint returned, with mild flexion contractures. He was taken again to the operating room, and granulomatous tenosynovitis was identified and resected. Additionally, innumerable rice bodies were washed out. No crystals were reported by the laboratory. We are currently awaiting the antibiotic sensitivities. Although still uncommon, with the widening use of potent immunosuppressive therapies, NTM musculoskeletal infections are increasingly recognized, but there is still a protracted delay in diagnosis. Hopefully, the images presented here will heighten awareness of these infections and prompt appropriate diagnostic evaluation, which often requires tissue-sampling.

Brian F. Mandell, MD, PhD
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AUGUST

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August 5–7
Washington, DC

CLEVELAND BREAST CANCER SUMMIT: COLLABORATING FOR A CURE
August 12
Cleveland, OH

INTERPROFESSIONAL APPROACH TO MANAGEMENT OF CRITICALLY ILL PATIENTS WITH LIVER DISEASE
August 15–16
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INTENSIVE REVIEW OF CARDIOLOGY
August 19–21
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PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
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Cleveland, OH

HOSPITAL MEDICINE
September 8–9
Beachwood, OH, and live stream

SPASTICITY AND NEUROREHABILITATION: PEDIATRIC AND ADULT SYMPOSIUM
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Warrensville Heights, OH

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THE PRACTICE OF ECHOCARDIOGRAPHY AT CLEVELAND CLINIC 2022
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Live stream

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September 22–23
Cleveland, OH, and live stream

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Warrensville Heights, OH

GLOBAL EP 2022
September 23–24
Cleveland, OH

INTENSIVE REVIEW OF GASTROENTEROLOGY AND HEPATOLOGY
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Las Vegas, NV

CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE
September 28–30
Cleveland, OH

CLEVELAND CLINIC NEPHROLOGY UPDATE
September 29–October 1
Cleveland, OH

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ADVANCING CARDIOVASCULAR CARE: CURRENT AND EVOLVING MANAGEMENT STRATEGIES
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Dublin, OH

PRACTICAL MANAGEMENT OF STROKE
October 7
Cleveland, OH

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 7–9
Cleveland, OH

CARDIOVASCULAR UPDATE FOR THE PRIMARY CARE PROVIDER
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Cleveland, OH

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SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
December 3–4
Lake Tahoe, NV

2023

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A 69-year-old man was referred to our hospital with a 6-month history of progressive swelling in the right middle finger without systemic symptoms. There was no previous trauma or surgery to the finger. The patient had previously been diagnosed with rheumatoid arthritis treated with methotrexate and hypertension treated with cilnidipine (a calcium channel blocker).

Physical examination revealed non-tender, sausage-like swelling of the right middle finger (Figure 1) with no nail abnormality or rash suggestive of psoriasis. Laboratory testing revealed a white blood cell count of 5.4 × 10⁹/L (reference range 4.5–10.9) and a C-reactive protein level of 0.07 mg/dL (reference range 0.0–0.5). Hand radiography revealed soft-tissue swelling of the right middle finger without joint erosions or periostitis.

Dactylitis is rare in patients with rheumatoid arthritis

Magnetic resonance imaging (MRI) revealed soft-tissue swelling and thickening around the digital flexor tendon showing high intensity on short time inversion recovery (Figure 2A), and ultrasonography revealed low echoic area and power Doppler signals around the digital flexor tendon (Figure 2B), consistent with inflammation. Dactylitis is rare in patients with rheumatoid arthritis, and thus, the examination differed from that of typical rheumatoid arthritis. The patient did not show signs of other inflammatory diseases associated with dactylitis. We performed a biopsy around the digital flexor tendon of the affected finger to exclude infection.

Histology revealed exudative synovitis with lymphocyte and plasma cell infiltration. Tissue culture initially yielded no bacteria; however, mycobacterial culture was positive for Mycobacterium intracellulare. The patient was diagnosed with dactylitis due to M intracellulare infection and treated with rifampin, ethambutol, and clarithromycin. The finger swelling markedly improved over 6 months.
Dactylitis is the inflammation of a finger or toe with swelling of the entire digit rather than just a knuckle joint. Dactylitis can be classified based on the involved tissue of the digit, ie, bone only, bone and soft tissue, or soft tissue only. In addition, dactylitis may be classified according to the etiology as noninflammatory, inflammatory infectious, and inflammatory noninfectious.

Spondyloarthritis dactylitis has been described as sausage-like in appearance and involves pain and swelling of the fingers or toes, mostly along the flexor tendons. Related disorders include psoriatic arthritis, ankylosing spondylitis, enteropathic arthritis, and reactive arthritis.

MRI and ultrasonography show an increase in the volar bone-to-skin distance in dactylitic fingers that can be due to synovial thickening around the flexor tendons and may also show fluid collection in the tendon sheaths, indicating flexor tenosynovitis and adjacent soft-tissue swelling with small-joint synovitis.

Although rare, tuberculous dactylitis can be the result of extrapulmonary tuberculosis with involvement of the digit and soft tissue. Radiographs typically show bone erosion (spina ventosa) and MRI shows that the lesion often extends to the soft tissue of the digit through cortical defects forming a sinus tract.

The differential diagnosis of dactylitis includes syphilitic dactylitis, a manifestation of congenital syphilis; sarcoid dactylitis, with infiltration of the phalangeal soft tissue by noncaseating granulomas; sickle cell dactylitis, or “hand-foot syndrome,” associated with infarction of bone marrow, usually in children; and reactive distal dactylitis of the anterior fat pad, mostly due to group A beta-hemolytic streptococci. Dactylitis can also be associated with gout, resulting from deposition of monosodium urate crystals in the soft tissue of the involved digits and from infection.

**Mycobacterium intracellulare infection of a finger**

Nontuberculous mycobacteria (NTM) cause pulmonary disease in 90% of cases. NTM musculoskeletal infection is uncommon, but NTM tenosynovitis has been repeatedly reported. Wrist and hands are the most frequently reported sites of tenosynovitis, and some have described the presence of multiple granulomatous “rice bodies.” As seen in our patient, M intracellulare can infect a single digit and cause tenosynovitis-associated dactylitis.

Use of anti-tumor necrosis factor agents, high-dose corticosteroids, leflunomide, cyclophosphamide, azathioprine, cyclosporine, mycophenolate, and chlorambucil have been associated with NTM infection of soft tissue or joints.

**Disclosures**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
REFERENCES


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- Critical Care Management of Post Liver Transplant Patients
- Sepsis in Critically Ill Patients with Liver Disease
- Mechanical Ventilation in the Critically Ill Patient with Liver Disease
- Nutrition in Critically Ill Patients with Liver Disease
- Lessons Learned – Building a Liver Intensive Therapy Unit
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- Nuts and Bolts of Co-Management

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- Acute Kidney Injury in Patients with Liver Disease
- Strategies for Solid Organ Recipients (Liver & Kidney) with Cardiac: Role of Combined Cardiac Interventions
- Hemodynamic Challenges
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Which ICU patients need stress ulcer prophylaxis?

ABSTRACT

Critically ill patients are at an increased risk for developing stress ulcers of the mucosa of the upper gastrointestinal (GI) tract. Bleeding from stress ulcers was previously associated with a longer stay in the intensive care unit and an increased risk of death. Thus, most patients admitted to the intensive care unit receive stress ulcer prophylaxis. However, there is a growing concern that acid-suppression drugs may be associated with increased frequency of nosocomial pneumonia and *Clostridioides difficile* infection. In this article, the authors address controversies regarding stress ulcer prophylaxis in critically ill patients and provide guidance for its appropriate use in this setting.

KEY POINTS

- Although 75% of critically ill patients who do not receive stress ulcer prophylaxis develop stress ulcers, only a minority of these ulcers bleed.
- Positive pressure ventilation for more than 48 hours and coagulopathy are two major independent predictors of clinically important GI bleeding in critically ill patients.
- Although stress ulcer prophylaxis has not been shown to reduce mortality risk, it decreases the risk of clinically significant bleeding and does not increase risk of *C difficile* infection or pneumonia.
- The beneficial effects of stress ulcer prophylaxis on GI bleeding argue for its use in critically ill patients with risk factors for developing stress ulcers.

Most critically ill patients are at an increased risk for developing erosions and ulceration of the mucosa of the gastrointestinal (GI) tract. The exact physiology is not fully known, but postulated mechanisms include splanchnic and GI tract hypoperfusion, mucosal ischemia or disruption leading to decreased mucus secretion, and increased acid production with subsequent GI tract injury. Although about 75% of critically ill patients who do not receive stress ulcer prophylaxis develop stress ulceration, only a minority of these ulcers bleed.

Stress ulcers in critically ill patients can be divided into 3 categories, each with separate definitions and incidence rates (Table 1). Earlier studies suggested an association between stress ulceration and an increase in mortality risk and length of stay in the intensive care unit (ICU), which led to a significant emphasis on providing prophylaxis to most critically ill patients. But stress ulcer prophylaxis may not be benign, as reports of an association with increased risk of pneumonia and *Clostridioides difficile* infection spurred debate as to its role in critically ill patients.

In this article, we address controversies regarding the use of stress ulcer prophylaxis in critically ill patients. We will discuss risk factors associated with the development of stress ulcers and GI bleeding in critical illness, review evidence comparing different prophylactic agents, and provide guidance for appropriate use of stress ulcer prophylaxis in this population.
STRESS ULCER PROPHYLAXIS IN THE ICU

Which Patients Are at Increased Risk?

Numerous risk factors are associated with the development of stress ulcers in ICU patients. Perhaps the biggest risks were identified in the Canadian Critical Care Trials Group, a multicenter prospective cohort study of 2,252 critically ill patients. This study found that positive pressure ventilation for more than 48 hours (odds ratio [OR] 15.6, \( P < .001 \)) and bleeding diathesis (OR 4.3, \( P < .001 \)) are major independent predictors of clinically important GI bleeding in these patients. The incidence of stress-related GI bleeding when these risk factors were present was 3.7% vs 0.1% in patients with no risk factors. Subsequent studies have identified other risk factors associated with clinically important GI bleeding in critically ill patients (Table 2). However, as no single variable is an independent predictor of clinically important GI bleeding, the decision to use prophylaxis should be tailored to the individual patient.

What Is the Effect of Stress Ulcer Prophylaxis on Outcomes?

The effect of stress ulcer prophylaxis on mortality in patients in the ICU was evaluated in the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial, a multicenter European randomized controlled trial that included 3,298 ICU patients with at least 1 predefined risk factor for GI bleeding. Notably, 20% of these patients had coagulopathy, and 79% were receiving positive pressure ventilation. Interestingly, 90-day mortality rates were similar between groups: 31.1% in the prophylaxis group vs 30.4% in the placebo group (\( P = .76 \)).

These results have been replicated in other studies and at least 2 meta-analyses, stirring the debate as to whether stress ulcer prophylaxis is beneficial. Advocates argue that despite similar 90-day mortality rates between the treatment and placebo groups, studies evaluating this question may be subject to type II error (a false-negative error of omission) because of a potentially real but small mortality benefit related to prophylaxis. In addition, advocates point out that the rate of clinically significant GI bleeding was 41% lower in patients treated with proton pump inhibitors (PPIs) than in the placebo group (2.5% vs 4.2%), a finding that has been replicated in meta-analyses.

It should be noted that in the intervention arm of the SUP-ICU trial, more patients in the PPI group required transfusion than in the placebo group (2.5% vs 4.2%), a finding that has been replicated in meta-analyses.

Which Agent Should I Use?

Agents used for stress ulcer prophylaxis include PPIs, histamine-2 receptor blockers, and sucralfate. The

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**TABLE 1**

**Categories, definition, and incidence of stress ulcers in critically ill patients**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress ulceration with occult bleeding</td>
<td>Fecal samples with guaiac-positive test for blood</td>
<td>15%–50%</td>
</tr>
<tr>
<td>Stress ulceration with overt gastrointestinal bleeding</td>
<td>Hematemesis, bloody nasogastric tube aspirate, or melena</td>
<td>1.5%–8.5%</td>
</tr>
</tbody>
</table>
| Stress ulceration with clinically important gastrointestinal bleeding | Overt gastrointestinal bleeding plus 1 or more of the following within 24 hours:  
  - Decrease in systolic, mean arterial blood pressure, or diastolic blood pressure of ≥ 20 mm Hg  
  - Orthostatic hypotension (systolic blood pressure > 10 mm Hg) or postural tachycardia (increase in pulse ≥ 20 beats/minute)  
  - Drop in hemoglobin ≥ 2 g/dL  
  - Received transfusion of ≥ 2 units of packed red blood cells  
  - Need for vasopressors or invasive interventions (eg, endoscopy) | 1%–3%       |

Based on information in references 1 and 3–9.
choice should be tailored to the patient’s needs, comorbidities, and potential risk factors for pneumonia and *C. difficile* infection. A Cochrane meta-analysis of 18 studies (N = 1,636) reported that PPIs were more effective in suppressing gastric acid than histamine-2 receptor blockers (risk ratio [RR] 2.90, 95% confidence interval [CI] 1.83–4.58; absolute risk 4.8%, 95% CI 2.1–9.0].\(^{17}\) A 2020 randomized controlled trial of critically ill patients receiving positive pressure ventilation (N = 26,982) showed a statistically significant decrease in GI bleeding in patients taking PPIs compared with those taking histamine-2 receptor blockers (1.3% vs 1.8%, \(P = .009\)).\(^{18}\)

Although PPIs may be more effective than histamine-2 receptor blockers in preventing GI bleeding,\(^{17,18}\) there has been a concern for increased risk of pneumonia and *C. difficile* infection associated with PPIs. This concern was primarily based on a large, propensity-matched cohort study of patients on positive pressure ventilation for more than 24 hours (N = 35,312).\(^{11}\) The study showed a higher incidence of pneumonia in patients treated with a PPI than in those treated with a histamine-2 receptor blocker (38.6% vs 27%, \(P < .001\)), and a higher incidence of *C. difficile* infection with a PPI vs a histamine-2 receptor blocker (3.8% vs 2.2, \(P < .001\)).\(^{1}\)

However, the PEPTIC trial (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit)\(^{18}\) largely dispelled this concern after finding no increase in *C. difficile* infection (0.3% with a PPI vs 0.43% with a histamine-2 receptor blocker; RR 0.74, 95% CI 0.51–1.09) or in pneumonia (6.5% with a PPI vs 5.8% with a histamine-2 receptor blocker; RR 1.18, 95% CI 0.87–1.59). The PEPTIC trial results are supported by those of the SUP-ICU trial,\(^{3}\) which found no increased incidence of infectious events (composite end point of nosocomial pneumonia or *C. difficile* infection) between PPI and placebo (16.8 vs 16.9; RR 0.99, 95% CI 0.84–1.16).

In addition, data from 3 meta-analyses also did not show an increase in the risk of infectious complications (including *C. difficile* infection and pneumonia) between PPIs and histamine-2 receptor blockers.\(^{11,19,20}\) Given these data, we prefer an oral PPI to a histamine-2 receptor blocker when indicated in high-risk patients who can receive enteral nutrition to decrease their risk of clinically significant GI bleeding. Table 3 shows dosing recommendations.\(^{21}\) We do not use intravenous PPIs unless a patient is actively bleeding from a stress ulcer or cannot tolerate enteral nutrition, because intravenous PPI is significantly more expensive than oral PPI therapy.\(^{22}\) In rare cases in which PPIs and histamine-2 receptor blockers cannot be used for prophylaxis (eg, because of drug intolerance or interactions), sucralfate may be considered as an alternative.

### TABLE 2

<table>
<thead>
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<th>Major risk factors (prophylaxis recommended)</th>
</tr>
</thead>
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<td>Positive pressure ventilation &gt; 48 hours, including extracorporeal life support</td>
</tr>
<tr>
<td>Coagulopathy (platelet count &lt; 50 × 10⁹/L, international normalized ratio &gt; 1.5, activated partial thromboplastin time &gt; 2 times normal)(^a)</td>
</tr>
<tr>
<td>History of gastrointestinal ulceration or bleeding within past year</td>
</tr>
<tr>
<td>Acute traumatic brain or spinal cord injury</td>
</tr>
<tr>
<td>Major thermal injury (≥ 35% of total body surface area)</td>
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</table>

<table>
<thead>
<tr>
<th>Minor risk factors (prophylaxis recommended if ≥ 2 minor criteria are present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Intensive care unit stay &gt; 1 week</td>
</tr>
<tr>
<td>Occult gastrointestinal bleeding for ≥ 6 days</td>
</tr>
<tr>
<td>Glucocorticoid therapy (&gt; 250 mg of hydrocortisone or the equivalent)</td>
</tr>
<tr>
<td>Use of antplatelet or nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Renal failure or renal replacement therapy</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>History of peptic ulcer disease</td>
</tr>
<tr>
<td>Extracorporeal life support</td>
</tr>
<tr>
<td>Organ transplantation</td>
</tr>
</tbody>
</table>

\(^a\)Independent predictors of clinically important gastrointestinal bleeding in critically ill patients.

Based on information in references 3, 5, 6, 8, and 12.

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**DOES ENTERAL NUTRITION REDUCE THE RISK OF DEVELOPING STRESS ULCERS?**

Emerging data show that the incidence of stress ulcers may be lower in patients receiving enteral nutrition in the ICU. In these patients, it is unclear whether stress ulcer prophylaxis is indicated. In a meta-analysis, Huang et al\(^{23}\) concluded that prophylaxis provides no added benefit to patients receiving enteral nutrition. They found no statistically significant difference in the rate of GI bleeding. They reported that prophylaxis had no effect on overall mortality, duration of positive pressure ventilation, incidence of *C. difficile* infection, or ICU length of stay.\(^{23}\) Early enteral nutrition is recommended as it promotes gut integrity, decreases infectious morbidity, and may lower mortality risk.\(^{24}\) Because there are no data from prospective randomized controlled trials on enteral nutrition as...
a sole means of stress ulcer prophylaxis, we believe that enteral feeding should not replace prophylaxis in high-risk critically ill patients.

■ WHAT IS THE OPTIMAL DURATION OF STRESS ULCER PROPHYLAXIS IN ICU PATIENTS?

The optimal duration of stress ulcer prophylaxis in ICU patients is unclear. While most experts agree that prophylaxis should be used if risk factors are present, there is limited agreement on when to stop it.25 A practical approach would be to evaluate indicators associated with a high risk for developing stress ulcers. Once these stressors have been mitigated, prophylaxis could possibly be de-escalated. This approach, while not validated, may be reasonable given the low risk of bleeding from stress ulcers in non-ICU hospitalized patients (0.29%).26

■ DISCLOSURES

Dr. Bass has disclosed consulting for AbbVie Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.


■ THE BOTTOM LINE

In some critically ill patients, the risk of clinically significant GI bleeding is high. Stress ulcer prophylaxis does not reduce mortality rates. But on the other hand, it decreases the risk of clinically significant bleeding and does not increase the risk of C difficile infection or pneumonia. Based on these findings, we believe that prophylaxis should be considered in critically ill patients with risk factors for stress ulcers. Frequent reassessment and de-escalation of therapy are warranted when the patient is at lower risk for bleeding.

### TABLE 3

Dosing recommendations for stress ulcer prophylaxis

<table>
<thead>
<tr>
<th>Route</th>
<th>Proton pump inhibitor</th>
<th>Histamine-2 receptor blocker</th>
<th>Sucralfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>Pantoprazole 40 mg/day</td>
<td>Famotidine 20 mg every 12 hours</td>
<td>Sucralfate 1 g every 6 hours</td>
</tr>
<tr>
<td>Enteral</td>
<td>Pantoprazole 40 mg/day</td>
<td>Famotidine 20 mg every 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

Based on information in reference 21.


Address: Mariam Saeed, MD, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; saeedm@ccf.org
Unraveling a challenging diagnosis: Role of a TNF inhibitor

A 48-year-old male industrial electrician presented for consultation with a 5-year history of pain and swelling of the dorsum of the right hand, with limited mobility of the right wrist and flexion of the fourth finger. The hand inflammation had begun as a red nodule on the dorsum of the second metacarpophalangeal joint, which slowly progressed to a soft, doughy-looking, subcutaneous mass encompassing the dorsum of the right hand (Figure 1).

The patient's previous mycobacterial and fungal cultures, stains for organisms, and purified protein derivative testing for tuberculosis were negative. Also, chest radiography and thoracic computed tomography were normal. The pathologist suggested the diagnosis of chronic cutaneous sarcoidosis with tenosynovitis. The patient was treated with prednisone 15 mg daily and methotrexate 15 mg weekly with daily folate supplementation. However, the hand pain and swelling persisted, and new areas of inflammation appeared. Biopsies from right olecranon bursitis 2 years later (patient still on prednisone and methotrexate) and from a right forearm mass 3 years later again revealed noncaseating granulomata with negative cultures.

When we saw the patient, because previous mycobacterial and fungal cultures were negative on 3 different occasions, and because histologic re-evaluation of previous slides revealed noncaseating granulomatous inflammation with multinucleated giant cells, the initial diagnosis of sarcoidosis was still considered likely. Hence, infliximab, a monoclonal antibody that binds to tumor necrosis factor-alpha (TNF-alpha), was added to treat the presumably refractory sarcoidosis.

One week after the second infusion, the swelling and redness of the right hand became noticeably worse. Infliximab was discontinued, and diagnostic tenosynovectomy was performed, along with another deep biopsy of the right dorsal hand mass (the patient’s fourth biopsy). Rice bodies were extruded through...
the surgical incision (Figure 2). Stains for bacteria, mycobacteria, and fungus were negative. However, an acid-fast bacillus grew on culture and was identified as *Mycobacterium marinum* by sequence identification. Infliximab was presumed to have unmasked the underlying chronic infection.5,6 Methotrexate was discontinued, and the patient was weaned from prednisone. The microbiology laboratory was alerted to include sustained cultures at lower temperatures, and *M marinum* grew at 23 days. Based on in vitro minimum inhibitory concentration values, the patient was started on rifampin, ethambutol, and azithromycin.

Eight months later, the patient required surgical repair of a ruptured right middle finger extensor tendon (Figure 3). One year after that repair, while still receiving antibiotics, he experienced swelling of the right olecranon bursa, requiring excision. Ziehl-Neelsen stain of smears from mycobacterial growth indicator bottles revealed *M marinum* microcolonies, and the tissue tested positive for *M marinum* by sequence identification. At that time, the patient was started on trimethoprim-sulfamethoxazole based on its reported efficacy in eradicating treatment-refractory *M marinum* infection, and the other antimycobacterial antibiotics were discontinued. Treatment was continued for 2 years after the complete resolution of symptoms and findings.

**FEATURES OF M MARINUM INFECTION**

*M marinum* is a nontuberculous mycobacterium that usually infects humans by exposure to contaminated fresh or marine water through damaged skin. Notably, apart from this patient’s exposure as an industrial electrician to cooling water pools for induction furnaces, he had no clear history of exposure to any recognized water source for *M marinum* infection.

*M marinum* infection can present as a nodular granulomatous dermatitis resembling cutaneous sarcoidosis7 or as tenosynovitis. It often starts as a solitary violaceous or red plaque or nodule, sometimes with a crusted or verrucous surface, which can spread along lymphatics, similarly to lymphangitic sporotrichosis.7

In immunocompetent patients, the infection is usually limited to the skin and soft tissues, whereas disseminated *M marinum* infections can occur in patients with HIV/AIDS and other immunocompromised states. Infected synovial fluid, bursae, or tendon sheaths may contain rice bodies, ie, small, loose pellets that resemble polished grains of white rice. They are composed of cellular debris or sloughed infarcted synovium, surrounded by fibrin, sometimes with a collagenous core. In the past, rice bodies were mainly associated with poorly controlled rheumatoid arthritis. Currently, they are more often associated with chronic (especially mycobacterial) infection.

*M marinum* grows optimally at 32°C (89.6°F), and growth is inhibited at 37°C (98.6°F). The infection involves the colder parts of the body, especially the extremities. Ziehl-Neelsen stain of biopsy specimens is rarely positive. Therefore, cultures should be obtained and observed for at least 6 weeks and are ultimately positive in up to 80% of patients.7 In our patient’s case, all previous cultures before presentation to our clinic were reportedly negative, presumably because
of the low number of organisms in the clinical specimens and incubation of the tissue at 37°C (not at 28°C–32°C) in the microbiology laboratory due to lack of suspicion for M marinum infection.

TNF-alpha plays an essential role in granuloma formation, limiting the spread of mycobacterial infection. When a TNF-alpha inhibitor was started in this patient, it permitted rapid multiplication of organisms, leading to a positive acid-fast bacillus culture and detection of M marinum by sequence identification, ultimately revealing the diagnosis.5,6

■ WHEN TO SUSPECT M MARINUM INFECTION

M marinum should be considered when a patient presents with nonhealing nodular skin lesions in the distal extremities. The differential diagnosis of such lesions should also include granulomatous fungal infections such as sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis. Other chronic skin infections with a similar presentation are cutaneous tuberculosis, other nontuberculous mycobacterial infections, leishmaniasis, and nocardiosis. Cutaneous sarcoidosis should be considered in the differential diagnosis, as in our patient’s case, but sarcoidosis remains a diagnosis of exclusion.

In our patient, the absence of exposure to fish tanks or outdoor water and the repeatedly negative mycobacterial and fungal cultures swayed us from initially suspecting the correct diagnosis. Eventually, an unexpected response to TNF-alpha antagonist therapy facilitated recognition of the correct diagnosis. Infections with M marinum in patients receiving TNF-alpha antagonists and other biologic agents have been well described.5,6

■ TREATMENT CHALLENGES

Therapy of M marinum is not standardized.7 The organism is generally resistant to isoniazid, pyrazinamide, and para-aminosalicylic acid. In a study of 63 clinical cases, rifamycins and clarithromycin were the most potent agents against M marinum.8 There is no consensus on the duration of therapy, as there are no randomized controlled trials. Combination therapy is recommended for immunosuppressed patients. In addition, surgical debridement is often needed to facilitate cure. In immunocompetent patients, treatment should continue for at least 2 months after all skin lesions have healed. Immunocompromised patients require therapy with 2 agents for at least 6 months after the resolution of all skin lesions.

Acknowledgment: The author thanks the patient for permission to share his information.

■ DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

■ REFERENCES


Address: Soumya Chatterjee, MD, MS, FRCP, FACP, FACR, Department of Rheumatic and Immunologic Diseases, Orthopaedic and Rheumatologic Institute, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chattes@ccf.org
A 43-year-old woman presented to the outpatient breast clinic with a 2-week history of pain and skin tightness over the right breast. She had no history of breast-related surgeries or trauma and was not on any regular medication. Physical examination revealed a subcutaneous cord-like, fibrous, tender lesion running diagonally from the upper outer quadrant of the right breast to the right flank, causing skin retraction and a groove over the outer half of the right breast when the right arm was stretched upward (Figure 1).

Doppler ultrasonography revealed a noncompressible, dilated, subcutaneous vein without flow, supporting the diagnosis of Mondor disease of the breast, which commonly presents superficially in the lateral part of the breast. Mammography revealed no abnormality. The lesion and pain resolved within 4 weeks of presentation without medication, and 6-months follow-up showed no recurrence (Figure 2).

**Mondor disease of the breast**

Mondor disease of the breast is a benign clinical condition characterized by thrombophlebitis of the superficial veins of the anterolateral thoracoabdominal wall, occurring most commonly in women in the third to fifth decades,\(^1\,^2\) with incidence ranging from 0.08% to 0.94% in breast studies in Greece, Ghana, and China.\(^2\,^3\) Diagnosis is usually based on history and physical examination and can be ultrasonographically confirmed.\(^1\) In 45% of cases, primary Mondor disease of the chest wall is idiopathic. Secondary Mondor disease involves predisposing or underlying factors,
the most common causes being traumatic (22%) and iatrogenic (20%).

Although association with breast cancer is less frequent (5%), Mondor disease can occasionally be caused by breast cancer (11.7%) and does not rule out the presence of a tumor. Therefore, a thorough breast evaluation including diagnostic imaging is recommended. In addition to local manifestations, concomitant symptoms such as fever and malaise should be considered to rule out the possibility of underlying systemic inflammatory disease.

Mondor disease of the breast is typically a self-limiting condition, with spontaneous resolution in 4 to 8 weeks. Pain may be managed with anti-inflammatory and analgesic drugs. It is important for the clinician to recognize this condition, provide reassurance, and avoid unnecessary investigation.

■ DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

■ REFERENCES


Address: Toshiyuki Yamaguchi, MD, Department of Surgery, Asama Nanorku Komoro Medical Center. 3-3-21, Aioicho, Komoro-shi, Nagano 384-8588, Japan; koseihp@ctknet.ne.jp
Women’s health update: A literature review impacting primary care

ABSTRACT

The authors review studies on key issues in women’s health with potential impact on internal medicine practice. The reviewed articles discuss cardiovascular disease risks, bone health, breast cancer genetics, cervical cancer prevention, depression in the peripartum period, pelvic pain, and emergency contraception. The key issues in women’s health continue to be cardiovascular disease risk, bone health, breast cancer risk, cervical cancer prevention, postpartum depression, pelvic pain, and emergency contraception. The authors review studies on these topics with potential impact on internal medicine practice.

CARDIOVASCULAR DISEASE RISK STRATIFICATION: MIGRAINES WITH AURA, MENOPAUSAL VASOMOTOR SYMPTOMS

A 49-year-old woman has had migraines accompanied by aura for a year and recently developed hot flashes that awaken her from sleep 4 nights each week. Her sister also experiences migraines and was started on a statin as her doctor noted her increased risk for heart disease. The patient asks if she needs medication to reduce her own risk.

Migraines with aura and cardiovascular risk

Migraines with aura have been associated with higher adjusted incidence of cardiovascular disease (CVD) in women but how this risk compares with other risk factors has not been known. A study by Kurth and colleagues evaluated the association of migraine with aura and risk of CVD. A total of 27,858 US female health professionals (mean age 54.7), without CVD at baseline, provided lipid measurements. At baseline, 1,435 (5.2%) self-reported a history of migraine with aura, 2,177 reported migraine without aura, and 24,246 had no migraine. The primary outcome was major CVD, including first myocardial infarction, stroke, or CVD death. Participants were followed for a mean 22.6 years.

For women with migraine with aura, the adjusted incidence rate of major CVD events was 3.36 (95% confidence interval [CI] 2.72–3.99) per 1,000 person years compared with 2.11 (95% CI 1.98–2.24) for migraine without aura, a statistically significant difference ($P < .001$). The risk associated with migraine with aura was significantly higher than that associated with obesity, low high-density lipoprotein cholesterol, or high triglycerides but not significantly different than participants with elevated systolic blood pressure, high total cholesterol, or family history of myocardial infarction prior to age 60. The CVD incidence rates associated with current smoking and diabetes was significantly higher than those with migraine with aura ($P = .02$).

An important limitation of this study is that data were self-reported. In addition, information regarding management of migraines and other risk factors was not available. While this paper demonstrates increased risk for cardiovascular events in women with migraine with aura, to date, evidence is limited with respect to targeted use of aspirin or statins for prevention in this population.
Menopausal vasomotor symptoms and cardiovascular risk

Prior studies have suggested that vasomotor symptoms (eg, hot flashes, night sweats) are associated with an unfavorable CVD risk profile, but the association with clinical CVD has been less clear.17−23 Zhu and colleagues2 published a pooled analysis of 23,365 women in 6 prospective studies that contributed to the InterLACE (International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events) Consortium. Predictors included frequency, severity, and timing of vasomotor symptoms; the primary outcome was incidence of CVD. Using Cox proportional hazard models, hazard ratios were estimated for the association of vasomotor symptoms with CVD incidence. Vasomotor symptom severity was measured as never, mild, moderate, or severe.

There was no association between the frequency of vasomotor symptoms and CVD.2 Severe vasomotor symptoms were associated with an increased risk of CVD. The hazard ratio for the association between CVD and hot flashes, night sweats, and any vasomotor symptoms was 1.83 (95% CI 1.22−2.73), 1.59 (95% CI 1.07−2.37), and 2.11 (95% CI 1.62−2.76), respectively. Early or late onset of symptoms were associated with increased CVD incidence when compared with no symptoms. In conclusion, severe vasomotor symptoms, not frequency, are associated with an increased risk for CVD.

History of migraine with aura or menopausal vasomotor symptoms and risk assessment

Women with migraine with aura had a higher adjusted CVD incidence than women with migraine without aura or women without migraine.2 The degree of risk was similar to that associated with elevated systolic blood pressure or high total cholesterol. Severity of vasomotor symptoms, but not frequency, may also help with identifying women at higher risk for CVD.

Our approach is to consider migraine with aura and menopausal vasomotor symptoms as risk factors when engaging in shared decision-making with patients to reduce cardiovascular risk.

Bone health

A 73-year-old woman has been taking alendronate for 3 years, however, recently read that alendronate could increase fracture risks. She asked if she should stop or shorten therapy duration.

Atypical femur fractures vs fracture prevention

Bisphosphonates reduce hip fracture risk and are first-line medication for osteoporosis treatment,24,25 however, have been associated with atypical femoral fractures and osteonecrosis of the jaw.26 When communicating with patients about bisphosphonate use, discussing the magnitude of benefits and risks fosters shared decision-making.

Black and colleagues3 evaluated the association between bisphosphonate use and atypical femoral fracture in female patients ages 50 and over who were receiving bisphosphonates between 2007 and 2017 and were enrolled in the Kaiser Permanente Southern California healthcare system. Atypical femoral fracture was the primary outcome, and bisphosphonate-associated atypical fractures were compared with other prevented fractures when bisphosphonate use was terminated.

In 196,129 women who used bisphosphonates at any time during the study period, 277 experienced atypical femoral fractures (1.74 fractures per 10,000 patient years).3 The incidence of atypical fractures increased as duration of bisphosphonate use increased. The hazard ratio for duration of use (compared with use < 3 months) was 8.86 (95% CI 2.79−28.20) for 3 to 5 years and 43.51 (95% CI 13.70−138.15) for 8 or more years. Race impacted risk (hazard ratio for Asian vs White patients 4.84; 95% CI 3.57−6.56), as did shorter height, higher weight, and glucocorticoid use. Atypical femoral fractures rapidly decreased with bisphosphonate discontinuation,3 although the absolute risk of atypical femur fracture remained very low compared with reduction in risk of hip, vertebral, and humerus fractures with continuation of bisphosphonate treatment.4

In 10,000 White women treated for 3 years, there would be 149 hip fractures prevented and 2 atypical femoral fracture would occur.3 In 10,000 Asian women treated for 3 years, 91 hip fractures would be prevented and 8 atypical femoral fracture would occur.

In conclusion, atypical femoral fracture risk increased with longer duration of bisphosphonate treatment and declined rapidly after discontinuation. The absolute risk of atypical femoral fracture remains low compared to the reduction in hip, vertebral, and humerus fractures with bisphosphonate treatment.
Optimal duration of bisphosphonate therapy

Although the optimal duration of treatment with bisphosphonates remains uncertain, the 2017 American College of Physicians guidelines recommend treating osteoporotic women with pharmacologic therapy for 5 years and to consider a longer duration of treatment in higher-risk individuals.27 Determining the continuation of bisphosphonate treatment after 5 years is complicated. In a recent retrospective study of 29,685 women who had taken bisphosphonates for 5 years, authors evaluated the impact of stopping therapy, continuing for 2 years, or continuing for 5 more years on hip fracture incidence.5 There was no difference in hip fracture incidence for patients who continued for 5 more years, compared with patients who stopped after 5 years. However, hip fracture risk was lower in those who continued for only 2 additional years and then stopped. Discontinuation of bisphosphonates at different time intervals needs additional study.

Should this patient continue bisphosphonate therapy?

Although atypical femoral fractures are associated with bisphosphonate use, the absolute risk remains low compared with the reduction in hip and other fractures. Our patient should continue bisphosphonate treatment and should complete at least 5 years of treatment. Decision-making about continuing treatment beyond 5 years remains complicated and should be evaluated at that time.

PERIPARTUM DEPRESSION MANAGEMENT AND DIAGNOSIS

A 34-year-old woman, pregnant for the first time and in her first trimester, indicated that she is having increasing symptoms of both anxiety and depression. The Edinburgh Postnatal Depression Scale was administered resulting in a score of 11. During the visit, the patient wonders if she should continue to take duloxetine, prescribed for her diagnosis of relapsing-remitting depression, during pregnancy.

Depression in pregnancy is common,28 is often undertreated,29 and has been associated with adverse outcomes for the mother, developing fetus, and newborn.30,31 The 10-item Edinburgh Postnatal Depression Scale is universally accepted, used, and recommended by the US Preventive Services Task Force.32,33 However, the US Preventive Services Task Force does not specify a cutoff value for depression diagnosis in pregnant and postpartum patients.33,34

Depression screening during pregnancy and postpartum

The Edinburgh Postnatal Depression Scale screening accuracy in pregnant and postpartum women was evaluated in a systematic review and meta-analysis of individual participant data from 58 studies (15,557 women at least 18 years of age, 2,069 with major depression).6 Data included both Edinburgh Postnatal Depression Scale scores and major depression classification based on validated interviews. Assessments were conducted no more than 2 weeks apart, either during pregnancy or within 12 months of giving birth.

Overall, combined sensitivity and specificity for depression diagnosis were maximized at a cutoff value of ≥ 11 (81% and 88%, respectively).6 Accuracy was similar in pregnant and postpartum women. A cutoff value of ≥ 13 was less sensitive but more specific (66% and 95%, respectively) and may be more useful in identifying women with a high symptom burden.

Is duloxetine safe in pregnancy?

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor used in the treatment of depression, fibromyalgia, chronic musculoskeletal pain, and generalized anxiety disorder—all conditions that commonly affect women of childbearing age.35 Limited safety data exist with respect to adverse pregnancy outcomes.

Huybrechts et al conducted a population-based cohort study using data from the United States Medicaid Analytic eXtract from 2004 to 2013 to evaluate the risk of adverse maternal and infant outcomes following in utero exposure to duloxetine.

The study population included pregnant women ages 18 to 55 and their live-born infants who were exposed to duloxetine.7 Exposure was defined as filling at least 1 outpatient prescription for duloxetine. Authors considered 4 reference groups:

• Women not exposed to duloxetine
• Women exposed to selective serotonin reuptake inhibitors
• Women exposed to another serotonin-norepinephrine reuptake inhibitor (venlafaxine)
• Women exposed to duloxetine before but not during pregnancy.

Primary outcomes included congenital malformations, preterm birth, cardiac malformations, small for gestational age infant, pre-eclampsia, and postpartum hemorrhage.7 Several potential confounding variables were considered, and propensity score stratification was used to account for imbalances between groups.

Compared with unexposed pregnancies, there was
BREAST CANCER RISK GENES

Between 5% to 10% of patients with breast cancer have a pathologic genetic variant, thus the US Preventive Services Task Force recommends that women with a personal or family history of breast or ovarian cancer be screened with one of several breast cancer risk assessment tools and offered genetic counseling and possibly genetic testing based on the results. Since the identification of BRCA1 and BRCA2 in the mid-1990s, genetic testing for cancer susceptibility has become more affordable and more common. Several multigene panel tests are available for clinician use. These panels include breast cancer risk genes as well as variants of uncertain significance, leading to challenges in interpretation.40

Genes most associated with breast cancer

Two studies addressed genetic variants and breast cancer risk.8,9 Hu et al8 and the Breast Cancer Association Consortium9 published population-based case-control studies with similar results. Hu et al compared 32,247 US breast cancer patients with 32,544 healthy controls by sending the same multigene panel with 28 cancer-predisposition genes from both groups.8 Most participants in the sample (75%) identified as White.9 The Breast Cancer Association Consortium study included 60,466 breast cancer patients and 53,461 controls from 27 mostly European countries and used a similar panel with 34 putative susceptibility genes in their analysis.9 In both studies, the multigene panel analysis was applied to previously collected DNA samples that were entered into consortium databases with patient consent.8,9

Several genes were found to be significantly associated with strong or moderate breast cancer risk: BRCA1, BRCA2, PALB2, CHEK2, and ATM.8,9,41,42 BRCA1, BRCA2, and PALB2 conferred the highest breast cancer risk, aligning with current guidelines to discuss risk-reducing mastectomy with those patients.41,42 CHEK2 and ATM were associated with elevated, but more moderate, risk. In the study by Hu et al,8 BRCA1, BRCA2, and PALB2 conferred the strongest risk for breast cancer, with odds ratios ranging from 3.83 for PALB2 (95% CI 2.68–5.63, P < .001) to 7.62 for BRCA1 (95% CI 5.33–11.27, P < .001). More moderate risk for breast cancer was associated with CHEK2 (odds ratio 2.47, 95% CI 2.02–3.05, P < .001) and ATM (odds ratio 1.82, 95% CI 1.46–2.27, P < .001) genes. Notably, in both studies, the majority of variants of uncertain significance were not associated with breast cancer risk.8,9

Does this patient need to be re-tested for breast cancer risk genes?

Additional genes have been identified since this
patient’s test 15 years ago. While ideally, the person who experienced breast cancer (in this case, the patient’s sister) would be re-tested, this is not always possible for a given patient. The patient’s family history meets guidelines for genetic testing, and it is reasonable to offer repeat testing to look for these additional culprit genes. Additionally, she may be a candidate for chemoprevention or breast magnetic resonance imaging depending on results of individualized risk assessment, regardless of the genetic testing outcome.

CERVICAL CANCER PREVENTION

A 41-year-old patient returned to your office after seeing her obstetrician-gynecologist for management of cervical intraepithelial neoplasia (CIN) 2. She asked if there is anything to do to reduce her cervical cancer risk. She shared that she had been uncertain about vaccinating her 11-year-old daughter but was now reconsidering, asking, “Does this vaccine really prevent cervical cancer?”

Human papillomavirus virus vaccination indications

The US Food and Drug Administration approved a quadrivalent human papillomavirus (HPV) vaccine in 2006 while the currently used 9-valent version was subsequently approved and prevents infection with 7 cancer-associated HPV types (16, 18, 31, 33, 45, 52, 58) and 2 genital wart-associated HPV types (6, 11). Individuals ages 9 through 45 may be vaccinated, though the Advisory Committee on Immunization Practices recommends routine vaccination only for persons ages 9 through 26 and shared decision-making for catch-up vaccination in adults ages 27 to 45. In 2018, only 51% of US adolescents were up-to-date with the HPV vaccine series.

HPV vaccination has now been demonstrated to reduce the risk of cancer, as well as invasive CIN

HPV vaccine as adjuvant therapy for high-grade cervical intraepithelial neoplasia
Receipt of the quadrivalent HPV vaccine may reduce the risk of recurrent, high-grade CIN when used as adjuvant therapy for cervical dysplasia. Lichter et al performed a systematic review and meta-analysis to evaluate the efficacy of adjuvant HPV vaccination in preventing recurrence after surgical excision by studying 2,984 women in 6 studies who had received a diagnosis of CIN 2 or greater. Patients with invasive disease, immunodeficiency, or autoimmune conditions were excluded. All patients underwent surgical excision, and only the intervention group members also received adjuvant HPV vaccination. Comparison group members received placebo or surgical management alone. At 6 to 48 months, recurrence of CIN 2 or greater was significantly decreased in HPV vaccine recipients (RR 0.36, 95% CI 0.23–0.55) with a number needed to treat for benefit (NNTb) of 28. Recurrence of CIN 1 or greater irrespective of HPV type was decreased (RR 0.67, 95% CI 0.52–0.85; NNTb 30), and recurrence of CIN 2 or greater with HPV 16 or 18 was also decreased (RR 0.41, 95% CI 0.20–0.85, NNTb 83).

HPV vaccination for primary prevention of cervical cancer

Previous studies of HPV vaccination used the surrogate endpoint of prevention of high-grade cervical cancer lesions to evaluate efficacy. In this registry-based cohort study, Lei et al evaluated the rate of invasive cervical cancer in 1,672,983 Swedish girls and women ages 10 to 30 from 2006 to 2017 received either ≥1 dose of the quadrivalent HPV vaccination or no HPV immunization. After adjustment for covariates, cervical cancer incidence was reduced in the intervention group by 88% if the immunization occurred prior to age 17, as demonstrated by an incidence rate ratio of cervical cancer of 0.12 (95% CI 0.00–0.34); for those immunized between ages 17 and 30, cervical cancer incidence was reduced by 53%, with an adjusted incidence rate ratio of 0.38 (95% CI 0.12–0.72).

Should this patient and her daughter receive HPV vaccination?

Given the safety of HPV vaccination and relatively low NNTb, this patient should receive HPV vaccination. As her daughter is under 17, now is the ideal time for cervical cancer prevention with HPV immunization.

EMERGENCY CONTRACEPTION

A 31-year-old woman participated in unprotected intercourse 2 days before presenting at the clinic. She tried to obtain ulipristal from the pharmacy, but it was not in stock. She heard that intrauterine devices (IUDs) are effective emergency contraception and asked for “the one that leads to lighter periods.”

Levonorgestrel IUD as emergency contraception

Observational studies have suggested that levonorgestrel IUDs may be effective for emergency contraception. Turok et al performed a randomized, controlled trial comparing levonorgestrel and copper IUDs for...
emergency contraception. Inclusion criteria included women ages 18 to 35, fluent in English or Spanish, requesting emergency contraception after unprotected sexual intercourse within the previous 5 days (120 hours). Other eligibility involved participants with a desire to initiate use of an IUD, to prevent pregnancy for at least 1 year, negative urine pregnancy test, history of regular menstrual cycles, and known date of last menstrual period. Women were excluded if they were breast feeding, had vaginal bleeding of unknown origin, intrauterine infection within 3 months, untreated gonorrhoeal or chlamydia infection within prior 30 days, used oral emergency contraception within the preceding 5 days, or had copper allergy.

The intervention cohort received IUD (levonorgestrel 52 mg), and the control group received copper IUDs. The primary outcome was a positive urine pregnancy test 1 month after IUD insertion using a noninferiority margin of 2.5 percentage points; secondary outcomes included IUD discontinuation, participant satisfaction, and bleeding outcomes.

Over one-quarter of patients had a body mass index > 30 kg/m²; 711 women presented to 6 different sites in Utah seeking emergency contraception. For the primary outcome of pregnancy, there was 1 pregnancy in 317 participants who received the levonorgestrel IUD and 0 pregnancies in 321 participants who received the copper IUD—the between-group absolute incidence was 0.3, which was not statistically significant. There was no difference between groups in rates of IUD expulsion, removal, or need for medical care within 1 month of IUD placement. Satisfaction rates were similar.

**Can this patient be offered a 52-mg levonorgestrel IUD for emergency contraception?**

This study demonstrates that levonorgestrel 52-mg IUD is noninferior to the copper IUD in providing emergency contraception. As this patient reports an interest in lighter menses, the levonorgestrel IUD may be an appropriate therapeutic option to offer in shared decision-making, particularly when body mass index limits the effectiveness of other emergency contraception options. However, the US Food and Drug Administration has not yet approved levonorgestrel IUD for emergency contraception, which may limit its use for this indication.

**CURRENT TREATMENT OF CHRONIC PELVIC PAIN**

A female patient presented for follow-up of chronic pelvic pain. She previously underwent extensive evaluation, including laparoscopy, which did not reveal the cause of her symptoms. Her aunt takes gabapentin for chronic pain, and she asks if this is a good treatment option for her.

Chronic pelvic pain refers to noncyclic pain localized to the pelvis, lasting 3 to 6 months, and is associated with substantially reduced quality of life for affected individuals. While comprehensive history taking, physical examination, and testing may identify a specific etiology, often, the etiology is complex involving pelvic floor disorders, may overlap with other chronic pain syndromes such as irritable bowel syndrome or bladder pain syndrome, or may not have an identifiable cause. Many individuals who have experienced trauma suffer from chronic pelvic pain.

**Gabapentin for chronic pelvic pain**

Current pathophysiologic models focus on a common pathway involving the central pain response, and gabapentin is often chosen as treatment based on its efficacy in other chronic pain conditions. Small trials have shown modest improvement in pain for patients with chronic pelvic pain treated with gabapentin.

Horne et al performed a larger multicenter, randomized, double-blind, placebo-controlled trial in 39 hospital centers in the United Kingdom to assess the efficacy and safety of gabapentin for the treatment of chronic pelvic pain in women with no structural or infectious cause of symptoms. Participants were included (n = 306) if they had experienced chronic pelvic pain for at least 3 months with or without dysmenorrhea, were using contraception, and had no evidence of pelvic pathology on laparoscopy performed at least 2 weeks and less than 36 months before enrollment. Similar to previous trials, intervention group participants received gabapentin, titrated to a maximum dose of 2,700 mg/day; control group participants received matching placebo. The primary outcome was a reduction in pain on a rating scale (0–10) and reported adverse events at 16 weeks.

At baseline, the majority of participants experienced dysmenorrhea, were using hormonal contraception, identified as White, and had previously used non-steroidal anti-inflammatory drugs and opiates as rescue medications. Baseline pain scores between groups were similar, with average scores of 5.5 in both groups and worst scores of 8.4 and 8.6 in treatment and placebo groups on a 10-point scale.

At 16 weeks, there was no difference between groups in either worst pain score or average pain scores. Participants in the gabapentin cohort had a mean decrease in average pain scores of 1.1 (standard deviation [SD]
2.0) and decrease in worst pain scores of 1.4 (SD 2.3); the placebo cohort reported decreases of 0.9 (SD 1.8) in average pain score and 1.2 (SD 2.1) in worst pain score. Significantly more participants in the gabapentin cohort reported adverse events that included dizziness (54% vs. 28%, risk ratio 1.91, \(P = .0002\)), drowsiness (52% vs 29%, risk ratio 1.71, \(P = .002\)), and visual disturbances (22% vs 11%, risk ratio 2.25, \(P = .01\)).

Strengths of the trial include its size; prior trials included fewer than 100 patients each. The trial ended after 16 weeks, which may have limited its ability to detect a difference with longer-term use as seen in the smaller studies. However, none of the gabapentin trials offer insight into participants’ comorbid pain conditions or participation in multidisciplinary treatment approaches, a limitation in their generalizability.

### Should this patient be offered gabapentin?
In Horne et al., gabapentin did not result in lower pain scores but led to more dizziness, drowsiness, and visual disturbances than placebo, and earlier, smaller studies showed modest benefit. Clinicians considering the use of gabapentin to treat chronic pelvic pain should note the side effects and potential modest effects when discussing with patients and determining next steps in shared decision-making.

### TAKE-HOME POINTS

- Migraine with aura and severe vasomotor menopausal symptoms can be considered when determining a patient’s cardiovascular disease risk.
- Consider overall benefits and risks of bisphosphonates when counseling patients, specifically the low incidence of atypical femoral fracture compared with hip fractures.
- Obtain breast cancer genetics evaluation in patients meeting National Comprehensive Cancer Network criteria who have either never had genetic testing or did not have testing for BRCA1, BRCA2, PALB2, CHEK2, and ATM genes.
- Compared with unexposed pregnancies, duloxetine exposure confers no increased risk of congenital malformations, preterm birth, or pre-eclampsia. There is a small increase in risk for postpartum hemorrhage with late-pregnancy exposure (adjusted relative risk 1.53, 95% CI 1.08–2.18). Duloxetine is unlikely to be a major teratogen.
- The Edinburgh Pregnancy Depression Scale can be used to diagnose depression in pregnant and postpartum patients.
- HPV vaccination for primary prevention of cervical cancer can be considered as adjuvant therapy for women being treated for CIN 2 or greater.
- The levonorgestrel intrauterine device appears to be noninferior to the copper intrauterine device for emergency contraception; however, it is not yet approved for this indication by the United States Food and Drug Administration.
- Current evidence suggests caution when using gabapentin to treat chronic pelvic pain in women, with shared decision-making to discuss potential side effects and expected benefit.

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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data. BMJ 2012; 344:e1401. doi:10.1136/bmj.e1401

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Acute anxiety and tachycardia in a hospitalized 59-year-old woman

A 59-year-old woman was hospitalized after 3 days of neck pain, painful swallowing, headache, and fever. Three years earlier she had received a liver transplant because of chronic liver disease due to hepatitis C, and afterward had contracted posttransplant lymphoproliferative disease. Because she needed frequent blood tests, a subclavian port had been placed 7 months before the current presentation and last accessed 6 weeks ago. She also had stage 3 chronic kidney disease. She had no history of thyroid disease or alcohol or tobacco use.

Her medications at home included the following:

- Tacrolimus 1 mg by mouth twice a day
- Oxycodone 30 mg by mouth every 6 hours as needed
- Oxymorphone 40 mg by mouth every 12 hours as needed
- Modafinil 200 mg by mouth as needed
- Promethazine 12.5 mg by mouth as needed
- A multivitamin, fish oil, vitamin D, and calcium supplements daily.

On examination, her temperature was 38.7°C (101.7°F), heart rate 103 beats per minute, blood pressure 129/64 mm Hg, and respiratory rate 22 breaths per minute. She was alert and oriented and answered questions appropriately.

Her neck was tender to palpation all over but particularly in the left anterior area. There were no palpable masses or swollen glands or lymph nodes. The area around the subclavian port was red and tender. Cardiovascular and pulmonary examinations were normal. She had a surgical scar on the abdominal wall. The rest of the abdominal examination was normal.

Initial laboratory results are listed in Table 1.

Contrast-enhanced computed tomography (CT) of the head and neck revealed soft-tissue inflammation tracking from the left anterior chest wall, encompassing the thyroid, and reaching into the retropharyngeal space (Figure 1).

Blood cultures from the subclavian port grew methicillin-resistant Staphylococcus aureus after 15 hours, as did cultures from the peripheral blood after 30 hours.

Improvement, then a turn for the worse

The team removed her subclavian port, started intravenous vancomycin, and admitted her to the hospital. Three days later, contrast-enhanced CT showed marked improvement: the thyroid gland was smaller, and the inflammatory fat-stranding previously seen surrounding the gland had resolved.

However, on the patient’s fourth day in the hospital, she became increasingly short of breath, confused, agitated, and anxious. She had no focal neurologic deficits, but her mental status waxed and waned, with intermittent delirium and loss of orientation to time.

Her temperature was still 38.4°C (101.1°F), but her heart rate had risen to 153 beats per minute, blood pressure 153/107 mm Hg, and respiratory rate 33 breaths per minute. Other new findings on physical examination were the following:

- Fine inspiratory crackles at the bases of both lungs
- Eyelid lag (the top eyelids remaining high when the patient looks down)
- Pitting edema in both ankles, rated 1+ (mild) on a scale of 4
- Generalized hyperreflexia.

Electrocardiography revealed sinus tachycardia without ST-T-wave changes. Her white blood cell count was 12.8 × 10^9/L (reference range 3.4–9.6) with 78% neutrophils (reference range 40%–60%). Trans-thoracic echocardiography revealed an ejection fraction of 45% but no wall-motion abnormalities. CT angiography of the chest was negative for pulmonary embolism.

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Differential Diagnosis

Which one of the following conditions is the most likely diagnosis?

- Thyrotoxicosis, thyroid storm
- Pheochromocytoma
- Adrenal crisis
- Delirium tremens (withdrawal from heavy alcohol use)

**Pheochromocytoma** can cause many symptoms similar to those of thyroid storm, but they are often paroxysmal and brief. A systematic review by Soltani et al. found that headache, which our patient did not have, was the second most common symptom of pheochromocytoma (after hypertension), with a pooled sensitivity of 60.4% among 25 studies. Absence of the classic triad of headache, tachycardia, and diaphoresis had a negative likelihood ratio of 0.139 (95% confidence interval 0.059–0.331) for the diagnosis of pheochromocytoma.

Further, the patient had symptoms that are not

<table>
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<th>Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reference range</th>
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<tr>
<td>Hemoglobin</td>
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<td>White blood cell count</td>
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<td>Segmented neutrophils</td>
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<tr>
<td>Platelet count</td>
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<td>157–371 × 10&lt;sup&gt;9&lt;/sup&gt;/L</td>
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<td>Thyroid-stimulating hormone (TSH)</td>
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<td>Thyroxine (free T&lt;sub&gt;4&lt;/sub&gt;)</td>
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<td>Glucose</td>
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<tr>
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<td>6.3–7.9 g/dL</td>
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<td>Bilirubin</td>
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<td>≤ 1.2 g/dL</td>
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<td>Gamma-glutamyl transferase</td>
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<td>Lactate dehydrogenase</td>
<td>216 U/L</td>
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<tr>
<td>Prothrombin time</td>
<td>10.3 seconds</td>
<td>9.4–12.5 seconds</td>
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</tbody>
</table>

<sup>a</sup>Abnormal results are shown in bold.
common in pheochromocytoma such as eyelid lag, hyperreflexia, altered mental status, and lower extremity edema, overall making this diagnosis less likely.

Adrenal crisis can also present with nonspecific signs such as fever, confusion, and tachycardia. However, patients with adrenal crisis commonly have low blood pressure (not high, as in this patient) worsened by dehydration due to vomiting and diarrhea. Other features of adrenal crisis not seen in this patient are lethargy (not agitation) and a constellation of laboratory abnormalities (eg, hyperkalemia, hypercalcemia, hypoglycemia, hyponatremia). Also, this patient had not received glucocorticoids in the near past, which would have suggested adrenal insufficiency from steroid withdrawal.

Delirium tremens is not likely without other features of alcohol use disorder or withdrawal: nausea, vomiting, diaphoresis, tremors, fatigue, pallor, and mydriasis, and laboratory findings such as elevated aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, carbohydrate-deficient transferrin, and mean corpuscular volume, a mildly low platelet count, and hypomagnesemia.

Thyroid storm should be suspected in this patient in view of her rapid deterioration and findings that suggest thyrotoxicosis such as altered mental status, confusion, anxiety, sinus tachycardia, hyperthermia, hypertension, tachypnea, pulmonary crackles (likely due to pulmonary edema from acute heart failure), lower extremity pitting edema, eyelid lag, and hyperreflexia.

**HYPERTHYROIDISM AND THYROID STORM**

Hyperthyroidism is a general term that means the thyroid gland is producing thyroid hormone above normal levels.

Thyrotoxicosis is the manifestation of excessive concentrations of circulating thyroid hormone in the body due to any cause.

Thyroid storm is extreme thyrotoxicosis with physiologic decompensation resulting in severe multisystem dysfunction, often to the point of failure. Because mortality rates range from 20% to 30%, it should always be strongly suspected in patients with known thyrotoxicosis who have evidence of systemic decompensation, and in patients displaying signs and symptoms of thyrotoxicosis without a previous diagnosis of this disorder.4

**Common features of thyroid storm**

- Central nervous system: anxiety, confusion, delirium, generalized tremors, coma
- Cardiovascular: tachyarrhythmia (most commonly atrial fibrillation), Means-Lerman scratch (a murmur produced by a hyperdynamic pericardium rub-
Scoring systems to diagnose thyroid storm are available, but the diagnosis is based on the clinical picture and the physician’s judgment

Scoring systems to distinguish thyrotoxicosis from thyroid storm, such as the Burch-Wartofsky Point Scale and the Japan Thyroid Association Criteria, are widely available in apps and online. They are sensitive but lack specificity and remain unvalidated.

The Burch-Wartofsky Scale awards points for fever, central nervous system effects, gastrointestinal and hepatic dysfunction, tachycardia, heart failure, and atrial fibrillation, and for any precipitating event. A score of 45 or higher is considered highly consistent with thyroid storm, 25 through 44 suggests an impending storm, and less than 25 makes a diagnosis of thyroid storm unlikely. If we enter the data for our patient, her Burch-Wartofsky score was 65 and was therefore highly consistent with thyroid storm.

LABORATORY FINDINGS IN HYPERTHYROIDISM

Which one of the following would further support the diagnosis of hyperthyroidism?

- Low uptake on radioactive iodine uptake scanning
- Thyroperoxidase antibodies in the serum
- Elevated reverse triiodothyronine (T3) level
- A low thyroid-stimulating hormone (TSH) level and high free thyroxine (T4) level

Radioactive iodine uptake can be high or low in cases of thyroid storm. High uptake may represent rapid thyroidal turnover of iodine. On the other hand, iodine uptake may be low in patients experiencing thyroid storm who previously had thyroiditis, had received exogenous thyroid hormone, had been exposed to intravenous contrast, or had used amiodarone.

Thyroperoxidase antibodies in the serum suggest underlying autoimmune thyroid disease. While most commonly found in patients with Hashimoto thyroiditis, they may also be present in Graves disease. Their titers correlate with risk of progression to overt hypothyroidism but do not reflect thyroid function or thyroid storm.

**Reverse T3** is metabolically inactive and has limited clinical value for routine testing of thyroid function.

**Low TSH and high free T4 levels.** A low (suppressed) TSH level (< 0.05 mIU/L) combined with elevated free T4 (> 1.6 ng/dL) support the diagnosis of thyrotoxicosis. However, no T3 or T4 cutoff level exists for diagnosing thyroid storm.

Though scoring systems to diagnose thyroid storm are available, ultimately the diagnosis is based on the overall clinical picture and the physician’s judgment. Levels of thyroid hormones during thyroid storm may be in some cases similar to those in a person with stable hyperthyroidism, and therefore, T3 and T4 levels are not reliable as diagnostic criteria.

Other, nonspecific laboratory findings during thyroid storm may include mild hyperglycemia (due to inhibition of insulin release and increased glycolysis caused by catecholamines), mild hypercalcemia (secondary to increased bone resorption), elevated aminotransferase and alkaline phosphatase levels (related to liver dysfunction or from increased bone turnover), and leukocytosis or, conversely, leukopenia.

CAUSES AND TRIGGERS OF THYROID STORM

Which of the following most likely placed this patient at risk of thyroid storm?

- Vancomycin
- Liver transplant
- Absence of preexisting thyroid illness
- Contrast-enhanced CT
- Systemic infection

Underlying causes of thyrotoxicosis

- Primary hyperthyroidism: Graves disease, toxic multinodular goiter, toxic adenoma, functioning thyroid carcinoma metastases, activating mutation of the TSH receptor, struma ovarii
- Secondary hyperthyroidism: TSH-secreting pituitary adenoma, chorionic gonadotropin-secreting tumors, gestational thyrotoxicosis
- Thyrotoxicosis without hyperthyroidism: subacute thyroiditis, silent thyroiditis including postpartum
thyroiditis, ingestion of excess thyroid hormone (thyrotoxicosis factitia), and other causes of thyroid destruction such as amiodarone, radiation, and adenoma infarction.

**Precipitants of thyroid storm**

- Surgery: thyroid surgery (“surgical storm”), non-thyroid surgery, manipulation of the thyroid gland
- Cerebrovascular causes: myocardial infarction, venous thromboembolism, cerebrovascular disease
- Neoplasms: struma ovarii, metastatic thyroid cancer
- Endocrine diseases: Graves disease, thyroiditis, multinodular goiter, solitary toxic adenoma, diabetic ketoacidosis, hypoglycemia
- Drugs: interferon, amiodarone, abrupt cessation of thionamide therapy (rare), interleukin 2 therapy, anesthetics, salicylates, pseudoephedrine
- Others: systemic infections, thyroiditis, pregnancy, parturition, trauma, burns, radiocontrast dye, emotional stress
- No known precipitant in many patients.

The most likely risk factor in our patient

Considering the many possible causes of thyrotoxicosis and risk factors for thyroid storm, which was the most likely risk factor in our patient?

Vancomycin and liver transplant per se are not known risk factors for thyroid storm, but some anesthetic drugs used during surgical procedures are known triggers. The etiology of the patient’s liver disease and the medications used to treat it should be carefully reviewed, as medications used to treat viral hepatitis such as interferon alfa or interleukin 2 have been associated with thyrotoxicosis.

Absence of preexisting thyroidal illness does not increase the risk of thyroid storm, but it also does not preclude it. Although thyroid storm usually occurs in the setting of hyperthyroidism such as Graves disease, it can happen in normothyroid patients. However, a precipitating event such as surgery, infection, myocardial infarction, cerebrovascular events, or exposure to iodinated contrast dye is typically needed to jump-start the process.

Contrast-enhanced CT. Exogenous iodine, as in CT contrast media, should suppress synthesis and release of thyroid hormone (the Wolff-Chaikoff effect). But this effect is only temporary, and within a few days to weeks hyperthyroidism can develop (the Jod-Basedow phenomenon), particularly in patients with subclinical multinodular goiter or Graves disease.

Infection can lead to an increase in cytokines including tumor necrosis factor alpha, interleukin 1, and interleukin 6 as part of an inflammatory response. This results in increased expression of proteins involved in thyroid hormone metabolism and transport and also of cell receptors, ultimately triggering thyroid storm.

Therefore, receiving multiple doses of iodinated radiocontrast dye and systemic infection were the likely precipitants of thyroid storm in our patient.

### INITIAL TREATMENT

Which one of the following is the most appropriate next step in this patient’s treatment?

- □ A beta-blocker and a thionamide
- □ An iodide solution
- □ Anticoagulation
- □ Aspirin

An iodide solution would not be appropriate, as it can exacerbate hyperthyroidism unless a thionamide is given at least 1 hour beforehand to block iodine organification (incorporation into thyroglobulin) and resultant new thyroid hormone synthesis.

Although thyroid storm usually occurs in the setting of hyperthyroidism such as Graves disease, it can happen in normothyroid patients as well.

Anticoagulation would also be inappropriate, unless thyroid storm were precipitated by pulmonary embolism or myocardial infarction, or if the patient develops atrial fibrillation. Petersen and Hansen found that atrial fibrillation is common in thyrotoxicosis, but the risk of stroke was not higher in patients with thyrotoxicosis with atrial fibrillation than in those with thyrotoxicosis without atrial fibrillation. Thus, the decision to start anticoagulation should be guided by the same risk-stratification criteria as in a patient without thyroid storm.

Aspirin is not recommended, owing to the possibility of it decreasing protein binding and thus increasing levels of free active thyroid hormone. Acetaminophen is preferred if antipyretic therapy is required.

A beta-blocker, propylthiouracil (a thionamide), and glucocorticoids were started in our patient. These medications, along with supportive care, led to improvement in her symptoms and cardiac function.
Optimal treatment of thyroid storm

Patients with thyroid storm are critically ill and have a high mortality risk. Therefore, treatment and resuscitative measures should begin as early as possible.

Management of thyroid storm involves the same principles that apply to uncomplicated hyperthyroidism, but additional medications and higher and more frequent dosing are often required. Optimal treatment of thyroid storm has the following 5 main goals:

- Reduce thyroid hormone synthesis and secretion
- Block thyroid hormone actions at the cellular level
- Reverse systemic decompensation (e.g., hyperthermia, dehydration, congestive heart failure, arrhythmia)
- Treat the precipitating event
- Establish long-term therapy.

These goals can be achieved with a regimen commonly consisting of multiple medications with different mechanisms of action, as described below.

Thionamides

Both propylthiouracil and methimazole effectively inhibit hormone synthesis and can be used to treat thyroid storm. However, propylthiouracil has the added benefit of decreasing peripheral T₄-to-T₃ conversion in a dose-dependent fashion. Since T₃ is the active form of thyroid hormone, propylthiouracil is in theory superior to methimazole in treating thyroid storm. Once patients are clinically stable, their propylthiouracil can be changed to methimazole, which requires less frequent dosing and has a lower risk of hepatotoxicity. Methimazole should be avoided in the first trimester of pregnancy as it has been found to cause birth defects.

Exogenous iodine

Exogenous iodine decreases the release of preformed hormone, but new hormone synthesis must first be blocked with a thionamide, as underlying thyroid pathology may otherwise result in increased T₃ and T₄ production. Additionally, the thyroid iodide transport system adapts to increased levels of iodine and eventually escapes inhibition within 2 weeks, which may exacerbate thyrotoxicosis. Also, inhibiting the thyroid gland with exogenous iodine may delay the patient’s treatment with radioactive iodine.

Glucocorticoids

Glucocorticoids decrease peripheral conversion of T₄ to T₃, and ameliorate the partial adrenal insufficiency commonly seen during thyroid storm that is due to excessive metabolic degradation of corticosteroids and that increases the risk for acute cortisol deficiency because of increased cortisol turnover and diminished reserves.

Beta-blockers

Beta-blockers are a cornerstone in the management of thyroid storm, as they blunt the associated adrenergic surge, ie, a sudden and dramatic increase in catecholamines leading to severe increases in blood pressure and heart rate. Dose requirements may be high as a result of increased drug metabolism from hyperthyroidism.

The most commonly used beta-blocker is propranolol, a nonselective drug that also decreases peripheral T₄-to-T₃ conversion, which usually requires a daily dose of 240 to 480 mg. Cardioselective beta-blockers such as atenolol or metoprolol can be considered, especially if the patient has relative contraindications to nonselective beta-blockers such as asthma or chronic obstructive pulmonary disease. In patients with decompensated heart failure, esmolol may be preferable, as it has a better safety profile in this population due to its very short half-life (9 minutes), so that any adverse effects may be quickly reversed.

Of note: controlling tachycardia in thyroid storm may improve heart failure. Dosing of beta-blockers should be titrated to the desired effect and guided by the patient’s clinical condition.

In patients with absolute contraindications to beta-blockers, a nondihydropyridine calcium channel blocker such as diltiazem may control the heart rate.

Bile acid sequestrants

Thyroid hormones are metabolized in the liver, where they are first conjugated with glucuronide and sulfate, then excreted in the bile into the intestine, and finally reabsorbed through the portal system. Therefore, bile acid sequestrants such as cholestyramine have been found to reduce thyroid hormone levels in patients with thyrotoxicosis by interfering with enterohepatic circulation and recycling of thyroid hormone.
Plasmapheresis and surgery

In refractory cases, plasmapheresis or emergency surgery may be needed.\(^{12,31}\) Plasmapheresis removes thyroid hormones, catecholamines, autoantibodies (in the case of Graves disease), and cytokines that trigger inflammation, all of which are undesirable in thyroid storm.\(^{32}\)

If surgery is determined to be the best approach and the patient is receiving an iodide solution (eg, saturated solution of potassium iodide, Lugol solution), the surgery should be done within 8 to 10 days to avoid the Jod-Basedow phenomenon.\(^{2,9}\) If an iodine solution is not used, there is no additional increased risk in deferring surgery. Surgery in patients with elevated thyroid hormones, however, has extraordinary cardiovascular risks such as ischemic heart disease, atrial fibrillation, and congestive cardiac failure that require careful attention from the anesthesiology team.

Supportive care

Supportive care may include one or a combination of the following:

**Antipyretics.** Distress from pyrexia may be relieved with acetaminophen, which is preferred over salicylates, which affect protein binding and may increase the level of free thyroid hormone.\(^{2}\) Peripheral cooling with ice packs and cooling blankets can also be implemented.

**Volume resuscitation.** Dehydration is often due to insensible fluid loss, diarrhea, and vomiting.\(^{19}\) Also, several factors, including increased production of metabolic end products in a hypermetabolic state and direct stimulation of potassium channels in arterial smooth muscles by thyroid hormones, favor a state of general vasodilation.\(^{34}\) Volume management and electrolyte replacement are appropriate based on the patient’s condition and fluid status, keeping in mind that overenthusiastic administration of fluids could worsen heart failure.

Sedatives are used to manage delirium and agitation.

**FURTHER CARE**

5 After the patient is clinically stable, which one of the following would be the most appropriate next step in her management?

- [ ] Continue propylthiouracil indefinitely
- [ ] Thyroidectomy
- [ ] Discontinue propylthiouracil, start methimazole, and evaluate for preexisting thyroid pathology such as Graves disease
- [ ] Radioactive iodine treatment

Surgical consultation for thyroidectomy, antithyroid drugs, and radioactive iodine treatment should all be considered for definitive therapy if the patient is found to have underlying thyroid disease such as Graves disease.\(^{4}\) However, in our patient’s case, stabilizing her condition is the priority, while long-term therapy can be formulated later.

**Stopping propylthiouracil, starting methimazole**

Once a patient with thyrotoxicosis is in stable condition, propylthiouracil should be replaced by methimazole, which has a better safety profile. Common side effects of both medications include pruritus, rash, urticaria, arthritis, fever, nausea, and vomiting. More serious side effects include agranulocytosis, antineutrophil cytoplasmic antibody-positive vasculitis, and hepatotoxicity, all of which are more frequent with propylthiouracil. Additionally, hepatotoxicity due to propylthiouracil use is associated with hepatocellular inflammation and necrosis, likely explaining higher rates of liver failure with this drug compared with methimazole, which is associated with cholestatic dysfunction.\(^{35}\)

Propylthiouracil should be discontinued at any time if aminotransferase levels reach more than 3 times the upper limit of normal, or if elevated levels at the onset of therapy increase further.\(^{4}\) These levels should then be monitored weekly until they return to normal.

**Stopping other drugs**

Glucocorticoids and iodine therapy should be discontinued once the patient’s condition is stable. Beta-blockers should be tapered and discontinued when thyroid function studies return to normal. Thiouramides need to be titrated to maintain a euthyroid state, usually over weeks to months.\(^{20}\)

Thyroid storm mortality rates have been decreasing in recent years, partly due to advances in treatment and earlier recognition of this medical emergency.\(^{36}\) However, even when death is prevented, significant morbidity in the form of end-organ damage may lead to long-term complications.

**CASE CONCLUSION**

Our patient’s condition stabilized with medical treatment. She underwent a workup for underlying thyroid disease after discharge from the hospital, but none was found. Likely precipitants of her thyroid storm were repeated exposure to intravenous iodine-containing contrast and systemic infection.
TAKE-HOME POINTS

- Thyroid storm requires a high level of suspicion (particularly in patients with preexisting thyroid disease), prompt recognition, and intensive medical therapy, in view of its high mortality rate. Its symptoms are not specific.
- Most cases of thyroid storm happen in the setting of underlying Graves disease; however, it may also occur in patients with normal thyroid function if they are exposed to the right triggers.
- TSH is the best single test to evaluate thyroid function.

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Hormone levels in patients experiencing thyroid storm are comparable to those in patients with stable thyrotoxicosis. Therefore, no cutoff values for the diagnosis exist.

Management of thyroid storm is complex, based on the specifics of each case, and usually involves multiple treatments.

DISCLOSURES

Dr. Stancampiano has disclosed work as principal or co-investigator of funded research for Gilead Sciences. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.


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Metastatic bone disease: Early referral for multidisciplinary care

ABSTRACT

It is estimated that more than half of all cancers develop bony metastases, exacting a substantial cost in terms of patient quality of life and healthcare expenses. Prompt diagnosis and management have been shown to reduce morbidity and costs. When a patient with a history of cancer presents with musculoskeletal pain, heightened awareness of the risk of bone metastasis should prompt immediate referral to an orthopedic specialist. A multidisciplinary approach is needed to identify an appropriate treatment plan for the patient based on the prognosis, fracture status, and extent of skeletal disease.

KEY POINTS

More than 50% of patients with cancer survive their disease for at least 10 years, making durable reconstruction in metastatic skeletal disease more important.

Most patients with metastatic bone disease present to an orthopedic team after a pathologic fracture has already occurred, increasing the likelihood of discomfort and morbidity.

Awareness of the diagnostic and therapeutic challenges associated with metastatic bone disease is essential for timely referral to an orthopedic specialist.

CONSIDERING THE NUMBERS

The estimated cost directly attributed to care of bone metastasis in the United States is greater than $12.6 billion annually, which accounts for 17% of total cancer care. In 2012, Medicare paid $100 million in hospital charges to cover the cost of prophylactic internal fixation of the femur as a result of metastasis. The rate of new cases of cancer in the United States currently stands at 442.4 per 100,000 men and women per year. In January 2019, the US National Cancer Institute predicted 16.9 million cancer survivors in the United States with a projected increase to 22.2 million by 2030. Similarly, in the United Kingdom, the number of people...
living with cancer is rising by 3% each year, with survivorship projected to increase by 1 million per decade from 2010 to 2040. In 2015, an estimated 2.5 million people were living with cancer in the United Kingdom, with a predicted rise to 4 million by 2030. In the United Kingdom, 375,000 new cancer cases are diagnosed every year, or about 1,000 new cases daily.

In the early 1970s, the median survival time for patients with metastatic disease was 1 year. By 2007 it was 6 years, and by 2011 it was 10 years. Today, it is estimated that over 50% of patients survive their disease beyond 10 years. With this increased longevity, the age of patients with metastatic bone disease and rates of survival are on the rise.

Incidence of bone metastasis
Bone is the third most common organ affected by metastatic cancer after the lung and liver.

Although it is difficult to fully appreciate the incidence of metastatic bone disease, it is estimated that more than 50% of all cancers develop bone metastases, with the variability in the literature ranging from 12% to 70%. In 2008, the incidence of metastatic bone disease in the United States was approximately 280,000 patients per year with an upper estimate of 322,000. This is likely to have increased significantly since then.

Although almost any carcinoma can metastasize to bone, those that do so most frequently are prostate, breast, renal, lung, thyroid, and blood (multiple myeloma) in origin. Some autopsy studies have demonstrated skeletal metastases in 90% of men who die of prostate cancer. Bone is the most common site of metastasis in patients with breast cancer, and up to 70% of women with metastatic breast cancer have some form of skeletal involvement.

Quality of life
The quality of life in patients with skeletal metastases is compromised by skeletal-related events, ie, intractable pain, forced immobilization, hypercalcemia, spinal cord compression, and pathologic fractures. Bony metastasis is often the most symptomatic and disabling manifestation of secondary cancer. Approximately 68% of patients with skeletal metastasis have pain, and 10% to 20% of those with long-bone metastases eventually sustain pathologic fractures. Pathologic fracture may be the first sign of disease and the index finding leading to the diagnosis of cancer. In 3% to 4% of patients who present with pathologic fracture, the primary site is not discovered. In most cancer types, the morbidity rate in patients with multiple skeletal-related events is higher than in patients with single events. Additionally, the presence of extraosseous disease in the context of skeletal-related events is a powerful predictor of poor outcomes.

Bone metastasis typically occurs via hematogenous spread and therefore tends to seed in more heavily vascularized parts of the skeleton. The most frequent sites for metastases are the spine, pelvis, proximal femur, proximal humerus, skull, and ribs, and involvement of any of these sites can significantly affect activities of daily living, quality of life, functional status, and overall prognosis.

Healthcare costs
The management of patients with skeletal events due to bone metastasis has important implications for healthcare costs. Early intervention for patients with metastatic bone disease has been shown to reduce patient morbidity as well as overall cost. A prompt, proactive response has been shown to reduce complication rates, length of stay, need for community care, and overall treatment costs, and this is specifically true of pathologic fracture. A prophylactic approach has shown to be safer and much more cost-effective compared with traditional management, or acute fixation, after a completed fracture.

Patients are living longer with advances in systemic therapy, targeted therapy, and radiotherapy treatments, thus making durable reconstruction of a metastatic skeletal location more important. The appropriate surgical approach and choice of implant have the potential to reduce healthcare costs.

EARLY RECOGNITION OF BONE METASTASIS: CHALLENGES AND CONSIDERATIONS

Patients with metastatic bone disease commonly present to orthopedic surgeons in 1 of 3 ways: an oncologist refers the patient after noting disease during a routine investigation; the patient is admitted with a pathologic or impending pathologic fracture; or a primary care physician refers the patient for evaluation of musculoskeletal pain.

Unfortunately, most patients have already sustained a pathologic fracture by the time they present to an orthopedic team and thus have a greater likelihood of severe discomfort and increased morbidity during the treatment process. A fracture event may create complexity that limits treatment options. Heightened awareness in the primary care setting of possible metastatic bone disease is essential in patients who present with musculoskeletal pain and a history of cancer or previous radiotherapy.
Bone cancer pain
The primary symptom often described by patients is pain, and this is especially relevant in a patient with cancer.20

Bone cancer pain can be very complex and has an associated intricate pathogenesis.21 It is often described as a dull ache that is deep and intense in nature, exacerbated by weight-bearing, and often worse at night. Red flags for bone metastasis include a chronic dull ache that continues to worsen over time, pain associated with weight-bearing, night pain, pain on direct palpation, and unexplained localized pain in a patient over age 45. A sudden change to more intense or severe pain usually indicates a pathologic fracture, particularly in the context of minimal trauma.

Patients who live with cancer ultimately deal with considerable suffering and pain; therefore, sudden changes in the quality or quantity of pain should be acted on swiftly.22,23 Significant symptoms that accompany pain include unexplained weight loss, night sweats, and any red flag symptoms of back pain (eg, nighttime pain during movement, band-like bilateral nerve root pain or radiculopathy, unsteady gait, progressive weakness of limbs, bowel and bladder symptoms).

Time to metastasis
Few epidemiologic studies establish the median time from primary cancer diagnosis to bone metastasis. The results vary by country, ethnicity, primary cancer type, patient age, and initial treatment received. In broad terms, the highest risk of metastatic bone disease is within the first 3 to 5 years of the initial diagnosis, before the cancer reaches a stable state, ie, no increase or decrease in severity or extent.9,21 However, bony metastasis can present as late as 20 years after the primary diagnosis, so a history of cancer at any stage is important.24

Progression to fracture
Patients with known cancer involving the skeleton or those who have had previous radiotherapy to skeletal metastatic deposits are at particular risk of pathologic fracture. Several landmark studies have suggested that the risk of pathologic fracture after radiotherapy can range from 13% to 41%.25,26 One study suggested that after radiotherapy, 26% of patients develop disease progression at the bony site,27 and another study noted that 35% of fractures develop at just 6 months after radiotherapy.28 For this reason, patients who receive radiotherapy for bony metastasis should be assessed by an appropriate specialist to determine the need for further stabilization or surgical treatment.

Evaluation
Patients who present in a primary care or hospital setting with suspected metastatic bone disease need preliminary investigations in addition to an initial thorough examination. Certain blood tests (eg, alkaline phosphatase, lactate dehydrogenase, calcium, blood cell count, basic tumor markers) and plain radiographs can supplement the history and physical examination.22 Although no blood test is specific for bone metastasis, increased calcium and alkaline phosphatase levels can supplement the clinical picture of metastatic bone disease.

Because bone lesions may not become apparent on radiography until 50% to 70% of the bone has been destroyed, initial radiographs may not show an obvious abnormality. A patient with bony lesions may experience symptoms related to hypercalcemia such as nausea, vomiting, polyuria, muscle weakness, constipation, and confusion, and metastasis to the spine may cause neurologic compromise. Urgent referral to an oncologist, orthopedic surgeon, or neurosurgeon is warranted if cauda equina syndrome is suspected.29 Delays in appropriate treatment can lead to increased morbidity, complications, and challenges that would not have been present earlier in the disease process such as changes in bony anatomy with wider destruction, increased frailty of the patient, and missed opportunity for less-invasive treatment options.

NEXT STEPS: STOP, THINK, STAGE
When bone metastasis is suspected or confirmed, the next step is to establish the origin and nature of the lesion, the degree of disease dissemination, the patient’s overall health and prognosis, and the effect of the lesion on the bone.30 Analysis of this information requires a multidisciplinary effort to allow for effective decision-making as to the most appropriate management (Figure 1).

The multidisciplinary team
Management of metastatic bone disease requires input from a team of specialists to determine the best treatment options for the individual patient. The team should consist of a medical oncologist, radiation oncologist, radiologist, pathologist, orthopedic surgeon with an interest in bone metastasis, anesthesiologist, palliative care specialist, rehabilitation specialist, cancer nurse specialist, and, most important, the patient and family.15
**Origin and nature of the bone lesion**
The origin and nature of a bone lesion plays a key role in the decision-making process. All bony lesions are treated as primary bone tumors, or sarcoma, until proven otherwise. Applying this principle ensures that no primary bone tumor receives delayed or inappropriate treatment.

**Initial investigation: Imaging and biopsy**
The initial investigation includes a computed tomography (chest, abdomen, pelvis), whole-body nuclear bone scan, positron emission tomography, and magnetic resonance imaging of the affected area. Biopsy is becoming a more important and better recognized diagnostic step. Today, most patients who present with a bone lesion should be considered for biopsy in order to obtain a histologic diagnosis, regardless of whether metastatic bone disease is suspected. Biopsy has been reported to reveal a benign diagnosis, infection, a different primary cancer, or change of immunophenotype between the primary disease and the metastasis.

Bone scan, positron emission tomography, and computed tomography are increasing in use, are readily available, and can determine the degree of disease dissemination. This is important because metastatic bone disease can range from a solitary lesion to widespread bone involvement.

**Prognosis**
Estimating a patient’s life expectancy and overall prognosis will significantly frame the support and input the patient requires. As a general rule, a patient should have a life expectancy greater than 6 weeks if surgical management is to be considered. With this prognosis, the surgical procedure must permit immediate weight-bearing. If the procedure requires partial weight-bearing or no weight-bearing postoperatively, the minimum prognosis must be at least 3 to 6 months. A life expectancy greater than 6 months justifies and requires comprehensive surgery (Figure 1).

**THE HOLISTIC APPROACH TO MANAGEMENT**
The key principles of management of metastatic bone disease are to control pain, maintain or improve quality of life, allow early mobilization, create a durable orthopedic construct to replace or augment bone, and prevent disease progression if possible.
Painless, smaller lesions
It is generally accepted that painless, smaller lesions with little risk of fracture respond well to radiotherapy alone, but a pathologic fracture will likely require some form of surgical stabilization. A delicate balance is required to avoid overtreatment and undertreatment of these lesions, especially with procedures that have longer recovery times or incur greater morbidity. The clear benefit of operating on early impending fractures must be weighed against the risks of surgery, anticipated prognosis, and overall benefit to the patient.\(^\text{33}\)

The primary aim of treating asymptomatic small lesions is disease control and prevention of skeletal-related events. The mainstay of treatment is systemic control such as hormonal therapy, immunotherapy or targeted therapies, chemotherapy, or agents that improve bone strength combined with potential radiotherapy for local control. For smaller symptomatic lesions and at more difficult surgical locations, percutaneous ablation techniques with interventional radiology have been shown to be effective.\(^\text{34}\)

Larger, symptomatic lesions
For lesions that are larger and more symptomatic, the aim of treatment is not only to control disease but also to maintain mobility and improve pain.\(^\text{32}\) The need for surgical intervention must be considered in addition to local radiotherapy and systemic medical control of the disease.

Although postoperative radiotherapy has played a role in management, evidence supporting its use is weak, and the associated risks are quite high (eg, wound infection, skin irritation, osteoporosis, and failure of metalwork). Because radiotherapy itself is a risk factor for propagating pathologic fractures, its use needs to be weighed against the potential benefits.\(^\text{35}\)

\section*{NONSURGICAL MANAGEMENT}
Antiresorptive drugs are the mainstay of nonsurgical treatment of bone metastasis, and bisphosphonates and denosumab are the most commonly used.

Bisphosphonates and denosumab
Bisphosphonates affect osteoclast activity and survival.\(^\text{36}\) Zoledronate is approved for use in solid tumors and multiple myeloma, and pamidronate is approved for bone metastases from breast cancer and multiple myeloma. Ibandronate is effective in breast cancer patients. Zoledronate is particularly useful in hypercalcemia associated with bony metastasis. Monitoring is required for complications such as kidney failure, hypocalcemia, and osteonecrosis of the jaw.

Denosumab reduces osteoclast activity and is generally well tolerated. It can be used in patients with renal failure since it is not nephrotoxic. It has been shown to prolong the time to first skeletal-related event in patients with metastatic breast and prostate cancer.\(^\text{37}\)

Radiotherapy
Radiotherapy is used primarily for pain management, spinal cord compression, and pathologic fractures. Pain relief is achieved within the first 2 weeks and is almost complete in 50% of patients. The dose, technique, and schedule depend on several factors. Short courses of treatment are often used in Europe and Canada, while longer courses are preferred in the United States.\(^\text{37}\)

Other methods
Other methods of pain relief should follow the World Health Organization analgesic ladder\(^\text{38}\) and range from anti-inflammatory drugs to opiate-based treatment. Guidelines for more detailed pain management options in cancer patients have been published\(^\text{39}\) and may require input from specialized pain services.

\section*{SURGICAL MANAGEMENT}
When surgical intervention is necessary, the intervention should be a single procedure that will last the patient’s life span while allowing immediate weight-bearing and mobility.\(^\text{17}\) Pathologic fractures caused by metastatic bone disease will not heal, even with radiotherapy. The surgical intervention must be appropriate for the stage of disease, condition of the patient, and the patient’s preferences and wishes. In general, surgical options include the use of intramedullary nails, ridged plate and screws, bone cement supplementation, and endoprostheses, or a combination of these.\(^\text{11,17,31}\)

Current research favors early diagnosis and a prophylactic surgical approach in managing bony metastases in patients with impending pathologic fractures. Many studies have shown that in appropriate patients, a prophylactic procedure (compared to a procedure performed after fracture) leads to reduced blood loss, reduced length of hospital stay, quicker return to baseline mobility, and, overall, a better 2-year survival rate.\(^\text{40}\)

The surgical approaches have evolved with advances in technology and prosthesis design. Fixation alone may not necessarily be the most appropriate option. For example, there is a popular notion that surgical management involves only prophylactic intramedullary nail stabilization. But more recent
studies have shown that in appropriate patients, the use of massive endoprostheses for the treatment of bone metastases is a reliable method of limb reconstruction. This option is associated with low complication and failure rates, can restore good function, allows for early weight-bearing, alleviates pain, and sometimes allows for complete resection of the tumor.

Observational studies have shown sustained improvement in pain relief and function up to 1 year after surgery in patients with metastatic bone disease, irrespective of prognosis. Studies have also indicated that patients with low-volume bony oligometastatic disease (< 5 metastases throughout the body) have enhanced survival and better disease prognosis with appropriate surgical intervention. While these arguments show that the burden of disease and morbidity should not be underestimated, there still exists little awareness and appreciation in hospital and primary care settings regarding possible management options for skeletal-related events due to bone metastasis.

**TAKE-HOME MESSAGES**

- Metastatic bone disease is associated with high rates of mortality and morbidity and has a significant impact on quality of life. A holistic, team-based approach to management is essential to providing appropriate, expeditious, and aggressive treatment. Delay in referral and treatment is associated with increased morbidity.
- Awareness of the signs of metastatic bone disease and early referral for specialist input are essential. To improve overall outcomes and quality of life for patients with cancer, treatment strategies need to be planned comprehensively and tailored to the individual patient.
- A prophylactic approach to management of metastatic bone disease leads to better pain relief and function.
- Healthcare systems need a well-defined and easily accessible platform for primary care physicians and oncologists to expeditiously refer patients for further assessment and management.

**REFERENCES**


Dr. Nystrom has disclosed consulting, teaching, and speaking for Onkos Surgical. Dr. Mesko has disclosed consulting for Bone Support, Onkos Surgical, and Stryker Orthopaedics, and teaching and speaking for KCI and Onkos Surgical. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.


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An unexpected turn: A 71-year-old man with myocardial infarction

A 71-year-old man who had been previously well was brought to the emergency department by ambulance after experiencing several days of confusion and low back pain and a fall while showering. It was difficult to obtain a history owing to his altered mental status, but he said he had no chest pain or shortness of breath. His medical records were not available.

The patient’s temperature was 36.8°C (101.5°F), pulse rate 98 beats per minute, respiratory rate 16 breaths per minute, and blood pressure 100/60 mm Hg. He was somnolent but had no focal weakness or sensory deficits. Cardiac and pulmonary examinations were normal.

An electrocardiogram in the emergency department revealed ST-segment elevation in leads II, III, and aVF and ST-segment depression in V1, V2, V3, and aVL (Figure 1).

**FURTHER STUDIES**

Laboratory test results were as follows:
- White blood cell count 12.0 × 10^9/L (reference range 3.9–11.7) with a neutrophilic predominance
- Hemoglobin 13.7 g/dL (13.3–17.7)
- Creatinine 1.3 mg/dL (0.7–1.3)
- Lactate 3.4 mmol/L (0.5–2.2)
- High-sensitivity troponin I 48.3 ng/L (< 4).

Computed tomography (CT) of the brain did not show any acute abnormalities, and CT aortography excluded aortic dissection.

The patient was taken emergently for cardiac catheterization for ST-segment elevation myocardial infarction (STEMI). Coronary angiography revealed a left dominant circulation with the posterior descending artery and posterolateral branches arising from the left circumflex artery. A large filling defect was seen in the left dominant circumflex artery, and there were distal cutoffs in multiple obtuse marginal branches (Figure 2).

Balloon angioplasty followed by aspiration thrombectomy at the site of the filling defect improved coronary blood flow. The aspirated material had a yellow, organized, fibrinous appearance that was atypical for red thrombus (composed largely of red blood cells and clotting factors) or white thrombus (composed of platelets), both of which are seen during aspiration thrombectomy in acute coronary syndrome.

Intravascular ultrasonography showed no evidence of atherosclerotic disease in the left circumflex or left posterior descending arteries. Intracoronary nitroglycerin did not increase the caliber of the coronary vessels or resolve the filling defects.

**DIFFERENTIAL DIAGNOSIS**

1 Which of the following is the most likely cause of the coronary artery obstruction in this patient?
- Atherosclerotic plaque rupture with formation of intracoronary thrombus
- Coronary embolization
- Spontaneous coronary artery dissection
- Coronary vasospasm

Atherosclerotic plaque rupture leading to formation of an intracoronary thrombus is the most common cause of STEMI, but in this patient, coronary angiography did not demonstrate significant coronary atherosclerosis, and intravascular ultrasonography did not reveal a culprit plaque that had ruptured, eroded, or fissured. Furthermore, thrombectomy of the occlusive coronary thrombus in the posterior descending...
artery returned fibrinous material that was not consistent with the appearance of a typical red or white thrombus of an atherosclerotic plaque rupture.

Spontaneous coronary artery dissection usually affects middle-aged women (90% of patients); it also accounts for 15% of myocardial infarctions during pregnancy or the peripartum periods. Furthermore, the patient had no angiographic or intravascular ultrasonographic evidence of artery dissection.

Coronary vasospasm can cause angina and infarction, often in association with ST-segment elevation. Angiography can reveal concomitant atherosclerosis or isolated vasospasm, neither of which was detected. The finding of occlusive filling defects on coronary angiography that improved with balloon angioplasty and aspiration excludes vasospasm as the primary cause of STEMI.

Embolism. The multiple distal cutoffs in the obtuse marginal branches are most consistent with an embolic event throughout the left dominant circumflex coronary artery.

CASE CONTINUED: RETURN FOR CATHETERIZATION

The patient was admitted to the coronary care unit. Over the next 24 hours, his temperature increased to 38.9 °C (102.0 °F), his white blood cell count increased to 29.7 × 10⁹/L, and he developed hypoxic respiratory failure, acute kidney injury, and refractory shock despite antibiotics, vasopressors, and fluids.

Transthoracic echocardiography showed an ejection fraction of less than 20% and akinesis of the inferior, posterior, and lateral walls of the left ventricle. The patient’s clinical team thought that this degree of cardiac dysfunction was disproportionate to an inferoposterolateral infarct from a single lesion in the left circumflex artery and small distal cutoffs in obtuse marginal branches. Given the unclear etiology of the patient’s shock and poor response to fluids, antibiotics, and vasopressors, he was taken back to the cardiac catheterization laboratory on hospital day 2 for right and left heart catheterization.

Right heart catheterization showed elevated right-sided and left-sided filling pressures, with the following values:
- Pulmonary capillary wedge pressure 32 mm Hg (reference range < 12)
- Cardiac index 1.7 (2.5–4.5)
- Cardiac output 4.2 L (4–8)
- Systemic vascular resistance 1,200 dynes/seconds/cm⁻⁵ (800–1,200) on multiple vasopressors
- Mean right atrial pressure 15 mm Hg (2–6).

Left heart catheterization showed normal flow through the previously occluded left dominant circumflex coronary artery.

Figure 1. The patient’s electrocardiogram in the emergency department showed ST-segment elevation (arrows) in leads II, III, and aVF, and ST-segment depressions (triangles) in V₁, V₂, V₃, and aVL.
flex artery and its obtuse marginal branches. However, multiple new cutoffs were noted in the distal obtuse marginal arteries, consistent with repeat coronary embolization.

**INTERPRETING THE HEMODYNAMIC MEASUREMENTS**

The patient’s hemodynamic measurements point to which of the following mechanisms of shock?

- Distributive
- Cardiogenic
- Mixed distributive and cardiogenic
- Hypovolemic

Right heart catheterization is performed by advancing a balloon-tipped catheter through the right-sided chambers of the heart in the direction of blood flow and measuring filling pressures, oxygen saturation, and cardiac output. Cardiac output is calculated using the thermodilution or Fick method. Systemic vascular resistance is calculated based on the mean arterial pressure, central venous pressure, and cardiac output.

Hemodynamic measurements that can be used to determine the mechanism of shock (Table 1). The different types of shock include the following:

- **Distributive shock** occurs when blood vessels are abnormally dilated, such as in sepsis or anaphylaxis. The cardiac output is usually normal or high, the systemic vascular resistance is low, and the pulmonary capillary wedge pressure is low.

- **Cardiogenic shock** occurs when the heart fails to pump adequately, such as after myocardial infarction. The cardiac output is low, the systemic vascular resistance is high, and the pulmonary capillary wedge pressure is usually high.

- **Hypovolemic shock** occurs when there is not enough volume in the intravascular space, such as after hemorrhage. The cardiac output is normal to low, systemic vascular resistance is normal to high, and pulmonary capillary wedge pressure is low.

The patient required multiple vasopressors to normalize his systemic vascular resistance, which indicated a vasodilatory state. The combination of low cardiac output and normal systemic vascular resistance on multiple vasopressors suggested mixed cardiogenic and distributive shock.

**CASE CONTINUED:**

**REFRACTORY SHOCK, NEW RESULTS**

An intra-aortic balloon pump was placed to provide mechanical support to the left ventricle. However, the patient developed progressive hypotension and persistent lactic acidosis despite the balloon pump, inotropic support, vasopressors, mechanical ventilation, and continuous venovenous hemofiltration.

**Blood cultures obtained on admission returned positive for Staphylococcus aureus**

Repeat transthoracic echocardiography demonstrated progressive left ventricular dysfunction and a new, small pericardial effusion. No valvular dysfunction or vegetations were seen.

Repeat brain CT angiography demonstrated a new subarachnoid hemorrhage that was larger on the left side than on the right, and layered along the frontal sulci near the vertex without hydrocephalus or herniation.

Serial electrocardiograms demonstrated persistent ST-segment elevations in leads II, III, and aVF; new ST elevations in V4 and V5; and resolution of the ST depressions in aVL, V1, V2, and V3 (Figure 3).

Blood cultures obtained on admission returned positive for Staphylococcus aureus.
MYOCARDIAL INFARCTION

■ INTERPRETING THE NEW ELECTROCARDIOGRAPHIC RESULTS

What is the most likely cause of this patient’s persistent ST-segment elevation at the 48-hour time point?

- Recurrent ST-segment elevation myocardial infarction
- Pericarditis
- Ventricular aneurysm
- Subarachnoid hemorrhage

Recurrent ST-segment elevation myocardial infarction. After STEMI, the ST-segment and reciprocal changes typically resolve within 48 hours. The persistence of ST-segment elevation after the reciprocal changes (ST depressions) had resolved was not consistent with recurrent STEMI in the same distribution.

Ventricular aneurysm or an akinetic ventricular wall can lead to persistent ST-segment elevation following STEMI, but neither finding was detected on echocardiography or angiographic ventriculography.

In subarachnoid hemorrhage, the most common electrocardiographic waveform changes are U waves and T-wave abnormalities. ST-segment elevation is not characteristic.

Pericarditis. A key challenge at this juncture was distinguishing whether the patient was having a recurrent myocardial infarction or pericarditis. His initial electrocardiogram (Figure 1) was consistent with an inferoposterolateral myocardial infarction and could be explained by the distribution of emboli in the coronary anatomy. His left dominant coronary circulation supplied 3 major myocardial territories via the left circumflex artery and its branches: obtuse marginals supplied the lateral wall, the posterior descending artery supplied the inferior wall, and posterolateral branches supplied the posterior wall. ST-segment elevations in V₆ were caused by emboli in the obtuse marginal branches supplying the lateral wall. Embolization into the posterolateral branches supplying the posterior wall caused depressions in V₁, V₂, and V₃. Embolization in the posterior descending artery supplying the inferior wall caused elevations in II, III, and aVF and reciprocal depression in aVL.

In contrast, pericarditis is frequently associated with diffuse concave ST-segment elevation without reciprocal T-wave inversions or Q waves. (Occasionally, pericarditis manifests in focal leads). In this patient, the reciprocal depressions in aVL in the initial electrocardiogram had resolved, and new ST-segment elevations were present in V₄ and V₅ (Figure 3). The diffuse ST-segment elevations in a nonfocal coronary distribution, the absence of reciprocal ST depressions, and the presence of a new pericardial effusion were consistent with pericarditis.

■ CASE CONTINUED: A DEFINITIVE DIAGNOSIS

On hospital day 3, the patient underwent transesophageal echocardiography, which showed an 8-mm vegetation on the aortic valve without aortic regurgitation (Figure 4). The patient was diagnosed with S aureus endocarditis complicated by coronary and cerebral embolization; cerebral embolization was suspected to be the cause of the subarachnoid hem-

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MYOCARDIAL INFARCTION

### TABLE 1

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<td>Mechanism</td>
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<td>Distributive</td>
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<td>Cardiogenic</td>
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<td>Hypovolemic</td>
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orrhage on CT. Magnetic resonance imaging of the spine excluded spinal infection.

The patient underwent aortic valve replacement. Intraoperatively, he was found to have purulent pericarditis, with pericardial fluid that grew *S. aureus*. The aortic valve had a 1 cm × 2 cm vegetation on the non-coronary leaflet. A bioprosthetic aortic valve was implanted.

The patient could not be weaned from cardiopulmonary bypass and was placed on extracorporeal membrane oxygenation. On day 5 of hospitalization, he developed refractory sepsis and died.

■ SEPTIC CORONARY EMBOLIZATION

Infective endocarditis accounts for 1.58 million disability-adjusted life-years globally per year. Autopsy reports have shown that as many as 60% of patients who die with infective endocarditis have microemboli in the coronary circulation. However, only 3% to 11% of patients with infective endocarditis present with signs and symptoms of myocardial infarction attributed to macroemboli.

The lower incidence of septic macroemboli causing coronary occlusion may be because of the brisk flow past the coronary ostia, the caliber differences between the aorta and the coronary arteries, the acute angle at which the coronary arteries branch from the aorta, and the favorable positioning of the coronary ostia behind the aortic valve cusps during systole, which may protect them from emboli. The risk of embolization is highest in patients with *S. aureus* endocarditis and aortic valve endocarditis.

Several case reports and small case series describe coronary embolism as a complication of infective endocarditis. A review found that a murmur was present in almost 90% of cases. In a case series, 13 of 14 patients had moderate to severe valvular regurgitation on echocardiography.

Emboli most commonly enter the left coronary artery and travel to the left anterior descending artery, which generally has minimal angulation in its takeoff from the left main artery. In contrast, the circumflex artery typically branches at a 90-degree angle from the left main artery.

Patients with STEMI from septic coronary emboli have a higher mortality rate than those with atherosclerotic myocardial infarction, both in the hospital (41% vs 3%–6%) and at 30 days (43% vs 2%–10%).

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**Figure 3.** On repeat electrocardiography 48 hours after presentation, the ST-segment elevations in leads II, III, and aVF were still present. The ST-segment depressions in aVL and V₁–V₃ had resolved, and new ST-segment elevations were present in V₄ and V₅ (arrows).
Treatment

Evidence-based recommendations are available to guide antibiotic selection in infective endocarditis, but none exist on the management of septic coronary embolization.

Expert opinion supports early coronary angiography even when infective endocarditis is suspected, since coronary embolism is clinically indistinguishable from atherosclerotic plaque rupture at the time of presentation. Intravascular ultrasonography may be used to distinguish plaque erosion from embolus.

Aspiration thrombectomy with or without balloon angioplasty can be done to restore normal coronary blood flow. However, angioplasty with stenting may establish a nidus of infection in the vessel wall.

In this patient’s case, the initial presentation suggested typical STEMI due to atherosclerotic coronary artery disease. However, the angiographic, hemodynamic, and microbiologic data directed the clinicians toward a rarer cause of acute coronary syndrome—infective endocarditis. Infections of cardiac valves commonly cause morbidity through direct cardiac invasion and distant emboli. This patient’s case reminds us that emboli from heart valve vegetations sometimes take an unexpected turn.

■ TAKE-HOME POINTS

- If angiography for STEMI does not reveal evidence of atherosclerotic plaque rupture, consider other causes of STEMI including coronary vasospasm, dissection, and embolization.
- Fever, leukocytosis, and vessel cutoffs on angiography are early clues to septic coronary emboli; later test results, including blood cultures, vegetations on echocardiography, and mixed shock on hemodynamic measurements provide additional evidence for endocarditis.
- Patients with STEMI from septic coronary emboli have higher in-hospital and 30-day mortality rates than patients with atherosclerotic myocardial infarction.

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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