Exercises in Clinical Reasoning

Against All Odds

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In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (italics) is integrated throughout the discussion.

A 59-year-old man presented with fever and myalgia. Two months before presentation, fevers, chills, fatigue, and night sweats began. This was followed by pain over the right posterior thigh that was persistent, progressive, and exacerbated by squatting or exercise.

Fever with myalgia is frequently self-limited, as in upper respiratory infections, but if protracted, may signal a systemic disorder. Pain over the right posterior thigh, particularly in the absence of fever and with a more lateral distribution, suggests meralgia paresthetica, an entrapment of the lateral femoral cutaneous nerve by a fascial sling. Alternatively, his discomfort may originate from a spinal or radicular process at L2, L3, or L4. It is important to confirm that squatting was impaired by pain and not weakness, as the latter signals a myopathy.

One month before presentation, he noticed painful whitening of his fingers when exposed to cold, which resolved upon warming. He had lost 5 kg despite a normal appetite. He had no headache, cough, dyspnea, chest pain, abdominal pain, diarrhea, nausea, vomiting, or arthralgia.

The patient had a history of benign prostatic hyperplasia. His only medication was acetaminophen. He had smoked one pack of cigarettes daily for 40 years and drank one can of beer daily. He had not traveled outside of Japan. He lived with his wife and worked as a garbage collector at commercial buildings, but stopped his job 2 weeks earlier due to severe fatigue.

Discoloration of the fingers with exposure to cold suggests Raynaud's phenomenon. Chilblains, an ill-characterized, chronic, recurrent, cold-induced acral ischemic syndrome, can produce this presentation as well. A concomitant ischemic myopathy of his thigh would suggest a large vessel disorder such as atherosclerosis, giant cell arteritis, or Takayasu's arteritis.

On exam, he reported severe right posterior thigh pain. His temperature was 38.8°C, his blood pressure was 102/68 mmHg, his pulse was 112 beats per minute, and his respiratory rate was 20 breaths per minute. His right posterior thigh was tender to palpation but not warm, erythematous, or swollen; there was no palpable mass. Muscle strength was intact in both the upper and lower extremities with limitation of right hip extension and knee flexion due to pain. The remainder of the examination was normal.

His vital signs are compatible with a systemic inflammatory response or sepsis, prioritizing the search for infection. The absence of heart murmurs is important, because any patient with fever, systemic symptoms, and ischemic phenomena may have endocarditis. The right posterior thigh is tender, but does not have any signs of inflammation, which might be expected in a patient reporting this much pain. His impaired motion confined to hip extension and knee flexion is likely explained by pain rather than motor weakness. The absence of sensory abnormalities makes spinal cord, radicular, and neuropathic processes less likely. However, neuropathic pain emanating from the sacral plexus must remain on the differential.

Pyomyositis, commonly caused by *Staphylococcus aureus*, could be responsible for severe pain in the involved extremity, although it should have revealed some local inflammation on examination after 2 months. The course of bacterial pyomyositis is usually much more acute compared to this case. No mention is made of peripheral pulses, but this pain sounds more disabling than expected in an ischemic process, in which the distal leg would also be expected to be cold. A sarcoma or other tumor affecting the soft tissues of the leg should be considered, but does not provide an explanation for the hand discoloration. A mass or indolent abscess in the right thigh is most likely. I once cared for a patient with acute leukemia who presented with severe thigh pain, caused by expansile bone marrow in the femur.

The discussant expands upon the three major categories of disease for undefined systemic disorders—infection, malignancy, and autoimmunity. He cites specific examples to anchor his reasoning in each category—pyomyositis, sarcoma, and vasculitis—and weighs the supporting and conflicting features of each condition, drawing upon his illness scripts. Illness scripts (mental representations of disease in a clinician's mind) contain textbook knowledge of diseases combined with personal experiences, such as the discussant's anecdote with leukemia. Anecdote-driven reasoning (also termed instances or exemplars¹) has a sizeable impact on clinicians' real-world reasoning despite its limitations (e.g., availability bias).

The hemoglobin concentration was 11.8 g per deciliter, with normal mean corpuscular volume; the white blood cell count was 12,200 per cubic millimeter with 81% neutro-

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phils, 11% lymphocytes, 6% monocytes, and 2% eosinophils; and the platelet count was 218,000 per cubic millimeter. The peripheral-blood smear showed no abnormal cells. The erythrocyte sedimentation rate and C-reactive protein level were 92 mm per hour (normal value <20) and 4.13 mg per deciliter (normal value <0.3), respectively. Laboratory tests revealed the following serum concentrations: aspartate aminotransferase, 161 U per liter (normal range, 9–38); alanine aminotransferase, 107 U per liter (normal range, 4–36); lactate dehydrogenase, 886 U per liter (normal range, 125–237); and creatine kinase (CK) 6,912 U per liter (normal range, 50–230). Electrolytes, protein, albumin, renal function tests, and thyroid-stimulating hormone were normal. The antinuclear antibody was less than 1:40, but antibody to the Ro (SSA) was positive at 78.6 U per milliliter (normal range, <7). Assays for antibodies to double-stranded DNA, Smith, RNP, La (SSB), Scl-70, and Jo-1 were negative. Rheumatoid factor, antineutrophil cytoplasmic antibodies, and cryoglobulins were also negative. Serum and urine protein electrophoresis were normal, as were serum complement C3 and C4 levels. Antibodies to hepatitis B virus, hepatitis C virus, and human immunodeficiency virus were absent. Blood cultures showed no growth. Urinalysis was negative. Chest radiograph followed by chest computed tomographic scan showed no evidence of mediastinal lymphadenopathy or parenchymal disease. A magnetic resonance imaging (MRI) of the right thigh revealed high T2 signal within the hamstrings (Fig. 1).

The elevated CK suggests that myonecrosis could account for the elevated transaminases and LDH, although the latter could also be originating from a lymphoma. Pleomorphic conditions such as sarcoidosis or lymphoma often show abnormalities on chest imaging such as mediastinal lymphadenopathy or parenchymal disease. An isolated anti-SSA with numerous negative rheumatological investigations is likely an incidental finding or a false positive; perhaps it warrants repeating. Autoantibodies are seen in many asymptomatic and disease-free patients, although sometimes they can predict ensuing ailments. Systemic lupus erythematosus appears very unlikely given the negative ANA.

The differential for this MRI finding includes a subacute infection, an unusually localized manifestation of a rheumatologic disorder, or a tumor. The absence of external inflammation and aggressiveness of the associated organisms makes

bacterial pyomyositis unlikely. The location would be excellent for a rhabdomyosarcoma, and the severity of pain might be explained by neuroinvasion. The upper extremity symptomatology remains a mystery.

Without a sufficient degree of match between the problem representation (not explicitly articulated here but possibly “a previously healthy 59-year-old man with a 40 pack-year smoking history with fevers, anemia, inflammation, and an undefined focal myopathic process”) and potential illness scripts, the discussant starts invoking atypical versions of infectious, autoimmune, or malignant conditions but with varying degrees of specificity. The lack of certainty at this point is a sign of diagnostic sophistication: recognizing the mismatch between the patient and his mental files, the discussant remains open to unusual presentations rather than discounting a category or condition altogether. The temporal correlation of the upper extremity symptoms with the thigh pain and the association with autoimmune conditions favor a single explanation for both phenomena (Occam’s Razor), but the discussant has not yet committed to this constraint.

On open biopsy of the right posterior thigh, the muscle appeared grossly pale. Microscopic examination demonstrated inflammatory infiltrates consisting of lymphocytes and plasma cells (Fig. 2). Necrotic muscle fibers and regeneration were seen throughout the fascicle. There were no neutrophilic infiltrates or granulomata. These findings were consistent with inflammatory myositis. Gram stain, fungal stain, and acid-fast bacilli stain were negative. Bacterial culture and tissue polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were negative.

Although the pale muscle suggests ischemia, no vasculitis was appreciated. The findings are compatible with an inflammatory myositis, but the cardinal clinical feature of dermatomyositis or polymyositis—skeletal muscle weakness—is absent. An open surgical procedure should have found evidence of a sarcoma. Tuberculosis almost never involves the skeletal muscle. Observation and symptomatic treatment would be prudent, reacting to clinical events as they occur.

Figure 1. MRI of the bilateral thighs. Axial view of a T2-weighted MRI shows increased signal intensity (white arrow) in the right hamstrings.

Figure 2. Muscle biopsy specimen (hematoxylin and eosin). The specimen shows necrotic muscle fiber with inflammatory infiltrates with lymphocytes and plasma cells. There were no findings of vasculitis.

Empiric antibiotics or immunosuppressants are best avoided until further information becomes available.

The patient continued to have myalgia and daily fevers to 39°C. Myositis-specific autoantibody to PL-7 (threonyl-tRNA synthetase antibody) was positive (normal, undetectable). Early polymyositis was diagnosed, and prednisone 60 mg daily was prescribed. During the next month, intermittent low-grade fevers continued, but the myalgia improved somewhat. Creatine kinase decreased from 6,912 to 1,608 U per liter. Repeat MRI showed enlargement of the original lesion in the right hamstrings and new lesions in the surrounding tissues (Fig. 3).

It is never a surprise when a patient, irrespective of the underlying diagnosis, shows early clinical improvement on high-dose prednisone which invariably mitigates symptoms that are related to inflammation. This temporary response, however, can mask a tumor or indolent infection, and the clinical and radiologic progression after high-dose steroids favors these categories over an autoimmune process.

Clinicians frequently administer therapeutic trials of steroids in scenarios when diagnostic certainty cannot be achieved in highly symptomatic patients—e.g., diffuse rash, unexplained wheezing, or suspected gout. Therapeutic trials have two potential benefits—bringing relief to patients and serving as a diagnostic test for the clinician—but also carry risks of temporarily concealing conditions or fostering infection. Here the discussant cautions against such a trial but does use the clinical response to prioritize the three categories of disease.

On the 25th hospital day, intravenous immunoglobulin was initiated for suspected refractory polymyositis. The creatine kinase decreased slightly, mild tenderness and limitation in mobility remained, and there was no change on follow-up MRI. On the 30th day, slow tapering of prednisone was started. Muscle cultures for fungi and mycobacteria returned negative. On the 40th hospital day, fever to 40°C developed, and painful erythema with warmth was detected over the right posterior thigh (Fig. 4).

Given the ongoing focality, the unremitting high fever, and absence of evidence of malignancy, I would favor an indolent or atypical infectious myositis. There is no history of a tick bite to

Figure 4. Photograph of the patient's swollen, erythematous right thigh.

suggest *Rickettsia tsutsugamushi* infection, which would be culture-negative and could cause this degree of discomfort.

Transcutaneous aspirates of a subcutaneous fluid collection (which was contiguous with the deep muscle and fascia on MRI) were purulent, and microscopic examination revealed abundant acid-fast bacilli. PCR and cultures confirmed *M. tuberculosis*. Treatment with isoniazid, rifampin, pyrazinamide, and ethambutol was started for tuberculous pyomyositis. The patient defervesced within 2 weeks. QuantiFERON later returned positive.

Steroids were tapered off. His pain, CK elevation, and MRI imaging improved over the next 3 months. His recovery was complicated by rupture of the subcutaneous tuberculous abscess through a sinus tract to the skin. The drainage was acid-fast smear positive, resulting in the prolongation of his antituberculous chemotherapy. The resulting ulceration and drainage required more than 6 months to resolve completely.

Although tuberculosis affecting skeletal muscle is rare, this outcome again displays the incredibly pleomorphic behavior of this organism. It also shows that some pearls—tuberculosis never affects skeletal muscle—turn out to be glass beads on further inspection.

COMMENTARY

In this challenging case, both the team of treating physicians and a very experienced clinician were unable to arrive at the rare diagnosis of tuberculous myositis. The discussant repeatedly raised the possibility of an indolent infection, and he considered tuberculosis. Layered upon his accurate understanding of skeletal muscle as a very rare site for TB was normal chest imaging followed by a negative acid-fast stain, negative MTB PCR, and negative mycobacterial cultures from an open biopsy. An earlier PPD or a QuantiFERON test may have changed the course of this case, but it is impossible to know if these tests would have been diagnostic in the initial weeks of the illness.

The aphorism that TB (or syphilis or endocarditis etc.) is “protean” or “can do anything” is helpful as a general guide in diagnosis. However, at some point, a clinician may find himself or

Figure 3. Repeated MRI of thigh shows worsening findings of muscle inflammation (white arrows).

herself below the diagnostic threshold for the disease and must concede in order to seriously consider and pursue alternatives. Clinicians are comfortable with the empiric treatment of TB when confronted with a lymphocytic, exudative, non-malignant pleural effusion with negative mycobacterial studies (e.g., AFB stain, culture, PCR, and ADA). However, given the very limited experience any clinician would have with tuberculosis myositis (indeed, one article is entitled "Tuberculous myositis: a rare but existing clinical entity"²), it is unrealistic to expect that analogous reasoning would be sufficient to drive empiric treatment when faced with an uncertain muscular disorder.

Many cases in practice initially defy diagnosis.^{3,4} Zermansky wrote that "a failure to achieve a diagnosis is not a reason to invent one" but goes on to say "neither is it a reason to deny the patient help."⁵ This dual tension leads physicians to undertake therapeutic trials without a firmly affixed diagnostic label. Glasziou provides criteria to consider when the "test of treatment" strategy can be reasonably used to arrive at a final diagnosis: when a single diagnosis is highly probable but not certain, when an available treatment works for most patients with that diagnosis, and when there is a measurable short-term outcome or surrogate.⁶ Examples include steroids for polymyalgia rheumatica, acetaminophen for elbow pain, and proton pump inhibitors for GERD. Clinicians also feel compelled to initiate empiric treatment in highly symptomatic patients when palliation is not possible without directed treatment. As the potency and risk of the proposed treatment increases (e.g., cytotoxics or chemotherapy), the need for diagnostic certainty approaches 100%, but exceptions are prevalent.

Faced with a progressive illness and a suffering patient, the clinicians in this case hesitantly assigned a diagnosis of inflammatory myopathy on the basis of serologic results and possible Raynaud's phenomena. The atypical features for that diagnosis were outlined by the discussant, and it is likely that the treating clinicians were aware of these inconsistencies in the diagnosis as well. Whether this was an episode of premature closure or a conscious lowering of the diagnostic and treatment threshold for autoimmune myopathy is hard to say and is a judgment that is nearly impossible to make in retrospect.

An evolving literature has elevated delayed and missed diagnoses to an important patient safety issue.⁷ As taxonomies and frameworks are developed, we will have to consider that some cases which appear to be diagnostic errors emerge from a more complex context where the limits of diagnosis are reasonably reached and only the passage of time can be relied upon to establish the diagnosis—to the frustration of patient and physician alike.

CLINICAL TEACHING POINTS

1. *M. tuberculosis* disproportionately affects underdeveloped nations and communities worldwide, but there are highly developed nations such as Japan in which it remains

endemic. In 2009, there were 24,170 newly diagnosed cases reported in Japan.⁸

2. MTB infection is extremely rare in the myocardium, skeletal muscle (occurring in <1% cases of tuberculosis⁹), pancreas, and thyroid.¹⁰
3. Tuberculous myositis is diagnosed on the basis of histopathology and culture results. According to the largest case series from Taiwan², chest radiographs were abnormal in half of patients, most patients required surgical debridement and drainage, and the mortality rate was 14%, with corticosteroids administration prior to the tuberculous myositis diagnosis being a poor prognostic factor. Tuberculous myositis cases with negative initial smear and culture results have been reported.¹¹

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