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Chest pain, weakness, and elevated cardiac enzymes: How would you treat?

You are making rounds in the hospital one Saturday morning when you receive a call from the emergency department saying a 68-year-old man is having chest pain, weakness, and “positive cardiac enzymes.” His electrocardiogram (ECG) reading is reported as unremarkable. Because it is the weekend and no cardiology consultation is available at your hospital, the family medicine resident wants to know if you would like to admit the patient to your service or transfer him to a larger hospital. You decide that you can best make this decision by going to the emergency department and personally evaluating the patient.

History of present illness
• Approximately 4 weeks of generalized extremity pain and weakness; left-sided, nonexertional chest pain, which is much less severe than his extremity pains
• Symptoms are most prominent in the proximal upper extremities, especially with movement; the right side is more affected than the left
• Dyspnea on exertion
• Seen twice in local urgent care facilities in the past 10 days; diagnosed with congestive heart failure; treated with furosemide, digoxin, and an unknown antibiotic without relief
• 20- to 30-pound weight loss over the past year

Review of systems
• Up to the day of admission has been ambulatory and able to care for himself despite his weakness
• No fever, chills, or rash; but has night sweats
• Smokes; does not drink alcohol
• Retired; lives with his wife

Physical examination
• Alert, appears mildly uncomfortable
• Temperature 101°F, respirations 32, blood pressure 164/72, pulse 80
• 3/5 strength in proximal upper and lower extremities (can barely lift arms and legs off the bed; movement also limited by pain)
• Normal distal strength (hand grips and dorsi/plantar flexion of foot)
• Normal sensation, reflexes, cranial nerves, and mental status; no neck weakness
• No abnormal joint findings; has pink discoloration over extensor surface of
MCP joint, which patient dismisses as scars from previous abrasions that have been present “for a long time”
• Heart, lungs unremarkable; no peripheral edema

Laboratory studies completed in the emergency department
• ECG: normal
• Chest x-ray: bibasilar peribronchial infiltrates
• Hemoglobin/hematocrit: normal
• White blood count: 27,000 with 92% neutrophils
• Erythrocyte sedimentation rate: normal
• Urinalysis: negative for blood
• Brain natriuretic peptide: normal
• Creatine kinase (CK): 2205 IU/L (normal range 35–232)
• Troponin-I: 0.6 ng/mL. [Reference range: <0.05 = Negative
0.05−0.09 = Equivocal
0.10−0.49 = Suspicious
0.50 = Consistent with myocardial injury]

Q: What is your presumptive diagnosis? What is your management plan?

A:

Is this acute non-ST elevation myocardial infarction (NSTEMI)?
The American College of Cardiology and the American Heart Association define myocardial infarction primarily as elevated cardiac-specific enzymes troponin-I and troponin-T in the appropriate clinical setting. Elevated cardiac troponins have a sensitivity approaching 100% for myocardial damage. Specificity is much lower for acute ischemic cardiac disease, however, particularly for patients with a low pretest probability (45% false-positive rate in one series of 1000 consecutive patients presenting to a large urban emergency department with symptoms of acute coronary ischemia).4

Mechanisms other than atherosclerotic coronary artery disease that can elevate cardiac troponins:
• Increased cardiac demand (eg, sepsis, hypovolemia)
• Nonatherosclerotic ischemia (eg, cocaine or other sympathomimetic agents, coronary vasospasm)
• Direct myocardial injury (eg, cardiac contusion, myocarditis)
• Myocardial strain (eg, congestive heart failure, pulmonary embolus)
• Chronic renal insufficiency (mechanism unclear).4

In light of this patient’s history and physical exam findings, you doubt he’s having an acute cardiac event. The most remarkable features are his weakness, muscle pain, and markedly elevated CK.

Though you have ruled out anemia and several other possibilities, the differential diagnosis of weakness is still broad. You decide to explore the differential diagnosis of elevated CK, a more specific finding in this case.

Pursuing the differential
You consult UpToDate, searching under “creatine kinase,” and find an article entitled “Muscle enzymes in the evaluation of neuromuscular disease.” You conclude that the most likely cause of your patient’s problems is an idiopathic inflammatory myopathy: polymyositis, dermatomyositis, or inclusion-body myositis.6

Other possibilities include post-viral myositis and myositis associated with connective tissue disease, hypothyroidism, or drug reactions.
D-penicillamine, zidovudine (AZT), and viral or bacterial infection may produce inflammatory myopathy similar to polymyositis. A history of exposure to myotoxic drugs (such as statins) and toxins has been excluded.

The absence of a family history for neuromuscular disease and the relatively recent onset of symptoms rule out an inherited muscular dystrophy or congenital muscle enzyme deficiency.

Myasthenia gravis presents with extraocular muscle involvement. Guillain-Barré syndrome is characterized by ascending muscle weakness. Lyme disease may cause weakness secondary to peripheral neuropathy but it does not produce evidence of muscle inflammation such as elevation of the CK. West Nile virus encephalitis may present with muscle weakness and flaccid paralysis. Trichinellosis may also cause muscle inflammation with weakness and elevation of CK, but it is rare in the United States.

You repeat parts of your physical exam and confirm that his proximal upper extremity muscles are much weaker than his distal muscles.

In practice settings where specialty consultation is not always immediately available, your diagnostic skills may be challenged by uncommon presentations of disease. In this case, the challenge is “chest pain and positive cardiac enzymes” in a patient who does not appear to have a primary cardiac problem.

Q: What is your management plan at this point?
A:

- Diagnostic plan: serial ECGs and cardiac enzymes: an echocardiogram
- Therapeutic plan: pain control; antibiotics for possible pneumonia; consider steroids
- Assistance from consultants (who are you going to ask for help?): physiatrist consult for electromyography (EMG); cardiology consult; neurology consult
- Patient education (explain to the patient and his family the current diagnostic possibilities and your management plan)
- Provider education (learn more about myopathies!)

You request specialty consultations: Neurology: possible polymyositis; recommends rheumatology consultation, multiple labs (most of which are sent out to a reference lab and return only several days later)

Cardiology: ECG normal; cardiologist does not see evidence for congestive heart failure or coronary artery disease

Physical medicine and rehabilitation: EMG performed; findings consistent with inflammatory myopathy

Rheumatology: recommends proceeding with muscle biopsy to differentiate polymyositis and inclusion-body myositis

Surgery: performs muscle biopsy which is sent to a regional neuropathologist; reveals inflammatory myopathy with prominent perivascular lymphocytic inflammation strongly suggestive of dermatomyositis.
Further case management and resolution
You administer solumedrol intravenously 1 g/d for 3 days, then change to prednisone orally 1 mg/kg/d. The patient improves steadily with 3 months of oral steroid therapy. He tests positive for anti-Jo antibodies but his pulmonary symptoms resolve. He undergoes an outpatient evaluation for cancer screening. Colonoscopy, esophagogastroduodenoscopy and chest/abdominal/pelvic computed tomography scans are negative for evidence of malignancy.

Other ways in which you may encounter inflammatory myopathies
Dermatomyositis usually causes a characteristic rash that facilitates early diagnosis (though it did not appear in this case). As shown in FIGURES 1 AND 2, patients may have either a heliotrope rash (blue-purple to dusky eryhematosous discoloration on the upper eyelids, with or without edema), or Gottron’s papules (slightly raised violaceous papules and plaques overlying bony prominences, particularly the joints in the fingers and the knuckles).

A variety of less specific skin and nail changes can occur. Dermatomyositis may present with skin lesions alone (dermatomyositis sine myositis) or rarely with myopathy alone (dermatomyositis sine dermatitis). In our case, multiple examiners failed to detect any classic dermatologic abnormalities, though the pinkish skin changes over the extensor aspect of the MCP joints were, in retrospect, suggestive of dermatomyositis. The weakness associated with this disease may be mild, moderate, or severe enough to result in quadripareisis. Dermatomyositis usually occurs alone but may be present with scleroderma and mixed connective tissue disease.
Inclusion-body myositis is often misdiagnosed as polymyositis or dermatomyositis until identified by muscle biopsy findings (see How inflammatory myopathies develop), although suspicion is raised with a poor response to steroid therapy. Some patients report falling as a result of quadriceps weakness. On occasion the weakness can be asymmetric or distal (rare with dermatomyositis or polymyositis). Diagnosis is always made by muscle biopsy. Disease progression is slow but steady and most patients end up requiring a walker or assistive device. Polymyositis is generally seen after the second decade of life. Both children and adults may be affected by dermatomyositis. There have been rare familial occurrences.

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Commonly associated clinical findings

Extramuscular manifestations of inflammatory myopathies. Dermatomyositis is a systemic inflammatory disorder that may extend beyond the dermatologic and muscular systems, and patients can exhibit such symptoms as fever, malaise, and weight loss.

Arthralgia and Raynaud’s phenomenon may occur with associated connective tissue disease.

Dysphagia indicates involvement of the oropharyngeal striated muscles and the upper esophagus.

Cardiac disturbances include atrioventricular conduction defects, tachyarrhythmias, myocarditis, heart failure, and possibly hypertension from long-term steroid use. The elevated troponin-I seen in our index case may have been evidence of a mild myocarditis, though the echocardiogram was normal.

Calcinoisis (deposition of calcium in the skin or muscles) occurs in up to 40% of children with dermatomyositis but is unusual in adults. Pulmonary symptoms may be due to weakness of the thoracic muscles, interstitial lung disease, or aspiration. One retrospective study of 156 consecutive patients with dermatomyositis/polymyositis based on clinical criteria found a 23.1% incidence of interstitial lung disease.

Malignant disorders. The frequency of cancer is increased in association with these diseases. Studies have placed the highest risk of concomitant malignancy with dermatomyositis and the least risk with polymyositis. (The relative risk for malignancy in dermatomyositis as compared with polymyositis was 2.4.) Malignancy associated with dermatomyositis or polymyositis is twice as likely in women than in men.

Risk of associated malignancy was highest within the first year of diagnosis. Therefore, consider a diagnostic evaluation for malignancy at the time myopathy is diagnosed. The optimal diagnostic regimen in this setting is unknown. In one retrospective French study of 40 consecutive adult patients with inflammatory myopathy (33 with dermatomyositis and 7 with polymyositis) between the years 1981 and 2000, malignancy was present at the time of myopathy diagnosis in 16 patients (13 with dermatomyositis and 3 with polymyositis). An Australian population-
based, retrospective cohort study of 537 individuals with biopsy-proven idiopathic inflammatory myopathy from 1981–1995 demonstrated 116 cases of malignancy in 104 patients. The risk was highest in dermatomyositis (standardized incidence ratio [SIR] 6.2), next highest in inclusion-body myositis (SIR 2.4), and lowest in polymyositis (SIR 2.0).

**Diagnosis: What helps, what doesn’t**

Suspect inflammatory myopathy by the constellation of clinical findings; confirm it by looking for elevated muscle enzymes and characteristic findings on EMG and muscle biopsy (see How inflammatory myopathies develop).

The most sensitive muscle enzyme for inflammatory myopathy is CK, levels of which usually parallel disease activity and may be used to assess response to therapy. Needle EMG demonstrates increased spontaneous activity with fibrillations; complex repetitive discharges; positive sharp waves; and voluntary motor units consisting of low-amplitude polyphasic units of short duration. EMG findings alone are not diagnostic.

Serologic tests are commonly done but their clinical usefulness is controversial. Antinuclear antibodies are found in about 80% of cases but are nonspecific and not clinically useful. Myositis-specific antibodies (MSAs) have been described in about 30% of idiopathic inflammatory myopathies but are also of uncertain diagnostic and pathogenic importance. The most prevalent MSA, anti-Jo, is present in only about 20% of cases and correlates with interstitial lung disease, but has uncertain usefulness in differentiating between dermatomyositis, polymyositis, and inclusion-body myositis.

Differentiate between the inflammatory myopathies based on characteristic pathological findings on muscle biopsy (previously discussed). Muscle biopsy is the definitive test for establishing the diagnosis. In our case presentation, the regional neuropathologist thought the biopsy result was most consistent with dermatomyositis despite the clinical paucity of skin abnormalities, though our consulting neurologist favored a diagnosis of polymyositis on clinical grounds.

**How inflammatory myopathies develop**

Evidence suggests the inflammatory myopathies are autoimmune disorders. They are often associated with connective tissue diseases and other systemic autoimmune conditions. Viral infections such as coxsackie, influenza, paramyxovirus, mumps, cytomegalovirus, and Epstein-Barr have been indirectly associated with chronic and acute myositis and may trigger the autoimmune process.

Specific muscle or capillary target antigens have not been identified, and the agents that initiate self-sensitization are still unknown. Other features of these disorders are their association with auto-antibodies, certain histocompatibility genes, T-cell–mediated myocytotoxicity, and complement-mediated microangiopathy.

Dermatomyositis appears to be primarily a B-cell mediated microangiopathy. Antibodies directed against the endothelium of the endomysial capillaries lead to the primary histological changes in the blood vessels. The disease manifests when the complement system is activated to form the membrane attack complex (MAC).

Polymyositis and inclusion-body myositis appear to result from a cytotoxic T-cell response directed specifically against muscle fibers. CD-8+ cells are induced via T-cell activation to invade MHC-I antigen-expressing muscle cells. Usually most muscle cells do not express MHC Class I or II antigens. Histology demonstrates infiltration of individual muscle fibers by inflammatory cells. Inclusion-body myositis is differentiated from polymyositis by the presence of nuclear and cytoplasmic vacuoles.

**Treatment recommendations**

Corticosteroids are the most efficacious treatment for dermatomyositis (strength of recommendation [SOR]: B). One empirical regimen is to give prednisone 1 mg/kg/d as initial therapy; maintain this therapy for 1 month after symptoms and CK have normalized; then slowly taper (SOR: C). Twenty-five percent of
patients will not respond to steroids; others will not tolerate the side effects of steroid therapy.\textsuperscript{10}

Immunosuppressive drugs such as azothioprine, methotrexate, cyclosporine, mycophenolate mofetil and cyclophosphamide may be used as second-line treatment (SOR: C). Intravenous immunoglobulin may have some efficacy (SOR: B).\textsuperscript{14} Plasmapheresis does not appear to be effective (SOR: B).\textsuperscript{17}

### Determinants of prognosis

Most patients will improve over several weeks or months with therapy, although a third or more are left with mild to severe muscle damage. Dermatomyositis responds better than polymyositis; inclusion-body myositis is the most difficult to treat. Poor prognostic factors include older age, association with cancer, pulmonary fibrosis, dysphagia with aspiration pneumonia, cardiac involvement, steroid-resistant disease, and calcinosis in dermatomyositis.\textsuperscript{6,10} Studies have demonstrated 5-year survival rates between 77\% and 92\%.\textsuperscript{16,19} The main causes of death were related to malignancy and cardiac or pulmonary complications.\textsuperscript{6}

**REFERENCES**


