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CLINICAL CARE CONUNDRUMS

Aching for a Diagnosis

The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

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A 23-year-old Caucasian man presented to an outpatient clinic with a sore throat and associated subjective fevers. His evaluation included a negative rapid streptococcus test; nevertheless, he was empirically treated with amoxicillin. The following day, he experienced increasing sore throat and presented to the emergency department (ED). He was treated with prednisone and morphine sulfate and discharged home with azithromycin.

Initial considerations in a healthy young man who presents with fever and pharyngitis should focus on common infectious etiologies. Viral illnesses are the most frequent causes of sore throat and fever. These often manifest as mononucleosis-like illnesses and include Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In this age group, it is also critical to consider sexually transmitted diseases (STDs) such as gonorrhea, human immunodeficiency virus (HIV), herpes simplex virus, and syphilis. Consideration of streptococcal pharyngitis is important. Since the rapid streptococcal antigen test is neither sensitive nor specific, confirmation of infection should be based on clinical findings and a culture of the pharynx for group A S*treptococcus*. Other common etiologies of fever and pharyngitis include acute or chronic sinusitis with postnasal drainage. Due to the progressive nature of the sore throat, there should be an evaluation for difficulty swallowing, problems phonating, or neck discomfort, any of which would be concerning for a retropharyngeal abscess. Additional history should be obtained with focus on sexual history, previous STDs, recent sick contacts, and other supporting signs and symptoms of viral illnesses.

Eight days after the initial onset of symptoms, the patient developed acute low back pain. The back pain was midline, severe, and constant around the lumbar spine. There was no saddle anesthesia, bowel or bladder dysfunction, or weakness or numbness in the extremities. He also noted swelling of the left fourth metacarpophalangeal joint and an erythematous rash on his right knee and anterior tibial region of the right leg. He continued to experience subjective fevers, sore throat, and swollen neck glands. Due to the severity and discomfort of symptoms, the patient returned to the ED.

With no history of trauma, the subsequent development of acute low back pain may be related to the patient's sore throat and fever. Monoarticular arthritis with contralateral skin lesions should raise suspicion for a systemic process, particularly infection or a rheumatologic syndrome. Infectious etiologies would include rheumatic fever, endocarditis with septic emboli, and osteomyelitis. Rheumatologic causes, such as ankylosing spondylitis and juvenile rheumatoid arthritis (RA), are also possibilities. The infectious evaluation should include an assessment of a history of intravenous drug use (IVDU) and underlying valvular disorders, which will increase the risk for endocarditis and therefore septic emboli. Acute HIV infection can be seen as early as 1 to 2 weeks postexposure and should be considered as well. Appropriate testing would include both conventional HIV antibody tests and HIV viral load assay. Lastly, in considering the patient's symptoms, obtaining his travel history to identify risk for Lyme disease would also be appropriate.

The patient did not report any further positive findings on review of systems. He did not have any significant past medical history and did not take any chronic medications. He had no sick contacts. He rarely drank alcohol and denied IVDU and sexual activity over the past year. He was previously involved in monogamous relationships with women. His last HIV test, 1 year prior, was negative. He did not have any history of STDs. He was a graduate student in computer science and lived in southern California. He had recently traveled to central California and France for 2 weeks, staying in larger cities. He had not been hiking during that time. His family history was significant for hypertension.

The travel history is provocative for 3 diseases of the reticuloendothelial system with possible systemic manifestations. First, toxoplasmosis, which is endemic in France where rare or raw beef and lamb are frequently consumed. It may present as a mononucleosis-like illness and rarely as atypical pneumonia. Second, tuberculosis, which is also endemic in France, especially in major cities. Although most commonly a self-limited respiratory disease, it may disseminate with systemic symptoms. Third, primary

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coccidioidomycosis, which is prevalent in the central valleys of California. The climate and wind patterns lead to aerosolization of the spores and make this a common respiratory pathogen.

The physical exam should include a detailed evaluation of the eyes for uveitis and iritis, seen in some rheumatologic disorders. A pharyngeal exam with assessment for exudate can support streptococcal pharyngitis or diphtheria. Evaluation for lymphadenopathy, while nonspecific, would be important for streptococcal pharyngitis, rheumatic fever, and juvenile RA. Further characterizing the rash is essential in distinguishing viral exanthems from the fleeting salmon-colored maculopapular rash of juvenile RA. Assessment for peripheral stigmata of endocarditis should be done. A thorough joint exam should evaluate evidence of inflammatory or infectious joint disease.

On physical exam, he was a thin man who appeared anxious but in no acute distress. His temperature was 36.7°C, blood pressure 111/68 mm Hg, heart rate 83 beats/minute, respiratory rate 16 breaths/minute, and oxygen saturation 99% on room air. Erythema was noted in the posterior oropharynx with no tonsillar exudate. There were several subcentimeter, nontender, and mobile lymph nodes in the anterior cervical chain bilaterally. The cardiovascular exam revealed normal sinus rhythm with a 2/6 systolic murmur at the apex, without radiation. His lungs were clear to auscultation. Skin exam revealed 2 blanching erythematous, indurated, and tender lesions on the right pretibial region, 2-cm and 4-cm in diameter. Two other similar, but smaller, lesions were noted on the left upper extremity and left ankle. His lumbar spine was slightly tender to touch. A complete joint exam was normal, including the left fourth metacarpophalangeal joint. Neurological exam, including bilateral strength, sensation, reflexes, and gait, was unremarkable.

Younger patients are subject to social-acceptance bias and can deny sexual activity on initial inquiry. An objective evaluation for STDs with serologic workup should still be pursued. The cervical lymphadenopathy and tonsillar erythema continue to suggest a viral illness. While the systolic murmur may be physiologic, subjective fevers, disseminated cutaneous lesions, and arthritis warrant evaluation for bacterial endocarditis with blood cultures and an echocardiogram.

On exam, there is no evidence of true joint involvement and this decreases the likelihood of rheumatologic conditions, such as ankylosing spondylitis and juvenile RA. However, the skin lesions are suspicious for erythema nodosum (EN), which should prompt a biopsy and an evaluation for infectious etiologies. Serologies should include evaluation of *Chlamydia*, *Mycoplasma*, *Coccidioides*, and *Histoplasma*. I would also examine the feet carefully for potential transcutaneous inoculation by microorganisms that can produce a rash similar to EN. For instance, penetrating skin trauma can lead to pseudomonal infection. *Brucella* (from ingesting unpasteurized milk or milk products), *Bartonella* (from the scratches of feline animals), and *Francisella tularensis* (from rabbit exposure) can also produce skin lesions that mimic EN. These are best distinguished through a detailed history, concomitant serologic workup, and biopsy. Other noninfectious etiologies of EN can include inflammatory bowel disease, Behcet's, and sarcoidosis; however, the patient does not currently report any symptoms supporting these diagnoses. In addition to the above evaluation, complete blood count with differential, liver function tests, creatinine, and urinalysis should be obtained.

The patient's white blood cell (WBC) count was 12,100/μL with 73% neutrophils, 14% lymphocytes, and 12% monocytes. Hemoglobin was 11.8 g/dL and platelet count 292,000/μL. Chemistry panel and liver function tests were unremarkable. Erythrocyte sedimentation rate (ESR) was 71 mm/hour (range, 0–10). Urinalysis was negative for protein and red blood cells. Chest x-ray did not illustrate any abnormalities. Computed tomography (CT) of the lumbar spine revealed a small posterior disc bulge at L4-5 and L5-S1.

The moderate leukocytosis with neutrophilic predominance and monocytosis raises concern for a systemic inflammatory process; the elevated ESR further supports this. Monocytosis can be seen in a number of infectious, autoimmune, and malignant conditions. Tuberculosis, brucellosis, bacterial endocarditis, syphilis, infectious mononucleosis, and viral illnesses are among the infections typically characterized by monocytosis. Autoimmune illnesses, such as systemic lupus erythematosus and RA can also have similar presentations. The patient does not have any features of an underlying malignancy, such as weight loss or night sweats; however, if the autoimmune and infectious evaluations are negative, Hodgkin's disease and certain leukemias should be considered. There is no evidence of osteomyelitis on the spine CT, which decreases the possibility of (but does not exclude) infectious or rheumatologic conditions of the spine. I would suggest a comprehensive laboratory evaluation for the discussed infectious and rheumatologic disorders.

The patient's back pain was controlled with antiinflammatory medications overnight. Due to the patient's stable condition and lack of a diagnosis, empiric antibiotics were not initiated. An extensive workup was sent, including antistreptolysin O, polymerase chain reaction for *Chlamydia*, *Neisseria gonorrhoeae*, EBV, and parvovirus B19 DNA, serologies for *Coccidioides* immunoglobulin G (IgG) and IgM, urinary antigen for *Histoplasma*, HIV enzyme-linked immunosorbent assay (ELISA) and Western blot, serum angiotensin-converting enzyme level, C-reactive protein, rheumatoid factor, antinuclear antibody, and anti–double-stranded DNA antibodies.

Without a clear diagnosis, I would recommend against treatment with empiric antibiotics. At this point, I agree with waiting for the results of the pending workup.

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On hospital day 1, the patient developed severe acute left ankle pain. On examination, the joint was exquisitely tender with decreased range of motion. Arthrocentesis was promptly performed. The synovial fluid WBC count was 1370/μL with a differential of 82% neutrophils and 18% monocytes. No crystals were identified and the bacterial Gram stain was negative. He was treated with antiinflammatory medications. Bacterial blood cultures, obtained from the day of admission, were negative.

The arthrocentesis reveals a polymorphonuclear-predominant fluid; however, the WBC count in the fluid is only mildly elevated. While the elevated monocyte count could again be consistent with viral arthropathies or juvenile RA, there is currently no systemic evidence of either illness. It is important to await the results of the final cultures, but the low WBC count and negative Gram stain decrease the probability of a septic joint. Empiric antibiotics to cover Gram-positive organisms and gonococci would not be unreasonable, pending joint fluid culture results. The monocytosis could also be consistent with a fungal arthritis.

On hospital day 2, the results of the rheumatologic and infectious evaluation were negative with the exception of C-reactive protein, which was 11.8 mg/dL (normal, <0.8), antinuclear antibody titer of 1:160 (normal, <1:40), *Coccidioides* IgM enzyme immunoassay (EIA) 0.710 (negative, <0.150), and *Coccidioides* tube-precipitin (TP) immunodiffusion (ID) antibody-positive. *Coccidioides* IgG EIA was negative.

The serologic tests are consistent with primary coccidioidomycosis. This is often a challenging diagnosis due to the nonspecific signs and symptoms, such as cough, fever, myalgias, and fatigue. Since screening EIAs are sensitive but not specific, concern for coccidioidomycosis or abnormal EIA results should prompt confirmatory testing with complement fixation titers (CF) and TP ID. Treatment with fluconazole should be initiated. Since the patient does not have central nervous system (CNS) symptoms, I would not recommend lumbar puncture at this point. However, a bone scan should be done for assessment of the back pain.

The patient was diagnosed with primary coccidioidomycosis infection with immune-complex–mediated arthritis and EN. A bone scan was negative. The patient was treated with fluconazole and discharged with 3 months of therapy. At follow-up clinic visits after completion of therapy, his symptoms had resolved and his titers had normalized.

Discussion

The diagnosis of coccidioidomycosis is often challenging due to its protean manifestations. Four clinical syndromes are commonly seen: (1) acute pneumonia, (2) chronic progressive pneumonia, (3) pulmonary cavities and nodules, and (4) extrapulmonary disease involving the skin, lymph nodes, bones, joints, and meninges. The most common clinical manifestation, acute pneumonia, may be indistinguishable from other causes of community-acquired pneumonia (CAP). In a study of CAP in Arizona, 29% of cases were positive for coccidioidal infection through serologic evaluation.[1] Features suggestive of coccidioidal infection include fatigue, severe headache, and pleuritic chest pain. Adenopathy in the hilar or paratracheal regions can be seen in 25% of infections.[2] Chronic progressive pneumonia refers to infections in which symptoms, including cough, hemoptysis, and weight loss, persist for longer than 3 months. Pulmonary nodules and cavities are residual manifestations of primary pulmonary infection and occur in 2% to 8% of cases. Extrapulmonary disease develops in less than 5% of immunocompetent patients with primary pulmonary infection, with higher prevalence in patients of African American and Filipino decent. Immunocompromised patients are at increased risk for extrapulmonary infection. The most serious site of extrapulmonary disease is the meninges. Coccidioidal meningitis carries nearly 100% mortality rate if left untreated. The presentation is variable with up to 75% of cases reporting headache. While coccidioidal pneumonia also frequently presents with headache, symptoms including altered mental status, focal neurological deficits, and persistent or progressive headache are more suggestive of meningeal disease.[3]

Patients with any presentation of coccidioidomycosis can display immune-mediated manifestations such as EN, arthralgias (desert rheumatism), and in some cases mild conjunctivitis.[4] It is hypothesized that these findings occur due to a hypersensitivity reaction to coccidioidomycosis.[4] EN is an inflammatory process of the subcutaneous fat, which presents as tender and erythematous nodules typically on the lower extremities. EN is not a disease entity or site of metastatic infection, but a response to underlying illness. Its recognition should trigger a search for the primary etiology, as guided by the patient's history and clinical presentation. The differential diagnosis for EN is broad and includes rheumatologic, infectious, medication-related, inflammatory, and idiopathic processes (Table 1). Coccidioidomycosis should be strongly considered based on geographical location, with the vast majority of cases seen in southern California, Arizona, Nevada, New Mexico, and Texas. While the pathophysiology of EN has not been completely elucidated, the lesions may reflect a vigorous immune response conferring a protective advantage. Interestingly, a study of pregnant women with coccidioidomycosis revealed a decreased incidence of disseminated disease in patients with EN.[5,6]

Coccidioidomycosis is also associated with immune-mediated arthralgias and arthritis. These manifestations occur in up to one-third of patients with concomitant EN. Arthritis may be monoarticular or polyarticular, often affecting large joints such as the knees or ankles. It is important to note that septic arthritis can also occur and should be differentiated from rheumatism by joint aspiration.

The diagnosis of coccidioidomycosis can be made by serologic testing, direct isolation of the organism on culture, or visualization on tissue biopsy. Of these methods, serologic testing is most commonly utilized. The 2007 Infectious Disease Society of America (IDSA) and American Thoracic Society guidelines recommend diagnostic testing in hospitalized patients with CAP who reside in or have recently traveled (within 2

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TABLE 1. Differential Diagnosis of Erythema Nodosum

Rheumatologic/autoimmune
• Systemic lupus erythematosus
• Wegener's granulomatosis
• Sarcoidosis
Infectious
• *Streptococcus pyogenes* causing pharyngitis (most common)
• *Borrelia burgdorferi*
• *Mycoplasma pneumoniae*
• *Bartonella henselae*
• *Shigella*
• *Campylobacter jejuni*
• *Salmonella*
• *Yersinia enterocolitica*
• *Chlamydia*
• *Brucella*
• *Escherichia coli*
• *Treponema pallidum*
• *Mycobacterium leprae*
• *Neisseria gonorrhoeae*
• *Mycobacterium tuberculosis*
• Human immunodeficiency virus
• Epstein-Barr virus
• *Cytomegalovirus*
• Influenza
• Varicella Zoster virus
• *Coccidioides immitis*
• *Histoplasma capsulatum*
• *Blastomyces dermatitidis*
• Dermatophytic fungal infections (rare)
Gastrointestinal
• Ulcerative colitis
• Crohn's disease
• Celiac disease
• Behcet's disease
Medications
• Oral contraceptives
• Proton pump inhibitors
• Sulfonamides
• Leukotriene modifiers (montelukast)
• Hepatitis B vaccine
• Isoretinoin
Miscellaneous
• Hodgkins lymphoma
• Sweet's syndrome

weeks) to endemic areas.[7] There are multiple approaches to serologic diagnosis based on identification of IgM or IgG antibodies to various coccidioidal antigens. During the early phase of infection, TP ID and EIA can be utilized to detect IgM antibodies. While EIA testing has 92% sensitivity, it has high rates of false-positive results, and therefore confirmatory testing with ID is recommended. ID has variable sensitivity, but 90% of patients will test positive by 3 weeks of infection.[8] During the later phase of the infection, IgG antibodies are detected either quantitatively by CF or qualitatively by ID and EIA. CF can provide information on the severity of illness and prognosis based on titer levels, as well as serving as a marker for response to treatment.[2] Positive titers greater than 1:32 suggest disseminated disease. In addition, CF titer in the cerebrospinal fluid is the test of choice in diagnosis of coccidioidal meningitis. An evaluation for disseminated disease should be initiated if the patient has any risk factors or clinically concerning symptoms for bone or CNS involvement. This evaluation includes a bone scan and lumbar puncture. All patients should be assessed for immunocompromised status.

The management of coccidioidomycosis is based on the extent of infection, the severity of illness, and the immune status of the patient. In 95% of cases of uncomplicated pulmonary disease in an immunocompetent host, the symptoms will resolve without treatment with antifungal agents.[9] The decision to treat uncomplicated pulmonary disease is based on severity of illness. While there is no consensus recommendation, commonly used indicators for treatment include persistent fever, age >55 years, symptoms greater than 2 months, hilar adenopathy, diffuse pulmonary infiltrates, weight loss, and inability to work.[9] In patients with chronic progressive pneumonia or extrapulmonary involvement, treatment with antifungal medications should be initiated. While fluconazole remains the preferred treatment in coccidioidal pneumonia and meningitis, amphotericin B preparations should be considered for diffuse coccidioidal pneumonia and disseminated disease, including refractory meningitis.[9] The use of newer azoles, particularly posaconazole, has been studied in a limited number of patients with refractory coccidioidomycosis with improvement in symptoms.[10] Frequent follow-up visits are recommended to detect progression of disease or to document resolution, with improving symptoms and decreasing titers. Duration of therapy in uncomplicated cases should be at least 3 months. Treatment of extrapulmonary disease can span years, and in the case of meningitis lifetime treatment is recommended given the high rate of relapse.

While the patient and the clinicians were aching for a diagnosis after the initial negative evaluation, recognition of the immunologic manifestations of coccidioidomycosis was essential in this case. Coccidioidomycosis should be considered in patients presenting with EN, regardless of presence of concurrent pulmonary symptoms; particularly in patients living in or with recent travel to endemic areas. Furthermore, the severity of symptoms can guide the decision and duration of treatment.

Teaching Points

1. Coccidioidomycosis has 4 main clinical presentations: (1) acute pneumonia, (2) chronic progressive pneumonia, (3) pulmonary cavities and nodules, and (4) extrapulmonary disease.
2. Independent of pulmonary symptoms, coccidioidomycosis can present with immune-mediated manifestations, such as EN and arthritis.
3. The diagnosis of coccidioidomycosis often relies on serologic testing for early and late infection.
4. Treatment of coccidioidomycosis is based on risk factors and severity of symptoms. High-risk and symptomatic patients can be treated with fluconazole or amphotericin B.

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Pretibial Myxedema

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An 83-year-old female reported increased swelling of her legs over the past 2 years. She noted temperature intolerance, low energy, and constipation, but denied any hair loss or nail changes. On exam, she had marked bilateral lower extremity edema that was predominately nonpitting. Overlying the edema there were thickened, well-defined plaques with a peau d'orange appearance surrounded by brown, thin plaques on the pretibial areas sparing the dorsum of the feet (Figure 1). A punch biopsy was obtained and demonstrated increased deposition of mucin throughout the dermis along with fragmentation and increased numbers of elastic fibers consistent with a diagnosis of pretibial myxedema. Measured thyrotropin level was elevated at 3.9 μU/mL (normal, 0.3-3.8 μU/mL), consistent with hypothyroidism. This is a severe example of pretibial myxedema, or infiltrative dermopathy, which can occur, more commonly, in the setting of Graves' disease or, in rare circumstances, hypothyroidism.[1] Myxedema results from the accumulation of hyaluronic acid and chondroitin sulfate in the dermis.[2] Treatment is difficult and includes topical glucocorticoids under occlusion and, if indicated, thyroid corrective therapy.[3]

FIGURE 1. Pretibial myxedema. Note thickened, well-defined plaques with a peau d'orange appearance surrounded by brown, thin plaques on the pretibial areas sparing the dorsum of the feet.

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