CQ

CASE QUIZ

E.P.C.M.S.

A 16-Year-girl with Recurrent Culture Negative Urinary Tract Infections

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A 16 year-old Latina girl presents to the Walk in Clinic with a 5-day history of increasing shortness of breath along with a mild, non-productive cough. She denies having any fever, chills, chest pain, or palpitations. No sick contacts are identified, and she denies any recent travel. On further questioning, the patient reports that she first experienced shortness of breath 1 year ago, and that it has been gradually progressive since then. Her shortness of breath has particularly worsened over the last 5 days. She recalls being treated with antibiotics as an outpatient by her primary care provider for numerous urinary tract infections over the past years, on each of these occasions her urinalysis was positive for "red blood cells, white bold cells and lots of protein." Review of her chart confirms her statement and that her urines where negative for leukocyte esterase and bacterial nitrates. Cultures had been sent and were negative. Her PCP treated her presumptively with antibiotics for UTI, including coverage for Chlamydia. She also has a history of heavy menstrual periods, for which she has been on oral contraceptive pills (OCPs). Her family history is positive for diabetes mellitus and ischemic heart disease. Except for the OCPs, she is no chronic medications. She denies any sexual activity, smoking, alcohol or illicit drug use, and she has no known allergies (drug or otherwise).

On physical examination, she appears to be in no acute distress. She is moderately obese, with a body mass index (BMI) of 25. Her blood pressure is 170/95 mm Hg, her heart rate is 106 bpm, her respiratory rate is 18 breaths/min, and her temperature is 98.6°F (37°C). She has an oxygen saturation of 97% while breathing room air. Auscultation of her chest reveals fine end expiratory crackles bilaterally at the bases (Lung fields 8, 9, 10 B). Her cardiovascular examination shows normal first and second heart sounds, with no jugular venous distention, murmurs, rubs, or gallops. There are, however, several enlarged, nontender cervical and axillary lymph nodes bilaterally. She has no rashes. The neurologic examination is nonfocal. Her peripheral pulses are palpable. Examination of her lower extremities elicits mild bilateral pitting pedal edema. The rest of her examination reveals no significant findings.

Her electrocardiogram is remarkable for sinus tachycardia. The initial laboratory workup reveals a creatinine of 1.6 mg/dL (141.44 µmol/L), proteinuria (>300 g/L), and hematuria (50-100 red blood cells per high-power field). She is found to have anemia, with a hemoglobin and hematocrit of 8.1 g/dL (81 g/L) and 25.4% (0.254), respectively. Her mean corpuscular volume is 77 µm3 (77 fL), with iron levels of less than 10 g/dL, a total iron binding capacity of 197 µg/dL (35.26 µmol/L), and a ferritin level of 68 ng/mL (152.8 pmol/L). The D-dimer is positive at 4.73 µg/mL (4.73 mg/L), and the erythrocyte sedimentation rate (ESR) is elevated at 50 mm/hr. A chest x-ray (Figure 1) shows a right-sided pleural effusion and a patchy linear opacity at the base of the left lung that is consistent with atelectasis/scar tissue. Computed tomography (CT) scanning of the thorax shows bilateral small pleural effusions that are greater on the right than the left, significantly enlarged axillary and subpectoral lymph nodes bilaterally, and a small pericardial effusion.

Questions to Think About:

Does this patient have true history of recurrent UTIs?

What diagnosis does her most current presentation, described in this vignette suggest?
A. recurrent urinary infections with a fastidious organism
B. HIV infection manifesting as AIDS nephritis
C. Systemic lupus
D. Goodpasture's syndrome
E. Wegner's Syndrome

Answer on page 12

A 16-Year-girl with Recurrent Culture Negative Urinary Tract Infections (Continued)

Discussion

C. The patient has systemic lupus erythematosus with lupus nephritis. The constellation of serositis, hypertension, diffuse lymphadenopathy, azotemia, and proteinuria in this patient was highly suspicious for a systemic autoimmune disease. Further laboratory workup revealed a positive result for antinuclear antibodies (ANA) 1:640, including those against double-stranded DNA (ds-DNA); IgG titer of 300 IU/mL, and an anti-Smith finding (156 EU/mL) which, when correlated with the clinical picture, are consistent with a diagnosis of systemic lupus erythematosus. Other relevant findings included a decreased complement level, with C3 and C4 levels of 46.2 mg/dL (0.462 g/L) and 5.3 mg/dL (0.053 g/L), respectively; a positive Coombs test; hypoalbuminemia (3.1 g/dL [31 g/L]); and a negative lupus anticoagulant antibody finding. Biopsy of the kidney was performed, which showed diffuse proliferative lupus nephritis class IV, with moderate activity and no chronicity; moderate interstitial inflammation was also seen.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that primarily affects the connective tissue. Because the disease affects the connective tissue, multiple organ systems, including the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body are affected as well. As is typical of other autoimmune disorders, the immune system attacks the body's own cells and tissue, which results in a continuous inflammatory response and tissue damage. SLE is more common, and more severe, in nonwhite patients. The highest prevalence among ethnic groups is in blacks.[1] This particular patient was of Afro-Dominican descent. SLE is up to 10 times more common in women than in men and typically occurs during child-bearing age, with a peak age of onset between 15 and 45 years. The disease course is as variable as it is unpredictable, with periods of illness, or "flares," alternating with periods of remission. Estrogen may play a role in the pathophysiology of SLE, but this has not yet been proven conclusively. Women exposed to estrogen-containing OCPs, however, do have an increased risk of developing SLE, especially if they started using them recently.[2]

SLE is characterized by a wide spectrum of signs and symptoms due to the ongoing presence of a variety of antigens, auto-antibodies, and immune complexes, which result in accumulated tissue damage to the point of clinical manifestation. The American College of Rheumatology (ACR) diagnostic criteria for lupus includes 11 manifestations. These criteria include:

- Serositis (pleuritis, pericarditis)
- Oral ulcers
- Arthritis (nonerosive)
- Photosensitivity (exposure to UV radiation causes skin manifestations)
- Blood dyscrasias (hemolytic anemia, leukopenia, thrombocytopenia)
- Renal manifestations (proteinuria, casts)
- Positive ANA finding
- Immunologic disorders (anti-Smith antibodies positive, antiphospholipid antibody positive, false positive test for syphilis, presence of anti–double-stranded DNA antibodies)
- Neurologic manifestations (seizures, focal signs, psychosis)
- Malar (butterfly) rash
- Discoid rash

The presence of 4 or more of these criteria, either serially or simultaneously, is diagnostic of SLE.[3] About 80% of patients have skin involvement manifesting as photosensitivity, malar (butterfly) and discoid rash (thick, red, scaly patches on the skin), ulcers in the oral and nasal cavities or in the vagina, or alopecia, all of which are part of ACR diagnostic criteria. However, an absence of skin manifestation, as described in this patient, should not lower clinical suspicion for lupus because its symptoms vary and come and go unpredictably. Diagnosing SLE can thus be elusive, with some patients suffering from unexplained symptoms of untreated SLE for years, such as the initial (and chronic) complaints of fever, malaise, joint pains, myalgias, and fatigue, as well as temporary loss of cognitive abilities.

When SLE is diagnosed, it is important to establish the severity and potential reversibility of the illness in order to institute appropriate therapy. Treatment options usually focus on the suppression of symptoms rather than treating the cause, since there is not an actual "cure" for the disease. Renal disease remains the most serious complication of SLE. It affects 30%-60% of patients.[4] Renal involvement is characterized by proteinuria (> 0.5 g/24h) and/or active urinary sediment (> 5 red blood cells per high-power field, pyuria, or cell casts). In patients with inactive sediment and > 500 mg/day of proteinuria, monitoring is recommended with urinalysis every 3-6 months for 3 years; every 3 months is preferred in patients with anti–double-stranded DNA antibodies and/or hypocomplementemia.[5]

Prompt renal biopsy is required in all lupus patients with evidence of kidney involvement to determine the histologic subtype of lupus nephritis.[6] The typical histologic picture is of a membranous glomerulonephritis, with "wire-loop" abnormalities that result from the granular appearance (on immunohistochemical staining) of immune-complex deposition along the glomerular basement membrane. The World Health Organization (WHO) classification of glomerulonephritis in SLE includes grades I to VI.[7] Pathology reports also reflect the extent of inflammatory (reversible) and chronic (irreversible scarring) changes. In general, treatment for lupus nephritis is not recommended in patients with class I or II disease or in those with extensive irreversible changes. In contrast, aggressive immunosuppression is recommended for patients with disease class III, IV, or V with inflammatory proliferative lesions, because a majority of those individuals, if untreated, develop end-stage renal disease (ESRD).[8] However, ESRD is seen in fewer than 5% of SLE cases, due to earlier detection and subsequent prompt management of the disease. Lupus nephritis tends to be an ongoing disease, with flares often requiring repeat biopsy and repeated treatment over time.

Pleural inflammation is a common feature of SLE and is the most common pulmonary manifestation of SLE. It causes chest pain, shortness of breath, and cough. Pleural effusions are typical findings and are usually ANA-positive exudates with low complement.[9] Less frequent pulmonary complications of SLE include interstitial lung disease and pulmonary hypertension.

The most common hematologic manifestation of SLE is anemia, usually normochromic normocytic, which is often overlooked in young menstruating women. Iron deficiency may also develop. Leukopenia and thrombocytopenia are common as well, which

Continued on page 13

may be due to the primary disease process or may be a side effect of the subsequent pharmacologic treatment for the disease. Leukopenia almost always consists of lymphopenia, not granulocytopenia.[10] Patients with SLE may also have signs and symptoms of a thrombotic disorder known as antiphospholipid syndrome, wherein autoantibodies to phospholipids are present in the serum. Serum levels of anticardiolipin antibodies should also be checked in patients suspected of having SLE. The presence of these antibodies may result in a false positive test for syphilis. Lymphadenopathy is not an uncommon presentation in SLE; it occurs in 15%-26% of patients. However, diffuse lymphadenopathy is very rare and is reported in very few cases.[11,12] It is not one of the ACR criteria for the diagnosis of SLE. Lymph node biopsy may be warranted to exclude alternative diagnoses. The patient in this case underwent lymph node biopsy, which showed no evidence of lymphoproliferative disorder.

Treatment of SLE is aimed at controlling acute flares and using maintenance strategies that suppress symptoms to an acceptable level, while preventing further organ damage. For milder manifestations of SLE, such as arthritis, dermatitis, and constitutional symptoms, NSAIDs, hydroxychloroquine, and low-dose steroids have been used with success. Severe forms of the disease, including those with more life-threatening courses (including lupus nephritis), require a combination therapy of high-dose systemic glucocorticoids and cyclophosphamide or mycophenolate mofetil to induce remission, followed by longer-term, intense immunosuppressive therapy to maintain response.[17]

The patient in this case began treatment with high-dose oral corticosteroids and mycophenolate mofetil. After 1 week, her condition improved, with significantly decreased shortness of breath. She was discharged to home with renal, rheumatologic, and primary care outpatient follow-up but unfortunately progressed to end-stage renal failure.

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