

MORNING REPORT

A Burmese Woman with Fever

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A 44-year-old woman presents with a three-week history of intermittent fevers, malaise, proximal myalgias, and arthralgias of her shoulders, knees, and hands. She also reports a 15-pound weight loss and nonproductive cough.

Her past medical history is unremarkable. She takes no medications regularly. Family history is unknown. She reports no tobacco, alcohol, or illicit drug use. She is a recent immigrant from Myanmar (Burma) and does not speak English; history is obtained via telephone interpreter.

Fevers are a common presenting complaint. Infections, particularly viral syndromes, are the most common source of fevers encountered by internists. Malignancies and collagen vascular diseases are the other two broad categories that may cause fever. Most febrile illnesses are readily diagnosed through presenting symptoms, a focused physical assessment, and, if needed, simple diagnostic testing.

More history is needed; this can pose a challenge in a non-English speaking patient. Experts recommend using trained medical interpreters rather than communicating through English-speaking family and friends. Social factors, including travel history, sick contacts, occupational exposures, and risk factors for human immunodeficiency virus (HIV) and tuberculosis (TB), will be important. A complete review of systems should be performed.

On further history, she reports immigrating to the United States from Myanmar one year prior. She had previously lived in a refugee camp on the Thailand/Myanmar border for 20 years. She now resides in Tennessee. She has no known exposure to TB and works in the book-binding industry.

Given the patient's travel history, there are concerns about infectious causes of her fever. Infections such as dengue, typhoid, leptospirosis, and malaria are endemic to South-east Asia. She is also at risk for acute viral hepatitis, TB, and HIV. Now that she lives in the United States, indolent fungal or tick-borne infections should be considered; histoplasmosis and ehrlichiosis, for example, may be seen in Tennessee.

On examination, attention should first be directed to the vital signs, looking for evidence of severe sepsis, which might change the initial management. Other potentially useful elements of the physical exam include the presence or absence of lymphadenopathy, pulmonary rales, heart murmur, splenomegaly, joint effusions, or skin findings.

On presentation, her temperature is 101.2°F (38.4°C), blood pressure is 112/66 mm Hg, heart rate is 87 beats per minute, and oxygen saturation is 99% on room air. Physical exam is notable for tender lymphadenopathy of posterior cervical, axillary, supraclavicular, and inguinal nodes bilaterally. She has a grade II/VI systolic murmur at the left upper sternal border that does not radiate. The remainder of her exam is unremarkable.

The presence of fever is confirmed. Her diffuse lymphadenopathy is concerning but non-specific. Infection with bacterial, viral, mycobacterial, fungal, protozoan, and spirochetal organisms can result in generalized lymphadenopathy. Non-infectious causes of peripheral lymphadenopathy include malignancy, particularly lymphoma or leukemia; lymphoproliferative disorders; immunologic processes such as serum sickness; endocrine disor-

ders such as hypothyroidism and adrenal insufficiency; and rheumatologic diseases such as systemic lupus erythematosus, rheumatoid arthritis, Still's disease, or dermatomyositis. Any of these illnesses may be associated with fevers, myalgias, and arthralgias.

The remainder of the exam is normal, aside from a systolic murmur, the description of which suggests a flow murmur. When evaluating a febrile patient, key findings are often not detected during the initial assessment; as the work-up proceeds, it may be necessary to repeat a detailed history and physical examination to look for additional clues. The next steps of diagnostic testing should include a complete blood count with differential, routine chemistries, bacterial cultures, urinalysis, chest x-ray, and testing for mycobacterial and HIV infection. If initial testing is unrevealing, or if blood cultures are positive, an echocardiogram should be considered to evaluate for endocarditis.

Laboratory studies reveal a hemoglobin of 9.9 g/dL and WBC count of $2.7 \times 10^9/\mu\text{L}$ (differential is notable for significant lymphopenia representing 1% of total leukocytes). Aspartate aminotransferase and alkaline phosphatase are mildly elevated at 64 U/L and 123 U/L, respectively. Renal function, electrolytes, and creatine phosphokinase are within normal limits.

The patient's CBC shows lymphopenia and anemia. These findings could be consistent with any of our three general diagnostic categories. The slight elevation in AST is likewise non-specific; if it persists, evaluation with a viral hepatitis panel and imaging would be warranted.

While the initial cultures and
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imaging are pending, consideration is indicated for withholding antibiotic therapy if there is no evident source of bacterial infection or hemodynamic instability. Given her cough and fever, she should be in respiratory isolation until pulmonary tuberculosis is excluded. She needs a hematologic work-up to better characterize her anemia and leukopenia. Leukopenia, particularly lymphopenia, can be seen in viral infections, hematologic and disseminated malignancies, and rheumatologic processes.

The patient is admitted, and the initial concern is for chronic bacterial, mycobacterial, or fungal infection. Blood, urine, and sputum bacterial cultures are without growth. Her CD4 count is 11 at presentation, but HIV RNA viral load is undetectable. A PPD is negative, as are urine, sputum, and blood cultures for acid-fast bacilli. Given her heart murmur, she undergoes a high-quality transthoracic echocardiogram, which shows no valvular vegetations. CT imaging of the chest, abdomen, and pelvis shows only diffuse lymphadenopathy. Excisional biopsy of a cervical lymph node reveals necrosis but no evidence of neoplastic or infectious process. An infectious work-up is negative for viral hepatitis, CMV, *Histoplasma*, *Blastomyces*, *Ehrlichia*, *Mycoplasma*, *Legionella*, *Bartonella*, *Brucella*, and syphilis.

Extensive testing for infection has been unrevealing. At this point, the patient meets criteria for fever of unknown origin (FUO). This has classically been defined by the presence of fever greater than 38.3°C on several occasions, persisting for at least three weeks without clear etiology after intensive diagnostic testing.

The approach to FUO in this relatively young, previously healthy, recent immigrant from Southeast Asia

should be systematic and not biased by the fact that she is from an area of multiple endemic infections. While it is appropriate to consider her infection risk in the context of her social and travel history, the overall fever work-up may not differ significantly from the approach to fever in any other HIV-negative adult patient. Since an infection has not been identified to date, evaluation for non-infectious causes of fever should be pursued, and the history and exam should be revisited.

Given the patient's age and gender, the suspicion for a rheumatologic disease is increased. We have not been given information about her erythrocyte sedimentation rate or presence of rheumatoid factor or antinuclear antibodies; these laboratory tests are recommended as part of the initial diagnostic evaluation of FUO and might help make a diagnosis of rheumatoid arthritis or systemic lupus erythematosus (SLE). Other collagen vascular diseases, such as Still's disease or vasculitis, are more challenging to diagnose but are less likely in the absence of skin findings. Malignancy remains on the list, but an excisional lymph node biopsy was negative, and no primary tumor was detected on imaging. Miscellaneous conditions, such as sarcoidosis and factitious disorder, should also be considered.

Her leukopenia persists, and hemoglobin decreases to a nadir of 7.3 g/dL. She undergoes bone marrow biopsy, which shows low-normocellular bone marrow with trilineage hematopoiesis and no evidence of infection or infiltrative disease. Her creatinine gradually rises from 0.7 mg/dL to 1.8 mg/dL. This is associated with an albumin of 1.3 g/dL and nephrotic-range proteinuria of 3.5 grams/24 hours. She has a markedly elevated

ferritin of 3058 ng/mL and low complement levels. Rheumatologic evaluation reveals an ANA titer of more than 1:160 with a smooth pattern, as well as positive anti-double stranded DNA, anti-Smith, and anti-SSA antibodies. A diagnosis of SLE is made.

SLE is a chronic inflammatory autoimmune disease characterized by a wide range of clinical manifestations. Diagnosis is often challenging, as patients may present mainly with constitutional complaints, as with this patient, or with single or multi-organ system involvement. The American College of Rheumatology has proposed 11 diagnostic criteria for lupus, of which four or more are required to confirm the diagnosis. These criteria include: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis or pericarditis), renal disease (nephritic or nephrotic syndrome), neurologic manifestations (seizures or psychosis), hematologic abnormalities (leukopenia, lymphopenia, thrombocytopenia, and/or hemolytic anemia), positive immunologic markers (antiphospholipid antibody, anti-DNA, anti-Smith, or false-positive serologic test for syphilis), and an abnormal titer of ANA. Though not part of the formal criteria, fever is seen in more than one third of patients at disease onset, and multi-focal lymphadenopathy is detectable in more than one fourth of patients with SLE.

She is started on high-dose steroids and hydroxychloroquine. Given her renal failure, she undergoes renal biopsy, which shows class IV-V lupus nephritis and fibrinoid necrosis. Immunosuppressive therapy and renin-angiotensin blockade are initiated on an outpatient basis.

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Several therapeutic agents exist for the management of end organ disease in SLE. Non-steroidal anti-inflammatory drugs are commonly used to treat musculoskeletal complaints, and anti-malarial drugs such as hydroxychloroquine are effective in treating joint and skin manifestations. Glucocorticoids are used for more significant organ involvement, usually renal and neurologic disease. A variety of immunosuppressive drugs have been studied, including cyclophosphamide, cyclosporine, methotrexate, azathioprine, mycophenolate, and rituximab.

One of the most serious complications of SLE is renal involvement, which manifests as an abnormal urinalysis with or without an abnormal serum creatinine level. The most common finding is proteinuria, with definitive diagnosis made by renal biopsy. Six classes of lupus nephritis have been described based on the pathologic patterns found on biopsy. This patient was found to have a combination of class IV disease (diffuse lupus nephritis) and class V disease (membranous lupus nephritis). Nephrotic syndrome is frequently seen with these two

classes of glomerular disease, and therefore angiotensin blockade is indicated in addition to immunosuppressive therapy.

Key Points

1. The etiology of fever typically falls within one of three general categories: infection, malignancy, or collagen vascular disease.
2. Important findings are often missed during the initial evaluation of a patient with fever of unknown origin; repeating a detailed history and physical exam may provide valuable clues to the diagnosis.
3. SLE is a multi-system autoimmune disease that commonly presents with fever and generalized lymphadenopathy; the diagnosis may be overlooked without a broad differential diagnosis.

References

1. Hart D, Bowen J, DeJesus R, Maldonado A, Jima F. Using medical interpreters. *Minnesota Medicine* 2010;4.
2. Ellis RD, Fukuda MM, McDaniel P, et al. Causes of fever in adults on the Thai-Myanmar border. *J*

Trop Med Hyg 2006; 74:108-13.

3. Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. *Am Fam Physician* 2002; 66:2103-11.
4. Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet* 1997; 350:575-80.
5. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25:1271-7.
6. Calguneri M, Ozturk MA, Ozbalkan Z, et al. Frequency of lymphadenopathy in rheumatoid arthritis and systemic lupus erythematosus. *J Int Med Research* 2003; 31:345-9.
7. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine* 1993; 72:113-24.
8. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; 65:521-30.

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