

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 Rash Decision

A 38-year-old HIV+ Ohio man with a recent CD4+ count of 534 cells/mL presented to his physician with 3 weeks of fever as high as 102°F. He noted mild myalgias, pruritus, and an occasional cough but no headache, sore throat, dyspnea, rash, or gastrointestinal or genitourinary complaints. He had been seen elsewhere 2 weeks previously, when he had reported a single episode of receptive oral sex with a male partner several weeks earlier. He had been prescribed ciprofloxacin and azithromycin, but a throat swab came back negative for *Chlamydia* and *Neisseria gonorrhoeae*, and he reported no change in his symptoms after the course of antibiotics. He denied smoking or using street drugs. His only medications were citalopram and trazodone for depression.

This is a HIV+ man with a mild degree of immunosuppression with a fever of unknown origin (FUO). It is not yet known if the requisite basic infectious evaluation has been completed to meet this definition, but the duration certainly qualifies, and regardless of semantics, the FUO framework is a helpful starting point. The primary considerations in FUO are infections, neoplasms, and autoimmune illnesses. Autoimmune diseases are relatively less common in HIV patients. Although pruritis is quite common in HIV alone, it may also herald renal failure, cholestasis, or a malignancy (usually hematologic). Drugs must also be considered as a cause of unexplained fever; the pruritis might suggest an allergic reaction, although I do not think of citalopram or trazodone as having this effect. The failure to respond to broad-spectrum antimicrobials (along with the duration) lowers my suspicion for common infections such as pneumonia, urinary tract infection, or cellulitis. Among sexually transmitted diseases, syphilis can be protean and merits consideration.

On examination he appeared well. His temperature was 102.4°F, pulse 111 beats/min, blood pressure 138/78 mm Hg. The head, neck, cardiovascular system, and lungs appeared normal on examination. The abdomen was soft and nontender without organomegaly; skin, extremities, and neurological system were unremarkable. Rectal examination showed small anal condylomata. Hemoglobin was 14.3 g/dL, white blood cell count 6200/cm³, and platelet count 230,000/cm³. Serum electrolytes and lactate dehydrogenase were normal. The results of his liver function tests (LFTs) demonstrated a serum aspartate transaminase

of 60 U/L (normal, 7-40 U/L), alanine transaminase of 125 U/L (normal, 5-50 U/L), alkaline phosphatase 218 U/L (normal, 40-150 U/L), and total bilirubin 2.1 mg/dL (normal, 0.0-1.5 mg/dL). Urinalysis demonstrated 2+ bilirubin and was otherwise normal. His erythrocyte sedimentation rate was 32 mm/hr (normal, 0-15 mm/hr).

After 3 weeks of illness, his CBC demonstrates no signs of chronic illness (such as anemia of a chronic disease or a reactive leukocytosis or thrombocytosis). The results of his liver function tests showed moderate elevation, slightly more cholestatic than hepatocellular. This finding may reflect a disease process involving the liver, but such abnormal findings are often nonspecific in acute and chronic illnesses. With an unremitting fever, infectious complications in the liver merit early consideration. The time course rules out common biliary disorders such as cholangitis or cholecystitis. Pyogenic or amoebic liver abscesses are possible (homosexual men are at increased risk for the latter), but the absence of pain or abdominal tenderness is atypical. This biochemical profile can also be seen in chronic (but not acute) viral infections of the liver. Chronic hepatitis B and C predispose to hepatocellular carcinoma (HCC), which can be associated with fever. Cancers that infiltrate the liver, such as lymphoma or carcinoma, could also account for this picture. Indolent infections such as tuberculosis (TB) and syphilis are also possible, so associated signs of these systemic diseases should be sought. I do not believe either of his antibiotics is commonly associated with LFT abnormalities, and his CD4 count is too high for HIV cholangiopathy. In sum, a host of liver diseases are possible, but an extrahepatic systemic disease deserves equal attention.

His CD4+ count was 537 cells/mL, and his HIV RNA viral load was 44,300 copies/mL. Radiographs of the chest were normal. Two sets of blood cultures were negative. The rapid plasma reagin (RPR) was nonreactive. The results of serologies for acute hepatitis A, B, C, and E, chronic hepatitis B and C, and toxoplasmosis were negative. Testing for both Epstein-Barr virus and cytomegalovirus showed evidence of remote infection. Results of serologies for bartonella species, human herpesviruses 6 and 7, and parvovirus B19 were negative.

The negative RPR makes disseminated (secondary) syphilis improbable, provided the prozone phenomenon has been excluded. An extensive serological workup is common in the evaluation of fever of unknown origin, although the threat of false-positive results always looms when many studies are sent simultaneously. This must be considered in advance here, as his relatively preserved CD4 count affords him significant protection against many opportunistic infections. His HIV infection, however, regardless of CD4 count, increases his risk for TB and lymphoma, which remain high on my list. Both may be residing primarily in the liver. In FUO, the abdominal CT is frequently a high-yield test (primarily by demonstrating unsuspected tumors and abscesses), even in the absence of symptoms, and would certainly be of interest here given the liver function test results. Imaging could diagnose febrile tumors such as lymphoma, HCC, or renal cell carcinoma. In the event that imaging is unrevealing, causes of granulomatous hepatitis should be entertained. The constellation of cough, LFT abnormalities, and fever is compatible with Q fever. As with any FUO case, I would also carefully revisit this patient's history to discern where he was born, where he has been, and what activities or exposures he is engaged in.

He was seen 2 days later with fever of 104°F and new papules over his sternal area. Over the next week, he had intermittent fevers and severe fatigue. The rash progressed, predominantly involving his chest and back, but also his legs, arms, and face (see Fig. 1). The lesions spared his palms and soles. The exanthem was intensely pruritic and maculopapular, consisting of lesions with a diameter of 0.5 cm or less, with some scaling. There were no vesicles or pustular lesions. There were no other new findings on examination. His transaminase and bilirubin had normalized, and his CBC and electrolytes were unchanged. Repeat blood cultures held for extended incubation were negative. Computerized tomography of the chest, abdomen, and pelvis demonstrated mild lymphadenopathy at the porta hepatis with increased portocaval and periaortic lymphadenopathy.

The only LFT abnormality that persists is the elevated alkaline phosphatase, which suggests (1) that liver involvement was not specific and that there is a disease process involving the bone, (2) that there is a persistent infiltrative disorder of the liver such



FIGURE 1. Truncal rash.

as infection or malignancy or, less likely, amyloidosis or sarcoidosis, or (3) that the porta hepatis lymphadenopathy is causing biliary obstruction. The underlying diagnosis must explain the rash, intraabdominal lymphadenopathy, and fever. The time course does somewhat limit the extensive differential of fever and rash. After 3 weeks of illness, some of the most life-threatening entities such as meningococcal disease, Rocky Mountain spotted fever, and toxic shock syndrome are unlikely. Concern remains for infections that are more indolent, such as mycobacteria, fungi, or spirochetes. The most striking elements of the rash are the extensive distribution, rapid progression, large number, and discreteness of the lesions, which collectively point more toward disseminated fungal (eg, histoplasmosis, as he lives in Ohio), spirochetal, rickettsial, or viral etiologies, rather than bacterial or mycobacterial entities. The absence of vesicles detracts from the diagnosis of a disseminated herpes virus such as herpes simplex or varicella. I believe that this rash is too disseminated to be caused by a common mycobacterial illness. This extent of cutaneous metastases would usually accompany a far more ill patient with an obvious primary cancer (none is seen on imaging, including the liver), and it appears too extensive to be caused by a paraneoplastic phenomenon such as Sweet's syndrome. A systemic vasculitis or another autoimmune disease remains possible, but there is minimal evidence of visceral organ involvement. All the aforementioned diseases could explain the intraabdominal lymphadenopathy, but my suspicion is highest for infection. I

would biopsy and culture the skin lesions, repeat the RPR and/or send a treponemal-specific test, place a PPD skin test, and send fungal studies (serum serologies and urine antigens) for evaluation. If the results of these noninvasive studies are unrevealing, I would consider a liver biopsy.

The patient's medications were discontinued, and a skin biopsy of the rash from his chest showed atypical lymphohistiocytic infiltrates without acute inflammatory cells and with negative Gomori methenamine silver (GMS), acid-fast bacilli (AFB), and Fite (for Nocardia) stains. The infiltrates were predominantly T cells with a 1:1 CD4:CD8 ratio. This was read as suspicious for cytotoxic (CD8) mycosis fungoides.

I do not have reason to doubt the pathologist's impression of mycosis fungoides on histopathologic grounds, but from a clinical standpoint, I do not think mycosis fungoides is a disease that has a prolonged febrile prodrome or an explosive cutaneous onset. Rather, it is frequently preceded by nonspecific skin findings over a long period. Thinking broadly and pathophysiologically and noting that T cells are the predominant lymphocytes in skin, I wonder if they could represent a nonmalignant, immunological reaction in the skin. The stains, although not perfectly sensitive, make mycobacterial and fungal diseases less likely, although incubation of cultures is necessary.

Over the next 10 days (bringing the total duration of the patient's illness to 6 weeks), the skin lesions increased in number. In the physician's office at his next follow-up, the patient had a temperature of 104.1°F, was uncomfortable, shivering, and ill-appearing. His blood pressure was 108/66 mm Hg, and his pulse 114 beats/min. He complained of severe shooting pains, predominantly in his pretibial regions and arms. Examination showed no other new findings, including no focal neurological findings. The results of the T-cell rearrangement study from the skin biopsy showed evidence of a monoclonal T-cell population. He was admitted to the hospital for further evaluation and treatment.

The extremity dysesthesias could represent a lesion of the spinal cord (including the CSF/meninges), a polyradiculopathy, or a polyneuropathy. Unfortunately, this does not add a tremendous amount of

diagnostic resolution, as infection, malignancy, and autoimmune syndromes, such as vasculitis, may all involve the nervous system in these ways. In general, I associate monoclonal lymphocyte responses with hematological malignancies and polyclonal responses with the less specific inflammation that could accompany infection, autoimmunity, or solid malignancies. His age, fever, and rapid progression seem atypical for mycosis fungoides, but given the monoclonal T cells, this must now be considered. Adult T-cell leukemia/lymphoma, with its prominent skin manifestations and its association with HTLV-1, is an alternative T-cell malignancy that could explain the fever, neurological symptoms, and possible visceral involvement (elevated alkaline phosphatase, which could reflect liver or bone). In cases that are diagnostic challenges, one of the highest-yield maneuvers is to repeat the preceding evaluation, starting with the history, exam, and basic labs, and if necessary, to review or repeat the imaging or skin biopsy. Given the elevated alkaline phosphatase, disseminated rash, new neurological symptoms, and his HIV status, I remain particularly concerned about syphilis and would do further testing (accounting for the prozone phenomenon) before proceeding with the malignancy evaluation.

A lumbar puncture demonstrated clear cerebrospinal fluid, with 2 leukocytes and 195 erythrocytes/cm³, protein of 26 mg/dL, and glucose of 52 mg/dL. Bacterial and fungal cultures of the fluid were negative. The results of colonoscopy were normal. A bone marrow biopsy demonstrated ring granulomas. GMS, AFB, Fite, and Steiner (for spirochetes) stains were negative, cultures of the aspirate were negative for bacteria, and smears were negative for fungi and mycobacteria. Antibody tests for human T-cell lymphotropic virus types I and II, Coxiella burnetii, and Bartonella henselae were negative. The dermatology consultant believed the absence of lymphadenopathy and the pruritic nature of the lesions was atypical for cytotoxic T-cell lymphoma (CTCL). Before initiating therapy for CTCL, she suggested repeating the skin biopsy and RPR.

The repeat RPR was positive at 1:64 dilutions, and a confirmatory fluorescent treponemal antibody absorption test showed a positive result. He was prescribed intramuscular benzathine penicillin 2.4 million units weekly for 3 weeks, with almost immediate defervescence and slower resolution of his rash and shooting pains in his limbs.

The repeat skin biopsy done during the hospitalization demonstrated lichenoid-type dermatitis with interstitial and perivascular lymphohistiocytic infiltrates and granulomas. Steiner stains for spirochetes were positive. Immunohistochemical stains ruled out a lymphoproliferative process. One year later his RPR was nonreactive.

COMMENTARY

Fever of unknown origin (FUO) was first defined by Petersdorf and Beeson in 1961 as a temperature higher than 38.3°C on several occasions lasting longer than 3 weeks and defying diagnosis despite 1 week of inpatient investigation.¹ Dramatic changes in medical practice have rendered this definition outdated, with more recent proposals allowing thoughtful outpatient investigation to serve as a surrogate for hospitalization. Some have proposed that HIV-associated FUO be considered a distinct entity, with the most complete North American series finding the etiology of the HIV-associated FUO in 56 of 70 patients.² The mean CD4+ count in this series was 58/cm³. Disseminated *M. avium* was the most frequently diagnosed cause, followed by *P. jirovecii* pneumonia, cytomegalovirus infection, disseminated histoplasmosis, and lymphoma. Of 14 patients with fever of no definable etiology, 12 eventually proved to have self-limiting illness.

Despite numerous attempts to reduce the investigation of the patient with FUO to an algorithm, the approach must be individualized. A thorough history and careful, serial physical examinations are frequently and appropriately stressed as the foundation, followed by thoughtful selection of laboratory and imaging studies. Although FUO has a lengthy differential diagnosis, it often proves to be, as Mackowiak and Durack stress, an unusual manifestation of a common disease, rather than a typical presentation of a rare disease.³ A relatively uncommon disease in conjunction with an initially negative diagnostic test result, as was the case with this patient, may lead to a protracted diagnostic puzzle.

Syphilis is a rare cause of FUO. In 6 large studies of a total of 947 patients published over a 40-year period, only 2 cases of syphilis (1 secondary and 1 neurosyphilis) were reported.^{1,4-8} Syphilis as a cause of prolonged cryptic fever appears to have been seen with greater frequency in the preantibiotic era.⁹ In the first half of the 20th century, syphilis was known as the great imitator, with its unusual manifestations recognized and indeed

expected. As a result of the dramatically lower incidence of syphilis in recent decades, these lessons have largely been forgotten, however, which may lead to diagnostic confusion when syphilis presents atypically. The manifestations of secondary syphilis are protean, including a variety of rashes, aphthous ulcers, arthralgias, pharyngitis, weight loss, fever, meningitis, ocular symptoms, cranial nerve palsies, glomerulonephritis, hepatitis, and periostitis (which afflicted this patient, who complained of “severe shooting pains” in his arms and shins).

After declining in the last decade of the 20th century, the rates of primary and secondary syphilis are rising in the United States.¹⁰ Oral sex is a clear risk factor for syphilis transmission, particularly for men who have sex with men.¹¹ Because of the patient’s exposure history and clinical picture, his outpatient physician considered the diagnosis of secondary syphilis early in the course of his illness. The diagnosis was not entertained further when an RPR test, highly sensitive at this stage of the disease, returned nonreactive. Likewise, when a rash subsequently appeared, the lack of palm and sole involvement dissuaded multiple clinicians from reconsidering the diagnosis of syphilis. A skin biopsy that appeared to lead in a distinctly different direction understandably confused the picture still further. Even at the time of the lumbar puncture, VDRL of the CSF was not ordered.

In retrospect, the chief confounder in the case was the false-negative RPR test, as the discussant suspected early on. Although nontreponemal tests are generally accurate in individuals with HIV, delayed seropositivity and false-negatives have been reported in this population.¹² The false-negative could have also been a result of the prozone phenomenon, an unusual event, occurring in fewer than 2% of cases of secondary syphilis and attributed to a mismatch between antibody and very high antigen level. The prozone reaction can be corrected for by requesting dilution of the serum prior to repeating the test. Simple lab error must be considered as well, but without access to this patient’s serum from his original testing, the cause of his initial false-negative test cannot be known with certainty.

An unusual presentation in conjunction with failure to recognize the causes of rare false-negative testing for secondary syphilis led to a delayed diagnosis in this patient. Although syphilis and mycosis fungoides have previously been reported to mimic one another both clinically and histopathologically,

the potential for secondary syphilis to be misdiagnosed in this fashion is not generally appreciated.^{13–15} Recognition of the possibility of secondary syphilis occurred just in time to spare this patient the “rash decision” of treating him with cytotoxic therapy directed against CTCL.

Teaching Points

- HIV-associated FUO can be a diagnostic challenge, but an etiology can be found in most cases.
- Syphilis continues to be an unusual cause of FUO and can have protean manifestations affecting nearly every organ system
- The sensitivity of RPR is extremely high in secondary syphilis, but false-negative tests can be seen in HIV because of both the prozone phenomenon and a delayed rise in antibodies.

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