

## **Fever and rash in a 36 year-old female**

Drew J. Chiesa, D.O.

Kennedy Memorial Hospital, Cherry Hill, NJ, University of Medicine and Dentistry of New Jersey-School of Osteopathic Medicine

### **CASE**

A 36 year-old female presented to the hospital complaining of fever and rash 24 to 36 hours prior to arrival to the emergency room. The patient had presented to the hospital twice over the past several weeks with a similar presentation of diffuse rash, fever, arthralgias, and myalgias. She had an extensive workup performed on previous admissions, all of which were negative. Previous workup included; Lyme titers, ASO, Influenza A and B, RPR, Rocky Mountain Spotted Fever titer, Ehrlichia titer, Parvovirus titer, malaria smear, and Clostridium difficile toxin. On further questioning, the patient reported a history of rashes attributed to lupus. However, the current rash, described as diffuse and non-blanchable, began on her abdomen, moved to the axilla, and progressed to the entire body. She stated that on her first admission to the hospital, the rash began on her lower extremities, and on her second admission, the rash began on the abdomen. The patient did complain of fevers as high as 104 degrees while at home, along with diffuse joint pain, nausea and non-bilious, non-bloody emesis for approximately 4 to 5 days. She denied pruritis, diarrhea, abdominal pain, chest pain, shortness of breath, bleeding, or meningeal symptoms. The patient denied any recent travel or exotic foods. She was up-to-date on immunizations. The patient reported she had taken doxycycline empirically upon discharge from the hospital a few weeks prior for a suspected tick-borne illness. Doxycycline was completed 3 days prior, and no adverse reactions to the medication were noted. No other new medications were recently started. She denied any new detergents or soaps or any recent sick contacts while at home. The patient stated she had no recent tick or mosquito bites, however, she did state that she had been outside in a wooded area recently. She had not had a menstrual cycle in approximately seven months, and did not have any children. The patient did have pets at home. She had a past medical history of systemic lupus erythematosus that was diagnosed 10 years prior, and Class V membranous lupus nephritis diagnosed via kidney biopsy in 2000 at a suburban community hospital of Philadelphia. She was status-post Cytoxan treatment for 14 sessions that was completed in approximately 2001. Social history revealed that she was an immigrant from Laos, but had been living the United States for the past 30 years. She lived at home with her fiancée. The patient had a 2 ½ pack year history of smoking, and denied alcohol or recreational drug use. Outpatient medications included Prednisone and Percocet. Her vital signs showed a temperature of 100.9 degrees Fahrenheit, a pulse of 53 beats per minute, a blood pressure of 89/52, and a pulse oximetry of 98% on room air. On physical exam, the patient was ill-appearing, lung exam was clear, and cardiac exam showed a regular rate and rhythm without any murmur, gallops, or rubs. Musculoskeletal and neurologic exam were unremarkable, including a negative Kurnig and Brudinski sign. Skin exam showed a diffuse petechial rash on her face, extremities, and trunk, however, the rash was greatest on her back. The rash was nonblanching and there was no palpable purpura. Osteopathic exam revealed dysfunctions of T4-7 RrSl. Her BMP was unremarkable, but her CBC did show a white count of 1,600, a hemoglobin of 9.6, a hematocrit of 27.8, a MCV of 88, and a platelet count of 83,000. She did have a slight left shift. Other labs noted included a D-dimer of 1.20, and an AST/ALT of 49 and 24 respectively. PTT was 34.6, INR was 1.0, and a CRP was 0.5. A urinalysis revealed positive

protein, large blood with 30-40 RBCs, no bacteria, and no WBC. EKG showed normal sinus rhythm with a first degree AV block; a new finding compared to previous EKGs. Chest X-ray showed no active disease. The patient was admitted to the hospital for the diffuse petechial rash, pancytopenia, and fevers.

### **STRATEGIES AND EVIDENCE**

The patient was admitted to the intensive care unit and empirically started on Maxipime and Doxycycline. The patient was placed on reverse isolation and a dose of Neupogen was given for an ANC of 600. Blood and fungal cultures, and a urine culture and sensitivity were obtained. Consults were placed to Infectious Disease and Hematology. Infectious Disease assessment was the patient's symptoms may have been due to a relapsing tick-borne disease versus a viral etiology. Additional lab work was ordered including, titers for ehrlichiosis IgM/IgG, Brucellosis IgM/IgG, Parvovirus B19 IgM/IgG, EBV, Babesiosis, anti-ds DNA, C3/C4, HIV, hepatitis panel, and a vasculitis panel were sent. Hematology assessment was the patient's pancytopenia may have been due to a viral infection versus a primary hematologic etiology. Hematology also ordered additional laboratory work including, a hemolytic panel and a Coombs test. The patient was transferred out of the intensive care unit to the telemetry floor on day 4 of her hospitalization. That evening, the patient had Type I 2<sup>nd</sup> degree AV block (Wenkebach) with tachy-brady like activity. A 2-D echo was performed which revealed, a normal left and right ventricular systolic function with trace mitral regurgitation and tricuspid regurgitation. Lab work ordered was negative for HIV, hepatitis A,B, and C, EBV, babesia, parvovirus B19, and brucellosis. Her vasculitis panel was negative. There was no evidence of hemolysis, and the Coombs test was negative. However, the ds-DNA was positive, which confirmed she had lupus, in addition to a low C3/C4, which was consistent with glomerulonephritis. Also of note, her Ehrlichia chaffeensis antibody IgG was positive with a titer of 1:1024. Repeat AST/ALT remained elevated at 70 and 53, respectively. The patient continued to have episodes of bradycardia with type I 2<sup>nd</sup> degree AV block during her hospital stay. Cardiology was consulted, and after discussion with an electrophysiologist, it was recommended that if the bradycardia persisted after adequate treatment for Ehrlichiosis, the patient may require a permanent pacemaker. The patient then began to show signs of progression to a lower AV nodal block with continued bradycardia, and a permanent pacemaker was eventually placed. After permanent pacemaker was placed, the patient had episodes of NSVT/Torsades dePointe secondary to electrolyte abnormalities. However, even after electrolytes were adequately replaced, the patient continued to have episodes of NSVT. It was recommended by cardiology to have the patient transferred to a tertiary care center for a cardiac MRI and electrophysiology evaluation for possible myocarditis secondary to Ehrlichiosis. Also during this time, the patient remained pancytopenic. A bone marrow biopsy was performed, which was positive for myelodysplasia. The patient refused any further medical workup and eventually signed out against medical advice.

### **REASON FOR PRESENTATION**

Human monocytic ehrlichiosis typically present as an acute illness. However, there is a wide spectrum of disease, from subclinical and self-limited, to subacute or chronic infection. Most ehrlichial diseases have an incubation period of one to two weeks, but shorter periods may be seen. Most patients are febrile and have nonspecific complaints such as myalgias, malaise,

nausea, and vomiting, which occurs in up to 25-50% of cases<sup>1</sup>. The rash, which can be macular, papular, maculopapular, or petechial occurs in a minority of patients. Diagnosis of human monocytic ehrlichiosis is usually a clinical diagnosis. However, there are other scientific methods to diagnose this disease. In this patient, human monocytic ehrlichiosis was confirmed serologically using the indirect fluorescent antibody (IFA) test. The current case definition of human monocytic ehrlichiosis used by the CDC requires at least a four-fold rise in IFA titer against *E. chaffeensis* between the acute and convalescent stage with a minimum titer considered to be indicative of current or previous infection<sup>2</sup>. In most laboratories, the minimum titer ranges from 1:64 to 1:80. In this patient, the titer was 1:1024, showing that she was between the acute and convalescent stage of the disease. The IFA test has been shown to be 94-100% sensitive<sup>2</sup>. This patient also presented to the hospital with a newly diagnosed first degree AV block that advanced, which eventually required permanent pacemaker placement. There was concern that myocarditis may have precipitated these events. Myocardial involvement has been frequently documented with Rocky Mountain Spotted Fever, but not as frequently with ehrlichiosis. Typically, patients with Rocky Mountain Spotted Fever present with heart failure, MI, cardiac arrhythmias, or conduction disturbances, and most cases are fatal. However, myocarditis with ehrlichiosis is a rare finding with only two previously reported cases, one of which was fatal<sup>3,4</sup>. The pathogenesis of cardiac involvement is completely unknown. While immunohistological staining demonstrated ehrlichiosis in the cytoplasm of inflammatory cells in the autopsy of the myocardial tissue in one case, it is uncertain whether ehrlichiosis directly induces myocardial damage, or if it induces transient immunosuppression and concomitant inflammatory cell dysfunction causing nonspecific damage to myocytes<sup>3</sup>. Acute myocarditis should be suspected whenever a patient presents with unexplained cardiac abnormalities of new onset such as CHF, MI, arrhythmias, or other cardiac disturbances. Other settings in which a diagnosis of myocarditis should be considered is when systemic manifestations of a viral, bacterial, rickettsial, fungal, or parasitic infection are associated with new abnormalities in cardiovascular function. In this patient, myocarditis was suspected since new conduction disturbances along with arrhythmias and a diagnosis of rickettsial disease was found. There may have been an association with the patient's cardiac abnormalities and SLE. SLE is a multisystem disorder with numerous potential adverse effects on the cardiovascular system<sup>5</sup>. Conduction disturbances have been reported in the literature to occur primarily from the progression of SLE, and secondarily from pharmacotherapy used to treat SLE<sup>5</sup>. EKG abnormalities, such as first degree AV block in patients with SLE may be clues to more significant cardiac disease due to chronic inflammation and fibrosis in longstanding autoimmune disease. This patient had a new first degree AV block discovered on the EKG performed in the emergency room, but had also received Cytoxan treatments for her lupus nephritis. The patient was also on chronic prednisone for SLE, which could have contributed to her conduction abnormalities. Of note, the patient received doxycycline prior to and during her admission. Doxycycline has been known to exacerbate SLE and its symptoms.

## **CONCLUSIONS**

It is unclear whether the patient's conduction abnormalities were related to ehrlichiosis or SLE. The patient did have serology strongly positive for ehrlichiosis, however, it has been shown that there can be false positive readings in patients with SLE. Also considered was her rash could have been a lupus flare. Myocarditis is an uncommon, often asymptomatic manifestation of SLE

with a prevalence of approximately 8-25%.<sup>6</sup> Global hypokinesia may be an echo indication of myocarditis and is present in approximately 6% of patients with SLE.<sup>6</sup> In this patient, her echo was basically unremarkable. Since the patient never had the cardiac MRI or EP study, we can only speculate about what caused her conduction abnormalities.

---

<sup>1</sup> Bakken JS, Krueth J, et al. Clinical and laboratory characteristics of human ehrlichiosis. *JAMA*. 1996; 275: 199-214.

<sup>2</sup> Dumlar, JS, Madigan JE, et al. Ehrlichiosis in humans: epidemiology, clinical presentation, diagnosis, and treatment. *Clinical Infectious Disease*. 2007; 45: 764-78.

<sup>3</sup> Jahangir, A, Kolbert C, et al. Fatal pancarditis associated with human granulocytic ehrlichiosis in a 44 year-old man. *Clinical Infectious Disease*. 1998; 27: 1424-27.

<sup>4</sup> Williams JD, Snow RM, Arciniegas JG. Myocardial involvement in a patient with human ehrlichiosis. *American Journal of Medicine*. 1995; 98: 414-15.

<sup>5</sup> Moder, KG, Tazellar HD, et al. Cardiac involvement in systemic lupus erythematosus. *Journal of American College of Cardiology*. 1999; 74: 275-87.

<sup>6</sup> Borenstein DG, Fye WB, et al. The myocarditis of systemic lupus erythematosus. *Annals of Internal Medicine*. 2002; 89: 619-625.