Kikuchi Disease: A Unique Case of Fever of Unknown Origin

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Introduction

In the setting of fever of unknown origin and diffuse lymphadenopathy, it is important to rule out rheumatologic causes, malignancies, as well as atypical infectious causes. Fever of unknown origin and lymphadenopathy can be associated with a number of infectious etiologies, including herpes simplex virus, Epstein-Barr virus, cytomegalovirus, *Bartonella henselae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, and *Francisella tularensis*.[1-3] Neoplasms such as non-Hodgkin lymphoma, Hodgkin lymphoma, and various forms of metastatic carcinoma can present with similar symptoms as well.[1-4]

Kikuchi disease is an uncommon disease, typically with a higher incidence in Asian populations.[2] While this disease can appear at any age, there is a greater predisposition for it to appear between the second and third decade of life. Additionally, it typically has a slightly greater predisposition to appear in females with a 1:1.1 to 1:1.4 male to female ratio. Because of these epidemiological facts, the diagnosis of Kikuchi is challenging. We present a patient with an atypical presentation of a rare disease.

Case Report

A 58-year-old white male was transferred to our hospital for further evaluation of his fever of unknown origin. Initially, he presented to another hospital with a three-week history of fever, chills, myalgias, and overt fatigue. The patient endorsed these as new symptoms, saying he never experienced similar ones. His past medical history was significant for mitral valve prolapse, recurrent hernias, hyperlipidemia, and prostate cancer status post resection. He had no past medical history of other malignancies or rheumatologic disease. He was married, worked as an electrical engineer, had never been a smoker or experimented with illicit drugs, and had five to seven drinks of alcohol per week.

The patient's family history was significant for Burkitt lymphoma in a brother. He confirmed travel to Arizona several months prior to the onset of his symptoms. Workup at the outside hospital was not suggestive of any specific etiology for his persistent fever. He had negative blood cultures, urinalysis, and chest x-ray. He had negative serologies for Cryptococcus, cytomegalovirus (CMV), Bartonella, Brucella, Coxiella, Rickettsia, Tularemia, and Ehrlichia. He was negative for Cryptococcus antigen and had a negative polymerase chain reaction (PCR) assay for Epstein-Barr virus (EBV). He was also negative for extractable nuclear antigen and anti-double-stranded DNA and had a normal serum protein electrophoresis and rheumatoid factor.

A bone marrow biopsy with flow cytometry was negative for malignancy as well as acid-fast bacilli staining. Treatment with vancomycin, nafcillin, gentamycin,

ceftriaxone, daptomycin, doxycycline, and fluconazole were employed, but his fever and associated symptoms lingered. Additionally, an abdominal laparoscopic lymph node biopsy suggested reactive lymphadenitis. Finally, a transesophageal echocardiogram confirmed mitral valve prolapse but showed no evidence of any vegetations. Concerned for a more serious or rare etiology, he was transferred to our institution for further management.

Assessment. On admission, the patient was in no acute distress and answered questions appropriately, albeit with a flat affect. Vital signs included a temperature of 36.7°C, pulse of 87 beats/minute, blood pressure of 113/74 mmHg, 18 resting respirations, and an oxygen saturation of 96% on room air. A small, palpable sub-centimeter left submandibular lymph node and a small, palpable sub-centimeter left supraclavicular lymph node, both mobile and non-tender, were noted on his head and neck. Lungs were clear to auscultation bilaterally. Cardiac exam showed his heart had a normal rate and rhythm with a grade IV/VI holosystolic murmur, auscultated best at the apex, with radiation to the axilla. Abdominal examination was notable for laparoscopic port incisions, which were clean, dry, and intact. A diffuse maculo-papular rash with sparing of palms and soles, but with facial involvement, was noted. No focal neurological deficits were noted.

Admission laboratory results showed mild anemia with a hemoglobin of 11.9 g/dL, leukopenia with a white blood cell count of 1700 U/L, but with bands comprising 18% and lymphocytes 21%. An increase in lactate dehydrogenase was noted with a level of 982 U/L. A peripheral blood smear showed normocytic/normochromic anemia without schistocytes, absolute neutropenia without abnormalities, and mild thrombocytopenia. He had an elevated erythrocyte sedimentation rate of 30 mm/hr. Blood and urine cultures were repeated, though there was no growth in either.

Due to the rash seen on admission, dermatology was consulted and they obtained skin shave and punch biopsies. Surgical pathology of skin biopsies showed vacuolar interface dermatitis and purpura, consistent with a possible autoimmune etiology. Additional serology testing returned negative for Blastomyces, Coccidioides, human immunodeficiency virus (HIV), and hepatitis A, B, and C. A cytomegalovirus PCR was negative as well. With no evidence of infective etiologies for the persistent fever, hematology suggested a positron emission tomography (PET) scan to evaluate the lymphadenopathy.

Diagnosis. A PET scan indicated extensive lymphadenopathy pattern suggestive of lymphoma (Figure 1). Thus, biopsy of additional nodes was suggested. The biopsy showed necrotizing lymphadenitis in mesenteric and axillary nodes and karyorrhectic debris in the axillary node only (Figures 2 and 3). These findings were consistent with Kikuchi disease. Flow cytometry of the lymph node biopsies showed normal B-cell populations with no evidence of monoclonal expansion, normal antigen expression, and normal CD4:CD8 ratios. A bone marrow aspiration with flow cytometry to exclude leukemia showed a normocellular marrow with trilineage hematopoiesis, mild dyserythropoiesis, and 1% blasts, along with markedly decreased iron stores consistent with iron deficiency anemia.

Discussion

Kikuchi disease has a world-wide distribution with a wide age of presentation. Dorfman and Berry reported a mean age of 30 in their review of 108 cases, with a range of 11-75 years of age.[5] The primary manifestation of Kikuchi disease is

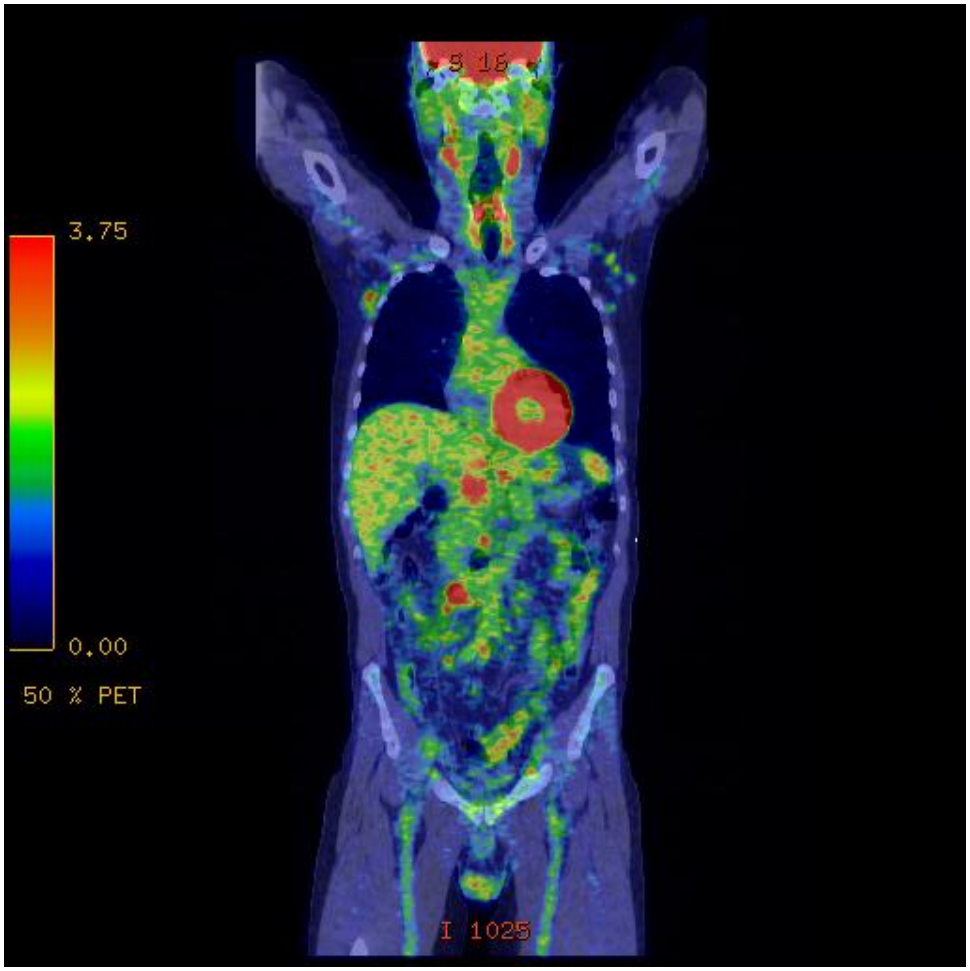

Figure 1. Multifocal areas of increased uptake on PET scan.

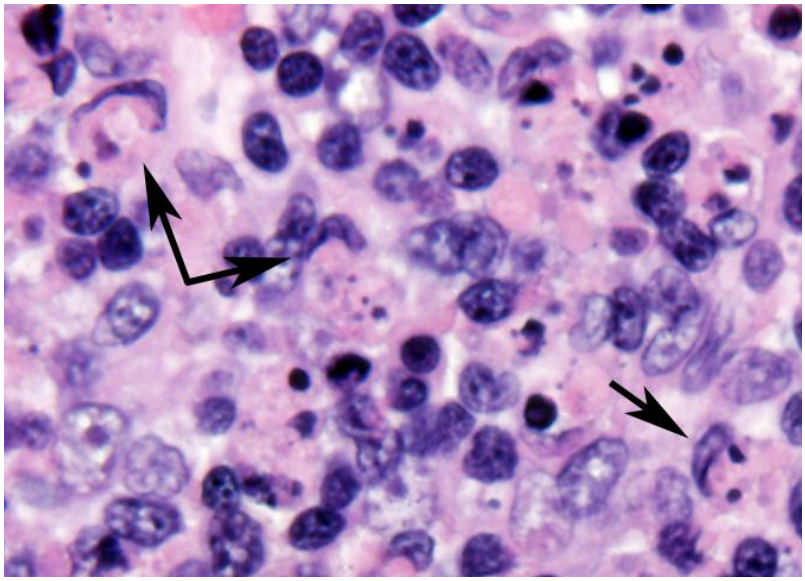

Figure 2. Lymph node biopsy with necrotizing lymphadenitis.

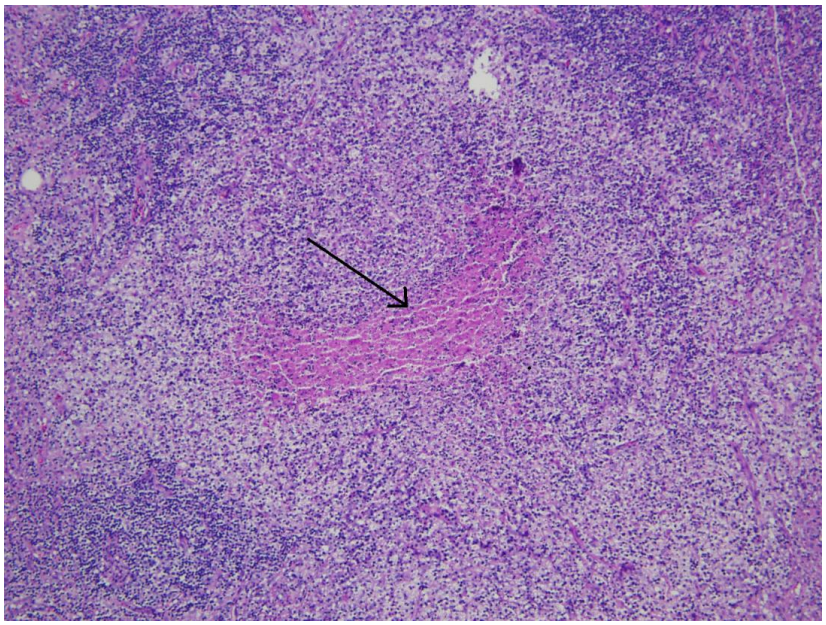

Figure 3. Lymph node biopsy with necrosis.

lymphadenopathy, which primarily occurs in the cervical and supraclavicular region, and is typically unilateral.[1,6-8] However, lymphadenopathy has been described in other case reports of axillary, thoracic, peripancreatic, retroperitoneal, and inguinal lymph nodes.[1,2,6,7] Most cases have relatively small lymphadenopathy, usually with nodes less than 2 cm wide.[1,2] Fever is also a common manifestation and can be the presenting symptom.[1] Skin rashes can take a number of forms including erythematous papules, plaques, acneiform or morbilliform lesions, and facial erythema,[2] and importantly, often can be suggestive of autoimmune pathology on biopsy.[9] Along with the clinical rash presentation[1,2] and association with co-existing lupus,[7,10] it is important to exclude rheumatologic causes as part of the differential diagnosis or as possible comorbidities with Kikuchi disease.

Kikuchi disease has some unique histopathologic findings, primarily in the form of irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, distortion of nodal architecture, histiocytic proliferation at the margin of necrotic areas, and karyorrhectic foci formed by different cellular types, including histiocytes, plasmacytoid monocytes, immunoblasts and small and large lymphocytes.[11] However, atypia commonly can be present in the reactive immunoblastic components and can be mistaken for lymphoma.

In this particular case, the patient received a thorough workup at the outside facility prior to transfer, including a lymph node biopsy. The diagnosis was not made initially, likely due to the rarity of the disease combined with the fact that this patient was atypical from an epidemiologic standpoint.

There is no treatment or therapy that has proven effective in the treatment of Kikuchi disease. Typically, there is complete resolution of symptoms within one to six months of presentation.[5] A relatively low recurrence rate has been reported, roughly 3-4%.[5] Recurrence may be reduced with prednisolone, but the evidence is insufficient to recommend its use routinely. Antibiotics such as ciprofloxacin and minocycline may have some benefit, though the evidence is

scarce.[12] Symptomatic measures aimed to relieve the distressing local and systemic complaints should be employed. Analgesic-antipyretics and nonsteroidal anti-inflammatory drugs may alleviate lymph node tenderness and fever. Because of the association with systemic lupus erythematosus, it is important to maintain follow-up even after the resolution of symptoms to ensure lupus does not develop.

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