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Kikuchi-Fugimoto's Disease in Sickle Cell Disease: Report of Two Cases

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Abstract

Kikuchi-Fugimoto's Disease (KFD), also known as histiocytic necrotizing lymphadenitis, is most frequently seen in young women and has been associated with autoimmune disorders such as polymyositis and systemic lupus erythematosus. It is a generally self-limiting disease with recovery time ranging from weeks to months. A typical presentation of KFD includes painful cervical lymphadenopathy, usually consisting of unilateral involvement of the posterior cervical chain. To date, this condition has not been described in patients with sickle cell disease. We present two cases of KFD, one in a patient with sickle beta⁰ thalassemia (S β^0 thal) and one in a patient with sickle cell anemia with hereditary persistence of fetal hemoglobin (HbS-HPFH). Both patients were young adult African American females who presented with fever and unilateral tender cervical lymphadenopathy. Extensive infectious disease testing including cultures and viral serologies were all negative. Imaging was negative for abscesses. The first patient had a preceding history of benign carcinoid tumor and idiopathic thrombocytopenic purpura. The second patient had no history of autoimmune syndromes but was on hydroxyurea therapy at the time of her presentation; the first had never taken hydroxyurea. Treatment strategies included prednisone therapy in the first case and watchful monitoring in the second. Recovery time was approximately 2 months for each patient. Both developed thyroid disease subsequent to their episode of KFD. Currently both patients are asymptomatic with no recurrence of KFD or active autoimmune disease.

Keywords

Kikuchi Disease; Sickle Cell Disease; Histiocytic Necrotizing Lymphadenitis

Introduction

Kikuchi-Fugimoto's Disease (KFD), also known as histiocytic necrotizing lymphadenitis, is an entity that has been described since the 1970's and has frequently been associated with

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autoimmune disorders such as arthritis, polymyositis, uveitis, and systemic lupus erythematosus.¹⁻⁴ The disease is generally self-limiting, but recovery can take weeks to months. KFD affects predominantly young adult women, with a male to female ratio of 1:4; children are also affected.⁵⁻⁷

A classical presentation of KFD includes painful cervical lymphadenopathy, usually consisting of unilateral involvement of the posterior cervical chain.⁸ Fevers are common, but skin rash, splenomegaly, parotid gland enlargement, and meningitis are sometimes seen.⁸ Histopathologic evaluation remains the mainstay of diagnosis of KFD. The involved lymph node reveals a proliferation of histiocytes with karyorrhectic nuclear debris and/or geographic necrosis; there is also a proliferation of lymphocytes and plasmacytoid monocytic/dendritic cells. Mature neutrophils, eosinophils and plasma cells are usually rare or absent. To date, KFD has not been described in patients with sickle hemoglobinopathies. We now present two cases of Kikuchi's disease in patients with sickle cell disease (SCD).

Case Reports

Case 1

African female with hemoglobin S Beta⁰ Thalassemia (S β^0 thal) disease whose past medical history consisted of idiopathic thrombocytopenia complicated by a liver hematoma that was resected later that year. In 2002, she developed a benign carcinoid tumor of 5 millimeters, for which she underwent a polypectomy with negative margins. No recurrence has been identified to date. Later in 2002, during evaluation after a motor vehicle accident, she was found to have a multi-nodular thyroid goiter during computer-assisted tomography of her cervical spine. One month later, she presented with questionable mediastinal lymphadenopathy, bilateral axillary adenopathy, bilateral pleural effusions, heterogeneous thyromegaly with multiple cysts, and normal thyroid function tests. Pleural fluid was not obtained during this evaluation. Subsequent scans 3 months later showed complete resolution of pleural effusions and lymphadenopathy. In 2003, she presented to a local emergency department with a 5-day history of low grade fevers, malaise, headache, abdominal pain, and diffuse body aches in arms and legs, not typical of her sickle cell pain. Blood cultures, Chlamydia and gonorrhea assays by PCR, as well as mononucleosis latex agglutination test were all negative. Chest X-ray was interpreted as showing signs of early pneumonia, and the patient was discharged home on antibiotics. Her antithyroglobulin was positive during this evaluation. One month later, the patient presented to clinic with fevers up to 100.2°F, chills, persistent fatigue, cough, and pain in her elbows, hips, back and chest. She also had a three-day history of tender neck lymphadenopathy and was admitted for further evaluation.

On the initial admission examination, she had a temperature of 101.8° F, pulse rate of 73, normal respirations, and blood pressure of 115/72. Physical exam was positive for a III/VI systolic ejection murmur at the left upper sternal border radiating to the carotids and bilateral posterior cervical and occipital lymphadenopathy, the largest node being 1.5 centimeters (cm) tender and fixed. She had no hepatomegaly or splenomegaly and no joint swelling.

On laboratory examination, her hemoglobin level was 7.2 grams/deciliter, with a hematocrit of 26. Platelet counts were stable, between 200-300,000/microliter. Serologic tests were negative for Epstein Bar Virus (EBV) IgM, hepatitis B and C virus antibodies, and antibodies to parvovirus B19, Lyme disease causative agent, mycoplasma, and Human Immunodeficiency Virus (HIV). Echocardiogram during this admission revealed mild mitral regurgitation which resolved on followup echocardiogram 3 months later.

Biopsy of her left occipital lymph node was done and showed histiocytic necrotizing lymphadenitis, or Kikuchi-Fujimoto's Disease (Figure 1A-C). Computed tomography (CT) of her chest, abdomen, and pelvis revealed small reactive lymph nodes and no additional masses. The lymph node biopsy revealed no evidence of lymphoma or malignancy. Five hydroxy-indoleacetic acid (5-HIAA) and chromogranin levels did not suggest the presence of recurrent or metastatic carcinoid. The patient was treated with 30 milligrams (mg) daily of prednisone. Fevers dissipated over the next 48 hours, and she was discharged on a prednisone taper over a two month time period. She experienced a full recovery within 2 months and has had no recurrence to date. In 2007, the patient developed Grave's disease with exophthalmos. However, at a clinic visit in 2008, the patient presented with complaints similar to her initial episode of thyroiditis. Evaluation at that time revealed a euthyroid state by serum thyroid testing, and ultrasound of her thyroid showed no change in the size of the pre-existing nodules. No further evidence of autoimmune disease was found by serologic tests.

Case 2

African American female with hemoglobin S and hereditary persistence of fetal hemoglobin (HbS-HPFH) presented to the outpatient sickle cell clinic with a one -week history of high fevers of 103-104°F and tender cervical lymphadenopathy. Two weeks prior to her clinic visit, she had presented to an outside hospital with similar symptoms and had been discharged with a presumptive diagnosis of infectious mononucleosis. During that hospitalization, she had had an extensive evaluation for infectious disease work up prior to discharge and was negative for cytomegalovirus (CMV), acute EBV, HIV, and rapid strep. In the clinic she had fever of 104°F and increasing neck pain. Her physical exam revealed an ill appearing female with mild tachycardia, but no tachypnea and oxygen saturation of 98% on room air. She had palpable left cervical nodes, the largest measured 4 cm and described as tender, smooth, soft, and movable. Contrary to most cases with HbS-HPFH, this patient had no palpable splenomegaly. No additional lymphadenopathy was found. Laboratory examination revealed erythrocyte sedimentation rate (ESR) of 110, C-reactive protein of 5, normal thyroid panel, negative blood cultures and toxoplasma antibodies. Her baseline hemoglobin was 6.5 which is lower than the baseline for patients with HbS-HPFH. She was admitted for further evaluation.

She was started on empiric antibiotics and blood cultures remained negative, but high fever persisted. Patient underwent left cervical lymph node biopsy and pathology reported a 1.4×1.3×0.9 cm lymph node, negative for lymphoma, infectious etiologies, but consistent with histiocytic necrotizing lymphadenitis or KFD (see Figure 2). The patient's fevers eventually resolved without additional therapy. Three weeks later, she had recurrent fevers,

but her lymphadenopathy continued to resolve during this second febrile episode. Eight weeks after initial episode, her fevers and lymphadenopathy completely resolved. Two months later, the patient developed hyperthyroidism, which resolved without therapy nine weeks later. As of her last clinic visit, she has not had any recurrent symptoms,

Discussion

Kikuchi-Fujimoto's disease is a rare cause of fever of unknown etiology. Young women are more often affected than men. Several reports describe its association with systemic lupus erythematosus and other autoimmune disorders.^{3,9} However, this condition has not been reported in patients with SCD.

Many treatment approaches to KFD have been suggested. Hydroxychloroquine, intravenous immunoglobulin, antivirals, and glucocorticoids have been proposed on the basis of reports of successful treatment of KFD.^{5, 10} Patient 1 received steroids as part of her treatment course and had a somewhat shorter course of symptoms, compared to Patient 2, who was not treated with steroids. However, KFD is considered a self-limited disease, and symptoms tend to abate over weeks to months without treatment. It is especially notable that both patients developed some autoimmune manifestations after diagnosis of KFD. Patient 1 developed Grave's disease three years after diagnosis; however, her most recent thyroid scan and hormone levels revealed a euthyroid state. At her most recent clinical visit, she also reported symptoms of diffuse joint pain and stiffness, but no rash. Laboratory studies at that time showed an anti-nuclear antibody (ANA) titer of 1:160 (weakly positive), and the patient's symptoms improved with a brief course of prednisone. It is possible that she is developing early signs of lupus, and she will be closely monitored for further manifestations. Patient 2 presented with palpitations two months after her recovery from KFD and diagnosed with acute thyroiditis. Her symptoms resolved without treatment, and she currently shows no other signs of KFD recurrence or autoimmune phenomena. Of note, patient 2 had started to take hydroxyurea for management of her sickle cell disease one month prior to the onset of her KFD symptoms. During her episode of KFD, the hydroxyurea was held. To date, there has not been any reported association with hydroxyurea and necrotizing lymphadenitis. It is unclear if initiation of hydroxyurea therapy had any relationship to this patient's disease, as she has resumed taking hydroxyurea and is tolerating the medication well.

KFD is a rare condition, but its strong association with autoimmune disorders warrants that special attention is paid to possible signs and symptoms of autoimmune diseases in patients who are diagnosed with it. As shown in these two patients, autoimmune events do occur in KFD patients, but the timing and type of such manifestations can be variable. Periodic monitoring for connective tissue disease, lupus, and thyroid conditions may be warranted. This may be especially true in the setting of SCD, since that hemoglobinopathy affects primarily people of African origin, a population with an increased incidence of lupus and other autoimmune disorders.

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Figure 1.

Case 1 H&E and CD68 staining of cervical lymph node biopsy.

A: The eosinophilic areas are foci of patchy necrosis. (H&E stain, 40x)

B: Proliferation of histiocytes with increased karyorrhectic nuclear debris. (H&E stain, 400x)

C: Many cells are positive for CD68, a histiocytic cell antigen marker, confirming the proliferation of histiocytes in the areas shown. (CD68 immunohistochemical stain, 400x). CD14 stain was not reported.

Figure 2.

Case 2 H&E, CD68, and MPO stains of cervical lymph node biopsy. .

A: Patchy necrosis in the paracortical area of the lymph node. (H&E Stain, 40x) B: Positive CD 68 staining in many cells adjacent to the necrotic area of the lymph node. (CD68 immunohistochemical stain, 40x). CD14 stain was not reported.

C: Myeloperoxidase (MPO), an antigen marker for granulocytes, is positive in many histiocytic cells in this lymph node, such as neutrophils, eosinophils and their precursors. This antigen marker is usually negative in histiocytes proliferated due to other etiologies; however, for unknown reasons, it is positive in histiocytes in Kikuchi-Fujimoto's disease (Myeloperoxidase stain).