Kikuchi-Fujimoto disease diagnosed by correlating skin and lymph node biopsies

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INTRODUCTION

Kikuchi-Fujimoto disease is a rare, self-limited benign necrotizing lymphadenitis that typically manifests as fever and lymphadenopathy with or without extension to other organs including the skin, eyes, and bone marrow.[1,2] The rash may be variable in appearance, although most commonly presents with erythematous macules, papules, and plaques involving the face, upper extremities, and trunk.[3] Because the laboratory findings and imaging are nonspecific, the diagnosis depends on histologic examination. Characteristic histopathologic features of Kikuchi-Fujimoto disease include abundant nuclear debris surrounded by a brisk histiocytic infiltrate with varying degrees of lymphocytes and immunoblasts. Neutrophils are typically absent.[2] The etiology of Kikuchi-Fujimoto disease is unknown, although various infections including Epstein-Barr virus (EBV), parvovirus B-19, HIV, and human herpesvirus 6 have been implicated. An association with systemic lupus erythematosus (SLE) has also been reported, although the nature of the relationship is unclear.[3] We report a case of Kikuchi-Fujimoto disease in the setting of EBV infection diagnosed following correlation between skin and lymph node biopsies.

Abbreviations used:

EBV: Epstein-Barr virus
SLE: systemic lupus erythematosus

CASE REPORT

A 40-year-old Hispanic woman presented with a 3- to 4-week history of recalcitrant fevers, weight loss, and pruritic rash. Examination found well-demarcated pink-tan to slightly violaceous edematous nodules without scale scattered on the face, trunk, and extremities (Fig 1, *A* and *B*). She was also noted to have bulky submandibular lymphadenopathy on admission. Her medical history was unremarkable except for a urinary tract infection diagnosed 3 weeks before admission, which was treated with trimethoprim-sulfamethoxazole and a second unknown antibiotic. Her laboratory workup was remarkable for a positive low-titer antinuclear antibody count of 1:80 in a speckled pattern, although her other autoimmune antibodies were negative, and her complement levels were normal. Her infection workup was notable for a positive EBV viral capsid antigen antibody IgG and 2 positive HIV screening tests with subsequent negative confirmatory testing, favored to represent a false-positive HIV test caused by cross-reactivity with EBV. A cutaneous 4-mm punch biopsy was performed and found focal vacuolar interface dermatitis with papillary to mid dermal perivascular and interstitial lymphohistiocytic infiltrate with karyorrhexis (Fig 2). The histiocytic infiltrate was highlighted by CD68 and myeloperoxidase. Most of the lymphocytes were $CD3^+$ T cells with rare scattered $CD20^+$ positive B cells. Infectious agent stains including Gomori methenamine-silver nitrate and acid-fast Bacilli were negative. A lymph node biopsy was also performed and found necrotizing lymphadenitis with an appearance similar to that of the skin biopsy (Fig 3). Features of EBV lymphadenitis in the setting of acute infection were absent, as histology will typically show follicular and paracortical hyperplasia with Reed-Sternberg–like cells.[4] Lymph node flow

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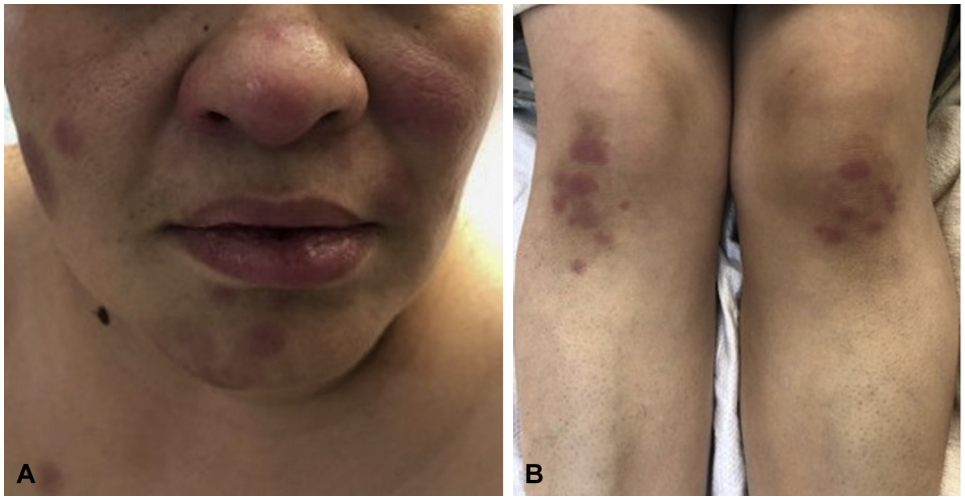

Fig 1. Clinical images taken at time of inpatient dermatology consultation. **A**, Well-circumscribed indurated pink to violaceous nodules scattered on the face and chest. **B**, Well-circumscribed indurated pink to violaceous nodules scattered on the extremities.

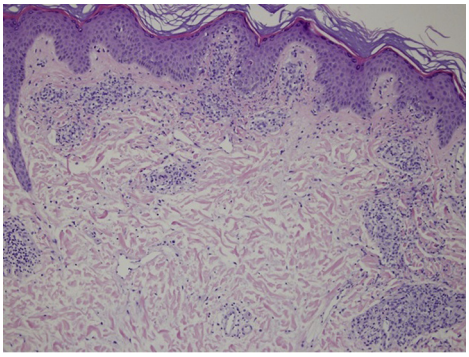

Fig 2. Section of punch biopsy from right knee shows focal vacuolar interface dermatitis with papillary to mid dermal perivascular and interstitial lymphohistiocytic infiltrate with karyorrhexis. (Hematoxylin-eosin stain; original magnification: ×100.)

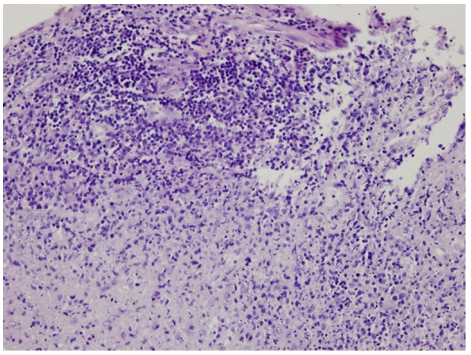

Fig 3. Section of excisional lymph node biopsy shows necrotizing lymphadenitis. (Hematoxylin-eosin stain; original magnification: ×200.)

cytometry was negative for a monotypic B-cell population or an aberrant or expanded T-cell population. Bone marrow biopsy and flow cytometry were similarly negative for any hematologic abnormality. Given the constellation of clinical findings in combination with the patient's unique skin and lymph node histology, a diagnosis of Kikuchi-Fujimoto disease was made. The patient's symptoms self-resolved over several weeks after her hospital discharge, further supporting the diagnosis.

DISCUSSION

The diagnosis of Kikuchi-Fujimoto disease can be clinically challenging and relies on histologic interpretation. Although excisional lymph node biopsy is required for diagnosis, dermatopathology can also reinforce the findings. Pathology findings will consistently show karyorrhectic debris with a surrounding lymphohistiocytic infiltrate, and cutaneous biopsies may also have an interface dermatitis.[3] The main clinical and histologic mimickers of Kikuchi-Fujimoto disease include SLE, infection, and lymphoid malignancies. Because Kikuchi-Fujimoto is benign and self-limited, early and accurate diagnosis is imperative to prevent unwarranted procedures and inappropriate treatments. A study from Pileri et al[5] reported a unique finding of myeloperoxidase co-expression by $CD68^{+}$ histiocytes in lymph node biopsies from patients with Kikuchi-Fujimoto. This peculiar phenotype, as also demonstrated by our skin biopsy, can be used for differentiation from malignant lymphoma and plasmacytoid monocyte tumors.[5] A CD8-predominant lymphocytic infiltrate and sparse plasma cell population have been found to be helpful

histologic clues to differentiate Kikuchi-Fujimoto disease from SLE. Notably, serologies may be unreliable, as Kikuchi-Fujimoto can occur in the setting of autoimmune disease including mixed connective tissue diseases and SLE. Patients with Kikuchi-Fujimoto disease require long-term monitoring for the development of SLE, which has been reported to occur in up to 25% of cases. Kikuchi-Fujimoto disease may precede, postdate, or coincide with SLE diagnosis.[6] Patients with positive serologies who experience arthralgias, skin manifestations, and weight loss are most at risk for the development of SLE.[3]

The initial differential diagnosis for this patient included lymphoma, lupus, and infection including HIV. Her laboratory results were inconclusive given the positive low titer antinuclear antibody level, EBV viral capsid antigen antibody IgG indicative of past infection, and false-positive HIV tests. Kikuchi-Fujimoto disease was suggested as a unifying etiology only after the lymph node and skin biopsies displaying nonneutrophilic karyorrhexis were correlated. Infectious disease proposed possible EBV infection as a trigger for the Kikuchi-Fujimoto disease and as an explanation for the false-positive HIV tests. As expected, this patient improved without treatment.

This case shows the difficulty in diagnosing Kikuchi-Fujimoto disease, a rare entity that dermatologists may encounter, and the ability of histology to confirm the diagnosis.

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