Kikuchi-Fujimoto Disease

A Review

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Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a relatively rare condition characterized by subacute necrotizing regional lymphadenopathy. This is a benign and self-limited disease, frequently associated with mild fever, and occasionally with other systemic symptoms.1–3 The disease was first described in Asia by Kikuchi4 and Fujimoto et al5 in 1972, and afterwards in the United States6,7 and Europe.8 Despite many studies in the literature, the etiology and pathogenesis of KFD remain unknown. Clinicians, as well as many pathologists, are unfamiliar with this entity, which can pose significant diagnostic challenges as it can easily be mistaken for other benign lymphadenopathies or infectious lymphadenitis as well as lymphomas. Herein, we provide a review of clinical and histopathologic aspects of this entity.

EPIDEMIOLOGY

Kikuchi-Fujimoto disease was first described4,5 in Japanese patients and has a higher prevalence among Asians.1–3 Pileri et al8 described the first case series outside of Asia, with a predominantly European cohort. Since then, KFD has been reported worldwide in a variety of ethnic backgrounds.1 It usually affects young adults (younger than 40 years), but it can occur in any age group.1–3 Most reports show female predominance; however, some studies from Asian countries suggest that the male to female ratio is closer to 1:1.9,10

CLINICAL FEATURES

Kikuchi-Fujimoto disease is self-limiting with acute to subacute course, evolving during several weeks. Patients most commonly present with posterior cervical lymphadenopathy (60%–90% of cases), frequently with concomitant involvement of axillary and/or supraclavicular lymph nodes. Affected lymph nodes are tender and painful. Generalized lymphadenopathy is rarely reported (1%–22% of cases).1–3,11 Lymphadenopathy is most commonly associated with fever (35%–77% of cases); other infrequent symptoms include weight loss, nausea and vomiting, weakness, headache, arthralgia, night sweats, upper respiratory symptoms, and sore throat.3 Hepatomegaly and splenomegaly rarely occur (less than 5% of cases).11 The disease uncommonly occurs in extranodal locations, most frequently in the skin, and occasionally in bone marrow and liver.1,12–14 Cutaneous involvement mostly affects the face and upper body, manifesting as rashes, nodules, erythematous papules, indurated erythematous lesions, erythema multiforme, and erythematous maculopapular lesions.1–3,11,15,16 Most commonly patients have normal laboratory findings. In some cases, there is mild anemia, mildly elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Other findings include leukopenia (especially granulocytopenia; 20%–58% of cases) and leukocytosis (2%–5% of cases), with atypical lymphocytes in the peripheral blood reported in up to one-third of patients. Other laboratory abnormalities seen in some of these patients include elevated serum lactate dehydrogenase and elevated aminotransferases.3

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ETIOLOGY AND PATHOGENESIS

Many studies in the literature have tried to elucidate the cause of KFD, but at present it remains unclear. The 2 most common theories explored in the literature are infectious and autoimmune. The clinical picture of KFD is similar to that of viral infection, and, like viral infection, the disease does not respond to antibiotics. Moreover, histopathologic features (ie, paracortical expansion, immunoblastic proliferation, necrosis in paracortex, predominance of T cells, and circulating atypical/reactive lymphocytes in the peripheral blood) are similar to those seen in viral infections.1–3 Numerous viruses have been proposed as possible etiologic agents of KFD, including Epstein-Barr virus; herpes simplex virus; varicella zoster virus; human herpesviruses 6, 7, and 8; parvovirus B19; paramyxovirus; parainfluenza virus; rubella; cytomegalovirus; hepatitis B virus; human immunodeficiency virus; human T-lymphotropic virus type 1; and dengue virus. However, no study in the literature has definitively proven a causal relationship between a virus and KFD or identified viral particles ultrastructurally.1,3,17,18 Other infectious agents studied include Brucella, Bartonella henselae, Yersinia enterocolitica, Toxoplasma gondii, Entamoeba histolytica, and Mycobacterium szulgai.3,18

It has been postulated that KFD represents an exuberant T-cell–mediated immune response to a variety of antigens in genetically susceptible people.1 Compared with the general population, patients with KFD more frequently have particular human leukocyte antigen (HLA) class II alleles, specifically HLA-DRP1 and HLA-DRP1. These alleles are more prevalent in Asians and are extremely rare or absent in whites, which may account for the more common occurrence of this entity among Asian people.13 Kikuchi-Fujimoto disease has also been described in association with a number of systemic diseases, most commonly autoimmune conditions such as systemic lupus erythematosus (SLE). Wegener granulomatosis, Sjögren syndrome, Graves disease, Still disease, etc.3,20 The cytoplasm of stimulated lymphocytes and histiocytes of KFD patients contains tubular reticular structures that, by electron microscopy, bear similarity to structures that have been described in the endothelial cells and lymphocytes of patients with SLE and other autoimmune disorders.21 Immunohistochemical staining has been consistently negative in KFD patients.1–3,7 Despite negative serology in KFD, there is a degree of clinical and morphologic overlap between KFD and SLE that requires particular consideration. In a study by Dumas et al32 that included 91 KFD patients, 11 patients (12%) had a history of SLE. These cases likely represent lupus lymphadenitis, as the 2 disorders are histologically indistinguishable in some cases.

A number of case reports have described KFD in association with different pathologic conditions (eg, meningitis,23 status epilepticus,24 interstitial lung diseases,25 myocarditis,26 acute renal failure,27 hemophagocytic syndrome,28 and sickle cell anemia29) and malignancies (breast,30 stomach,31 and oral cavity32), as well as in patients with pacemakers3 and breast implants,33 suggesting that these foreign bodies might represent triggers for the development of disease.

### Histologic Differential Diagnosis of Kikuchi-Fujimoto Disease

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HISTOPATHOLOGIC FEATURES AND IMMUNOHISTOCHEMISTRY

Histologically, lymph nodes usually have partially preserved architecture with follicular hyperplasia. The paracortex is expanded and shows patchy, well-circumscribed areas of necrosis. Necrotic foci show abundant karyorrhectic nuclear debris and a large accumulation of histiocytes at the edge of necrosis. Occasionally, there are only isolated apoptotic cells scattered throughout large sheets of histiocytes, admixed with cellular debris and nuclear dust. In the necrotic foci there are frequent so-called crescentic histiocytes. Among the histiocytes, there are scattered small lymphocytes, activated T cells, and some plasma cells. Neutrophils and eosinophils are conspicuously absent, an important clue in diagnosis of this entity (Figure 1, A through C). At the edge of necrotic areas, there are clusters of plasmacytoid dendritic cells, as well as immunoblasts. Moreover, thrombosed vessels can frequently be seen at the periphery of necrosis.3,4,35

Three evolving histologic patterns of KFD have been proposed: proliferative, necrotizing, and xanthomatous. The initial proliferative pattern is characterized by an expanded paracortex with sheets of histiocytes and plasmacytoid dendritic cells, admixed with small lymphocytes and karyorrhectic nuclear debris. The necrotic phase is characterized by the presence of necrosis. In the xanthomatous phase, there is predominance of foamy histiocytes in the lesions, regardless of presence or absence of necrosis36 (Figure 1, D).

The diagnosis of Kikuchi-Fujimoto disease is made predominantly on basis of morphologic evaluation. As in many benign and malignant lymph node disorders, low-power pattern recognition is critical in this disease. Immunohistochemical staining is sometimes useful, especially in cases with limited tissue (ie, core biopsies or small biopsies), where it is often difficult to appreciate a pattern of lymph node involvement. The histiocytes in KFD are positive for lysozyme, myeloperoxidase, CD68, CD163, and CD4. The lymphocytes in the lesions are mostly CD3–positive T cells demonstrating a predominance of CD8
compared with CD4, with very few CD20-positive B cells. Plasmacytoid dendritic cells are highlighted with CD123 (Figure 2, A and B).2,34

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of KFD includes infectious lymphadenitis of different etiologies, autoimmune lymphadenopathy (primarily SLE lymphadenopathy), and non-Hodgkin lymphoma. The histologic differential diagnosis of KFD is given in the Table.

Multiple infectious agents can cause necrotizing lymphadenitis, which may mimic KFD. In necrotizing lymphadenitis of tuberculosis, histoplasmosis, leprosy, and cat-scratch disease, there is proliferation of epithelioid histiocytes with granuloma formation, as well as scattered giant cells. In cases of syphilitic necrotizing lymphadenitis, there is usually prominent perivascular plasma cell infiltration. In lymphadenitis caused by Y enterocolitica, there are prominent eosinophils, whereas in bacterial infections there are usually abundant neutrophils. Moreover, neutrophils and viral inclusions are seen in cases of herpes simplex necrotizing lymphadenitis. Special stains and immunohistochemical stains are sometimes helpful in identifying the infectious agents. Correlation with serologic and molecular studies is usually necessary to confirm the diagnosis. Occasionally, infectious mononucleosis lymphadenitis can enter the differential diagnosis of KFD. Infectious mononucleosis usually shows marked follicular hyperplasia and paracortical expansion with an increase in immunoblasts and scattered Hodgkin- and Reed-Sternberg–like cells. Single-cell apoptosis and foci of necrosis are also commonly seen. Epstein-Barr virus–encoded RNA in situ hybridization is usually strongly and diffusely positive and resolves the diagnostic dilemma.34

Systemic lupus erythematosus lymphadenopathy is the most difficult differential diagnosis to resolve, and in some cases it is histologically and immunohistochemically indistinguishable from KFD. Systemic lupus erythematosus lymphadenopathy shows focal or confluent paracortical necrosis, surrounded by lipid-laden histiocytes. Within the necrotic foci, there are numerous apoptotic cells. Similar to KFD, there is an absence of neutrophils and eosinophils. In a subset of cases, hematoxylin bodies are seen, composed of aggregates of nuclear DNA, polysaccharides, and immunoglobulin. Hematoxylin bodies are the most specific histologic feature of SLE lymphadenopathy. Moreover, blood vessels showing Azzopardi phenomenon (hematoxylin-staining nuclear material) can sometimes be seen in the areas of necrosis (Figure 3, A through D). Given the
Figure 2. Kikuchi-Fujimoto disease. A, CD123 showing increase in plasmacytoid dendritic cells, with prominent clustering on the edges of necrotic foci. B, Histiocytes are positive for myeloperoxidase immunohistochemical stain (original magnifications ×100 [A] and ×200 [B]).

Figure 3. Systemic lupus erythematosus (SLE). A, Paracortical sheet of histiocytes with karyorrhectic debris in an SLE patient with enlarged cervical lymph node; morphologic findings are indistinguishable from Kikuchi-Fujimoto disease. B, Histiocytes stain positive for myeloperoxidase immunohistochemical stain. C, Another case of SLE lymphadenopathy showing extensive necrosis with apoptotic debris and hematoxylin bodies. D, Azzopardi effect (hematoxylin and eosin, original magnifications ×200 [A] and ×400 [C and D]; original magnification ×200 [B]).
histologic similarity of SLE lymphadenopathy to KFD, it is prudent to always put SLE in the differential diagnosis to alert clinicians that clinical and laboratory correlation is needed to distinguish between these 2 entities.1–3,34

Kikuchi-Fujimoto disease can easily be confused with lymphoma. Proliferation of immunoblasts and plasmacytoid dendritic cells at the edges of necrotic foci, as well as obliteration of sinuses, can mimic involvement by both T-cell and B-cell non-Hodgkin lymphoma.36 Immunohistochemical stains are helpful in challenging cases. B-cell lymphomas are easy to eliminate because of very few B cells in the involved areas. T-cell lymphomas can pose a more difficult diagnostic challenge because most lymphoid cells in the lesions are T cells. Positivity of histiocytes for myeloperoxidase is a helpful clue. However, positivity for myeloperoxidase can sometimes be misinterpreted as myeloid sarcoma. In KFD, no immunohistochemical stain is a substitute for a good-sized, well-fixed hematoxylin and eosin–stained section.

Diagnosis of KFD is especially difficult in small or needle-core biopsies, where the pattern of involvement cannot be well appreciated. Figure 4 shows a case of KFD from our practice diagnosed on a needle core biopsy that nicely illustrates challenges and pitfalls of this diagnosis on a small specimen. Several small needle core biopsies of a cervical lymph node were completely effaced by an atypical lymphohistiocytic infiltrate that on high power showed sheets of large atypical cells with irregular nuclei, focally prominent nucleoli and moderately abundant cytoplasm; there are frequent apoptotic bodies. C, Area of necrosis with karyorrhectic debris is present. D and E, Most cells in the infiltrate are histiocytes, as shown by CD68 immunohistochemistry (D), which coexpress myeloperoxidase (E). F, CD123 highlights clusters of plasmacytoid dendritic cells (hematoxylin and eosin, original magnifications ×10 [A] and ×400 [B and C]; original magnifications ×10 [D] and ×100 [E and F]).

TREATMENT AND PROGNOSIS

Kikuchi-Fujimoto disease is a self-limited disease that usually resolves within a few months. It has a low recurrence rate of 3% to 4%,1–3 and only several fatal cases have been reported.26,37,38 Treatment aims at relieving...
symptoms (rest, analgesics, and antipyretics), as there is no specific therapy for these patients. Patients with relapsing disease or a more severe clinical course might benefit from corticosteroid therapy.

**CONCLUSIONS**

Kikuchi-Fujimoto disease poses significant diagnostic challenges to pathologists and clinicians. Pathologists should be familiar with this entity to avoid a misdiagnosis of lymphoma, which could lead to unnecessary and aggressive therapy. Excisional lymph node biopsy is the optimal specimen for diagnosis of KFD; however, immunohistochemical stains can be helpful in cases with limited material. From a clinical standpoint, one of the most important differential diagnoses is SLE, which should be ruled out in all patients diagnosed with KFD.

**References**