Enigmatic Kikuchi-Fujimoto Disease

A Comprehensive Review

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Abstract

To determine the clinicopathologic significance of Kikuchi-Fujimoto disease (KFD) and review the literature on this condition, we conducted a MEDLINE search of English-language articles published between 1972 and December 2003.

KFD has a worldwide distribution, and Asiatic people have a higher prevalence. Its pathogenesis remains controversial. Patients are young and seek care because of acute tender, cervical lymphadenopathy and low-grade fever. Histologic findings include paracortical areas of coagulative necrosis with abundant karyorrhectic debris. Karyorrhectic foci consist of various types of histiocytes, plasmacytoid monocytes, immunoblasts, and small and large lymphocytes. There is an abundance of T cells with predominance of CD8+ over CD4+ T cells. Differential diagnosis includes lymphoma, lymphadenitis associated with systemic lupus erythematosus, and even adenocarcinoma. KFD is an uncommon, self-limited, and perhaps underdiagnosed process with an excellent prognosis. Accurate clinicopathologic recognition is crucial, particularly because KFD can be mistaken for malignant lymphoma.

Kikuchi-Fujimoto disease (KFD; so-called histiocytic necrotizing lymphadenitis) is an enigmatic, benign, and self-limited syndrome characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever and night sweats. Initially described in Japan, KFD was first reported almost simultaneously by Kikuchi and by Fujimoto and associates in 1972 as a lymphadenitis with focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris.[1] Clinicians and pathologists are unfamiliar with this entity. We provide a comprehensive review of KFD with special emphasis on the clinicopathologic significance of this condition.

Literature Review

We reviewed relevant articles published in English-language medical journals from 1972 (when KFD was first reported) to the present day through a MEDLINE search using the keywords "kikuchi" and "histiocytic necrotizing lymphadenitis." In addition to original and review articles and editorials, we included outstanding case reports and letters.

Epidemiology

KFD is known to have a worldwide distribution with a higher prevalence among Japanese and other Asiatic people.[1-5] It is scarcely known in the Western hemisphere. In fact, the first description of the disorder outside Asia was made by Pileri and colleagues[6] in 1982 (with Kikuchi as a coauthor). Cases reported by Pileri et al[6] included 23 from the former

West Germany and individual cases from Iran, Italy, South Korea, and Spain. It since has been reported worldwide.[7-18] Affected patients most often are adults younger than 40 years (range, 19 months to 75 years).[16,18-21] A recent series from Taiwan of 61 patients with KFD revealed a mean age of 21 years.[22] In general, a female preponderance has been reported (female/male ratio, 4:1).[17,19,20] Yet recent reports from Eastern countries seem to indicate that the female preponderance was overemphasized in the past and that the actual ratio is closer to 1:1.[17,22]

Cause and Pathogenesis

There is much speculation about the cause of KFD; a viral or autoimmune cause has been suggested. Some initial reports hinted at *Yersinia enterocolitica* and *Toxoplasma gondii* as possible causative agents of KFD, mainly on the basis of positive serologic test results. But subsequent studies failed to support these hypotheses. In addition, the histologic features of lymphadenitis associated with these microorganisms clearly differ from those of KFD[23-25] **Table 1**.

The role of Epstein-Barr virus (EBV), as well as other viruses, in the pathogenesis of KFD remains controversial. Serologic tests including antibodies to EBV, cytomegalovirus, and a host of other viruses have consistently proven noncontributory.[1] A viral infection is, nevertheless, possible by virtue of clinical manifestations, as described by Unger and colleagues[2] (upper respiratory prodrome, atypical lymphocytosis, and lack of response to antibiotic therapy), and certain histopathologic features (ie, proliferation of immunoblasts, presence of necrotic zones localized to T-cell areas, expansion of the paracortex, and predominance of T cells as revealed by immunologic marker studies). However, no viral particles have been identified ultrastructurally. Histologic, ultrastructural, and immunohistochemical findings might support a hyperimmune reaction, perhaps to several organisms. It is possible that KFD might represent an exuberant T cell–mediated immune response in genetically susceptible people to a variety of nonspecific stimuli. Some HLA class II genes are more frequent in patients with KFD. In particular, the incidence of DPA1*01 and DPB1*0202 alleles is significantly higher in patients with KFD than in healthy control subjects. These genes are extremely rare or absent among Caucasians but relatively common among Asiatic people (eg, French, 0.4%; Italian, 0.8%; Korean, 9.9%; and Japanese, 4.5%). This might provide an admissible explanation about the aforementioned epidemiologic pattern.[37]

Among others, EBV and herpesviruses 6 and 8 have been suggested as potential causative agents of KFD. With regard to EBV, there are 2 studies—including 11 cases of KFD—that detected EBV by means of in situ hybridization for EBV-encoded RNA expression[19,26] and polymerase chain reaction–based methods (Epstein-Barr nuclear antigen-1 DNA).[19] However, there have been several other studies that, by using the same and other molecular pathology procedures (eg, Southern blot analysis) to localize the virus genome, have concluded that neither EBV nor herpesvirus 6 or herpesvirus 8 has a putative role in the pathogenesis of KFD. This conclusion is based on the facts that most cases were negative and that, if positive results were observed, the percentage of viral detection in control subjects also was augmented.[27-33]

Table 1
Microorganisms More Frequently Reported to Have a Causative Role in KFD

Microorganism	Supportive Data	Contrary Data
Yersinia enterocolitica	Positive IIF assay applied to lymphatic tissue in 1 case[24]; positive serologic results reported[23]	Histologic features of mesenteric lymphadenitis differ from those of KFD
Toxoplasma gondii	Positive serologic results reported[25]	Histologic features of toxoplasmic lymphadenitis differ from those of KFD
Epstein-Barr virus	Detected by ISH[19,26] and PCR[19,27]	Not detected by ISH,[27-29] SB,[30] or PCR[31]; 50% positive detection in KFD but also 50% positive detection in control samples by PCR[30]
HHV-6	Detected by PCR[32]	Not detected by PCR[27] or SB[32]; 100% positive detection in KFD but also 50% positive detection in control samples by ISH[32]
HHV-8	23% incidence rate by PCR[33]	Not detected in KFD, but 100% detection in control samples by PCR[29]
HTLV-1	Positive serologic results reported[34,35]	Not detected by ISH or PCR[26]
Hepatitis B virus	None	Not detected by ISH[28]
Parvovirus B19	Detected by immunohistochemical analysis in 1 case[36]	Not detected by immunohistochemical analysis[26]
Herpes simplex, CMV, varicella zoster	None	Not detected by PCR[30,31]

CMV, cytomegalovirus; HHV, human herpesvirus; HTLV-1, human T-lymphotropic virus type 1; IIF, indirect immunofluorescence; ISH, in situ hybridization; KFD, Kikuchi-Fujimoto disease; PCR, polymerase chain reaction; SB, Southern blotting.

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Electron microscopic studies have identified tubular reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes in patients with KFD.[1] Because these structures also have been noted within endothelial cells and lymphocytes of patients with systemic lupus erythematosus (SLE) and other autoimmune disorders, Imamura and coworkers[38] hypothesized that KFD might reflect a self-limited SLE-like autoimmune condition induced by virus-infected transformed lymphocytes. Yet the results of serologic studies testing antinuclear antibodies, rheumatoid factor, and other immunologic parameters consistently have been negative in these patients,[1] providing no support for an autoimmune nature of the disease. Nevertheless, as we will comment, the association between KFD and SLE has been reported with a frequency probably greater than that expected by chance alone.

Some physicochemical factors have been pointed out anecdotally as triggers that might lead to KFD. One case of a patient who underwent a pacemaker implantation 6 weeks before the onset of KFD has recently been described.[39] In addition, the simultaneous occurrence of KFD and silicone lymphadenopathy in an axillary lymph node of a patient with a leaking silicone breast implant was reported in 1996.[40] In this patient, a lymph node biopsy revealed silicone lymphadenopathy along with the classic morphologic and immunophenotypic features of KFD.[40]

Although the mechanism of cell death involved in KFD has not been studied extensively, some works have proposed that it is characterized by apoptosis.[41-45] The finding of nuclear debris, which is one of the characteristic features of KFD, might indicate cell death by apoptosis. By means of an in situ end-labeling procedure, Felgar et al[41] noticed that the lymphocytes within and surrounding the typical areas of necrosis in affected lymph nodes from patients with KFD had nuclear fragmentation, a typical feature of early apoptosis. Furthermore, it has been reported that CD8+ T lymphocytes seem to be the lymphocytes that undergo apoptosis.[41,43-45] T-cell–restricted intracellular antigen–1 (TIA-1) cytotoxic granules were detected within the cytoplasm of apoptotic bodies in KFD necrotizing lesions.[41] In double stainings, TIA-1+ lymphocytes were found to be CD8+ rather than CD4+.[43]

On the other hand, several immunohistochemical studies have established that the predominant proliferating cell in KFD lymph nodes is the CD8+ T lymphocyte.[16-18,46,47] To elucidate the apoptotic mechanism related to this condition and the type of cells involved, Ohshima and coworkers[45] studied perforin and Fas pathways as CD8+ T-cell cytotoxic mechanisms that could induce apoptosis in target cells in patients with KFD. According to their observations, proliferating CD8+ T cells might act as "killers" and "victims" in the apoptotic process via the Fas and perforin pathways. The high Fas/FasL (ligand) frequency among CD8+ T cells rather than CD4+ T cells would support this hypothesis. Interestingly, these authors found a high frequency of Fas/FasL in histiocytes. They also suggested that there is an activated CD8+ T-cell proliferating/dying functional balance that might be beneficial to eradicate the responsible agent.[45]

CD123^{bright} plasmacytoid predendritic cells—the so-called plasmacytoid monocytes or plasmacytoid T cells—have been reported to be a striking histopathologic finding of KFD. Plasmacytoid cells represent a population composed mainly of lymphoid (and also myeloid) cells that at an immature stage produce type I interferon in response to viral infection and, depending on microenvironmental stimuli, differentiate into potent antigen-presenting cells. These cells would have a role in the pathogenesis of KFD via their migration from bone marrow to affected lymph nodes, where they might produce large amounts of type I interferon, thus promoting a T-helper 1 T-cell response and the aforementioned cytotoxic immune reaction.[20,48-51]

Monocyte and macrophage lineage cells have been proposed as enhancers of the apoptotic event. The existence of a Fas/FasL interaction in these cells might imply a histiocyte-dependent death of CD8+ T cells, which could amplify the background process. Abe and coworkers[52] recently demonstrated the presence of receptor-binding cancer antigen expressed on SISo cells (RCAS1) in the macrophages from lymph nodes of patients with KFD. RCAS1 seems to be an apoptosis-associated protein that induces apoptosis in activated T cells and erythroid progenitor cells. The authors suggested that the high presence of RCAS1 on macrophages might contribute to the aforementioned histiocyte-dependent CD8+ T-cell death.[52]

Serum concentrations of some inflammation mediators such as interferon (IFN)-γ, FasL, and interleukin-6 have been reported to be increased during the acute phase of KFD, returning to normal levels during the convalescent phase, thus raising the possibility that these cytokines could have a role in the pathogenesis of this condition.[53,54] Ohshima et al[55] noticed an abundance of cytokines and chemokines such as IFN-γ, interleukin-18, monokine induced by IFN-γ, and Cys-X-Cys chemokine IFN-γ–inducible protein-10 (which are related to the aforementioned perforin and Fas pathways) in lymphocytes and histiocytes in KFD lymph nodes. Nonspecific lymphadenitis cases were used as control cases. These immunologic pathways might, therefore, be closely involved in the apoptotic process of the disease.[55]

Clinical Manifestations

The onset of KFD is acute or subacute, evolving during a period of 2 to 3 weeks. Cervical lymphadenopathy is

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present in 56% to 98% of cases, more commonly consisting of tender lymph nodes involving the posterior cervical triangle (88.5%), generally unilateral (88.5%). Lymph node size ranges from 0.5 to 4 cm (93.4%), and occasionally, lymph nodes are larger than 6 cm. Painful lymphadenopathy is seen in up to 59% of patients. Generalized lymphadenopathy has been reported in 1% to 22% of cases.[1,2,16-18,22] Involvement of mediastinal, peritoneal, and retroperitoneal regions is uncommon.[7] In addition to lymphadenopathy, 30% to 50% of patients with KFD might have fever, usually low-grade, associated with upper respiratory symptoms. Less frequent symptoms include weight loss, nausea, vomiting, sore throat, and night sweats.[1,2,10,19,22] It should be mentioned that systemic symptoms are found more frequently when extranodal involvement is present.[19]

Laboratory Evaluation

The results of a wide range of laboratory studies usually are normal in KFD. Some patients have anemia and a slight elevation of the erythrocyte sedimentation rate. Mild leukopenia has been observed in 25% to 58% of patients, whereas leukocytosis is found in 2% to 5% of cases. Moreover, 25% to 31% of patients have atypical peripheral blood lymphocytes,[1,2,16-18,22] which might support the aforementioned speculated viral cause. The mechanism of granulocytopenia in a patient with KFD has been studied using an in vitro culture system.[1] The number of granulocyte precursor cells (colony forming units in culture [CFU-C]) in the bone marrow was found to be decreased. While T lymphocytes from the patient had no significant suppressor effect on the CFU-C, the patient's serum blocked CFU-C in vitro.[1] The authors proposed that one or more inhibitory factors might cause granulocytopenia in patients with KFD. Finally, serum levels of lactate dehydrogenase and aminotransferases are increased in some patients with KFD.[30] In 2002 we saw a patient with typical clinical and histopathologic findings of KFD who, in addition to anemia, leukopenia, and an increased serum lactate dehydrogenase level, had moderate thrombocytopenia with a normal bone marrow examination (unpublished data).

Unusual Features and Associated Conditions

Involvement of extranodal sites by KFD is uncommon, but skin and bone marrow involvement and liver dysfunction have been reported.[19,56-58]

It is worth mentioning that 6 of 7 initially reported cases of cutaneous involvement occurred in males and that the facial skin was the most common localization. The patients had had a disease with a more severe clinical course, yet all recovered without complications. Skin lesions in KFD seem to be nonspecific. A wide variety of dermatological patterns have been observed, including rashes; nodules; erythematous, crusted papules; scattered, indurated, erythematous lesions; erythema multiforme; and erythematous maculopapular eruptions, all mainly affecting the face and upper body.[59-63] A recent article described a patient with papulopustular whole-body skin involvement.[64] Oral ulcers and lip edema with desquamation and erosions have been reported anecdotally.[19,65] Finally, a patient was described whose recalcitrant psoriasis cleared spontaneously during the clinical course of KFD.[66]

A few patients have had generalized lymphadenopathy and hepatosplenomegaly as the initial manifestations of KFD. KFD also has been reported as a cause of prolonged fever of unknown origin.[67-69] It has been reported rarely in HIV-positive patients[70,71] and in association with the human T-cell leukemia/lymphoma (lymphotropic) virus type 1 (HTLV-1). One patient with HTLV-1 had a recurrent clinical form of KFD along with aseptic meningitis.[34,35] Charalabopoulos et al[72] described a case of KFD associated with brucellosis. A recent article from Thailand suggested an association between *Mycobacterium szulgai* lymphadenitis and KFD on the basis of the coexistence of characteristic histologic features of KFD in lymph nodes and a positive culture.[73] On the other hand, SLE has developed in some patients thought to have true KFD, suggesting to some investigators that KFD could be an incomplete form of an autoimmune condition. The patients, however, may have had SLE from the beginning, taking into account the histopathologic considerations discussed later.[74-77] The diagnosis of KFD can precede, postdate, or coincide with the diagnosis of SLE.[75] With regard to this topic, in 2003, Hu and coworkers[78] reported a clinicopathologic analysis of 18 cases of KFD plus SLE and tried to clarify the relationship between the conditions. They concluded that KFD is not related to SLE and that the KFD-like lymphadenitis coexisting with SLE should be regarded as a lupus lymphadenitis on the basis of several histologic criteria. Nevertheless, 6 cases of pre-SLE or post-SLE necrotizing lymphadenitis were found to be true KFD.[78]

In addition to SLE, other autoimmune conditions and manifestations such as antiphospholipid syndrome, polymyositis, systemic juvenile idiopathic arthritis, bilateral uveitis, arthritis, cutaneous necrotizing vasculitis, and pulmonary hemorrhage have been linked to KFD.[79-85] Whether these patients had true KFD or another autoimmune necrotizing lymphadenitis such as that associated with SLE remains unproven. Furthermore, some fatal cases, which had been reported as KFD, were found to be related to potentially life-threatening autoimmune conditions.[85,86]

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There have been other reports of unusual features of KFD, including parotid gland involvement,[87,88] thyroiditis,[88] carcinoma,[89] and diffuse large B-cell lymphoma.[90] Some cases of KFD have been associated with the hemophagocytic syndrome.[36,81,91,92] A review by Kelly and coworkers[91] on this association concluded that the diseases should be considered as a continuum rather than as separate entities.

Diagnosis

KFD generally is diagnosed on the basis of an excisional biopsy of affected lymph nodes. This disorder does not have a characteristic appearance on ultrasonographic or computed tomographic (CT) examination. The findings of CT and magnetic resonance imaging of KFD can be variable and mimic not only lymphoma but also various nodal diseases with necrosis, including metastasis and tuberculosis.[93-95] By using CT and magnetic resonance imaging, Miller and Perez-Jaffe[96] found a distinctive lymphadenopathy pattern in patients with KFD consisting of many small clustered lymph nodes. However, these observations must be interpreted cautiously because the study was carried out with a small number of patients.[96]

The usefulness of fine-needle aspiration cytology (FNAC) to establish a cytologic diagnosis of KFD has been limited and, in general, it is less useful than excisional lymph node biopsy. It has been said, however, that surgical biopsy would be unnecessary if a firm diagnosis could be made by using FNAC.[97-100] Thus, the results from 2 studies including histologic sections and excisional biopsy specimens led to the conclusion that in patients with typical clinical features and characteristic cytologic findings in lymph node aspirates, FNAC alone would suffice for diagnosing KFD.[97,100] Nevertheless, the overall diagnostic accuracy of FNAC for KFD has been estimated at 56.3%.[101] Therefore excisional lymph node biopsy should be mandatory if clear-cut clinical and cytologic KFD findings are absent.

We speculate that KFD might be an underdiagnosed disorder. It is possible that some (or many) young patients with (a "minor form" of) KFD who have a short history of low-grade fever and small cervical lymphadenopathy are given a presumptive diagnosis of a viral process, especially when their physical examination findings are normal, atypical lymphocytes are seen in a peripheral blood smear, and no lymph node biopsy is available.

Histologic Features

KFD can be diagnosed with confidence if careful attention is given to the architectural features and the characteristic cytologic composition of lymph node biopsy specimens. The characteristic histopathologic findings of KFD include irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large numbers of different types of histiocytes at the margin of the necrotic areas. The degree of necrosis varies considerably from one case to another **Image 1**. Thrombosed vessels usually are seen around the areas of necrosis. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes, but also immunoblasts, some of which may be atypical, and small and large lymphocytes. The number of plasmacytoid monocytes, small and large lymphocytes, and immunoblasts is variable **Image 2**. Atypia in the reactive immunoblastic component is not uncommon and can be mistaken for lymphoma when a proliferation of plasmacytoid monocytes, immunoblasts, and small lymphocytes is seen without necrosis. Various types of histiocytes can be observed, including nonphagocytic histiocytes, the so-called crescentic histiocytes **Image 3**, tingible body macrophages, and foamy histiocytes. There usually are areas of paracortical hyperplasia with small and large lymphoid cells and, occasionally, large, pale, interdigitating dendritic cells. Neutrophils characteristically are absent, and plasma cells are absent or scarce.[16-18]

Histiocytes and plasmacytoid monocytes make the most distinctive cell types found within the karyorrhectic foci. In fact, it has been considered that the earliest recognizable foci and minimum diagnostic criterion of KFD are paracortical clusters of plasmacytoid monocytes with interspersed karyorrhexis and crescentic histiocytes.[16]

Reactive lymphoid follicles are present in 50% to 60% of cases, and follicular hyperplasia has been found in approximately 10% of cases.[16-18] It has been reported that the

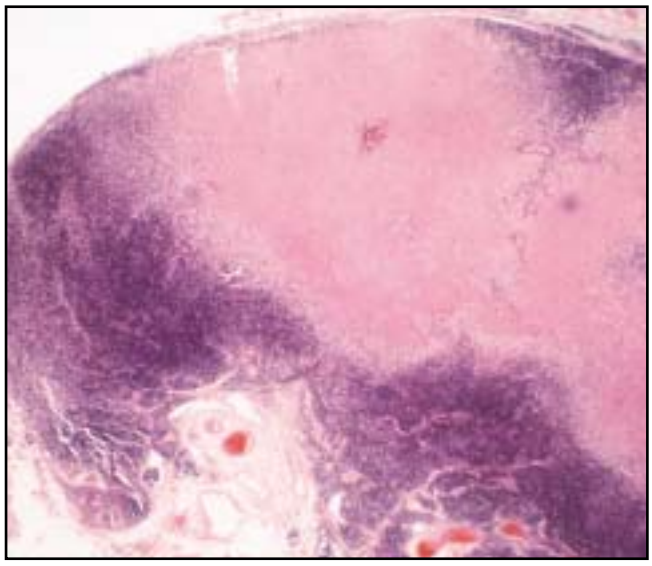

Image 1 Kikuchi-Fujimoto disease. Extensive paracortical area of coagulative necrosis (H&E, original magnification ×40).

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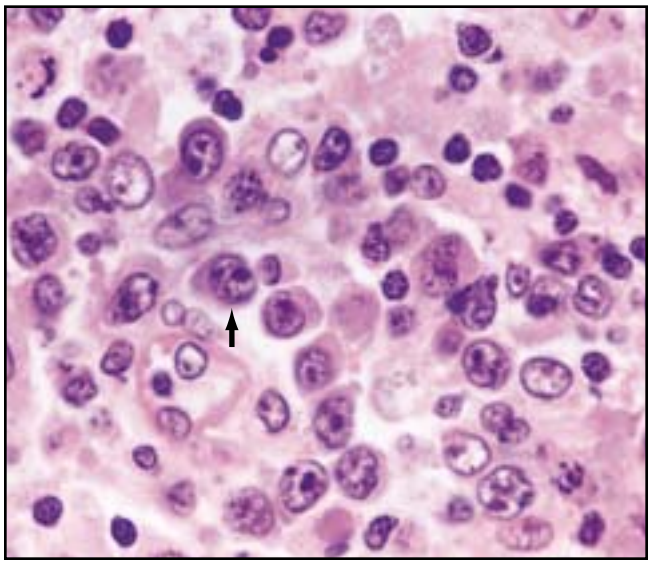

Image 2 Kikuchi-Fujimoto disease. Large lymphoid cells and immunoblasts, some of which have wide cytoplasm with an eccentric nucleus (arrow) (H&E, original magnification ×600).

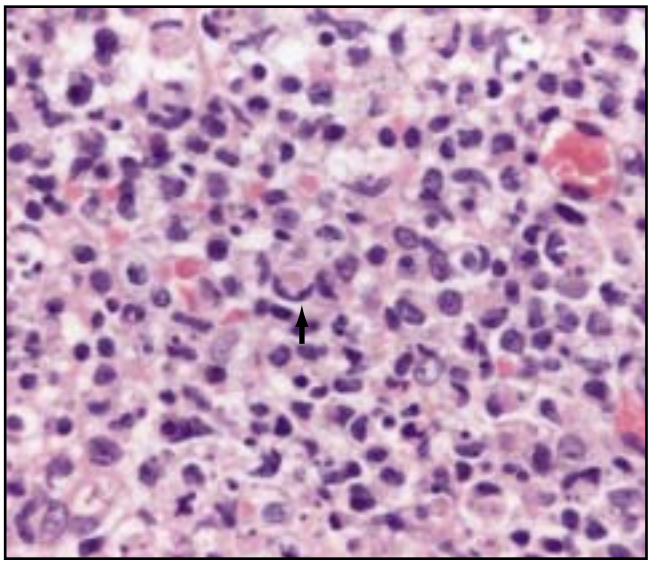

Image 3 Kikuchi-Fujimoto disease. Karyorrhectic foci with large numbers of histiocytes, including crescentic histiocytes (arrow), and some lymphoid cells (H&E, original magnification ×400).

karyorrhectic process can extend beyond the confines of the nodal capsule.[16] Chamulack and colleagues[102] reported the occurrence of karyorrhexis in the perinodal tissue in 2 of 10 cases of KFD. Tsang and coworkers[16] confirmed this finding in 15 of 75 cases. The process might even obliterate the perinodal lymphatics. Biopsies of skin lesions from patients with KFD with cutaneous involvement have revealed dermal infiltration by apoptotic plasmacytoid monocytes[60] and other cell infiltrates that essentially are composed of the same components as affected lymph nodes, including histiocytic aggregates, atypical lymphoid cells, karyorrhectic debris, and patchy necrosis.[19,61] The same features, along with lupus dermatitis–like histologic findings, were reported by Spies et al[63] in 1999 in a series of 5 patients affected by necrotizing lymphadenitis consistent with KFD and unspecific skin rashes. The authors suggested that this histologic pattern might be highly specific of KFD cutaneous involvement. Yet only 1 of the patients was reportedly followed up during 4 months without showing clinical features suggestive of SLE.[63]

Kuo[17] proposed classification of the histopathologic features of KFD into 3 evolving histologic stages: proliferative, necrotizing, and xanthomatous. The proliferative stage consists basically of various histiocytes, plasmacytoid monocytes, and a variable number of lymphoid cells with karyorrhectic nuclear fragments and eosinophilic apoptosis debris. If cellular aggregates in a given lymph node showed any degree of coagulative necrosis, the case was classified as necrotizing. If foamy histiocytes predominated in the KFD lesions, the case was classified as xanthomatous regardless of the presence or absence of necrosis. The most common type was the necrotizing type, accounting for slightly more than half of the cases. As Kuo[17] pointed out, the 3 histologic types might represent different stages of the disease or might reflect differences in cause or host reaction. Judging from the histologic changes, KFD perhaps begins as proliferative, progresses to necrotizing, and finally resolves into xanthomatous. However, sequential biopsy specimens were not available in the study by Kuo[17] to verify this postulated concept. Also, data on the duration of the disease did not correlate with the progression of the 3 histologic types.

Immunohistochemical Features

The immunophenotype of KFD typically consists of a predominance of T cells, with very few B cells. There is a predominance of CD8+ cells over CD4+ cells, along with a decreased ratio in the affected areas of the lymph node **Image 4**, owing to the aforementioned intense CD8+ T-cell apoptosis in the necrotic foci. The histiocytes express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO), and CD68 **Image 5**. This observation suggests that peripheral blood CD68+/MPO+ monocytes might be attracted to lymph nodes to fulfill the role of lacking granulocytes. It seems that the MPO needed for the inflammatory and cell-death mechanisms is supplied in this particular case by histiocytes. Striking plasmacytoid monocytes also are positive for cutaneous lymphocyte-associated antigen and CD68 but not for MPO.[49] They also express CD4 and CD74 and are positively stained by the pan-macrophage monoclonal antibody Kim1P. On the other hand, immunoblast cells in KFD-affected foci have the T-cytotoxic phenotype.[16-18,46,47]

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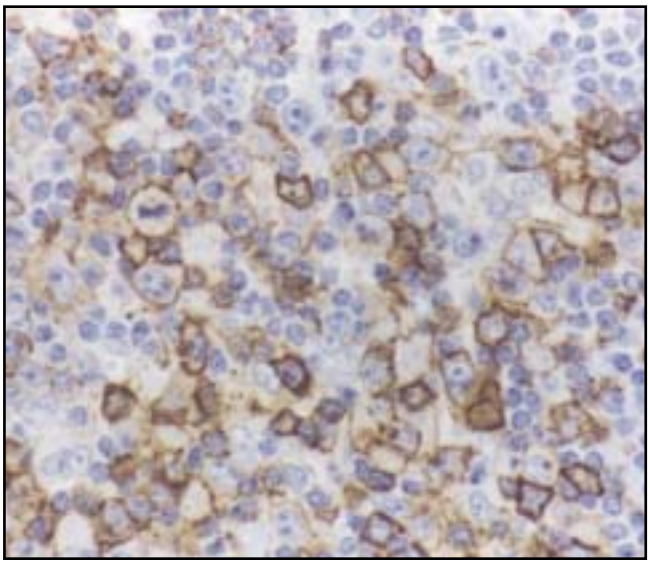

Image 4 Kikuchi-Fujimoto disease. CD8 immunostaining showing a characteristic membrane pattern of T cells. Most CD8+ T (cytotoxic) cells are constituted by lymphoid cells and large immunoblasts (avidin-biotin-immunoperoxidase technique; EnVision, DakoCytomation, Carpinteria, CA) (CD8, original magnification ×400).

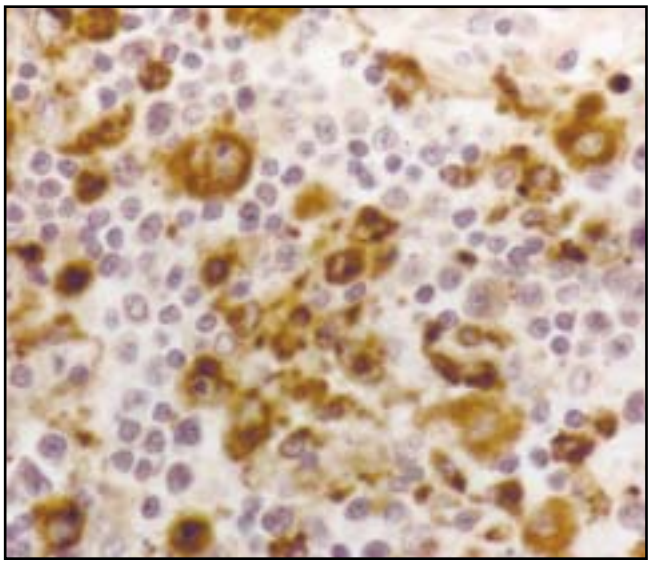

Image 5 Kikuchi-Fujimoto disease. The histiocytes in the karyorrhectic foci are positive for the CD68 antigen (avidin-biotin-immunoperoxidase technique; EnVision, DakoCytomation, Carpinteria, CA) (CD68, original magnification ×400).

Although KFD is considered to be a paracortical T-zone process, it is not uncommon to observe some reactive lymphoid follicles in the background, which can be interpreted as residual follicles or as a participation of the B-cell component in the disease process.[16] Some authors have observed monocytoid B-cell clusters in some cases of KFD.[1,2,16,18] Pileri and associates[6] reported focal distention of sinuses by monocytoid B lymphocytes ("immature sinus histiocytes") in some patients with KFD.

In cases of KFD with cutaneous involvement, immunohistochemical analysis of skin lesions has revealed essentially the same findings as those in lymph nodes.[58,61]

Differential Diagnosis

Although KFD is considered uncommon, at least in Western countries, this disorder must be included in the differential diagnosis of "lymph node enlargement" because its course and treatment differ dramatically from those of lymphoma, tuberculosis, and SLE. The histologic differential diagnosis of KFD includes mainly reactive lesions such as lymphadenitis associated with SLE, lymphadenitis associated with herpes simplex and other microorganisms, non-Hodgkin lymphoma, plasmacytoid T-cell leukemia, Kawasaki disease, nodal colonization by acute myeloid leukemia, and even metastatic adenocarcinoma. **Table 2** provides clues to the differential diagnosis of KFD.[1,2,16-18,20,49,102,103]

SLE can be associated with lymphadenitis characterized by prominent foci of necrosis, mimicking the necrotizing type of KFD. Features that can be seen in SLE-associated lymphadenitis but not in KFD include hematoxylin-bodies, believed to represent degenerated nuclei that have reacted with antinuclear antibodies, and the Azzopardi phenomenon (ie, encrustation of blood vessel walls with nuclear material). Moreover, the finding of sparse cytotoxic T cells seems to tip the balance in favor of SLE-associated lymphadenitis, in contrast with the CD8+ lymphocyte abundance seen in lymph nodes in KFD.[78] These striking features might not be identified in every case of SLE-associated lymphadenitis, however, and the diagnosis cannot always be ruled out on histologic grounds alone.[16-18] Nevertheless, even though there is little information in the literature about lupus-associated lymphadenitis, its immunophenotype seems to be virtually identical to that of KFD, including the CD68+/MPO+ histiocytic pattern.[18,49] Finally, the presence of a large number of plasma cells in a given lymph node with features resembling those of KFD favors SLE-associated lymphadenitis over KFD.[20]

Herpes simplex–associated lymphadenitis can be characterized by histiocytic infiltrates and necrotic debris, findings that otherwise are characteristic of KFD. Yet, the histiocytic infiltrate usually is less striking than that in KFD, neutrophils often are observed, and the finding of viral inclusions confirms the diagnosis of herpes simplex–associated lymphadenitis. The immunophenotype of KFD might be similar to that of a viral lymphadenitis, but the findings in the latter are not specific.[18] Histiocytes from herpes

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Table 2
Clues to the Differential Diagnosis of Kikuchi-Fujimoto Disease

Condition	Clinical Features	Histologic Features	Immunohistochemical and Genetic Features
SLE-associated lymphadenopathy	Elevation of ANA titers; SLE features in the follow-up	Hematoxylin bodies; Azzopardi phenomenon; sparse CD8 T cells; abundance of plasma cells	
Herpes simplex–associated lymphadenopathy	Skin and mucous membranes have ulcerative lesions near sites of lymphadenopathy	Presence of neutrophils; viral inclusions; no striking polymorphous histiocytic infiltrate	Histiocytes MPO–
Non-Hodgkin lymphoma		No striking polymorphous histiocytic infiltrate; most T-cell lymphomas CD4+	Histiocytes MPO–; T-cell arrangement gene–positive
Plasmacytoid T-cell leukemia	Elderly men who have or will develop MML	Proliferation of PC-like cells; no striking polymorphous histiocytic infiltrate	PC-like cells MPO–
Kawasaki disease	Mostly children younger than 5 y; typical skin involvement	Geographic necrosis; fibrinoid thrombosis; no striking polymorphous histiocytic infiltrate; presence of neutrophils; PC absent or not prominent	
Nodal colonization by AML		No striking polymorphous histiocytic infiltrate; lacking CD8 T cells	CD34+; neutrophilic elastase–positive; HLA-DR+
Metastatic adenocarcinoma		Signet-ring cells containing mucin rather than nuclear debris	Presence of cytokeratin; absence of histiocyte-associated antigens
Infectious lymphadenitis		Occasional presence of granulomas; usual presence of polymorphonuclear leukocytes	Histiocytes MPO–

AML, acute myeloid leukemia; ANA, antinuclear antibodies; MML, myelomonocytic leukemia; MPO, myeloperoxidase; PC, plasmacytoid cells; SLE, systemic lupus erythematosus.

simplex–associated lymphadenopathy and other nonspecific reactive or granulomatous lymphadenopathies are MPO–, in contrast with the histiocytes in KFD, which are MPO+.[49]

Recognition of KFD is crucial, especially because it can be mistaken for malignant lymphoma.[1,16-18] The case of a patient misdiagnosed as having large-cell lymphoma and subjected to 1 course of cytotoxic therapy before histologic sections were submitted to an expert pathologist in consultation was mentioned in an editorial in 1987.[1] In fact, numerous immunoblasts can be found in tissue specimens from patients with KFD, raising the question of diffuse large-cell lymphoma. The common presence of atypia in the immunoblasts and their occasional occurrence in clusters and sheets might lead the unwary to an erroneous diagnosis of malignant lymphoma. This impression might be reinforced further by the admixed histiocytes with twisted nuclei, which can be misinterpreted as atypical lymphoid cells. The histiocytes, however, can be distinguished from lymphoid cells by their delicate nuclear membrane. In addition, polymerase chain reaction for T-cell gene rearrangement might be useful for differentiating KFD from peripheral T-cell lymphoma. In any case, the polymorphous background and mixture of histiocytes (which, peculiarly, are MPO+/CD68+,[49] in contrast with the MPO– staining of the histiocytes from malignant lymphoma) would be exceptional findings in this hematologic neoplasm. In countries in the Western hemisphere, most lymphomas are of B-cell lineage, and among T-cell lymphomas, CD4 expression is more common than CD8, whereas a predominance of CD8 positivity is characteristic of KFD.[18] Plasmacytoid cells also can facilitate a clear distinction of KFD, especially in the early stages of the disease, from a large cell or high-grade lymphoma.[47] Likewise, histologic findings of skin lesions from patients with KFD can mimic cutaneous malignant T-cell lymphoma.

Plasmacytoid T-cell leukemia—the so-called plasmacytoid monocyte tumor—is a rare clinicopathologic entity, mostly described in elderly men, which is characterized clinically by lymphadenopathy, hepatosplenomegaly, and weight loss. Affected lymph nodes display T-zone expansion by plasmacytoid-like cells, later developing acute or chronic myelomonocytic leukemia. Ruling out this condition can be straightforward because proliferative plasmacytoid cells do not express MPO, in contrast with the varied KFD histiocytic component that is strikingly MPO+.[49,51,104]

Because KFD might be associated with histiocytes resembling signet-ring cells, the so-called signet-ring histiocytes, the diagnosis of metastatic adenocarcinoma occasionally, although rarely, is considered.[16,18] Distinguishing these cells from signet-ring carcinoma cells can be a diagnostic challenge. However, metastatic adenocarcinoma is composed of cells with atypical nuclei and that contain mucin rather than cellular debris.

The histologic and immunohistochemical diagnostic challenges of KFD have been evidenced in a series of 25

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patients studied initially by referring pathologists in the United Kingdom.[105] The diagnosis of KFD was suspected by the referring pathologist in only 3 cases. The most common suggested diagnosis was non-Hodgkin lymphoma.

Clinical Course and Management

KFD typically is self-limited, and lasts 1 to 4 months. A low, but possible, recurrence rate of 3% to 4% has been reported.[1,2,16-18,35,106] A few cases have been described with recurrent disease during an 8- to 9-year period.[28,107] Only 3 fatal cases have been reported, occurring in the active phase of probably "genuine" KFD. One patient was a 38-year-old man with fever and generalized lymphadenopathy in whom an abrupt onset of heart failure developed, and he eventually died. Postmortem examination revealed that the heart was dilated and flabby, with multiple microscopic foci of necrosis and mild fatty changes.[108] Another case was that of a 19-month-old child who died unexpectedly after a febrile illness. On the necropsy study, typical histopathologic findings of KFD were seen in lymph nodes and extranodal sites.[21] Finally, fatal KFD also was reported in an Asiatic transplant recipient.[109]

There is no specific treatment for patients with KFD. However, because the disease is self-limited, only symptomatic treatment measures to relieve distressing local and systemic complaints should be used (ie, analgesics, antipyretics, and rest). The patient mentioned earlier (unpublished data) had a clinical course characterized by multiple flares of bulky cervical lymphadenopathy and fever. She eventually needed low-dose corticosteroid treatment to achieve clinical remission. Therefore, on the basis of some pathogenetic and immunologic considerations, one might argue, and there exists the possibility, that some patients with KFD with a more severe clinical course or with relapsing signs and symptoms could benefit temporarily from corticosteroids as other authors have pointed out.[110] Takada and coworkers[111] recently reported a case of KFD that dramatically resolved with oral minocycline treatment, suggesting that the causative agent of KFD might be especially sensitive to this antibiotic.

Conclusions

KFD is an extremely uncommon, self-limited, and perhaps underdiagnosed process of unknown cause with an excellent prognosis that seems to be more prevalent among Asiatic people. The clinical, histopathologic, and immunohistochemical features seem to point to a viral cause, an extreme that has not been proven. Recognition of this condition is crucial, especially because it can be mistaken for malignant lymphoma or, rarely, adenocarcinoma. Awareness of this disorder not only by clinicians but also by pathologists might help prevent misdiagnosis and inappropriate treatment. The diagnosis of KFD merits active consideration in any nodal biopsy showing fragmentation, necrosis, and karyorrhexis, especially in young people with posterior cervical lymphadenopathy.

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