Kikuchi-Fujimoto Disease

Is Epstein-Barr Virus the Culprit?

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A histologically distinct form of subacute necrotizing lymphadenitis was first described in Japan in 1972 by Kikuchi1 and independently by Fujimoto and colleagues.2 Although apparently more common in Asia, the disease has been reported in many areas of the world, including Europe, the United States, and Australia. The disease first described by Kikuchi1 and Fujimoto et al2 has been called Kikuchi disease, Kikuchi-Fujimoto disease, histiocytic necrotizing lymphadenitis, Kikuchi necrotizing lymphadenitis, phagocytic necrotizing lymphadenitis, subacute necrotizing lymphadenitis, and necrotizing lymphadenitis.

Kikuchi-Fujimoto disease (KFD) occurs most often in young women (mean age, 30 years; male/female ratio, 1:4).3 The most common clinical manifestation is cervical adenopathy with or without fever; additional findings may include fever, sore throat, weight loss, sweats, chills, myalgia, arthralgia, splenomegaly, and skin rash.3,4 Laboratory abnormalities may include leukopenia, an elevated serum transaminase level, and an elevated serum lactate dehydrogenase level.5 In almost all cases, the course is benign and followed by complete recovery within 1 to 3 months.6,7 Recurrence of disease may occur but is infrequent, and fatalities are exceptional.3,8-10

The typical nodal KFD lesion is paracortical and composed of patchy zones of eosinophilic fibrinoid necrosis with nuclear dust surrounded by a mixed lymphohistiocytic infiltrate composed of debris-laden macrophages, foamy histiocytes, immunoblasts, and atypical mononuclear cells with irregular twisted nuclei.3 Additional histologic findings useful for the differential diagnosis include the absence of granulocytes, the absence of granulomata and multinucleated giant cells, the rarity of plasma cells, and the presence of clusters of unusual “plasmacytoid” monocytes.3,11 Although originally described as plasmacytoid T cells,12,13 more recent immunophenotypic evidence indicates that these cells are most likely monocytic in origin.11,14 Immunohistochemical studies indicate that the lesions are composed primarily of CD15+ histiocytes, CD4+ T cells (in early stages), and CD8+ T cells (in late stages) with relatively few B cells and NK cells.3,5,15,16

In addition to the mature necrotizing lesion, 3 other lesions have been described: (1) an early proliferative lymphohistiocytic lesion with numerous atypical mononuclear cells, (2) a prenecrotizing phagocytic lesion with numerous histiocytes and single cell necrosis, and (3) a late postnecrotic xanthomatous (foamy cell) form.7,17 In 1 case of KFD, the first lymph node biopsy revealed a proliferative lesion, while a biopsy 1 month later revealed a necrotizing lesion.18 This illustrative case indicates that KFD may progress from an early proliferative phase to a necrotizing phase and, finally, to a xanthomatous (resolving) stage.

The numerous atypical mononuclear cells and immunoblasts characteristic of the early proliferative lymphohistiocytic lesion of KFD may lead to an erroneous diagnosis of malignant lymphoma.3,4 No association between KFD and malignant lymphoma has been reported. Features useful for distinguishing the proliferative KFD lesion from malignant lymphoma include incomplete architectural effacement with patent sinuses, intervening areas with a reactive “mottled” appearance, presence of numerous reactive histiocytes without a starry-sky pattern, and a relatively low mitotic rate.19

Several features of KFD suggest that the cause is likely to be infectious or autoimmune. The clinical manifestations of fever, chills, lymphadenitis, rash, arthralgia, and myalgia in young women is certainly suggestive of an infectious or autoimmune disease. Imamura et al19 first suggested that KFD might be a lupus-like autoimmune condition triggered by viral infection. Indeed, the histologic features of KFD in some cases may be difficult to distinguish from systemic lupus erythematosus (SLE)-associated lymphadenitis.3,20 Although at diagnosis KFD is not associated typically with
serologic evidence of autoimmune disease, in 2 cases reviewed by Dorfman and Berry, SLE subsequently developed and led to a recommendation that patients with KFD be observed carefully for development of SLE. A KFD-like lesion occurring in a patient with silicone lymphadenopathy suggested that KFD may represent a nonspecific autoimmune-like reaction. Several cases of KFD occurring in association with SLE have been described. Given the similarities of KFD lymphadenitis with lupus lymphadenitis, KFD-like lymphadenitis in the setting of SLE or another autoimmune process may simply represent an abnormal autoimmune reaction, as suggested by Sever et al.

Another plausible candidate for the cause of KFD is an infectious agent. The clinical manifestations of the disease resemble those of a subacute infection. Peripheral blood abnormalities noted in some cases (monocytosis, lymphocytosis, atypical lymphocytes, and neutropenia) are suggestive of a mononucleosis-like viral infection. The benign course and complete recovery seem more consistent with a self-limited infectious process than a lupus-like autoimmune condition. The histologic features are suggestive of an evolving infectious process with an initial lymphoproliferative phase, a slowly evolving necrotizing phase, and a final resolving xanthomatous phase. The histologic changes of KFD must be differentiated from infectious lymphadenitis due to Toxoplasma gondii, Yersinia enterocolitica, Bartonella henselae, Epstein-Barr virus (EBV), and HIV-1. Many features of KFD also are similar to that of EBV-associated hemophagocytic syndrome.

Special tissue stains for microorganisms, including Gram, Giemsa, periodic acid–Schiff, Ziehl-Neelsen, and Warthin-Starry are negative in KFD. A single case report describes a 36-year-old Indian man with histopathologic evidence of KFD and Y enterocolitica infection (positive indirect immunofluorescence but negative serologic results) whose condition slowly improved after antibiotic treatment, but 1 year later, he died of recurrent disease.

Serologic results have been reported inconsistently and in most cases do not indicate a specific cause. However, in some cases, serologic evidence of acute infection with Y enterocolitica, Toxoplasma organisms, parvovirus B19, HTLV-1, human herpesvirus (HHV) 6, 30 and EBV has been reported. However, the detection of a single increased titer to an infectious agent should be interpreted with great caution. Serologic titers to numerous ubiquitous infectious agents may be nonspecifically increased in some patients during unrelated illness. In some infections, such as EBV or hepatitis B virus infection, elevated antiviral titers may persist long after convalescence from primary infection. Truly relevant serologic results include detection of an elevated IgM titer or a 4-fold increase in the IgG titer occurring during the disease process.

More recently, the search for a causative infectious agent in KFD has used the highly sensitive and specific techniques of polymerase chain reaction (PCR) and in situ hybridization (ISH). HHV-6 was detected by ISH in a lymph node from a 37-year-old woman with KFD and SLE who also had serologic evidence of active HHV-6 infection. In a later report, HHV-6 DNA was detected in 26 of 27 cases of KFD by PCR and in 10 of 10 cases by ISH. However, since Southern blot results were negative and HHV-6 also was detected in reactive lymphoid tissue, the authors concluded that the role of HHV-6 in KFD was unclear. Two more recent studies failed to detect HHV-6 DNA in KFD by PCR. In the report by Chiu et al, no evidence of HTLV-1 infection by PCR or parvovirus B19 infection by immunostaining was obtained. Huh et al recently reported the presence of HHV-8 DNA in 6 (23%) of 26 cases of KFD by PCR, while 0 of 40 reactive tissues were positive. It is important that this intriguing result be confirmed independently by other investigators.

Arguably the most commonly detected infectious agent in KFD is EBV. Other studies have failed to detect EBV in KFD by PCR, ISH, or both. The study by Chiu et al is important since the authors used 3 independent techniques for the detection of EBV in tissue: (1) colorimetric EBV-encoded RNA (EBER) ISH, (2) EBV DNA PCR (EBV BamHIW repeat sequence), and (3) immunohistochemical staining with monoclonal antibodies against EBV latent membrane protein-1 (LMP-1), early antigen-diffuse (EA[D]), BZLF-1 replication activator (ZEBRA), and Epstein-Barr nuclear antigen-2 (EBNA-2). This highly sensitive strategy of probing for viral DNA, RNA, and protein is laudable. In the cases in which results of both DNA PCR and RNA ISH assays are positive (9 of 10 cases), one can safely conclude that the tissue contains EBV. The evaluation of EBV protein expression by immunohistochemistry allows for in situ detection of type II latent-infected (EBNA-2–positive and LMP-1–positive) and lytic-infected (BZLF-1–positive and EA[D]-positive) cells. The results presented by Chiu et al indicate that in only 1 case was lytic (EA[D]-positive and BZLF-1–positive) infection detected. In the remaining 9 cases, no EBV protein expression (including EBNA-2 and LMP-1) was detected, a result most consistent with type I latency.

If one assumes that EBER expression is present in most if not all forms of EBV infection, EBER ISH can be particularly useful by localizing infection to individual identifiable cells and by allowing an estimation of the degree of infection. The use of EBER ISH for identification of EBV infected cells led to the important discovery that EBV infects Reed-Sternberg cells in Hodgkin disease. In the case of KFD, by estimating the degree of infection, EBER ISH has had a major role in assessing the likelihood that EBV is an
important causative factor rather than an innocent bystander. For example, despite an EBV PCR detection rate of 55%, the low numbers of EBER ISH–positive cells contributed greatly to the conclusion by Hollingsworth et al36 that EBV is not likely to be an important causative agent in KFD. A similar argument was advanced in an earlier study in which, despite an EBV PCR positivity rate of 27%, the authors concluded that EBV is not actively involved in the pathogenesis of KFD since the number of EBER ISH–positive cells was low.41 Hollingsworth et al36 and Anagnostopoulos et al41 also make the important point that since EBV is detected commonly in reactive lymphoid tissues, detection of EBV in lesional tissues is not conclusive evidence that EBV is relevant to pathogenesis.

In the report by Chiu et al,38 although the number of EBER ISH–positive cells is not quantified rigorously, the authors make some important observations. The number of EBV-positive lymphocytes is maximal in the proliferative stage and steadily decreases through the necrotizing stage to the xanthomatous stage. Remarkably, as the number of EBER-positive lymphocytes declines, the number of CD68+ histiocytes containing ingested EBER-positive cells steadily increases as the disease progresses. These important observations seem to question the validity of basing judgments about the role of EBV in KFD on the number of EBV-infected cells within a given lesion.

Yen et al54 originally suggested that the presence of a limited number of EBV-infected cells in a given lesion of KFD should not exclude the possibility that EBV has an important role in some cases of KFD. In the face of the vigorous immune response so characteristic of KFD, the initial lymphoproliferative phase with increased numbers of EBV-infected lymphocytes would give way to the hyperimmune necrotizing phase with cytotoxic T lymphocyte–mediated killing of EBV-infected cells, engulfment by histiocytes, and, finally, the xanthomatous reparative phase. Biopsies in KFD are probably obtained most often during the necrotizing or xanthomatous phase, rather than the proliferative phase, by which time the offending agent is likely to be markedly reduced in number. The work by Chiu et al58 once again places EBV on center stage as a possible causative factor in Kikuchi-Fujimoto disease.

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References