

Kikuchi-Fujimoto disease

Histiocytic necrotizing lymphadenitis

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ABSTRACT

يعد مرض كيكوتشي فوجيموتو أو التهاب الغدة اللمفاوية الناخر من الأمراض الذاتية المحدودة، حيث أن مسببات هذا المرض معقدة وغير واضحة. يحاكي هذا المرض من الناحية السريرية والمجهريّة الأمراض اللمفاوية الخبيثة وغيرها من الأمراض غير الخبيثة. إن عملية التعرف على هذا المرض عملية بالغة في الأهمية لأن الخطأ في تشخيصه كمرض لمفاوي له عواقب سريرية كبيرة. وعلى الرغم من أن مرض كيكوتشي فوجيموتو يعد من الأمراض المعروفة في الأدب الطبي إلا أن كثير من الأطباء غير مدركين لوجوده. لقد قمنا في هذا المقال باستعراض حيثيات المرض مع التركيز بشكل خاص على المسببات والتشخيص التفريقي.

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a self-limited disease of complex and unclear etiology. Clinically and microscopically, it may mimic malignant lymphoma and other non-malignant diseases. Recognition of this entity is crucial, as mistaking this disease as lymphoma has major clinical consequences. Although KFD is a well-recognized entity in the literature, many clinicians and pathologists are still unaware of its existence. In this article, a review of KFD is provided with special emphasis on the pathogenesis and pathological differential diagnosis of this disease.

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Kikuchi-Fujimoto disease was first described in Japan by Kikuchi and Fujimoto in 1972,^{1,2} and has been called Kikuchi disease, necrotizing lymphadenitis, histiocytic necrotizing lymphadenitis, histiocytic necrotizing lymphadenitis without granulocytic infiltration, Kikuchi necrotizing lymphadenitis, subacute necrotizing lymphadenitis, and phagocytic necrotizing lymphadenitis. Its etiology is unknown, but it has been associated with many viruses,^{3,4} bacteria,^{5,6} and protozoal organisms.^{7,8} An autoimmune mechanism has also been suggested. In the literature, it is clear that KFD is one of the important mimic of lymphoma and other non-malignant diseases, and mistaken frequently with these diseases on clinical and pathological levels. The diagnostic difficulty in distinguishing KFD from lymphoma has been emphasized in many series and case reports, in which approximately 50% of the referring cases of KFD were initially referred with a diagnosis of lymphoma, or suggestive of lymphoma before being sent for consultation.^{9,10} The aim of this article is to review the literature on this disease with emphases on the differential diagnosis in our society, and to explore the possible etiology.

Epidemiology. A female predominance has been demonstrated initially, however, recent reports indicate that the female predominance was overemphasized, and the actual male to female ratio is close to 1:1.^{11,12} Kikuchi-Fujimoto disease is rare in children, however, it is well documented in the literature.¹³⁻²¹ The gender distribution in children seems to be different from adult with a reported male to female ratio of 1.8:1.¹⁶ Kikuchi-Fujimoto disease is originally thought to occur only in Asians, it is now recognized in many other geographic regions including North America,^{3,22-24} South America,²⁵⁻²⁷ Australia,²⁸ Africa,²⁹ and Europe.³⁰ However, it is still frequently reported in Asian countries including Japan, and considered rare in Europe and America.^{3,11,12,18,19,30} Kikuchi-Fujimoto disease has been described in the Kingdom of Saudi Arabia (KSA) as case reports and series. More than 60 cases have been

reported so far, including Saudi patients and other nationals,^{9,31-39} and it has also been described in many other Arab countries including Lebanon,⁴⁰ Egypt,⁴¹ Kuwait,⁴² Qatar,⁴³ Jordan,⁴⁴ and Tunisia.⁴⁵

Clinical features. Kikuchi-Fujimoto disease usually present as tender and painful cervical lymphadenopathy with fever. The onset is usually acute or subacute. Lymph node size has been found to range from 0.5-4 cm.⁴⁶ The common location of the lymphadenopathy is the neck, however, rarely it can affect other locations like the axilla,^{9,47-50} mediastinum,⁵¹ and retroperitoneum.⁵² Very rarely, KFD can present as generalized lymphadenopathy.⁵²⁻⁵⁵ Extranodal involvement by KFD is rare, but cutaneous involvement is well-documented in the literature.⁵⁶⁻⁵⁸ Fever is usually low-grade and present in approximately 50% of the patients, and is usually associated with upper respiratory symptoms. Usually, the fever subsides within one week, however, it may persist for months. Less frequent symptoms include nausea, vomiting, night sweat, fatigue, arthralgia, and weight loss.^{46,53,59} Hepatomegaly and splenomegaly are rarely seen in KFD.^{59,60} The disease course is usually spontaneously favorable in few weeks or months, and rarely requires corticosteroids therapy.^{11,60} Recurrence of the disease is rare.^{61,62} Laboratory findings in KFD include leucopenia (43%), high erythrocyte sedimentation rate (40%), and anemia (23%).⁶³

The patients described in KSA have similar clinical presentations where cervical lymphadenopathy represents the most common presenting feature, commonly associated with fever. A female predominance is clear in those cases reported in KSA with an overall male to female ratio of 1:2.3. The age range was between 13 and 50 years. Most of the patients recover without treatment with only 3 documented patients who evolved into systemic lupus erythematosus (SLE). The clinical features and the follow up of those patients are summarized in Table 1. In a study reported from Qatar, the age range was between 18 and 36 years with a female predominance.⁴³ The patients reported from the Arab countries have similar clinical presentation with fever and lymphadenopathies as the most common presenting features.⁴⁰⁻⁴⁵

Morphologic features. The lymph nodes involved by KFD are usually less than 4 cm in greatest dimension, although a larger lymph node up to 8 cm have been reported, and most commonly in children.^{16,64-66} Zuo et al¹⁶ reported that 5 out of 36 children with KFD have lymph node enlargement larger than 5 cm. The typical morphological appearance of lymph node involved by KFD is patchy paracortical involvement by necrosis (Figures 1a-1e) with variable proportions of benign C-shaped or crescentic histiocytes, transformed lymphocytes (immunoblasts), plasmacytoid dendritic

cells (plasmacytoid monocytes) and small lymphocytes surrounding the necrotic areas with variable amount of nuclear debris or apoptotic bodies (karyorrhexis). Classically, granulocytes are absent and plasma cells are either absent, or very scant. Kuo⁶⁷ proposed a histopathological classification of KFD that includes 3 forms: proliferative, necrotic, and xanthomatous. The most frequent form and accounts for more than 50% of the cases is the necrotic form. The least frequent form is the xanthomatous.^{67,68} According to Kuo,⁶⁷ KFD is characterized by sequential events that start with the proliferative form, and end by xanthomatous form, however, this remains as a speculation as there is no evidence in the form of serial lymph node evaluation that could indicate this sequence of changes. Recognition of the different forms of KFD is very important in the differential diagnosis as the proliferative form can closely mimic lymphoma, where the necrotic form frequently mimics SLE lymphadenitis (Figure 1f), and infectious process like tuberculosis.

Immunohistochemical profile. The immunohistochemical profile of KFD typically consists of a predominance of T-cells, with very few B-cells. There is a predominance of CD8-positive cells over CD4-positive cells (Figures 2a & 2b).^{46,60,69,70} It has been demonstrated that in KFD, it is predominantly CD8-positive cytotoxic T- cells that undergo apoptosis in the necrotic foci, however, most of the proliferating cells is also CD8-positive T-cells.⁷⁰ The histiocytes of KFD express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO), and CD68.^{71,72} Plasmacytoid dendritic cells (plasmacytoid monocytes) are positive for CD123, CD303, CD68, HLA-DR, CD4 and CD74, and are positively stained by the pan-macrophage monoclonal antibody Kim1P but negative for MPO, Fascin, a mature DC marker, as well as CD13 and CD33.^{69,73} Immunoblast cells in KFD-affected foci have the T-cytotoxic phenotype and are positive for CD8, T cell-restricted intracellular antigen-1 (TIA-1), CD3 and CD45RO.^{69,72} Some authors have observed B-cell clusters in some cases of KFD.⁶⁷ Immunostaining for the apoptosis-regulating proteins Bcl-2 and p53 are usually negative.⁹

Differential diagnosis. Kikuchi-Fujimoto disease must be included in the differential diagnosis of lymphadenopathy since its course and treatment is completely different from lymphoma and infectious diseases in particular, tuberculosis. The pathological differential diagnosis of KFD includes Hodgkin's and non-Hodgkin's lymphoma, myeloid leukemia, lupus lymphadenitis, tuberculosis, herpes simplex, Kawasaki's disease, and even metastatic carcinoma.^{74,75} In our society, the most important differential diagnosis includes lymphoma, SLE and tuberculosis.

Table 1 - Summary of previous studies that report Kikuchi-Fujimoto disease in the Kingdom of Saudi Arabia.

Author	Patients	Age (range of average)	Male/female	Lymph adenopathy (n)	Other symptoms (n)	Summary of clinical course
Amir et al ³¹	2	24-30	0:2	Cervical (2)	Fever (2)	Both patients recovered without sequelae. The 2 patients are non-twin sisters with identical human leukocyte antigen
Louis et al ³³	2	16-36	1:1	Cervical (2)	Fever (2)	Both patients recovered without sequelae
Al Salloum ³⁴	1	10	1:0	Cervical	Fever, loss of weight	A diagnosis of systemic lupus erythematosus (SLE) with lupus nephritis was made 2 months later
Sabir et al	1	29	0:1	Cervical	Fever	Patient recovered without sequelae
Al-Maghrabi et al ⁹	15	13-46	4:11	Cervical (14) Axillary (1)	Fever (15)	Patients recovered without sequelae after one to 10 years of follow up
Abba et al ³⁵	13	14-36	6:7	Cervical (10), Hilar (1), Axillary (1), Generalized (1)	Fever (8), loss of weight (1)	Patients recovered without sequelae after 6 months to 4 years of follow up. Four patients were lost to follow-up
Al-Nazer et al ³⁶	6	15-32	3:3	Cervical (10)	Fever (5), weight loss (2)	Patients recovered without sequelae after one to 12 years of follow up
Chavis et al ³⁷	1	32	0:1	Cervical (1)	Fever (1)	Concomitant lacrimal gland inflammation
El-Ramahi et al ³⁸	8	20-50	0:8	Cervical (8) Axillary (1)	Fever (7)	Two of the patients evolved into SLE The other patients recovered without sequelae
Al-Dousary et al ³⁹	6	22-35	1:5	Cervical (5) Axillary (1)	Fever (1), weight loss (1)	All 5 patients with available follow up recovered without sequelae after 4-6 months of follow up
Kutty et al ³²	5	30	2:3	Cervical (5)	Fever (5), weight loss (2)	Not available

Lymphoma. Kikuchi-Fujimoto disease must be differentiated from malignant lymphoma, either non-Hodgkin or Hodgkin, because both entities may share similar clinical presentations,⁷⁶ radiological,⁷⁷ and sometimes, pathological features.^{9,10,78} Recognition of this entity is crucial, because mistaking this disease as malignant lymphoma has major clinical consequences. In the literature, it is clear that KFD is commonly mistaken for malignant lymphoma, clinically and pathologically. It is interesting to know that KFD was not reported to be associated with increased risk of lymphoma with long periods of follow-up. Although KFD has been reported from most of the countries around the world, and almost 40 years has passed since it was first recognized, it is still continued to be a significant mimic of lymphoma.^{10,15,46,48,79} Immunoblasts proliferation and the presence of clusters of plasmacytoid dendritic cells could potentially mimic a large-cell lymphoma, especially peripheral T-cell lymphoma. This impression might be reinforced further by the admixed histiocytes with twisted nuclei, which can be misinterpreted as atypical lymphocytes.⁶⁹ The histiocytes, however, can be distinguished from lymphoid cells by their delicate nuclear membrane. In some cases, large transformed lymphocytes with immunoblasts morphology are markedly increased, in a background of karyorrhectic debris and scattered tangible-body macrophages, which resemble high-grade lymphoma.⁴⁶ The expansion of paracortex is usually present in both entities. Neutrophils

and eosinophils are characteristically absent, and plasma cells are scarce or absent in KFD.^{12,46,69,79}

The pathological diagnostic challenges of KFD have been evidenced in a series reported by Menasce et al,⁸⁰ where only 3 out of 25 patients with KFD have been diagnosed correctly by the initial refereeing pathologists. The most common suspected diagnosis was non-Hodgkin's lymphoma including T-cell lymphoma, high-grade lymphoma (immunoblastic and histiocytic) and malignant lymphoma, not otherwise specified. Hodgkin's lymphoma was suggested in 4 cases of that series. Patients misdiagnosed as having lymphoma can be subjected to unnecessary cytotoxic therapy.⁶⁹ In our previous study,⁹ we showed that 3 of 4 cases sent to our institution for consultation had been misdiagnosed initially as lymphoma, or identified as suggestive of lymphoma.

Morphological features that favor KFD over lymphoma are the patchy nonexpansile distribution of the lesions with incomplete architectural effacement with patent sinuses, abundance of karyorrhectic debris, presence of admixed medium-sized cells with round nuclei (plasmacytoid dendritic cells), numerous reactive histiocytes without a starry-sky pattern, relatively low mitotic rate, and presence of intervening areas with reactive appearance.^{75,79} Kikuchi-Fujimoto disease may mimic Classic Hodgkin lymphoma because both could cause necrosis and have histiocytic infiltrate.^{10,46,81} However, the presence of large Reed-Sternberg cells

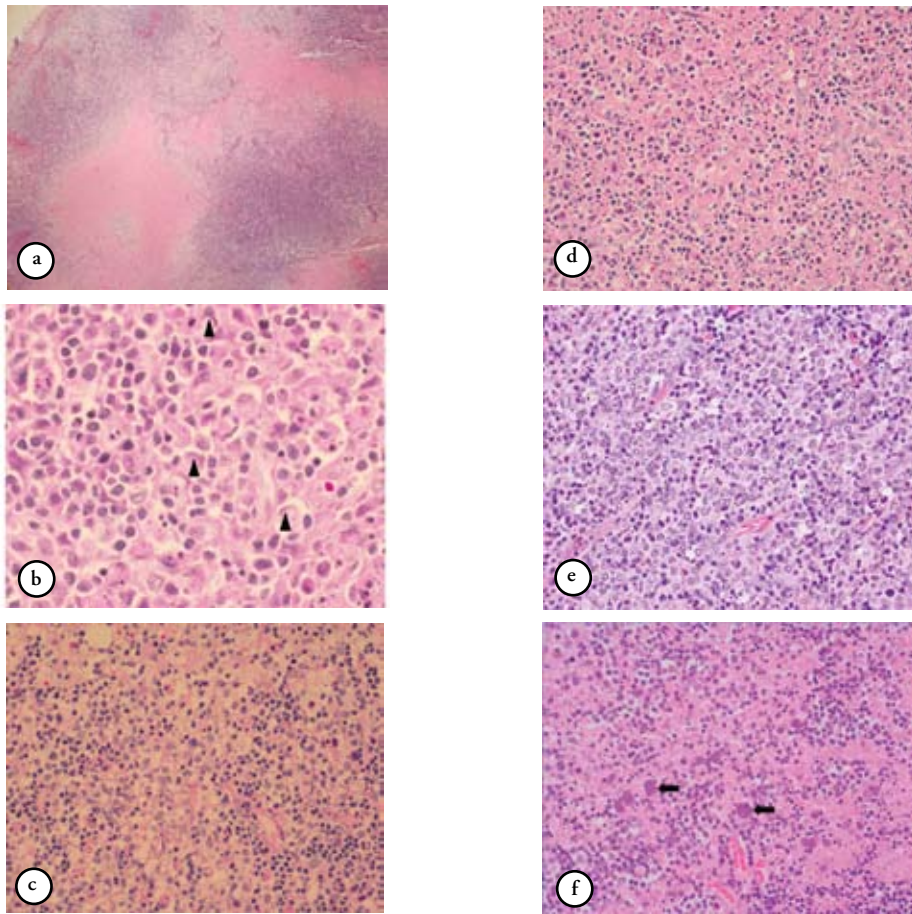


Figure 1 - Lymph node involved by Kikuchi-Fujimoto disease (KFD) showing: a) low power shows patchy necrotizing areas in the paracortical region (hematoxylin-eosin [HE], original magnification x100); b) necrotic form of KFD. Higher power shows the lesion composed of mononuclear cells associated with characteristic karyorrhectic debris (arrow heads) (HE, original magnification x200); c) necrotic form of KFD. High power shows karyorrhectic debris and numerous histiocytes, some of them have crescentic nuclei; (HE, original magnification x400); d) a proliferative form of KFD. High power shows proliferative pattern of KFD with numerous transformed lymphocytes (immunoblasts) and plasmacytoid monocytes with some characteristic karyorrhectic debris. This pattern mimics large cell lymphoma. Immunohistochemistry study and PCR for T-cell receptor clonality were used in this case to support the diagnosis of KFD and rule out lymphoma (HE, original magnification x400); e) a xanthomatous form of KFD. High power shows mainly histiocytes, some with xanthomatous appearance associated with some karyorrhectic debris (HE, original magnification x400). f) lymph node involved by lupus lymphadenitis reveals similar necrosis with karyorrhectic debris; however, there are many hematoxylin-bodies (arrows) which favor the diagnosis of SLE (HE, original magnification x400)

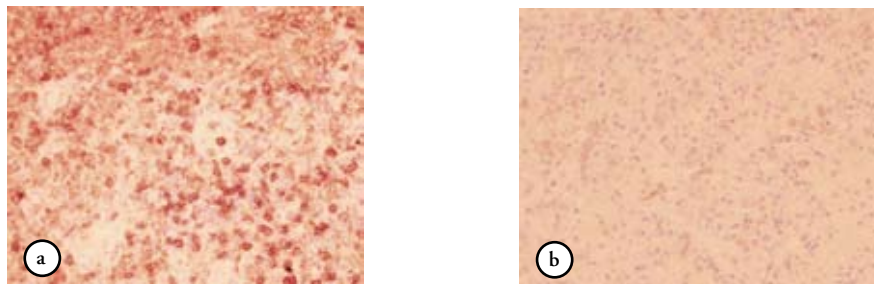


Figure 2 - Lymph node involved by Kikuchi-Fujimoto disease showing: a) immunohistochemistry stain for CD8 reveals many positive cells (original magnification x400); b) immunohistochemistry stain for CD4 reveals only few positive cells (original magnification x400).

or variants, and numerous eosinophils, as well as neutrophils, are very helpful to diagnose Hodgkin's lymphoma.⁴⁶

Immunohistochemistry study is helpful to support the diagnosis of KFD. In T-cell lymphomas, CD4 expression is more common than CD8, whereas a predominance of CD8-positivity is typical of KFD. In addition, the histiocytes in KFD are MPO-positive/CD68-positive, which is in contrast with the MPO-negative staining of the histiocytes from malignant lymphoma.⁷⁴ 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. The Ki-M1P detects plasmacytoid cells, and was found to be a reliable delineation of these cells against other similar cell types, such as blasts of high-grade B- and T-cell lymphoma.⁸² Lack of expression of B-cell markers including CD20, CD79a or PAX5 within the large-cell population would make a lymphoma of B-cell lineage unlikely. The absence of large Reed-Sternberg cells or variants, which are stained with CD15 and CD30, is helpful to differentiate from Hodgkin's lymphoma.

In difficult cases, ancillary test such as flow cytometry and molecular study by polymerase chain (PCR) reaction for T-cell gene rearrangement might be useful for differentiating KFD from T-cell lymphoma. Absence of a monoclonal T-cell receptor rearrangement excludes the possibility of T-cell lymphoma, and supports the diagnosis of KFD.⁸³

Recently, radiological ultrasonographic characteristics that help to differentiate the 2 entities have been proposed.⁸⁴ Cervical lymphadenopathies in patients with KFD tend to have smaller size, less round, less micronodular reticular echotexture, and more signs of matting and cortical widening than those with lymphoma.⁸⁴

Tuberculosis. Kikuchi-Fujimoto disease can mimic clinically, radiologically, and pathologically tuberculosis.^{22,27,85-91} Many cases of KFD have been initially misdiagnosed as tuberculosis and treated with antituberculous medications.^{85,86} On the other hand, there are cases that have been called and treated as KFD and found to be tuberculosis on review diagnosis, and confirmed by the presence of acid-fast bacilli and Ziehl-Nielsen.⁹² However, the association between KFD and TB has been reported as well.⁹³

Tuberculosis commonly affects cervical lymph nodes. The typical features of tuberculous lymphadenitis include necrotizing (caseating) inflammation associated with epithelioid granulomata. Tuberculosis in its classic form with the epithelioid granulomata and multinucleated giant cells are relatively straightforward diagnosis. However, in non-reactive tuberculosis, microscopically there are large areas of necrosis not typical of caseation,

but often contain nuclear debris, fibrin, and red blood cells, and usually surrounded by poorly defined zone of macrophages. Usually there are no granulomata or multinucleated giant cells in this pattern of TB. Confirmation of the diagnosis is by demonstration of *Mycobacterium tuberculosis* (acid-fast bacilli) by stain or culture.

In our previous study, we reported a case of KFD referred to our institution that has been initially misdiagnosed as TB. Al-Dousary et al⁹⁴ reported that 4 out of 6 cases of KFD have been initially clinically diagnosed as tuberculous lymphadenitis. Tuberculin tests in most of the reported cases of KFD in KSA are negative.^{32,33} In KSA where TB is endemic, biopsy of lymph nodes with extensive areas of necrosis should be interpreted very carefully as TB is the most common cause of lymph node necrosis in this area of the world. Special stains for acid-fast bacilli should be carried out on any necrotizing lymphadenitis even if it is not associated with granulomata to avoid missing the non-reactive form of TB. Other typical microscopic features of KFD will be sufficient in most of the time to avoid misdiagnosis with TB.⁹

Systemic lupus erythematosus. Systemic lupus erythematosus represents one of the most challenging differential diagnosis of KFD. The KFD and SLE can have similar clinical presentation with fever and lymphadenopathy. Involved lymph nodes in KFD and SLE have common morphological features, and sometimes very difficult if not impossible to differentiate between them on histological bases alone.^{54,63,90,95-98} Involved lymph nodes in both diseases show classically the non-neutrophilic necrotizing lymphadenitis with paracortical necrosis with karyorrhectic debris and inflammatory cell response, including histiocytic infiltrate. Microscopic features that favor lupus lymphadenitis include: the presence of hematoxylin-bodies (Figure 1f), which most likely represent degenerated nuclei that have reacted with antinuclear antibodies, thrombosed blood vessels, the presence of plasma cells and the presence of basophilic necrotic material in blood vessels wall (Azzopardi phenomena). Immunohistochemistry can help by demonstrating predominance of CD8-positive cells in KFD, while they are usually very sparse in SLE.^{99,100} Even in the absence of the above features that favor SLE, clinicians should be notified of this possibility, and exclusion of SLE clinically is recommended to prevent delay in the treatment. Clinical evaluation of the patients should include careful clinical history, examination, and laboratory investigation data, including evaluation of antinuclear antibodies and complement levels (C3 and C4).^{11,57,63,96,101,102}

In addition to resembling SLE, KFD has been reported to be associated with SLE. Kikuchi-Fujimoto

disease may occur in patients with pre-existing SLE,^{54,101} may occur simultaneously with SLE,^{63,89,95,103,104} or evolve into SLE.^{11,57} Systemic lupus erythematosus was found to be associated with KFD more frequently in patients from Asia than Europe.⁶³ Patients with KFD should be followed clinically mainly because of the increased risk of evolvement into SLE but not into lymphoma.

Etiology and pathogenesis. The etiology of KFD is complex and still is not clear, however, many features of KFD suggest that the most likely cause of KFD is infectious or autoimmune. Some authors suggest that KFD may be an autoimmune disease that is triggered by a viral infection.^{105,106} Many viruses have been incriminated in the pathogenesis of KFD including Epstein-Barr virus (EBV), human immunodeficiency virus (HIV-1), parvovirus B19, human T-cell lymphotropic virus (HTLV-1), human herpes viruses (HHV6, HHV-7, HHV-8).^{3,16,66,107-115} Recent studies that discussed the possible role of viruses in the pathogenesis of KFD is summarized in Table 2.

From these studies it seems that EBV is the most commonly detected virus in KFD, however, there are conflicting data regarding the role of EBV in the pathogenesis of KFD. There are studies that support this involvement,^{3,4,16,66,107-109} and there are conflicting data.¹¹¹⁻¹¹³ Different sensitive techniques have been used for detection of viruses in KFD including PCR, in situ hybridization (ISH), and immunohistochemistry (IHC). The EBV was detected in KFD in more than 50% of the cases by many authors using PCR or ISH, or both.^{3,66,107} Although EBV has been detected frequently in KFD, some authors suggest that EBV is not likely to be an important etiologic agent in the pathogenesis of KFD because of the low numbers of Epstein-Barr virus-encoded RNA (EBER) ISH-positive cells detected in KFD.^{116,117} It has been demonstrated that EBER ISH-positive cells are usually more in the early proliferative phase of the disease, and steadily decrease through the necrotizing to the late xanthomatous stage,¹⁰⁷ which may explain the low number of EBER ISH-positive cells

Table 2 - Summary of viruses that are reported in association with Kikuchi-Fujimoto disease.

Author	Technique	Virus	Result
Chiu et al ¹⁰⁷	PCR, ISH	EBV	Detected in 10 out of 10 patients
		HTLV-1	Not detected in any of 10 patients
		Parvovirus B19	Not detected in any of 10 patients
Kim et al ¹⁰⁸	ISH	EBV	Detected in 8 out of 35 (22.9%) of patients
Zou et al ¹⁶	IHC	EBV	Detected in 2 out of 36 patients
		HSV-2	Detected in 1 out of 36 patients
Hudnall et al ³	PCR, ISH, IHC	EBV	Detected in 18 out of 30 patients by PCR, 10 out of 30 by ISH, and in 1/30 by IHC
		HHV-6	Detected in 2 out of 30 patients
		HHV-7	Detected in 3 out of 30 patients
		CMV	Detected in 1 out of 30 patients
		HSV-1	Not detected
		HSV-2	Detected in 1 out of 30 patients
Maeda et al ¹⁰⁹	PCR	EBV	Detected in 6 out of 20 cases (30%)
		HHV-6	Detected in 3 out of 20 patients
		HHV-7	Detected in 2 out of 20 patients
		HHV-8	Not detected in any of 20 patients
		CMV	Not detected in any of 20 patients
Stephan et al ⁶⁶	PCR, ISH	EBV	Detected in 2 out of 2 patients by ISH and PCR
George et al ¹¹¹	ISH, PCR	EBV	Detected in 2 out of 24 cases by ISH
		HHV-8	Not detected in any of 29 patients
Vassallo et al ¹¹³	ISH	EBV	Not detected by ISH in one patient
Krueger et al ¹¹⁴	ISH	HHV-6	Detected in 12 out of 14 (87.5%) patients
Cho et al ⁴	PCR, IHC	HHV-6	Detected in 21 out of 50 (42%) patients, and in 8 out 20 (40%) control samples
		HHV-7	Detected in 32 out of 50 (64%) patients, and in 9 out 20 (45%) control samples
		HHV-8	Detected in 3 out of 50 (6%) patients
Zhang et al ¹¹⁵	PCR, ISH, IHC	Parvovirus B19	Detected in 87.1% by PCR, 69.7% by ISH, and 57.6% by IHC of patients, and only in 56.3% by PCR, 31.3% by ISH, and 25% by IHC of control samples by the respective methods

PCR - polymerase chain reaction, ISH - in situ hybridization, EBV - Epstein-Barr virus, IHC - immunohistochemistry, HSV - herpes simplex virus, HHV - human herpes virus, CMV - cytomegalovirus, HTLV - human T-cell lymphotropic virus

in KFD because necrotizing stage is the most common stage, at which KFD is usually diagnosed.

By evaluating EBV DNA by PCR and ISH in patients with KFD from UK, USA, and KSA, Hudnall et al³ demonstrated that EBV DNA-positivity was significantly greater in KFD cases from the US (80%), and UK (75%) as compared with cases from KSA (33%), and suggested that this either reflect that EBV is more commonly associated with KFD in the US and UK than in KSA, or it may reflect a geographical difference in the rate of lymph node EBV-positivity in the general population.

Although HHV-6 was detected and suggested to play a role in the pathogenesis of KFD by some authors,^{114,118} most of the studies tested HHV-6 in KFD, and compared that with reactive lymph node controls concluded that is unlikely to be involved in the pathogenesis of KFD.^{3,4,109}

All the other viruses that have been tested in KFD include HIV-1, parvovirus B19, HTLV-1, HHV-7, HHV-8, hepatitis B virus, varicella zoster, HSV-1 and HSV-2 are also very unlikely to play any significant role in the pathogenesis of KFD. They have been reported in KFD either as serological positivity, which is non-specific or in few cases, which are not different from the detection rate in negative control cases, and represent most likely coincidental findings rather than true association. Kikuchi-Fujimoto disease has also been described in association with different diseases and disorders, such as hemophagocytic syndrome,¹¹⁹⁻¹²¹ psoriasis vulgaris,¹²² antiphospholipid syndrome,¹²³ aseptic meningitis,¹²⁴ parotiditis,¹²⁵ subdural hematoma,²² MFH,¹²⁶ papillary conjunctivitis,¹²⁷ pyomyositis,¹²⁸ arthritis,¹²⁹ bilateral anterior uveitis,¹³⁰ cerebellar ataxia,¹³¹ Still's disease,¹³² Sjögren's syndrome,¹³³ Well's syndrome,¹³⁴ and with some non-viral infections like *Brucella melitensis* infection,⁵ *Toxoplasma gondii* infection,¹³⁵ and *Giardia lamblia* intestinalis.⁷ However, this association remains at the level of case reports with no documented pathogenetic link.

It is known that KFD is frequently reported in Asian countries including Japan, however, it is rare in Europe and North America. Tanaka et al¹³⁶ found DPA1*01, and DPB1*0202 allele frequencies are significantly higher in KFD patients than in normal controls. The frequency of DPB1*0202 alleles is known to be extremely low or absent in Caucasians (for example: French [0.4%]; Italian [0.8%]); and Negroid, but relatively frequent in Asians (for example: Korean [9.9%]; and Japanese [4.5%]).¹³⁶ They concluded that KFD may have a positive relation to this allele.

In conclusion, EBV may play a role in the pathogenesis of KFD at least in a subset of cases. It is also possible that triggering infection may induce

autoimmune reaction. So it seems that combination infection and immunoreactions are the most likely pathogenetic pathway in KFD. Susceptibility for the disease may be influenced by HLA allele.

Clinical course and management. Kikuchi-Fujimoto disease is typically self-limited disease, usually resolve within one to 4 months, but a recurrence rate of 3-13% has been reported.^{11,62} Compared to non-recurrent cases, recurrent cases were reported to have more extranodal involvement, and remained symptomatic for a rather longer duration.⁶² Less than 3% of the patients will evolve into SLE some years later.^{11,62} No risk to other family members,¹³⁷ but KFD has been reported in 2 human leukocyte antigen-identical non-twin sisters.³¹ Although KFD has a benign course, rare fatal cases have been reported.^{103,138} There is no specific treatment for patients with KFD. Only symptomatic measures to relieve distressing local and systemic complaints should be used, which include analgesics and antipyretics. Corticosteroids have been used in severe, relapse, and recurrent cases, and found to be effective.^{16,59,60}

In conclusion, KFD is rare, self-limited, and perhaps under-diagnosed process of unclear etiology with an excellent prognosis that seems to be more prevalent among Asian people. The disease should be considered in the differential diagnosis of cervical lymphadenopathy with fever, and in any excised lymph node with non-granulomatous, non-neutrophilic necrotizing lymphadenitis. The diagnosis is made only by identifying characteristic pathologic features from involved tissue. A hyper-immune reaction of immune cells to EBV is most probably involved in the pathogenesis of KFD. Awareness of this disorder by clinicians and pathologists is crucial to avoid misdiagnosis and inappropriate treatment. The disease is well-documented in KSA, and described among Saudi and non-Saudi nationals. Second opinion of the pathology specimens is very important to avoid misdiagnosis of this entity. Patients with KFD do not carry increased risk of lymphoma, however, some of them may progress to SLE or other autoimmune diseases, and that is why KFD patients need clinical follow-up.

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