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Kikuchi-Fujimoto's Disease: A Rare and Underdiagnosed Condition with Possible Renal Involvement

In depth review

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ABSTRACT
Kikuchi-Fujimoto disease (KFD), or Histiocytic Necrotizing Lymphadenitis, is a rare disease, with worldwide distribution but is best known in Japan and South Asia. The most common feature is cervical lymphadenopathy, accompanied by tenderness or high fever, with night sweats, but it can also be asymptomatic or with a very wide range of symptoms. The diagnosis is histopathological, on excisional biopsy. The Kikuchi-Fujmoto disease can mimic lymphoma but also tuberculosis and some autoimmune diseases, or be associated with them. Nephrologists need to be aware of it, considering the potential renal involvement. The association with systemic lupus erythematosus (SLE) is the most frequent but not the only one. Early diagnosis of this disease can prevent unnecessary investigations and aggressive therapies.

KEYWORDS: Kikuchi-Fujimoto disease, Histiocytic Necrotizing Lymphadenitis, renal involvement, autoimmune disease, excisional biopsy, differential diagnosis

Introduction

The Kikuchi-Fujimoto disease is a rare condition [1] discovered in 1972 by Kikuchi and Fujimoto and is also known as histiocytic necrotizing lymphadenitis. It has a worldwide distribution but is more prevalent in Japan and Asia, with isolated cases in Europe and the USA, often because it is undiagnosed. Any age can be affected; the reported cases are between 6 years and 85 years old, most often young adults under 30, with a previously overestimated female preponderance by a 4:1 ratio, but the actual ratio is about 1:1 [1]. The etiology is not clear; a viral or autoimmune cause has been suggested. The contribution of genetic or environmental factors to the development of Kikuchi-Fujimoto disease remains unclear too. KFD associated with connective tissue disease, especially systemic lupus erythematosus (SLE), causes an exacerbation of the patient's symptoms, requiring treatment, and also reports cases with serious, potentially life-threatening sequelae.

Etiopathogenesis

This rare disease has an unclear etiology; both the role of infection as a trigger of lymphadenopathy and the possible autoimmune etiology are still debated. There are many pathogens associated with cases of KFD, the most frequently involved are herpes virus 6, EBV, and Toxoplasma gondii, but also Brucellosis, Bartonella henselae, Entamoeba histolytica, Yersinia enterocolitica, Parvovirus B19, Mycobacterium szulgai, and HTLV 1 [2]. KFD has also been found to be associated with Covid 19 infection [3, 4]. It is also true that KFD is often not related to any type of infection. A differential diagnosis of lymphadenopathy with many conditions is very important to avoid misdiagnosis of KFD (Table 1), as this has happened in the past when patients have received chemotherapy or tuberculosis treatments, so it is important for the histologist not to confuse KFD with lymphoma or something else.

Non-Hodgkin lymphoma	Toxoplasmosis
Hodgkin lymphoma	Turalemia
Metastatic carcinoma	Epstein–Barr virus
Herpes simplex virus	Cytomegalovirus
Group A streptococcus infection	Mycobacterium tuberculosis
Staphlyococcus aureus infection	Cat scratch disease (Bartonella henselae)
Lymphadenitis of SLE	HIV 1 and 2
Parvovirus	Sarcoidosis
Reactive Lympahadenitis in local infection	Syphilis
Kaposi 's Sarcoma	Atypycal Mycobatteriosis
Kawasaki Disease	Leprosy

Table 1. Etiological differences of lymphadenopathies.

SLE is the most common autoimmune disease in connection with Kikuchi but not the only one, KFD is fund also associated with: Polymyositis, Scleroderma, Still's disease, Rheumatoid Arthritis, Hashimoto Thyroiditis, and Sjogren's Syndrome; Lymphoma can also be associated with KFD. It has also been identified in the presence of a silicone implant and after vaccinations: in 2022, has been reported also the first case of KFD related to the BNT162b2 mRNA COVID-19 vaccine and the concomitant onset of hemophagocytic lymphohistiocytosis and Kikuchi disease [5].

Clinical manifestations

Tender cervical, unilateral or bilateral lymphadenopathy, located in the posterior cervical triangle, is the most common feature of KFD (56-98%). The enlarged lymph nodes range from 0.5 cm to 4 cm in diameter, rarely up to 6 cm [1]. Lymphadenopathy is reported as painful in about 50% of cases and generalized lymphadenopathy may be found in 1-22%; although rarely, it can be localized in the peritoneal or retroperitoneal and mediastinal area. Right hilar, axillary lymphadenopathy is also reported, as well as in the pelvic region. KFD is a cause of prolonged fever of unknown origin; fever is present in 30% to 50% of the cases and, it is associated with frequent upper respiratory symptoms and odynophagia. Less common symptoms include nausea, vomiting, headaches, arthralgia, weight loss, night sweats, and fatigue during the latter parts of the day. It is also possible that skin involvement of the face, upper limbs, and trunk may precede or accompany lymphadenopathy. The skin lesions can be of various types: urticaria, plaques, nodules, rash, and papules. In case the lesions persist skin biopsy is mandatory to rule out associated vasculitis or otherwise. Hepatosplenomegaly is rare. Nervous system involvement is also rare but possible as encephalitis, acute cerebellar ataxia, and septic meningitis.

KFD can involve heart and lungs, eyes with panuveitis, and impairment of visual acuity, although rarely. Kidney involvement is also possible, in both in the condition of multiorgan extranodal involvement and as direct damage, often not documented by renal biopsy, or it is associated with a subsequent concurrent diagnosis of SLE. Cases have been reported of KFD associated with ADPKD [6], acute pyelonephritis, and antiphospholipid syndrome. The renal involvement has been seen as either glomerular: podocyte damage or tubular damage alone or together. Activation of histiocytes by KFD may result in acute renal failure due to acute tubular necrosis and also nephrotic syndrome due to podocyte damage. There is also an association between KFD and Hemolytic Uremic Syndrome [7] with severe renal involvement confirmed by renal biopsy with diffuse endothelial damage, and arteriolar lumen obstruction, resulting in complete ischemia of the glomeruli.

Diagnosis

- **Laboratory test.** To date, there is no specific laboratory test that aids in the diagnosis. Leukopenia is present in 30-70% of cases. Other nonspecific abnormal laboratory tests are increased erythrocyte sedimentation rate with low C-reactive protein in 30-50% of cases, anemia, and atypical peripheral blood lymphocytes, and serum hepatic transaminase activities and lactate dehydrogenase levels are also often increased. A high antinuclear antibody titer can also be The presence of ANAs and anti-DNA antibodies is significantly associated with the development of SLE.
- **Radiological Investigations**. There are no radiological or ultrasound characteristics that could lead to the diagnosis. Chest Rx should always be performed to rule out tuberculosis or malignancy; CT and ultrasound are always performed but there are no imaging features that can lead to the final diagnosis, so they are important in guiding lymph node biopsy.

- **Histopathology.** Surgical consultation is indicated for a diagnostic excisional lymph node biopsy. Excisional biopsy is the gold standard to arrive at the diagnosis of KSD while FNAC alone has an estimated diagnostic accuracy of about 56.3%. It is important for an experienced histologist not to confuse the histology of KSD with lymphoma or anything else. In KFD the lymph nodes demonstrate paracortical areas of apoptotic necrosis with plasmacytoid dendritic cells, karyorrhectic debris, the proliferation of histiocytes, and CD8(+) T cells but no neutrophils and infrequent B cells, no presence of Reed-Sternberg cells, relatively low mitotic rates. Three phases of evolution are found in the histology of KFD: the proliferative phase, followed by the necrotized phase, and finally the xanthomatous phase [2]. The positivity of CD8 cells highlights their role as effector and target cells, while very abundant histiocytes are enhancers; the consequent abundant apoptosis that occurs induces the necrotizing lesions.
- The differential diagnosis between KFD and lymphoma is not difficult even if in the early stages of the disease the absence of necrosis and the abundant immunoblasts can lead to an erroneous diagnosis of lymphoma. The differential diagnosis with lymphoma is found in KFD: absence of Reed-Sternberg cells, incomplete architectural obliteration with patent sinuses, the presence of numerous reactive histiocytes, and relatively low mitotic rates. It could be difficult a differential diagnosis between KFD and SLE lymphadenitis, both can have similar clinical and histological findings. KFD often is in association with SLE; KFD may precede, occur concurrently, or follow the diagnosis of SLE, in this case, it is important to check C3, C4, anti-Sm, and LE cells to rule out SLE. Of course, the finding of lymph nodes with necrosis must rule out tuberculosis lymphadenitis, particularly in those areas of the world where it is still very frequent. In favor of the diagnosis of tuberculosis, we find granulomas with epithelioid cells and Langerhans cells, and the presence of caseous necrosis while we do not find karyorrhectic debris as in KFD. The investigation must always be completed with the search, in all cases, for special stains for acid-fast bacilli.

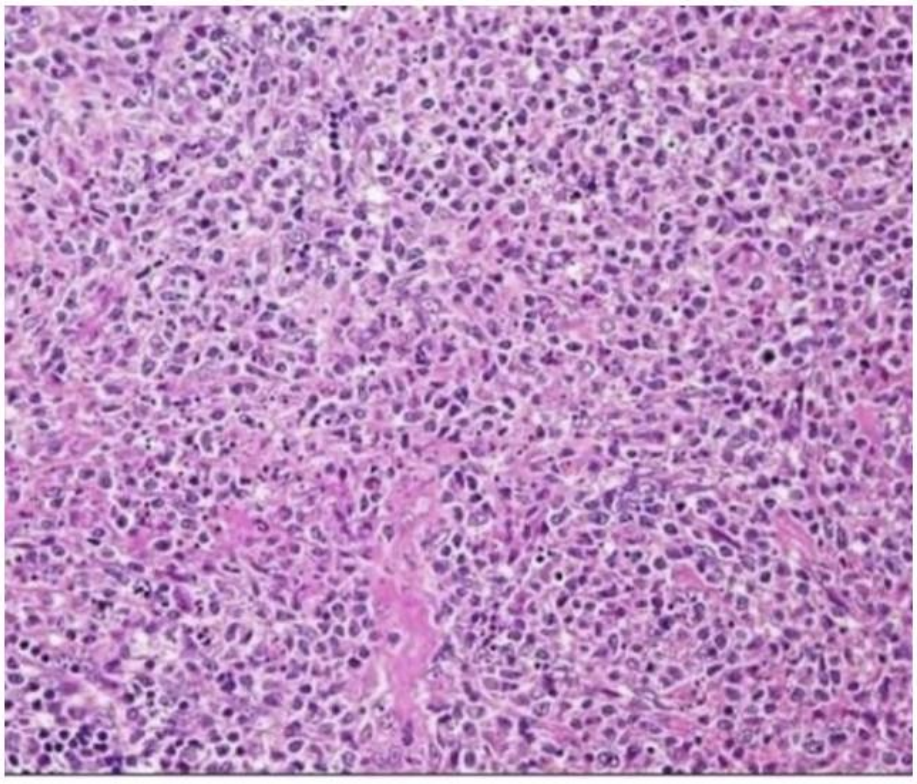

Figure 1. From excisional lymph node biopsy is visible abundant histiocytosis and necrosis [8].

Prognosis

KFD is a benign, self-limiting disease, typically resolved within a few weeks to months. Its persistence in chronic is rare; there is, however, the possibility of recurrence in 3-4% of cases, the reappearance of the disease can occur from a few months up to 16-18 years from the first manifestation. The overall prognosis is good, with extremely rare complications such as Hemophagocytic lymphohistiocytosis (HLH). Although it is a self-limiting disease, a long-term follow-up, even for years, is very important, due to the possible appearance of an autoimmune disease. The most frequent is SLE, which has been reported to manifest from a few months to a few years after the onset of Kikuchi lymphadenopathy. Mortality is very rare but is possible when there is extranodal involvement, in particular when the kidney or the heart is involved due to necrosis or the lung is involved due to pulmonary hemorrhage; otherwise, mortality can be due to disseminated intravascular coagulopathy.

Therapy

There are no guidelines for the therapy of KFD. Asymptomatic patients are often not treated with pharmacological therapy but observed over time, ruling out association with autoimmune disease. When KFD is symptomatic, there is, generally, a benefit to nonsteroidal anti-inflammatory therapy. However, patients with atypical and refractory symptoms may require steroid therapy.

Hydroxychloroquine is also prescribed, it interferes in complement-dependent antigen-antibody reactions, and inhibits neutrophil transport and eosinophil chemotaxis. It also described the prescription of intravenous immunoglobulins, Anankira, in cases of steroid resistance.

Conclusions

Although rare, KFD is underdiagnosed, particularly in Europe, due to mixed non-specific symptoms at presentation and a lack of knowledge among general practitioners and specialists. It must be present in the cultural background of nephrologists, to be able to make differential diagnoses in patients with nephropathy presenting with fever of unknown etiology and cervical lymphadenopathy. This is particularly crucial in patients of Asian origin and those who are immunosuppressed, which the nephrologist is used to managing. At the moment there are very few nephrological reports of KFD in the literature, partly due to the many missed diagnoses.

Many questions still have incomplete answers: the role of infections in Kikuchi-Fujimoto disease is not known, just as the relationship between Kikuchi-Fujimoto disease and autoimmune diseases. Autoimmune diseases are often present at the time of diagnosis or may appear months or years later. Therapy also remains an open discussion: whether and when to treat with steroids and whether antibiotic therapy has any real benefit. The gold standard for diagnosis is lymph node histology with excision biopsy. A multidisciplinary clinical approach is important to achieve an early diagnosis of KFD and avoid inadequate and aggressive therapy.

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