Kikuchi-Fujimoto disease: a clinicopathologic update

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Key words

Kikuchi-Fujimoto disease • Histiocytic necrotizing lymphadenitis • Cervical adenopathy • Fever

Summary

Kikuchi-Fujimoto disease (KFD), also known as “histiocytic necrotizing lymphadenitis”, is a rare lymphadenitis of unknown origin, but with an excellent prognosis. It is more common in Asia, but isolated cases are also reported in America, Africa and Europe. The disease can have an acute or subacute course, usually develops in 1 to 3 weeks, with spontaneous resolution in 1-4 months. The main clinical sign is cervical lymphadenopathy, especially in the posterior cervical triangle with bulky and painful lymph nodes, usually affecting only one side; rare cases of generalized lymphadenopathy can be seen. This common clinical presentation can also be accompanied by nausea, vomiting, weight loss, weakness, headache and arthralgia. An extranodal extension of the disease, including involvement of skin, eye, and bone marrow localizations, has been rarely described. Most patients have leukopenia or neutropenia with a relative leukocytosis. At an ultrasound exploration of the affected lymph nodes, a hypoechoic aspect can be seen, with an external, thick and irregular hyper-echoic ring. As there are no specific tests for KFD, the final diagnosis is histologically-based from lymph node excisional biopsy. Histological examination shows paracortical foci of coagulative necrosis containing karyorrhectic debris, which are surrounded by numerous CD68+/myeloperoxidase (MPO)+ histiocytes, CD68+/CD123+ plasmacytoid dendritic cells, and a minority of small- to large-sized CD8+ lymphocytes and immunoblasts. Differential diagnosis mainly includes systemic lupus erythematosus (SLE)-related lymphadenopathy and large cell lymphoma. The histological absence of neutrophils, plasmacells, as well as hematoxylin bodies, is a feature which argues against the diagnosis of SLE. In addition, the absence of auto-antibodies and anti-nuclear antibodies is useful in ruling out an autoimmune disorder. Early diagnosis of KFD is crucial to prevent the patients undergo extensive investigations related to suspected malignant lymphomas or other diseases.

Introduction

Kikuchi-Fujimoto disease (KFD), also known as “histiocytic necrotizing lymphadenitis”, is an extremely rare lymphadenitis mainly involving the posterior cervical lymph nodes, frequently associated with fever, nocturnal sweating, shivering and leucopenia. The etiology is still unknown, but the clinical course is benign with spontaneous regression without any specific therapy in most cases. Although it has a worldwide distribution, there is a high prevalence in Asia, while isolated cases are also reported in USA, Africa and Europe. This disease was firstly described by Kikuchi ¹ in 1972, and simultaneously, but independently, by Fujimoto 1972 ². Awareness of the possibility that this lymphadenitis can occasionally occur in caucasian population is important for both clinicians and pathologists to prevent a misdiagnosis and inappropriate treatment. The aim of the present paper is to provide a brief update about KFD to both clinicians and pathologists, with emphasis on the clinical and pathological features useful to achieve a correct diagnosis in daily practice.

Epidemiology

KFD is a very uncommon cosmopolitan disease with higher prevalence in Japanese and Asiatic people ³, but...
sporadic cases have also been reported from Europe. This geographic predominance may be related to the presence of certain HLA class II alleles, HLA-DPA1 and HLA-DPAB1, which are more prevalent in Asian patients affected by KFD. These genes are extremely rare or absent among Caucasian people. KFD has been observed in both females and males of all ages, and in all races. The average age of patients with KFD is 21-25 years. Although KFD has been reported in patients ranging in age from 6 to 80 years, young adults between 20 and 40 years are most frequently affected. A female predominance (M:F=4:1) has been reported, but recent studies don’t confirm these data, reporting a ratio closer to 1:1. Interestingly, only rarely KFD is diagnosed in childhood.

**Etiology**

The etiology of KFD is currently unknown, but there is increasing evidence that a viral infection or an autoimmune disease can trigger the onset of the disease. Epstein-Barr virus, herpes simplex, herpes virus 6, 7, 8, cytomegalovirus, parvovirus B19, paramyxovirus, parainfluenza virus, rubella, hepatitis-B, HIV, human T-lymphotropic virus type 1 (HTLV-1) and Dengue virus have been all suggested to be implicated in the etiopathogenesis of the disease, but their role has never been demonstrated. Viral etiology has been strongly suggested, based on clinical similarities with viral infections, including flu-like respiratory prodromes and no response to antibiotic therapy, as well as on its morphologic features, such as necrosis in the T-cell zones of lymph nodes, infiltration by immunoblasts, expansion of paracortex, immunologic evidence of T cell predominance, and the presence of tubular inclusions on electronic microscopy in the cytoplasm of lymphocytes and histiocytes. Other infectious agents, such as Yersinia enterocolitidis, Brucella, Bartonella henselae, Entameoba histolitica, micobacterium szulgai and toxoplasma gondii, have been proposed, but subsequent studies failed to support this hypothesis.

**Associated-diseases**

KFD has been reported in association with different systemic diseases, mainly autoimmune conditions such as, Wegener granulomatosis, leukocytoclastic vasculitis, antiphospholipidic syndrome, Sjogren syndrome, arthritis, thyroiditis, Graves disease, conjunctivitis, optic neuritis, bilateral panuveitis, polymyositis with pulmonary involvement, autoimmune hepatitis, relapsing polycondratitis. Still’s disease, and systemic lupus eritematosus (SLE). However the possibility that the lymphadenopathy diagnosed as KFD could represent an autoimmune necrotizing lymphadenitis, such as that associated with SLE (see below), cannot be completely ruled out. With regard to this topic, the association between KFD and SLE merits a separate comment. In a series of 91 patients affected by KFD, 11 patients (12% of the cases) had a history of SLE. Notably, in all but one case, the diagnosis of KFD was rendered concomitantly and in the year following diagnosis in 2 cases. Although some authors have reported that KFD can seldom precede, occur at the same time or immediately after the diagnosis of SLE, the association between these two different diseases still remains unclear. This is mainly due to the fact that they may share, not only some clinical (lymphadenopathy, rash, pyrexia of unknown origin, arthralgia), but also several morphological features. Accordingly the diagnosis of concomitant SLE in the patients with KFD should be rendered with extreme caution. In fact it is likely that many KFD in SLE patients should be better regarded as “lupus lymphadenitis”.

Apart from autoimmune disorders, KFD has also been reported in patients with several other pathological conditions, such as meningitis, status epilepticus, raised intracranial pressure due to subdural effusions, interstitial lung diseases, cryptogenetic organizing pneumonia, myocarditis, acute renal failure, AIDS, systemic phacomatosis pigmentovascularis, hemophagocytic syndrome, cerebellar ataxia, sickle cell anemia, symptomatic CD4 lymphocytopenia. Whether these pathological conditions are unusual forms of visceral involvement by KFD, or they merely represent the clinicopathologic context in which KFD arises, is still to be established. Interestingly, KFD has also been reported in patients with breast, oral cavity, and gastric cancer. There have been also speculations about the possibility that KFD may be a manifestation of an early stage of T-cell lymphoma, and recently one case of KFD displaying (2:16) chromosomal translocation has also been published. Lastly, rare cases of KFD have been also described in patients with implanted pacemakers or silicone breasts implants, suggesting that these materials may act as potential agents triggering hyperimmune reactions.

Interestingly a few cases of KFD have been reported in pregnancy, with no complications for both mother and child. However the possibility of a recurrent or an evolution of KFD in a fatal hemophagocytic syndrome has been seldom described, respectively, during pregnancy or post partum. In addition KFD has also been reported in association with a miscarriage and the follow-up of patient revealed an evolution into a SLE-like syndrome.

**Clinical symptoms**

KFD is a self-limiting disease which can have an acute or subacute course, evolving over two or three weeks. Only rare cases of KFD have been reported in an Asian patient who presented with recurrent episodes for five years before a diagnosis was made. The most common clinical manifestation is cervical lymphadenopathy...
(60-98% of cases). The disease is usually unilateral, and occurs in the lymph nodes located in the posterior cervical triangle. Lymph nodes, relatively small in size (< 3 cm), are tender, mobile and painful (60% of cases) \(^3\). Rarely lymph nodes may be larger than 6 cm in their greatest diameter, and firm in consistency. In a large series about 50% of patients presented polyadenopathy \(^1\) with concomitant involvement of axillary and supraclavicular lymph nodes, respectively, in 14% and 12% of patients \(^5\). Only rarely generalized lymphadenopathy has been reported (1-22% of cases), but enlargement of mediastinal, peritoneal, retroperitoneal, mesenteric, and groin lymph nodes is exceptional \(^3\). Occasionally KFD may present as an isolated axillary lymphoadenopathy as the unique clinical manifestation of the disease \(^6\). Lymphadenopathy can be associated with fever in 30-50% of cases, while weight loss, nausea, vomiting, upper respiratory symptoms, sore throat, weakness, fatigue, headache, arthralgia and night sweats, are less frequent symptoms (Tab. I). Interestingly, some patients may have prolonged fever of unknown origin, as the only presenting symptom \(^61-64\). A minority of patients may present both lymphadenopathy and hepatosplenomegaly as the initial clinical manifestation. In this regard, hepatomegaly and splenomegaly have been reported in isolated cases, 3% and 2%, respectively, in a series of 244 cases of KFD \(^8\). An extranodal extension of the disease is uncommon, with involvement of skin and bone marrow. Cutaneous lesions include rashes, erythematous papules, plaques aciform or morbilliform lesions and facial erythema \(^3\). These skin lesions, often occurring in the face, trunk and limbs, could be present concurrently or precede the lymphadenopathy. Interestingly, isolated cases of pseudo-appendicitis due to KFD have been reported with the necessity of abdominal surgery to establish the final diagnosis \(^65,66\).

**Laboratory and radiological findings**

Laboratory investigation usually shows normal results, but a few patients have a slight elevated erythrocyte sedimentation rate. Leukopenia (especially granulocytopenia) occurs in up to 25% to 58% of patients, whereas leukocytosis can be seen in 2% to 5% of \(^3\). Some authors have postulated that inhibitory factors in serum may be responsible for granulocytopenia in KFD \(^1\). Aminotransferase and alanine aminotransferase may be elevated \(^67\). KFD does not have a characteristic radiological appearance \(^68\) and imaging, such as computed tomography or magnetic resonance, are not useful in distinguishing lymphadenopathy of KFD from other causes. On ultrasound examination, the affected lymph nodes may appear hypoechoic, with an external, thick and irregular hyperechoic ring \(^69\). In a study on 96 retrospective CT scans of patients with histologically proven KFD, Kwon et al. \(^59\) showed multiple involved lymph nodes, most of them (94%) being smaller than 2.5 cm. This finding may help in ruling out lymphoma which typically produces a few number but larger nodes, perinodal infiltration, and necrosis \(^3\). However imaging tests are performed on daily practice to identify suitable site for lymph node biopsy or excision.

<table>
<thead>
<tr>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Fever</td>
<td>35-77.3%</td>
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<tr>
<td>Asthenia</td>
<td>74.4%</td>
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<tr>
<td>Fatigue</td>
<td>4.5-22.7%</td>
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<tr>
<td>Rash</td>
<td>10%</td>
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<tr>
<td>Arthralgia</td>
<td>7-4.5%</td>
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<tr>
<td>Headache</td>
<td>18.2%</td>
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<td>Myalgia</td>
<td>4.5%</td>
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<th>Physical examination</th>
<th>percentage</th>
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<tr>
<td>Lymphonodes enlargement</td>
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</tr>
<tr>
<td>Unilateral cervical</td>
<td>54.5%</td>
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<tr>
<td>Bilateral cervical</td>
<td>23.6%</td>
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<tr>
<td>Both cervical and axillary</td>
<td>27.2%</td>
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<tr>
<td>Axillary alone</td>
<td>4.55%</td>
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<tr>
<td>Hepatomegaly</td>
<td>3-9.1%</td>
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<tr>
<td>Splenomegaly</td>
<td>2-4.5%</td>
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<thead>
<tr>
<th>Laboratory findings</th>
<th>percentage</th>
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<tr>
<td>Anemia</td>
<td>54.5%</td>
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<tr>
<td>Leucopenia</td>
<td>9.1-32%</td>
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<tr>
<td>Leucocytosis</td>
<td>13.6%</td>
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<tr>
<td>Thrombocytopenia</td>
<td>4.5%</td>
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<tr>
<td>Elevated C-reactive protein</td>
<td>22.7%</td>
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<tr>
<td>High erythrocyte sedimentation rate</td>
<td>31.8%</td>
</tr>
<tr>
<td>Increased lactate dehydrogenase</td>
<td>31.8%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>27.2%</td>
</tr>
<tr>
<td>ANA positivity</td>
<td>13.3-45.2%</td>
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<tr>
<td>Anti-DNA antibodies</td>
<td>18%</td>
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<th>Histology (biopsy of the lymph node)</th>
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<td>Paracortical expansion with foci of incipient necrosis laden with karyorrhectic debris both within and outside macrophages. The macrophages with ingested debris are classically described as crescentic because the nucleus is pushed to the periphery (74). Neutrophils are absent. The necrotic foci are usually surrounded by macrophages (CD68+/MPO+), plasmacytoid dendritic cells (CD68+/CD123+) and CD8+ lymphoid cells (43)</td>
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<thead>
<tr>
<th>Recurrence</th>
<th>percentage</th>
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<tr>
<td>3-21%</td>
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<th>Causes of death (0.5-2%)</th>
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<tr>
<td>Pulmonary hemorrhage, fatal hematopoietic syndrome, cerebral hemorrhage secondary to thrombocytopenia, heart failure, graft failure following renal, liver and pancreatic transplants (8,87,94-96).</td>
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Diagnosis

Fine-needle aspiration biopsy (FNAB) is potentially a good test for diagnosis of KFD when the following features are present: i) polymorphous lymphoid cell population; ii) abundant karyorrhectic debris; iii) numerous small-sized histiocytes with eccentrically-placed round to oval or a crescentic nuclei, with or without ingested nuclear debris. Unfortunately false-positive and false-negative rate is reported in 37.5% and 50%, respectively, with an overall accuracy about 56% 71. FNA or ultrasound-guided core biopsy (USCB) are limited due to the potential sampling error related to marked variation within a single lymph node, or among different lymph nodes 72. The diagnosis of KFD is still based on histological examination from surgically excised lymph node (excisional biopsy). The presence of the following morphological features are highly suggestive for diagnosis 73 74: i) focal, irregularly-shaped, paracortically-based areas of coagulative (eosinophilic) necrosis containing abundant karyorrhectic debris (Figs. 1A, B); ii) numerous histiocytes (Fig. 2A), plasmacytoid dendritic cells (Fig. 2B), and a minority of small- to large-sized lymphocytes and immunoblasts within and/or surrounding the aforementioned necrotic areas. Notably, both plasma cells and neutrophils are absent or scarce. This finding is very helpful in the differential diagnosis with other necrotic lymphadenites. Histiocytes can be represented by phagocytic (Fig. 1B) or non-phagocytic cells with peripherally placed nuclei (also known as “crescentic histiocytes”), as well as foamy histiocytes. Interestingly, histiocytes, apart from CD68, also express myeloperoxidase (MPO), a typical marker of myeloid cell lineage (Figs. 3A, B) 75. Lymphocytes and immunoblasts are mainly T-cells with cytotoxic phenotype (CD8+) 6 76, while plasmacytoid dendritic cells (previously termed as “plasmacytoid monocytes or plasmacytoid T cells”) are small-sized cells with eccentrically placed nuclei, which express both CD68 and CD123 77 78. As KFD is considered to be a paracortical T-zone reactive process, it is not uncommon the presence of reactive lymphoid follicles (in 50% to 60% of cases) 6. Some authors have suggested that there is possibility of classify KFD into three different evolving morphological phases: i) the proliferative phase characterized by the presence of histiocytes, plasmacytoid dendritic cells, lymphocytes and apoptotic cells (Fig. 4A); ii) the necrotizing phase, in which the aforementioned cellular aggregates undergo coagulative necrosis (Fig. 4B); iii) the xanthomatous phase, characterized by a predominant infiltration of foamy histiocytes 76 (Fig. 4C). Some studies have suggested that the paracortical necrosis - the hallmark of KFD- be the result of cytotoxic lymphocyte-mediated apoptotic cell death 79 80. In this regard, it has been
suggested that two different, perforin- and Fas-based, molecular mechanisms of T-cell-mediated cytotoxicity may be involved in the apoptotic process \(^8\), and CD8+ lymphocytes may kill or be killed in this scenario \(^8\)\(^9\). It has been postulated that plasmacytoid dendritic cells can produce type I interferon in response to viral infection, promoting a T-helper response which results with the cytotoxic immune reaction \(^8\). In addition molecular studies, conducted in some cases of KFD, have shown that five genes (IFI44L, CXCL10, GBP1, EPST1 and IFFI27) that belong to the family of interferon-induced genes are up-regulated, as well as nearly all apoptosis-associated genes (including caspase, BCL2) \(^8\). Apart from these genes, it seems that cytokine and chemokine pathways of interferon gamma, interleukin 18, MIG, and interferon gamma-induced protein 10 might play an important role in the pathogenesis of apoptosis associated with KFD \(^8\)\(^9\).

**Differential diagnosis**

In a large series of 186 cases of reactive lymphadenopathies, KFD represented 1.6% \(^8\). Its recognition and separation from other benign or malignant processes is crucial, because its treatment and prognosis differ dramatically from the others disorders. Due to its morphological features differential diagnosis mainly includes reactive lymphadenitis associated with SLE and non-Hodgkin lymphomas \(^9\). Among these entities, the former poses serious diagnostic problems. In fact it is widely known that SLE can be associated with a necrotizing lymphadenitis which closely resembles KFD. Several authors agree that the identification of neutrophils and hematoxyphilic material (also known as “haematoxylin bodies”) in the necrotic foci are all features favoring the diagnosis of SLE-lymphadenitis. Hematoxylin bodies are mainly composed of DNA derived from karyorrhectic nuclear material, presumably from lymphocytes, and can also be found in the sinusoids and on the wall of blood vessels. The presence of sparse CD8+ lymphocytes and numerous plasma cells, especially in the interfollicular areas, as well as vasculitis in the perinodal tissue are all features which favor SLE-associated lymphadenitis \(^9\). Although haematoxylin bodies are considered practically pathognomonic of SLE-lymphadenitis, they are not invariably present. Accordingly, the above mentioned histologic features should, however, be interpreted in the clinical context of a given patient (presence or absence of SLE-related signs, such as fever,
Fig. 3. Histiocytes are stained both with CD68 (A) and myeloperoxidase (B), while plasmacytoid dendritic cells are stained with CD123 (C).

Fig. 4. The different morphological phases of Kikuchi-Fujimoto disease. (A) Proliferative phase with histiocytes, plasmacytoid dendritic cells, and apoptotic cells; (B) Necrotizing phase with a small necrotic focus; (C) Xanthomatous phase with a predominant infiltration of foamy histiocytes.
vasculitis, hemophagocytic syndrome; laboratory tests, such as very high serum anti-nuclear antibodies-ANA titer). As KFD may contain clusters of immunoblasts and lymphocytes, sometimes with nuclear atypia, it can be confused with large cell T-lymphoma. It has been reported that up 30% of cases of KFD was erroneously diagnosed as lymphoma. Awareness of the possibility that KFD can mimic a CD8+/T cell lymphoma is crucial to avoid a misdiagnosis of malignancy. In fact in Western countries most of T-cell lymphomas (peripheral T-cell lymphomas NAS; angio-immunoblastic T cell lymphoma) are CD4-positive rather than CD8-positive, and neoplastic cells are variably admixed with plasmacells, eosinophils and histiocytes.

Recurrence

Most cases of KFD resolve spontaneously with only occasional recurrence described in the literature. A recurrence rate of 3-21% has been reported over a period of 2-14 years following initial presentation. Van den Bergh et al. reported a case relapse of KFD three months after initial diagnosis with portohepatitis and portacaval node enlargement as the dominant adenopathy associated with fibromyalgia and chronic fatigue syndrome. Komagamine et al. described a patient with aseptic meningitis in association with KFD spontaneously resolved without any complication. In an analysis of 65 published cases of recurrent KDF, while those with recurrences similarly affect young (average age = 27 years), Asians (80%), women (76%), 73% had multiple sites of involvement and 32% of those tested had underlying autoimmune conditions.

Prognosis

Although KFD is usually a self-limiting disease with a benign course, rare fatal cases due to pulmonary hemorrhage, DIC, fatal hemophagocytic syndrome, heart failure as well graft failure following renal, liver and pancreatic transplants have been reported. One patient with recurrent KFD died of intracranial hemorrhage secondary to thrombocytopenia. One analysis of 244 cases of KFD reported an overall mortality rate of 2.1%, which contradicts the widely held belief that the disease is generally benign and non-fatal. A female patient died of heart failure, in the context of other hematologic autoimmune complications including hemolytic anemia. Another patient died of pulmonary hemorrhage and a 24-week pregnant woman died from multiorgan failure after developing KFD-triggered hemophagocytic syndrome. Three patients developed KFD after transplantation and died of respiratory failure. These patients were immunesuppressed and there were probably other factors than KFD involved in their illness.

Treatment

KFD is a self-limiting condition undergoing resolution spontaneously in most patients (64%) within 1 to 4 months. Supportive measures are the mainstay of therapy. Patients with symptoms and/or fever or involvement of extranodal tissues, such as central nervous system, skin and eyes, can benefit from short pulses of corticosteroids, nonsteroidal anti-inflammatory drugs, analgesic and antipyretics. In most cases KFD responds well to glucocorticoids therapy, especially prednisone with deescalating dosages, rapidly obtaining recovery from disease. Good results have also been gained with immunoglobulins, hydroxychloroquine, minocycline, and ciprofloxacin. Treatment with corticosteroids was necessary in 16% in Kucukardali’s experience. In a French study on 91 patients with KFD, systemic corticosteroids were prescribed in 32% of cases, hydroxychloroquine in 17.6% and intravenous immunoglobulin in 3 patients. The patients must be offered a regular follow-up in order to monitor the manifestation of SLE, because some patients may manifest autoimmune diseases some years later, and a prospective study is required to determine the risk factors for the development of SLE.

Conclusions

KFD disease is a rare, likely under-diagnosed, disease due to the possibility that some cases may manifest with mild clinical signs, including low-grade fever and small cervical adenopathy, and are wrongly diagnosed as viral infections. Early recognition is necessary to avoid unnecessary investigation to exclude malignant lymphomas or related disorders. The course is favorable usually without any adverse event. In rare circumstance may recur. Awareness of the disease by clinicians and pathologists is crucial not only to suspect the diagnosis, but mainly to avoid a misdiagnosis of malignancy.

References

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