Original Research Article

Histiocytic Necrotizing Lymphadenitis or Kikuchi–Fujimoto Disease: Clinical experiences in North Africa

Abstract

Introduction Kikuchi-Fujimoto disease or Kikuchi disease (KD) or histiocytic necrotizing lymphadenitis is an uncommon disease more frequent in Asia. It is diagnosed with lymph node histopathological findings.

Objective To perform a systematic review of Kikuchi's disease (KD) cases and describe clinical manifestations and associated etiology in the Tunisian population.

Methods We conducted a multicentric descriptive study collecting patients with histologically proven KD. Clinical data, laboratory results, histopathologic examination, associated pathologies, and patient evolution were included.

Results The search included 9 patients. They were 7 women and 2 males with a median age of 45 years old [24-72]. Common clinical manifestations were fever (n=8) and arthralgia (n=7). Lymph nodes mainly were bilateral (n=8), multiple (n=9), and in the cervical region (n=8) and axillary area (n=6). Laboratory results showed inflammatory syndrome and elevated lactate dehydrogenase. Areas of necrosis, karyorrhectic debris, and accumulation of histiocytes were specific histologic findings noted for all patients. Systemic Lupus Erythematosus was associated with KD in 2 patients and with Sjögren disease in one of them. Other associated pathologies were Lymphohistiocytic activation syndrome, lymphocytic meningitis, sepsis from a urinary tract infection, and idiopathic interstitial lung disease. Corticosteroids were prescribed in 4 cases. The other 5 cases had spontaneous regression of symptoms. The outcomes were favorable with recovery in 3 cases. Five patients developed Hodgkin lymphoma, myelodysplastic syndrome, and lupus nephropathy after KD diagnosis.

Conclusions KD is exceptional in North Africa. The study noted the same clinical and histological findings in the literature. SLE was the most associated pathology. No ethnic variability was detected.

Keywords: Kikuchi disease, Kikuchi-Fujimoto disease, Histiocytic necrotizing lymphadenitis, Systemic lupus erythematosus, lymphadenopathy.

1. Introduction

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is an uncommon disease. It was described for the first time in Japan in 1972 by Masahiro Kikuchi and Y. Fujimoto [1]. It is mostly described in Asian young adults but it has been reported worldwide. It is a benign and self-limited disorder [1, 2]. The disease usually presents with a fever, cervical lymphadenopathy, and non-specific systemic

symptoms [2, 3]. The pathogenesis of Kikuchi disease (KD) is not well known and raises the problem of several differential diagnoses. Histological study of the affected adenopathy and immunophenotyping are the main components to establish the diagnosis [4]. The clinical findings suggest an autoimmune, viral, or bacterial etiology [1, 3], yet specific etiologic agents remain unknown. Clinicians and pathologists are unfamiliar with this entity, which frequently causes significant diagnostic challenges [2], and a better knowledge of this disease may improve the patient's outcome. This study aims to describe the different clinical presentations of KD in Tunisia, the difficulties of diagnosis, and the evolutive patterns of the patients.

2. Patients and Methods

We conducted a retrospective review of patients diagnosed with KD from January 2001 to December 2022 at the internal medicine department and the infectious disease department of Farhat Hached Hospital of Sousse and the internal medicine department of Sahloul Hospital in Tunisia.

KD was diagnosed when histological findings of lymph-node biopsy show: patchy paracortical necrosis, histiocytes with crescentic nuclei and other cells (predominantly T-cells), karyorrhexis, and scarce plasma cells in the absence of neutrophils and granulomas.[5]

Clinical manifestations of patients were described. The complementary examinations were carried out and histological findings have been collected. Associated etiology and patient evolution were reported.

3. Results

Of the 9 patients, diagnosed with KD during the study period, there were 7 females and 2 males patients (3.5:1). Their ages ranged from 24 to 72 years old with a median age of 45 years old. All patients showed up with lymphadenitis, and fever in 8 of 9 patients. The other common clinical manifestations consisted of polyarthralgia (n=7), headache (n=4), night sweats (n=4), asthenia (n=3), anorexia (n=3), weight loss (n=3), facial erythema (n=3), chills (n=2), and facial telangiectasia (n=1).

The lymph nodes were mainly in the cervical region (n=8), in the axillary area (n=6), in the inguinal area (n =3), retroperitoneal ganglia (n=3), mediastinal adenopathy (n=2), and hepatic hilar lymph nodes (n=2) (Table 1). The enlarged lymph nodes were mostly bilateral (n=8), and multiple (n=9). The average size of the adenopathies was ≥ 2cm in diameter (n=5). The involved lymph nodes were firm (7/8), tender (4/8), and movable (6/8) (Table 1).

The initial laboratory results, for the patients on admission, showed an accelerated erythrocyte sedimentary rate (ESR) in all patients and elevated C-reactive protein

(CRP) in 7 patients (7/8), anemia in 3 patients, thrombopenia in 3 patients, elevated lactate dehydrogenase (LDH) in 7/8 patients and hepatic cytolysis in 3 patients. Serum Protein Electrophoresis was analyzed in 6 cases and showed inflammatory profile in 4 cases. Positive anti-nuclear antibody (ANA), with a significant level, was present in 3 of 8 patients. Analysis of serum complement levels revealed low C3 and C4 levels in 2/6 patients. No concomitant viral infections (Human immunodeficiency virus, Cytomegalovirus, Epstein–Barr virus, Parvovirus B19) were documented.

The diagnosis was made in all the cases by histopathologic examination of a lymph node biopsy. The histologic findings were mainly for all patients, areas of necrosis, nuclear debris, and accumulation of histiocytes (figure 1). Other histologic features were observed such as immunoblasts (n=3), follicular hyperplasia (n=2), activated lymphocytes (n=2), and thrombosed vessels (n=1). Alterated neutrophils (n=1), eosinophils (n=1), small calcification areas (n=1), and hemophagocytic histiocytes (n=1).

A concomitant diagnosis of Systemic Lupus Erythematosus (SLE) was made during hospitalization in 2 cases associated with Sjögren syndrome (SS) in one of them. Other associated pathologies were Lymphohistiocytic activation syndrome (n=1), lymphocytic meningitis with normal glucorrahchia and normal proteinorrhachia (n=1), sepsis from a urinary tract infection (n=1), and idiopathic interstitial lung disease (n=1). For the three remaining patients, KD was the only present pathology.

For 5 patients, no treatment has been required, with spontaneous regression of symptoms. Corticosteroids were prescribed in 4 cases at a dose of 1 mg/kg per day of prednisone with a progressive decrease in the dose. The duration of corticosteroid therapy was variable depending on the pathology associated with KD. One patient received non-steroidal anti-inflammatory drugs and 1 patient received chloroquine for SLE. The duration of follow-up ranged from 2 months to 15 years. The outcomes were: favorable with recovery in 3 cases, two patients developed Hodgkin lymphoma (HL) respectively 2 years and 17 years after KD diagnosis, one patient developed myelodysplastic syndrome one year later, and lupus nephropathy 15 years later (n=1). One patient is still being followed for SLE and SS, and the last one was lost to follow-up (Table 2).

Table1. Characteristics of involved lymph nodes

Characteristics	n
Laterality of lymphadenopathy	
Bilateral	8
Unilateral	1
Location	
Cervical	8
Axillary	6
Inguinal	3
Retroperitoneal	3
Mediastinal	2
Hepatic	2
Location in the cervical area	

Jugulodigastric	5
Supraclavicular	4
Spinal	3
Retroauricular	2
Submandibular	1
Size of lymph nodes	
> 2cm	5
≤ 2 cm	4

Table 2. Baseline characteristics of Kikuchi's disease patients	
Characteristics	Median [min-max]
Age	45 [24-72]
Characteristics	n
Sex	
Female	7
Male	2
Clinical symptoms	
Lymph nodes	9
Fever	8
Polyarthralgia	7
Night sweating	4
Headache	4
Body weight loss	3
Chills	2
Laboratory features	
Inflammatory syndrome (C-RP> 10 mg/l; ESR)	9/9
Thrombocytopenia (<150 000/mm3)	7/8
Elevated liver enzymes	3/9
Increased LDH	7/8
ANA (+)	3/8
Treatment	
No treatment	5
Corticosteroids	4
NSAIDs	1
Hydroxychloroquine	1
Associated diseases	
SLE	1
SLE + SS	1
Macrophage activation syndrome	1
Lymphocytic Meningitis	1
Interstitial lung disease	1
Urinary tract infection with sepsis	1
Outcome	
Recovery	3
Hodgkin lymphoma	2
Myelodysplastic syndrome	1
SLE with nephropathy	1
Lost to follow up	1
Still being followed	1

ANA = Anti-nuclear antibody; CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; LDH =Lactate dehydrogenase; NSAIDs = non-steroidal anti-inflammatory drugs; SLE = Systemic Lupus Erythematosus ; SS= Sjögren syndrome

4. Discussion

The Kikuchi-Fujimoto disease is also known as histiocytic necrotizing lymphadenitis. It is a rare benign self-limiting inflammatory disease with acute to sub-acute course, evolving over several weeks [2,6]. KD has a very low recurrence rate (~ 3%) [7,10]. The disease was first described in Japanese patients in 1972 and it is known to affect most commonly Asiatic people which could be probably related to Human leukocyte antigen (HLA). Some studies showed a connection between KD and HLA-DPB1 and HLA-DPA1 alleles which are common in the Asian population [6]. Ten years later, in 1982, Pieri and colleagues, with Kikuchi as a co-author, made the first description of the disorder outside Asia [9]. Some case studies in the United States (US) and Europe found that the disease has been reported worldwide in all racial groups and in a variety of ethnic backgrounds [2, 6].

KD usually happens to occur in young adults, in their second and third decades [1], generally under 40 years [2, 6, 9]. A female predominance has been initially reported in most studies with a female-to-male ratio of 4:1, yet recent reports suggest that the actual ratio is closer to 1:1 [2, 6].

The most common clinical presentation is posterior cervical lymphadenopathy in 60 to 90% of cases, generally unilateral (88.5%). It was rarely isolated and polyadenopathy was found in 1 to 2% of cases with frequent involvement of the supraclavicular and/or axillary lymph nodes. Affected lymph nodes are tender and painful [2, 8, 9]. The size of cervical lymph nodes has been reported to vary from 0.5cm to 4cm. However, lymph node sizes can range from 5 cm to 6 cm and are rarely larger than 6cm [6, 9]. Involvement of mediastinal, peritoneal, and retroperitoneal regions is uncommon [9]. In that study, deep lymph nodes were observed (mediastinal, retroperitoneal, and hepatic). Lymphadenopathy is associated with fever in 35 to 77% of cases lasting about 4 to 6 weeks [2, 10]. Other symptoms could be associated, including weight loss, weakness, headache, night sweats, arthralgia, nausea, vomiting, sore throat, and upper respiratory symptoms [2, 9]. In about 40% of cases, KD patients are likely to experience erythema, commonly in the trunk, limbs, and cheeks as well as an ulcer on the mucous membrane, purpura, malar erythema, alopecia, and lupus-like skin lesions [6, 10]. Lipoedema with desquamation and erosions have been reported [9]. A skin lesion biopsy might further reveal the presence of vacuities [6]. Hepatomegaly and splenomegaly are observed in less than 5% of cases [2]. Occasionally, KD could occur in the bone marrow [2, 6]. The literature describes pulmonary, cardiac, and neurologic involvement, mostly meningitis as one of our cases [8].

A wide range of studies showed normal laboratory findings. In some cases, some abnormalities are observed. It could be mild anemia, mildly elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Other findings include leukopenia (especially granulocytopenia 20-58% of cases) and leucocytosis (2-5% of cases) with

atypical lymphocytes in the peripheral blood reported in up to one-third of patients. The mechanism of granulocytopenia has been studied using an in vitro culture system. The number of granulocyte precursor cells in the bone marrow was found to be decreased [9]. Other laboratory findings are seen in some cases, elevated lactate dehydrogenase (LDH) and alanine aminotransferase (ALT) [2,7].

The diagnosis is based on the histologic findings of an excisional biopsy. This disorder does not have a characteristic appearance on ultrasonographic or computed tomographic (CT) examination [9]. Fine needle aspiration does not provide a definitive diagnosis because the assessment of the lymph node architecture is crucial for the diagnosis [1], thus the histological diagnosis is based on 2 important elements, the architectural features and the cytology [9]. The classic histologic findings consist of a partially preserved architecture with hyperplasia, a well-circumscribed paracortical area of necrosis with fibrin deposits, and abundant apoptotic karyorrhexis nuclear debris. The karyorrhectic foci are formed predominantly of histiocytes, plasmacytoid monocytes, but also immunoblasts, some of which may be atypical, and small and large lymphocytes [9]. Some of the histiocytes occasionally show the characteristic “crescentic” nuclei. Neutrophils and eosinophils are conspicuously absent, which is an important clue in diagnosing this entity [1, 2, 9]. Moreover, thrombosed vessels can frequently be seen at the periphery of necrosis [9]. However, histologic appearance is variable, and three evolving histologic patterns have been proposed: the proliferative, necrotizing, and xanthomatous patterns. An expanded paracortex with sheets of histiocytes and plasmacytoid dendritic cells admixed with small lymphocytes and karyorrhectic nuclear debris is found in the initial proliferative pattern. A necrotic phase of the histology is characterized by the presence of necrotic tissue on the lymph nodes. An abundance of foamy histiocytes, with or without necrosis found in the xanthomatous phase [1, 2, 6]. The necrotizing form appears to be the most commonly seen. It unclear whether these subtypes correlate with progression from early to more advanced stages or reflect distinct subtypes of KD [1].

The differential diagnosis in KL cases is broad and includes infectious lymphadenitis [2] and 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 [9]. In necrotizing lymphadenitis of tuberculosis, histoplasmosis, leprosy, and cat-scratch disease, there is a proliferation of epitheloid histiocytes with granuloma formation. In bacterial infections, there are usually abundant neutrophils; eosinophils are prominent in lymphadenitis caused by Y *enterolitica*. Prominent perivascular plasma cell infiltration is observed in syphilitic necrotizing lymphadenitis [2]. Correlation with serologic and molecular studies is usually necessary to confirm the diagnosis [2]. SLE lymphadenopathy is the most difficult differential diagnosis, in some cases, it is difficult to distinguish histological abnormalities from KD. In particular, hematoxylin bodies are seen, composed of aggregates of nuclear DNA, polysaccharides, and immunoglobulins. Hematoxylin bodies are the most specific histologic feature of SLE

lymphadenitis and they are not present in KD [1, 2]. KD and non-Hodgkin's lymphoma (NHL) share certain histopathological features, such as the proliferation of immunoblasts and plasmacytoid dendritic cells at the edges of necrotic foci as well as obliteration of sinuses, thus immuno-staining would be helpful as the positivity of histiocytes for myeloperoxidase can be used to exclude T-cell lymphomas and can offer useful clues regarding infectious agents [2,10].

The etiology of KD is largely unknown and many studies in the literature have tried to understand the underlying causes of the disease. There is much speculation about the cause of KD. A viral or autoimmune cause has been suggested. Numerous viruses have been proposed as possible etiologic agents of KD, including Epstein-Barr virus; herpes simplex virus; varicella-zoster virus; human herpes viruses 6, 7, and 8; parvovirus B19; paramyxovirus; parainfluenza virus; rubella; cytomegalovirus; hepatitis B virus; human immunodeficiency virus; human T-lymphotropic virus type 1; and dengue virus [2]. Most of the studies have failed to confirm an association between KD and any viral infection [1, 2, 3]. It has been postulated that a viral infection could function as a trigger for KD, which then progresses to clinically evident lymphadenopathy only after the viral infection has resolved [1]. The second theory explored in the literature is autoimmune etiology [2]. The Kikuchi-Fujimoto disease has also been described in association with a number of systemic diseases, most commonly autoimmune conditions such as systemic lupus erythematosus (SLE), Wegener granulomatosis, Sjogren syndrome, Graves disease, Still disease, etc [2]. Multiple studies have reported an association between KD and SLE, raising suspicion that KD may represent a subclinical form of SLE lymphadenitis; it is advised that patients diagnosed with KD undergo clinical evaluation for SLE [1, 4]. Sopeña and colleagues performed a systematic review of all cases of the association between KD and SLE. The search found 158 adults with proven KD-SLE. SLE had been diagnosed before KD in 18% of cases, simultaneously in 51%, and after KD in 31%. No significant differences were found in terms of clinical and laboratory manifestations except for a lower frequency of lupus nephritis [11]. In that study, one patient developed lupus nephritis 15 years later.

The disease usually resolves within months [1- 4 months] without any specific treatment [6, 9]. The relapse rate is between 3 to 4% [6, 7]. Only 3 fatal cases have been reported, one patient was a 38-year-old man who died after acute heart failure, the post-mortem examination revealed that the heart was dilated and flabby, with multiple microscopic foci of necrosis. The second one was a 19-month-old child who died unexpectedly after a febrile illness. In the necropsy study, typical histopathologic findings of KD were seen in lymph nodes and extranodal sites. Finally, fatal KD also was reported in an Asiatic transplant recipient [9]. Sometimes, a strong immunological reaction is accompanied by histolytic proliferation, hemophagocytosis, and systemic inflammatory response causing Hemophagocytic lymphohistiocytosis (HLH), a relatively rare condition, which can be found in KD patients [6]. The risk with this entity is the onset of a life-threatening disseminated intravascular coagulation. The mortality rate of HLH is 20-42%. It is managed with

intravenous immunoglobulin and methylprednisolone [6]. There is no specific treatment for KD, symptomatic treatment could be prescribed especially when the systemic manifestations are distressing. No therapeutic recommendations for the management of the disease are available [10]. Therefore, on the basis of some pathogenetic and immunologic considerations, non-steroidal anti-inflammatory drugs (NSAIDs), hormones, and immunosuppressants could be considered to manage the symptoms [9, 10].In chronic cases, treatment involves corticosteroids, intravenous immunoglobulin, or hydroxychloroquine [6].

Conclusion

This study is the first multicentric one in North Africa where KD is exceptional. The same clinical and histological findings of the literature were found so no ethnic variability was detected. The second common result was the association of KD to SLE.

Availability of data and materials

The figures did not be used in any other publication

References

[1].F Rosado,Y Tang, R Hasserjian, et al.Kikuchi-Fujimoto lymphadenitis: role of parvovirus B-19, Epstein-Barr virus, human herpesvirus 6, and human herpesvirus 8. Human Pathology (2013) 44, 255–259.

[2]. M Perry and S Choi. Kikuchi-Fujimoto Disease. Arch Pathol Lab Med—Vol 142, November 2018.

[3]. Y Chong, CKang. Causative agents of Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis): A meta-analysis. International Journal of Pediatric Otorhinolaryngology 78 (2014) 1890–1897.

[4]. D R André, F Vicente, J Chaves, et al. Kikuchi-Fujimoto Syndrome: A Rare Entity to Consider. European Journal of Case Reports in Internal Medicine. . EJCRIM 2020;7: doi:10.12890/2020_001456.

[5] Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol 1988;5:329–45.

[6].Ahmed Z, Quadir H, Hakobyan K, et al. (August 09, 2021) Kikuchi-Fujimoto Disease: A Rare Cause of Cervical Lymphadenopathy. Cureus 13(8):e17021. DOI 10.7759/cureus.17021

[7].C.Y Cheng, W.H Sheng, Y.C Lo et al.Clinical Presentations, Laboratory Results and Outcomes of Patients with Kikuchi’s Disease: Emphasis on the Association

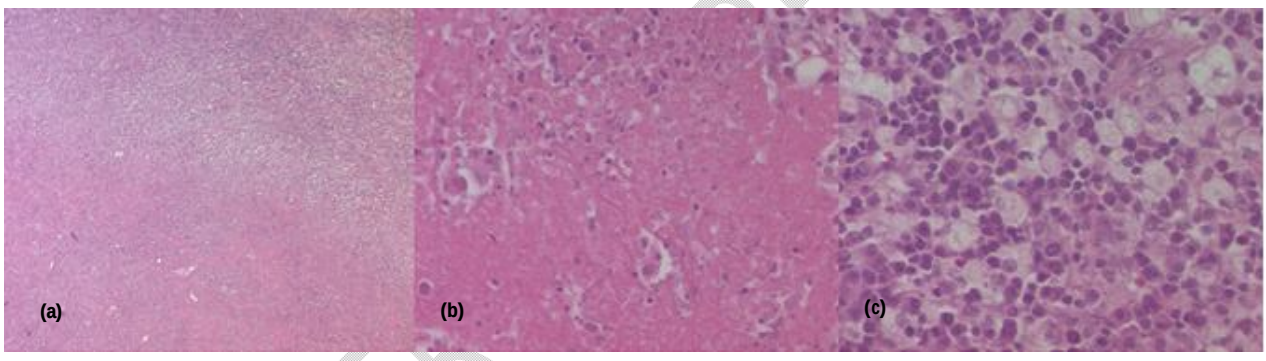
Between Recurrent Kikuchi's Disease and Autoimmune Diseases.J Microbiol Immunol Infect 2010; 43(5):366–371.

[8]. G Dumas, V Prendki, J Haroche, et al.Kikuchi-Fujimoto DiseaseRetrospective Study of 91 Cases and Review of the Literature.Medicine. Volume 93, Number 24, November 2014

[9]. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimotodisease: a comprehensive review. Am J Clin Pathol. 2004; 122(1):141–152.

[10].Xu S, Sun W, Liu J: Kikuchi-Fujimoto disease: a case report and the evaluation of diagnostic procedures.BMC Oral Health. 2019, 19:223. 10.1186/s12903-019-0920-4

[11]. Sopeña B, Rivera A, Chamorro A et al.Clinical association between Kikuchi's disease and systemic lupuserythematosus: A systematic literature review. Seminars in Arthritis and Rheumatism (2017).



- Figure 1: (a) H&E, original magnification x 50. Irregularly shaped, pale areas composed of histiocytes, plasmacytoid dendritic cells, eosinophilic granular material and abundant karyorrhectic debris (nuclear dust), often surrounding a central zone of overt necrosis. (b) H&E, original magnification x 400. Areas of necrosis with karyorrhectic debris. (c) H&E, original magnification x 400. Regions between pale areas include small lymphocytes admixed with immunoblasts and clusters of plasmacytoid dendritic cells, causing a mottled or starry sky appearance.