Kikuchi-Fujimoto Disease

Retrospective Study of 91 Cases and Review of the Literature

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Abstract: Kikuchi-Fujimoto disease (KFD) is a rare cause of lymphadenopathy, most often cervical. It has been mainly described in Asia. There are few data available on this disease in Europe. We conducted this retrospective, observational, multicenter study to describe KFD in France and to determine the characteristics of severe forms of the disease and forms associated with systemic lupus erythematosus (SLE). We included 91 cases of KFD, diagnosed between January 1989 and January 2011 in 13 French hospital centers (median age, 30 ± 10.4 yr; 77% female). The ethnic origins of the patients were European (33%), Afro-Caribbean (32%), North African (15.4%), and Asian (13%). Eighteen patients had a history of systemic disease, including 11 with SLE. Lymph node involvement was cervical (90%), often in the context of polyadenopathy (52%), and it was associated with hepatomegaly and splenomegaly in 14.8% of cases. Deeper sites of involvement were noted in 18% of cases. Constitutional signs consisted mainly of fever (67%), asthenia (74.4%), and weight loss (51.2%). Other manifestations included skin rash (32.9%), arthromyalgia (34.1%), 2 cases of aseptic meningitis, and 3 cases of hemophagocytic lymphohistiocytosis. Biological signs included lymphocytopenia (63.8%) and increase of acute phase reactants (56.4%). Antinuclear antibodies (ANAs) and anti-DNA antibodies were present in 45.2% and 18% of the patients sampled, respectively. Concomitant viral infection was detected in 8 patients (8.8%). Systemic corticosteroids were prescribed in 32% of cases, hydroxychloroquine in 17.6%, and intravenous immunoglobulin in 3 patients. The disease course was always favorable. Recurrence was observed in 21% of cases. In the 33 patients with ANA at diagnosis, SLE was known in 11 patients, diagnosed concomitantly in 10 cases and in the year following diagnosis in 2 cases; 6 patients did not have SLE, and 4 patients were lost to follow-up (median follow-up, 19 mo; range, 3–39 mo). The presence of weight loss, arthralgia, skin lesions, and ANA was associated with the development of SLE ($p < 0.05$). Male sex and lymphopenia were associated with severe forms of KFD ($p < 0.05$). KFD can occur in all populations, irrespective of ethnic origin. Deep forms are common. An association with SLE should be investigated. A prospective study is required to determine the risk factors for the development of SLE.

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Abbreviations: ALAT = alanine aminotransferase, ANAs = antinuclear antibodies, ASAT = aspartate aminotransferase, CRP = C-reactive protein, CMV = cytomegalovirus, ENT = ear, nose, and throat surgery, EBV = Epstein-Barr virus, FDG-PET-CT = F-18 fluorodeoxyglucose positron emission tomography/computed tomography, HLH = hemophagocytic lymphohistiocytosis, HIV = human immunodeficiency virus, IVIG = intravenous immunoglobulin, KFD = Kikuchi-Fujimoto disease, LDH = lactate dehydrogenase, NSAIDs = nonsteroidal antiinflammatory drugs, PCR = polymerase chain reaction, SLE = systemic lupus erythematosus, TDM = tomodensitometry.

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare and benign cause of lymphadenopathy. Since the first description of the disease by the Japanese pathologists Kikuchi and Fujimoto,[20,39] its etiology has remained unknown, although environmental factors, in particular viruses, have been suspected.[11,53] Links between KFD and other autoimmune diseases, particularly systemic lupus erythematosus (SLE), have been reported.[15,24]

KFD classically affects young women. The distribution is ubiquitous, with an over-representation of Asian patients, possibly linked to some haplotypes.[70] KFD is characterized by localized lymphadenopathy, fever, frequent upper respiratory symptoms, and odynophagia. The onset is typically subacute or acute, with a short course of symptoms.[4] Nevertheless, KFD has been already described as a cause of fever of unknown origin.[58] Other symptoms are less frequent, including chills, night sweats, arthralgia, and loss of weight.[44] Involvement of the posterior cervical group is the most common feature. However, all areas can be involved.[14] Usually, lymph nodes appeared painful, tender with a moderate size. Atypical presentations[4] and extranodal involvement are possible, mainly cutaneous manifestations[75] and aseptic meningitis.[17] Generalized forms sometimes associated with splenic or hepatic enlargement have been already described.

Laboratory findings are usually normal except for inflammatory syndrome or mild cytopenias, sometimes associated with hemophagocytosis.[8]

The clinical picture is not specific and may be consistent with several diagnoses as viral infection (as mononucleosis), bacterial adenitis (mainly tuberculosis or cat scratch disease), malignant lymphoma, or metastatic cancer, especially when constitutional symptoms are marked. Although KFD is not well recognized, it should be included in the differential diagnosis of ''febrile lymphadenopathy.''

Diagnosis is confirmed by analysis of an affected lymph node. Biopsy is generally preferred to fine-needle aspiration.[4] Characteristic features include paracortical areas of necrosis, abundant karyorrhexis and mononuclear cells reaction (histiocytes, plasmacytoid monocytes, small lymphoid cells and immunoblast) around the necrosis foci. Granulocytes and plasma cells are typically rare or absent. Immunohistochemical analysis is helpful to rule out malignant lymphoma. It reveals a predominance of T cells, mostly CD8+, and histiocytes, which express myeloperoxidase (MPO) and CD68 antigens.[46]

Distinguishing KFD lymphadenopathy and SLE-associated adenitis can be a challenge, because both share clinical and pathologic findings. Moreover, the diagnosis of SLE can precede, follow, or coincide with the diagnosis of KFD. However, some pathologic features could be helpful for the distinction.[60] The outcome is usually favorable, although rare cases of fatal progression have been described.[7]

Most of the data in the literature regarding this disease have come from histopathologic studies, most often conducted in Asian populations.[49,77] Thus, we conducted the present study to describe the characteristics of KFD in a Western country. Our secondary objectives were to compare severe forms of KFD with mild forms and to compare the forms of KFD associated with SLE with those that were not.

PATIENTS AND METHODS

Patients

This was a retrospective, observational, multicenter study of cases of KFD diagnosed between January 1989 and January 2011 in 13 hospital centers in France (departments of internal medicine, rheumatology, hematology, infectious diseases or Ear, Nose, and Throat surgery [ENT]). The cases were collected using the coding system of the French healthcare system and the databases of the anatomopathology departments of the 13 centers.

The inclusion criteria, were age >16 years and histopathologic lesions according to the Kikuchi criteria[38] present in all the cases: well-circumscribed focal lesions situated in the lymph node cortex or paracortex; severe necrosis with karyorrhexis or other apoptotic images; the absence of large numbers of polymorphonuclear neutrophils or eosinophils; occasional, sometimes foamy histiocytes, predominantly around the areas of necrosis, as well as lymphoid hyperplasia. The exclusion criterion was a suspected or subsequently confirmed alternative diagnosis (mainly lymphoma or infectious adenitis). In particular, none of the examined lymph nodes was suggestive of SLE adenitis. In particular, there was no evidence of hematoxylin bodies or prominent plasma cells, both features typically found in SLE adenitis.

As in the Kuo definition,[46] we classified histologic variant into the following types: proliferative (composed of various histiocytes, plasmacytoid monocytes and a variable number of lymphoid cells with karyorrhectic nuclear fragments and eosinophilic apoptotic debris), xanthomatous (when foamy histiocytes predominated), and necrotizing (if cellular aggregates in a given lymph node showed any degree of coagulative necrosis).

Study Design and Population

The following data were collected using a standardized form: demographic features including patient origin, previous history of systemic disease, particularly SLE, clinical signs and symptoms at diagnosis (fever, anorexia and its severity, night sweats, shivering, location, number and sensitivity of lymphadenopathies, cutaneous lesions, hepatomegaly and/or splenomegaly, articular or ENT signs [odynophagia, pharyngitis]).

The following laboratory investigations were performed: hemogram; C-reactive protein (CRP); aspartate aminotransferase (ASAT); alanine aminotransferase (ALAT); lactate dehydrogenase (LDH); serology (Epstein-Barr virus [EBV], cytomegalovirus [CMV], parvovirus B19, HIV1 and 2, toxoplasmosis, PCR: EBV, human herpes virus 8; antinuclear antibodies [ANAs] and antinative DNA antibodies.

The therapeutic protocols and evolution of the disease (cure, recurrence, or diagnosis of a concomitant systemic disease) were recorded. Severe forms of KFD were compared with mild forms, and forms of KFD associated with SLE were compared with KFD forms that were not.

Definitions

Severity: Clinical manifestations resulting in severe functional effects or affecting the vital prognosis (weight loss >5 kg, neuromeningeal involvement, hemophagocytic lymphohistiocytosis [HLH] defined according to the criteria of HLH-2004[26]) were defined as severe.[7,36,55]

Deep forms: Forms of KFD termed ''deep'' were characterized by the presence of deep adenopathy on tomodensitometry (TDM) or F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) or the presence of clinical or radiologic organomegaly (hepatomegaly, splenomegaly).[35,47,72]

Recurrence: Recurrence was defined as the reappearance of localized adenopathy and clinical manifestations, identical or not to those observed initially and, if necessary, proven by a new lymph node biopsy.

Diagnosis of a systemic disease, in particular SLE, was based on the 1997 criteria of the American College of Rheumatology.[27]

Literature Review

A search was performed for articles published in the literature between January 1990 and January 2013 in the MED-LINE database (National Library of Medicine, Bethesda, MD), using the following Keywords: 'Kikuchi disease' or 'necrotizing lymphadenitis' only and with the phrases 'neurological involvement', 'aseptic meningitis', 'systemic lupus erythematous', 'hemophagocytic lymphohistiocytosis', 'computed TDM' or 'FDG-PET-CT'. The search included articles published in English and in French.

Statistical Analysis

Descriptive statistics were expressed as means or medians for continuous variables and frequencies (percentage) for categorical variables. Univariate analysis was performed using the Fisher exact test to compare categorical variables and the Mann-Whitney nonparametric test to compare continuous variables. A $p < 0.05$ was considered as statistically significant. Factors associated with severe forms of KFD or associated with SLE were identified by univariate analysis. All the statistical analyses were performed using R software, v. 2.15.1.

RESULTS

Patient Characteristics

Ninety-one patients were included in the study. The main characteristics of these patients are shown in Table 1. Ward origins were as follows: internal medicine (n = 61; 67%), hematology (n = 13; 13%), infectious diseases (n = 9; 9.9%), rheumatology (n = 5; 5.5%), and ENT surgery (n = 3; 0.03%). The median age at diagnosis was 30 years (range, 23–35 yr). The geographic origins of the patients were African (n = 29), North African (n = 14), and European (n = 30). Twelve patients were Asian. Seventy patients (76.9%) were female. Eighteen patients had a history of systemic disease (see Table 1), including 11 with SLE. Two were infected with HIV and were in the stage C. Two patients were homozygous sickle cell carriers (that is, Hb SS), and 1 had end-stage renal failure and was receiving dialysis. One female subject was pregnant.

Clinical and Biological Symptoms

Constitutional signs were observed in 79 cases (86.8%). These consisted of asthenia (n = 64) and/or anorexia (n = 46) and/or weight loss (n = 43), fever (n = 59), night sweats (n = 34) and chills (n = 20). Lymph node involvement was principally cervical (n = 82), more often multiple (n = 47) than localized (n = 40) and sometimes deep (n = 14). Deep involvement was mediastinal (n = 4), intraabdominal (n = 10) or hepatosplenic (n = 12, of which 3 cases were isolated) (see Table 1).

Extranodal symptoms included cutaneous (skin rash, maculopapular erythema, oral ulceration) (n = 27), arthralgia (n = 29), and aseptic meningitis (n = 2). Examination of cerebrospinal fluid showed hypercellularity with a predominance of lymphocytes (38 and 100 cells/mm^3), normoglycorrachia, and hyperproteinorrachia (2 g/L) in 1 case.

HLH was present in 3 cases, and severe KFD was present in 20 cases (22%).

The main biological abnormalities are shown in Table 1. Increase acute phase reactants (that is, sedimentary rate >20 mm in the first hour or CRP >10 mg/L) was present in 56.4% of cases (n = 44; not recorded [NR] = 13) with a mean CRP of 30 ± 32.7 mg/L (n = 63; NR = 28), lymphopenia in

63.8%, thrombocytopenia in 19%, elevated LDH in 81.5% and hepatic cytolysis in 24.4%.

A significant titer (>1/320) of ANA was present in 33 cases (45.2%; NR = 18) and anti-DNA antibodies in 11 cases (18%; NR = 30). Mixed cryoglobulinemia was observed in 2 patients (including 1 with SLE). Eight concomitant viral infections were documented: EBV (n = 4) (seroconversion in 2 cases and new PCR-positive in the other 2); parvovirus B19 (n = 2); herpes virus 6 (n = 1) (PCR) and Coxsackie A (n = 1) (see Table 1). Two patients were infected with HIV with CD4 < 50/mm^3 and were not receiving antiretroviral treatment, 1 because of a recent diagnosis and the other because of nonadherence in drug taking.

Histopathology

The diagnosis was made in all the cases by histopathologic examination of a lymph node biopsy. The histologic subtypes were as follows: necrotic (76.5%); xantho-granulomatous (19.1%), and proliferative (4.4%). Liver biopsy showed severe necrosis with karyorrhexis. Skin biopsy revealed vacuolization of the basal membrane and dermal infiltrates consisting of small-sized lymphocytes and histiocytes, without any vascular changes.

Evolution and Treatment

The median time to diagnosis was 1.6 months (range, 1–3 mo; n = 75). All patients had a favorable outcome. We observed 1 perforation of the nasal septum, concurrent with KFD, in a SLE patient. One left axillary venous thrombosis complicated the evolution of axillary adenitis.

Generally (61.5%; n = 56), no treatment has been required, with spontaneous regression of clinical symptoms and normalization of biological parameters. Because of a marked symptomatology or association with SLE, treatment was started in 35 cases (38.5%): corticosteroids (n = 29) at a dose of 0.5–1 mg/kg of prednisone, for periods ranging from 10 days to 2 months; nonsteroidal antiinflammatory drugs (NSAIDs) (n = 6); or intravenous immunoglobulin (IVIG) (n = 3). Sixteen patients have been treated by hydroxychloroquine: SLE was recently diagnosed for 11 patients, 5 patients were previously treated for SLE and for 3 patients KFD was the single diagnosis. For the 8 patients previously treated by low dose corticosteroids, the dose was increased. Thirty-six patients received empirical antimicrobial therapy before diagnosis.

Clinical recurrence was observed in 16 patients (21.3%, NR = 14) with a time to relapse of 3.5 months (1–11.5). One of the patients infected with HIV had a recurrence of KFD documented from lymph node biopsy in the month following spontaneous cure and the initiation of antiretroviral treatment. Diagnosis of both KFD and SLE was made in 10 patients. Of the 33 patients who had significant titer of ANAs during the first episode, 11 had known SLE, 10 had a concomitant diagnosis of SLE, 2 developed SLE in the year following the diagnosis of KFD, 6 did not develop SLE, and the other 4 were lost to follow-up (median follow-up, 19 mo; range, 3–39 mo).

The presence of weight loss, arthralgia, skin lesions and ANA was associated with the development of SLE ($p < 0.05$) (Table 2).

Table 3 shows determinants of severe forms of KFD. Male sex and lymphopenia were associated with the more severe forms ($p < 0.05$).

TABLE 1. Baseline characteristics of Kikuchi-Fujimoto patients

	N (%) (n = 91)	NR[*]
Epidemiologic features		
Age,yr[†]	30 (23−35)	−
Female sex	70 (76.9)	−
Geographic origin		4
Europe	30 (33)	
Afro-Caribbean	29 (32)	
North Africa	14 (15.4)	
Asia	12 (13.2)	
South America	2 (2.2)	
Unknown	4 (4.4)	
Co-morbid disease		
SLE	11 (12)	−
Systemic sclerosis	2	−
Hashimoto thyroiditis	1	−
Sharp syndrome	1	−
Others[*,‡]	10	−
Clinical features		
Asthenia	64 (74.4)	5
Anorexia	46 (55.4)	8
Weight loss	43 (51.2)	7
Fever ($\geq 38°$c)	59 (67)	3
Night sweats	34 (43)	12
Chills	20 (26.7)	16
Cervical lymph node	82 (90.1)	−
Axillary lymph node	36 (39.6)	3
Lymph nodes, other localization	29 (32)	2
Lymph nodes (>2 localizations)	47 (52)	4
Tender lymph nodes	53 (68.8)	14
Hepatomegaly, splenomegaly	12 (14.8)	10
Skin rash	27 (32.9)	9
Arthralgia	29 (34.1)	6
Odynophagia	26 (30.9)	7
Deep form	17 (18)	−
Severe form	20 (22)	−
Laboratory features		
Inflammatory syndrome (C-RP> 10 mg/l; ESR> 20mm)	44 (56.4)	13
Neutropenia (PNN< 1500/mm3)	28 (35)	8
Lymphopenia (< 1500/mm3)	53 (63.8)	8
Thrombocytopenia (<150 000/mm3)	12 (19)	28
Elevated liver enzymes (ALAT> 42U/l)	20 (24.4)	49
Increased LDH (>460UI/l)	44 (81.5)	37
ANA	33 (45.2)	18
Anti ds-DNA	11 (18)	30
Positive viral serology[§]	8 (8.8)	−
Treatment		
NSAIDs	6 (6.6)	−
Corticosteroids	29 (31.9)	−
Hydroxychloroquine	16 (17.6)	−
IVIG	3 (3.3)	−
Antibiotics	36 (39.6)	−
Outcome		
SLE	12 (13)	−
Recurrence	16 (20.7)	14

Abbreviations: ANA = Anti nuclear antibody; CRP = C-reactive protein; ds-DNA = double stranded DNA antibody; ESR = Erythrocyte sedimentation rate; IVIG = Intravenous Immunoglobulins; LDH = Lactate deshydrogenase; NSAIDs = non-steroidal anti-inflammatory drugs; SLE = Systemic Lupus Erythematosus.

[*] not recorded.

[†] Median (Q1-Q3).

[‡] rheumatoid arthritis (1), Antiphospholipid syndrome (1), severe Raynaud's phenomenon (2), mixed connective (1), HIV(2), Sickle cells disease (2), end stage chronic kidney disease (1).

[§] Epstein Barr Virus (EBV) = 4; Parvovirus B19 = 2, Human Herpes virus 6 (HHV6) = 1, Coxsackie A=1.

TABLE 2. Kikuchi-Fujimoto Disease Patients With and Without Systemic Lupus Erythematosus de Novo

	KFD With SLE de novo (n = 12) N (%)	KFD Without SLE* (n = 68) N (%)	p
Epidemiologic features			
Age,yr[†]	27.5 (16–34)	30 (23–35)	NS
Male sex	2 (17)	17 (25)	NS
Clinical features			
Weight loss	10 (83)	25 (40)	<0.01
Fever (≥ 38°c)	11 (92)	41 (62)	NS
Night sweats	5 (56)	27 (44)	NS
Cervical lymph nodes	11 (92)	62 (91)	NS
Axillary lymph nodes	6 (50)	25 (37)	NS
Hepato-Splenomegaly	2 (18)	6 (10)	NS
Cutaneous rash	7 (58)	15 (25)	0.03
Arthralgia	7 (64)	17 (27)	0.03
Odynophagia	5 (42)	18 (29)	NS
Deep form	2 (17)	9 (13)	NS
Severe form	5 (42)	12 (18)	NS
Recurrence	3 (25)	10 (19)	NS
Laboratory features			
Inflammatory syndrome (CRP> 5 mg/l; ESR > 20mm)	6 (67)	32 (54)	NS
Neutropenia (PNN< 1500/mm3)	4 (36)	21 (34)	NS
Lymphopenia (< 1500/mm3)	9 (75)	36 (60)	NS
Thrombocytopenia (<150 000/mm3)	3 (33)	8 (17)	NS
Elevated liver enzymes (ALAT> 42U/l)	3 (50)	16 (53)	NS
Increased LDH (>460UI/l)	8 (89)	31 (78)	NS
ANA	11 (100)	11 (22)	<0.01
Anti ds-DNA	5 (63)	1 (2)	<0.01
Positive viral serology	1 (8)	5 (7)	NS
Treatment			
NSAIDs	1 (8)	5 (7)	NS
Corticosteroids	9 (75)	12 (18)	<0.01
Hydroxychloroquine	8 (67)	3 (4)	<0.01
IVIG	0 (0)	2 (3)	NS
Antibiotics	6 (50)	28 (41)	NS

Abbreviations: ANA = Anti nuclear antibody; CRP = C-reactive protein; ds-DNA = double stranded DNA antibody; ESR = Erythrocyte sedimentation rate; IVIG = Intravenous Immunoglobulins; LDH = Lactate deshydrogenase; NSAIDs = non-steroidal anti-inflammatory drugs; SLE = Systemic Lupus Erythematosus.
* patients with previous SLE where excluded of analysis.
[†] Median (Q1-Q3).

DISCUSSION

Kikuchi-Fujimoto disease has mostly been described in Asia, probably due to HLA haplotypes, with series reporting as far as 276 patients[38] (Table 4). To our knowledge, the present study of 91 cases is the largest clinical study of KFD in Western countries. Dorfman et al[14] reported 108 cases but data were mainly histopathologic. Our study confirmed, as in Asia, the female predominance of KFD, as well as the preferential involvement during the third decade of life.[14,38,41,44,49,59,73,77] Constitutional symptoms were most often predominant, with fever, in a same proportion to that already described in the literature.[44] We observed a large proportion of severe symptoms (22%), certainly due to recruitment in hospital wards. Lymph node involvement was mainly cervical (90%), rarely isolated and polyadenopathy was found in half of the cases. Cutaneous lesions were present in one-third of the cases, complicating the differential diagnosis with SLE,[3] particularly in patients with facial involvement. These lesions consisted of a skin rash, but macules, papules or plaques were also possible, in agreement with the existing data.[3] They could precede the appearance of adenopathies or appear concomitantly. The face, trunk and upper limbs are the preferential sites.[3,75] Mucous eruptions

are more rare.[32,76] Skin biopsy could be useful[32,40,45] as in 1 case in our study: it showed dermal histiocytic (or lympha-histiocytic) infiltrates, presence of necrotic keratinocytes in the epidermis, non-neutrophilic karyorrhexis, papillary dermal edema and basal vascular changes.[32,45,69] In our study, skin involvement was not associated with a risk of recurrence or with severe forms of KFD, in contrast to the study by Sumiyoshi and Kuo. The frequency of arthralgia (34.1%) was higher than that usually described, from 5–10%. 64% of our patients who progressed to SLE had arthralgia at diagnosis (p = 0.003; see Table 2).

We only report 2 cases of visceral forms. In the literature, pulmonary,[21,30] cardiac,[7] and neurologic[56] involvement have been described, mostly meningitidis (n = 22).[2,13,17,43,44,52,56,74] Histologic examination of solid organs has rarely been performed. One of our patients underwent a liver biopsy, which revealed characteristics similar to those described in lymph node biopsies. Forms with associated HLH are also rare, with fewer than 20 cases published, mainly in children and adolescents.[48] The clinical signs are marked,[51] with eventually a fatal evolution.[36] Lee et al[48] reported 12 cases, of which 4 fulfilled the criteria of HLH-2004,[26] with favorable outcome with high-dose corticotherapy (8 cases), IVIG (6 cases), etoposide

TABLE 3. Characteristics of Kikuchi-Fujimoto Disease Patients With and Without severe forms

	KFD With severe forms (n = 20) N (%)	KFD Without severe forms (n = 71) N (%)	p
Epidemiologic features			
Age,yr[*]	31 (23–35)	30 (22–35)	NS
SLE	3 (15)	7 (9.8)	NS
Other rheumatoid diseases	5 (24)	17 (24)	NS
Geographic origin			
Europe	5 (25)	25 (35)	NS
Afro-Caribbean	7 (35)	22 (30)	NS
North Africa	8 (40)	6 (8.4)	<0.01
Asia	–	12 (17)	–
South America	–	2 (2.8)	–
Clinical features			
Asthenia	18 (86)	46 (64.8)	0.08
Anorexia	17 (81)	29 (41)	<0.01
Loss of weight	17 (81)	26 (36.6)	<0.01
Fever (≥ 38°c)	16 (76.2)	43 (60.5)	NS
Night sweats	12 (57.1)	22 (31)	0.03
Cervical lymph node	18 (86)	64 (90.1)	NS
Axillary lymph node	10 (47.6)	26 (36.6)	NS
Hepato-splenomegaly	7 (33.3)	5 (7)	<0.01
Cutaneous rash	8 (38)	19 (26.8)	NS
Odynophagia	6 (28.6)	20 (28)	NS
Arthralgia	10 (47.6)	19 (26.8)	NS
Deep form	6 (28.6)	11 (15.5)	NS
Laboratory features			
Inflammatory syndrome	11 (52.4)	33 (46.5)	NS
Neutropenia	5 (23.8)	23 (32.4)	NS
Lymphopenia	16 (76.2)	37 (52)	0.05
Thrombocytopenia	5 (23.8)	7 (10)	NS
Elevated liver enzymes	8 (38)	12 (17)	NS
Increased LDH	13 (62)	31 (43.6)	NS
ANA	5 (23.8)	6 (8.4)	NS
Anti ds-DNA	10 (47.6)	20 (28)	0.08
Positive viral serology	3 (14.3)	5 (7)	NS
Outcome			
Recurrence	3 (14.3)	13 (18.3)	NS
SLE diagnosis	3 (15)	7 (10)	NS

Abbreviations: ANA = Anti nuclear antibody; CRP = C-reactive protein; ds-DNA = double stranded DNA antibody; ESR = Erythrocyte sedimentation rate; LDH = Lactate deshydrogenase; SLE = Systemic Lupus Erythematosus.
[*] Median (Q1-Q3).

(2 cases) and cyclosporine (1 case). In our series, 1 patient received intravenous corticoids and no evolution toward SLE or recurrence was observed.

Disease course was always favorable, spontaneously (n = 56; 61.5%) or with analgesics and/or antipyretics. This rate is lower than in the literature, ranging between 87.2% and 95%,[64,67] but is close to the 64% reported by Kucukardali et al.[44] In our series, 20% of the patients had recurrence of KFD, but no predictive factors were found. Neither the ethnic origin of the patient nor the association with lupus appeared to influence the risk of recurrence (p = NS).

When treatment is necessary, short-duration oral corticosteroid therapy is the treatment of choice,[4,5] allowing for rapid control of the disease,[1] although there are no recommendations regarding the method of administration. The severity of symptoms might justify high doses of methylprednisolone.[8] We used IVIG (0.4 g/kg, 2 days) with success in 3 patients with severe disease. They have already been used in spite of the absence of recommendations[55] as they have an immunomodulatory role[37] which makes it a treatment of choice in many autoimmune and inflammatory diseases.[22] Hydroxychloroquine, alone or in association with other treatments, mainly corticosteroids, was used in 17.6% of our patients (see Table 1). Interestingly, it has been successfully used in patients with symptomatic KFD which was not associated with SLE.[9,63] The antiinflammatory and immunomodulatory nature of this treatment, notably on antigen presentation and protein degradation, could explain this success.[18,19,57] Furthermore, the low toxicity of this treatment, administered for a short duration in low cumulative doses, could make it a treatment of choice for symptomatic forms of KFD.

An original feature of our study was the predominance of subjects of African origin, in contrast with the classic over-representation of Asian patients.[44,54] In the study by Dorfman,[14] performed in North American subjects (n = 88), Afro-Caribbean subjects only represented a minority of patients (n = 6). This difference could be explained in part by the demography of the Ile de France region, which is characterized by a large proportion of migrants originating from old French colonies.[34] One also may hypothesize that genetic susceptibility to autoimmune diseases could explain the large number of African patients in our population.

TABLE 4. Comparison of Kikuchi-Fujimoto disease manifestations between previous and present series

	Dumas et al.	Cheng et al.	Young Song et al.	Yu et al.	Kuo	Tsang et al.	Treilleux et al.	Kikuchi et al.	Dorfman et al.	Pileri et al.	Turner et al.
Reference	Present report	(11)	(58)	(85)	(46)	(79)	(78)	(38)	(16)	(60)	(81)
Year of publication	2014	2010	2009	2005	1995	1994	1991	1990	1988	1982	1982
Number of patients	91	195	102	58	79	75	11	276	108	27	30
Country	France	Taiwan	Korea	Taiwan	Taiwan	Hong-Kong	France	Japan	USA/other countries	Germany	USA
Age (yr)	30	24.6	26.7	24.9	26.8	25.5	23	26.9	30	26.6	28
Sex ratio M/F	1/3	1/2.6	1/3.6	1/1.76	1/1.1	1/2.75	1/2.7	1/1.56	1/4	1/2.85	1/9
Caucasian (%)	33	0	0	0	0	–	63.6	–	63	96	63
Afro-Caribbean (%)	31.9	0	0	0	0	–	36.4	–	5	–	0
Asian (%)	13.2	100	100	100	100	100	0	100	–	4	20
Localized nodes (%)	48	74.9	10.8	94.8	97	94.6	90	97.5	86	55.5	76.7
Generalized nodes (%)	52	23.1	3.9	5.2	1.3	5.3	–	11.3	12	22.2	23.3
Fever (%)	67	37.9	73.5	43	48.4	38.5	45.5	30.2	33	50	6.7
Night sweats (%)	43	5.6	8.8	2	–	–	36.4	–	6,5	–	3
Arthralgia (%)	34.1	2.6	6.9	3	–	–	27.3	–	3,7	–	–
Rash (%)	32.9	4.1	2	3	1.26	–	9	–	3,7	–	3.3
Hepato-splenomegaly (%)	14.8	–	–	3	–	–	–	–	8,3	28.5	10
Leucopenia (%)	34.9	23.1	53.5	29	42.9	45.5	18	58.3	20	25	16.7
ANA at diagnosis (%)	42.2	8.9	30.4†	–	2.5	6	–	–	7	–	–
Inflammatory syndrome (%)*	56.4	78.9	–	14	–	–	–	–	–	71	–
Corticosteroid Treatment (%)	31.9	–	12.7	7	–	–	–	–	–	–	–
Associated viral disease (%)	8.8	0	–	–	–	–	–	–	–	–	–
Recurrence (%)	17.6	7	20.6	0	3.3	3	18.2	4	5	–	–

ANA = Anti nuclear antibody.
* defined by elevated ESR or C-RP.
† data available in 46 patients.

TABLE 5. Minimal diagnostic assessment in KFD

Comprehensive history, Repeated physical examination
Routine blood exams
    Complete blood count, routine blood chemistry, including bilirubin, Lactate dehydrogenase, liver enzymes, erythrocyte sedimentation rate,
      C-reactive protein, routine blood culture
    Urinalysis
Serologic tests
    HIV, EBV, CMV, Toxoplasma gondii, HHV6, HHV8
Auto-immunity
    Antinuclear antibodies, rheumatoid factor
Chest radiograph
Lymph node biopsy
    With standard coloration, immunohistochemistry, Standard culture, Ziehl-Neelsen, culture for Mycobacterium tuberculosis.
Optional (clinical setting-differential diagnosis)
    Cat scratch disease serology or PCR, parvovirus B19, Yersinia enterocolitica serology
    HSV, CMV, VZV (serology and/or PCR)[*]
    CT scan
    FDG-CT scan[†]

[*] no supportive data.
[†] if fever of unknown origin or clinical study protocol.
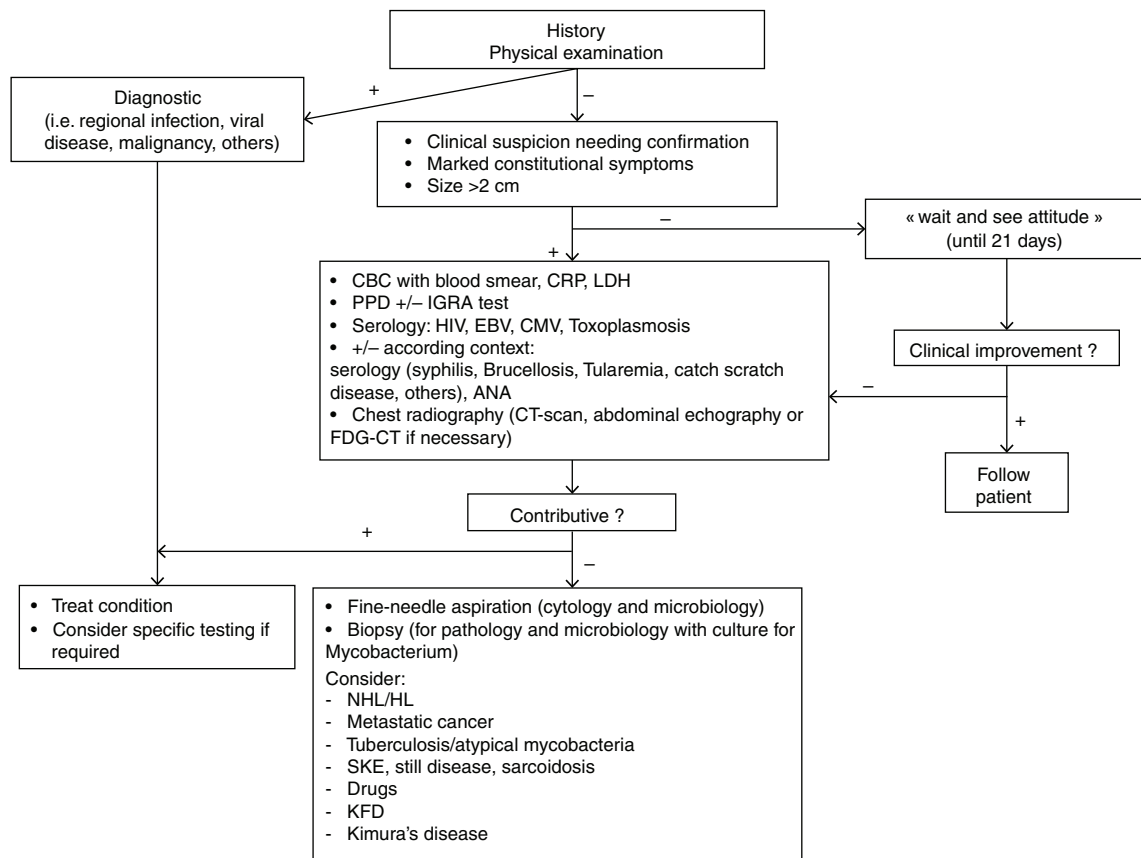
FIGURE 1. Cervical lymphadenopathy: diagnosis algorithm. Abbreviations: ANA = antinuclear antibody; CBC = complete blood count; CMV = cytomegalovirus; CRP = C-reactive protein; CT = computed tomography; EBV = Epstein-Barr virus; FDG-CT = F-18 fluorodeoxyglucose positron emission tomography/computed tomography; HIV = human immunodeficiency virus; HL = Hodgkin lymphoma; IGRA test = interferon gamma release assay; KFD = Kikuchi-Fujimoto disease; LDH = lactate dehydrogenase; NHL = non-Hodgkin lymphoma; PPD = purified protein derivative; SLE = systemic lupus erythematosus.

Few data are available on deep forms of KFD. In our study, the frequency of deep forms (18%) was higher than usually described (5%).[4,14,44,73] It is likely that deep and systemic forms of KFD were underestimated because CT or FDG-PET/CT were rarely performed. Dorfman[16] and Tsang[71] reported a small percentage of deep (3%) or generalized (5%) lymph node involvement (see Table 4). Kucukardali[44] reported rare cases of mesenteric involvement. More recently, Rimar,[64] in a study of KFD in Israel, reported 21% retroperitoneal involvement and 26% generalized lymphadenopathies, compared with 22% in the study by Pileri[61] and 11% in the Japanese study by Kikuchi.[38] There are no data, however, on the prognostic value of this presentation. FDG-PET/CT generally performed for the investigation of prolonged fever or if lymphoma is suspected, could help to individualize deep involvement. A FDG-PET/CT study performed in 9 patients with proven KFD demonstrated the existence of 2 profiles: a superficial presentation (n = 6) with small, primarily cervical lymph nodes and a more diffuse and deep one (n = 3).[62]

We observed severe form of KFD in 20 patients, more frequently in men, in the presence of night sweats, hepatomegaly, splenomegaly or lymphopenia or of a North-African origin (see Table 3, p < 0.05). The greater severity of KFD in men has never been described before. Night sweats, hepatomegaly and splenomegaly suggest a more generalized form of the disease, which can mimic lymphoma. Lymphopenia has rarely been studied in KFD, in which leuko-neutropenia and lymphocytosis have been more classically described.[4,44] In a study of 20 patients with both KFD and SLE, authors found lymphopenia in 15.[68] However, in our study, no significant difference in lymphocyte count was found between patients with lupus and the others. Subjects of North African origin appeared have a higher risk of more severe forms of KFD, which has never been described before, but could be linked to a HLA susceptibility.

We described a large number of cases of SLE associated with the diagnosis of KFD, 25% of our patients, which is higher than the 13% described recently.[44] Half of our patients were already followed up for SLE, and SLE was reported in the remaining patients following a diagnosis of KFD (see Table 1). No clinico-biological or prognostic differences were observed between patients with previous or de novo SLE. Arthralgia, cutaneous manifestations, weight loss, ANAs and anti-DNA antibodies were significantly associated with the development of SLE (see Table 2). No studies have previously documented a link between weight loss and a disease course toward SLE. The other factors, in part, concurred with the definition of SLE. In our study, we showed no association between SLE and deep or severe forms of KFD, in contrast to what has been suggested previously.[25] No influence of the geographic origin of the patients was observed. On the contrary, Kucukardali[44] showed a higher frequency of both SLE and KFD in Asian patients. Lymph nodes during SLE are uncommon, ranging from 12% to 26% of cases.[6,66] The exact prevalence of this association is unknown because SLE lymphadenopathies are rarely biopsied.[66] Nevertheless, many studies have reported SLE flare-ups concomitant with the diagnosis of KFD.[10,29,42] Secondly, association of SLE and non-Hodgkin lymphoma have already been described.[78] Also, lymph node biopsy is needed in case of diagnostic uncertainty. The common clinical presentation of these diseases, as highlighted in our study, can mislead the clinician. The detection of significant levels of ANA might be useful. These antibodies have prognostic value for the risk of recurrence and evolution toward SLE.[67] Of the 33 patients with positive ANAs in our study, a diagnosis of SLE was made in 2

patients in the year following diagnosis, and 6 patients did not develop SLE.

To our knowledge, none of the large series published to date has described cases of infection or seroconversion occurring at the time of diagnosis with KFD. In our study, 8 patients had documented recent viral infection, concomitant with the diagnosis of KFD, despite the nonsystematic character of viral assessment (see Table 1). The most frequently detected viruses were EBV and parvovirus B19. There was also a single case of concomitant infection with Coxsackie A. 2 patients were infected with HIV, for which an association with KFD has rarely been reported.[31,65] The link between KFD and infection has been the subject of debate for many years,[14,16,31,33] and previous studies attempting to demonstrate a causal link have failed.[12,23,28,50,65] The microorganisms most frequently implicated have been EBV, herpes viruses (particularly human herpes virus 6), parvovirus B19, and *Toxoplasma gondii*.[2,4]

In light of these data, it appears pertinent, when attempting to diagnose histiocytic necrotizing lymphadenitis, to propose minimal assessments to rule out the main differential diagnoses, and to look for an associated disease (Table 5). Figure 1 shows our management strategy for cervical lymphadenopathy.

We acknowledge some limitations in the current study. Our analysis was performed as a retrospective review, with potential bias. Additionally, the initial assessment was not standardized, especially for viral screening and imaging procedures. Prospective enrollment and data collection from the time of diagnosis would be ideal, but is more difficult to achieve with rare diseases.

In conclusion, this study updates the clinical presentations of KFD, which is not only found in young Asian women. Deep or systemic forms are not uncommon. Weight loss, arthralgia, cutaneous manifestations, and ANA antibodies were associated with the development of SLE. Subjects of North African origin appeared to have an increased risk of severe KFD, probably due to HLA susceptibility. A prospective study is ongoing in order to better identify the etiologic factors and to validate these important observations.

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