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Review Article

Kikuchi-Fujimoto disease associated with Sjogren's syndrome: a case report and review of the literature

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Abstract: Kikuchi-Fujimoto disease (KFD), known as subacute necrotizing histiocytic lymphadenitis, is an extremely rare, benign and self-limited disease, and has been infrequently reported with autoimmune diseases. Here we report a 17-year-old girl pathologically diagnosed as KFD who suffered recurrence of KFD and developed into Sjogren's syndrome (SS) after four years and then performed a systematic literature search about KFD associated with SS in which seven patients was reviewed in detail. The results show that SS may be prior to, simultaneous with or following KFD and it developed mainly in young (average age: 25 years), female patients (4/5) after KFD with an average latency of 43 months. Therefore, long follow-up and appropriate clinical and laboratory workup are highly encouraged to exclude underlying SS conditions in young women with KFD.

Keywords: Kikuchi-Fujimoto disease, lymphadenopathy, Sjogren's syndrome

Introduction

Kikuchi-Fujimoto disease (KFD), also named as histiocytic necrotizing lymphadenitis, is firstly described independently in 1972 by Kikuchi and Fujimoto et al, usually characterized by cervical lymphadenopathy and prolonged high fever [1, 2]. It is difficult to accurately diagnose KFD, which can resemble lymphoma, tuberculosis, and systemic lupus erythematosus (SLE), based on physical findings or imaging alone. The lymph node (LN) biopsy may histologically confirm the disease by identifying eccentric, crescentshaped nuclei of histiocytes, karyorrhectic debris, and plasmacytoid monocytes in the form of nodules, with a paucity of neutrophils [3]. Clinically, KFD is rarely associated with autoimmune diseases, in particular, such as SLE [4]. We herein present the case of a female Chinese patient with KFD who recurred and developed Sjogren's syndrome (SS) manifestations after four years.

Material and methods

Case presentation

A 17-year-old Chinese girl presented to our hospital with one-month history of recurrently bilateral cervical lymphadenopathy associated with high fever (40°C), sore throat, dizziness, oral ulcer, and slight weight loss, and without improved antibiotics treatment in September 2009. She had a past medical history of allergic rhinitis for one year. Laboratory findings showed that the levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and alanine transaminase increased, while hemoglobin, leukocyte count, platelet count, aspartate aminotransferase, serum ferritin, serum urea, creatinine, tumor markers, and analysis of urine and stool were within normal limits. Serum antinuclear antibody (ANA), anti-extractable nuclear antigen antibody (anti-ENA), anti-double-stranded-DNA (anti-dsDNA), anti-Sm, anti-Ro, anti-La, anti-neutrophilic cytoplasmic antibody, rheumatoid factor, anti-tuberculosis antibody, anti-typhus antibody, and anti-streptolysin were negative (**Table 1**). The RNA-negative of enterovirus and IgM-negative and low-titer IgG-positive of Coxsackie virus B, Epstein-Barr virus and cytomegalovirus were found. The ultrasonography showed multiple enlargement of bilateral cervical, left axillary and retroperitoneal LNs with the largest measuring 2.2 cm. Due to prolonged high fever of unknown origin, ^{18}F-fluoro-

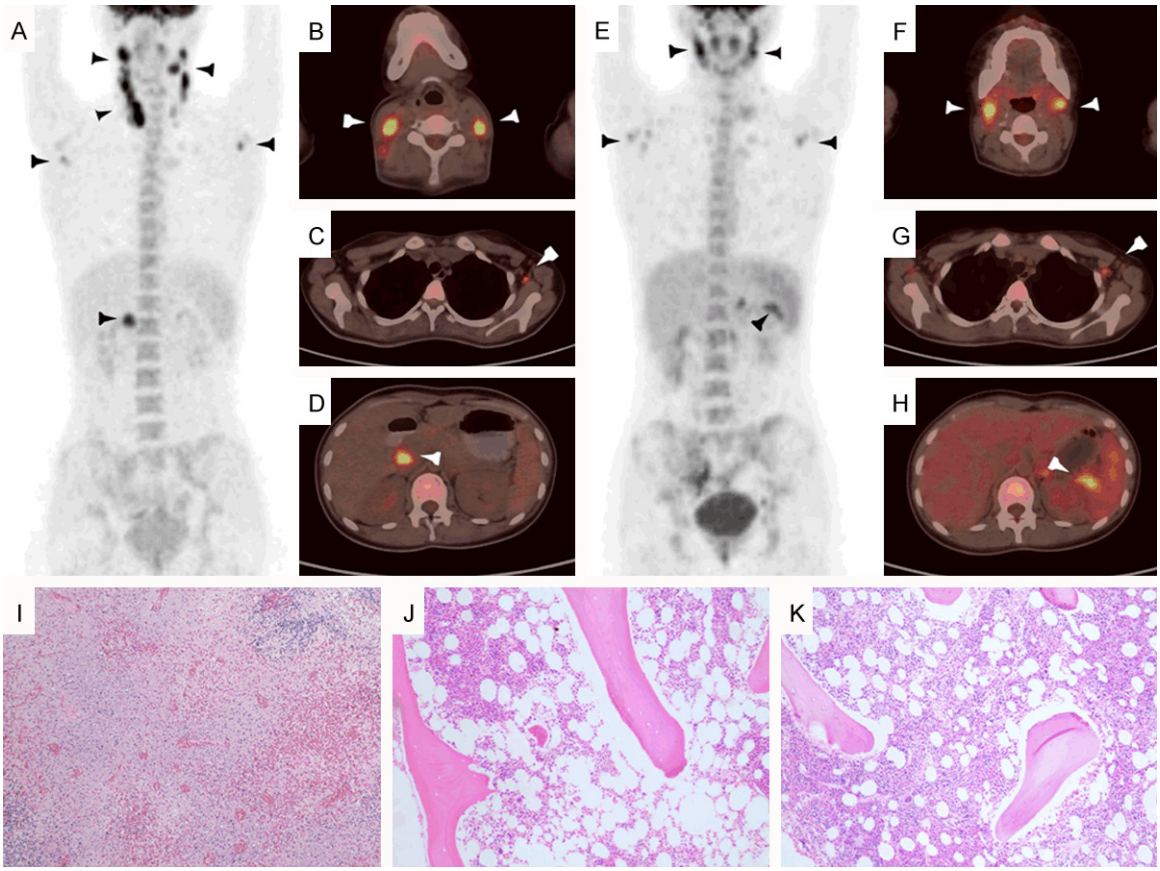

Figure 1. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and biopsy specimens of cervical lymph node (LN) and bone marrow (BM). The first maximum intensity projection (MIP) (A) and axial images show intense accumulation of ^{18}F-FDG (arrows) in bilateral cervical (B) and axillary (C), and hepatic hilar LNs (D) in initial diagnosis of Kikuchi-Fujimoto disease (KFD). The second MIP (E) and axial images show extensive uptake of ^{18}F-FDG (arrows) in bilateral cervical (F) and axillary (G), and splenic hilar LNs (H) in recurrence of KFD associated with Sjogren's syndrome after 4 years. Histopathological images show the disrupt structure with plenty of lymphohistiocytic cells, karyorrhectic nuclear debris, and extensive necrosis in LN (I), and actively benign proliferation of hematopoietic cell in BM (J, K) (H&E × 100).

deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan was performed and revealed multiple enlargement of LNs in bilaterally cervical and axillary, and hepatic hilar regions with high uptake of ^{18}F-FDG (location with highest uptake: right neck; size: 1.76 × 1.06 cm; maximum standard uptake value, SUVmax: 8.5) (**Figure 1A-D**). For excluding lymphoma, right cervical LN and bone marrow biopsy were advised and performed. Histological and immunohistochemical examinations exhibited disrupt structure with plenty of lymphohistiocytic cells expressing both CD68 and MPO, karyorrhectic nuclear debris, and extensive necrosis in LN and actively benign proliferation of hematopoietic cell in bone marrow (**Figure 1I**, **1J**). Consequently, KFD was diagnosed, and then all symptoms and laboratory data improved after methylprednisonlone was intravenously administered (40 mg/d) for 8 days and taken orally (16 mg bid) for 3 months.

Four years later, she returned with high fever (41°C), right cervical lymphadenopathy, fatigue, oral ulcer, dental caries, alopecia, vulvav ulcer, and Raynaud's phenomenon for one week in September 2013. Laboratory data revealed mild anemia, leukopenia, increased levels of ESR and CRP, and positive results of ANA (1:80), anti-Ro and anti-Ro52 antibody (**Table 1**). The PET/CT findings showed generally multiple enlargement of LNs with extensive accumulation of ^{18}F-FDG, which of highest uptake located in right neck with 7.26 of SUVmax (**Figure 1E-H**). Schirmer's test was negative,

Table 1. Evolution of laboratory data in present case

Laboratory data	Initial KFD (Sep-2009)	Recurrent KFD with SS (Sep-2013)	Follow-up (Nov-2014)
Hemoglobin (131-172 g/L)	120	108	124
Leukocyte (4-10 × 10^9/L)	4.8	3.4	5.3
Platelet (83-303 × 10^9/L)	208	218	184
ALT (5-35 U/L)	55	10	12
AST (8-40 U/L)	18	16	15
Ferritin (7-323 ng/mL)	236.1	90.4	ND
ESR (0-20 mm/h)	73	64	9
CRP (0-8 mg/dL)	14.2	78.9	1.6
RF	-	-	-
ANA	-	+(1:80)	+(1:80)
Anti-ENA	-	-	+
Anti-dsDNA	-	-	+(weak)
Anti-Ro	-	+	+
Anti-Ro52	-	+	+
ANCA	-	-	ND

ALT, alanine transaminase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; Anti-dsDNA, anti-double-stranded DNA; Anti-ENA, anti-extractable nuclear antigen antibody; AST, aspartate transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; KFD, Kikuchi-Fujimoto disease; ND, not done; RF, rheumatoid factor; SS, Sjogren's syndrome; +, positive; -, negative.

while sialoscintigraphy with technetium-99m was positive without visualization of bilateral submandibular glands (**Figure 2A**). Lip biopsy displayed slight plasma cells in the mesenchyme of labial gland (**Figure 2B**). Bone marrow biopsy showed active proliferation of hematopoietic cell without malignant signs (**Figure 1K**). And so, the recurrent KFD with SS was clinically considered. Unfortunately, LN biopsy was no implemented by reason of patient's disapproval. She spontaneously recovered to normal body temperature two weeks later. Subsequently, the traditional Chinese medicine and total glucosides of paeony were intermittently taken, and fatigue and dental caries were suffered repeatedly up to now. The positive ANA (1:80), anti-ENA, anti-Ro and anti-Ro52 and weak positive anti-dsDNA were observed in November 2014 (**Table 1**).

Literature search

A systematic literature search was performed using subject terms "Kikuchi-Fujimoto and Sjogren" and "necrotizing histiocytic lymphadenitis and Sjogren" in PubMed and Embase to identify articles. The language was restricted to English. For recruited patients in collected articles, the race, gender, age of KFD onset, duration of KFD, latent period between KFD and SS, autoimmunity, steroid treatment, clinical outcome, and follow-up were reviewed in detail. This case was approved by the institutional review board.

Results

In total, six articles were identified by the search criteria, of which one non-English article was excluded from the review. Finally, five articles with seven patients (including our patient) were analyzed (**Table 2**) [5-9]. The SS was diagnosed simultaneously in a 24-year-old woman, 26 years before in a 42-year-old woman, and after the onset of KFD in five patients, whose ratio of females to males was 4:1, and age range and latent period were from 7 to 42 years (mean ± standard deviation: 25.0 ± 13.5 years) and 2 month to 10 years (mean ± standard deviation: 43 ± 46 months), respectively.

Discussion

KFD is considered an extremely rare, benign and self-limited disease, known as subacute necrotizing histiocytic lymphadenitis. It has a worldwide distribution with higher prevalence among Asian, and usually happens to occur in young adults below 40 with a fourfold female predominance. Although the exact etiology of KFD is still unknown, it may be associated with CMV, EBV infection, or SLE and other autoimmune diseases [3]. However, we no repeated these virus or autoimmune serologies confirming the possible etiology. Cervical lymphadenopathy and fever, usually low-grad, and elevated ESR and CRP are the commonly clinical manifestations and laboratory findings of patients with KFD, as observed in our patient [3, 4].

Up to now, KFD is often identified difficultly because of its very low incidence, non-specifically clinical manifestations, laboratory tests and radiologic findings. Therefore, it is frequently misdiagnosed as malignant lymphoma

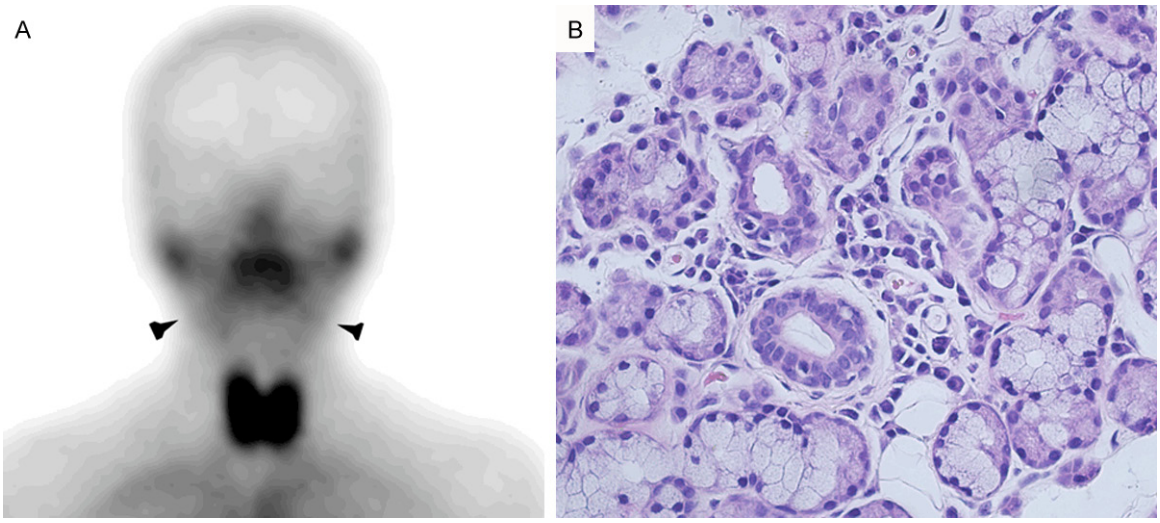

Figure 2. Sialoscintigraphy with technetium-99m and lip biopsy specimen. Sialoscintigraphy image (A) shows no visualization of bilateral submandibular glands (arrows). Lip biopsy (B) displays slight plasma cells in the mesenchyme of labial gland (H&E × 400).

or some other form of inflammatory disease and diagnosed finally by biopsy from an affected LN [10]. It is worth mentioning that the PET/CT imaging findings showed systemic lymphadenopathy with high accumulation of ^{18}F-FDG and guided the affected LN biopsy in our patient. In contrast to conventional imaging methods, ^{18}F-FDG PET/CT reflects glucose metabolism and enables estimation of the disease activity of lesions [11]. And so, it can be a useful tool to localize an appropriate biopsy site, especially in cases with a negative result using conventional imaging methods. In general, KFD resolves spontaneously within 1 to 4 months. Sometimes, but rarely, steroids can be used temporarily, especially in severe extranodal involvement or generalized clinical course, as evidenced herein [3].

The present case relapsed high fever, multiple lymphadenopathy and oral ulcer with dental caries, Raynaud's phenomenon, positive ANA, anti-Ro, anti-Ro52 antibody and sialoscintigraphy four years after initial diagnosis of KFD. Although LN biopsy was unavailable, the recurrent KFD was considered, based on clinical manifestations and PET/CT findings similar to those in the first onset. Additionally, the profiles of autoantibody, sialoscintigraphy and lip biopsy in our patient suggested a diagnosis of SS. KFD has a variably reported recurrence rate ranging from 3% to as high as 14.6% in some series [3, 12]. A study analyzed 66 cases with recurrent KFD and found that 32% of those tested had underlying autoimmune conditions [9]. KFD has been infrequently reported with autoimmune diseases, such as SLE, mixed connective tissue disease, anti-phospholipid syndrome, thyroiditis, polymyositis, scleroderma, autoimmune hepatitis and adult-onset Still's disease [4].

To the best of our knowledge, few studies also have suggested that KFD may be associated with SS. Through a systematic search, we reviewed five literatures and analyzed seven patients with KFD and SS (including our patient). Miyashita et al reported a Japanese woman who was diagnosed with SS when she was 16 years old developed painful indurated erythema 26 years later that were histologically consistent with KFD [5]. Soy et al reported a 24-year-old woman diagnosed simultaneously as SS and severe KFD who required high dosed of steroids plus hydroxychloroquine [6]. Ogata et al reported a 7-year-old boy with KFD developed into SS two months later who improved within one month after treatment with prednisolone and mizoribine and relapsed with positive anti-Ro after 1.5 years [7]. Bogusz et al reported a 42-year-old African woman with KFD presented SS 19 months later and recurrence of KFD after almost 8 years [9]. In addition, a recent case series with long follow-up data identified 2 women who developed SS after 2 and 10 years, respectively, following the diag-

Table 2. Summary of clinical manifestations of reported KFD association with SS cases

Author (year)	Race	Gender	KFD					SS			
			Age (y)	Duration (month)	Autoimmunity	Steroid treatment	Clinical outcome	Latency (month)	Autoimmunity	Steroid treatment	Follow-up
Miyashita et al (2003)	Japanese	Female	42	1	RF+, ANA (1:2560)+, anti-Ro+, anti-La+	Y (PRE)	Improvement within 3 weeks	312 (before)	ANA (1:1024)+, anti-Ro+, anti-La+	Y (PRE)	Recurrence of 6 times in 26 years
Soy et al (2007)	NR	Female	24	NR	RF+, ANA (1:1280)+, anti-Ro+, anti-La+	Y (PRE & HCQ)	Improvement	0 (coexist)	RF+, ANA (1:1280)+, anti-Ro+, anti-La+	Y (PRE & HCQ)	Asymptomatic for 10 months
Ogata et al (2010)	NR	Male	7	5	RF-, ANA-	Y (PRE)	Improvement after 3 months	2 (after)	ANA (1:40)+, anti-Ro+, anti-La+, anti-Sm+, anti-PL+, anti-RNP+	Y (PRE & MZR)	Improvement after 1 month and anti-Ro+ after 16 months
Sopena et al (2012)	NR	Female	27	NR	ANA-	NR	NR	120 (after)	ANA (1:160)+, anti-Ro+	NR	ANA (1:2560)+ and anti-Ro+ after 6 years
	NR	Female	32	NR	ANA (1:320)+, anti-Ro+	NR	Recurrence of 3 times after SS	24 (after)	NR	NR	ANA(1:640)+ and anti-Ro+ after 3 years
Bogusz et al (2013)	African	Female	42	NR	NR	NR	Recurrence after almost 8 years	19 (after)	RF-, ANA (1:640)+, anti-Ro+	N	NR
Present case	Chinese	Female	17	4	RF-, ANCA-, ANA-	Y (MP)	Improvement after 3 months and recurrence after 4 years	48 (after)	RF-, ANCA-, ANA (1:80)+, anti-Ro+	N (TGP & TCM)	ANA (1:80)+, anti-ENA+, anti-Ro+ , anti-Ro52+ and weak anti-dsDNA+ after 14 months

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; anti-dsDNA, anti-double-stranded DNA; anti-ENA, anti-extractable nuclear antigen antibody; anti-PL, anti-phospholipid; anti-RNP, anti-ribonucleoprotein antibody; HCQ, hydroxychloroquine; KFD, Kikuchi-Fujimoto disease; MP, methylprednisonlone; MZR, mizoribine; NR, no reported; N, no; PRE, prednisonlone; RF, rheumatoid factor; SS, Sjogren's syndrome; TGP, total glucosides of paeony; TCM, traditional Chinese medicine; Y, yes; +, positive; -, negative.

nosis of KFD [8]. Accordingly, the SS can occur prior to, concurrent with or, especially, behind KFD diagnosis. For the five patients with SS after the onset of KFD, the ratio of females to males was 4:1, and the average age and latent period were 25 years and 43 months, respectively.

Conclusion

In conclusion, we present a infrequent case with KFD that recurred and developed into SS after four years. The findings of literature review suggest that SS is likely to be associated with KFD, which may be prior to, simultaneous with or following KFD with a long latency, especially in young women. Therefore, long follow-up and appropriate clinical and laboratory workup are highly encouraged to exclude underlying SS conditions for young female patients with KFD.

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Disclosure of conflict of interest

None.

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