Cutaneous Kikuchi disease-like inflammatory pattern in mycoplasma infection

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ABSTRACT:

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Kikuchi-Fujimoto disease (KFD) is a rare, self-resolving disease, which typically presents with fever and cervical lymphadenopathy. Histopathology is essential for its diagnosis. KFD is confirmed to be associated with multiple conditions, including autoimmune and infection. We present a Thai girl with cutaneous lesions, of which histopathology is compatible with KFD, without lymphadenopathy, thus the patient is diagnosed with Kikuchi disease-like inflammatory pattern.

Key words: Kikuchi disease, lymphadenopathy, Kikuchi disease-like inflammatory pattern, Mycoplasma infection

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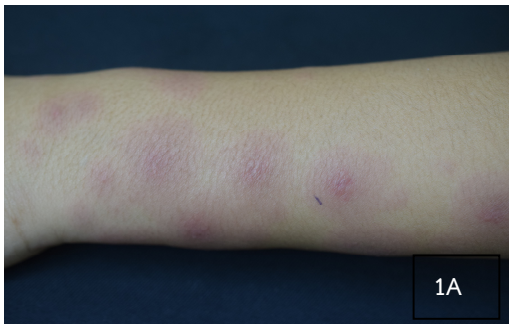

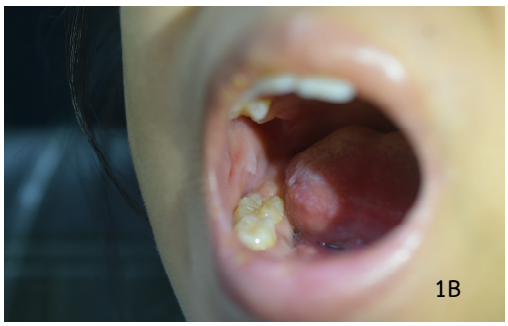

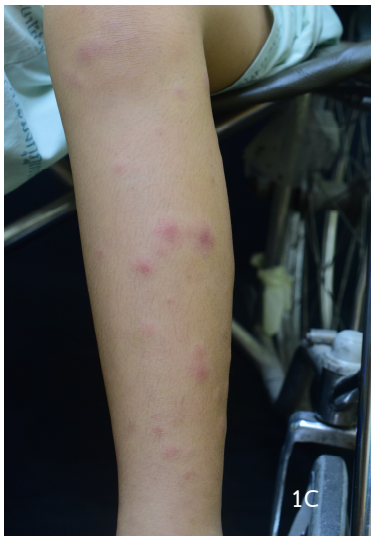

Figure 1 A-C Multiple painful erythematous dermal nodules with ill-defined borders and vesicles on the forearm and lower legs with a clean based erosion on the right buccal mucosa

Introduction

Kikuchi-Fujimoto disease (KFD) is a rare, self-resolving disease, which typically presents with fever and cervical lymphadenopathy[1,2]. The disease can affect other organs as well, such as skin, liver, spleen, and bone marrow[3]. Kikuchi disease, which has a high prevalence among Asians, was first described by Kikuchi and Fujimoto independently in 1972[2]. The disease mostly affects young adults aged between 20 and 40 years old and is rarely seen in children.[3] A variety of infections and inflammatory diseases were reported to be associated with KFD. As no particular guideline of treatment is established, the mainstay of treatment are supportive treatments with antipyretic, non-steroidal inflammatory drugs (NSAIDs) or systemic steroids.

Case report

A healthy 9-year-old Asian girl presented with fever and painful rashes for one week prior to admission. In the first two day of fever, the patient had dry cough without other respiratory tract symptoms. Three days prior to admission, the girl developed rashes on her face, extremities, oral mucosa and genital mucosa which were all painful. She received intravenous levofloxacin 250 mg/day and oral acyclovir 1600 mg/day for four days prior to admission but shown no sign of improvement. She was referred to Phramongkutklao hospital and was re-

evaluated for the condition. Since she showed no evidence of infection, all antibiotics were off.

Physical examination revealed a body temperature of 38.4°C, blood pressure of 104/62 mmHg, and pulse rate of 130 beats/min.

There were multiple painful erythematous dermal nodules with ill-defined borders on both legs and multiple erythematous dermal nodules with ill-defined borders, central hyperpigmentation, and vesicles on the upper extremities (Fig. 1A and 1B). There were also multiple painful clean based erosions with well-defined borders on the right buccal mucosa and right labia majora. (Fig. 1C). No lymphadenopathy or hepatosplenomegaly were observed. The remainder of the physical examination was unremarkable.

Basic laboratory investigations including complete blood count, renal function test and liver function test were normal. Antinuclear antibodies (ANA) titer was 1:160 (fine speckle pattern) whereas anti-dsDNA was negative. The C3 and C4 were in normal level. The erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) level were elevated. The chest radiography revealed no active pulmonary condition.

Skin biopsies from lesions on the patient's left forearm and left lower leg showed nodular infiltration of the dermis and subcutis with lymphocytes, and histiocytes. Dermal necrosis with non-neutrophilic karyorrhexis and crescentic histiocytes without vascular destruction were observed (Fig. 2A-C).

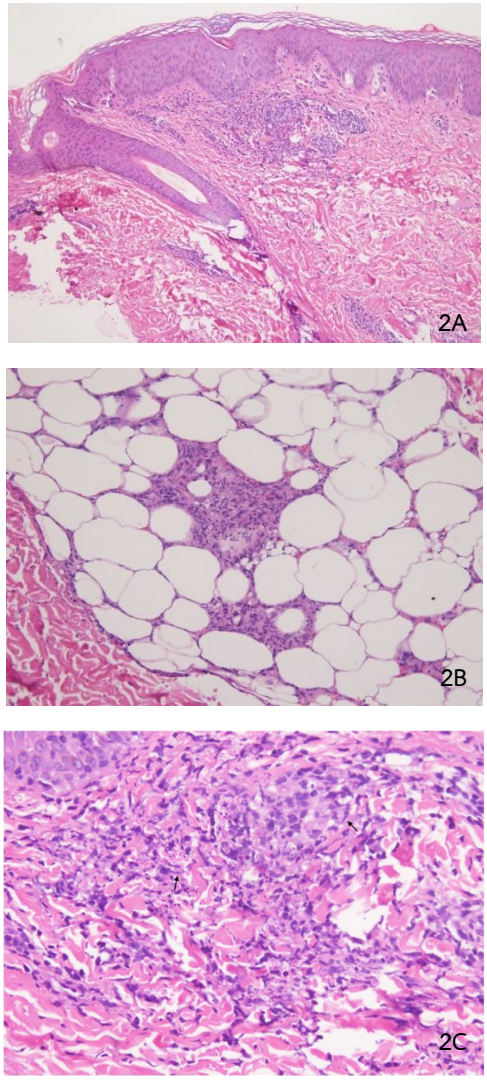

Figure 2 A-C Nodular infiltration of the dermis and subcutis with lymphocytes, histiocytes, non-neutrophilic karyorrhexis and crescentic histiocytes (arrow) without vascular destruction.
(Figure 2A-C: H&E, 200x, 200x and 400x, respectively)

Immunohistochemical stains revealed a population of histiocytes which were positive for CD68 (Fig. 3) and negative for Epstein-Barr Virus-Encoded RNA (EBER), CD3, CD4, CD8, CD20, and CD30. The histopathological features were compatible with cutaneous Kikuchi-Fujimoto disease. Serum polymerase chain reaction (PCR) was negative for herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpes virus-6 (HHV-6), HHV-7, human parvovirus B19 and cytomegalovirus (CMV). Serum anti- *Mycoplasma pneumoniae* IgM were borderline result at admission and turned positive after two weeks of follow-up.

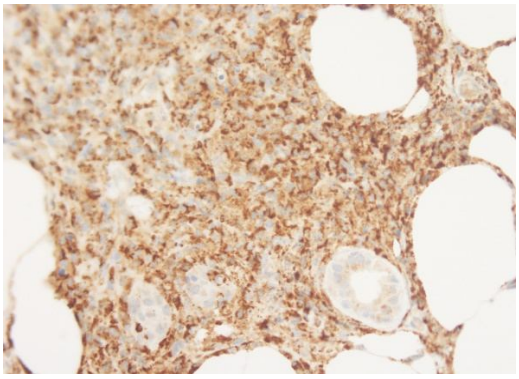

Figure 3 Immunohistochemical stains revealed CD68 positivity in histiocytes (CD68, x400).

Due to our patient had only cutaneous manifestations and fever without lymph node involvement, the final diagnosis in our case should be used the term Kikuchi disease-like inflammatory pattern (KLIP).

Supportive treatment with anti-pyretic drugs was provided. All symptoms improved and subsided within one week. After two months of follow-up, the patient remained well without further treatment.

Discussion

Kikuchi-Fujimoto disease, or histiocytic necrotizing lymphadenitis is a rare, benign disorder which has self-limiting course[2]. This condition usually occurs in young Asian females[2,4]. The typical clinical presentations are fever and painful lymphadenopathy, especially in cervical or axillary area[3,5]. Other infrequent systemic manifestations are weight loss, nausea and vomiting, as well as weakness, headache, arthralgia, night sweats and hepatosplenomegaly[1, 5].

Cutaneous manifestations have been reported in 16.6 percent of the cases[4]. The lesions are variable. Among the most common findings are erythematous macules, papules or patches, which are usually located on the face, trunk and extremities of the patients diagnosed with Kikuchi disease[6].

Less common cutaneous findings, including malar erythema, oral ulcer, conjunctival injection, alopecia and photosensitivity have been reported[1]. Skin lesions could be present along with or preceding lymphadenopathy. Such symptoms could sometimes occur immediately after lymphadenopathy as well[1].

The disease's etiology is yet unknown. A number of associated conditions have been implicated as etiologic factors such as autoimmune diseases, infections and malignancies as shown in Table 1.

Table 1 Conditions associated with KFD[1,3]

Infections	**Virus:**
	Epstein-Barr virus
	Herpes simplex virus
	Varicella zoster virus
	Human herpesviruses 6, 7, and 8
	Parvovirus B19
	Paramyxovirus
	Parainfluenza virus
	Rubella
	Cytomegalovirus
	Hepatitis B virus
	Human immunodeficiency virus Human T-lymphotropic virus type 1 dengue virus
	Bacteria and parasite:
	Brucella
	Bartonella henselae
	Yersinia enterocolitica
	Streptococcus pneumoniae, Toxoplasma gondii
	Entamoeba histolytica, Mycobacterium szulgai
Autoimmune diseases	Systemic lupus erythematosus (SLE)
	Still disease
	Graves disease
	Sjogren syndrome
	Wegener granulomatosis
Malignancies	Breast
	Stomach
	Oral cavity

Table 2 The differences and similarities between KLIP and KFD[1-4,6,7,9,10]

	KLIP	KFD
Cutanenous lesions	Heterogenous cutaneous presentations: erythematous macules, papules or patches on face, trunk, and extremities	Same
Internal organ involvement	No	Hepato-splenomegaly, eye involvement, arthrtitis, bone marrow involvement
Histopathologic change in skin or lymph nodes	Same as KFD	Necrosis containing abundant non-neutrophilic karyorrhectic debris, numerous histiocytes with crescentic nuclei, plasmacytoid dendritic cells
	Sometime has lichenoid interface dermatitis or cutaneous mucinosis.	
Associated disease	Cutaneous LE*, SLE**, Behcet's disease, dermatomyositis, vasculitis, hematologic malignancy	SLE**, mixed connective tissue disease, Still's disease
Prognosis	Without associated-disease, self-limited within one to four months	Without associated-disease, self-limited within one to four months
	75% of KLIP patients were diagnosed with SLE, mostly responded well to treatment	More recurrences in ANA positive KFD patients

*LE – lupus erythematosus

**SLE – systemic lupus erythematosus

Histopathology is essential for the diagnosis. The presence of focal areas of necrosis containing abundant non-neutrophilic karyorrhectic debris, numerous histiocytes with crescentic nuclei, plasmacytoid dendritic cells, and few small- to large-sized lymphocytes are the clues for diagnosis. These findings are similar to histopathologic findings in lymph nodes[1,3]. The nature of the target cells releasing nuclear debris is unknown. The karyorrhectic debris may be from the lymphoid and/or myeloid cells infiltrate[7].

The epidermal change with interface vacuolar change or interface lichenoid change can be found in more than 50 percent of the cases[4]. The presence of interface dermatitis in KFD is not specific for lupus erythematosus. This finding can be seen in both KFD associated and non-associated with lupus erythematosus[4]. Other less common epidermal changes are non-specific such as atrophic epidermis, follicular plugging, hyperkeratosis, spongiosis and intraepidermal vesicles[1].

The Immunohistochemistry shows all the histiocytes were positive for CD68 and CD163[5].

Most of the patients have normal laboratory findings[5]. Possible laboratory abnormalities include anemia, leukopenia, leukocytosis, thrombocytopenia, elevated CRP, elevated ESR, increased lactate dehydrogenase and increased alanine aminotransferase[3].

ANA positivity has been reported in 13.3 to 45.2 percent of patient with KFD[3,8]. The risk for development of future connective tissue diseases in KFD patients with a positive ANA is inconclusive and no reports have shown a significant correlation between positive ANA in KFD and the developed systemic lupus erythematosus (SLE) [9,10]. A small number of patients with a positive ANA subsequently developed SLE in the follow-up period[6,9,10].

The positive ANA was also significantly higher in patients with recurrent KFD compared to the non-recurrence group[10].

Thai Lan-Huong, et al used the term Kikuchi disease-like inflammatory pattern (KLIP) in the patients who have only cutaneous lesions without lymph nodes involvement[4]. The cutaneous manifestations in KLIP are variable, similar to KFD[4]. The histopathological findings from skin lesion have characteristic non-neutrophilic karyorhexis as histopathologic change in KFD. The KLIP and KFD may involve a pathogenic process which limited to the skin for KLIP and had systemic involvement in KFD[4]. KFD is typically self-remitting disease in one to four months[6,9]. Recurrent episodes of KFD have been reported in 20.6 percent of the cases[10]. The presence of fatigue, extranodal involvement and long symptomatic duration were significant predictive factors of recurrence[10].

Symptomatic treatments such as NSAIDs and anti-pyretics are usually the initial treatment. Systemic corticosteroid can be used in generalized KFD or severe extranodal involvement[2].

Our patient presented with fever and cutaneous lesions, of which histopathology is compatible with KFD without lymphadenopathy. This condition is compatible with KLIP, which has similar pathogenesis to KFD, but different clinical courses as shown in Table 2.

The etiology of our patient's condition is unknown. Most laboratory investigations were normal, except the positive ANA test and positive serum *Mycoplasma pneumoniae*-IgM. The physical examinations and laboratory findings of our patient does not meet the criteria of Systemic Lupus International Collaborating Clinics (SLICC). We assume the condition in our patient may be aggravated by mycoplasma infection. However, as mention above about association of SLE and KLIP, this patient needs long term follow up for any sign of autoimmune disease.

In summary, we presented a case of KLIP, which was possibly triggered by *Mycoplasma*

pneumoniae infection. The disease spontaneously resolved following symptomatic treatments.

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