Kikuchi-Fujimoto's Disease, Histiocytic Necrotizing Lymphadenitis, Mimicking Systemic Lupus Erythematosus

PIROON MOOTSIKAPUN, M.D.*,
JITTIMA SIRIJERACHAI, M.D.*,
RATANAVADEE NANAGARA, M.D.*

Abstract

Kikuchi-Fujimoto's disease (KFD) or histiocytic necrotizing lymphadenitis is a self-limiting condition characterized by fever, neutropenia and lymphadenopathy. It is rarely associated with systemic lupus erythematosus (SLE). The authors reported a case of Kikuchi's necrotizing lymphadenitis who presented with fever, generalized lymphadenopathy, moderate leukopenia, polyarthritis, vasculitis-like lesions and oral ulcers compatible with SLE but serologic tests for autoimmune disease were all negative. The clinical symptoms resolved spontaneously within 3 months without any treatment. Because there is an association between KFD and SLE, great care should be taken with a patient who presents with either KFD or SLE.

Key word : Kikuchi-Fujimoto's Disease, Histiocytic Necrotizing Lymphadenitis, Systemic Lupus Erythematosus

**MOOTSIKAPUN P,
SIRIJERACHAI J, NANAGARA R
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Kikuchi-Fujimoto's Disease (KFD), histiocytic necrotizing lymphadenitis is a rare self-limiting condition first described in Japan by Kikuchi in 1972[1] followed by Fujimoto et al[2] in the same year. In the first decade, reports were confined only to Oriental but later expanded to Caucasians as well[3-11].

Characteristically, the patients are young women with cervical adenopathy which may be tender and sometimes associated with fever and neutropenia. The course is invariably benign. The lymphadenopathy resolves spontaneously, usually within 2-3 months although it may be protracted in some cases. The etiology of KFD is controversial. Its diag-

* Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

nosis is confirmed histologically. It may also be misdiagnosed as malignant lymphoma[7] but no association with any malignancy has been found. KFD has been rarely reported associated with systemic lupus erythematosus (SLE)[12-16] and can precede, coincide and proceed with the diagnosis of SLE. Clinical and pathological results of these two conditions may be indistinguishable.

The authors reported a case of Kikuchi-Fujimoto's necrotizing lymphadenitis clinically resembling SLE, for whom the correct diagnosis was established only after pathologic examination of a lymph node biopsy specimen was performed. KFD should be ruled out in a patient who presents like SLE because of different prognosis and management.

CASE REPORT

A 21 year-old Thai man presented with a six-week history of bilateral cervical and epitrocheal lymphadenitis and a two-week history of polyarthritis with oral ulcers. He had flu-like symptoms during the first week of his illness, which resolved spontaneously without any treatment. By the time that arthritis occurred, asymptomatic bloodstained seminal fluid was also noticed. He had been symptomatically treated with naproxen 250 mg twice a day for one week with some improvement of his painful joint symptom. He denied a history of photosensitivity, alopecia, weight loss, or homosexual behavior. He was an engineering student and had lived in Khon Kaen province for 3 years.

His general appearance was quite good and body temperature was normal. There were vasculitis-like skin lesions at his lower lip and multiple painless oral ulcers at the hard palate. Multiple discrete lymph node enlargements were palpated at the posterior cervical, submental, submandibular and epitrocheal region, with variable sizes (diameter ranged from 1-2 cm), firm consistency and mild tenderness. All of the proximal interphalangeal (PIP) joints were swollen, warm, with pain on motion, making deformity of fusiform shape as seen in rheumatoid arthritis. Neither hepatosplenomegaly nor genital ulcer was detected.

His complete blood count revealed a total white blood count of 1.8 x 10^9/L (44% neutrophils, 49% lymphocytes, 4% monocytes and 3% eosinophils), the hemoglobin concentration14.1 g/dl, platelet count was adequate and the erythrocyte sedimentation rate was 32 mm/h. Urinalysis was normal. Total serum protein, albumin and globulin were 7.4, 4.4 and 3.0 g/dl, respectively. Liver enzymes (SGOT and SGPT) were within normal limit. FANA, RF, LE cell, VDRL, HBsAg and anti-HIV were all negative. Serum C3 was 52.1 mg/dl (normal range 60-140 mg/dl).

Biopsy of his cervical lymph node and bone marrow aspiration were performed. Bone marrow smear revealed a slight increase in mature monocytes and histiocytes with some evidence of phagocytic activity. Presumptive diagnosis of immune complex disease secondary to viral infection was made. No medication was given while awaiting the result of the biopsy. On the consecutive week, he felt better. The vasculitic lesions and oral ulcers disappeared. The enlarged lymph glands regressed about half the size without tenderness. All PIP joints were still swollen, slightly stiff but not warm as initially. Blood stained seminal fluid was resolved. The repeated CBC showed a hemoglobin concentration 15.2 g/dl, total white blood count of 4.2 x 10^9/L with 49 per cent neutrophils, 33 per cent lymphocytes, 14 per cent monocytes and 4 per cent eosinophils.

Pathologic examination of the excised lymph gland revealed a necrotizing process (Fig. 1) predominantly at the subcapsular area with marked karyorhexis and phagocytosis by histiocytes (Fig. 2). There was prominent mononuclear cell infiltration without polymorphonuclear cell infiltration. Brightly eosinophilic fibrin deposits were present. According to these pathologic findings, the diagnosis of Kikuchi-Fujimoto's disease was made and no drug was administered at all.

One month after diagnosis was made the remaining enlarged lymph glands and polyarthritis had completely resolved and he was generally well. His white blood cell count was 6.2 x 10^9 /L. Erythrocyte sedimentation rate declined to 9 mm/h. Bone marrow aspiration was repeated and the smear revealed normal findings.

DISCUSSION

Kikuchi-Fujimoto's syndrome (KFD) or histiocytic necrotizing lymphadenitis has been increasing both in Oriental and Caucasian populations including Hong Kong, South Korea, India, Saudi Arabia, Puerto Rico, Brazil, Argentina, South Africa, Canada and the U.S. It is usually a benign self-limited condition although one patient died of cardiac complication[17]. It may rarely recur[18]. Most of the cases are female, with a mean age of 28 years (range 7-75 years). But one-fourth of the cases reported were male, like the presented case. The patients typi-

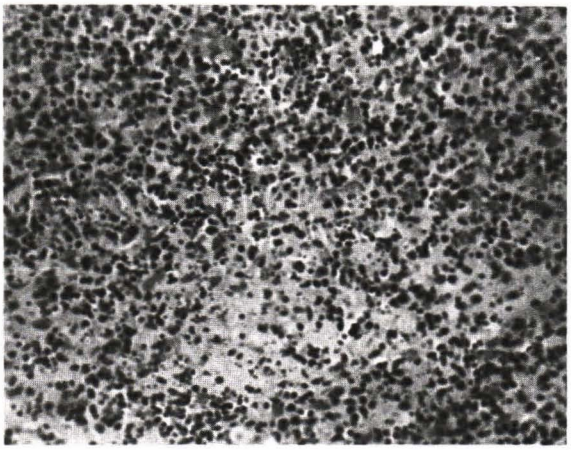

Fig. 1. Pathology of the excised lymph node (10x). Necrotizing process in lymph node of the KFD patient.

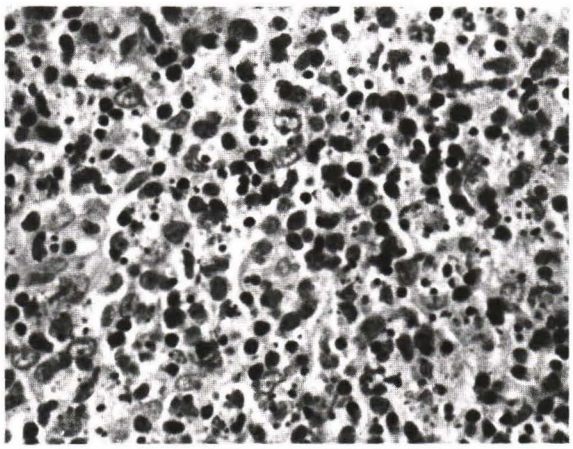

Fig. 2. Pathology of the excised lymph gland (100x) The area with marked karyorrhexis and phagocytosis by histiocytes.

cally present with localized unilateral cervical lymphadenopathy, which may or may not be tender but generalized lymphadenopathy may be occasionally found. Although the cervical lymph nodes are most frequently involved, those from other sites have also been reported, including the axillary, inguinal, and para-aortic groups[7-11]. They are discrete and vary in size ranging from 0.8-3 cm, but could be enlarged to 6 cm[3-6]. Rarely they are matted, mimicking tuberculous lymphadenitis[19], or occult misleading the initial diagnosis as fever of unknown origin[8-11] or acute abdomen[3]. Fever presents in one-third of the patients[3-6]. Other associated clinical findings include mild splenomegaly or hepatomegaly, weight loss, night sweats, nausea, vomiting, myalgia, epididymitis, pharyngitis and nonspecific dermatitis[3-6].

The histologic features of KFD are characterized by partial effacement of the normal architecture, with only a few small lymphoid follicles[3-6]. Most frequently, the paracortical and cortical areas consist of confluent areas of eosinophilic necrosis with prominent clusters of nuclear karyorrhexis, associated with histiocytes, macrophages, and plasmacytoid T cells, which Immunohistochemically are cytotoxic/suppressor T lymphocytes in necrotic tissue and helper/inducer T lymphocytes in the surrounding non-necrotic lymphoid tissue[3-6,20-22]. There are rare B cells and natural killer (NK) cells present. Granulocytes are absent and plasma cells are rarely seen[3-6].

Because of the high incidence of KFD in young females and its clinical findings, it is usually diagnosed as SLE at first. In fact, about 30 cases of KFD have been reported as associated with SLE worldwide, prior, simultaneous or after the diagnosis of SLE. The authors reported a male with KFD whose presentation including fever, generalized mild painful lymphadenopathy, vasculitis-like skin lesions at the lower lip, oral ulcers typically at the hard palate, and polyarthritis of small joints of hands, resembled SLE but all serologic evaluation of autoimmune diseases were negative. The diagnosis of KFD was from histopathology of the lymph node. Although these two conditions have been considered indistinguishable histologically[3-6,12-16], the haematoxylin bodies that are the typical finding in SLE were not found in the presented case. However, the patients should have a long-term follow-up because some patients develop SLE later[12-16]. Associations have also been noted with Still disease[23,24].

Over half of the KFD patients have normal white blood cell counts but mild to moderate leukopenia is occasionally associated with KFD[3-6] as demonstrated in the presented patient. Leukopenia in the presented patient may have resulted from increasing hemophagocytic activity in bone marrow, which was once reported[25] and it subsequently remitted spontaneously.

The etiology of KFD is controversial. The tubuloreticular structures seen in relationship to inter-

feron production have been demonstrated in the histiocytes of KFD[4]. This suggests a hyperimmune reaction to some unknown etiologic agent, and it has also been demonstrated in endothelial cells or lymphocytes of patients with SLE and other autoimmune disorders[26]. These findings suggest that KFD may be a self-limited, lupus-like, autoimmune condition resulting from virus-infected activated lymphocytes. Unfortunately, repeated efforts have failed to show any significant relationship with Epstein-Barr virus and Herpes virus 6[27]. The initial event may be a localized exuberant activation of T cells and histiocytes, perhaps secondary to a viral antigen or even possibly a superantigen. These activated T cells are subject to a mechanism of down-regulation, perhaps by the histiocyte's production of interferon[28]. It is possible that the plasmacytoid T cells are instructed to undergo prompt cell death as they differentiate in the proximity of interferon-producing histiocytes. The cellular debris is then removed by macrophages.

Treatment of Kikuchi's necrotizing lymphadenitis is only supportive. The majority of the patients will recover spontaneously within two to four months, but the longest course reported in the literature was 21 months[6]. Only a few cases may relapse or develop SLE but are not associated with any malignancy[10].

In conclusion, KFD may present like SLE but has different management and prognosis. It may also be associated with SLE. Patients with SLE should be assessed for KFD. Vice versa, patients with KFD should be assessed for SLE and have a long-term follow-up considering possible onset of SLE. Moreover, KFD should be ruled out in SLE flare-up accompanied by lymphadenopathy.

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โรคคิคูชิฟูจิโมโตหรือต่อมน้ำเหลืองอักเสบย่อยสลายจากฮิสติโอไซต์ที่มีอาการเหมือนโรคลูปุส

ภิรุญ มุตสิกพันธุ์, พ.บ.,*
จิตติมา ศิริจีระชัย, พ.บ., รัตนวดี ณ นคร, พ.บ.**

อาการทางคลินิกของต่อมน้ำเหลืองอักเสบย่อยสลายจากฮิสติโอไซต์หรือโรคคิคูชิฟูจิโมโตเป็นโรคที่มีอาการไข้ เม็ดเลือดขาวต่ำ ต่อมน้ำเหลืองโต แต่อาการจะหายเอง พบมีความสัมพันธ์กับโรคลูปุสได้แต่ไม่บ่อย รายงานนี้เสนอผู้ป่วยที่มาพบแพทย์ด้วยเรื่องไข้ ต่อมน้ำเหลืองโตทั่วไป เม็ดเลือดขาวต่ำ ข้ออักเสบหลายข้อ และมีผื่นผิวหนังเหมือนจากเส้นเลือดอักเสบและแผลในปาก การตรวจเลือดเกี่ยวกับภาวะโรคภูมิแพ้ตัวเองให้ผลลบทั้งหมด อาการต่าง ๆ ที่พบหายไปเองภายใน 3 เดือน โดยที่ไม่ได้มีการรักษาจำเพาะใด ๆ เนื่องจากมีความสัมพันธ์ระหว่างโรคคิคูชิฟูจิโมโตกับโรคลูปุสดังนั้นจึงควรมองหาโรคดังกล่าวอีกอย่างหนึ่งในผู้ป่วยที่มาด้วยเรื่องโรคคิคูชิฟูจิโมโตหรือโรคลูปุส

คำสำคัญ : โรคคิคูชิฟูจิโมโต, ต่อมน้ำเหลืองอักเสบย่อยสลายจากฮิสติโอไซต์, โรคลูปุส

ภิรุญ มุตสิกพันธุ์, จิตติมา ศิริจีระชัย, รัตนวดี ณ นคร
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 1037–1041

* ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ขอนแก่น 40002