Kikuchi-Fujimoto Disease

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ABSTRACT: **Background:** Kikuchi-Fujimoto disease is a benign and self-limited disease, first reported in Japan in 1972. The characteristic features of this disorder include lymphadenopathy and fever.

Objectives: To summarize our experience with Kikuchi disease with regard to clinical manifestations and outcome.

Methods: The patients included in the study were those diagnosed with Kikuchi disease during the years 2005–2008 in two departments of internal medicine at Sheba Medical Center.

Results: We identified five patients with Kikuchi disease; four were women and the mean age was 22.6 years. All the patients had cervical lymphadenopathy; three had other sites of lymphadenopathy. Four of the patients had fever higher than 39ºC. Two of them had splenomegaly and three reported weight loss. Three of the five patients experienced a relapse of the disease and were treated with steroids or non-steroidal anti-inflammatory agents. The diagnosis was confirmed in all the patients by an excisional biopsy of lymph node.

Conclusions: Kikuchi disease must be considered in every young patient with fever and lymphadenopathy. The disease usually has a benign course.

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KEY WORDS: Kikuchi-Fujimoto disease, lymphadenopathy, fever, benign course, symptomatic treatment

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is a rare, benign and self-limited disorder that was first described in Japan in 1972 almost simultaneously by Kikuchi and Fujimoto [1,2]. The two most characteristic features of this disorder are regional tender lymphadenopathy (mostly cervical) and fever. Other findings include night sweats, weight loss, nausea, vomiting and sore throat [3]. The disease is more frequent among Asians, especially Japanese, and was thought to be much more common among women, with a female to male ratio of about 4:1. Recent reports, however, suggest that the actual ratio is closer to 1:1 [4,5]. Most of the patients are under the age of 30 [6]. The etiology is unknown, but some reports suggest an immunologic and infectious pathogenesis. Diagnosis is based on excisional biopsy of enlarged lymph nodes.

In this article we present five patients with Kikuchi disease who were diagnosed in our medical center. Their clinical course, laboratory data and radiologic evaluation are described. The pathologic findings, differential diagnosis and prognosis of this entity are discussed.

PATIENTS AND METHODS

A retrospective analysis of the records of the patients diagnosed with Kikuchi-Fujimoto disease in our departments of internal medicine during the years 2005 to 2008 was performed. The clinical presentation and the clinical course of the patients are described, as is the laboratory and radiologic evaluation.

PATIENT 1

The first patient was a 21 year old woman of Moroccan-Syrian origin who presented with fever of 6 weeks duration, up to 39ºC, accompanied by unilateral submandibular lymphadenopathy. She reported 5 kg weight loss over that period, abdominal pain, arthralgia and minimal complaints of sore throat. She was in contact with a friend who had infectious mononucleosis and had initially attributed her symptoms to Epstein-Barr virus.

On examination her vital signs were normal. She had enlarged tender left submandibular lymph nodes and enlarged and tender supraclavicular and axillary lymph nodes. The spleen was palpated 3 cm below the rib cage. Laboratory and radiologic evaluation are presented in Tables 1 and 2. A biopsy of supraclavicular lymph node was performed and Kikuchi's disease was diagnosed.

The patient was discharged on treatment with non-steroidal anti-inflammatory drugs and prednisone. Five days after prednisone cessation, there was a relapse of the cervical lymphadenopathy and fever. She was readmitted and was treated with solumedrol.

PATIENT 2

The second patient was a 20 year old man of Moroccan origin who presented with fever of 4 weeks duration, up to 39.5ºC, and unilateral cervical lymphadenopathy. He was treated by his family physician with amoxicillin and amoxicillin + clavulanic acid.

He reported losing 6 kg during that period. His weight at admission was 66 kg, so he lost 8.5% of his weight in one month. At admission, vital signs were normal. Palpation

Table 1. Laboratory evaluation of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ESR	109	60	90	30	20
CRP	48.6			4.21	
WBC	4.6	3.3	6.4	5	5
Hb	12	12.5	12.2	12.2	11.5
LDH	174	338	178	215	
HIV	Negative		Negative	Negative	
anti-HA IgM	Negative				
HBsAg	Negative				
anti HCV	Negative				
CMV Ab IgM	Negative		Negative		
EBV EBNA Ab IgG	Positive				
EBV VCA Ab IgG	Positive				
EBV VCA Ab IgM	Negative	Negative			
EBV ELISA IgM	Positive		Negative		
EBV EBNA	Positive				
Blood culture	Negative	Negative	Negative		
ANF	Positive		Negative		
RF	Negative		Negative		
P&C ANCA			Negative		

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, Hb = hemoglobin, WBC = white blood cells, LDH = lactate dehydrogenase, HIV = human immunodeficiency virus, Ig = immunoglobulin, HCV = hepatitis C virus, CMV = cytomegalovirus, EBV = Epstein-Barr virus, EBNA = Epstein-Barr nuclear antigen, VCA = viral capsid antigen, ELISA = enzyme-linked immunosorbent assay, ANF = antinuclear factor, RF = rheumatoid factor, ANCA = anti-neutrophil cytoplasmic antibodies, P = perinuclear, C = cytoplasmic

revealed bilateral cervical lymphadenopathy. An enlarged spleen was palpated 2 cm below the rib cage. Ear, nose and throat examination was normal. He underwent a lymph node biopsy of an enlarged cervical lymph node [Figures 1 and 2] and was diagnosed with Kikuchi's disease.

He was discharged from the hospital and was invited for follow-up as an outpatient. but was tragically killed in the second Lebanon war, before his appointment at the hospital outpatient clinic.

PATIENT 3

The third patient was a 23 year old woman of Russian origin who was admitted to hospital due to fever, up to 40ºC, of 2 weeks duration, cervical lymphadenopathy and weight loss. Two months earlier she returned from a trip to India. A week before admission she suffered from abdominal pain and diarrhea. Her history was vague regarding a diagnosis of celiac disease.

On admission her vital signs were normal, except for tachycardia (100 beats/min). She had mildly enlarged cervical lymphadenopathy and small axillary lymph nodes. Serology tests for West Nile fever, Dengue, Toxoplasma, Rubella, Borrelia, and Brucella were all negative. Due to her so-called celiac disease, and suspected lymphoma secondary to celiac disease, a laparoscopic biopsy of two lymph nodes at the mesentery of the terminal ileum and a lymph node from the hilum of the liver was performed. The diagnosis of Kikuchi was established from the lymph nodes.

One year later she had a relapse of the disease, with high fever up to 40°C of 2 weeks duration and weight loss of 3 kg, 1 month after returning from Thailand. On physical examination, cervical lymphadenopathy was found, and abdominal ultrasonography demonstrated enlarged lymph nodes. Some of them were suspected to be necrotic. She was treated with prednisone which led to a rapid improvement.

PATIENT 4

The fourth patient was a 34 year old woman of Sephardic origin who presented with unilateral cervical lymphadenopathy of 10 months duration that had become larger and tender over the previous 2 months. At that time she noticed additional enlarged lymph nodes on the same side of her neck. A week prior to her admission she had fever, up to 39.7ºC. She reported having arthralgia of her right wrist and both shoulders. She was treated in the health fund clinic with amoxicillin + clavulanic acid, with no improvement.

Table 2. Radiologic evaluation of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Chest X-rays	Normal	Normal, except for swelling at the left side of the neck	Normal	Normal	
Abdominal ultrasound	Enlarged spleen (13 cm)	Enlarged lymph nodes at the upper retroperitoneum: at the gastrohepatic ligament, portal hilum	Two areas of lymph nodes demonstrated at the retroperitoneum, and the hilum of the liver	ND	
Neck ultrasound	ND	ND	ND	A collection of enlarged, vascular, hypoechogenic lymph nodes on the right side	
CT	A few lymph nodes at the retroperitoneum and the base of the neck	A lymph node near the inferior vena cava at the retroperitoneum. Neck – multiple lymph nodes with fat infiltration	Enlarged lymph nodes at the upper retroperitoneum: at the gastrohepatic ligament, portal hilum, and at the mesenterium	Enlarged lymph nodes at the right side of the neck	Sub-auricular, bilateral lymphadenopathy

Figure 1. Hematoxylin & eosin x 200. Area of necrosis (upper left) surrounded by cellular infiltrates and numerous cellular debris and nuclear dust.

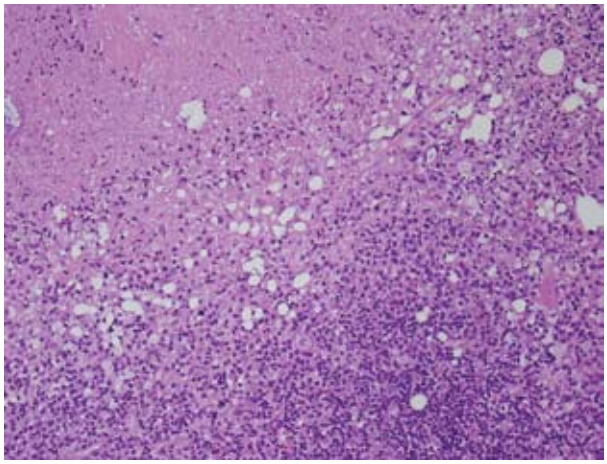
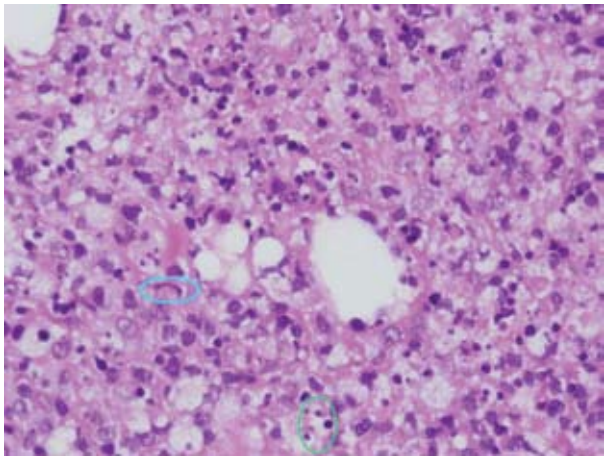


Figure 2. H&E x 600. Cell infiltrates composed of pale-staining histiocytes, some of them with "crescentic" nuclei resembling signet-ring cells (marked by horizontal blue ellipse), small lymphocytes, immunoblasts and numerous apoptotic cells and nuclear dust (marked by vertical green ellipse). No granulocytes or eosinophils are demonstrated.



On admission her vital signs were normal, except for tachycardia (110 bpm). She had tender cervical lymphadenopathy. A biopsy of an enlarged lymph node was performed and Kikuchi disease was diagnosed. The fever and arthralgia resolved after treatment with antipyretic drugs and she became asymptomatic.

PATIENT 5

The last patient was a 15 year old girl who presented with right cervical lymphadenopathy without fever. She was treated by her family physician with augmentin, but there was no improvement. Palpation revealed right cervical lymphadenopathy of about 3 cm. Ear, nose and throat examination was normal. Serology for cytomegalovirus and Toxoplasma were suggestive of past illness. She was treated with clindamycin but there was no improvement. She underwent a lymph node biopsy and was diagnosed with Kikuchi disease.

During the following 3 years she presented repeatedly with bilateral submandibular lymphadenopathy, headaches and fever, and was treated with NSAIDs. She later became asymptomatic.

DISCUSSION

Kikuchi disease is known to have a worldwide distribution with higher prevalence among Japanese and other Asiatic people. Kikuchi disease among Israelis was described recently by Rimar et al. [7]. In this article we describe the patients who were diagnosed and treated in two departments of internal medicine in Sheba Medical Center during a 4 year period (2005–2008).

Age at diagnosis in our patients ranged from 15 to 34 years, with a mean age of 22.6. There is a definite trend of presentation at young age, as demonstrated in many of the published series. In their work of 108 cases of Kikuchi disease, Dorfman and Berry [6] reported a mean age of 30 (range 11–75). Kucukardali et al. [8] reported a mean age of 25 (range 1–64) in their research of 244 cases, and Lin and co-authors [4] reported a mean age of 21 (range 6–46).

Four of our patients were women. Earlier reports of Kikuchi disease described a female predominance of 4:1. In recent reports, however, the ratio is closer to 1:1 with a slight female predominance [4-7].

Lymph node enlargement is an important manifestation of Kikuchi disease; the majority of cases present with cervical and unilateral lymphadenopathy [5,6,8,9]. Only 3 of 108 cases reported by Dorfman and Berry [6], and 7 of the 61 cases reported by Lin et al. [4] had bilateral cervical lymphadenopathy. All of our patients presented with enlarged cervical lymph nodes. Four of the patients had unilateral lymphadenopathy, and one had bilateral cervical lymphadenopathy. Other sites of lymphadenopathy reported in the literature are axillary, supraclavicular, mediastinal, inguinal, intraparotid, celiac, peripancreatic and retroperitoneal – all in sporadic patients [6- 9]. Three of our patients had lymphadenopathy that involved lymph nodes other than cervical. The dimension of the lymph nodes in our study ranged from smaller than 1 cm to 2–4 cm. In other publications lymph nodes ranged from 0.5 to 9 cm, were rarely larger than 6 cm [3], and 75% were < 2 cm [5].

Fever is another important manifestation of Kikuchi disease. It was reported in about 30–40% of patients [4-6]. In the

NSAID = non-steroidal anti-inflammatory drug

Israeli series described by Rimar et al. [7], 73% of the patients had fever. Four of our patients had fever higher than 39ºC.

Two of our patients had splenomegaly on physical examination and imaging evaluation. Weight loss is reported in 5–9% of Kikuchi patients [6,8]; 3 of our patients reported weight loss prior to their diagnosis. Two of our patients reported arthralgia. Reports in the medical literature are of a smaller scale, ranging from 4 to 7% [6,8].

Laboratory investigation is usually unremarkable and less suggestive for establishing a diagnosis of Kikuchi disease, but negative results might help to exclude other conditions. One of our patients had leukopenia, which is considered one of the most common laboratory findings among Kikuchi patients and ranges from 23% to 58% [5,9].

One patient had positive antinuclear antibodies and was later diagnosed with mild systemic lupus erythematosus.

In our series three patients (60%) had a relapse of the disease. Such a high rate of recurrent disease is unusual, and recurrent Kikuchi disease is estimated to occur in about 3% of patients [7,10]. The explanation for this finding is not clear.

The etiology and pathogenesis of Kikuchi disease are also not clear. Various infections have been postulated to be the cause. Most studies raise the possibility of immune system involvement. Apoptotic cell death appears to be the principal finding in the histogenesis of this disease [11]. The recurrent disease in the third patient and the many patients with Kikuchi disease described in the Far East raise the possibility of an unknown infectious agent as the causative agent. The diagnosis of this disease is done by excisional biopsy of affected lymph nodes.

Although Kikuchi is a rare disease, it should be considered in the differential diagnosis of "lymph node enlargement." Its course, treatment and follow-up differ from most of the other diseases on that list. The differential diagnosis of Kikuchi disease includes lymphoma, tuberculosis, reactive lesions such as lymphadenitis associated with SLE or herpes simplex, non-Hodgkin's lymphoma, Kawasaki's disease, and metastatic adenocarcinoma [3,9]. The main diagnostic challenge is that lymphoma can be easily confused with Kikuchi [12]. It is important to distinguish one from the other because the course, treatment and prognosis of these disorders differ dramatically. It is assumed that some of the cases that were diagnosed as malignant lymphoma were actually more consistent with Kikuchi [2,14], and there are reports of patients receiving cytotoxic therapy for no apparent reason [14-16]. While there are histologic and immunohistochemical methods to differentiate between these two disorders, the clinician's awareness of Kikuchi disease is very important.

Distinguishing Kikuchi from SLE is sometimes problematic. Both entities share similar presenting symptoms and histologic characteristics. Furthermore, there is a well-known and documented relationship between these two entities [5,8,9].

Kikuchi disease has a benign course and is self-limited usually within 6 months from diagnosis [8]; it usually requires no specific treatment. Symptomatic treatment measures such as analgesics, antipyretics, etc. are used to relieve patients' complaints [9]. Severe cases may be treated with corticosteroids [8,17-19]. There is also a report on treatment with chloroquine and hydroxychloroquine [20] and intravenous immunoglobulin was also used effectively to treat a patient with severe Kikuchi disease [21]. It is important for patients with Kikuchi to undergo long-term follow-up, mainly for assessing and evaluating development of SLE and prompt detection of recurrences.

In summary, we present five diverse cases that demonstrate the wide range of clinical and laboratory presentation of Kikuchi disease. All cases were diagnosed in our institute over 4 years. This series and the cases described recently by Rimar and colleagues [7] suggest that only the combination of experienced pathologists, but primarily the awareness of clinicians, may lead to the prompt diagnosis of Kikuchi disease. The disease is probably more common than was previously believed in Israel.

SLE = systemic lupus erythematosus

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