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 39°C. 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.

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

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 39°C, 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°C, accompanied by unilateral submandibular lymphadenopathy. He reported 6 kg weight loss over that period, abdominal pain, arthralgia and minimal complaints of sore throat. He 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.
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 40°C, 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 39.7°C. 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.

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**Table 1. Laboratory evaluation of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>109</td>
<td>60</td>
<td>90</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>CRP</td>
<td>48.6</td>
<td></td>
<td></td>
<td>4.21</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>4.6</td>
<td>3.3</td>
<td>6.4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hb</td>
<td>12</td>
<td>12.5</td>
<td>12.2</td>
<td>12.2</td>
<td>11.5</td>
</tr>
<tr>
<td>LDH</td>
<td>174</td>
<td>338</td>
<td>178</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>anti-HA IgM</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbsAg</td>
<td>Negative</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>anti HCV</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV Ab IgM</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV EBNA Ab IgG</td>
<td>Positive</td>
<td></td>
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<tr>
<td>EBV VCA Ab IgG</td>
<td>Positive</td>
<td></td>
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</tr>
<tr>
<td>EBV VCA Ab IgM</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
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</tr>
<tr>
<td>EBV ELISA IgM</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
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</tr>
<tr>
<td>EBV EBNA</td>
<td>Positive</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANF</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P&amp;c ANCA</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Table 2. Radiologic evaluation of the patients**

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

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.
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.

References
12. Chamulak GA, Brynes RK, Nathwani BN. Kikuchi-Fujimoto disease


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**Capsule**

**Damaged intestinal epithelial integrity linked to microbial translocation in SIV infection**

Estes and co-researchers used monoclonal antibodies specific for the core antigen of lipopolysaccharide (LPS) to stain colon tissue sections obtained from necropsies of SIV-infected rhesus macaques that were euthanized at different phases of infection, including early acute infection and chronic infection, as well as sections from uninfected controls. In the uninfected animals and during early acute infection there was abundant staining for LPS in the intestinal lumen but little staining in the lamina propria of the large bowel. By contrast, in chronically infected animals there was abundant staining for intracellular and extracellular LPS in the lamina propria. Abundant LPS staining was also seen in the mesenteric and axillary lymph nodes and the livers of chronically infected animals, but not in those of uninfected animals or during early acute infection. Moreover, staining for the tight junction component claudin 3 showed that the integrity of the epithelial barrier was severely compromised in chronically infected animals. This damage began during the late acute phase of infection, and the degree of damage correlated with the degree of LPS translocation.

The authors then investigated whether this translocation was linked to immune activation. Using double-label immunohistochemical staining, they found colocalization of LPS and the proinflammatory mediators interferon-α and interleukin-18 in chronically infected animals. Importantly, both mediators could be observed in close proximity to LPS rather than to sites of local SIV replication. Confocal microscopy also revealed that macrophages were abundant in gastrointestinal tissue during the chronic stage of infection but that a high proportion of these had not taken up any LPS, suggesting that macrophage-based clearance is impaired. Taken together, these data provide direct evidence to support the hypothesis that the systemic immune activation that occurs during chronic HIV-1 infection is linked to the translocation of microbial products from the intestinal lumen, which in turn is linked to damage to the structural integrity of the gut epithelial layer and impaired clearance by macrophages.

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**Capsule**

**CRISPR Processing of invading viruses**

Many bacteria and archaea recognize invading viruses and plasmids. Foreign DNA is integrated into so-called clustered regularly interspaced short palindromic repeat (CRISPR) loci, and transcripts from these loci are processed into RNAs that can target the invading DNA or RNA for destruction. To investigate the molecular basis for this processing, Haurwitz and team screened CRISPR-associated (Cas) proteins in the opportunistic pathogen *Pseudomonas aeruginosa* and found they were capable of cleaving the CRISPR transcripts. The crystal structure of Cas4 with the CRISPR RNA transcript revealed how the protein specifically recognized RNA repeats, as well as the mechanism of endonucleolytic cleavage.

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Eitan Israeli

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“From a very early age I’ve had to interrupt my education to go to school”

George Bernard Shaw (1856-1950), Irish playwright, a co-founder of the London School of Economics, and Nobel Peace Prize laureate. Nearly all his writings deal sternly with prevailing social problems, but have a vein of comedy to make their stark themes more palatable. Shaw examined education, marriage, religion, government, health care, and class privilege. An ardent socialist, he was most angered by what he perceived as the exploitation of the working class.