Pyrexia of Unknown Origin: Kikuchi-Fujimoto Disease

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A case of Kikuchi-Fujimoto disease is presented in the context of pyrexia of unknown origin. Although no specific etiology has been identified, several reported cases are associated with a variety of viruses, toxoplasma, or systemic lupus erythematosus. We present a case and discuss the implications for management.

Kikuchi-Fujimoto disease, or histiocytic necrotizing lymphadenitis, is a benign, rare, self-limiting disease that was initially described in Japan by Kikuchi [1] and Fujimoto et al. [2] as a disease affecting young Asian females [3] (female-to-male ratio, 4:1) [4]. Later, this entity started to be described worldwide [5]. It presents as lymphadenopathy (mainly cervical), fever, and (less commonly) rash. Approximately 50% of patients with Kikuchi-Fujimoto disease show leukopenia, 5% have leukocytosis, and ≥25% have atypical lymphocytosis [5, 6]. Its initial clinical appearance is commonly similar to that of an infectious disease. Although no specific etiology has been identified, several reported cases have been associated with a variety of viruses, toxoplasma, or systemic lupus erythematosus [7]. We present a case and discuss the implications for management.

Case report. A 32-year-old woman presented with a 1-month history of a right posterior neck mass that did not respond to a 10-day course of antibiotic therapy. The patient reported experiencing fever, generalized weakness, and malaise. There was no history of exposure to tuberculosis or cats and no history of joint pain, skin rashes, hoarseness, or dysphasia.

A physical examination showed that the patient was febrile and had several lymph nodes in the posterior triangle of the neck that were nontender and rubbery. Findings of a systemic examination were normal.

A complete blood count showed leukopenia and an elevated erythrocyte sedimentation rate. The results of a liver function test and a renal function test were normal. Results of a monospot test, a Toxoplasma titer, and a PPD test were normal. Radiography showed upper mediastinal widening, and a CT scan of the chest showed paratracheal lymphadenopathy. Cultures of blood, urine, and stool samples showed no growth. The results of a Brucella agglutination test, a cold agglutinin test, and a Widal test were negative. The results of tests for antinuclear factor, double-stranded DNA, and Rh factor were negative. The results of virus studies for human herpesvirus types 1 and 2, rubella, mumps, and hepatitis were all negative, but test results for cytomegalovirus IgM and IgG were positive. Analysis of a bone marrow aspirate and a trephine biopsy specimen did not show any evidence of lymphoma or noncaseating granulomas. The patient underwent excisional biopsy of the right posterior lymph node. Gross examination of the lymph node biopsy specimen revealed an intact capsule. Microscopic examination (figures 1, 2, and 3) showed retained sinusoidal architecture, with a patent peripheral sinus and several small residual lymphoid follicles. There were discrete areas of necrosis with incomplete architectural effacement and abundant nuclear debris surrounded by transformed lymphocytes, histocytes, and plasmacytoid monocytes. Many foamy histocytes were present. Plasma cells were not identified in the interfolllicular region. There was no follicular hyperplasia. The findings of histological examination were therefore consistent with Kikuchi-Fujimoto disease.

Figure 1. Hematoxylin-eosin stain of a lymph node biopsy specimen showing large discrete areas of necrosis with karyorrhectic nuclear debris in the lymph node cortex and an intact lymph node capsule.
disease. Immunohistochemical studies performed on the lymph node specimen showed CD4+ plasmacytoid monocytes, CD8+ transformed lymphocytes, and CD45+ cells focally.

The patient was followed up for 16 months; at the time of writing, she is asymptomatic. Findings of additional chest radiographs were normal, and the patient’s total WBC count has remained within the normal range.

Discussion. The combination of pyrexia, neutropenia, and cervical lymphadenopathy, particularly in young Asian women, often leads to an initial, incorrect diagnosis of an infectious process. Several possible etiologies have been postulated and investigated because clinicians have suspected that an infectious process was at work on the basis of the transient and self-limited nature of Kikuchi-Fujimoto disease and the associated constitutional and upper respiratory tract infection–like symptoms. Among the infectious organisms that have been looked for are Yersinia enterocolitica, cytomegalovirus, human herpesvirus, varicella-zoster virus, parainfluenza virus, and Epstein-Barr virus [8]. However, studies have thus far failed to demonstrate a relationship between Kikuchi-Fujimoto disease and infection with either human herpesvirus or Epstein-Barr virus, and laboratory analysis is usually normal except for a transient leukocytopenia and elevated erythrocyte sedimentation rate [9]. A diagnosis of Kikuchi-Fujimoto disease starts with a high index of clinical suspicion and is confirmed by histological demonstration of histocytic necrotizing lymphadenitis [3, 10, 11].

Kikuchi-Fujimoto disease is therefore a clinicopathologic disease. Multiple foci of necrosis are seen in the lymph node cortex, with an intact lymph node capsule and patent subcapsular sinus. High magnification microscopy shows mostly histocytes with foamy cytoplasm, as was seen in our case [12]. The etiology of this disease is still unknown. It is usually considered to be a reactive lymphadenitis, an exuberant T cell immune response to multiple nonspecific stimuli that are usually associated with infection [13]. Epstein-Barr virus, toxoplasmosis, and human herpesvirus 6 have most often been linked to this disease as potential triggering agents [4, 14–17]. The absence of granulocytes in the areas of necrosis and the lack of follicular hyperplasia differentiate the lymphadenitis caused by Kikuchi-Fujimoto disease from that caused by cat-scratch disease and other bacterial infections.

Immunohistochemistry is also an important tool for diagnosing Kikuchi-Fujimoto disease and for distinguishing it from high grade B and T cell lymphoma [4,14, 18, 19]. Histologically, the lymph nodes of patients with Kikuchi-Fujimoto disease show mixed cellular proliferation consisting of lymphoid blast cells of varying size (so-called plasmacytoid cells), which are believed to be of monocyte lineage. A monoclonal antibody, Ki-M1P, used as a marker for cells belonging to the monocyte-macrophage lineage, has been used to detect the plasmacytoid cells present in the involved lymph nodes and to make reliable distinction of these cells from other similar cell types, such as blasts associated with high grade B and T cell lymphoma. Clinically, the presentation is usually cervical adenopathy ≤2 cm in size, which is associated with fever and night sweats in the majority of cases and is unresponsive to antibiotic or other medical treatment [3, 4, 20, 21]. The outcome of the disease is usually favorable, with spontaneous resolution of symptoms in most cases and recurrence in only a few instances. The course of the disease is 1–3 months if no complication arises. No specific therapy is indicated.

A review of cases reported in the literature (table 1) suggests that neutropenia and an elevated erythrocyte sedimentation rate

Figure 2. Hematoxylin-eosin stain of a lymph node biopsy specimen showing mostly histocytes and plasmacytoid monocytes, as well as abundant nuclear debris surrounded by transformed lymphocytes. Many foamy histocytes are present.

Figure 3. Hematoxylin-eosin stain of a lymph node biopsy specimen showing mostly histocytes, some with C-shaped nuclei, and scattered karyorrhetic debris.
<table>
<thead>
<tr>
<th>Study, patient no.</th>
<th>Date</th>
<th>Clincial findings</th>
<th>Laboratory findings</th>
</tr>
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<tbody>
<tr>
<td>Hamdan et al.</td>
<td>2002</td>
<td>Mass in the neck; polyarthralgia; general weakness; fever; duration of symptoms, 6 months</td>
<td>CBC and ESR, normal; LFT and RFT, normal; Blood culture, no growth; monospot and PPD tests, negative</td>
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<tr>
<td>Stephan et al.</td>
<td>2001</td>
<td>Painful swelling in the neck; fever; weakness; weight loss; duration of symptoms, 3 weeks</td>
<td>CBC: 4.14 WBCs/mm³, 55% N, 37% L, 5.7% M, 4% E; Hb level, 11.4 g/dL; ESR, 55 mm/h; CRP level, 34 mg/dL; peripheral cell antigen: CD3⁺ cell count, 1280 cells/mm³; CD4⁺ cell percentage, 28%; CD8⁺ cell percentage, 41%</td>
</tr>
<tr>
<td>Wurm et al.</td>
<td>2000</td>
<td>Fever; malaise; anorexia; cervical lymphadenopathy; duration of symptoms, 6 weeks</td>
<td>CBC: 2.7 WBCs/mm³; 13 neutrophils/mm³; Peripheral blood smears for malaria, normal; T cell analysis: T cell lymphopenia of CD4⁺, CD8⁺, and NK population</td>
</tr>
<tr>
<td>Graham</td>
<td>2002</td>
<td>Fever and rashes; joint pain; sore throat; cervical and inguinal lymphadenopathy; duration of symptoms, 5 weeks</td>
<td>13.3 WBCs/mm³; ESR, 125 mm/h; AST, 283 U/L; ALT, 374 U/L; ANA, negative; Rh factor and HbsAg, negative; RFT, normal</td>
</tr>
<tr>
<td>Amir et al.</td>
<td>2002</td>
<td>Fever; night sweats; anorexia; weight loss; cervical lymphadenopathy; duration of symptoms, 5 weeks</td>
<td>2.6 WBCs/mm³; Hb level, 11.8 g/dL; ESR, 50 mm/h; RFT, normal; AST, 67 U/L; ALT, 85 U/L; Rh factor, ANA, and dsDNA, negative</td>
</tr>
<tr>
<td>Patient 1</td>
<td>2002</td>
<td>Fever; fatigue; cervical lymphadenopathy</td>
<td>2.7 WBCs/mm³; Hb level, 11.9 g/dL; ESR, 92 mm/h; AST, 109 U/L; ALT, 95 U/L; Rh factor, ANA, and dsDNA, negative</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2002</td>
<td>Fever; fatigue; cervical lymphadenopathy</td>
<td>2.7 WBCs/mm³; Hb level, 11.9 g/dL; ESR, 92 mm/h; AST, 109 U/L; ALT, 95 U/L; Rh factor, ANA, and dsDNA, negative</td>
</tr>
</tbody>
</table>
Baumgartner et al. [26] 2002 Gradually progressive fullness in the posterior triangle of the neck; duration of symptoms, 6 weeks

4.2 WBCs/mm³; Hb level, 14.1 g/dl; LFT, RFT, and TFT, normal; rapid plasma regain test, nonreactive; ANA, positive (1:320); with a homogeneous pattern

Blood and urine cultures, no growth; HIV and Borrelia titers, negative

CXR, normal; CT of the neck showing negative bilateral posterior triangle lymphadenopathy, prominent on the right

Lymph node biopsy specimen, consistent with KFD

Al-Nazer et al. [24] 2002 6 patients, aged 15–32 years, presented with history of fever, weight loss, and cervical lymphadenopathy; duration of symptoms, >3 weeks

Patient 1

2.1 WBCs/mm³; Hb level, 9 g/dl; ESR, 78 mm/hr; Coombs test, positive

AST, 863 U/L; ALT, 1106 U/L; LDH, 2358 U/L; ANA, positive (1:320), with a homogeneous pattern

Blood and urine cultures, no growth; HIV and Borrelia titers, negative; rapid plasma regain test, nonreactive

CXR, normal

Lymp node biopsy specimen, consistent with KFD

Patient 2

5.8 WBCs/mm³; Hb level, 11.8 g/dl; ESR, 130 mm/hr; Coombs test, not done

AST, 22 U/L; ALT, 10 U/L; LDH, 164 U/L; ANA and dsDNA, negative

Blood and urine cultures, no growth; malaria and Widal tests, negative; Toxoplasma titer, not done

CXR, normal

Lymp node biopsy specimen, consistent with KFD

Patient 3

4.7 WBCs/mm³; Hb level, 11.6 g/dl; ESR, 8 mm/hr; Coombs test, not done

AST, 10 U/L; ALT, 25 U/L; LDH, 170 U/L; ANA and dsDNA, not done

Blood and urine cultures, no growth; malaria and Widal tests, negative; Toxoplasma titer, not done

CXR, normal

Lymp node biopsy specimen, consistent with KFD

Patient 4

3.4 WBCs/mm³; Hb level, 13.9 g/dl; ESR, 5 mm/hr; Coombs test, not done

AST, 29 U/L; ALT, 37 U/L; ANA and dsDNA, negative

Blood and urine cultures, no growth; malaria and Widal tests, negative; Toxoplasma titer, not done

CXR, normal

Lymp node biopsy specimen, consistent with KFD

Patient 5

2.7 WBCs/mm³; Hb level, 11.8 g/dl; ESR, 123 mm/hr; Coombs test, not done

AST, 34 U/L; ALT, 35 U/L; ANA and dsDNA, negative

Blood and urine cultures, no growth; malaria and Widal tests, negative; Toxoplasma titer, not done

CXR, normal

Bone marrow aspirate, normal; axillary lymph node biopsy specimen, consistent with KFD

Patient 6

1.4 WBCs/mm³; Hb level, 12 g/dl; ESR, 32 mm/hr; Coombs test, not done

AST, 27 U/L; ALT, 12 U/L; ANA and dsDNA, not done

Blood and urine cultures, no growth; malaria and Widal tests, not done

CXR, normal

Lymp node biopsy specimen, consistent with KFD

Norris et al. [10] 1996 Patient 1

Fever; weight loss; malaise; cervical lymphadenopathy; duration of symptoms, recurrent for 10 years

CBC, normal; ESR, 80 mm/hr

LDH, 443 U/L; AST and ALT, normal; ANA, dsDNA, and Rh factor, negative

Blood and urine cultures, no growth; HIV antibody titer, negative

Cervical lymph node biopsy specimen, normal

NOTE. ALT, alanine aminotransferase; ANA, antinuclear antibody test; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CXR, chest radiograph; dsDNA, double-stranded DNA; E, eosinophils; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HbsAg, hepatitis B surface antigen; L, lymphocytes; LDH, lactate dehydrogenase; LFT, liver function test; M, monocytes; N, neutrophils; NK, natural killer cells; RFT, renal function test; TFT, thyroid function test.

a The 2 patients reported in Amir et al. [6] were sisters.
were the major abnormal hematological findings, and only a few patients had atypical lymphocytes in the peripheral smear. All patients tested negative for malarial parasites. For all patients, cultures of blood and urine samples showed no growth. Results of monospot and PPD tests were usually negative. Antibody titers against *Toxoplasmosis gondii*, *Toxocara canis*, rubella virus, cytomegalovirus, herpes simplex virus, HIV types 1 and 2, *Yersinia* species, and hepatitis C virus were negative, except in the case of 1 patient, whose serological testing results were positive for hepatitis B antibody [6] and Epstein-Barr virus [22]. Ours is the first case so far reported in the literature in which there is an association with a serological test result positive for cytomegalovirus.

Biochemical and immunological studies showed a normal immunoglobulin level but an elevated aspartate aminotransferase or alanine aminotransferase level in 4 cases [6, 23, 24] and an elevated lactate dehydrogenase level in 5 cases [10, 24]; the rest of the patients had normal liver function test results. Tests for antinuclear factor, double-stranded DNA, and antineutrophil cytoplasmic antibodies were negative except in the cases of 2 patients with elevated antinuclear antibody levels [24, 25] and 1 patient with thyroid microsomal antibodies [26]. Chest radiography findings for all patients were normal (except for our patient, who had mild mediastinal widening), and CT of the neck, performed for 1 patient, showed bilateral posterior triangle lymphadenopathy. CT of the chest of our patient showed paratracheal lymphadenopathy. Bone marrow biopsy was performed for 3 patients (including ours) [22, 26], and all patients had normal results. HLA phenotyping [6] was performed for 2 sisters who each received a diagnosis of Kikuchi-Fujimoto Disease and who were found to have identical HLA haplotypes. Immunohistochemical studies performed for 5 patients (including ours) had positive results; in 2 cases, antibody against CD68 histocytes was found, and antibody to CD8+ T lymphocyte has been demonstrated in other reports. We have also noted that, in our specimen, focal positivity for CD45 cells and CD45-positive CD163+ histocytes was found, and antibody to CD8+ T lymphocyte has been demonstrated in other reports. We have also noted that, in our specimen, focal positivity for CD45 cells was demonstrable [22, 26].

**Conclusion.** Kikuchi-Fujimoto disease, although rare, should be included in the differential diagnosis for patients presenting with cervical lymphadenopathy and fever of unknown origin. Early recognition of this entity can minimize unnecessary investigations and therapeutic trials.

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**References**