Kikuchi-Fujimoto Disease With Prolonged Fever in Children

Kyung-Yil Lee, MD; Yeong-Heum Yeon, MD; and Byung-Churl Lee, MD

ABSTRACT. We reviewed 12 patients who had Kikuchi-Fujimoto disease (KFD) and presented with prolonged fever and lymphadenopathy. The clinical and laboratory aspects of the patients confirmed by excisional lymph node biopsy were analyzed. The mean age of the children was 11.0 ± 3.0 years (range: 6–15 years). The male-to-female ratio was 1.4:1. The median duration of fever before admission and the total duration of fever was 13 days (range: 7–65 days) and 19.5 days (range: 9–75 days), respectively. One patient had supraclavicular lymphadenopathy, 10 had cervical involvement, and 1 had axillary lymphadenopathy. All of the histologic findings of the lymph node biopsies showed the characteristic findings consistent with KFD, such as paracortical necrosis with karyorrhexis and an increase in the number of phagocytic histiocytes and atypical lymphocytes. As for the laboratory findings, leukopenia (3600 ± 900 per mm³), anemia (hemoglobin 11.4 ± 1.2 g/dL), an elevated erythrocyte sedimentation rate (44 ± 18 mm/hour), and a relatively low C-reactive protein level (1.3 ± 1.1 mg/dL) were noted. Eight patients received conservative therapy with antipyretics, and 3 patients were treated with prednisolone. KFD is a rare disease yet should be considered in the differential diagnosis for older children with prolonged fever and lymphadenopathy. Pediatrics 2004; 114:e752–e756. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0485; Kikuchi-Fujimoto disease, subacute necrotizing lymphadenitis, prednisolone.

Kikuchi-Fujimoto disease (KFD) is a self-limiting disease that has an unknown cause and was first described independently in 1972 by Kikuchi1 and Fujimoto et al2 in Japan. This disease has now been recognized in many other countries and has also been referred to as Kikuchi’s disease, histiocytic necrotizing lymphadenitis, focal histiocytic lymphadenitis, and subacute necrotizing lymphadenitis.3–10

The characteristic clinical presentation of the disorder includes cervical lymphadenopathy and prolonged fever. Its natural course is usually benign, and the clinical symptoms and signs disappear within a few months without specific treatment. Because the clinical findings and laboratory examinations are nonspecific, the correct diagnosis requires a histopathologic examination by lymph node biopsy. If the clinician is unaware of the disorder or if the lymphadenopathy is not prominent at presentation, then delayed diagnosis and unnecessary investigations for a “fever of unknown origin” can occur. KFD affects individuals of all ages, particularly young women, but there are just a few descriptions of this disease in the pediatric literature.11–16 In this study, we evaluated the clinical and laboratory characteristics of 12 patients with KFD confirmed by lymph node biopsy.

METHODS

We retrospectively analyzed the medical charts of 12 patients who had KFD and presented with a prolonged fever of >10 days. Seven patients were admitted to Catholic University of Korea, Daejeon St Mary’s Hospital (patients 1–7), and 5 patients were admitted to St Mary’s Hospital (patients 8–12) from 1996 through 2003. All patients’ disease was diagnosed histologically by an excision lymph node biopsy. All histologic findings from the biopsies were consistent with a diagnosis of KFD, manifesting as a paracortical patchy eosinophilic fibrinoid necrosis with karyorrhexis and an increase of lymphohistiocytic infiltrates. These infiltrates included mononuclear cells, histiocytes, and atypical lymphocytes (Figs 1 and 2, obtained from patient 2). The clinical characteristics, status of affected lymph nodes, associated symptoms, and laboratory findings from the medical records are presented.

RESULTS

Clinical Characteristics

The mean age of the patients was 11.0 ± 3.0 years, ranging from 6 to 15 years. The male-to-female ratio was 1.4:1. The median fever duration before hospital admission was 13 days (range: 7–65 days), and the median total duration of the fever was 19.5 days (range: 10–75 days). Lymphadenopathy (lymph node size ≥1 cm and showing tenderness) was noted at the cervical regions in 10 patients, in the axillary region in 1 patient, and in the supraclavicular region in 1 patient. In this series, the mean size of affected lymph nodes on biopsy was 1.5 × 2.0 cm. All patients experienced tenderness of the affected lymph node, regardless of the node’s size, during the febrile period. As for other extranodal manifestations, 1 patient (patient 2) had a transient skin rash on the trunk that was of a maculopapular nature, and 1 patient presented with weight loss and night sweats (patient 7; Table 1). All patients except 1 (patient 12) became afebrile within 2 days after lymph node biopsy. In 4 patients (patients 3, 4, 7, and 10), the fever subsided...
before lymph node biopsy. Two patients (patients 1 and 2) showed recurrent fever 3 to 4 days after lymph node excision; this fever lasted several days and quickly responded to prednisolone treatment (1 mg/kg for 5–7 days, and then tapered within 1 week), and the patients became afebrile within 1 day. However, 1 patient (patient 6) had fever recurrence 7 days after the first lymph node biopsy; this fever did not respond to prednisolone therapy, and the patient required a second lymph node excision. The other children showed no fever recurrence during the observation of at least 6 months.

**Laboratory Findings**

The white blood cell count of all patients indicated leukopenia (3600 ± 900 per mm³), together with the normal differential. The mean hemoglobin level was 11.4 ± 1.2 g/dL, which was lower than that of healthy children of the same age. The erythrocyte segmentation rate (ESR) was higher (44 ± 18 mm/hour) than normal, whereas the C-reactive protein (CRP) level was slightly elevated (1.3 ± 1.1 mg/dL). The lactate dehydrogenase (LDH) level was increased, although aminotransferase levels were not increased. The fluorescent antinuclear antibody test and antirheumatoid factor were negative for all patients. Elevated immunoglobulin G and immunoglobulin E values were noted in 4 of the evaluated patients (Table 2).

**DISCUSSION**

KFD is recognized as a distinctive clinicopathologic entity, and it has been well described in the pathology literature. However, only a few case reports about the disorder are available in the pediatrics literature. KFD is more prevalent in Asians, particularly in Far East nations including Korea. Tanaka et al reported that 2 HLA class II...
TABLE 1. Clinical Characteristics of KFD in Children

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Fever Duration, days</th>
<th>Biopsied Lymph Node (Size, cm)</th>
<th>Treatment Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A*</td>
<td>B†</td>
<td>C‡</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8/F</td>
<td>5</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>9/M</td>
<td>42</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>10/F</td>
<td>7</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>11/F</td>
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<td>9</td>
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<tr>
<td>5</td>
<td>12/M</td>
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<tr>
<td>12</td>
<td>13/F</td>
<td>7</td>
<td>18</td>
<td>6</td>
</tr>
</tbody>
</table>

F indicates female; M, male. * Fever duration before admission. † Total fever duration before lymph node excision. ‡ Fever duration after lymph node excision biopsy.

genes, the DPA*01 allele and the DPB1*0202 allele, which is common in Asians but not in whites, might be related to KFD. In Korea, Koh et al17 reported 24 cases in 1983, and Song et al18 reported the first case of a pediatric patient in 1990. Although KFD affects individuals over a wide range of ages, the overall proportion of pediatric patients has not yet been defined in the literature. In 1 series, Lin et al10 reported that 21 (34.4%) cases of a total of 61 cases were pediatric patients <16 years old.

Cervical lymphadenopathy and fever are the most common presentations of the disorder. However, the clinical presentation may vary from patient to patient. Some patients with lymphadenopathy complain of malaise, fatigue, night sweats, weight loss, and gastroenteric symptoms without any fever. Although lymphadenopathy usually affects the cervical lymph nodes, the axillary lymph nodes and lymph nodes in other regions can be affected.3–10,14,19 The lymph nodes, the axillary lymph nodes and lymph nodes in other regions can be affected.3–10,14,19 The size of the affected lymph nodes usually are 2 to 3 cm, but sometimes these nodes can be >5 cm. An affected lymph node is solid, movable, and painful but not suppurative. In our series, fever was the main complaint, and its nature in most patients was intermittent. Some patients, however, experienced a daily spiking fever of >40°C for a fairly long period (patients 2 and 6). Although multiple lymph nodes were observed in some patients on the affected side or on both sides of the neck by palpation or sonography, the main affected lymph node was usually solitary. One patient (patient 2) who presented with 10 days of fever at initial admission did not show any lymphadenopathy. However, at the second admission, he was eventually noticed to have a lymph node with tenderness at the right axillary region on the 40th day of fever. All patients in this series were observed to have tenderness of the lymph nodes during the febrile period regardless of the affected node’s size, suggesting that the fever is associated with active lymph node inflammation. In evaluating KFD patients with prolonged fever, a thorough examination of the lymph nodes located in other sites as well as the palpable regions is warranted.14,19 Hong et al20 in Korea recently reported that among 23 KFD children with cervical lymphadenopathy diagnosed by fine-needle aspiration cytology, lymph node tenderness was noted in 60% of the patients, fever was noted in 44%, and the mean age at the time of presentation was 8.1 ± 3.8 years (range: 14 months to 14 years). However, almost all patients in this series presented with fever, tenderness of the lymph node, and a higher mean age (11 ± 3 years). This suggested that the immune response and clinical course of the KFD might differ according to age. Lymphadenopathy with or without fever is commonly observed in young children and is frequently overlooked. These findings, along with the self-limited nature of the KFD, suggest that the disease may be more common than originally thought.

Extranodal involvement rarely occurs in KFD but includes skin lesions,21 arthritis,22 aseptic meningitis,11,23 and unexpected death.12,24 Two reports independently described that children with KFD experienced a severe clinical course with multiorgan failure after the use of multiple antituberculous drugs.13,15

The laboratory investigations of KFD revealed leukopenia and anemia. The ESR and LDH levels were increased, but the transaminase level was unaffected. Similar to adult data, the laboratory indices of almost all patients examined in the febrile period showed leukopenia, anemia, elevated ESR and LDH values, and normal transaminase values. In addition, a relatively low CRP value and elevated immunoglobulin G and immunoglobulin E values were noted (Table 2).

The cause of the KFD is unknown. Several infectious agents have been suggested, but none have been confirmed. The histologic and immunologic findings together with the typical clinical presentation suggest a hyperimmune reaction of immune cells to unidentified agents.3,4,25 An autoimmune contribution to the pathogenesis is suggested by observations showing that the disease can precede or
occur in association with systemic lupus erythematosus.4,7,10,26

A definitive diagnosis of KFD is determined by a lymph node biopsy. The histopathologic changes in KFD are known to pass through 3 stages associated with clinical features.7 The early proliferative stage with lymphohistocytic proliferation and numerous atypical mononuclear cells can be confused with a malignant lymphoma.1,4,27 Tuberculosis, Kawasaki disease, and systemic lupus erythematosus should also be differentiated from KFD.

There is no specific therapy for KFD. The majority of patients show improvement in symptoms and signs within a few months of presentation. In this study, 7 of 8 patients became afebrile after the excision biopsy. One patient (patient 5), who had the longest fever duration in our series and experienced a fever for 1 year, became afebrile after the excision biopsy. One patient (patient 6) had left cervical lymphadenopathy and 12 days of fever at his first presentation. After confirming diagnosis by a left lymph node excision biopsy, he became afebrile for 1 week. He was readmitted with recurrent fever and right cervical lymphadenopathy. He did not respond to treatment with non-steroidal anti-inflammatory drugs or prednisolone (1 mg/kg for 7 days). He eventually improved after a second excision biopsy of the right-side lymph node (3.0 × 4.0 cm). These findings suggest that the removal of the affected lymph node is not only diagnostic but also possibly therapeutic. Therefore, even in cases in which the lymph node excision poses technical difficulties such as a deep location in the neck, the removal of the main affected lymph node may be desirable. A beneficial effect of glucocorticoids has been reported in a small number of cases with severe or recurrent symptoms.11,28 Although KFD is a benign disease, the prolonged fever can be distressing to the patient and parents. One patient (patient 6) described above did not respond to prednisolone. Although 2 patients (patients 1 and 2) with a recurring fever after a lymph node excision quickly responded to prednisolone treatment, additional study will be needed for validating steroid treatment for this disease.

KFD is rare disease, but it should be considered when making a differential diagnosis of prolonged fever in children, particularly older children. The laboratory findings show leukopenia, anemia, elevated ESR and LDH values, and normal transaminases values. An early diagnosis by an excision biopsy of the affected lymph node can help minimize unnecessary examinations and halt inappropriate or even harmful treatment and may improve symptoms.

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