Kikuchi’s Disease With Multisystemic Involvement and Adverse Reaction to Drugs

Maria L. Murga Sierra, MD*; Eva Vegas, MD*; Javier E. Blanco-González, MD*; Almudena González, MD‡; Pilar Martínez, MD‡; and Maria A. Calero, MD§

ABSTRACT. Kikuchi’s disease (KD), or histiocytic necrotizing lymphadenitis, was initially described in Japan in 1972. In the following years, several series of cases involving patients of different ages, races, and geographic origins were reported, but pediatric reports have been rare.

The etiology of KD is unknown, although a viral or autoimmune hypothesis has been suggested. The most frequent clinical manifestation consists of local or generalized adenopathy, although in some cases, it is associated with more general symptoms, multiorgan involvement, and diverse analytic changes (leukopenia, elevated erythrocyte sedimentation rate, and C-reactive protein, as well as an increase of transaminases and serum lactic dehydrogenase).

Diagnosis is based on characteristic pathologic findings that permit differentiation of this disease from lymphoma, systemic lupus erythematosus, and infectious lymphadenopathies.

We present here the case of a 14-year-old boy who presented with severe systemic manifestations and transient fulminant hepatic failure in response to treatment with antituberculosis drugs. Pediatrics 1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e24; Kikuchi’s disease, lymphadenitis, liver failure, antituberculosis drugs.

ABBREVIATIONS. KD, Kikuchi’s disease; LDH, serum lactic dehydrogenase.

CASE REPORT

A 14-year-old white boy was admitted to our hospital after presenting with fever up to 39.8°C for 1 week, malaise, odynophagia, arthralgia, myalgia, abdominal pain, and pruritic skin eruption. Personal and family history was irrelevant. He did not recall any history of exposure to flies, ticks, cats, or dogs, and there was no indication of animals scratches. On physical examination, several multiple peripheral adenopathies were detected (cervical, axillary, and inguinal), the sizes of which ranged from 0.5 to 2.5 cm in diameter. In general, these nodes were indurated, mobile, and relatively tender. Liver and spleen were palpable 4 cm and 2 cm, respectively, below the costal margin. Erythrocyte sedimentation rate was 39 mm per hour, and C-reactive protein was 163 mg/dL. Biochemical analysis, coagulation, hepatic and renal functions, immunoglobulins, and complement count were normal (Tables 1, 2). Rheumatoid factor, antinuclear antibodies, direct Coombs test, and two Mantoux test results proved to be negative. Antibody titers against Epstein–Barr, cytomegalovirus, hepatitis, HIV, and Parvovirus B19, and serum polymerase chain reaction for herpesvirus type 6 were negative as well, as were results of serologic tests for syphilis, Brucella, toxoplasmosis, Leishmania, Rickettsia, Borrelia, and Bartonella henselae and quintana.

Results of chest roentgenography, echocardiography, and bone scan were normal; an abdominal ultrasound examination detected hepatosplenomegaly with uniform density and nephromegaly with increased cortical echogenicity.

The patient was treated with ceftriaxone and nonsteroid anti-inflammatory drugs the second week of fever, with apparent lack of remission. Furthermore, the condition worsened with an onset of somnolence, headache, and emesis during the third week, potentiated by the detection of aseptic meningitis as certified by cerebrospinal fluid analysis that disclosed 32 leukocytes (90% monocytes), 48 mg/dL protein, and 68 mg/dL glucose.

Biopsy of the bone marrow revealed a normal cellular content. An immunophenotypic study of the marrow and peripheral blood showed an inversion in the CD4/CD8 ratio and depletion of B lymphocytes (0.2% of total) (Table 2). However, these tests were not repeated.

Biopsy results of the lymph nodes were compatible with histopathology of histiocytic necrotizing lymphadenitis; ie, they showed wide areas of confluent necrosis in paracortical zones, marked karyorrhexis, crecentic histiocytes and immunohistocytic type cells in an absence of neutrophils, and an intact node capsule (Fig 2).

Cutaneous biopsy demonstrated lymphohistiocytic infiltrates, predominantly perivascular, without any necrosis of the adjacent vascular wall.

Into the fourth week of illness, we decided to begin empiric treatment with corticoids (intravenous methylprednisolone, 2 mg/kg per day) and three antituberculosis drugs (isoniazid, rifampicin, pyrazinamide) while awaiting definitive microbiologic test results (tuberculosis infection is common in our country). On the third day of treatment, jaundice, 8 cm hepatomegaly, and a generalized erythematous rash were observed, confirmed as a fulminant hepatic failure (serum glutamic pyruvate transaminase, 1180 U/L; serum glutamic oxaloacetic transaminase, 3220 U/L; total bilirubin, 4.9 mg/dL; albumin, 2.2 g/dL; international normalized ratio, 2.13; and fibrinogen, 125 mg/dL). No signs of bleeding or encephalopathy were found. Antituberculosis drug therapy was suspended once hepatic failure was detected (3 days in treatment). Hepatic function normalized 1 week later (Table 2).

The patient received intravenous methylprednisolone for 10 days. He was then put on oral prednisone, which was slowly tapered over 3 months. In the sixth week of illness (8 days of corticotherapy), fever, hepatosplenomegaly, and lymphadenopathy receded. Pancytopenia abated in 2 months that followed, whereas arthromalgia and nephromegaly persisted until 3 months later. A posteriori, after 2 years of follow-up, no symptoms or signs of disease relapse were detected.

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DISCUSSION
KD has been described primarily in people younger than 30 years of age, predominantly in women, and in Asian populations. The age range is broad (4–75 years), but only 5% to 10% of patients are younger than 21 years of age. In our country, descriptions of KD in the clinical literature are limited to isolated case reports, and only one of these involves a pediatric patient.

The most frequent clinical manifestation of KD is an isolated cervical lymphadenopathy, although other lymphatic regions may be affected. The multiple lymphadenopathy occurs (as in the example of our patient) in 1.3% to 22.2% of cases. It might be accompanied by other, more variable symptoms that generally consist of fever (30% to 50% of patients), fatigue, musculoskeletal pains, night sweating, loss of weight, and chest and abdominal pain. In the case of unsuspected occult lymphadenopathy, the patient may debut with fever of unknown origin.

Noncharacteristic skin lesions have been observed in ~30% of patients, and usually are described as nodules, papules, maculopapular, disseminated erythema, or urticarial. Cutaneous biopsy results may show diffuse dermal infiltration by apoptotic plasmacytoid monocytes, with perivascular and perianexal distribution. Our patient had a papular rash, and biopsy revealed similar histopathologic findings.

Hepatosplenomegaly associated with KD has been detected on a relatively frequent basis, whereas nephromegaly was reported previously in only one case of 40-year-old patient with intraabdominal lymph node involvement. Neurologic manifestations are rare and have been described only in iso-

TABLE 1. Immunologic Parameters in Peripheral Blood*

<table>
<thead>
<tr>
<th>Differential Leukocyte Count</th>
<th>Immunophenotype Peripheral Blood</th>
<th>Immunoglobulin Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>T-cell markers</td>
<td>IgG</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>CD3</td>
<td>45%</td>
</tr>
<tr>
<td>Band cell forms</td>
<td>CD4</td>
<td>7.5%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>CD8</td>
<td>58%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>CD4/CD8</td>
<td>2%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>B-cell markers</td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>CD19</td>
<td>0.2%</td>
</tr>
<tr>
<td>Medium and large</td>
<td>CD10/CD19</td>
<td>0.1%</td>
</tr>
<tr>
<td>Irregularly shaped nuclei</td>
<td>CD10/CD19</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

* These tests were performed on 21st day of illness.

TABLE 2. Laboratory Profiles

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>Day 7</th>
<th>Day 29</th>
<th>Day 36</th>
<th>Day 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cell count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells (cells × 10^9/L)</td>
<td>2.7</td>
<td>7.1</td>
<td>4.3</td>
<td>11.6</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.3</td>
<td>8.3</td>
<td>7.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Platelets (cells × 10^9/L)</td>
<td>107</td>
<td>110</td>
<td>188</td>
<td>289</td>
</tr>
<tr>
<td>Hepatic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum glutamic oxalacetic transaminase (U/L)</td>
<td>34</td>
<td>3220</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Serum glutamic pyruvate transaminase (U/L)</td>
<td>38</td>
<td>1180</td>
<td>62</td>
<td>26</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>250</td>
<td>5420</td>
<td>630</td>
<td>353</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>657</td>
<td>17540</td>
<td>810</td>
<td>485</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.3</td>
<td>4.9</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8</td>
<td>2.2</td>
<td>4.4</td>
<td>5.2</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.93</td>
<td>2.13</td>
<td>1.05</td>
<td>1.01</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>225</td>
<td>125</td>
<td>180</td>
<td>278</td>
</tr>
</tbody>
</table>
lated cases of patients with aseptic meningitis, acute cerebellar ataxia, and secondary intracranial hypertension to cervical venal obstruction.

Diagnosis of KD is based on histopathologic observations of lymph node material obtained by fine-needle aspiration or open biopsy. In our case, both methods yielded the same information. The characteristic histopathologic features of the disease are 1) focal necrosis, predominantly in the paracortical region with abundant karyorrhexis; 2) aggregates of atypical mononuclear cells around the zone of necrosis (crescentic histiocytes, plasmacytoid monocytes, and immunoblasts); 3) absence of neutrophils and paucity of plasma cells; and 4) usually intact lymph node capsule. The histologic differential diagnosis of KD includes other causes of necrotizing lymphadenitis including infectious (tuberculosis, toxoplasmosis, yersiniosis, cat scratch disease); autoimmune (systemic lupus erythematosus, Kawasaki's disease); and neoplastic diseases (lymphoma). In the present case, results of a thorough microbiologic examination proved negative, and lack of analytic results that would suggest autoimmune reaction helped diagnose KD. An immunophenotypic study of peripheral blood and bone marrow performed on our patient were compatible with these references.

The pathogenesis of KD is still unknown. However, the clinical presentation and histologic changes suggest hyperimmune reaction of T cells, activated by an unidentified pathogen. At present, it remains to be seen whether the immune response is initially sparked by an infectious agent or whether it reflects some underlying intrinsic defect of T cell immunity. The association of several infectious agents including bacteria (Brucella, Yersinia), parasites (toxoplasmosis), and viruses (Epstein–Barr, herpesvirus 6, Parvovirus B19) was suggested, but thus far, no etiologic relationship has been confirmed. The importance of autoimmune mechanisms in the pathogenesis of the disease has been demonstrated by the description of patients who developed connective tissue diseases (systemic lupus erythematosus, Still's disease) before or after being diagnosed with histiocytic necrotizing lymphadenitis. Moreover, the majority of patients do not develop autoimmune dysfunction, although the presence of positive antinuclear antibodies, rheumatoid factor, and direct Coombs results have been reported. In our patient, the determinations noted above were negative.

The most frequent analytic alterations in KD include leukopenia with neutropenia, anemia, and the presence of atypical lymphocytes in peripheral blood; therefore, pancytopenia observed in our patient was by all standards, exceptional. An increase in reagents of acute phase and LDH often are reported. Subsequently, a moderate increase in the level of transaminases has been described in the cases that are accompanied by the alteration of hepatic function. Hepatic failure in our patient can be interpreted as an extremely early adverse reaction to antituberculosis drugs. The possibility that the severe liver dysfunction described previously could have occurred in the absence of antituberculosis drugs cannot be excluded, but this seems unlikely given that hepatic function was normal before the drug therapy. The mechanisms of drug-induced hepatotoxicity resulting from antituberculosis agents are thought to involve direct cytotoxicity (by the drugs or its metabolites). Nonetheless, they are not yet fully discerned. An immune-related component is also believed to play a role, because several authors have documented or suggested immunologic effects. In view of our findings, we speculate that fulminant hepatic failure may have been expedited by the underlying hyperimmune reaction. This stems from the fact that, thus far, no case of KD with fulminant hepatic failure or with an adverse reaction to drugs has been reported.

Although two fatal cases of KD have been documented, spontaneous improvement and disappearance of symptoms are frequently the norm, usually within 1 to 6 months of initial onset. In 3% of patients, the disease may recur for many years. No treatment is necessary, and nonsteroidal antiinflammatory drugs are helpful in alleviating fever and the tenderness of lymph nodes. The use of corticosteroids has been recommended to prevent death, but only in severe cases with hyperpirexia, aseptic meningitis, or cerebellar ataxia. The aforementioned therapy also is reserved for cases with an important increase in LDH or antinuclear antibodies titer.

By and large, our patient's clinical profile reflects a severe case of KD, with important constitutional symptoms, exceptional systemic manifestations (rare pancytopenia and nephromegaly), and ensuing complications (aseptic meningitis and hepatic failure). It is also important to note that in previous studies, an adverse reaction to drugs and fulminant hepatic failure have not been associated with this disease.
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