Original Article

Clinical Presentations, Laboratory Results and Outcomes of Patients with Kikuchi’s Disease: Emphasis on the Association Between Recurrent Kikuchi’s Disease and Autoimmune Diseases

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BACKGROUND/PURPOSE: Kikuchi’s disease (KD), also known as histiocytic necrotizing lymphadenitis, is a benign and self-limiting disease of unknown etiology that mainly affects young women. There is limited data on the long-term prognosis of patients with KD.

METHODS: We describe the clinical manifestations and outcomes of 195 patients, diagnosed as having KD at National Taiwan University Hospital from March 1989 to September 2006.

RESULTS: All together, 53.3% of our patients presented with tender lymphadenopathy, 37.9% with fever and 16.9% with headache. The most common laboratory findings were elevated erythrocyte sedimentation rate (78.9%), elevated serum lactate dehydrogenase (52.5%), elevated C-reactive protein (38.3%), monocytosis (26.9%), elevated serum alanine aminotransferase (23.3%) and leukopenia (18.9%). A total of 183 patients followed a benign course, with spontaneous resolution of fever and lymphadenopathy. However, 14 patients (14.6%) with follow-up of more than 6 months had clinical recurrence of KD; hence, long-term follow-up is suggested. Five of these patients developed an autoimmune disease, namely, systemic lupus erythematosus (n = 2), Graves’ disease (n = 2), or mixed connective tissue disease (n = 1). One patient with recurrent KD died of intracranial hemorrhage due to thrombocytopenia.

CONCLUSION: The prognosis for KD patients is generally optimistic; however, a concurrent autoimmune disease or the risk of developing an autoimmune disease requires careful monitoring.

KEYWORDS: autoimmune disease, histiocytic necrotizing lymphadenitis, Kikuchi’s disease

Introduction

Kikuchi’s disease (KD), or histiocytic necrotizing lymphadenitis, is a benign and rare disease. The most common clinical manifestations are persistent fever and localized lymphadenopathy. The typical laboratory findings are leukopenia, monocytosis, and elevated lactate dehydrogenase (LDH) and alanine aminotransferase (ALT). The prognosis of KD is generally favorable. Almost all KD patients lead a self-limited course and the disease resolves...
spontaneously over a period of several weeks to months. However, a minority of KD patients may experience a poor clinical outcome attributable to systemic involvement and the risk of progression to systemic lupus erythematosus (SLE). In addition, there has been one case report of a patient who experienced a recurrence of KD more than 10 years after the first episode.

KD appears to be more common in Asia than in western countries, but limited information on the long-term prognosis of KD exists. We conducted a retrospective review of 195 KD patients diagnosed at National Taiwan University Hospital (NTUH) between March 1989 and September 2006, with an emphasis on long-term follow-up results (the longest follow-up period was 17 years).

**Methods**

We retrospectively reviewed the records of patients diagnosed as KD (ICD code: 289.3) at NTUH from March 1989 to September 2006. The data were collected from standard case record forms and included age, sex, clinical symptoms, position and characteristics of lymphadenopathy, laboratory data for hemograms, blood culture and blood biochemistry. Blood biochemistry included ALT, alkaline phosphatase, creatinine, LDH, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Serological tests included test for antibodies to Epstein-Barr virus, herpes simplex virus, herpes zoster virus, cytomegalovirus and human herpes virus 6. Autoimmune screening included serology for anti-nuclear antibodies (ANAs), anti-mitochondrial antibodies, rheumatoid factor, microsomal antibodies and serum complement levels. Lymph node biopsies were fixed in buffered formalin, embedded in paraffin, and then stained with hematoxylin and eosin.

A definite diagnosis of KD is based on characteristic pathologic findings on biopsy that differentiate this disease from others such as lymphoma, SLE and infectious lymphadenopathy. Characteristic histopathologic findings include necrotic and thrombotic blood vessels, and basophilic necrotic material deposited in vessel walls. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes, but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce. Only patients with a definite diagnosis of KD were enrolled in this study. Clinical recurrence was defined as recurrence of fever and lymphadenopathy in any region after the initial presentation of KD diminished, plus pathological results compatible with KD with no other disease present. Long-term follow-up was defined as more than 6 months.

**Statistical analysis**

Continuous variables were compared using Student’s *t* test or the Wilcoxon test and categorical variables with χ² test or Fisher’s exact test.

**Results**

In total, 54 male patients and 141 female patients were diagnosed with KD at NTUH during the study period. Their ages ranged from 6 to 55 years (mean = 24.6 ± 9.1 years). The most common initial presentations were tender lymphadenitis (53.3%), fever (37.9%), headache (16.9%), weight loss (10.3%), dry cough (9.2%) and generalized malaise (8.2%) (Table 1). The time between the detection of palpable lymphadenopathy and the first visit to the clinic was less than 1 week in 54 patients (27.7%), and longer than 1 month in 45 patients (23.1%).

Lymphadenitis was noted in the jugular area (77.4%), supraclavicular area (10.5%), submental area (9.4%), axillary area (2.6%) or other areas (2.6% in the occipital, preauricular, postauricular or inguinal areas). Unilateral cervical lymph node enlargement was detected in 74.9% of patients, including right neck lymphadenopathy in 43.2%, left neck lymphadenopathy in 56.8%, and bilateral cervical lymphadenopathy in 23.1% of patients. The enlarged lymph nodes were mostly located in the posterior triangle of neck (73.8%). The average size of the involved lymph nodes was > 2 cm in diameter in 59.8% of patients and shared the characteristics of firmness (57.4%), tenderness (53.3%), elasticity (47.7%) and mobility (25.6%) (Table 2).

Table 3 shows the initial laboratory results for the 195 KD patients on admission or outpatient visit. Of these, 28/148 patients (18.9%) were found to have leukopenia, 8/148 patients (5.4%) had thrombocytopenia, 36/134 patients (26.9%) had monocytosis, and 15/134 patients (11.2%) had atypical lymphocytes in their blood tests. Twenty-one out of the 90 patients (23.3%) had elevated...
ALT, 15/66 patients (22.7%) had elevated alkaline phosphatase, 42/80 patients (52.5%) had elevated LDH, 18/47 patients (38.3%) had elevated CRP, and 15/19 patients (78.9%) had an elevated ESR.

Four patients had elevated levels of ANA at initial presentation of KD, two of whom were diagnosed with SLE 1 and 4 months later with the presentation of malar rash, general malaise, myalgia, polyarthralgia and oral ulcers. One patient, who presented with pain in both knees had elevated ANA, was diagnosed with undifferentiated connective tissue disorder 7 years later. Two other patients were positive for rheumatoid factor and one of them was also positive for anti-dsDNA antibodies, but neither of them developed any other disease. No patient tested positive for anti-mitochondrial antibodies. Analysis of serum complement levels revealed low C3 levels in nine patients and low C4 levels in seven patients, but none subsequently developed autoimmune disease. One patient, whose abnormal thyroid function test showed hyperthyroidism also tested positive for microsomal antibodies, and was subsequently diagnosed with Graves’ disease 3 months later (Table 3).

Most patients (93.9%) without prolonged fever were followed up in the outpatient department and were given acetaminophen (66.5%), non-steroidal anti-inflammatory drugs (11.2%) or oral antibiotics (33.3%). Twenty patients (10.3%) received steroids. Seven patients (3.6%) had a protracted course of KD with persistent lymphadenopathy, and received prolonged treatment (>4 weeks).

The outcomes for our KD patients were mostly favorable. The duration of follow-up ranged from 1 week to 17 years, and 96 patients were followed up for more than 6 months (median=52 months). Most patients (92.9%) recovered, with spontaneous resolution of fever and impalpable lymphadenopathy. Nevertheless, 14/96 patients (14.6%) with long-term follow-up of more than 6 months
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had clinical recurrence of KD at least once (10 patients had 1 episode, 4 patients had 2 episodes), and the median duration of recurrence was 2 years (range, 7 months to 8 years). In addition, one patient, who was diagnosed as SLE, died of intracranial hemorrhage 4 months later.

Discussion

KD is a rare and mostly benign condition. Most patients with KD have a self-limited course of disease that resolves within 1 to 2 months.\(^8\) Previously the recurrence rate of KD was reported to be less than 3%, with all relapses observed within a few weeks from the initial episode.\(^3\) Compared with those previous studies, the recurrence rate of KD was higher in our patients, with a 14.6% recurrence rate during a median follow-up period of 2 years. In agreement with another study,\(^9\) our results revealed the presence of positive ANA in patients with KD, which predict the development of autoimmune diseases such as lupus, rheumatoid arthritis and Graves’ disease. Therefore, we suggest that long-term follow-up of patients with KD, at least every 6 months, is advisable.

A previous study described fever, fatigue and joint pain as the most frequent symptoms.\(^2\) Similarly, our patients complained of nonspecific symptoms such as fever, headache, weight loss and generalized malaise. Due to these nonspecific symptoms, KD is often under-diagnosed in clinical practice. The most commonly involved site of lymphadenitis in our patients was the cervical region, which is in agreement with the study of Yu et al in southern Taiwan.\(^10\) A female predominance is also noted. Leukopenia is a characteristic finding of KD (45–50%),\(^11,12\) but the frequency was lower (28%) in our study. Furthermore, some of our patients initially presented with monocytosis (36/134 cases) and atypical lymphocytosis (15/134 cases). In such instances, infectious mononucleosis like syndrome, Epstein-Barr virus or cytomegalovirus infection should be excluded first, as these diseases may present with overlapping symptoms and signs of lymphadenopathy, tonsillitis, splenomegaly and liver enzyme derangement. Despite similar presentations, our patients all tested negative for typical viral serology. Elevated LDH, CRP and ESR were noted in many of our patients, and these abnormal laboratory findings are also mentioned in previous studies.\(^2,11\) Comparing the clinical picture of patients who had recurrence of KD with that of patients who did not have recurrence did not reveal a reliable predictor for recurrence. The small number of cases with recurrence may have prevented us from finding a suitable marker of recurrence in our study.\(^13–17\)

The clinical presentation of KD overlaps a wide spectrum of other diseases such as adult Still’s disease,\(^18,19\) polymyositis,\(^20\) interstitial lung disease,\(^21\) scleroderma,\(^12\) vasculitis,\(^23\) uveitis,\(^24\) thyroiditis\(^25\) or drug hypersensitivity.\(^26,27\) In fact, autoimmunity is believed to play a role in KD, since cytotoxic T lymphocytes are apoptotic effectors

<table>
<thead>
<tr>
<th>Laboratory analysis</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Hemogram</td>
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<tr>
<td>Leukopenia (&lt;3,000/μL)</td>
<td>28/148 (18.9)</td>
</tr>
<tr>
<td>Neutropenia (ANC &lt; 1,500/μL)</td>
<td>31/134 (23.1)</td>
</tr>
<tr>
<td>Leukocytosis (&gt;11,000/μL)</td>
<td>2/148 (1.4)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150 x 10³/μL)</td>
<td>8/148 (5.4)</td>
</tr>
<tr>
<td>Monocytosis (&gt;10%)</td>
<td>36/134 (26.9)</td>
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<tr>
<td>Atypical lymphocytes</td>
<td>15/134 (11.2)</td>
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<tr>
<td>Biochemistry</td>
<td></td>
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<tr>
<td>Abnormal aminotransferase (ALT &gt; 40 U/L)</td>
<td>21/90 (23.3)</td>
</tr>
<tr>
<td>Elevated ALP (&gt;220 U/L)</td>
<td>15/66 (22.7)</td>
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<tr>
<td>Abnormal renal function (Cre&gt;1.3 mg/dL)</td>
<td>0/93 (0)</td>
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<tr>
<td>Elevated LDH (&gt;460 U/L)</td>
<td>42/80 (52.5)</td>
</tr>
<tr>
<td>Elevated CRP (&gt;0.08 mg/dL)</td>
<td>18/47 (38.3)</td>
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<tr>
<td>Elevated ESR (&gt;20 mm/hr)</td>
<td>15/19 (78.9)</td>
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<tr>
<td>Serology and immunology</td>
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<tr>
<td>Anti-nuclear antibody (≥1:320)</td>
<td>4/45 (8.9)</td>
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<tr>
<td>Anti-mitochondrial antibody (&gt;1:20)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Rheumatoid arthritis factor (&gt;20 IU/mL)</td>
<td>2/11 (18.2)</td>
</tr>
<tr>
<td>Microsomal antibody (&gt;1:80)</td>
<td>1/2 (50.0)</td>
</tr>
<tr>
<td>Elevated free T4 (&gt;1.75 ng/dL)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>Decreased TSH (&lt;0.1 μU/mL)</td>
<td>1/9 (11.1)</td>
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<tr>
<td>Decreased C3 (&lt;81.61 mg/dL)</td>
<td>9/33 (27.3)</td>
</tr>
<tr>
<td>Decreased C4 (&lt;16.73 mg/dL)</td>
<td>7/33 (21.2)</td>
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\(^{a}\)Data presented as number of positive cases/total number of cases studied (%). ANC = absolute neutrophil count; ALT = alanine aminotransferase; ALP = alkaline phosphatase; Cre = creatinine; LDH = lactate dehydrogenase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TSH = thyroid-stimulating hormone; C3/C4 = complement C3/C4.
(as well as target cells), and histiocytes can enhance apoptosis in the pathogenesis of KD. Clinically, KD and SLE share similar presentations (fever and lymphadenopathy) and similar histopathology (necrotic and thrombotic blood vessels, and basophilic necrotic material deposited in vessel walls). Indeed, Hu et al suggested that if Kikuchi’s lymphadenitis coexists with SLE, it should be regarded as lupus lymphadenitis. However, after careful evaluation, these diseases satisfied the diagnostic criteria for separate autoimmune conditions. Therefore, we suggest a comprehensive survey of all patients with suspected KD, including autoantibody testing and careful follow-up of the subgroup of patients with positive autoantibodies at initial presentation.

Although we report a relatively large number of patients in our retrospective study, there are several limitations. First, laboratory data for some patients was missing and bias in the analysis of these results is to be expected. Second, due to the limited number of patients with a recurrence of KD, our study was not sufficiently powered to be able to detect differences in the clinical characteristics that may predict recurrence or evolution into another autoimmune disease. However, our study highlights the importance of long-term follow-up for all patients presenting with KD.

In summary, KD is usually a benign disease with symptoms of fever and lymphadenopathy, but may occasionally be associated with SLE or other autoimmune diseases. Long-term follow-up of patients with KD is necessary even after all symptoms and signs have subsided.

References


