

# Histiocytic Necrotizing Lymphadenitis and Tuberculosis Infection in the Same Cervical Lymph Node

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**H**istiocytic necrotizing lymphadenitis, also known as Kikuchi disease, Kikuchi Fujimoto disease, and subacute necrotizing lymphadenitis, is a rare disease of unknown etiology.<sup>1</sup> It is a usually benign and self-limited disease that occurs primarily in young Asian women. It is characterized by adenopathy of the cervical lymph nodes, pyrexia, neutropenia, and mild upper respiratory tract symptoms.

Histiocytic necrotizing lymphadenitis has been established as a distinctive clinicopathologic entity<sup>2</sup> that may reflect a hyperimmune reaction of T cells and histiocytes to 1 or more unknown infectious agents or physical stimuli.<sup>1-3</sup> The disorder is widely acknowledged in Japan but is generally unknown in the United States.<sup>4</sup> This article presents a rare case of the concomitant occurrence of histiocytic necrotizing lymphadenitis and *Mycobacterium tuberculosis* infection in the same cervical lymph node.

## CASE PRESENTATION

### Patient Presentation

A 21-year-old Bangladeshi woman who was in the United States (New York) for 4 months was admitted with complaints of fever, chills, rigors, and night sweats of 3 weeks' duration. She also reported retrosternal chest pain that worsened on deep inspiration. She did not report cough, hemoptysis, malaise, weight loss, or anorexia. She had no significant past medical history and denied a history of smoking. She was unemployed and lived at home with 4 relatives who were in good health. She denied past exposure to tuberculosis and had never had a tuberculin skin test performed.

### Physical Examination

Pertinent physical examination findings included a well-nourished woman with right cervical lymphadenopathy. The enlarged lymph node measured 1 cm × 0.5 cm and was mobile, firm, nontender, and nonerythematous with no discharge. No other lymphadenop-

athy was palpable. No hepatosplenomegaly was noted. Her temperature ranged from 101°F (38.3°C) to 104°F (40°C).

### Diagnostic Evaluation

The erythrocyte sedimentation rate was elevated (95 mm/hr). IgG titers for cytomegalovirus (CMV), parvovirus B19, and Epstein-Barr virus capsid antibodies were positive (3.86, > 9, and 4.4, respectively). IgM titers for CMV, parvovirus B19, and Epstein-Barr virus antibodies were negative. A tuberculin skin test at 5 tuberculin units was positive (25 mm induration). Expecterated sputum for acid-fast bacilli (AFB) smear, amplification, and final culture results were negative for *M. tuberculosis* on more than 3 occasions. Titers for antinuclear antibody were negative. CD4+ absolute cell count was 627/mm<sup>3</sup> (normal, 648–1386/mm<sup>3</sup>), with a CD4+/CD8+ ratio of 1.07 (normal, 1.18–2.77). Results of HIV testing were negative. Liver function test results were within normal limits. A computed tomography scan of the chest revealed mediastinal and right hilar adenopathy with multiple bilateral lung nodules, the largest measuring approximately 7 mm in the superior segment of the right lower lobe.

### Management and Clinical Course

Based on these findings, empiric weight-adjusted antituberculous medication was initiated, consisting of

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isoniazid 300 mg orally once daily, rifampin 600 mg orally once daily, ethambutol 1000 mg orally once daily, and pyrazinamide 1500 mg orally once daily. After initiation of antituberculous medications, the patient remained febrile (101°F [38.3°C]–104°F [40°C]) despite 10 days of treatment with acetaminophen 650 mg orally 4 times daily.

An excisional biopsy of the right cervical lymph node demonstrated an atypical lymph node with eosinophilic foci containing histiocytes, large lymphoid cells, and karyorrhectic and eosinophilic granular debris. Epithelioid histiocytes and plasma cells also were noted. Mitotic figures were frequent. No organisms were seen on Ziehl-Neelsen staining for AFB or on staining for fungi. Immunohistochemical analysis showed large atypical cells that consisted of CD68+/CD4+ macrophages, epithelioid histiocytes, and plasmacytoid monocytes.

The majority of the background lymphocytes were CD8+ T cells negative for cytokeratin (CK) AE1/AE3. These immunohistochemistry findings were thought to be consistent with histiocytic necrotizing lymphadenitis. The patient was discharged home on the previously mentioned antituberculous medications. Tissue culture of the lymph node ultimately demonstrated growth of *M. tuberculosis*. She was followed on a monthly basis in the tuberculosis clinic and demonstrated complete resolution of fevers and other symptoms within 6 months.

## **DISCUSSION**

The Lymphoma Task Force, inaugurated under the auspices of the National Cancer Institute in 1964, identified sporadic cases that were erroneously interpreted as lymphoma but actually represented an unusual form of necrotizing lymphadenitis. An increased incidence of this type of necrotizing lymphadenitis was first recognized in Japan in 1967.<sup>5,6</sup> In 1972, this distinctive lymph node lesion was described simultaneously by Kikuchi<sup>7</sup> and Fujimoto.<sup>8</sup> The first report of histiocytic necrotizing lymphadenitis outside of Japan was by Pileri and colleagues in 1982.<sup>9</sup>

## **Etiology**

The etiology and pathogenesis of histiocytic necrotizing lymphadenitis remains unknown.<sup>1,4,10</sup> Histologic, serologic, and culture studies have not demonstrated an infectious etiology.<sup>4,11,12</sup> Specifically, no evidence has been found for Epstein-Barr virus,<sup>10,13,14</sup> human herpesvirus type 6,<sup>10</sup> or human T-lymphotropic virus 1<sup>13</sup> as etiologic agents. No other viral structure has been identified ultrastructurally.<sup>15,16</sup> Other etiologic possibilities under consideration include an autoimmune process

similar to Still's disease<sup>17,18</sup> and a self-limiting form of systemic lupus erythematosus.<sup>10</sup>

## **Epidemiology**

Although initially observed only in Asian populations, the disease has now been reported in various racial and ethnic groups<sup>4,9</sup> and in other parts of the world including Europe,<sup>9</sup> the United States,<sup>2</sup> and India.<sup>3</sup> Although there is a wide age range, the majority of patients usually are younger than 30 years,<sup>2,4,19</sup> with a 4:1 female:male ratio.<sup>1-3</sup> The incidence of histiocytic necrotizing lymphadenitis is presumed to be low, although in recent years it has been realized that numerous cases previously diagnosed as malignant lymphoma may actually be consistent with histiocytic necrotizing lymphadenitis.

## **Clinical Presentation**

The most common manifestation of histiocytic necrotizing lymphadenitis is tender adenopathy with a predilection for the posterior cervical lymph nodes.<sup>2</sup> Fever is a primary symptom and is seen in 30% to 50% of cases.<sup>4</sup> Other frequent symptoms include an upper respiratory prodrome and, less frequently, weight loss, nausea, vomiting, night sweats, and hepatosplenomegaly.<sup>2,15</sup> A massive release of cytokines, particularly interferon- $\gamma$  and tumor necrosis factor, account for these systemic symptoms.<sup>20</sup> The duration of symptoms ranges from 1 to 24 months, with a mean of approximately 3 months.<sup>2</sup>

## **Diagnosis**

The results of laboratory tests are seldom abnormal, but some patients demonstrate leukopenia,<sup>2</sup> lymphocytosis with atypical lymphocytes,<sup>2,21</sup> or an elevated erythrocyte sedimentation rate.<sup>21</sup> Abnormal results of liver function tests also have been reported.<sup>12,22</sup> Tests of autoimmunity are usually negative,<sup>2,21</sup> although 2 of the cases reported by Dorfman and Berry<sup>2</sup> subsequently developed systemic lupus erythematosus.

There are no diagnostic laboratory tests aside from lymph node biopsy to confirm the diagnosis of histiocytic necrotizing lymphadenitis. Fine needle aspiration cytology was not diagnostic in cases reported by Bhat et al.<sup>23</sup>

Although the microscopic appearance of the nodes affected by histiocytic necrotizing lymphadenitis can be variable, the principal histopathologic features can be described as follows:

- Patchy, circumscribed areas of eosinophilic material consistent with a necrotic process
- Significant karyorrhexis with fragments of

nuclear debris (“nuclear dust”) distributed in an irregular fashion throughout the area of necrosis

- Absence of granulocytes and paucity of plasma cells
- Presence of transformed lymphocytes (immunoblasts) predominantly of T-cell origin
- Presence of plasmacytoid T-cells or plasmacytoid monocytes

The condition has been misdiagnosed as one of several other causes of cervical lymphadenopathy, such as malignant lymphoma,<sup>2,11</sup> sarcoidosis, systemic lupus erythematosus,<sup>2</sup> tuberculosis,<sup>24,25</sup> yersinia infection, and toxoplasmosis<sup>26</sup>; however all of these entities can be effectively excluded by specific clinical, serologic, or histologic findings.<sup>2</sup>

In the case of histiocytic necrotizing lymphadenitis described by Yoo et al,<sup>25</sup> sputum studies revealed AFB, as did Ziehl-Neelsen stains of the cervical lymph node biopsy. However, the histology of the lesion was consistent with histiocytic necrotizing lymphadenitis, indicating the coexistence of AFB infection with histiocytic necrotizing lymphadenitis. In our case, the histologic findings were consistent with histiocytic necrotizing lymphadenitis, but the sputum results and Ziehl-Neelsen staining of the lymph node both were negative for AFB. However, culture of the lymph node yielded *M. tuberculosis*, showing the concomitant presence of this histology and *M. tuberculosis* infection. It is unclear whether mycobacterial infection actually causes histiocytic necrotizing lymphadenitis or whether this disorder is instead the result of immunologic stimulation from a variety of different infections and environmental stimuli as is suggested in the literature.<sup>4</sup>

Histiocytic necrotizing lymphadenitis can be distinguished from usual tuberculous lymphadenitis based on the presence of consistent crescentic histiocytes, nonphagocytic and twisted nuclei, plasmacytoid monocytes, and immunoblasts with karyorrhectic rather than caseous necrosis.<sup>4,25</sup> Nonetheless, an uncommon form of “non-reactive” tuberculous lymphadenopathy in patients with immunodeficiency disorders, malnutrition, and other debilitating diseases can mimic histiocytic necrotizing lymphadenitis.

#### **Clinical Course**

Symptoms of histiocytic necrotizing lymphadenitis usually resolve spontaneously in 1 to 4 months<sup>1,2,27,28</sup> but may persist for up to 24 months. The disease occasionally may recur after a long period.<sup>29</sup> Although no specific treatment has been identified, steroids have been

used in some cases to hasten recovery.<sup>30</sup> As the prognosis is usually good, some authors have advocated that the disease should be allowed to run its course without therapy.<sup>1</sup> Only 1 fatality has been reported and this was associated with cardiac complications (abrupt onset of congestive heart failure) attributed to the disease.<sup>31</sup>

#### **CONCLUSION**

This case demonstrates the coexistence of mycobacterial infection and histiocytic necrotizing lymphadenitis. It is unclear whether this represents a coincidental co-occurrence of these entities or whether the infectious agent led to the unusual immune response culminating in histiocytic necrotizing lymphadenitis. Additional evidence linking these two entities is necessary to further define their relationship. **HP**

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