

A Case of Brucellosis Associated With Histiocytic Necrotizing Lymphadenitis: A Diagnostic Pitfall

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Abstract

Human cases of brucellosis are rare in the United States and difficult to diagnose. We report a case of a young female who underwent a diagnostic investigation of fever of unknown origin, which included a lymph node biopsy. The biopsy was consistent with Kikuchi's Disease, or histiocytic necrotizing lymphadenitis, an entity where the major differential diagnosis is systemic lupus erythematosus. Interestingly, serologic studies supported the diagnosis of brucellosis. Brucellosis has rarely been associated with histiocytic necrotizing lymphadenitis. This association has never been reported in the United States, thus suggesting that brucellosis should be considered in the differential for histiocytic necrotizing lymphadenitis, along with lupus-like autoimmune disease. As the prognosis and treatment of histiocytic necrotizing lymphadenitis, brucellosis, and systemic lupus erythematosus are distinct, it is important to differentiate these entities.

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INTRODUCTION

Human brucellosis, though rare in the U.S. with only 100 cases per year reported [1], is the most common zoonosis in the world [2]. Humans can acquire the disease by: ingestion of raw dairy products or infected meat; by contact with secretions or blood of chronically-infected animals; or by inhalation of contaminated aerosols. The incubation period is usually two to four weeks, followed by an onset that can be acute or insidious [3]. The most common clinical manifestations of acute brucellosis are non-specific, and include intermittent fevers, arthralgias, and fatigue. However, the spectrum of disease includes asymptomatic to exhibiting diverse signs and symptoms related to almost any organ system [4]. Endocarditis is a relatively rare complication (<2%), but accounts for the most deaths [3]. The most common

focal complication is osteoarticular involvement, such as reactive arthritis, sacroiliitis, or spondylitis [2].

When there is a high index of suspicion, diagnosis is best made by culture of the organism from blood, or bone marrow, though poorly sensitive. A rise in antibody titers is suggestive of disease, but falsely positive results are possible. A positive serum agglutination test may be more specific [4]. A lymph node biopsy is not a routine part of the diagnostic work-up, and the histologic findings are not well described in the literature.

We report a case of fever of unknown origin in which serologic studies supported a diagnosis of brucellosis and lymph node biopsy showed histology consistent with histiocytic necrotizing lymphadenitis, which has rarely been associated with brucellosis.

CASE PRESENTATION

An active, otherwise healthy, 22-year-old female was admitted for further work-up of fever of unknown origin. She has a past medical history of acne, treated with doxycycline 50mg daily. She lives in central Pennsylvania, with no history of international travel. She was working in a laboratory that studies New Zealand mud snails. Otherwise, she had no farm animal contact and did not ingest any unpasteurized milk or cheese. There was no family history of autoimmunity or immunodeficiency.

Approximately two months prior to her presentation, she developed fevers, fatigue, malaise, myalgias, right upper quadrant pain and weight loss. Given her fevers and findings of a new pancytopenia, she was admitted to a local hospital. The work-up was largely unremarkable, including: serology for hepatitis A/B/C, Epstein-Barr Virus (EBV), Cytomegalovirus, and Lyme disease; Tuberculin skin test; antistreptolysin O titer; and a transthoracic echocardiogram. Contrast-enhanced CT of the abdomen and pelvis revealed mesenteric lymphadenopathy. She was transferred to our institution five days later for further management.

On examination, she was febrile to 39.3 °C, but other vital signs were within normal limits. She had tender cervical lymphadenopathy. Her heart rate was irregular with skipped beats, and without murmur. Upon examination of her abdomen, there was right upper quadrant tenderness and hepatomegaly, without rebound or guarding. Her musculoskeletal exam revealed bilateral first and second metacarpophalangeal joints that were mildly full and tender to palpation, with a patch of overlying erythema, as well as tender ankles. The remainder of the physical examination was normal.

On admission, the patient had pancytopenia and elevated liver function tests, as well as a borderline positive anti-histone antibody (Table 1). Her blood chemistry panel was normal. Blood cultures drawn while already on antibiotics were negative. She had first degree atrioventricular block on admission EKG that progressed to second degree heart block on hospital day 5. Results of transthoracic echocardiography and cardiac MRI showed no evidence of myocarditis or endocarditis.

She underwent cervical lymph node biopsy on hospital day 6 (Figure 1 A-H). Grossly, the left cervical lymph node biopsy showed areas of tan tissue juxtaposed with areas of yellow and apparently hemorrhagic areas. The histologic sections demonstrated a reactive-appearing lymph node with areas of extensive necrosis without suppuration, but with abundant karyorrhexis and debris (Figure 1A). The viable areas showed follicles and otherwise a heterogeneous mixture of small lymphocytes, occasional transformed lymphocytes,

plasma cells and histiocytes. The necrotic areas showed mostly necrotic cellular debris with admixed lymphocytes and histiocytes, including occasional histiocytes with crescentic nuclei (Figure 1B). Particularly the edge of the necrotic areas showed a focally prominent population that appeared to represent plasmacytoid dendritic cells (Figure 1C). Paraffin section immunohistochemical stains demonstrated B-cells predominantly in follicles, as well as numerous T-cells mostly outside of the follicles. There were prominent aggregates of CD123 positive plasmacytoid dendritic cells, particularly at the periphery of the necrotic regions (Figure 1D). There were numerous CD4 positive cells, outside of the necrotic areas, but fewer CD4 positive lymphocytes within the necrotic areas (Figure 1E). In contrast, CD8 positivity was more prominent within the necrotic areas, highlighting some viable cells as well as debris (Figure 1F). The numerous CD68 positive histiocytes, concentrated in and around the necrotic areas, were also myeloperoxidase positive, but there were only rare myeloperoxidase positive neutrophils (Figures 1G-H). Immunohistochemical stains for cytomegalovirus (CMV), *Bartonella henselae* and herpes simplex virus 1 and 2 were negative. AFB and Grocott stains were negative for acid fast bacilli and fungal organisms, respectively. There were no hematoxylin bodies or evidence of the Azzopardi phenomenon identified.

Table 1: Select laboratory values of the patient obtained at admission.

	Patient value	Reference range
WBC	1,000/L	3,800 – 10,600
Neutrophils	54%	44 - 77%
Bands	7%	0 - 5%
Lymphocytes	31%	13 - 44%
Monocytes	7%	4 - 13%
Atypical lymphocytes	1%	0%
Hemoglobin	7.9 gm/dL	11.6 - 14.6
Platelets	121,000/L	156,000 – 369,000
Creatinine	0.7 mg/dL	0.5 - 1.4
ALT	82 IU/L	14 - 54
AST	126 IU/L	15 - 41
Bilirubin	0.6 mg/dL	0.3 - 1.5
Alkaline Phosphatase	61 IU/L	38 - 126
HIV Antibody	negative	negative
Anti-histone antibody	1.2 U	<1.0

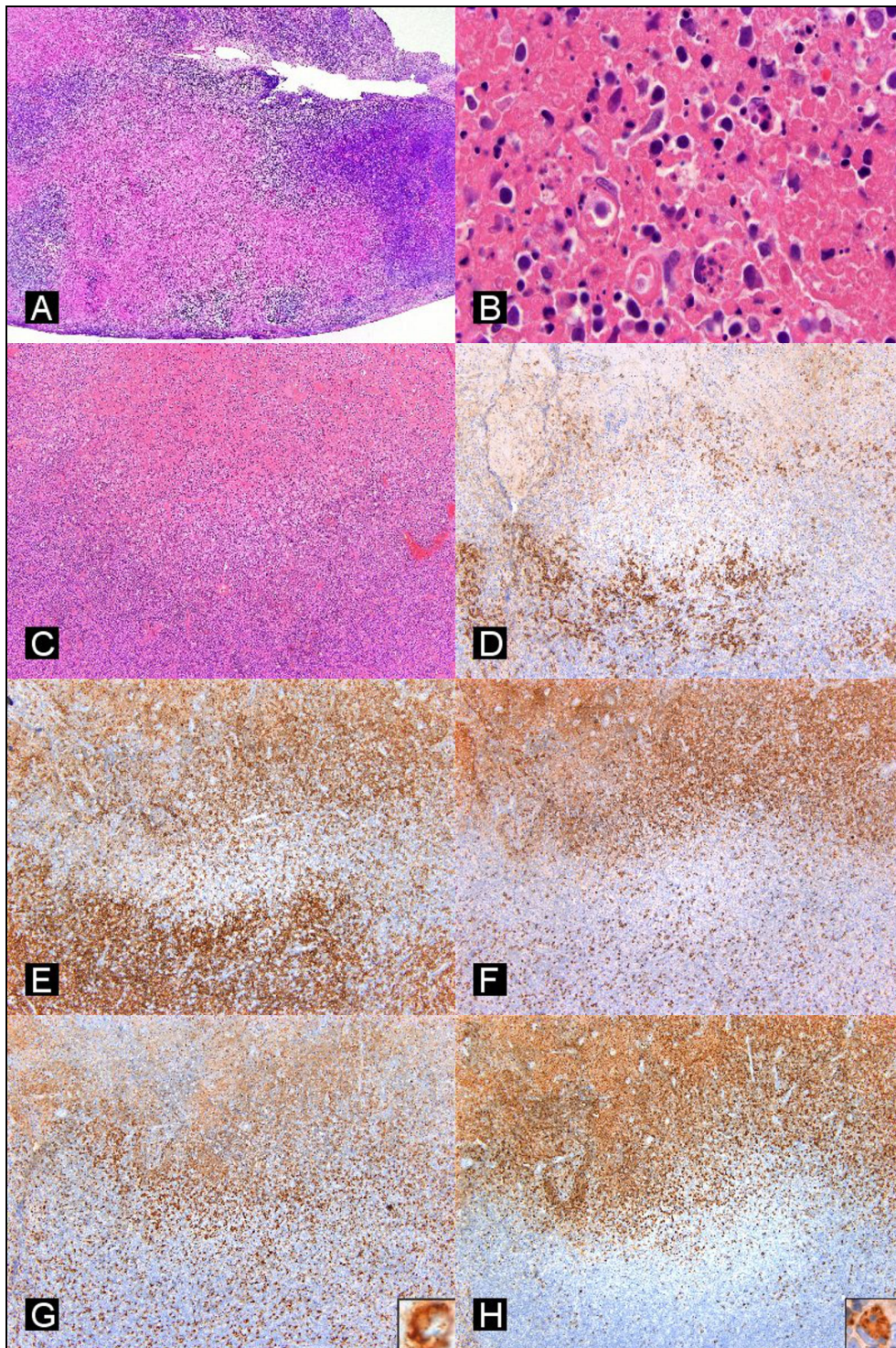


Figure 1: Cervical lymph node biopsy. **A:** A low magnification image demonstrates a reactive lymph node with areas of extensive eosinophilic necrosis. **B:** The necrotic areas showed some lymphoid cells and histiocytes, including some with crescentic nuclei but note the absence of neutrophils. **C:** The following immunohistologic stains (D-H) demonstrates this region of the histologic section with the necrotic area at the top of the image. **D:** CD123 highlights moderately numerous plasmacytoid dendritic cells at the periphery of the necrotic area. **E:** There were many CD4 positive T-lymphocytes in the more viable lymph node with fewer in the necrotic area. Many histiocytes are also more weakly CD4 positive. **F:** In contrast, there were few CD8 positive cells in the more viable area with more numerous positive cells and debris in the necrotic area. **G:** The necrotic area also demonstrated moderately numerous CD68 positive histiocytes. Inset: Crescentic macrophage is positive for CD 68. **H:** The histiocytes were also positive for myeloperoxidase (MPO). Inset: Crescentic macrophage is positive for MPO (A: H&E, 20x; B:H&E, 1000x; C:H&E 100x; D-H: immunostain with hematoxylin counterstain, 100x; insets: 1000x).

On hospital day 8, her Brucella IgM was reported as weakly positive with a value of 1.01 and IgG was 0.53 [reference range: <0.80 not detected, 0.80-1.09 equivocal, 1.10 or greater antibody detected (Figure 2)]. She was started on treatment for acute brucellosis with doxycycline 100mg twice daily, rifampin 300mg twice daily, and IV gentamicin 5mg/kg daily. Two

weeks later, her Brucella titers had increased to IgM 1.88 and IgG 1.04. Her pancytopenia and AV block completely resolved, as did her fevers, joint pains, and abdominal pain. She was continued on doxycycline and rifampin for an additional four months given her multiple organ involvement. Three months later, her Brucella titers were: IgM 0.64 and IgG 1.43.

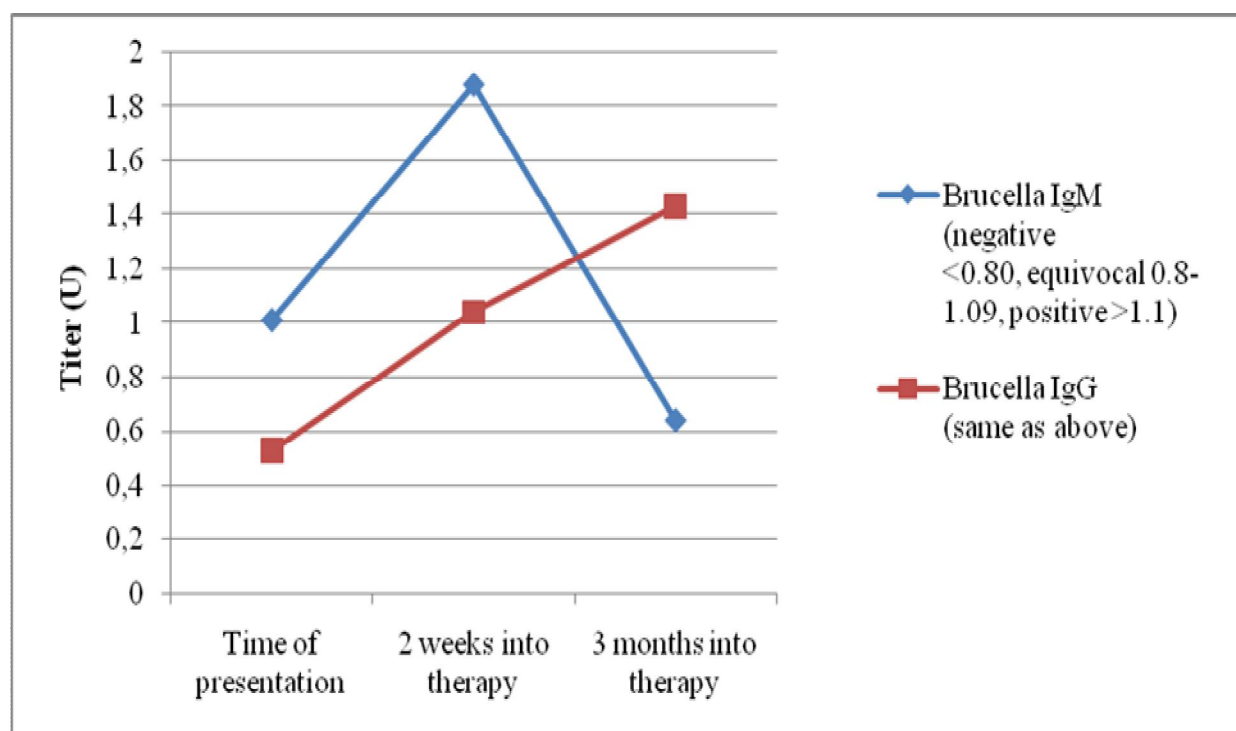


Figure 2: Depiction of early *Brucella* IgM and late IgG increase after antibiotic treatment.

DISCUSSION

This case illustrates a diagnostic dilemma regarding the possible clinical and histopathologic overlap between brucellosis and histiocytic necrotizing lymphadenitis (HNL). Brucellosis is frequently misdiagnosed, given its lack of specific symptoms, variety of presentations, and rarity in many parts of the world. Diagnosis is also difficult because of poor sensitivity of culture and lack of a definitive diagnostic test. In this case, her prior receipt of doxycycline may have inhibited the growth of *Brucella*. Although we were unable to make a definitive diagnosis, many of the patient's clinical features were compatible with this disease. An evaluation of her clinical findings revealed pancytopenia, hepatomegaly, lymphadenopathy, arthritis, and progressive cardiac conduction delay which all can be manifestations of acute brucellosis. Her symptoms, pancytopenia, and heart block resolved on antibiotic treatment for brucellosis. In addition, her

antibody titers trended as expected for an acute infection with recovery. However, she also had some clinical features that are atypical for brucellosis, including pleuritic chest pain, symmetric small joint polyarthritis, and weakly positive anti-histone antibody, suggestive of possible early connective tissue disease. Yet serologic autoimmune laboratory abnormalities have been reported in active brucellosis [5, 6], including weakly positive ANA (25%) and rheumatoid factor (38%) [7]. *Brucella* has also been known to cause reactive arthritis [2, 7, 8].

Lymph node biopsy is not routine, thus the full spectrum of morphologic changes seen in the lymph nodes of patients with brucellosis are not well-documented. It is thought that *Brucella* infection typically takes one of two forms. The first has sometimes been described as showing a "simple form," with follicular hyperplasia, sinus histiocytosis, or expanded areas of monocytoid B-cells, with increased

numbers of plasma cells. There may also be a proliferation of large, pale cells between the follicles. The second form, seen more frequently, may manifest with numerous clusters of epithelioid histiocytes, at times becoming confluent and rarely encroaching upon germinal centers [9]. For this patient, the lymph node findings demonstrate a necrotizing lymphadenitis that has many features of HNL or possibly lupus, including extensive areas of necrosis without suppuration. However, the patient's marked peripheral blood neutropenia may contribute to the lack of neutrophils in this setting.

Only two cases of brucellosis associated with the histopathologic findings of HNL have been described in the literature [10, 11]. In one case report, the authors describe that the patient, a 43-year-old male cattle, had a history of brucellosis diagnosed three months prior to his admission for fever, arthralgias, night sweats, painful enlargement of cervical and axillary lymph nodes, and hepatosplenomegaly. In order to evaluate the patient's persistent fever in light of decreasing titers and negative cultures, a lymph node biopsy was performed, showing findings characteristic of HNL, including paracortical areas with "karyorrhectic debris seen in both blastic and necrotizing areas, in a patchy pattern and contrasting with an absence of neutrophils, and histiocytes with crescentic nuclei were present" [10]. Immunohistochemical studies were not performed, but the morphological features are similar to the current case.

The differential diagnosis for this patient includes HNL, or Kikuchi's disease, as well as autoimmune disorders, including systemic lupus erythematosus and drug-induced lupus. HNL, initially described in 1972 by Masahiro Kikuchi, is characterized by self-limited episodes of cervical adenopathies, sometimes accompanied by fever, arthralgia, and rash [12]. The disease predominantly affects young women aged 20 to 30 years, and most reports are from East Asia. Because of the similarity in clinical manifestations and histologic findings in HNL and lupus, some authors have hypothesized that HNL could have an autoimmune origin or be a benign or self-limited form of lupus, given an overall incidence of lupus-like disease in HNL of 13-23% [12, 13]. Infections with bacteria or viruses in the right genetic constellation have been proposed as a trigger for autoimmune diseases like lupus and rheumatoid arthritis [14-16]. Therefore, *Brucella* infection itself, in the right setting, may trigger an HNL-like disease.

The current case, together with the previously described case of HNL-like brucellosis, suggests that these clinical and histologic findings may present a dilemma in the diagnosis of brucellosis. It is important to differentiate HNL, lupus, and brucellosis, since the

prognosis and treatments are distinct. However, brucellosis can be a difficult diagnosis to confirm, and this patient may have two concurrent diagnoses or may still develop lupus or connective tissue disease. Future studies with longer follow-up of brucellosis cases may help clarify whether HNL or other infections mimicking HNL leads to development of systemic lupus erythematosus, despite appropriate antimicrobial treatment.

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CONFLICTS OF INTEREST

Authors declare that they have no conflicts and disclosures.

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