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# Kikuchi Disease: The Great Masquerador - A Case Report and Review of the Literature

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## Abstract

We report the case of a 19-year-old Chinese woman who presented with fevers and cervical lymphadenopathy, mimicking infectious mononucleosis. Histology of the affected lymph nodes revealed necrotizing lymphadenitis, consistent with Kikuchi-Fujimoto disease. Remaining infectious work-up was negative. Kikuchi-Fujimoto should always be included in the differential diagnosis in cases of cervical lymphadenopathy, particularly in young Asian women, as it may mimic other clinical entities and further work-up for other underlying autoimmune processes should be pursued.

**Keywords:** Kikuchi disease; Cervical lymphadenopathy; Fever

## Introduction

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is a rare and self-limited syndrome characterized by tender cervical lymphadenopathy, usually in a young, previously healthy woman [1], although some recent reports indicate that the incidence among men and women is closer to equal than previously presumed [2,3]. The disease can mimic many other pathologic conditions, including EBV mononucleosis, lymphoma, metastases and tuberculous lymphadenitis, which represent one of the most frequent presentations of extrapulmonary tuberculosis [3]. The pathogenesis of Kikuchi is unknown. It has been hypothesized based on clinical presentation and immunological marker studies, however, that Kikuchi-Fujimoto disease is an immune response to an inciting viral exposure [4]. Diagnosis of Kikuchi disease relies on histology and microscopic examination of the lymph node, which is usually characterized by paracortical necrosis and infiltration of histiocytes [5]. Interestingly, there is also a strong association between Kikuchi-Fujimoto disease and autoimmune disorders, such as Hashimoto's Thyroiditis and systemic lupus erythematosus (SLE) [6]. Awareness of the disease is limited amongst clinicians, which often impedes the path to a timely diagnosis. Here, we present the case of a 19-

year-old female with Kikuchi disease, who originally presented with tender cervical lymphadenopathy and fevers mimicking infectious mononucleosis.

## Case Presentation

A 19-year-old Chinese female with no past medical history was initially referred to the Emergency Department (ED) by her primary care physician for fever and painful cervical lymphadenopathy of one-week duration, associated with mild sore throat and episodic night sweats. The patient was treated with oral azithromycin as outpatient for five days without improvement of symptoms. After reevaluation by her primary care physician, she received two doses of intravenous (IV) ceftriaxone, and was subsequently referred to the ED for further evaluation having failed outpatient antibiotic therapy for suspected bacterial pharyngitis.

Review of symptoms was otherwise negative. The patient denied weight loss, headache, cough, rhinorrhea, abdominal pain, nausea, vomiting, diarrhea, joint pain and skin rash. She denied recent illness, sick contacts, recent travel and exposure to animals or unusual bites. She further denied any sexual activity and drug or tobacco use. The patient had emigrated from China one year prior to symptom onset and endorsed that she had received all routine vaccines prior to arrival in the United States. She was unable to provide her PPD status or a history of BCG vaccine. Lastly, the patient endorsed that she had received the flu vaccine one month ago.

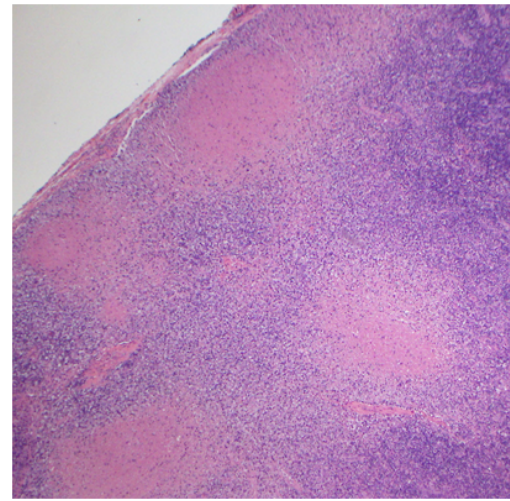
On admission, the patient was febrile to 101.3°F (38.5°C). Physical exam was notable only for left sided cervical and posterior cervical tender lymphadenopathy. Laboratory findings were unremarkable except for mild leukopenia (White Blood Cell count  $3.5 \times 10^9/L$  with 61% neutrophils, 32% lymphocytes, 4% monocytes and 0% eosinophils and basophils.) ESR was only mildly elevated at 33 mm/hr. Computerized Tomography of the neck with IV contrast revealed multiple symmetrically prominent lymph nodes with adjacent fat stranding, some of which appear to be necrotic (**Figure 1**). Urine and blood cultures were sent, and the patient was started on IV Ampicillin/Sulbactam pending Infectious Disease consult, as the clinical presentation was considered to be most consistent with infectious mononucleosis. The patient had a negative infectious disease workup that included

monospot test, EBV (early antigen IgG, nuclear Ag Ab IgG, VCA IgG and VCA IgM), CMV (antibody IgM and IgG) toxoplasmosis (toxoplasma antibody IgG and IgM) histoplasmosis (histoplasma galactomannan antigen, urine), tuberculosis (interferon-gama release assays) and HIV (PCR and viral load). Of note, EBV IgG antibodies were positive suggesting prior exposure, while the patient's urine and blood cultures were negative. The patient's TSH was within normal limits and the decision to pursue further autoimmune workup was deferred for the outpatient setting.

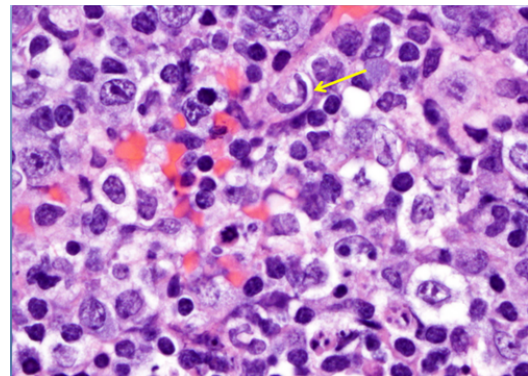


**Figure 1** CT neck with IV contrast demonstrating prominent necrotic cervical lymphadenopathy.

The patient continued to be febrile throughout her hospital course and her borderline leukopenia present on admission worsened. Four days after her admission, the patient underwent deep incisional cervical lymph node biopsy to rule out lymphoma, with Kikuchi disease high on the differential. Flow cytometry of the specimen found no evidence of non-Hodgkin lymphoma. Surgical pathology revealed necrotic lymphoid tissue with numerous apoptotic cells and interspersed B and T cells with necrotic areas surrounded by crescentic histiocytes overall consistent with a diagnosis of histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) (**Figure 2 and 3**). IV Ampicillin/Sulbactam was discontinued on the second day of admission and patient was managed supportively and discharged on day 5 of her hospitalization with instructions for close follow up and autoimmune workup as outpatient [7,8].



**Figure 2** A low power view of lymph node pathology showing typical circumscribed paracortical necrosis extending to the capsule.



**Figure 3** A high-power view of lymph node pathology showing numerous histiocytes, including characteristic crescentic or C-shaped histiocytes (arrow) and scattered apoptotic cells. No neutrophils are present.

## Discussion

Kikuchi disease, otherwise known as histiocytic necrotizing lymphadenitis, is a rare, idiopathic cause of lymphadenopathy that may be difficult to differentiate from other causes of lymphadenopathy such as mononucleosis, tuberculosis and lymphoma. The disease is most prevalent amongst young women (age <40) of Asian descent, however, it has been identified in all ethnicities, ages and in men. The most common clinical presentation is fever and cervical lymphadenopathy in a previously healthy young female. Rash, arthritis, fatigue and hepatosplenomegaly are other, less frequent, manifestations although there are case reports in the literature of more serious presentations such as meningitis, polymyositis and acute cerebellar syndromes [9,10]. Laboratory studies in people with Kikuchi disease are fairly non-specific. The most common finding is leukopenia,

followed by atypical lymphocytes; however, the majority of patients have a normal Complete Blood Cell count. Erythrocyte Sedimentation Rate also tends to be elevated in most patients [11] and there may also be abnormalities in liver enzymes and an elevated LDH.

While the pathogenesis of the disease is still unproven, the clinical presentation and the usually self-limited course suggest an immune response to an infectious agent. Numerous inciting infectious agents have been proposed, including, but not limited to EBV, HHV 6 and 8, HIV and parvovirus B19, however, no causal relationship has yet been established. Kikuchi disease shares an age and sex predilection (young, female), as well as histological similarities, with SLE. Although, histologic features are strikingly similar between SLE and Kikuchi; extensive necrosis, presence of hematoxylin bodies, plasma cells and/or neutrophils favor a diagnosis of SLE [12]. Interestingly, there is a rare but documented association between the disease and a subsequent diagnosis of SLE [13] leading some to postulate that the disease is an unusual presentation of SLE. However, it is also possible that some of these cases are actually lupus lymphadenitis misdiagnosed as Kikuchi disease [14,15].

Histopathological examination of involved lymph nodes is necessary to make a definitive diagnosis and to exclude other, possibly more severe diseases that it may mimic, such as lymphoma and hematologic malignancies. Microscopic examination of the node, depending on disease stage, will reveal paracortical foci often with areas of necrosis with lymphohistiocytic infiltration and a notable absence of neutrophils [16]. Histologic sections can sometimes be mistaken for an infectious etiology, but negative special stains, lack of neutrophils and/or granulomata make these entities much less likely. Features reminiscent of a non-Hodgkin lymphoma can sometimes be seen, but the patchy involvement of the lymph node, abundant karyorrhectic debris, a mixed cell population of crescentic histiocytes and negative flow cytometry findings would strongly favor Kikuchi's lymphadenitis.

Kikuchi is a self-limited disease with most symptoms resolving in one to four months [17] although 85 relapses have been reported [18,19]. There is no definitive treatment; however, people with severe symptoms have reportedly been treated with glucocorticoids and/or immune globulin for amelioration of symptoms. Relapses have been successfully treated with concomitant administration of glucocorticoids and hydroxychloroquine or with hydroxychloroquine monotherapy. Of note, necrotizing lymphadenitis and SLE show similar histologic features, however, a diagnosis of SLE was not supported clinically in this case. As the patient did not meet clinical criteria for a diagnosis of SLE accordingly to either the American College of Rheumatology (ACR) criteria [20] or the Systemic Lupus International Collaborating Clinics (SLICC) criteria [21], the decision was made to defer autoimmune workup to the outpatient setting.

## Conclusion

Kikuchi disease is a rare clinical entity mostly prevalent in women of Asian origin. Its etiology is unknown and further research is required for determination of possible pathogenesis pathways. Although the disease is usually characterized by a self-limited and benign course, it is associated with the potential for development of other autoimmune disorders and, as such, patients diagnosed with the disease warrant close follow up. Kikuchi-Fujimoto disease may mimic other clinical presentations and early clinical suspicion and awareness amongst practitioners is necessary to ensure accurate and prompt diagnosis, both to exclude other potential life-threatening disorders and to avoid mistreatment.

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