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SHORT REPORT

Kikuchi-Fujimoto disease: an amazing response to hydroxychloroquine

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Abstract Kikuchi-Fujimoto disease is a benign and self-limited disorder. The common clinical features are fever and cervical lymphadenitis. A 9-year-old girl with fever and cervical lymphadenitis was admitted because of persistent symptoms. A cervical lymph node biopsy showed the characteristic features of Kikuchi-Fujimoto disease. Herein, we will discuss the clinical features, diagnosis, and treatment of Kikuchi-Fujimoto disease and highlight the dramatic response when a patient was treated with hydroxychloroquine.

Keywords Kikuchi-Fujimoto disease · Kikuchi's disease · Necrotizing lymphadenitis · Hydroxychloroquine · Fever

Case report

A 9-year-old girl with no significant past medical history was sent to our Emergency Department on a weekend because of high-grade fever. In fact, she had been having intermittent fever for 25 days and some enlarged lymph nodes along the right-sided neck also developed in the beginning. She went to a local clinic several times and was diagnosed as acute pharyngotonsillitis with reactive lymphadenopathy. From the second visit, she was treated with oral cephalexin, but the problems persisted. However, she did not have significant signs or symptoms of upper airway infection, like rhinorrhea, sore throat, cough, dyspnea, or hoarseness. Other features of common infectious diseases, such as urinary tract infection, soft tissue infection, or diarrhea diseases, did not even occur, either.

When she was seen at our Emergency Department, her body temperature was 39°C. Nevertheless, she represented a fair appearance and activity. We found multiple soft lymph nodes from the right submandibular region to the lower neck, but the left side was normal. Physical examination was otherwise unremarkable. Blood analysis revealed mild leukopenia (2.73×10^9 leukocytes per liter) with normal differential formula. A neck computed tomography detected multiple lymph nodes from the right submandibular region to the right anterior cervical triangle. The largest one was 2 cm in diameter. She was then hospitalized.

Her fever persisted for 1 week despite treatment with clindamycin. She also underwent a cervical lymph node biopsy. The finding was necrotizing lymphadenitis composed of karyorrhectic debris, fibrinoid necrosis, and reactive mononuclear cells. Neutrophils and plasma cells were absent (Fig. 1). The histologic features were consistent with Kikuchi-Fujimoto disease. Therefore, clindamycin was discontinued, and hydroxychloroquine was prescribed. Within 6 h after her first dose of hydroxychloroquine, fever resolved completely. She remained in very good condition throughout the next 21 months.

Discussion

Kikuchi-Fujimoto disease was first described in 1972 by two Japanese pathologists, Kikuchi [4] and Fujimoto [2].

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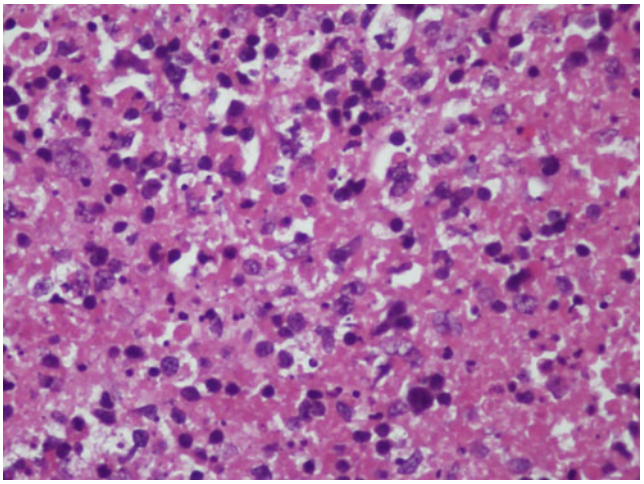

Fig. 1 High-power micrograph of a cervical lymph node biopsy specimen reveals necrotizing change. It is composed of karyorrhectic debris, fibrinoid necrosis, and reactive mononuclear cells. Neutrophils and plasma cells are absent

This disease was regarded as a benign and self-limited disorder. Initially, it was characterized by a certain type of lymphadenitis occurring predominantly in cervical lymph nodes of young Southeast Asian women. But now, it is reported that it occurs at any age, in both gender, or any ethnic group and can involve both nodal and extranodal sites [7]. Moreover, it has a worldwide geographic distribution.

Painful cervical lymphadenopathy is the most common clinical feature, although enlarged lymph nodes including axillary, abdominal, and inguinal lymph nodes may be isolated or generalized, but rare patients developed hepatosplenomegaly. Various kind of cutaneous manifestations were reported. Some patients may be febrile, but involvement of multiple organs is rare [7].

So far, there is no specific laboratory test to confirm the diagnosis of Kikuchi-Fujimoto disease. Although the neutropenia and leukocytosis have both been reported, the latter only occurred in a few patients. There were also patients with thrombocytopenia. As for autoimmune antibodies, studies to date were all negative. The correlation between Kikuchi-Fujimoto disease and microbiologic agents was also under research, but the results were not encouraging [7].

Histopathologically, the lymph node involvement is patchy. The lymphadenopathy is characterized by a collection of histiocytes, immunoblasts, plasmacytoid monocytes, and small lymphocytes surrounding the areas of fibrinoid necrosis. Abundant extracellular apoptotic debris is present. Contrarily, granulocytes are absent and plasma cells are rare or totally absent [7].

Differential diagnoses of Kikuchi-Fujimoto disease include the following entities: lymphoproliferative disease; infectious etiologies, such as herpes simplex virus, Epstein-Barr virus, cytomegalovirus, *Yersinia enterocolitica*, *Bartonella henselae* (cat-scratch disease), and *Toxoplasma gondii*; and autoimmune disease, such as systemic lupus erythematosus and Kawasaki disease [3, 5, 7, 8].

Both non-Hodgkin lymphoma and Hodgkin disease share similar clinical presentations and histologic features with Kikuchi-Fujimoto disease. However, the presence of large Reed-Sternberg cells or variants and numerous eosinophils, as well as neutrophils, may be helpful to distinguish the lymphoproliferative disease from Kikuchi-Fujimoto disease [3].

In general, viral lymphadenitis, in contrast to Kikuchi-Fujimoto disease, has less-prominent histiocytic infiltrates, more neutrophils, more plasma cell proliferations, and predominant $CD4^+$ T cells. In addition, the finding of viral inclusions confirms the diagnosis of herpes-simplex-associated lymphadenitis. Epstein-Barr-virus- and cytomegalovirus-associated lymphadenitis may present similar features, including proliferation of immunoblasts, follicular hyperplasia with characteristic mottled edges, prominent monocytoid B cells, abundant plasma cells, and varying degrees of necrosis [3]. *Y. enterocolitica* lymphadenitis is most typically mesenteric in location and is characterized by microabscesses that contain granulocytes, frequently involving germinal centers, as well as aggregates of epithelioid histiocytes. Lymphadenitis associated with cat-scratch disease displays stellate microabscesses containing numerous granulocytes, surrounded by palisading histiocytes. Toxoplasma lymphadenitis may present the specific finding of clusters of epithelioid histiocytes infiltrating germinal centers, as well as florid follicular hyperplasia and prominent monocytoid B cell proliferation within sinuses [7].

Lymphadenitis of systemic lupus erythematosus mimics Kikuchi-Fujimoto disease histologically. Features that support systemic lupus erythematosus include aggregates of degenerated nuclei that have reacted with antinuclear antibodies (hematoxylin bodies), aggregates of degenerated nuclear material in the blood vessel walls (Azzopardi phenomenon), the presence of numerous plasma cells, and sparse cytotoxic T cells [3]. In Kawasaki disease, the characteristic features of patchy necrosis associated with neutrophils and thrombosis of small vessels should clarify the diagnosis [7].

Kikuchi-Fujimoto disease is usually a self-limited disease, and its course in most patients is benign. Resolution of the symptoms is generally spontaneous and typically within 1 to 4 months. There are not many reports of recurrence in the medical literatures. However, a very small number of fatal cases have still been reported, including myocarditis [1], pulmonary hemorrhage [10], and systemic involvement [6].

To treat Kikuchi-Fujimoto disease, nonsteroidal anti-inflammatory agents were applied to control the symptoms. Glucocorticoids were also used alone or in combination with immunomodulators, including hydroxychloroquine, to treat patients with systemic lupus erythematosus and Kikuchi-Fujimoto disease [9]. Rezai et al. once only used hydroxychloroquine to treat a patient's first and second episodes of Kikuchi-Fujimoto disease, and the fever was resolved within 8–10 h after the administration of the first dose during both courses [8].

We also treated the patient with hydroxychloroquine alone, after several trials of nonsteroidal anti-inflammatory agents were in vain. We found that her fever was resolved within 6 h after the first dose. No glucocorticoids were used during the course of Kikuchi-Fujimoto disease. Her condition remained good throughout the next 21 months. To our knowledge, this is the first report in Taiwan in which hydroxychloroquine was used to treat a patient with Kikuchi-Fujimoto disease without any presence of another inflammatory process, such as systemic lupus erythematosus. Based on Rezai and our experiences, Kikuchi-Fujimoto disease responds to hydroxychloroquine quite well and very fast. Compared with glucocorticoids, the profile of hydroxychloroquine is safer, and it has less adverse effects. Therefore, we propose that hydroxychloroquine would be a good, even a prior, choice for the treatment of Kikuchi-Fujimoto disease.

Conflict of interest The authors report no conflicts of interest or any financial relationships.

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