Kikuchi-Fujimoto Disease: Hydroxychloroquine as a Treatment

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We describe a case of recurrent Kikuchi’s disease in a South Asian–American man that was treated successfully with chloroquine and on recurrence with hydroxychloroquine. Each treatment led to a very prompt response.

Case report. A 26-year-old South Asian–American man presented with a 1-month history of fever, chills, fatigue, weight loss (of 2.26 kg), and bilateral cervical adenopathy. Symptoms began with daily low-grade fever and small oral aphthous ulcers, which progressed to protracted high-grade fever, rigors, and bilateral cervical adenopathy. The patient received empiric courses of azithromycin and amoxicillin/clavulanate acid, but there was no response. He eventually developed nonbloody diarrhea, fever with a temperature as high as 40.7°C, dry cough, and night sweats. No other lymph nodes were enlarged, and he did not complain of neck pain, headaches, or a rash. An outpatient diagnostic workup, including serologic testing for syphilis and systemic lupus erythematosus (SLE), did not yield a diagnosis, and the patient was eventually hospitalized after a near-syncopal event.

The patient did not have a significant medical history, and he had no history of drug abuse. He had traveled to India 1 year prior to the development of symptoms. He did not receive treatment with prophylactic antimalarials before or during the trip. In India, the patient developed fever and chills that lasted 4 days and that resolved after treatment with a course of tetracycline. On physical examination, his temperature was 40°F. Findings of the examination were normal, except for the presence of 2 nontender, soft, mobile lymph nodes (size, 1 × 1.5 cm) in the right anterior cervical triangle and 1 nontender, soft, mobile lymph node (size, 2 × 3 cm) in the left posterior cervical triangle. Findings of the ear, nose, and throat examination were otherwise unremarkable. Fevers and chills persisted for 2 weeks despite treatment with broad-spectrum antibiotics. Treatment with antibiotics was eventually discontinued because of the possibility of drug-fever, without effect. The patient underwent a bone marrow biopsy and lymph node biopsy and, pending the results of both biopsies, received treatment with chloroquine for possible malaria infection. Blood smears for malaria organisms were negative. Within 8 h of his first dose of chloroquine, the patient’s fever completely resolved. He completed 4 days of treatment with chloroquine, which was followed by 14 days of treatment with primaquine for possible malaria. After the patient’s hospital discharge, his bone marrow biopsy specimen revealed a normocellular marrow with mildly megaloblastoid erythropoiesis and slight eosinophilia. No tumors or granulomas were seen. The peripheral blood smear appeared normal. The cervical lymph node architecture was effaced by well defined nodular infiltrates composed of a mixture of plasmacytoid monocytes, immunoblasts, small lymphocytes, histiocytes with twisted and crescentic nuclei, and abundant karyorrhectic debris, but no neutrophils. The histologic features were consistent with necrotizing lymphadenitis or Kikuchi-Fujimoto disease.

The patient was healthy until 1 year later, when he developed similar symptoms, including low-grade fever that progressed to high-grade fever (with a temperature of 40°C) and right-sided cervical adenopathy. After 1 week of worsening symptoms, he underwent a lymph node biopsy, the findings of which were, again, consistent with Kikuchi-Fujimoto disease (figures 1 and 2). Because of the patient’s prior history, a course of hydroxychloroquine (at a dosage of 200 mg twice per day orally for 14 days) was prescribed. His fever resolved again within 8–10 h after administration of the first dose. Serologic testing was negative for SLE. His condition remained good throughout the next 14 months.

Discussion. Kikuchi-Fujimoto disease was first described in 1972 by Kikuchi and Fujimoto in Japan [1]. They described a benign, self-limited syndrome of necrotizing lymphadenitis with distinctive histologic findings. The clinical symptoms are nonspecific and generally include cervical adenopathy and fever with a combination of other associated symptoms consisting of chills, sweats, malaise, nausea, vomiting, diarrhea, weight loss, fatigue, arthralgias, myalgias, hepatomegaly, and/or sple-
Figure 1. Low-power micrograph of a cervical lymph node biopsy specimen reveals that lymph node architecture is effaced by well-defined nodular infiltrates (hematoxylin-eosin stain; original magnification, ×100).

nomegaly [2]. Up to 30% of patients with Kikuchi-Fujimoto disease may also have cutaneous manifestations, such as morbilliform, drug eruption-like, rubella-like, urticarial, maculopapular, or erythematous rashes [3]. The disease was first reported in Asians; it has since been reported in persons of all races and ethnicities [1]. Most individuals with the disease are <30 years of age; however, patients of 11–80 years of age have been reported.

There are no specific diagnostic laboratory tests to confirm the diagnosis of Kikuchi-Fujimoto disease. Neutropenia, lymphocytosis, abnormal liver enzyme levels, an elevated lactate dehydrogenase level, and an elevated sedimentation rate have been reported [2]. The diagnosis is based on the presence of typical clinical symptoms and a lymph node biopsy specimen showing distinctive histologic features, which include patchy circumscribed necrosis with prominent karyorrhexis, bordered by histiocytes and transformed lymphoid cells [1].

The etiology of the disease is unknown. Viruses such as Epstein-Barr virus, parainfluenza virus, and human herpes virus type 6 have been implicated as causes, but culture and special staining have not confirmed these associations. Others have postulated that the disease may represent a hyperimmune response to various microbial, chemical, physical, or neoplastic agents [2].

The differential diagnosis of this disease includes tuberculosis, SLE, sarcoidosis, and lymphoma. The histopathologic findings, at times, can be mistaken for those characteristic of SLE. There have been case reports of Kikuchi-Fujimoto disease preceding the onset of, occurring simultaneously with, or occurring during the evolution of SLE [4].

The disease is usually benign and self-limited. No specific treatment has been reported to be effective. Resolution of the symptoms typically occurs within 1–4 months. Three to 4 percent of Kikuchi-Fujimoto disease patients experience 1 or more recurrent episodes. Treatment with nonsteroidal anti-inflammatory agents has been used to control symptoms. Therapy has been focused on patients with recurrent disease or severe symptoms. Jang et al. [5] administered glucocorticoids to 3 patients who had recurrent or prolonged symptoms, and observed a good response. Glucocorticoids have also been used alone or in combination with hydroxychloroquine to treat patients with SLE and Kikuchi-Fujimoto disease. Vila et al. [4] described a patient who presented with Kikuchi-Fujimoto disease 10 months prior to the development of SLE manifestations. This patient did not receive therapy at the time of presentation of Kikuchi-Fujimoto disease; however, he was treated with prednisone and hydroxychloroquine when SLE was diagnosed [4]. Similar cases—involving patients who have received diagnoses of Kikuchi-Fujimoto disease and SLE and who have responded to treatment with glucocorticoids and hydroxychloroquine—have been reported by Litwin et al. (6), Tumiati (7), and Bousquet et al. (8).

The patient described here is unique. After 14 months of follow-up there were no signs of SLE. To our knowledge, this
is the first report of a case in which hydroxychloroquine was used to treat a patient with recurrent Kikuchi-Fujimoto disease without the presence of another inflammatory process, such as SLE. During the patient’s first episode, chloroquine was used to treat possible malaria. Because of the patient’s impressive response, we chose to use hydroxychloroquine to treat his second episode of Kikuchi-Fujimoto disease. We postulate that the anti-inflammatory effects of hydroxychloroquine led to the improvement of his condition. We propose the use of hydroxychloroquine as an alternative treatment for Kikuchi-Fujimoto disease, given its superior safety profile, compared with that of glucocorticosteroids.

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References