

[CASE REPORT]

Recurrent Kikuchi-Fujimoto Disease Successfully Treated by the Concomitant Use of Hydroxychloroquine and Corticosteroids

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Abstract:

Kikuchi-Fujimoto disease (KFD) is a benign disease of unknown etiology characterized by lymphadenopathy and a fever. For the majority of patients with KFD, the course is self-limited; however, the optimum method of managing recurrent cases has not yet been established. We herein report a case of a 42-year-old Japanese woman with KFD (confirmed by a lymph node biopsy). Although high-dose prednisolone (PSL) rapidly induced remission, she experienced four recurrences on treatment tapering. Concomitant use of hydroxychloroquine (HCQ) with low-dose PSL induced continuous remission. This is the first case to suggest the effectiveness of HCQ for recurrent KFD in a Japanese patient.

Key words: Kikuchi-Fujimoto disease, histiocytic necrotizing lymphadenitis, hydroxychloroquine

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Introduction

Kikuchi-Fujimoto disease (KFD), also known as Kikuchi disease or histiocytic necrotizing lymphadenitis, is a lymphohistiocytic disorder of unknown etiology that was first described in Japan by Kikuchi (1) and Fujimoto (2) in 1972. KFD is characterized by lymphadenopathy accompanied by various symptoms, such as a fever, rash, and leukopenia. Although most cases of KFD have a self-limited clinical course, 3% to 7% of patients experience recurrent episodes (3). Treatment guidelines have not been established for KFD, so the therapeutic strategies are based on physicians' experiences and opinions. Watchful waiting without any medications might be the most common approach to treating KFD, due to its benign course. The short-term administration of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) may be effective for patients with severe symptoms (4). Although the optimum method of management for the few recurrent KFD cases has not yet

been established, some reports have described the effectiveness of hydroxychloroquine (HCQ) (5, 6).

HCQ is a weakly basic 4-aminoquinolone compound ordinarily used as an antimalarial agent. In addition to its antimalarial effects, HCQ has been shown to have disease-modifying effects on systemic lupus erythematosus (SLE) (7). Furthermore, HCQ is considered the first-line systemic agent for the treatment of cutaneous lupus (7). Of note, several reports have proposed a close clinical and pathological association between KFD and SLE (8-10). We therefore speculate that HCQ would be useful for treating KFD. To our knowledge, this is the first report of the successful treatment of a Japanese patient with recurrent KFD using HCQ.

Case Report

A 42-year-old Japanese woman was admitted to our hospital with fatigue and a rash. She had been diagnosed with KFD at a previous hospital 3 months earlier, where she had

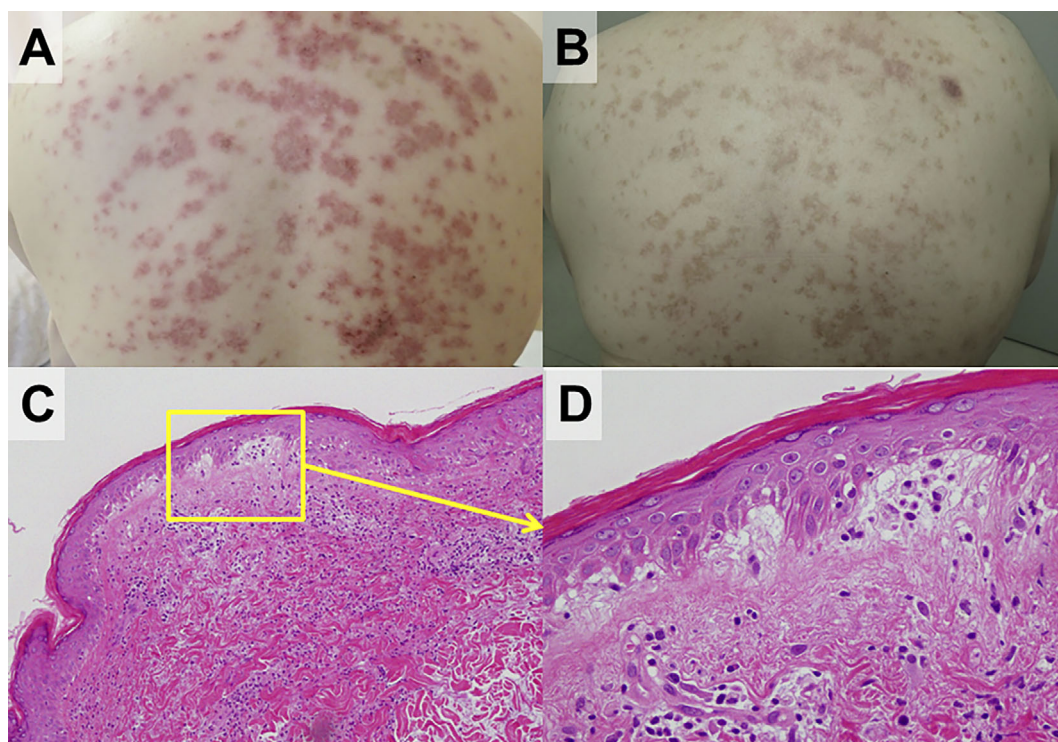


Figure 1. Skin rash of the back and its pathological findings. (A) Erythematous papules were distributed over a wide region of her back at the time of second admission to our hospital [before hydroxychloroquine (HCQ) administration]. (B) Erythematous papules were improved, and only brownish pigmentation was left (after HCQ administration). (C) A skin biopsy of the back revealed interface dermatitis. Vacuolar changes and scattered lymphocyte infiltration were detected in the epidermis (boxed-in area) [Hematoxylin and Eosin (H&E) staining, 100× magnification]. (D) Enlarged view of the boxed-in area (C) (H&E staining, 400× magnification).

presented with a fever (38°C), lymphadenopathy, arthralgia, fatigue, and a rash. Prednisolone (PSL) at 30 mg/day was orally administered. Although her fever and lymphadenopathy improved rapidly, the treatment was discontinued due to abdominal pain. Her symptoms - a fever, lymphadenopathy, and a rash - recurred 18 days after treatment cessation. PSL was resumed at 30 mg/day, and her symptoms again improved rapidly. The dosage of PSL was tapered. However, when the PSL dose was reduced to 15 mg/day, she again became febrile, and the dosage was increased again to 30 mg/day. A skin biopsy of an erythematous papule on her back revealed interface dermatitis with inflammatory cell infiltration at the dermo-epidermal junction. She was referred to our hospital because of her intractable and recurrent KFD and suspected concomitant underlying connective tissue disease (CTD).

At the time of admission to our hospital (first admission), she was afebrile under the administration of 25 mg/day of PSL. However, the rash and lymphadenopathy persisted, and erythematous skin lesions were distributed from her head to wide regions of the trunk. A further skin biopsy of an erythematous papule on her back was performed. Pathological findings revealed interface dermatitis-consistent with the previous biopsy result from the former hospital. A week after her admission, she again developed a fever of 38-40°C.

Laboratory tests showed leukopenia (2,100/mm³), increased lactate dehydrogenase (708 U/L), and soluble interleukin (IL)-2 receptor (745 U/L). C-reactive protein (CRP) was normal (0.05 mg/dL). The antinuclear antibody (ANA) titer was 40-fold (homogeneous pattern), the serum levels of C3 and C4 were normal, and antidouble-stranded DNA (dsDNA) antibody was also negative. Serum antibodies against Epstein-Barr virus, herpes simplex virus, and herpes zoster virus all showed patterns of previous infection. Cytomegalovirus antigenemia was negative. Although blood cultures for bacteria were all negative, IgA and IgG antibodies for chlamydia trichomoniasis were positive. Despite having no genital symptoms, azithromycin at 500 mg/day was administered, because we could not rule out possible chlamydial infection. However, her symptoms persisted.

A biopsy of a cervical lymph node was performed, revealing necrosis with abundant karyorrhectic debris and proliferation of histiocytes but no neutrophil infiltration, granulomatous formation, or atypical cells. These findings were consistent with KFD rather than malignant lymphoma or tuberculosis. We therefore diagnosed her with intractable and recurrent KFD without any underlying CTDs.

The dose of PSL was increased from 25 mg/day to 50 mg/day (0.8 mg/kg/day) for induction therapy, and her fever rapidly improved. Both the rash and cervical lymphadenopa-

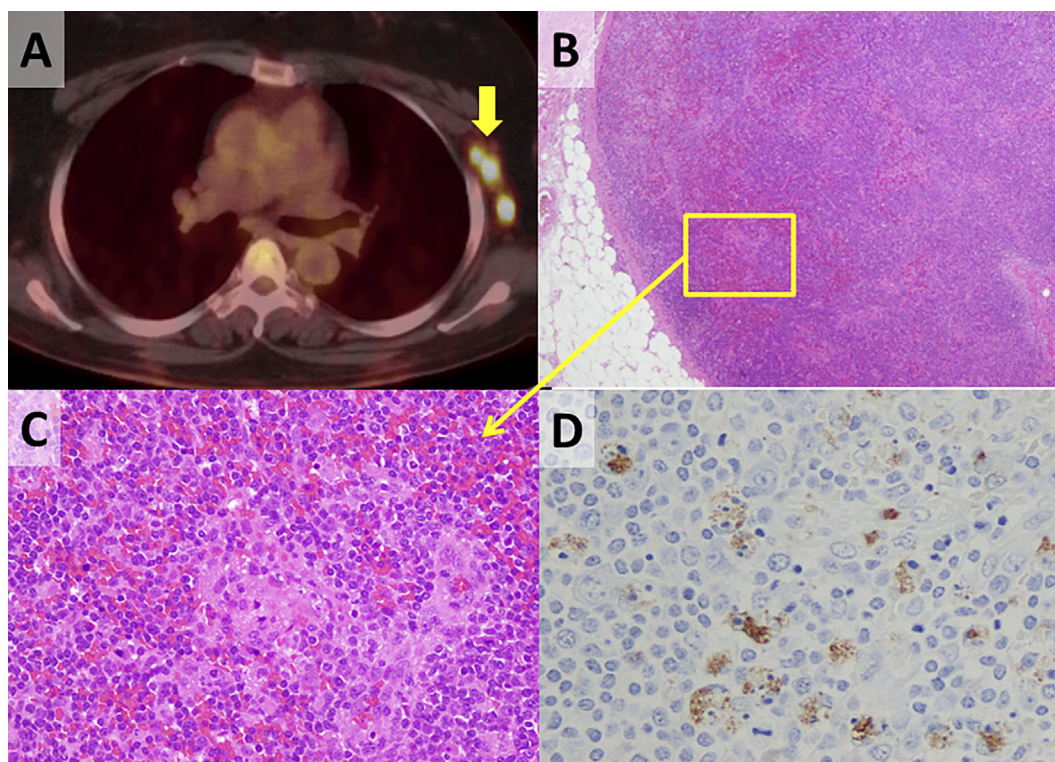


Figure 2. Axial lymphadenopathy and its pathological findings. (A) ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) imaging showed left axial lymphadenopathy and the marked uptake of FDG (SUV max: 23.4) (arrow). (B) Pathological findings of a left axial lymph node biopsy. The lymph node structure was destructed, and the marginal zone of the lymphoid follicle was unclear. There was necrosis along with proliferation of histiocytes without any atypical lymphocytes [Hematoxylin and Eosin (H&E) staining, 40 \times magnification]. (C) Enlarged view of the boxed-in area (B). There was a necrotizing area including histiocytic debris (H&E staining, 200 \times magnification). (D) Immunohistochemical staining for CD68 of the left axial lymph node. Abundant CD68-positive histiocytes were detected (400 \times magnification).

thy improved gradually. Therefore, PSL was tapered by 10% per every 2 or 4 weeks to a dosage of 12.5 mg/day without recurrence. However, 3 months after induction therapy with PSL dose at 11 mg/day, the rash recurred. Tapering of PSL was continued because she was afebrile and her general condition was good, while the rash gradually deteriorated. When the dose of PSL was reduced to 8 mg/day, she experienced arthralgia and developed a fever and lymphadenopathy. Despite the PSL dose being increased to 15 mg/day, her symptoms persisted.

She was admitted to our hospital again (second admission) with intractable recurrence of KFD. On a clinical examination, erythematous papules were seen diffusely across a wide region of her back (Fig. 1A). A skin biopsy revealed interface dermatitis characterized by vacuolar degenerations and scattered lymphocytes infiltration in the epidermis (Fig. 1C and D). Imaging with ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) revealed a marked abnormal accumulation [standardized uptake value (SUV max; 23.4)] at the swollen left axillary lymph nodes (Fig. 2A). A biopsy of the left axillary lymph node was performed to rule out the presence of a lymphoproliferative disease (LPD). The pathological features

of the lymph nodes accorded with the previous results showing necrosis and proliferation of histiocytes without any atypical lymphocytes (Fig. 2B and C). Immunohistochemical staining for CD68 showed abundant CD68-positive histiocytes (Fig. 2D). Laboratory tests showed leukopenia (2,600/ mm^3), increased lactate dehydrogenase (364 U/L), CRP (1.2 mg/dL), and soluble IL-2 receptor (622 U/L). The ANA titer was 80-fold (homogeneous pattern), anti-dsDNA antibody was negative, and the serum levels of C3 and C4 were also normal. She was therefore ultimately diagnosed with recurrence of KFD without LPD or underlying CTDs. The dose of PSL was again increased from 15 to 40 mg/day as a reinduction therapy. Because she had experienced recurrence of KFD four times following the tapering of PSL, concomitant use of HCQ was proposed as a maintenance therapy. After gaining her consent, HCQ at a dose of 200/400 mg on alternating days was added to her treatment with PSL at 35 mg/day.

Her skin lesions, lymphadenopathy, and laboratory data such as leukopenia and elevation of CRP and LDH gradually improved. Three months after starting HCQ administration, only brownish pigmentations were seen on her back (Fig. 1B). The dose of PSL was tapered under the concomi-

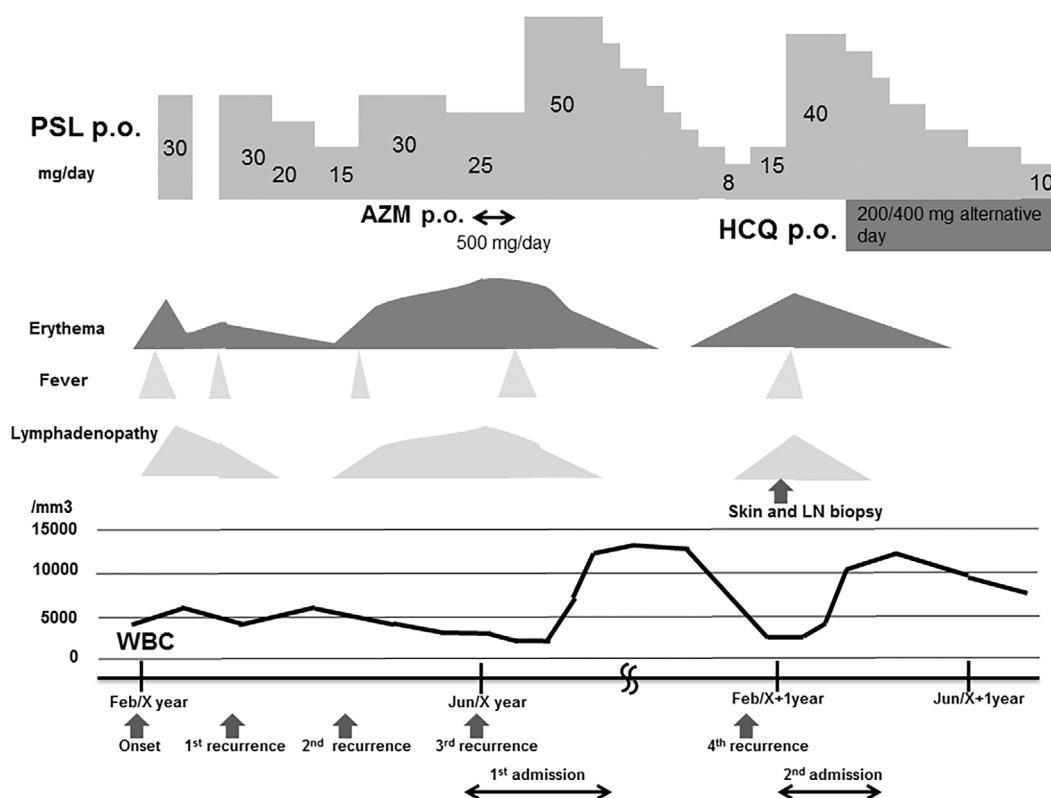


Figure 3. Clinical course. PSL: prednisolone, p.o.: per os, AZM: azithromycin, HCQ: hydroxychloroquine, LN: lymph node, WBC: white blood cell, 1st and 2nd admission: first and second admission to our hospital

tant use of HCQ. Combination of low-dose PSL (decreased to 10 mg/day) and HCQ led to continuous remission without adverse events or recurrence of KFD for over 6 months (Fig. 3).

Discussion

We encountered a case of KFD that recurred four times following tapering of PSL treatment. Continuous remission was eventually achieved by the concomitant use of HCQ with low-dose PSL. Following our successful experience in this case, we made two clinically important observations.

First, the clinical features of this case were consistent with those of previously reported cases of recurrent KFD. The presence of a fever, fatigue, extra-nodal involvements such as in the cutaneous regions, and a positive ANA test (all present in our case) have been identified as predictors of the recurrence of KFD (3). An association between KFD and underlying autoimmune disorders has been frequently described in the literature. Of such autoimmune disorders, SLE is the most often linked to KFD (4). Interestingly, it was reported that patients with KFD associated with SLE had a significantly higher frequency of KFD recurrence than those with isolated KFD (11). Our case therefore all of the previously described clinical predictors for KFD recurrence except for definite underlying CTDs, such as SLE. We therefore had to be alert for the possible recurrence of KFD. However, after the administration of HCQ, our patient expe-

rienced no KFD recurrence.

Second, in our case of intractable recurrent KFD, the concomitant use of HCQ with low-dose PSL led to continuous remission. To our knowledge, this is the first report of the successful treatment of recurrent KFD in a Japanese patient without any underlying CTDs such as SLE using HCQ. There have been several case reports suggesting that HCQ is effective for treating KFD patients both with SLE (12-14) and without SLE (5, 6, 15). A retrospective study showed that 67% (8/12 cases) of KFD patients with SLE and 4% (3/68 cases) of KFD patients without SLE had been treated by HCQ (16). In that retrospective study, NSAIDs were used in 6.6% of 91 KFD patients, corticosteroids in 31.9%, and intravenous immunoglobulin (IVIG) in 3.3% (16). Although some patients with KFD-SLE might be treated with cyclophosphamide, mycophenolate, IVIG, or rituximab depending on the severity of their clinical manifestations (11), the usefulness of these immunosuppressants or biologics for KFD has not been established. In particular, for KFD patients without SLE, only one case report has suggested the effectiveness of IVIG (17).

HCQ has been used for decades in certain countries to treat patients with various rheumatic diseases, such as SLE, Sjögren's syndrome (SS), rheumatoid arthritis, and antiphospholipid syndrome (7, 18, 19). In Japan, however, the use of HCQ to treat SLE and cutaneous lupus erythematosus was prohibited until 2015. Although the exact mode of action of HCQ on rheumatic diseases is still unclear, several potential

mechanisms have been suggested, including the reduction of cytokine production, inhibition of immune effector cells, and blocking of toll-like receptors (TLRs) (18). While the etiology of KFD has not been entirely clarified, several possibilities are suspected, such as infections—like Epstein-Barr virus, herpesvirus, human immunodeficiency virus, human T-lymphotrophic virus, and parvovirus B19 - or autoimmune mechanisms - like SLE, SS, thyroiditis, and leukocytoclastic vasculitis (4). In addition, various molecules have been shown to be associated with the pathogenesis of KFD, including interferon (IFN)-induced genes, apoptosis-associated genes, cytokine and chemokine pathways of IFN γ , interleukin (IL)-18, and chemokine (C-X-C motif) ligand (CXCL) 9 and 10 (4). These molecular mechanisms of KFD might be shared with certain CTDs, like SLE and SS. We can therefore speculate that HCQ would be as effective a treatment for KFD as for other CTDs through the modes of action common to these disorders.

In our case of intractable KFD, we choose HCQ for maintenance therapy instead of other immunosuppressive agents such as cyclophosphamide, cyclosporine A, and mycophenolate, for the following two reasons: First, the patient had severe cutaneous involvements showing vacuolar changes and scattered lymphocytes infiltration, which we suspected might be a viable therapeutic target of HCQ, although she did not have definite SLE based on the 1997 American College of Rheumatology (ACR) classification criteria for SLE (20). Second, although her KFD was recurrent and intractable, she had no major organ involvements, such as nephritis, central nervous system manifestations, or hemophagocytic lymphohistiocytosis, which require more aggressive immunosuppressive therapy with cyclophosphamide, cyclosporine A, or mycophenolate. As a result, HCQ dramatically suppressed the recurrence of the disease.

In conclusion, our findings in the present case support the efficacy of the concomitant use of HCQ alongside corticosteroid for recurrent KFD patients. HCQ may be as promising a therapeutic option for patients with refractory KFD in Japan as it is in other countries.

The patient presented in this report gave her informed consent prior to her inclusion.

The authors state that they have no Conflict of Interest (COI).

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