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Original Article

Pediatric Kikuchi-Fujimoto disease: A clinicopathologic study and the therapeutic effects of hydroxychloroquine

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KEYWORDS
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Abstract *Background:* To investigate the clinical features of Kikuchi-Fujimoto disease (KFD) in children, and place an emphasis on the therapeutic effects of hydroxychloroquine as monotherapy.
Methods: We retrospectively reviewed the medical records of all children diagnosed with KFD during the period January 1992 to September 2016 at a tertiary medical center in Taiwan.
Results: 40 patients were histopathologically confirmed as KFD, and the mean age of the patients was 13.9 ± 3.1 years. The male to female ratio was 1:1. The lymph node involvements were often cervical (95%) with features of unilateral predisposition (75%), polyadenopathy (84.4%) and tenderness (56.3%). Fever, cough, rhinorrhea, and tonsillitis were other common presentations. Laboratory findings included leukopenia (56.5%), monocytosis (63.6%), with positive results of EB-VCA IgG (88.9%), EB-VCA IgM (22.2%), EBEA IgG (22.2%) and EBNA IgG (88.9%). The univariate analyses of prolonged fever with lymphopenia, monocytosis, thrombocytopenia and necrotizing type in histopathology were disclosed as statistically significant ($P < 0.05$). Corticosteroids and hydroxychloroquine were administered in 15.6% of patients respectively, along with symptomatic treatments for the rest. Recurrence occurred in 13.0% of patients without corticosteroids or hydroxychloroquine treatment. There were neither recurrences nor relevant major adverse effects in all the five KFD cases treated with hydroxychloroquine.

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Conclusion: KFD should be suspected in children with febrile cervical lymphadenopathy, especially when concomitant with leukopenia and monocytosis. Lymphopenia, monocytosis, thrombocytopenia and necrotizing type in histopathology are reliable predictors for prolonged fever. Hydroxychloroquine may be an alternative choice to corticosteroids for its favorable effects and safety.

Introduction

Though the literature on Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis has continued to increase since its first descriptions in 1972,[1,2] the exact entity of this disease is still obscure. These studies were usually carried out across decades to obtain a large sample size owing to its rarity.[3–8] KFD is one of several differential diagnoses of lymphadenopathy, and the diagnosis is made only with histological confirmation.[9] There are still many queries about this disease, including the pathogenesis, pathognomonic factors other than histopathologic findings, and optimal treatment plans.

KFD has shown predilections for the young female population aged around 30 regardless of ethnicity.[4,9–11] Cervical lymphadenopathy, fever, and other nonspecific constitutional symptoms comprise most clinical settings.[3,4,6,12] Leukopenia, lymphopenia, thrombocytopenia, and elevated alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and lactate dehydrogenase (LDH) are common laboratory findings. There were numerous postulations about the pathogenesis of KFD and possible inciting agents,[4,9] including viral infections and autoimmune mechanisms. KFD is generally thought to be a benign disease with self-limiting courses; nevertheless, it may progress to a more severe state, with repeated recurrence or even demise occasionally.[11,13–19] Observation without treatment or with the use of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAID) are sufficient for most occurrences, but short courses of corticosteroids, intravenous immunoglobulin (IVIG) or hydroxychloroquine (HCQ) might be required in more complicated cases.[4,9]

KFD in the pediatric group shows some differences compared with adults, including predominance among young boys and clinical presentations.[6,20] We conduct this study to further delineate the characteristics of KFD in children, and emphasize the excellence of hydroxychloroquine treatment for KFD on the basis of our previous experience.[21]

Methods

The medical records of 40 children with KFD, under the age of 18 years, between January 1992 and September 2016 in the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan were retrospectively analyzed. The diagnosis of KFD was confirmed with lymph node excisional biopsy, composed of typical histopathologic features, i.e., paracortical well-circumscribed necrotic lesions consisting of karyorrhexis, fibrin deposits, plasmacytoid monocytes and infiltration of histiocytes in the absence of plasma cells or neutrophils. Based on Kuo's histopathological definition,[12] these were classified into three subtypes: proliferative type if containing various histiocytes, plasmacytoid monocytes, lymphoid cells with karyorrhectic nuclear fragments and eosinophilic apoptotic debris; necrotizing type with the existence of coagulative necrosis; and xanthomatous type if foamy histiocytes predominated.

Data collected during the first medical visit in this hospital included sex, age, characteristics of lymphadenopathy, symptoms and signs, laboratory studies, pathologic features, treatments and outcomes. The most abnormal data were representative when series of laboratory studies were repeated during the hospitalization. The Liaison Epstein–Barr virus (EBV)-viral capsid antigen (VCA) IgM, VCA IgG, and EBV nuclear antigen (EBNA) IgG chemiluminescent assays (DiaSorin S.p.A., Saluggia, Italy) used in our hospital had trustworthy sensitivity and specificity to correctly categorize relevant EBV infection states as 93.8% and 94.6%, respectively.[22] Clinical managements, including the use of corticosteroids or HCQ were retrieved and investigated for their clinical effects. Because there was no current recommended dose for KFD patients, the treatment criteria of HCQ is 5–7 mg/kg/day for 6 months in this study. Regarding the outcomes, we focused on the recurrence, defined as later symptomatic lymphadenopathies with or without febrile episodes, and relevant adverse effects after medical treatments.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and were compared between groups using the Mann–Whitney U test. Categorical variables, expressed by percentages, were compared with Fisher's exact test. A 2-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Baseline demographic characteristics, clinical features and laboratory data at initial presentation are shown in Tables 1 and 2. Forty children without duplication (20 boys and 20 girls) were evaluated during the study period, with the foremost pathological confirmations of the diagnosis of Kikuchi-Fujimoto disease. The ages ranged

Table 1 Characteristics of Kikuchi-Fujimoto disease in children.

Total patient no. (%)		
Age (y), mean ± SD		13.9 ± 3.1
Sex ratio (M/F)	Total	20:20
	0–6 yr	1:0
	7–12 yr	5:5
	13–18 yr	14:15
Lymphadenopathy		
Location	Cervical	38 (95)
	Axillary	1 (2.5)
	Inguinal	1 (2.5)
Unilateral		24/32 (75)
Multiple		27/32 (84.4)
Tenderness		18/32 (56.3)
Maximum size (cm), mean ± SD		2.3 ± 1.1
Clinical symptoms and signs		
Fever		16/32 (50.0)
Cough, rhinorrhea or sore throat		6/32 (18.8)
Headache		4/32 (12.5)
Anorexia		3/32 (9.4)
Tonsillitis		3/32 (9.4)
Chills		2/32 (6.3)
Rash		2/32 (6.3)
Weakness		2/32 (6.3)
Night sweat		1/32 (3.1)
Odynophagia		1/32 (3.1)
Hepatomegaly		1/32 (3.1)
Splenomegaly		1/32 (3.1)
Treatment and outcome		
Hospitalization		18/32 (56.3)
Oral prednisone		5/32 (15.6)
HCQ		5/32 (15.6)
Later recurrence	Treat with HCQ	0/5 (0)
	Treat with oral prednisone	0/5 (0)
	Others	3/23 (13.0)

Patients whose clinical data were unavailable for analysis were excluded.
M = male; F = female; HCQ = hydroxychloroquine.

Table 2 Laboratory and pathological findings of Kikuchi-Fujimoto disease in children.

Total patient no. (%)	
Hemogram	
Leukopenia (<4000/mm^3)	13/23 (56.5)
Leukocytosis (≧10,000/mm^3)	1/23 (4.3)
Neutropenia (ANC < 1500/mm^3)	12/22 (54.5)
Lymphopenia (<1500/mm^3)	12/22 (54.5)
Monocytosis (≧10%)	14/22 (63.6)
Anemia	5/23 (21.74)
2–9 yr (<11.5 g/dL)	
10–18 yr, male (<12.5 g/dL)	
10–18 yr, female (<12.0 g/dL)	
Thrombocytopenia (<150 × 10^3/mm^3)	7/23 (30.4)
Presence of atypical lymphocyte	4/22 (18.2)
Biochemistry	
Elevated ESR (≧12 mm/h)	5/8 (62.5)
Elevated CRP (≧1 mg/dL)	7/14 (50)
Elevated AST (≧35 U/L)	7/21 (33.3)
Elevated ALT (≧40 U/L)	3/20 (15)
Elevated LDH (≧213 U/L)	12/15 (80)
Serology and immunology	
ANA (≧1:80)	1/11 (9.1)
Decreased C3 (<79 mg/dL)	1/5 (20)
Decreased C4 (<16 mg/dL)	2/5 (40)
EB-VCA IgG (≧20 U/mL)	8/9 (88.9)
EB-VCA IgM (≧40 U/mL)	2/9 (22.2)
EBEA IgG (≧40 U/mL)	2/9 (22.2)
EBNA IgG (≧20 U/mL)	8/9 (88.9)
Histopathology	
Proliferative type	14/38 (36.8)
Necrotizing type	23/38 (60.5)
Xanthomatous type	1/38 (2.6)

Patients whose clinical data were unavailable for analysis were excluded.
ANC = absolute neutrophil count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; ANA = antinuclear antibody; EB = Epstein–Barr; EBNA = EBV nuclear antigen; EBEA = EBV early antigen; VCA = viral capsid antigen.

from 6 to 18 years with a mean of 13.9 ± 3.1 years. The male-female ratio was 1:1, and varied among different age groups.

The lymphadenopathies were mostly located in the cervical region (95%), and patients with the other two uncommon sites, inguinal and axillary regions, both had a prolonged diagnostic process. They were usually unilateral (75%), multiple (84.4%) with tenderness (56.3%), and the mean of maximum size was 2.3 ± 1.0 cm. Other common presentations included fever (50%), symptoms of upper respiratory tract infection, including cough, rhinorrhea or sore throat (18.8%), headache (12.5%), anorexia (9.4%) and tonsillitis (9.4%), while 62.5% of patients with fever had protracted febrile courses for more than 7 days with a mean duration of 21.0 ± 10.2 days.

Leukopenia (56.5%) and monocytosis (63.6%) were more prominent than leukocytosis, anemia and thrombocytopenia in the hemogram. ESR (62.5%), CRP (50%), and LDH (80%) were often elevated. Only one of the patients tested with anti-nuclear antibody (ANA) showed positive (>1:80), and one and two patients had decreased C3 and C4 levels respectively. Neither one in our study was diagnosed with systemic lupus erythematosus (SLE) or other autoimmune diseases during the follow-up period. In the nine cases tested with the EBV-specific antibody testing, past EBV infections (88.9%) were disclosed by positive EBNA IgG and EB-VCA IgG, and one acute EBV infection was revealed by positive EB-VCA IgM with negative EBNA IgG. The histopathology subtypes included proliferative type (36.8%), necrotizing type (60.5%), and xanthomatous type (2.6%) (Fig. 1).

Univariate analysis was exerted to analyze parameters associated with prolonged fever, as shown in Table 3. Lymphopenia, monocytosis, thrombocytopenia and necrotizing types in histopathology had significant associations with prolonged fever for more than 7 days ($P < 0.05$).

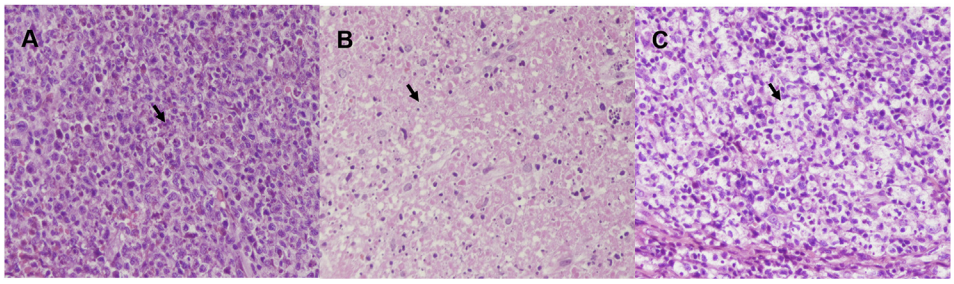

Figure 1. Histopathology of lymph node biopsy specimens. (A) Proliferative type containing karyorrhectic nuclear fragments (arrow), eosinophilic apoptotic debris and various histiocytes (Hematoxylin-Eosin stain, 200×). (B) Necrotizing type showing the existence of coagulative necrosis (arrow) (Hematoxylin-Eosin stain, 200×). (C) Xanthomatous type showing foamy histiocytes (arrow) (Hematoxylin-Eosin stain, 200×).

Table 3 Univariate analysis of prolonged fever[a] in children with KFD.

	Total patient no. (%)		
	Prolonged fever (N = 10)	No prolonged fever (N = 22)	*P*
Age (y), mean	12.2 ± 4.9	14.2 ± 2.3	0.158
Sex, female	5/10 (50)	9/22 (40.9)	0.712
LN size (cm), mean	2.7 ± 1.1	2.1 ± 1.0	0.181
Leukopenia	7/10 (70)	5/13 (38.5)	0.214
Lymphopenia	8/10 (80)	4/12 (33.3)	0.043[b]
Neutropenia	7/10 (70)	5/12 (41.7)	0.231
Monocytosis	9/10 (90)	5/12 (41.7)	0.031[b]
Thrombocytopenia	6/10 (60)	1/13 (7.7)	0.019[b]
Anemia	2/10 (20)	3/13 (23.1)	1.000
Elevated ESR	1/5 (20)	2/3 (66.7)	0.464
Elevated CRP	4/9 (44.4)	3/5 (60)	1.000
Elevated AST	6/10 (60)	8/11 (72.7)	0.659
Elevated ALT	9/10 (90)	8/10 (80)	1.000
Elevated LDH	2/9 (22.2)	1/6 (16.7)	1.000
Past EBV infection	7/8 (87.5)	1/1 (100)	1.000
NT in histopathology	9/10 (90)	10/20 (50)	0.049[b]

[a] Definition: fever more than 7 days.
[b] *P* value < 0.05 is statistically significant.
Patients whose clinical data were unavailable for analysis were excluded.
The definitions of laboratory finding are the same as in Table 2.
LN = lymph node; NT = necrotizing type.

Considering the recurrence, there was no parameter showing statistical significance (not shown in the table).

More than half of the patients (56.3%) were hospitalized during the courses of KFD, and the others received outpatient examinations and surgeries. Most KFD patient had self-limiting courses, and received antibiotics or medications for symptom relief, such as NSAID. Oral prednisolone and HCQ were administered in 5 cases (15.6%) respectively. The mean duration between initial diagnosis and the last follow-up was 42.9 months, ranging widely from 1 week to 20 years. Three patients had later recurrence, and neither of them had received prednisolone or HCQ.

After the favorable experience of using HCQ for one KFD patient with a protracted course,[21] another four patients were also administered with HCQ as the initial therapy, shown in Table 4. The actual dose and duration of treatment were not fully in accordance with the treatment criteria. The doses had been increased as tablets in two cases (case 1 and 4) for its intolerable bitter taste as powder. The duration varied widely from 3 to 9 months for individual concerns, i.e., safety or recurrence. All the five KFD patients treated with HCQ received ophthalmologic examinations biannually. A 9-year-old girl (case 4) is the only patient in this study received both corticosteroids and HCQ concurrently. Before this admission, corticosteroids were administered for one month in another hospital, and her fever persisted. The defervescence occurred abruptly after excisional biopsies and the initiation of HCQ in these cases. During the outpatient follow-up with a mean of 23 months, there was no later recurrence. Besides, apart from mild gastrointestinal upset, there was no major adverse effects of HCQ (including retinal damage and neuro-myotoxicity) noted.

Table 4 Summary of characteristics of KFD cases treated with hydroxychloroquine.

Case	Age (y)	Gender	Fever duration (days)	LN site and maxi. size (cm)	HCQ dosage (mg/kg/day)	Follow-up (months)	Later recurrence	Major adverse effects[b]
1	9	F	39	Cervical, 2.0	16.5	37	—	—
2	13	M	5	Cervical, 1.8	7.5	30	—	—
3	13	M	0	Cervical, 1.7	7.0	22	—	—
4	9	F	9	Cervical, 3.5	11.0	17	—[a]	—
5	12	M	11	Cervical, 2.0	6.5	9	—	—

[a] She took prednisolone in another hospital, and was admitted to our hospital for the recurrence.
[b] Adverse effects included retinal vascular disease, neuro-myotoxicity, peptic ulcer, weight gain, hypertension, hyperglycemia, imbalance of electrolytes, etc.
M = male; F = female; LN = lymph node; HCQ = hydroxychloroquine.

Discussion

The prevalence of KFD varies with age, ethnicity and gender,[4,10] and is mostly diagnosed in women of Asian descent between the ages of 20 and 35 years.[9] The female predominance has gradually shifted to male predominance in younger age groups, especially in pediatric KFD studies,[5,6,20,23–25] and our patients fit this trend as well. Kim et al. divided patients into five age groups, and the watershed of sex predominance was around the age of 15 years, at the timing of girls entering puberty. Therefore, the influence of female sex hormones may play a role in KFD.[6] Coincidentally with febrile lymphadenopathy in young females, an autoimmune disease or a particular infection apt to occur in this population are also possible explanations.

The classic presentations of KFD are characterized by cervical lymphadenopathy (79–94%), fever (35–67%), skin rash (4–32.9%), arthralgia (7–34.1%) and hepatosplenomegaly (3–14.8%), while laboratory studies include leukopenia (18.9–42.9%), lymphopenia (63.8%), thrombocytopenia (5.4–19%), along with elevated levels of liver function tests (23.3–24.4%), ESR (78.9%), CRP (38.3%) and LDH (52.5–81.5%).[3,4,6,10,12] Compared with adults, systemic manifestations such as fever and rash are more common in children.[6] These features grossly resembled our patient group. Lymphopenia, monocytosis and thrombocytopenia in our study had the potential to predict a prolonged febrile course, and these findings aid early recognition and selective consideration of advanced therapies.

No specific symptoms or signs above are pathognomonic. The only way to diagnose KFD is based on the histopathological evidence of lymph node biopsy, and fine-needle aspiration biopsy is less preferable than excisional biopsy for its limited diagnostic potential.[26] According to Kuo's classification,[12] our cases had similar distribution as previous studies: proliferative type (4.4–29.1%), necrotizing type (41.7–76.5%), and xanthomatous type (17.7–38.9%).[4,12,25] It is noteworthy that necrotizing type in histopathology was also a statistically significant parameter related to prolonged fever. These subtypes may represent different evolving stages of KFD or reflect the difference in etiology or host reaction,[27] and need further studies to be validated.

With similar clinical presentations and the lack of response to antibiotics, autoimmune diseases and viral infections are widely discussed in KFD patients for their possible causal relationships or they might present with the same disorder in different time sequences. Sopeña et al. conducted a case series with the mean follow-up for 119 months, and revealed 5 (29%) of 17 cases had autoimmune diseases prior to or simultaneously with the KFD diagnosis, and 4 (24%) additional cases thereafter.[8] SLE was mostly encountered,[3,5,10,24] and others such as Sjögren's syndrome and autoimmune thyroiditis have also been mentioned in several studies.[6,8,11] In a literature review of 244 KFD cases, higher ANA positivity rate (23% vs. 3%) and association with SLE (28% vs. 9%) were noted in cases from East Asia and the Far East than in those from Europe.[10] Compared with adults, pediatric KFD had resembling symptoms and opportunities to have autoimmune diseases, but lower ANA titers.[6] None of our cases had autoimmune diseases during the follow-up with a mean 42.9 months, though a few patients had positive ANA and decreased C3 and C4 levels. It could be underestimated due to the short duration of follow-up, and further evaluations should be continued.

Febrile lymphadenopathy with URI symptoms, tonsillitis and other constitutional symptoms after viral infection are comparable to that of KFD, and thus held the early diagnosis. However, studies investigating coexisting viral infections and KFD have raised the possibility about the association in between or merely random coincidence. Several pathogens had been studied, but none of them have compelling conclusions. From a literature of meta-analysis, while the polymerase chain reaction (PCR) positivity of EBV, human herpes virus types 6, 7, and parvovirus B19 reached over 26.3–56.9%, neither of them are associated to KFD than in normal controls with statistical significance.[28] In our EBV-specific antibody testing, except one with positive EB-VCA IgM alone indicating acute infection, the remaining eight cases had both positive EB-VCA IgG and EBNA IgG, which indicated past infections. Zou et al. had similar findings, with positive IgM and IgG of EBV in 3.4% and 82.8% of 29 pediatric KFD cases, respectively.[25] However, based on a large-scaled seroprevalence study with a total of 1411 serum samples in Taiwan, the seropositive rate of EB-VCA IgG was over 80.7–96.2% among the range of ages of our cases.[29] Thus the high prevalence of EBV past infection and small sample size in our study should be interpreted with caution. Monocytosis (63.6%), the presence of atypical lymphocytes (18.2%), and the presentations of tonsillitis (9.4%) in our patients deserved more attention. Infectious mononucleosis-like syndromes especially EBV infection should be excluded first before the diagnosis. Furthermore,

if all these results are reproducible in KFD patients, it might indicate a chance to clarify the relationships between EBV infections and KFD.

Observation is the most common approach in management of KFD for its benign nature most of the time. However, patients complicated with a more severe and protracted clinical course may benefit from corticosteroids, IVIG or HCQ.[4] HCQ is usually used in combination with corticosteroids for patients with SLE and KFD concomitantly. Rezai et al. reported the first KFD case using chloroquine to treat suspected malaria accidentally, and after one year, HCQ for the recurrence.[30] Despite recurrence after HCQ treatment as monotherapy being once reported in one case report,[15] it mostly brought KFD patients favorable outcomes.[14,21,30] Although there remain potential adverse effects including retinal damage and neuromyotoxicity, the exact risk of HCQ treatment is low except in individuals with G6PD deficiency.[31] Besides, there has been no major adverse event with the use of HCQ in the reporting system of our hospital, a tertiary medical center, for over two decades. The proposed mechanism of HCQ has been attributed to its alkalization of acidic intracellular vesicles, required for endosomal toll-like receptor activation. This proposed mechanism results in decreased inflammatory cytokine production and antigen processing necessary for antigen presentation of autoantigens.[31–33] All the five KFD patients treated with HCQ had excellent outcomes without later recurrence. Patients received corticosteroids had comparable performance as HCQ, while the recurrence rate reached 13.0% in the remaining cases. However, it was not until progressive clinical conditions that corticosteroids were administered concerning a long list of well-described, dose-dependent complications. In addition, half of patients in this study had fever, and 62.5% of them had protracted febrile courses for more than 1 week. Hence, due to the therapeutic effects without concession of its safety, HCQ may be considered in KFD patient. Although comparing with other managements, the case number is too small to be statistically significant, it is worth noting that the experience with favorable outcomes after HCQ treatment is accumulating. Further studies are still needed to verify its superiority.

This study has some limitations. First, the small sample size may limit the ability to identify significant differences between groups in statistical analysis. Second, our retrospective design and non-standardized initial assessment hindered the completeness of data acquisition and the inability to compare treatment effects of different therapies without bias. Third, the duration of follow-up varied widely, and the related prognostic outcome may be underestimated. Prudent interpretation is of the essence.

In conclusion, in children with KFD, necrotizing type in histopathology and several laboratory parameters could be reliable predictors for protracted febrile course. The use of HCQ may be considered as an alternative choice with safety to corticosteroids.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to the material discussed in this article.

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