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Case Report

Kikuchi-Fujimoto Disease Complicated with Reactive Hemophagocytic Lymphohistiocytosis

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Kikuchi-Fujimoto disease (KFD) is a benign cause of self-limiting subacute necrotizing lymphadenitis. KFD is rarely complicated with reactive hemophagocytic lymphohistiocytosis (HLH), and the clinical features of the simultaneous occurrence of these conditions are uncertain. A 30-year-old Japanese man with a persistent fever and sore throat presented to our hospital for treatment. Laboratory analysis showed bicytopenia, and radiological studies showed systemic lymphadenopathy accompanied by splenomegaly. A bone marrow examination showed hemophagocytic macrophages, suggesting HLH. Malignant lymphoma was suspected as a possible underlying disease, but the histology of the lymph nodes led to a final diagnosis of KFD and treatment with prednisolone (1 mg/kg/day), resulting in clinical improvement. This case highlighted the importance and difficulty of differentiating KFD from malignant lymphoma as an underlying condition of HLH. The literature review showed that patients with HLH-associated KFD may have higher serum ferritin and lactate dehydrogenase levels compared to typical KFD cases. Definite diagnosis based on pathological examination is essential for a better understanding of this rare disease. The presence of systemic lymphadenopathy does not exclude the possibility of KFD. This case serves to remind physicians that KFD is a potential etiology of HLH.

Key words: hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, histiocytic necrotizing lymphadenitis, Kikuchi disease, Kikuchi-Fujimoto disease

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is an autoimmune, self-limiting lymphadenitis, typically presenting as a persistent cervical lymphadenopathy accompanied by a fever. Although a viral etiology has long been suggested, the disorder remains idiopathic [1,2]. The clinical characteristics of KFD resemble those of malignant lymphoma (ML), and differentiating between the two is sometimes difficult [3,4]. Reactive hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening disease with various etiologies. Although ML occasionally induces HLH, KFD is rarely diagnosed as a primary disease underlying HLH, and the clinical features of HLH-associated KFD remain to be determined. We describe the case of a 30-year-old Japanese man diagnosed with HLH-associated KFD and present a literature review.

Case Presentation

A 30-year-old previously healthy Japanese man presented to our hospital with 2 weeks of high fever and a sore throat. He had been treated with 500 mg

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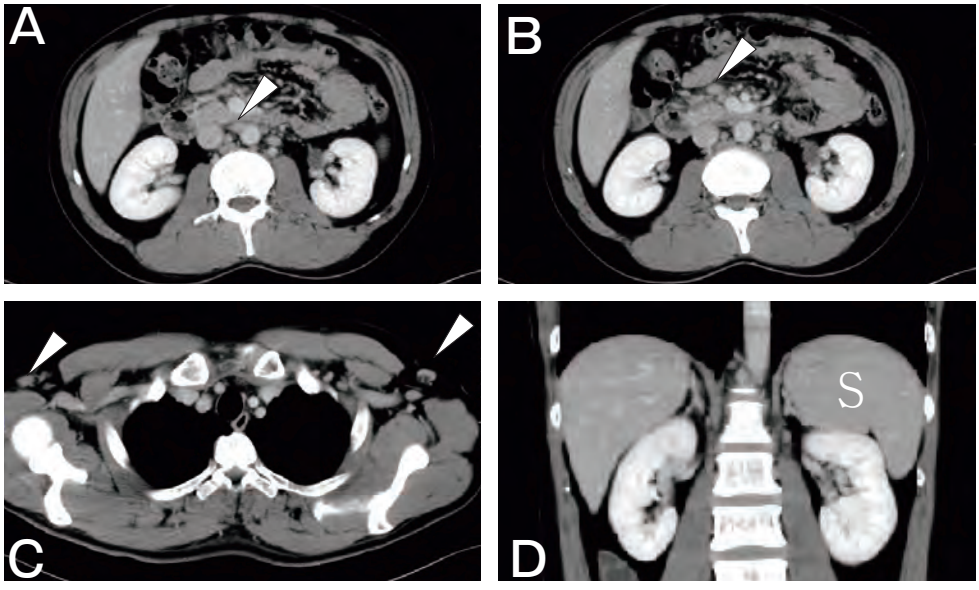

Fig. 1 Contrast-enhanced CT scan revealed enlarged lymph nodes at the para-aortic ((A), 12 mm), mesenteric ((B), 13 mm), and axillary regions ((C), 15 mm) (arrowheads), as well as splenomegaly ((D), 12. 5 cm; indicated by S).

per day of levofloxacin for 5 days with no clinical improvement. On admission, he complained of chills, sore throat, fatigue, and anorexia. He denied rigors, cough, sputum, rhinorrhea, weight loss, or night sweats. The review of systems was otherwise unremarkable. On physical examination, he had a temperature of 39.5℃, heart rate of 112 beats/min (regular), blood pressure of 157/98 mmHg, respiratory rate of 20 breaths/min, and oxygen saturation of 96% while breathing room air. He appeared mildly distressed. Physical examination revealed a non-tender lymph node at the cervical and left axillary region, but was otherwise unremarkable.

His laboratory data showed bicytopenia (white blood cell count, 1,500/μL; neutrophils, 65%; platelets, 130,000/μL) and elevated lactate dehydrogenase (LDH 1,111 IU/L) and transaminase levels (AST 128 IU/L; ALT 138 IU/L). His triglyceride, ferritin, and serum soluble interleukin-2 receptor levels were increased to 321 mg/dL, 1,730 ng/mL, and 1,210 U/mL, respectively. Serologic assays for Epstein-Barr virus (EBV) showed a past infection pattern (positive for viral capsid antigen (VCA)-IgG (1 : 20) and EBV nuclear antigen (EBNA) but negative for EBV VCA-IgM). The EBV-DNA copy number in whole blood, measured by real-time polymerase chain reaction (RT-PCR), was not elevated. Serologic tests for other common viral infections including human immunodeficiency virus (HIV), cytomegalovirus, parvovirus B19, herpes simplex virus, hepatitis A, hepatitis B, and hepatitis C did not suggest any acute infections. Antinuclear antibody, rheumatoid factor, and serum C3 and C4 levels were normal. Coagulation test results were almost normal. A contrast-enhanced computed tomography (CT) scan revealed enlarged cervical, para-aortic, mesenteric, axillary lymph nodes on both sides and moderate splenomegaly (Fig. 1). For the evaluation of bicytopenia, bone marrow aspiration was performed. The result showed hemophagocytic macrophages (Fig. 2), and a diagnosis of HLH was confirmed according to the

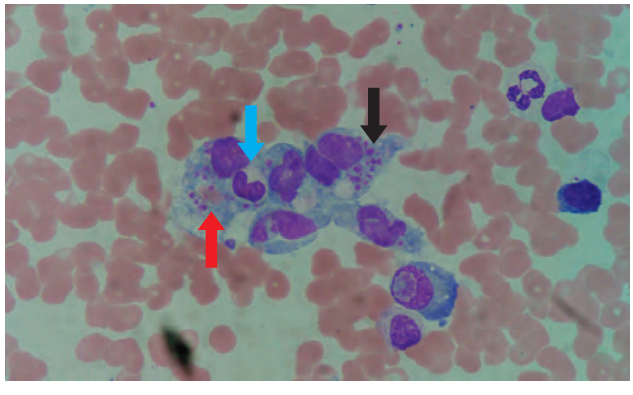

Fig. 2 A bone marrow aspirate showed hemophagocytic macrophage engulfing neutrophils (blue arrow), erythrocytes (red arrow), and platelets (black arrow) (MG-Giemsa staining).

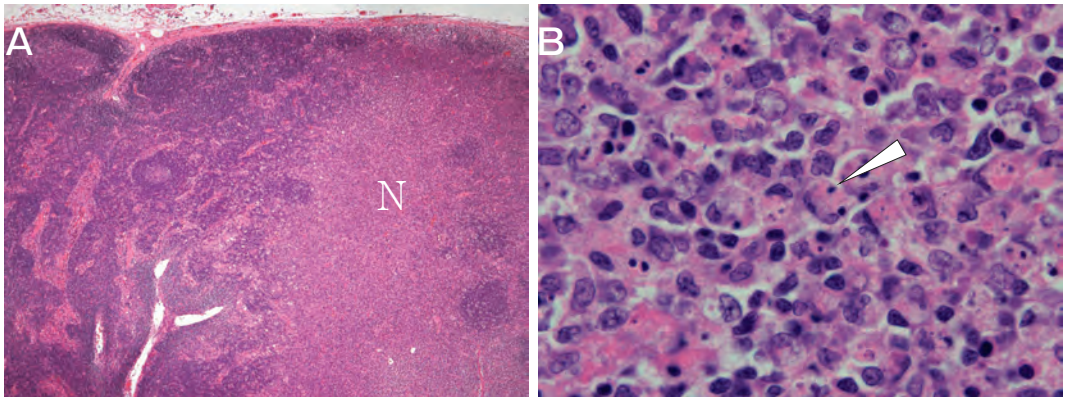

Fig. 3 Left axillary lymph node biopsy showed a paracortical necrotizing zone (N) accompanied by apoptotic necrosis with abundant karyorrhectic debris and a large number of histiocytes, including a few crescentic histiocytes (arrowhead) (hematoxylin and eosin staining, (A, B)).

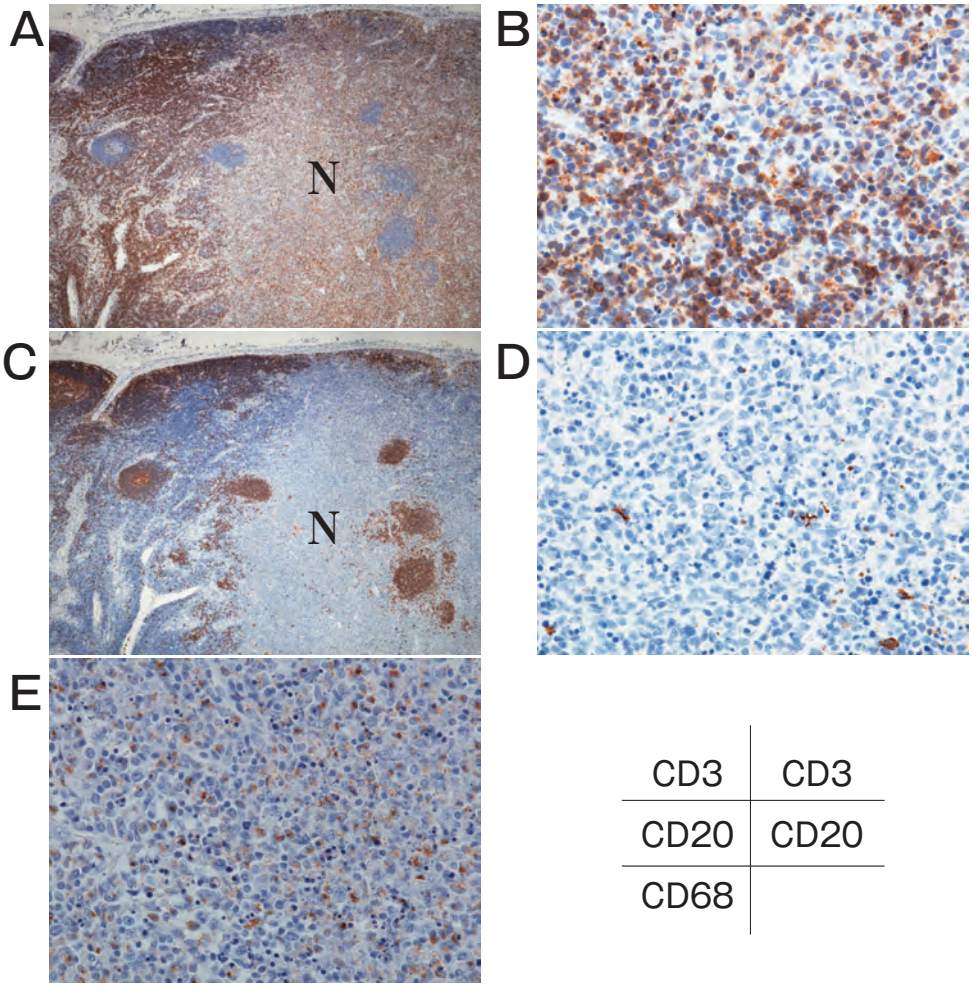

Fig. 4 Immunohistochemical study demonstrated a necrotizing zone with numerous CD3-positive T cells (CD3 immunostaining, (A, B)) and few CD20-positive B cells (CD20 immunostaining, (C, D)). CD68-positive histiocytes were noted in the necrotizing zone (CD68 immunostaining, (E)).

established clinical criteria [5].

The patient was initially treated with nonsteroidal anti-inflammatory drugs. However, the high fever persisted, and a left axillary lymph node biopsy was performed for further investigation. The histopathological examination showed typical findings of KFD (Fig. 3). No hemophagocytosis, granulomas, caseous necrosis, or evidence of malignancy was found. Immunohistochemical study showed that the necrotizing zone was infiltrated with numerous CD3-positive T cells. Although there were few CD20-positive B cells observed in the lymph node, CD68-positive histiocytes were noted in the necrotizing zone (Fig. 4). Flow cytometry and cytogenetic analysis of the lymph node showed no evidence of lymphoma or leukemia. Based on these histopathological findings, a definitive diagnosis of KFD was made.

Based on a final diagnosis of HLH-associated KFD, treatment was started with 1 mg/kg prednisolone (60 mg) daily tapered over 3 weeks by 10 mg every 3 days. His condition steadily improved following the treatment, and he was discharged on the 24th hospital day. A follow-up CT scan after 3 months showed improvement of the generalized lymphadenopathy and splenomegaly. The patient remains well after 6 months, without recurrence.

Discussion

KFD is typically a self-limiting disease that manifests as a persistent fever and painful cervical lymphadenopathy. Patients with HLH, on the other hand, usually have underlying diseases and may follow a severe and fatal course. According to a previous report summarizing 162 cases of HLH, 92 cases (56.8%) were induced by hematologic malignancies, mainly non-Hodgkin lymphomas (lymphoma-associated hemophagocytic syndrome), followed by infectious etiologies (24.4%) [6]. Chemo-immunotherapy (etoposide, corticosteroids, cyclosporin A, and, in selected patients, intrathecal methotrexate) has been given to patients with HLH [5]. The mortality rate has been reported to be as high as 20% [6].

HLH is rarely induced by KFD; however, there are many possible overlaps in the etiology and clinical features between the 2 conditions. A possible role of cytokines such as interferon-gamma and interleukin-6 in the pathogenesis of KFD [7,8], as well as HLH [9,10], was suggested in previous studies. These 2 diseases may be parts of a continuum of a single clinical condition, rather than different entities [11].

Due to the rarity of HLH-associated KFD, its clinical characteristics are still not well understood. We therefore performed a literature review and summarized 23 such cases including the present case (Table 1) [8-24]. The median age at diagnosis was 14 years, and the male-to-female ratio was 12 : 11. Almost all patients showed cytopenia and increased serum ferritin, LDH, and triglyceride levels. The median serum ferritin and LDH levels (1,168 ng/mL and 1,238 IU/L, respectively) were substantially higher in patients with HLH-associated KFD than in Japanese KFD patients without HLH (796 ng/mL and 245 IU/L, respectively) [4]. Complications of splenomegaly and hepatomegaly are rarely seen in KFD (2% and 3%, respectively) [3], but these conditions were observed in 12 (63%) and 8 (42%) cases of HLH-associated KFD, respectively. The high serum ferritin and LDH levels as well as organomegaly constitute helpful criteria for diagnosing HLH [25]. In contrast to the benign course of KFD, 3 patients with HLH-associated KFD (13%) died [16,21,22]. A previously healthy 5-year-old child was treated with a combination of etoposide and steroids, but eventually died of serious pancytopenia [22]. The second fatal case was a 24-year-old postpartum woman who developed disseminated intravascular coagulation and adult respiratory distress syndrome. Treatment with antibiotics, high-dose intravenous immunoglobulin (IVIG) and acyclovir did not work, and the authors emphasized the importance of the early diagnosis of HLH during pregnancy [16]. The third case was a 50-year-old man with systemic lupus erythematosus who eventually died after treatment with corticosteroids and broad-spectrum antibiotics. The importance of appropriate intensive immunosuppressive therapy was stressed [21].

HLH-associated KFD has a potentially fatal outcome, and early treatment is required. In the reviewed cases, the treatment included corticosteroids (19 cases), IVIG (9 cases) and etoposide (5 cases). Among these, corticosteroids can be considered an effective first-line treatment option for the disease; IVIG and etoposide could be alternative regimens.

In our case, the presence of systemic lymphade-

nopathy confused us and made it difficult to make a diagnosis of KFD. Complication with systemic lymphadenopathy is rarely seen in KFD, as it was observed in only 2 (2.9%) of the 69 Japanese KFD cases [4]. However, a histological examination successfully differentiated the disease from other etiologies and contributed to the definite diagnosis of KFD. Importantly, ML, the most common etiology of HLH, was excluded based on the findings of immunohistochemical staining and flow cytometry. Characteristic KFD histopathologic findings include irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture. Immunohistochemistry is also valuable in diagnosing KFD with a predominance of T-cells [26].

In conclusion, we present a rare case of HLH-associated KFD. Our literature review revealed that higher levels of serum ferritin and LDH as well as hepatosplenomegaly were more frequently observed in patients with HLH-associated KFD than in typical KFD cases. In contrast to the self-limiting course of KFD, the prognosis of the patients with HLH-associated KFD may be fatal. A definite diagnosis

Table 1 Summary of 23 cases of HLH-associated KFD

Case No.	Age/ Sex	Associated diseases	Treatment	Affected LN	Splenomegaly	Hepatomegaly	WBC (/μL)	Hb (g/dL)	Plt ($\times10^4$/μL)	Ferritin (ng/mL)	TG (mg/dL)	LDH (IU/L)	Outcome	Ref
1	17/F	Unknown	mPSL, IVIG, ACV	C, A, I	(+)	(−)	1,100	7.6	9.8	780	216	2,809	Improved	12
2	15/F	Infection (PVB19)	PSL	C	(+)	(+)	1,400	7.5	14.7	2,500	NA	1,941	Improved	13
3	15/F	Unknown	PSL	C, M	(−)	(−)	3,000	11.6	35.3	720	NA	337	Improved	8
4	37/F	SLE	PSL/mPSL	C, A	(−)	(+)	1,130	12.8	10.6	6,330	472	3,162	Improved	9
5	6/M	Infection (RSV), sickle cell	PSL/DEX, VP16, CyA	C	NA	NA	3,200	12.4	23.8	35,500	NA	8,340	Improved	14
6	10/F	Unknown	PSL, IVIG	C	NA	NA	1,400	9.7	21.9	1,083	207	852	Improved	15
7	14/M	Unknown	PSL, IVIG	C	(−)	(+)	1,450	12	9.8	128	146	1,238	Improved	15
8	24/F	Infection (EBV)	IVIG, ACV	C	(+)	(+)	2,600	NA	2.3	NA	NA	NA	Died	16
9	17/F	Unknown	IVIG	C	NA	NA	3,100	9.9	Normal	>1,000	NA	1,317	Improved	11
10	1/F	JIA	mPSL/PSL, IVIG, MTX, CyA	Generalized	(+)	(−)	4,100	5.8	8.9	41,500	362	NA	Improved	17
11	13/F	Unknown	mPSL/DEX, IVIG, VP16,	C	(−)	(−)	1,500	10.3	3.9	14,955	144	NA	Improved	18
12	2/M	JMML	PSL	NA	(+)	(+)	NA	Anemia	0.3	500	Raised	NA	Improved	19
13	40/M	Unknown	NSAIDs	C	(+)	(−)	2,700	13.2	8.2	NA	354	NA	Improved	20
14	13/M	Unknown	PSL	C, I	(+)	(+)	1,700	NA	13.5	NA	306	417	Improved	10
15	50/M	SLE	mPSL	C, A, I	(+)	(−)	2,040	8.4	9.6	NA	NA	3,056	Died	21
16	12/M	Unknown	PSL	C	NA	NA	2,500	10.5	22	1,003	80	1,105	Improved	22
17	14/M	Infection (EBV)	DEX, IVIG, ACV, VP16	C, A, I	(−)	(−)	3,200	9.1	16.9	2,541	177	682	Improved	22
18	5/F	Unknown	PSL/DEX, VP16	C, A, I, P	(+)	(+)	1,800	6.7	11	3,371	377	1,540	Died	22
19	14/F	Unknown	DEX, IVIG, VP16, CyA	C	(−)	(−)	2,400	9.8	10.8	472	78	627	Improved	22
20	8/M	Infection (EBV)	PSL	C, A, I, M	(+)	(+)	3,000	11.6	10.5	1,168	104	1,308	Improved	22
21	16/M	Infection (EBV)	No medication	C, A	(+)	(−)	1,240	12.6	13	892.9	275	NA	Improved	23
22	21/M	Sweet's syndrome	PSL	C	(−)	(−)	2,000	11.8	5.8	Normal	Normal	436	Improved	24
23	30/M	Unknown	PSL	C, A, I, P, M	(+)	(−)	1,500	12.5	13	1,730	197	1,111	Improved	Ours

NA, not available; LN, lymph node; PVB19, Parvovirus B19; EBV, Epstein-Barr virus; RSV, Respiratory syncytial virus; JIA, Systemic juvenile idiopathic arthritis; JMML, Juvenile myelomonocytic leukemia; ANA, antinuclear antibodies; SLE, Systemic lupus erythematosus; ACV, Acyclovir; IVIG, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs; DEX, Dexamethazone; VP16, Etoposide; MTX, Methotrexate; PSL, Prednisolone; mPSL, Methylprednisolone; CyA, Cyclosporine A. The affected lymph nodes are described as follows: C, cervical; A, axillary; I, inguinal; P, para-aortic; M, mesenteric.

based on pathological examination is essential for a better understanding of this rare disease. Additionally, physicians should not exclude KFD from the differential diagnosis of systemic lymphadenopathy.

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