Kikuchi-Fujimoto disease; evaluation of the prognostic factors and analysis of the pathologic findings

Running Head: Kikuchi disease

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Abstract

Conclusion. In Kikuchi-Fujimoto disease (KFD), low ratio of blastic cells (<70%) in the lymph node specimens and absence of atypical lymphocytes in the peripheral blood are the predictive factors which may protract the clinical course.

Objectives. Since KFD is a self-limiting disorder that does not require any specific management, its prognostic factors have received little attention. In the present study, we observed the clinical and pathological factors which may affect the period from onset to cure of KFD.

Methods: Forty three KFD patients that underwent lymph node biopsy and diagnosed by immunohistochemical staining at Okayama University Hospital and Okayama Medical Center from January 2001 to December 2013 were enrolled in this retrospective study.

Results: The total period from the onset to the cure of the disease was 1-37 months (mean, 6 months, median, 9.4 months). Low ratio of blastic cell proliferation area (<70%) in the lymph node specimens (p=0.011) and absence of atypical lymphocytes in the peripheral blood (p=0.026) were associated with relatively long duration of KFD.

Key Words: Kikuchi-Fujimoto disease, atypical lymphocytes, blastic cell, prognostic factors.

Introduction

The clinical characteristics of histiocytic necrotizing lymphadenitis, also known as Kikuchi-Fujimoto disease (KFD), are cervical lymphadenopathy with tenderness and fever, with a high prevalence among young Asian women. Typical histologic findings of KFD include paracortical areas of coagulative necrosis with abundant karyorrhectic debris, and karyorrhectic foci consist of various types of hystiocytes, immunoblasts, and small and large lymphocytes [**1**]. Since the prognosis of KFD is usually good with the condition resolving spontaneously within a period of several months [**2**], its prognostic factors have received little attention. However, it will often take more than a year from the onset of KFD to the cure of the disease, and the patients may feel uneasy and irritating. Therefore it may be convenient if there are some predictive factors which may affect the period from onset of KFD to cure of the disease. They may also be helpful to decide whether we undergo steroid therapy or not. The present study analyzed several prognostic factors including clinical characteristics, blood examination, and pathological findings. Among the pathological findings, we especially focused on the occupation of blastic cell proliferation and coagulative necrosis in each of the specimens.

Patients and methods

We identified 43 KFD cases by reviewing medical and pathological records between January 2001 and December 2013 at Okayama University Hospital and Okayama Medical Center. The 43 KFD cases in the present study were diagnosed by open surgical biopsy or cutting needle biopsy. The lymph node specimens obtained by biopsy were fixed in buffered formalin, embedded in paraffin, and then stained with hematoxylin and eosin. Automated immunostainers Ventana (Ventana Medical Systems, Tucson, AZ, USA) or Bond Max (Leica Biosystems, Melbourne, Australia) were used to perform immunohistochemical studies. The following primary antibodies were used: CD3 (LN10, Novocastra, UK; 1:200), CD4 (1F6, Nichirei, Japan; 1:40), CD8 (C8/144B, Nichirei; 1:100), CD20 (L26, Dako, Denmark; 1:200), CD68 (KP1, Dako; 1:200), Ki67 (MIB-1, Novocastra; 1:2500), lysozyme (LZM) (polyclonal, Dako; 1:1000), and myeloperoxidase (MPO) (polyclonal, Dako; 1:1500). LZM and MPO were stained using Ventana and CD3, CD4, CD8, CD20, CD68, and Ki67 were stained using Bond Max.

Results

Overall outcomes.

Of the 43 patients (**Table 1**), ages ranged from 11 to 59 years, and the mean age was 29 years. Fourteen (33%) were males and 29 (67%) were females. Twenty seven patients (63%) experienced fever over 37 °C, 24 (56%) felt pain, and 12 (28%) felt general fatigue. Twenty five (58%) patients had KFD at warm season in Japan (spring and summer; between March and August). In laboratory findings, the average of white blood cell counts (WBC) was 4119/μl (reference range, 3500-8500/μl), lactate dehydrogenase (LDH), 228.7 IU/L (120-240 IU/L), soluble interleukin-2 receptor (sIL-2R), 755.5 U/ml (122-496 U/ml), and C-reactive protein (CRP), 0.98 mg/dl (0.00-0.30 mg/dl), respectively. In 9 (21%) patients, atypical lymphocytes were observed in the periphery blood. Fourteen (33%) of 42 patients were smokers, and 9 (21%) of 42 were drinkers. Thirty eight (90%) of 42 patients took nonsteroidal anti-inflammatory drug (NSAID). Thirty one (72%) of 43 patients took antibiotic, and 12 (28%), steroid, respectively. The total period from the onset to the cure of the disease was 1-37 months (mean, 6 months, median, 9.4 months).

Affected lymph nodes were located in the cervical area in 42 of the 43 patients, and the remaining 1 patient had generalized lymphadenopathy, who was finally

diagnosed with concurrent systemic lupus erythematosus (SLE). Pathological studies showed large number of histiocytes, many of which were crescentic, at the margin of the necrotic area (**Figure 1a**). Immunohistochemical studies revealed that the infiltrated lymphocytes mainly consisted of CD3-positive T cells and there were only a few CD20-positive B cells. There was a predominance of CD8-positive large lymphoid cells with blastic features more than CD4-positive cells (**Figure 1b**). The CD8-positive large lymphoid cells revealed that the Ki67 labeling index was relatively high. In all cases, MPO (**Figure 1c**) was detected among LZM (**Figure 1d**) and CD68-positive histiocytes. The extent of the CD8-positive large lymphoid cell (blastic cell) occupation to the entire area of the specimens was over 70% in 10 (23%) cases (**Figure 2a**), and that of coagulative necrosis was over 50% in 7 (16%) cases (**Figure 2b**). All cases were clinically and pathologically consistent with KFD, and the accuracy of the diagnoses was confirmed by their clinical courses.

***Statistical analysis of prognostic factors*.**

In the present study, the subjects of which data was not perfect (sIL-2R, smoker or not, drinker or not, took NSAID or not) were looked upon as reference data and were excluded from multivariate analysis even if their data had a significant difference in univariate analysis. The results of univariate analyses for these characteristics are shown

in **Tale 1**. Onset in warm season, absence of atypical lymphocyte in peripheral blood, and blastic cell occupation to the entire area ≤70% in the histopathological studies were the factors which significantly protracted clinical course ($p<0.05$). Fever, general fatigue, and with steroid therapy had a tendency to protract clinical course ($p<0.1$). Although it was reference data, sIL-2R ≤1000 U/ml was also a negative prognostic factor ($p=0.0050$). Multivariate analyses to evaluate the simultaneous effects of variables which affect the period from the onset of KFD to cure of the disease (**Table 2**) showed absence of atypical lymphocyte in peripheral blood and blastic cell occupation to the entire area ≤70% in histopathological studies were independent factors which associated with protraction of the disease. There were no statistical significant factors which may cause recurrence of KFD (data not shown).

Discussion

The duration of KFD is generally reported as 1 to 4 months [**1**]. In the present study, the period from the onset to the cure of the disease was 1-37 months (mean, 6 months, median, 9.4 months). We speculated that in other studies many patients' follow-up might be suspended with improvement of their complaints, not with complete improvement of lymphadenopathy. Otherwise, the present study may suffer from selection bias because we enrolled biopsy-confirmed patients, and we tend not to perform surgical open biopsy in patients with mild symptoms or quick recovery.

There were no significant clinical characteristics which may affect the duration of KFD. Since an infectious etiology has been postulated, we had nominated the onset-season as a candidate of prognostic factors, and onset in warm season was one of the factors which significantly protracted clinical course by univariate analysis. However, viral infection is usually more common in winter than summer [**3**] and onset in warm season did not remain significant by multivariate analysis. On the other hand, absence of atypical lymphocytes in peripheral blood and small number of blastic cells in the lymph node specimens (≤70%) were statistically significant factors which may protract the duration of this disease. Although also the steroid therapy showed a tendency to protract the duration of KFD, it might affect the selection bias because we

tend to undergo steroid therapy for the patients with serious conditions. Most proliferating cells in KFD are CD8-positive T cells and most apoptotic cells are also CD8-positive cytotoxic T cells [**4**]. In other words, CD8-positive cytotoxic T cells transforming to blastic cells undergo both apoptosis and proliferation simultaneously in KFD [**5**]. The apoptosis of CD8-positive cells (=blastic cells) are induced by Fas and perforin pathways, and the activated CD8-positive T-cell proliferating/dying functional balance might be beneficial to eradicate the responsible agent [**6**]. Leukopenia with low CD4+/CD8+ cell ratio usually appears in the early stages of KFD. It may be mainly due to the apoptosis of CD4-positive smaller cells which may also be induced by blastic transformed CD8-positive cells [**7**]. These activated CD8-positive T cells may transude to peripheral blood and be recognized as atypical lymphocytes. In the present study, elevation of serum level of sIL-2R was a positive prognostic factor which may shorten the duration of KFD, and it might also reflect the activation of CD8-poisitive T cells [**8**], although the data of sIL-2R was not perfect. Thus the patients with atypical lymphocytes in the peripheral blood, large number of blastic cells in the lymph nodes, and perhaps elevation of serum level of sIL-2R, may recover from KFD earlier. Of course open surgical biopsy is desirable to confirm the amount of blastic cells in the lymph nodes, but cutting needle biopsy can be alternative method if the manipulation is

well done [**9, 10**]. Detection of atypical lymphocytes in the peripheral blood may be the most convenient method to predict the duration of KFD. The cell composition varies from case to case and with time: there is a tendency that necrosis and degenerated predominant type is observed a little later than immunoblastic predominant type [**7**]. However, many cases are mixed type and the amount of coagulative necrosis was not associated with the disease duration in the present study.

Some KFD cases are histological mimickers of SLE. Both clinically and histologically KFD and SLE exhibit a remarkable resemblance although no clearly identified relation has been found between KFD and SLE [**1**, **11**]. Even by pathological examination only the presence of hematoxylin bodies and paucity of neutrophils provide a strong support for discrimination of KFD from SLE [**12**]. Among the 43 KFD patients in the present study, 1 patient who had generalized lymphadenopathy was diagnosed with concurrent SLE. In a large study, the frequency of suspected SLE among KFD patients was 5 of 108 [**13**], and in another analysis, 32 of 244 KFD patients had SLE [**8**]. Generalized lymphadenopathy has been reported in 1% to 22% of KFD cases and is much less frequent now than in the past [**14**]. KFD should be followed up long-term considering the possible development of SLE [**11**].

Conclusion

In KFD, the patients with atypical lymphocytes in the peripheral blood and large number of blastic cells in the lymph nodes may recover from KFD earlier. Detection of atypical lymphocytes in the peripheral blood is the most convenient method to predict the duration of KFD.

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Figure Legends

Table 1. Univariate analysis of outcome for the duration of the 43 KFD patients

Characteristics		Number of patients (%)	Treatment period (months)	p-value
Age	>30 years	18 (42)	10.9	
	≤30	25 (58)	8.4	0.42
Sex	male	14 (33)	8.4	
	female	29 (67)	9.9	0.58
Fever	(+)	27 (63)	11.2	
	(-)	16 (37)	6.5	0.080
Pain	(+)	24 (56)	10.3	
	(-)	19 (44)	8.3	0.48
General fatigue	(+)	12 (28)	14.3	
	(-)	31 (72)	7.5	0.10
Onset	(spring, summer)	25 (58)	11.7	
	(autumn, winter)	18 (42)	6.3	**0.046**
WBC	>4000 (/μl)	23 (53)	10.3	
	≤4000	20 (47)	8.4	0.49
Atypical lymphocyte	(+)	9 (21)	5.4	
	(-)	34 (79)	10.5	**0.043**
LDH	>230 (IU/L)	18 (42)	9.3	
	≤230	25 (58)	9.5	0.95
sIL-2R	>1000 (U/ml)	4*	4.3	
	≤1000	18*	10.4	0.0050*
CRP	>1 (mg/dl)	10 (23)	9.0	
	≤1	33 (77)	9.5	0.85
Smoker	Yes	14*	8.6	
	No	28*	9.1	0.58*
Drinker	Yes	9*	14.1	
	No	33*	7.6	0.090*
NSAID	(+)	38*	9.8	
	(-)	4*	5.3	0.15*
Antibiotic	(+)	31 (72)	9.3	

	(-)	12 (28)	9.9	0.86
Steroid	(+)	12 (28)	14.1	
	(-)	31 (72)	7.6	0.087
Area of blast cell proliferation in the lymph nodes	>70%	10 (23)	5.6	
	≤70%	33 (77)	10.6	**0.040**
Area of Coagulative necrosis in the lymph nodes	>50%	7 (16)	14.0	
	≤50%	36 (84)	8.5	0.31

KFD, Kikuchi-Fujimoto disease; WBC, white blood cell; LDH, lactate dehydrogenase; sIL-2r, soluble interleukin-2 receptor; CRP, c-reactive protein; NSAID, nonsteroidal anti-inflammatory drug.

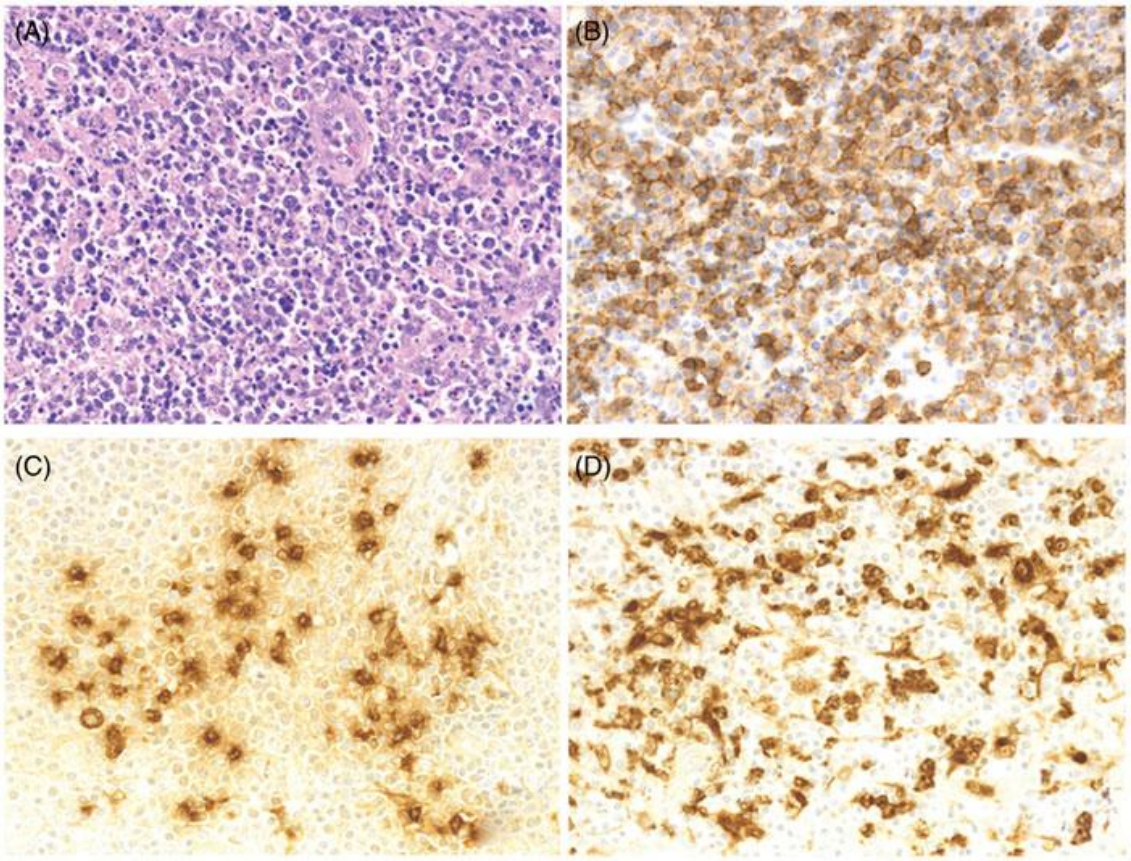
*The data were not perfect with some defect.

Table 2. Multivariate analysis of outcome for the duration of the 43 KFD patients

Prognostic factors	Standard regression coefficient	Standard error	95% confidence interval	P value
Fever (+)	0.099	3.40	-4.28-8.09	0.54
General fatigue (+)	0.18	3.96	-3.16-10.62	0.28
Onset (spring, summer)	0.22	2.48	-0.91-9.16	0.11
Atypical lymphocytes in peripheral blood (-)	0.32	3.14	0.91-13.65	**0.026**
Steroid (+)	0.29	3.56	-1.27-13.16	0.10
Area of Blastic cell proliferation in the lymph nodes ≤ 70%	0.39	3.19	2.13-15.09	**0.011**

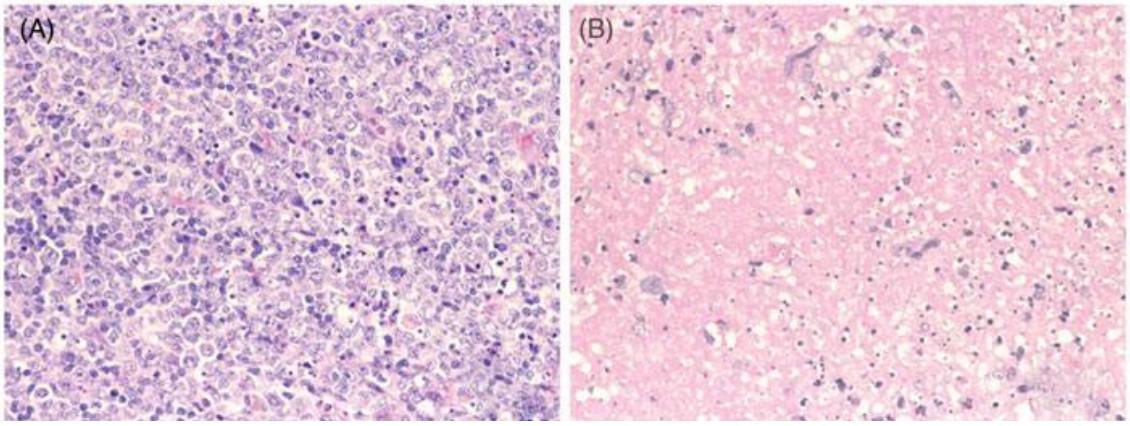
KFD, Kikuchi-Fujimoto disease.

Figure 1.



(**a**) Large number of histiocytes existed at the margin of the necrotic area, and many of them were crescentic (Hematoxylin and Eosin stain ×40). Immunohistochemical studies showed (**b**) there was a predominance of CD8-positive large lymphoid cells with blastic features, (**c**) myeloperoxidase was detected among (**d**) lysozyme-positive histiocytes. (×40)

Figure 2.



Representative pictures of high power view of Kikuchi-Fujimoto disease (Hematoxylin and Eosin stain ×40). (**a**) The case with occupation of blastic cells in the lymph node more than 70%. (**b**) The case with occupation of coagulative necrosis in the lymph node more than 50%.