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【 CASE REPORT 】

Recurrent Aseptic Meningitis Associated with Kikuchi's Disease (Histiocytic Necrotizing Lymphadenitis): A Case Report and Literature Review

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Abstract:

We herein report a 31-year-old man with recurrent aseptic meningitis associated with Kikuchi's disease. Although aseptic meningitis is the most common neurological complication of Kikuchi's disease, its characteristics remain unclear, especially in recurrent cases. A literature review revealed that aseptic meningitis associated with Kikuchi's disease was more likely to occur in men and was associated with a low cerebrospinal fluid (CSF)/serum glucose ratio. Lymphadenopathy tended to occur simultaneously or after the onset of meningitis. When encountering a patient with aseptic meningitis of unknown etiology, it may be worthwhile to focus on the CSF/serum glucose ratio and lymphadenopathy with a careful examination.

Key words: Kikuchi's disease, histiocytic necrotizing lymphadenitis, aseptic meningitis, recurrence, cerebrospinal fluid, lymphadenopathy

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Introduction

Kikuchi's disease, also known as subacute histiocytic necrotizing lymphadenitis, is a lymphadenitis of unknown cause that mainly affects young women. The main symptoms are a fever and lymphadenopathy accompanied by tenderness, and most cases resolve spontaneously. The recurrence rate has been reported to be 9-21% in recent years (1-4). Neurological complications, such as aseptic meningitis, cerebellar ataxia, and mononeuritis multiplex, occur in only 5% of all cases (5, 6). Aseptic meningitis is the most common neurological complication and is associated with 2.2-9.8% of cases of Kikuchi's disease (1, 2, 7). Although there are some case reports and a small number of case series regarding aseptic meningitis associated with Kikuchi's disease, there are few reports that summarize a large number of cases. In particular, only a few cases of recurrent aseptic meningitis associated with Kikuchi's disease have been reported because of its rarity; therefore, the clinical features of recurrent cases remain unclear.

We herein report a young man with recurrent aseptic meningitis associated with Kikuchi's disease. In addition, we reviewed the clinical features of 30 cases of aseptic meningitis associated with Kikuchi's disease previously reported in the literature in combination with our case. We also evaluated the characteristics of five cases of recurrent meningitis.

Case Report

A 31-year-old Japanese man who had been hospitalized for aseptic meningitis 5 months previously was admitted to our hospital because of a fever and headache that had lasted for three weeks. Three weeks prior, he noticed a fever ranging from 37 to 38℃ accompanied by a headache, and he was prescribed antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). His symptoms worsened despite taking medications, and his body temperature rose to 39℃. He visited the emergency department and was hospitalized with suspected meningitis recurrence. He had no known medical history except for aseptic meningitis accompanied by axillary and inguinal lymphadenopathy five months earlier. A cerebrospinal fluid (CSF) analysis revealed a 120/μL cell count (85% mononuclear cells and 15% poly-

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Table 1. Laboratory Data and CSF Analysis on Admission.

[Laboratory data]						[CSF analysis]	
White blood cells	3,200 /μL	Total protein	7.6	g/dL		Cell count	57 /μL
Band	6 %	Albumin	4.2	g/dL		Mononuclear	96 %
Segmented	62 %	Urea nitrogen	10	mg/dL		Polymorphonuclear	4 %
Lymphocyte	6 %	Creatinine	0.93	mg/dL		Protein	96 mg/dL
Monocyte	25 %	Na	136	mEq/L		Glucose	38 mg/dL
Atypical lymphocyte	1 %	K	4.3	mEq/L		CSF/serum glucose ratio	0.38
Hemoglobin	13.4 g/dL	Cl	101	mEq/L			
Platelet	192,000 /μL	FBS	99	mg/dL			
ESR	24 mm/h	AST	22	U/L			
C-reactive protein	1.77 mg/dL	ALT	15	U/L			
Antinuclear antibody	negative	LD	264	U/L			

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CSF: cerebrospinal fluid, ESR: erythrocyte sedimentation rate, FBS: fasting blood sugar, LD: lactate dehydrogenase

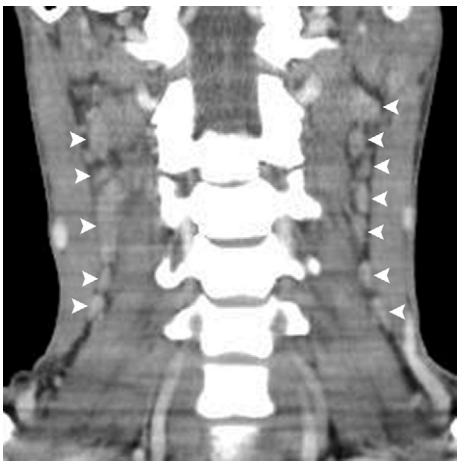

Figure 1. Contrast-enhanced computed tomography of the neck (coronal section) shows bilateral multiple cervical lymphadenopathies (white arrowheads).

morphonuclear cells), 140 mg/dL of protein, and 39 mg/dL of glucose (serum glucose: 90 mg/dL), although the meningeal signs were unremarkable. He was prescribed NSAIDs, and his signs and symptoms resolved within a week.

On a physical examination, he was alert and oriented. His blood pressure was 128/60 mmHg, pulse rate was 72 per minute, respiratory rate was 20 per minute, and body temperature was 38.5℃. The neurological findings, including meningeal signs, were unremarkable. Multiple bilateral cervical lymph nodes were enlarged with tenderness. A CSF analysis revealed pleocytosis with 96% mononuclear cells, elevated protein, and low CSF/serum glucose ratio (Table 1). CSF cultures for bacteria, mycobacteria, and fungus were negative. Polymerase chain reaction results for *Mycobacterium tuberculosis*, herpes simplex virus type 1/2, human herpesvirus type 6, Epstein-Barr virus, cytomegalovirus, and varicella-zoster virus were all negative. There were no detectable Mollaret cells in the CSF. Contrast-enhanced computed tomography showed multiple bilateral cervical lymphadenopathies (Fig. 1) and splenomegaly.

The presence of a subacute fever and painful lymphadenopathy in a young adult with leukopenia and aseptic meningitis suggested Kikuchi's disease. A cervical lymph node biopsy was performed, and a pathological examination revealed multiple histiocytic infiltrates and nuclear debris (Fig. 2); therefore, he was diagnosed with aseptic meningitis associated with Kikuchi's disease. NSAID therapy was selected as the initial treatment because the patient's general condition was stable and the clinical course was not long-term. He was treated with naproxen, and his symptoms subsided (Fig. 3). He was discharged on the ninth hospital day without any sequelae.

Discussion

We encountered a case of recurrent aseptic meningitis after an interval of five months from the initial episode and finally diagnosed the patient with Kikuchi's disease based on the pathological findings of the cervical lymph node. The major causes of recurrent aseptic meningitis are infections, drugs, tumors, and autoimmune diseases (8). Recurrent meningitis caused by herpes simplex virus type 2 is known as Mollaret meningitis. Mollaret meningitis was initially suspected based on the recurrence of aseptic meningitis, but the CSF findings were not consistent with this condition.

In September 2020, we searched MEDLINE, Web of Science, and Google Scholar for previous literature on aseptic meningitis associated with Kikuchi's disease using the terms "Kikuchi's disease," "Kikuchi disease," "Kikuchi-Fujimoto disease," "Kikuchi-Fujimoto's disease" or "necrotizing lymphadenitis," and "meningitis." We found 30 cases reported in 23 English- or Japanese-language articles that were available in full text (7, 9-30) (Table 2). Only four of these cases were found to have recurred after the complete resolution of aseptic meningitis. In this review, we identified three characteristics of aseptic meningitis associated with Kikuchi's disease: it may be more common in men than in women, the CSF/serum glucose ratio tends to be low, and lymphadeno-

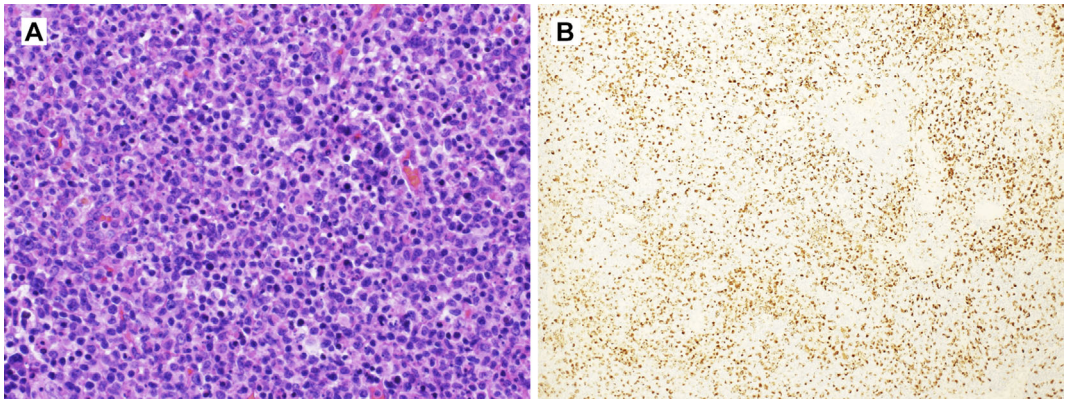

Figure 2. **A: Histopathology of the cervical lymph node reveals a histiocytic infiltrate and nuclear debris. There are no neutrophils in the lesion (Hematoxylin and Eosin staining, ×40). B: Immunohistochemistry of CD68, a histiocyte marker, is diffusely positive (×10).**

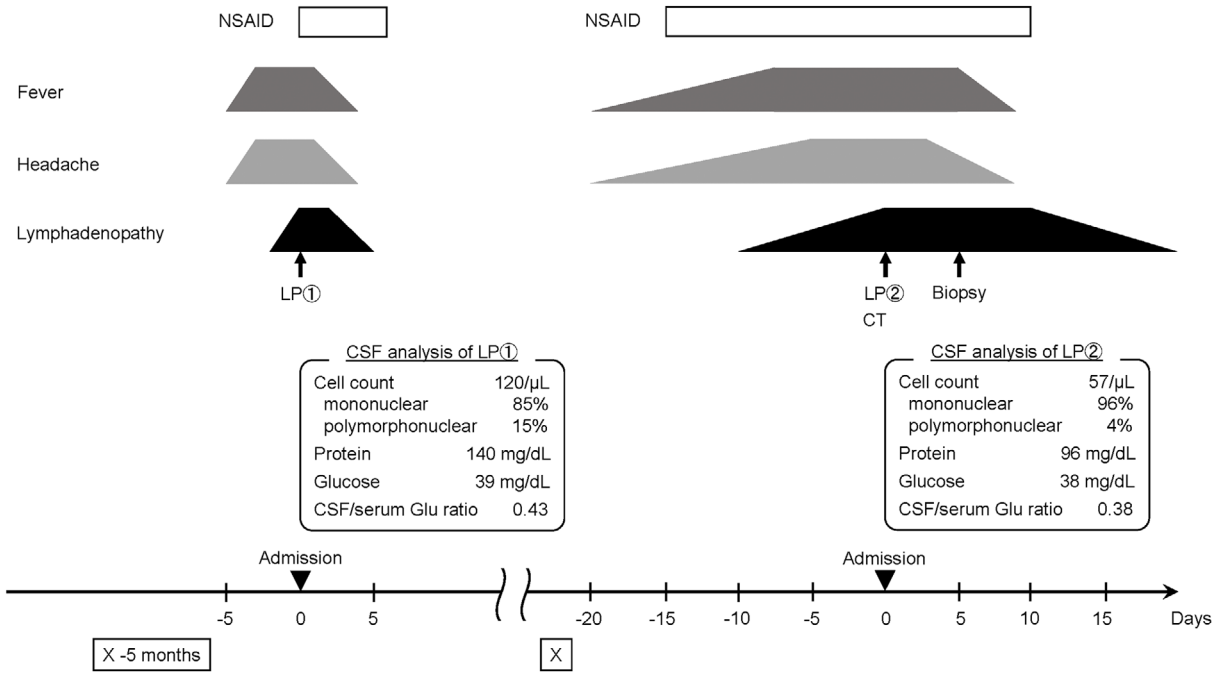

Figure 3. **Clinical course of the patient. CSF: cerebrospinal fluid, CT: computed tomography, Glu: glucose, LP: lumbar puncture, NSAID: non-steroidal anti-inflammatory drug**

pathy occurs simultaneously or later than meningitis in the clinical course of aseptic meningitis.

Generally, Kikuchi's disease is more likely to occur in women (72-77%) than in men (2, 3, 31). In contrast, 19 of the 31 cases (61%) with meningitis were men in our review. In a study that reviewed 91 cases of Kikuchi's disease, male sex was one of the factors associated with severe Kikuchi's disease, defined by the presence of weight loss, neurological complications, or hemophagocytic lymphohistiocytosis (2). The results of our review support this report. Men with Kikuchi's disease may be more likely to be severely affected by neurological complications, such as aseptic meningitis, than women. Kikuchi's disease has been reported to be associated with autoimmune diseases, particularly systemic lupus erythematosus (SLE) (32, 33). The complication rate of SLE has been reported in 13-25% of patients with Kikuchi's disease (2, 5). However, in our review, only one case of SLE was confirmed (12). Considering that the prevalence of SLE is dominant among women, Kikuchi's disease with aseptic meningitis and Kikuchi's disease with SLE might be different entities.

Both the CSF glucose level and CSF/serum glucose ratio were reduced in our case. In general, the CSF/serum glucose ratio is not reduced in viral aseptic meningitis; the median CSF/serum glucose ratio in 231 cases of viral meningitis was reported to be 0.56 (34). In our review, the median CSF/serum glucose ratio was 0.48 (n=15), which tended to be lower than that of viral meningitis. The CSF cell count and protein concentration varied widely among cases, and no consistent trend was found. It may be useful to focus on

Table 2. Literature Review of Cases of Aspetic Meningitis Associated with Kikuchi's Disease.

Case No. (Reference No.)	Age/ Sex	Symptoms and signs				Laboratory data			CSF findings				Treatment	
		AMS	Fever	Head-ache	Menin-gial sign	WBC (/μL)	CRP (mg/dL)	ESR (mm/h)	Cell count (/μL)	Glucose (mg/dL)	CSF/ serum glucose ratio	Protein (mg/dL)	NSAID	Corti-coste-roids
Recurrent cases														
1 (present case)	31/M	-	+	+	-	3,200	1.8	24	57	38	0.38	96	+	-
2 (9)	29/M	-	+	+	-	3,760	1.3	NA	37	34	NA	51	-	+
3 (10)	35/F	-	+	+	+	3,200	3.1	11	59	80	0.9	148	+	+
4 (11)	28/M	-	+	+	+	2,700	6.5	59	16	NA	0.75	28	+	-
5 (12)	29/F	-	+	+	-	3,190	15.1	44	295	63	NA	56	-	+
No recurrence														
6 (7)	25/M	-	+	+	-	4,700	(3+)	36	61	46	0.48	54	-	-
7 (7)	38/F	-	+	+	-	4,000	(+)	74	89	39	0.43	42	-	-
8 (7)	28/M	+	+	+	+	5,900	(-)	12	395	89	NA	227	-	+
9 (7)	23/M	-	+	+	+	4,000	(-)	7	108	48	0.51	75	+	+
10 (7)	21/M	-	+	+	-	4,300	(-)	24	179	65	0.60	200	-	-
11 (7)	13/M	-	+	+	+	7,600	2.1	17	1,685	47	NA	198	NA	NA
12 (7)	8/F	-	+	+	+	2,800	2.5	26	49	46	0.32	26	-	+
13 (13)	14/F	+	+	+	+	3,400	NA	NA	680	37	NA	73	-	+
14 (14)	46/M	+	+	+	-	2,600	6.0	76	135	44	NA	268	-	-
15 (15)	12/F	-	+	+	+	5,800	NA	105	100	55	NA	24	-	+
16 (7)	27/M	-	+	+	-	3,600	9.8	46	78	46	0.41	58	-	-
17 (16)	14/M	+	+	+	-	2,700	163	39	32	68	NA	48	+	+
18 (17)	37/F	-	+	+	+	2,800	11	94	75	NA	0.47	183	-	+
19 (18)	23/M	-	+	+	-	4,580	NA	37	283	44	0.56	86	-	-
20 (19)	34/M	+	+	+	-	3,800	90	54	380	74	NA	238	-	-
21 (20)	11/F	-	+	+	-	3,700	9.0	36	30	42	NA	90	-	+
22 (21)	28/M	-	-	+	+	4,300	3.5	36	318	60	0.4	285	-	+
23 (22)	32/M	-	-	+	-	3,700	NA	65	14	82	NA	63	-	+
24 (23)	30/M	-	+	+	-	NA	NA	NA	37	NA	NA	NA	-	+
25 (24)	19/F	-	+	+	-	6,060	NA	NA	8	NA	NA	NA	-	-
26 (25)	20/F	+	+	NA	+	14,100	NA	NA	NA	69	NA	299	NA	+
27 (26)	6/M	-	+	+	-	NA	NA	NA	160	NA	NA	NA	-	+
28 (27)	30/F	-	+	+	+	15,600	2.8	135	28	72	0.46	58	-	+
29 (28)	57/F	-	+	+	-	NA	3.6	43	30	66	0.55	80	-	+
30 (29)	8/M	-	+	+	+	NA	4.4	NA	33	67	0.56	47	+	-
31 (30)	18/M	+	+	+	-	3,470	4.1	NA	454	NA	NA	400	-	+

* The maximum values were listed if laboratory tests and CSF analysis were performed more than once.

AMS: altered mental status, CRP: C-reactive protein, CSF: cerebrospinal fluid, ESR: erythrocyte sedimentation rate, NA: not assessed, NSAID: non-steroidal anti-inflammatory drug, WBC: white blood cells

a low CSF/serum glucose ratio as a differentiator between aseptic meningitis associated with Kikuchi's disease and viral meningitis. The association between NSAID administration and aseptic meningitis is well known, and hyperglycemia due to corticosteroids is also common. However, NSAIDs were administered prior to lumbar puncture in 3 of the 31 cases listed. In addition, only 1 of the 15 patients with available data on the CSF/serum glucose ratio received corticosteroids prior to lumbar puncture. Therefore, these medications were unlikely to have affected the results of the CSF analysis. Multiple factors are thought to be involved in the reduction in the CSF glucose levels, including the inhibition of glucose entry into the subarachnoid space due to structural changes in the blood-brain barrier, increased glucose transport rates in the arachnoid villi, increased glycolysis by leukocytes, and increased metabolic rates in the brain and spinal cord (35). The median number of CSF cells in our case review was 77/μL, and its median in viral meningitis was reported to be 188/μL (34). Therefore, the promotion of glycolysis by increased leukocytes is unlikely to be the cause of the decreased CSF/serum glucose ratio in cases of aseptic meningitis associated with Kikuchi's disease, and other factors may be instead involved.

Finally, we discuss five cases of recurrent aseptic meningitis. Unfortunately, we were unable to detect any marked differences in clinical features, including CSF findings, be-

tween the recurrent and nonrecurrent cases. All of the cases were clinically diagnosed as Kikuchi's disease due to lymphadenopathy that occurred simultaneously with meningitis or occurred two to four weeks later, and all of the cases except one were confirmed histopathologically with a lymph node biopsy. Therefore, for patients with aseptic meningitis of unknown etiology, a careful examination for lymphadenopathy while considering Kikuchi's disease as a differential diagnosis may be helpful.

This review has several limitations. First, aseptic meningitis associated with mild Kikuchi's disease may recover spontaneously before a detailed examination can be conducted. In addition, undiagnosed cases of aseptic meningitis associated with Kikuchi's disease may exist, owing to the lack of a CSF analysis. In our review, 19 (63%) of the 30 patients received corticosteroids. This may suggest that the previously reported cases were relatively severe. The presence of publication bias needs to be considered in case reviews. Second, data on the CSF/serum glucose ratio were available in 15 of 31 cases, indicating that this information was unavailable in approximately half of the cases. Therefore, the aggregation of a large number of cases with no missing data will help determine the true clinical features of aseptic meningitis associated with Kikuchi's disease.

In conclusion, aseptic meningitis associated with Kikuchi's disease tended to occur more often in men than in women and was associated with a low CSF/serum glucose ratio according to previous reports. Follow-up is important, as meningitis can recur.

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

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