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°C 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°C. 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-
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 lymphadenopathy.

**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 |
| Band 6 % | Mononuclear cell count 57 /μL |
| Segmented 62 % | Urea nitrogen 10 mg/dL |
| Lymphocyte 6 % | Creatinine 0.93 mg/dL |
| Monocyte 25 % | Mononuclear protein 96 mg/dL |
| Atypical lymphocyte 1 % | Na 136 mEq/L |
| Hemoglobin 13.4 g/dL | Glucose 38 mg/dL |
| Platelet 192,000 /μL | K 4.3 mEq/L |
| 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
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

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**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: Immunohistchemistry of CD68, a histocyte 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.
Table 2. Literature Review of Cases of Aseptic Meningitis Associated with Kikuchi’s Disease.

| Case No. (Reference No.) | Year | Age/ Sex | Symptoms and signs | Laboratory data | CSF findings | Treatment |
|--------------------------|------|---------|-------------------|-----------------|-------------|-----------|
|                          |      |         |                   |                 |             |           |
|                          |      |         |                   |                 |             | **NSAID** |
| **Recurrent cases**      |      |         |                   |                 |             |           |
| 1 (present case)         | 2020 | 31/M    | - + + -           | 3,200 (1.8) 24  | 57 38 0.38 96 | + -       |
| 2 (9)                    | 2008 | 29/M    | - + -             | 3,760 (1.3) NA  | 37 34 NA 51 | - +       |
| 3 (10)                   | 2010 | 35/F    | - + + +           | 3,200 (3.1) 11 | 59 80 0.9 148 | + +       |
| 4 (11)                   | 2012 | 28/M    | - + +             | 2,700 (6.5) 59 | 16 NA 0.75 28 | + -       |
| 5 (12)                   | 2020 | 29/F    | - + + -           | 3,190 (15.1) 44| 295 63 NA 56 | - +       |
| **No recurrence**        |      |         |                   |                 |             |           |
| 6 (7)                    | 1979 | 25/M    | - + + -           | 4,700 (3+) 36  | 61 46 0.48 54 | - -       |
| 7 (7)                    | 1979 | 38/F    | - + + -           | 4,000 (+) 74   | 89 39 0.43 42 | - -       |
| 8 (7)                    | 1983 | 28/M    | + + + +           | 5,900 (-) 12   | 395 89 NA 227 | - +       |
| 9 (7)                    | 1986 | 23/M    | - + + +           | 4,000 (-) 7    | 108 48 0.51 75 | + +       |
| 10 (7)                   | 1987 | 21/M    | - + + -           | 4,300 (-) 24   | 179 65 0.60 200 | - -       |
| 11 (7)                   | 1989 | 13/M    | - + + +           | 7,600 (2.1) 17 | 1,685 (7) NA 198 | NA NA |
| 12 (7)                   | 1990 | 8/F     | + + + +           | 2,800 (2.5) 26 | 49 46 0.32 26 | - +       |
| 13 (13)                  | 1996 | 14/F    | + + + +           | 3,400 NA NA    | 680 37 NA 73 | - +       |
| 14 (14)                  | 1996 | 46/M    | + + + +           | 2,600 (6.0) 76 | 135 44 NA 268 | - -       |
| 15 (15)                  | 1998 | 12/F    | - + + +           | 5,800 NA 105   | 100 55 NA 24 | - +       |
| 16 (7)                   | 1999 | 27/M    | - + + -           | 3,600 (9.8) 46 | 78 46 0.41 58 | - -       |
| 17 (16)                  | 1999 | 14/M    | + + + +           | 2,700 (163) 39 | 32 68 NA 48 | + +       |
| 18 (17)                  | 2005 | 37/F    | - + + +           | 2,800 11 94    | 75 NA 0.47 183 | - +       |
| 19 (18)                  | 2005 | 23/M    | - + + +           | 4,580 NA 37    | 283 44 0.56 86 | - -       |
| 20 (19)                  | 2007 | 34/M    | + + + +           | 3,800 90 54    | 380 74 NA 238 | - -       |
| 21 (20)                  | 2011 | 11/F    | + + + +           | 3,700 9.0 36   | 30 42 NA 90 | + +       |
| 22 (21)                  | 2013 | 28/M    | - - + +           | 4,300 (3.5) 36 | 318 60 0.4 285 | - +       |
| 23 (22)                  | 2014 | 32/M    | - - + +           | 3,700 NA 65    | 14 82 NA 63 | - -       |
| 24 (23)                  | 2015 | 30/M    | - + + -           | NA NA NA 37    | NA NA NA NA | - +       |
| 25 (24)                  | 2017 | 19/F    | - + + -           | 6,060 NA NA 8 | NA NA NA NA | - -       |
| 26 (25)                  | 2018 | 20/F    | + + NA + 14,100   | 160 NA NA NA   | + +       |
| 27 (26)                  | 2018 | 6/M     | - + + -           | NA NA NA 160   | - -       |
| 28 (27)                  | 2018 | 30/F    | - + + +           | 15,600 (2.8) 135 | 28 72 0.46 58 | - +       |
| 29 (28)                  | 2019 | 57/F    | - + + -           | NA 3.6 43      | 30 66 0.55 80 | - +       |
| 30 (29)                  | 2019 | 8/M     | - + + -           | NA 4.4 NA 33   | 67 56 0.56 47 | + +       |
| 31 (30)                  | 2020 | 18/M    | + + + +           | 3,470 (4.1) NA | 454 58 NA 400 | + -       |

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

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

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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