Author's response to reviews

Title: Recurrent aseptic meningitis revealing Kikuchi-Fujimoto disease: case report and literature review

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Author's response to reviews: see over
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Dear Dr. Majithia:

Thank you for considering our paper for publication as a case report in *BMC Neurology*. We have changed the title of our manuscript; "Recurrent aseptic meningitis revealing Kikuchi-Fujimoto disease: Case report and literature review" to "Recurrent aseptic meningitis in association with Kikuchi-Fujimoto disease: Case report and literature review". The manuscript has been revised according to the reviewers’ comments. On the revised manuscript, the changes have been highlighted with a yellow marker.

We appreciate the reviewers' important suggestions, and believe that the manuscript has been improved by the revisions made. We hope that it has been suitable for publication in *BMC Neurology*.

Yours sincerely,
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We thank the reviewers very much for useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have fully considered the comments and have made necessary revisions.

We have changed the title of our manuscript: "Recurrent aseptic meningitis revealing Kikuchi-Fujimoto disease: Case report and literature review" to "Recurrent aseptic meningitis in association with Kikuchi-Fujimoto disease: Case report and literature review".

**In Response to Reviewer #1's Comments:**

1. *The authors mention in several places that aseptic meningitis in KFL “has not yet received significant attention”. This phrase could imply that it is a common medical problem that has been somewhat neglected. The authors acknowledge that aseptic meningitis is an extremely rare condition after all. Therefore, please avoid the mentioned phrase.*

   We appreciate the reviewer's comments. We have rewritten the abstract as "Recurrent aseptic meningitis in association with KFD is extremely rare, and remains a diagnostic challenge" and the introduction as "Recurrent aseptic meningitis associated with KFD is an extremely rare condition".

2. *Please delete from Discussion the sentence “Four of the 5 patients were Japanese, which may reflect a higher frequency of diagnosed KFD in Japan”. It is redundant in the face of the presented table.*

   We have deleted the sentence.

3. *Please delete from Conclusions the sentence “A controlled long-term study to investigate the efficacy of immune-moderating therapies in recurrent KFD-associated meningitis is needed”. Aseptic meningitis in KFL, as mentioned by the authors, is extremely rare. Although very interesting, I am not sure how resource-efficient a controlled long-term study on this subject would be.*

   We have deleted the sentence and rewritten the conclusion as following: Recurrent aseptic meningitis with KFD is extremely rare condition. However, awareness of KFD as the differential diagnosis for meningitis might assist with diagnosis of patients presenting with lymphadenopathy. Early excisional lymph node biopsy should be considered to avoid unnecessary treatments. Temporary corticosteroid treatment may be beneficial to patients that present with recurrent meningitis with KFD, although this treatment’s long-term efficacy remains uncertain. Because of the association with SLE, patient follow-up visit is necessary upon subsequent development of symptoms.
4. English needs to be heavily edited.

The revised version of our paper was edited by an English proofreading office.

5. Figure 1 is too large. Please change it to a smaller and more compact figure.

Dr. Kokubun joined us and rearranged the figures more refined.

6. Was atopy a feature of the previously reported cases of KFL/aseptic meningitis? Could this be a syndromic presentation (KFL+atopy+aseptic meningitis)?

We have discussed about atopic dermatitis and KFL/aseptic meningitis both in our patient and literature, and added the discussion section as following: Our patient had concurrent atopic dermatitis, and his serum IgE levels were elevated along with exacerbation from meningitis and lymphadenitis. Because IgE was not elevated in the CSF, his high serum IgE titre did not appear to play a pathogenic role in aseptic meningitis. A prior case with an elevation of serum IgE in recurrent aseptic meningitis with KFD has been reported [9]. In this study, we speculate that IgE elevation may be reflected the immunostimulatory condition that was activated upon KFD in a patient with atopic dermatitis. A striking histopathological feature of KFD is the clustering of the plasmacytoid dendritic cells at the margins of the necrotic foci of affected lymph node [1]. Plasmacytoid dendritic cells are known to produce type I interferon in response to viral infection and to induce human memory B cells to differentiate into plasma cells and produce immunoglobulin [15]. Type I interferon is known as a potential pathogenic agent in the SLE-related neurological involvement [16]. Moreover, the high titre of antinuclear antibodies had also been observed in another case [10]. The progression of recurrent aseptic meningitis with KFD may stem from pathogenic association with SLE or other autoimmune disorders. Further studies are necessary to clarify this hypothesis.

7. Please speculate on how KFL could be associated with aseptic meningitis? One causing the other or a third factor causing both? Any literature on this?

To date, there is no literature which discuss about mechanism of progressing meningitis in KFD. We have speculate the immunostimulatory condition that activated by KFD might trigger the meningitis in KFD. We have discussed as the the answer to comment #6.
8. Why did the patient stay in the hospital for 26 days? It sounds too long to me.

He stayed in the hospital for 14 days at the first admission and 12 days at the second admission. We have emphasized his admission day (day 12) on the second paragraph of the history.

9. KFL frequently presents with a rash. Do the authors think the rash in their case was the "rash of KFL" or a pure coincidence?

Various skin manifestations, such as rubella-like, drug eruption-like rashes, facial erythema, generalized erythema and purpures and so on, were reported possible as KFL skin lesion. (Yen HR., et al. Skin manifestations of Kikuchi-Fujimoto disease: case report and review. Eur J Pediatr 2004, 163:210-213.) So, we think the rash was the skin involvement of KFL. The clinical course of the rash that resolved spontaneously in parallel with the other signs and symptoms in KFL also support the speculation. To establish the diagnosis, skin biopsy of the rash is preferable in this case.

10. Was the specimen stained for CD68 too? Could you show the stains for MPO and CD68 (if performed) too?

We have done the stain of CD68 of the specimen and inserted the image and sentence as follows: Immunohistochemical study demonstrated that the histiocytes expressed CD68 and myeloperoxidase (Figure 2D, E).

11. Did the histiocytes have crescentic nuclei?

Yes, they did. We have also added "A portion of the phagocytic macrophage had crescent nuclei" in the pathological findings.

12. Please use thinner arrows in Figure 2. Could you show a x100 slide for panels B and C instead of x40?

According to the reviewer’s suggestion, we have rearranged Figure 2.

In Response to Reviewer #2's Comments:
1. The discussion section must be rearranged and ordered according the different issues: epidemiology, brief synthesis of the present report and published report, and current standard of differential diagnosis and treatment care.
We appreciated the reviewer's major suggestion. We had totally rewritten the background and discussion sections as following:

**Background**

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotising lymphadenitis, is recognised as a benign lymphadenopathy that has acute or sub-acute onset and is primarily localised within the cervical lymph nodes. KFD has various extranodal manifestations, including skin lesions, gastrointestinal symptoms or splenomegaly [1]. Neurological complications, including aseptic meningitis, mononeuritis multiplex or acute cerebellar ataxia, are not common [2], and a meta-analysis of 244 KFD cases in 181 published case reports demonstrated 11% of incidence of neurological involvements [3]. The most common neurological complication is aseptic meningitis, which is observed in 2.8-9.8% of KFD cases [4,5]. KFD usually resolves spontaneously within a few months, and the recurrence rate is 3-4% [6].

**Discussion**

Recurrent aseptic meningitis associated with KFD is an extremely rare condition, and only 4 sporadic cases have been reported [7-10]. In this study, we describe a KFD patient who presented with 7 episodes of recurrent meningitis. We also investigate the clinical and laboratory features of 4 patients previously reported in the literature. Since KFD was first described by both a pathologist and physician independently in 1972 [11,12], the aetiology of KFD remains largely unknown. The histopathological features of affected lymph nodes in KFD are, on occasion, notably similar to those of SLE [13]. Therefore, pathogenic linkage between the two disorders has been proposed [1,13]. Infectious agents, including toxoplasmosis, EBV, and HHV-6, have also been considered as possible causal agents, but several studies have failed to confirm their association [13,14]. There is no specific treatment for KFD because of its unknown aetiology. In general, the patients are treated symptomatically; for example, relief of local and systemic complaints with the use of analgesics, antipyretics and rest [13]. Furthermore, corticosteroids may be effective in severe cases or for a relapsing condition [1].

The aseptic meningitis associated with KFD was first reported in 1979 [14]. Today, 18 sporadic case reports have been documented in MEDLINE and Japan Medical Abstracts Society-website, with 4 of them reporting recurrence of meningitis [7-10]. The clinical profiles of our patient and the 4 patients reviewed in the literature are shown in Table 1. In all 5 cases the symptoms resolved within several months. Corticosteroids were administered in 3 out of the 5 patients. All of the 3 did not have early post-treatment relapse after receiving steroids. Steroid treatment may be beneficial for recurrent KFD with aseptic meningitis, although recommendation of steroid administration requires further investigation.

Our patient had concurrent atopic dermatitis, and his serum IgE levels were elevated along with exacerbation from meningitis and lymphadenitis. Because IgE was
not elevated in the CSF, his high serum IgE titre did not appear to play a pathogenic role in aseptic meningitis. A prior case with an elevation of serum IgE in recurrent aseptic meningitis with KFD has been reported [9]. In this study, we speculate that IgE elevation may be reflected the immunostimulatory condition that was activated upon KFD in a patient with atopic dermatitis. A striking histopathological feature of KFD is the clustering of the plasmacytoid dendritic cells at the margins of the necrotic foci of affected lymph node [1]. Plasmacytoid dendritic cells are known to produce type I interferon in response to viral infection and to induce human memory B cells to differentiate into plasma cells and produce immunoglobulin [15]. Type I interferon is known as a potential pathogenic agent in the SLE-related neurological involvement [16]. Moreover, the high titre of antinuclear antibodies had also been observed in another case [10]. The progression of recurrent aseptic meningitis with KFD may stem from pathogenic association with SLE or other autoimmune disorders. Further studies are necessary to clarify this hypothesis.