



Case report

Kikuchi-Fujimoto disease complicated by aseptic meningitis and hemophagocytosis successfully treated with intrathecal dexamethasone

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) is thought to be a self-limited disease featuring fever and cervical lymphadenopathy; most cases having a favorable outcome. Severe disease and death are occasionally reported. Here we report a case of KFD complicated by hemophagocytosis and aseptic meningitis. The symptoms and laboratory parameters improved after systemic glucocorticoids, intravenous immunoglobulin and one dose of intrathecal dexamethasone. Clinicians should aware of this disease and make early diagnosis by lymph node biopsy to avoid over-treatment.

1. Introduction

Kikuchi-Fujimoto disease (KFD) was firstly described by Kikuchi [1] and Fujimoto [2] in 1972. It is characterized by cervical lymphadenopathy accompanied by moderate fever, usually affecting young adults but can occur in any age. It is self-limited and the clinical presentations usually subside in a few weeks or months. The pathogenesis is thought to be autoimmune reaction triggered by a variety of antigens in genetically susceptible people [3]. Many viruses and other microorganisms including bacteria, mycobacteria and parasites have been proposed to be the possible etiologic agents of KFD [4, 5, 6]. Yet the relationship of microorganisms and KFD is inconclusive.

The diagnosis relies on the lymph node biopsy, which is histologically featured by subcortical coagulative necrosis, paracortical expanded and infiltrated by histiocytes with characteristic crescent-shaped nuclei, and massive apoptosis with abundant nuclear debris but absence of

granulocytes. By immunohistochemistry, the histiocytes are positive for lysozyme, myeloperoxidase, CD68 and CD163. The lymphocytes in the lesions are mostly T cells with CD8+ predominant. Plasmacytoid dendritic cells are highlighted with CD123 and CD303 [7,8].

KFD can be accompanied by many conditions including rheumatic diseases, tuberculosis and lymphoma [9]. KFD was also occasionally reported to be complicated with either hemophagocytosis [10, 11] or aseptic meningitis [12, 13]. No standard treatment was recommended. Severe diseases may benefit from glucocorticoids and/or hydroxychloroquine, and intravenous immunoglobulin (IVIG) will also be applied in certain cases [14, 15].

2. Case presentation

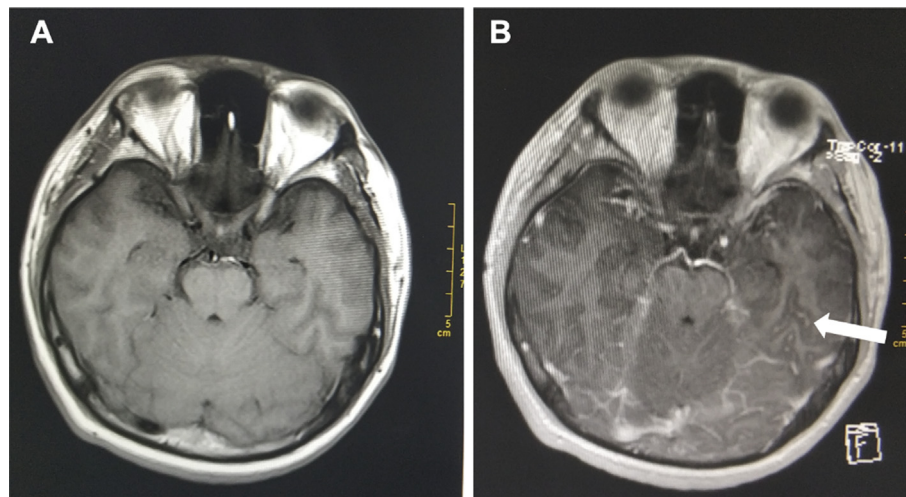
An 18-year old male presented with unremitting fever with peak temperature over 40 °C and simultaneous headache for 6 days. He is a

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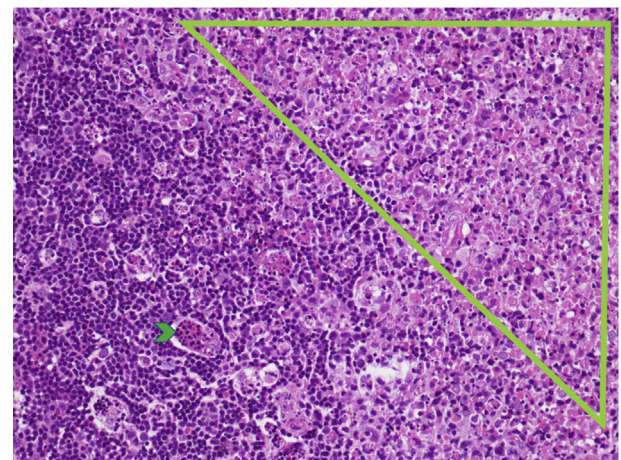
Table 1. Relevant laboratory tests results. WBC:white blood cells; Hb: hemoglobin; Neut: neutrophils; Lym:lymphocytes; ALT: alanine transaminase; AST: aspartate aminotransferase; CRP:C-reactive protein; TG:triglycerides; Fib:fibrinogen.

Items	11/25/2019	11/28/2019	12/1/2019	12/3/2019	12/5/2019
WBC(X10 ⁹ /L)	3.47↓	2.02↓	2.63↓	3.41↓	
Hb(g/L)	160	150	152	145	
PLT (X10 ⁹ /L)	232	203	174	197	
Neut#(X10 ⁹ /L)	2.19	1.35↓	1.72↓	1.99↓	
Lym#(X10 ⁹ /L)		0.6↓	0.69↓	1.11	
ALT (U/L)	26	32.8		146.1↑	162.6↑
AST (U/L)	19.5	46.3↑		156.2↑	108.3↑
CRP (mg/L)		40.75↑		21.43↑	43.15↑
Ferritin (ng/ml)		612.3↑		1410.4↑	
TG (mmol/L)					1.09
Fib (g/L)					2.81

**Figure 1.** Cranial MRI. A, T1 weighted image. B, Leptomeninges thickening and enhancement (white arrow) in contrast-enhanced T1 weighted image.

high school student in South China, and one of his classmates was known to have influenza A infection. On physical examination, he had cervical and inguinal lymphadenopathy with maximum diameter of 15mm. No meningeal irritation signs were detected. Relevant laboratory tests results are shown in Table 1. For microbiology, nasopharyngeal swab for influenza, parainfluenza, adenovirus and respiratory syncytial virus were negative. Blood screening for human immunodeficiency virus; hepatitis B, C, E; dengue virus; parvovirus B19; coxsackie virus; rubella; cytomegalovirus (CMV); Epstein-Barr virus (EBV); mycoplasma; Brucella; Cryptococcus; plasmodium was negative. Antinuclear antibodies were positive at 1:100 with speckled pattern. Extractable nuclear antibodies, anti-phospholipid antibodies, antineutrophil cytoplasmic antibodies were all negative. The bone marrow smear and tissue showed trilineage hematopoiesis; histocytes were readily identified, with hemophagocytosis. Both lungs were normal and the spleen was moderately enlarged radiologically.

The temperature did not respond to empirical treatment including oseltamivir, ceftriaxone and doxycycline. The patient was sent for cervical lymph node biopsy but he developed seizures and lost his consciousness suddenly just before the procedure. He was intubated and managed in intensive care unit, where the biopsy was finally done. Lumbar puncture was performed with an opening pressure of over 300 mm H₂O. The nucleated cells count in cerebrospinal fluid (CSF) was 454 (0–5) × 10⁶/L, with 75% mononuclear cells. The CSF protein level was 4001 (150–450) mg/L, while glucose and chlorides were within normal range. The cranial magnetic resonance images (MRI) showed leptomeninges thickened and enhancement (Figure 1). These features of

**Figure 2.** Histopathology of the cervical lymph node. Groups of apoptotic bodies were frequently seen (arrow head). Abundant pink cytoplasmic fragments and small blue dots of fragmented nuclei were shown in confluent necroptosis area (triangle). (hematoxylin and eosin, original magnification 200×).

central nervous system (CNS) involvement were worrisome for tuberculous meningitis, hence anti-tuberculosis therapy was initiated. Dexamethasone 12mg per day was given in dividing doses for hemophagocytosis.

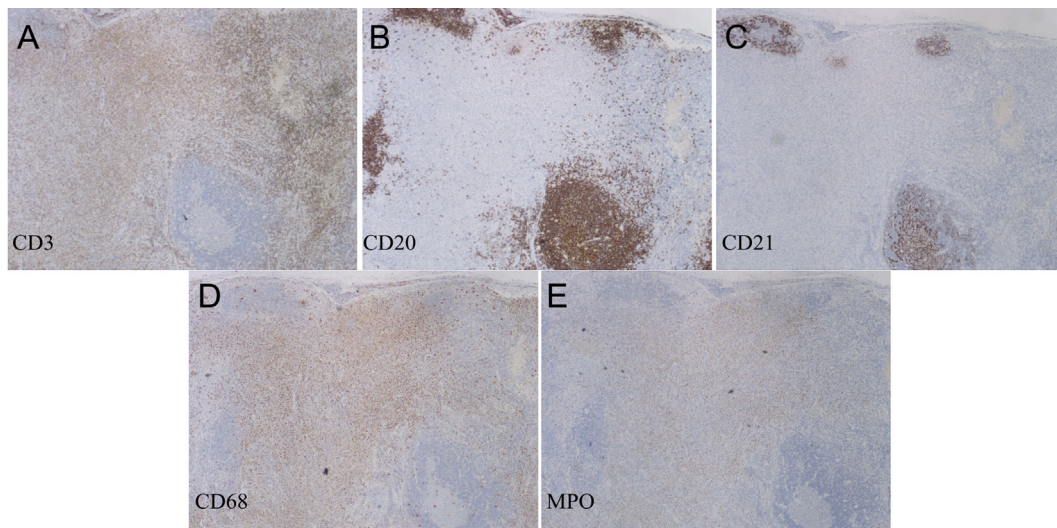


Figure 3. Immunohistochemistry of the cervical lymph node. A. Markedly expanded paracortex (CD3+ T cells). B. CD20 + B cells are limited to residual reactive follicles. C. The dendritic reticulum cell framework of the B-cell follicles is highlighted by the CD21 stain. D. Histiocyte marker CD68 is positive in the sheets of necrotic areas. E. Histiocytes are positive for myeloperoxidase, a feature of KFD. (original magnifications 40×).

The histopathology (Figure 2) and immunohistochemistry (Figure 3) of the lymph node were consistent with KFD. The preliminary microbiology screening for CSF turned out to be negative. Metagenomic next-generation sequencing (mNGS) was applied, only 2 sequences of udder nocardia and 4 sequences of cat flea rickettsia were detected, so it was interpreted as contamination.

Based on the comprehensive tests, the patient was diagnosed as KFD complicated by aseptic meningitis and hemophagocytosis. Methylprednisolone 48mg per day and IVIG (2 g/kg in total) were administered, together with hydroxychloroquine 200mg twice daily. The anti-infective agents were withdrawn. The patient's fever subsided and his consciousness returned. Lumbar puncture was repeated with the opening pressure of 215mmH₂O. 10mg dexamethasone was injected intrathecally in the meantime. The nucleated cells in CSF turned out to be $83 \times 10^6/L$, the protein was 498 mg/L, showing a significant improvement one week after the CNS episode. The CRP and ferritin level were also normalized. The patient was discharged and keeps follow up in the clinic with tapered methylprednisolone and hydroxychloroquine. The patient gave informed, written consent for all the diagnostic and therapeutic procedures, and for the publication of the case report.

3. Discussion

This young male adult presented with acute fever, lymphadenitis, splenomegaly and meningitis. With evidence of elevated liver enzymes, ferritin, and hemophagocytic phenomenon seen in bone marrow, the preliminary consider was hemophagocytic lymphohistiocytosis (HLH) [16]. However, the patient did not progress to severe hemocytopenia, hypertriglyceridemia or hypofibrinogenemia. Excluding infection and malignancies, the hemophagocytic phenomenon could potentially be due to rheumatic diseases, such as SLE, arthritis and adult onset Still disease. As arthralgia, typical skin rashes and specific autoantibodies were absent, the final diagnosis was KFD.

Previous literature summarized the CSF features of aseptic meningitis associated with KFD, including mononuclear pleocytosis, high protein level, normal glucose and chloride concentration [17], which were present in our case.

As the patient presented with both meningitis and hemophagocytosis, he was treated with intrathecal dexamethasone. To our knowledge, this therapy was not yet reported for KFD, but was part of the treatment regimen for HLH [16]. Consistent with published literatures, the patient's

CSF parameters improved within a short period. No further repeated CSF examination or intrathecal injection was planned.

4. Conclusion

Febrile aseptic meningitis presented in previously healthy young adults could be attributed to KFD. The CSF findings show very similar with tuberculous meningitis. Careful clinical examination and precise laboratory workup are important to guide personalized therapy so as to avoid over treatment and for better prognostication. Intrathecal therapy for these combined clinical features deserves further evaluation.

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Author contribution statement

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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