

Kikuchi-Fujimoto disease with aseptic meningitis

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= Abstract =

Kikuchi-Fujimoto disease was initially described as a self-limiting histiocytic necrotizing lymphadenitis in Japan in 1972, and is predominantly observed in women under the age of 30 year and in Asian populations. The pathogenesis is still poorly understood but is thought to include infections, and autoimmune and neoplastic diseases. The most common clinical manifestations are fever and painless cervical lymphadenitis. Diagnosis is based on the histopathological findings, characterized by focal necrosis in the paracortical region with abundant karyorrhexis, aggregates of atypical mononuclear cells around the zone of necrosis, absence of neutrophils and plasma cells, and usually intact lymph node capsule. There is no specific therapy for the condition, and aseptic meningitis can occur as one of the complications. Here, we report the case of a patient with Kikuchi-Fujimoto disease accompanied with aseptic meningitis, which may be confused as a case of tuberculous meningitis and lymphadenitis. (*Korean J Pediatr* 2009;52:622-626)

Key Words : Kikuchi-Fujimoto disease, Histiocytic necrotizing lymphadenitis, Aseptic meningitis

Introduction

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare, self-limiting disease that is most commonly seen in young adults of Asian heritage. It was first described by both Kikuchi¹⁾ and Fujimoto²⁾ in 1972 as a lymphadenitis with focal proliferation of reticular cells accompanied with numerous histiocyte and extensive nuclear debris. Since then, KFD has been increasingly reported in Japan and recently also in Europe, the United States and Asia³⁾. This rare, necrotizing form of cervical lymphadenitis preferentially affects young women under 30 years of age. The disease is occasionally reported in children. The pathogenesis is not well known yet but is thought to include a hyperimmune reaction or an autoimmune-mediated process in which apoptosis plays a major role⁴⁾. The most common clinical manifestations are low-grade fever, painless cervical lymphadenitis, malaise and fatigue. KFD has no specific

laboratory tests for the diagnosis, although elevated erythrocyte sedimentation rate, leukopenia and atypical lymphocytes are frequently observed in the peripheral blood. The diagnosis is based on histologic features in involved lymph node: focal necrosis in cortical and paracortical areas; karyorrhectic nuclear debris mixed with a polymorphous cell population including immunoblasts and histiocytoid cells, and the absence of granulocytic infiltrates⁵⁾. In a few cases, aseptic meningitis that suggested viral nature in KFD was reported occasionally in Korea^{6, 7)}. We describe the case of KFD with aseptic meningitis which was misdiagnosed with tuberculosis at first under 15 years of age.

Case Report

A previously healthy 13-year-old girl was admitted to the department of pediatrics in our hospital for the swellings of cervical lymph node developed 1 month ago and headache maintained for 2 weeks. She was anorexic with no weight loss and has suffered from severe headache especially during the night and her mother had noticed the swellings on the left side of her neck, which were painless and had gradually increased in size over the past 1 month. Her general practitioner initially treated her with antibiotics for a presumed upper respiratory tract infection, with no improvement in

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her symptoms and the nodes persisted. There was a history of tuberculosis in her mother that was diagnosed and treated for 9 months 3 years before the patient was born.

On physical examination, she had a body temperature of 38.1°C and multiple firm, movable and tender cervical lymph nodes of 2 to 1 cm in size in the posterior triangle of the neck. Signs of meningeal irritation were absent. There were no rashes or generalized lymphadenopathy. The examination of her other systems was normal.

On admission, the result of laboratory showed that the white blood cell (WBC) count was $4,150/\text{mm}^3$, the platelet count was $146 \times 10^3/\text{mm}^3$, and the C-reactive protein (CRP) level was 0.28 mg/dL. Other serum chemistry results all were normal. A lumbar puncture, performed on the 1st day of hospital, yielded clear cerebrospinal fluid (CSF) with an opening pressure of 18 cmH₂O, a glucose concentration of 56 mg/dL (simultaneously sampled blood glucose, 100 mg/dL), a protein concentration of 28 mg/dL and 65 white blood cells/mm³ (with 96% lymphocytes). Gram staining, latex agglutinin test for antigen of CSF samples and CSF culture for bacterial antigen were all negative. In order to rule out tuberculosis, Mantoux (PPD test), AFB test, *M. tuberculosis* by PCR hybridization in sputum, urine, CSF, and blood were performed and all negative.

Chest radiography showed no abnormality. Neck sonography showed multiple round or ovoid hypoechoic lymph nodes with suspicious marked hypoechoic area which is suggestive of focal necrosis at level V. The marked hypoechoic area suggested strong tuberculous lymphadenitis (Fig. 1).

On the basis of these radiologic results and with the given possibility of tuberculosis meningitis and lymphadenitis, Isoniazid, Rifampin, Pyrazinamide, and Streptomycin were started including ceftriaxone (100 mg/kg/day) until we got

the result of cultures in CSF, blood, urine, and sputum.

The patient's condition improved and her CSF findings were incompatible with a diagnosis of tuberculosis meningitis, leading to an additional lumbar puncture, 5 days later. CSF analysis revealed 50 white blood cells (with 93% lymphocytes), 26.1 mg/dL of protein, and 70 mg/dL of glucose. Antigens of CSF samples in Gram staining and latex agglutinin test were all not found. The CSF culture was negative. A third lumbar puncture was also performed on the 12th admission day to rule out tuberculosis meningitis. CSF analysis was 10 white blood cells (with 96% lymphocytes), 18.5 mg/dL of protein, and 55 mg/dL of glucose, respectively. The CSF culture and Herpes simplex virus PCR showed negative.

In order to rule out tuberculosis completely, AFB cultures to sputum, CSF, urine, and blood were performed in a total of 3 times and all negative. Fungus culture, stain and india ink to CSF were also performed in a total of 3 times and all negative. Cryptococcus antigen in blood and CSF was also not found. *M. tuberculosis* PCR–Hybridizations in sputum, urine, CSF, and blood were all negative 3 times. QuantiFe–Tb result was negative. Herpes simplex virus and Enterovirus in CSF were not isolated in CSF culture 3 times. EBV study was also done and revealed negative result as well.

We could get the diagnosis through the histopathology and cytology of the aspirated cervical lymphnode biopsy. It showed lymph node with small and large lymphocytes, immunoblasts, karyorrhexis and crescentic histiocytes, containing nuclear and cytoplasmic debris (Fig. 3). The findings were consistent with histiocytic necrotizing lymphadenitis, or KFD.

Consequently, tuberculosis meningitis and lymphadenitis

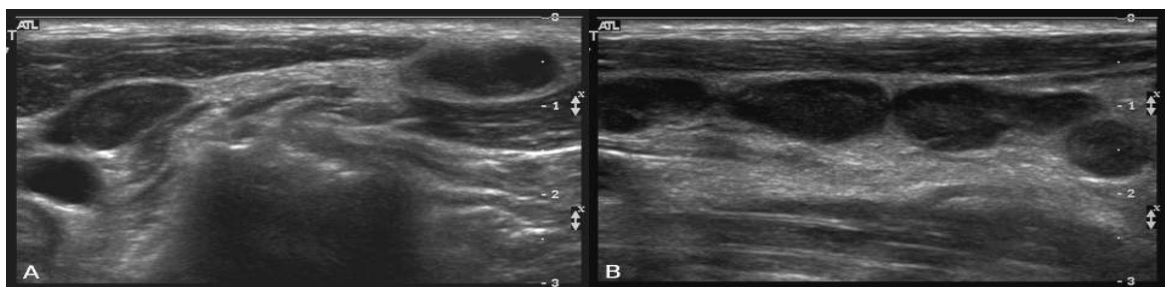


Fig. 1. Neck ultrasonography showed multiple round or ovoid hypoechoic lymph nodes with a suspicious marked hypoechoic area, suggestive of focal necrosis at level V.

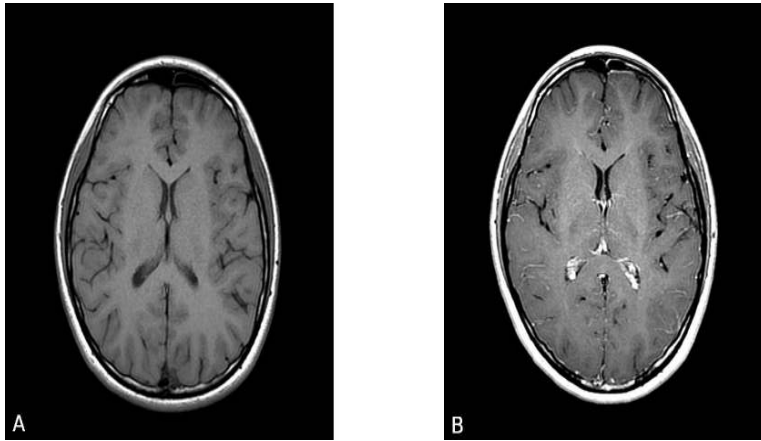


Fig. 2. Axial non-CE and CE T1W1 magnetic resonance images illustrate diffuse, mild leptomeningeal enhancement along the cerebral hemisphere and basal cistern.

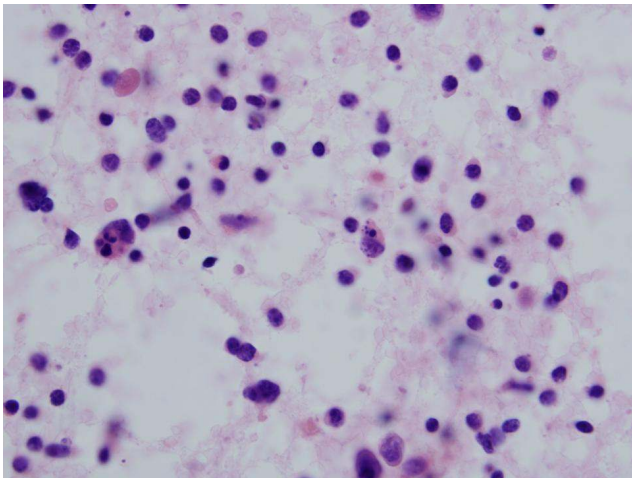


Fig. 3. Smear showing small and large lymphocytes, immunoblasts, karyorrhexis, and crescentic histiocytes containing nuclear and cytoplasmic debris (Papanicolaou stain, $\times 100$ magnification).

were excluded and the final diagnosis concluded KFD with aseptic meningitis according to the histopathologic and cytologic features in the cervical lymph node and CSF analysis.

On the 6th admission day, she suffered from stomatitis, uncontrollable high fever above 39°C and bullous, exanthematic eruptions on mouth, hands and feet. They were regarded as the adverse effects of tuberculosis medications. As tuberculosis medications were ceased, her fever, headache and skin lesion disappeared and she was discharged. Three weeks after discharge, her general condition was good, except excoriation of both hands and feet remained. The follow-up MRI showed remarkable improvement of leptomeningitis.

Discussion

A viral or autoimmune cause has been suggested about the etiology of KFD. Various etiological agents like EBV, HHV 6, HHV 8, parvovirus B19, cytomegalovirus, varicella zoster, dengue virus, as well as HIV and HTLV-1 have been linked to this disease^{8,9}. Some authors hypothesized that KFD may show a self limited autoimmune condition induced by virus-infected transformed lymphocytes because the disease has been noted within endothelial cells and lymphocytes of patients with systemic lupus erythematosus (SLE) and other autoimmune disorders^{1,2,10}. However, the etiology and pathogenesis of KFD is still clearly unknown.

Although diagnosis of KFD depends on histopathology, there are no specific and diagnostic clinical or radiological features for KFD. A chest film is still mandatory since tuberculosis and lymphoma should be ruled out. Computed tomography (CT) and magnetic resonance imaging are useful imaging modalities for patients with cervical lymphadenopathy, though sonography has been used. CT findings in KFD include multiplicity, homogeneity, and perinodal infiltration. Generally, CT features may mimic those of lymphoma. However, lymph nodes in KFD are not as large as those in lymphoma. CT scan of the affected lymphnode shows hypodense centers with peripheral ring enhancement corresponding to the central necrosis¹¹.

Laboratory tests did not establish a diagnosis of KFD. In laboratory investigations of KFD, leukopenia and anemia were revealed. The ESR and LDH levels were increased, but the transaminase level was unaffected. In addition, a relatively low CRP value and elevated immunoglobulin G and

immunoglobulin E values were noted.

This disease has often been misdiagnosed as tuberculosis, SLE, Kawasaki disease or malignant lymphoma, which delays treatment and worsens the patient's prognosis¹²⁾. A definitive diagnosis of KFD is determined by a lymph node biopsy. The characteristic histopathologic features of the disease are 1) focal necrosis, predominantly in the paracortical region with abundant karyorrhexis; 2) aggregates of atypical mononuclear cells around the zone of necrosis (crescentic histiocytes, plasmacytoid monocytes and immunoblasts); 3) absence of neutrophils and paucity of plasma cells; and 4) usually intact lymph node capsule¹³⁾. The value of fine needle aspiration (FNA) in the diagnosis of lymph node disorders is well recognized. The presence of abundant karyorrhectic debris in any lymph node aspirate should make one suspect this condition. Identification of numerous nondescript histiocytes in lymph node FNA smears is another pointer toward this diagnosis. The key to diagnosis is however the recognition of characteristic histiocytes having a crescent-shaped nucleus¹⁴⁾.

In the findings of sono-guided lymph node biopsy and brain MRI of present case on admission day, meningitis and lymphadenitis were considered as tuberculosis. In addition, the analytic results of her CSF suggested that it was related to aseptic meningitis. Therefore, laboratory investigations for tuberculosis were performed and antituberculosis-drug therapy was started at once for ten days until we got the test results on tuberculosis that were all negative. High fever, skin eruptions on the extremities, and stomatitis in her mouth that happened while taking tuberculosis medicines were decreased after they were ceased. They were regarded as the adverse effects of antituberculous drugs¹⁵⁾. It is recommended to use medications after we get the results of laboratory investigations for the disease of KFD.

There is no specific therapy for KFD. In the majority of cases it is a self-limiting disease. Recurrence has been reported in 3.3% cases but the mainstay of management is usually symptomatic treatment using analgesics-antipyretics or nonsteroidal anti-inflammatory drugs (NSAIDs) and allowing the disease to run its course. Systemic corticosteroids can be used as an effective option in cases unresponsive to initial use of aspirin or NSAIDs¹⁶⁾. Two weeks after the treatment of antibiotics and analgesics, her headache and fever had gone in this case.

By and large, our patient's clinical profile reflects a severe case of KFD, with important constitutional symptoms, exceptional manifestations (cutaneous eruptions, mucositis and

headache), and ensuring complication (aseptic meningitis). The diagnosis of aseptic meningitis could be challenged by KFD. The negative CSF culture for our patient suggested that aseptic meningitis could be one of significant complications in KFD patients.

The mechanisms of aseptic meningitis with KFD remain unclear. Host inflammatory response to KFD can be triggered by direct interaction of subcapsular cell wall components, such as peptidoglycans and lipoteichoic acids with host Toll-like receptors, initiating the production of proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin 1 β , and interleukin 6¹⁷⁾. Microbial toxins may also trigger host immune responses. It can be hypothesized that such mechanism could be involved in the occurrence of this aseptic meningitis, and more search is needed to discover the mechanism.

In conclusion, the early recognition of KFD makes us avoid unnecessary investigations and treatment. Active consideration of histologic and cytologic examination of the sample obtained with fine needle aspiration (FNA) in any nodal biopsy showing fragmentation, necrosis, and karyorrhexis, especially in children presenting with cervical lymphadenopathy and headache leads to the diagnosis of KFD with meningitis. To differentiate KFD with meningitis from tuberculosis meningitis with lymphadenitis is important because of differences in treatment choice and clinical outcome. It is needed to keep in mind that performance of a lymph node biopsy is a critical investigation, especially for differentiating KFD with meningitis from tuberculosis meningitis with lymphadenitis, in children presenting cervical lymph node enlargement and headache.

한글 요약

무균성 뇌수막염을 동반한 Kikuchi-Fujimoto 병

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키쿠치(Kikuchi) 병, 키쿠치-후지모토(Kikuchi-Fujimoto) 병, 혹은 조직구 괴사성 림프선염은 1972년 일본에서 키쿠치와 후지모토 두 사람에게 의해 처음 기술되었으며 흔히 아시아 지역에서 30세 미만의 여성들을 주로 침범하는 자가 관해 질환으로 기술되어져왔다. 이 질환의 병인은 여전히 잘 알려져 있지 않으나 감염성(EBV, HHV-6 and -8, HTLV-1, cytomegalovirus, varicella-zoster virus, tuberculosis, toxoplasmosis, yersiniosis,

cat scratch disease), 자가면역성(SLE, Kawasaki disease), 그리고 종양성 질환(lymphoma)이 포함되는 것으로 간주된다. 가장 흔한 임상증상은 발열과 통증 없는 경부 림프선염이다. 진단은 생검을 통한 조직병리학적으로 하게 되는데, 주로 풍부한 핵과괴(karyorrhexis)를 가진 괴질 주위 지역에서 나타나는 국소 괴사, 괴사 지역 주위로 비정형적인 단핵구들의 집합, 증성구 및 형질 세포의 결핍, 그리고 대개 림프절 캡슐의 보존 등으로 특징 지워진다. 절대적인 치료법은 없어 대증 치료를 하게 되며 치료 없이도 대개 1-6개월 안에 자가 관해되고 재발률도 3.3%에 불과하다. 키쿠치-후지모토 병의 합병증으로 피부, 심장, 골수 등을 침범할 수 있으며 간질관, 무균성 뇌수막염, 간비비대 등이 발생할 수 있으나 드물다. 본 증례에서는 입원 당시 결핵성 임파선염과 뇌수막염으로 오인되었던 무균성 뇌수막염을 동반한 키쿠치-후지모토 병을 경험하였기에 이에 보고하는 바이다.

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