

Case Report

Interstitial Pneumonitis: A Rare Manifestation of Kikuchi-Fujimoto Disease

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Abstract:

Background: Kikuchi-Fujimoto Disease (KFD) or subacute histiocytic necrotizing lymphadenitis is an uncommon cause of lymphadenopathy. The etiology of KFD remains unknown but it is postulated to be associated with post-viral infection and autoimmune processes. Most patients present with relapsing and remitting course of fever and lymphadenopathy, mostly cervical area. However, KFD patients could present with other uncommon manifestations including aseptic meningitis, hepatitis, uveitis, etc. Pulmonary involvement is rare in KFD and was reported by only a few groups. Herein, we report a case of KFD presenting with interstitial pneumonitis.

Case Presentation: A 32-year-old Thai female initially presented with prolonged fever and cervical lymphadenopathy. She was diagnosed with KFD proved by histopathology of cervical lymph node biopsy. Her KFD course was complicated with aseptic meningitis, recurrent fever and lymphadenopathy responded to systemic corticosteroid. She recently presented with dyspnea on exertion, cough and hypoxia. The chest computed tomography revealed diffuse ground glass and interstitial nodules. Extensive investigations for infectious etiologies were normal. Our patient was given therapeutic trial of systemic corticosteroid and her symptoms were completely resolved. Follow-up chest radiographic imaging became normal. **Conclusion:** Although pulmonary involvement in KFD is rare, physician should be aware of this complication in order to promptly diagnose and provide appropriate treatments.

Keywords : ● Kikuchi Fujimoto Disease ● Lymphadenopathy ● Interstitial pneumonitis

J Hematol Transfus Med 2018;28:289-94.

Received 26 July 2018 Accepted 14 August 2018

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รายงานผู้ป่วย

เนื้อเยื่อระหว่างถุงลมปอดอักเสบหนึ่งในอาการนำที่พบได้ยากของโรค Kikuchi-Fujimoto Disease

ธิตี อัครภาณุมาศ กฤษณา วุฒิการณ และ อุดมศักดิ์ บุญวรเศรษฐ์

บทคัดย่อ

ที่มาและความสำคัญ โรค คิคูชิฟูจิโมโต (Kikuchi-Fujimoto Disease ; KFD or subacute histiocytic necrotizing lymphadenitis) เป็นหนึ่งในสาเหตุที่พบได้น้อยของคนไข้ที่มีอาการต่อมน้ำเหลืองโต โดยสาเหตุการเกิดของโรคคิคูชิฟูจิโมโต ปัจจุบันยังไม่ทราบแน่ชัด แต่เชื่อว่ามี ความเกี่ยวข้องกับภาวะหลังการติดเชื้อไวรัสและระบบภูมิคุ้มกันของ ผู้ป่วย ส่วนมากผู้ป่วยจะมีอาการไข้และต่อมน้ำเหลืองโตเป็นๆ หายๆ โดยเฉพาะต่อมน้ำเหลืองบริเวณคอ อย่างไรก็ตาม มีผู้ป่วย คิคูชิฟูจิโมโต บางรายที่มาด้วยอาการซึ่งพบได้ไม่บ่อย เช่น เยื่อหุ้มสมองอักเสบ ตับอักเสบ ม่านตาอักเสบ รวมถึง ภาวะเนื้อเยื่อระหว่างถุงลมปอดอักเสบ ซึ่งภาวะดังกล่าว มีรายงานการพบได้น้อยมากในคนไข้โรคคิคูชิฟูจิโมโต ในที่นี้จึงได้รายงานคนไข้ในโรคคิคูชิฟูจิโมโต ที่มาด้วยอาการเนื้อเยื่อระหว่างถุงลมปอดอักเสบ

ตัวอย่างผู้ป่วย ผู้ป่วยหญิง อายุ 32 ปี มาด้วยอาการไข้เรื้อรัง และ ต่อมน้ำเหลืองโตบริเวณคอ ผู้ป่วยได้รับการวินิจฉัยเป็น โรคคิคูชิฟูจิโมโต ซึ่งยืนยันการวินิจฉัยทางพยาธิวิทยาโดยการตัดต่อมน้ำเหลืองบริเวณคอพบโรคดังกล่าว ผู้ป่วยรายนี้มีอาการเยื่อหุ้มสมองอักเสบ ไข้และต่อมน้ำเหลืองโตเป็นๆ หายๆ สอดคล้องกับการได้รับการรักษาด้วยสเตียรอยด์ หลังจากติดตามการรักษาต่อเนื่อง ผู้ป่วยมีอาการหายใจหอบเหนื่อยมากขึ้น มีไอ และ ออกซิเจนในเลือดต่ำ ผู้ป่วยได้รับการตรวจวินิจฉัยด้วยเอกซเรย์คอมพิวเตอร์ พบ ลักษณะที่ผิดปกติแบบกระจายทั่วทั้งปอดสองข้าง และมีจุดบริเวณเนื้อเยื่อระหว่างถุงลมปอด มีการตรวจสืบค้นเพิ่มเติมสำหรับสาเหตุการติดเชื้อ ซึ่งผลปกติทั้งหมด หลังจากผู้ป่วยได้รับการรักษาด้วยสเตียรอยด์ อาการโดยรวมของผู้ป่วยทั้งหมดดีขึ้น และติดตามการตรวจด้วยเอกซเรย์ไม่พบร่องรอยความผิดปกติ

สรุป ถึงแม้ว่าอาการ เนื้อเยื่อระหว่างถุงลมปอดอักเสบ จะพบได้น้อยในคนไข้คิคูชิฟูจิโมโตก็ตาม แต่แพทย์ควรนึกถึงภาวะแทรกซ้อนนี้ เพื่อที่จะได้รับการวินิจฉัยและให้การรักษาที่เหมาะสมแก่ผู้ป่วยได้ทันทั่วทั้งที่

คำสำคัญ : ● Kikuchi Fujimoto Disease ● Lymphadenopathy ● Interstitial pneumonitis

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:289-94.

Background

Kikuchi-Fujimoto disease (KFD) is a rare condition which patients present with fever and lymphadenopathy. In some occasion patients can have atypical presentation including aseptic meningitis, uveitis, hepatitis, etc. Pulmonary involvement has been rarely reported in KFD. We report a patient who presented with dyspnea on exertion, cough, hypoxia and investigation reveals lung involvement.

Case Report

A 32-year-old female presented to her general practitioner in 2008 with fever of unknown origin, generalized malaise and lower back pain for 1 month. Physical examination revealed low-grade fever and mildly painful multiple sub-centimeter cervical lymphadenopathy but no cutaneous rashes or articular abnormalities. CBC showed mild anemia with hemoglobin (Hb) of 9.6 g/dL, white cell count (WBC) of $10 \times 10^9/L$ with normal differential white cell and platelet of $423 \times 10^9/L$. A complete metabolic panel was normal. Erythrocyte sedimentation rate and C-reactive protein were markedly elevated at 96 mm/hour and 15.5 mg/dL respectively. Extensive infectious disease work up including blood cultures, PCR for mycobacterial tuberculosis, and serological tests for malaria, HIV, hepatitis, cytomegalovirus,

Epstein-Barr virus (EBV), bartonella, brucella and scrub typhus were negative. Autoimmune disease screen was positive for low titer antinuclear antibodies (1:80, homogeneous pattern) but were negative for anti-extractable nuclear antigen, rheumatoid factor, anti-phospholipid antibodies and anti-double stranded DNA antibodies. C3 was normal and C4 was marginally elevated at 57.3 mg/dL (range 15-57). During this time, she remained febrile and had progressively enlarged cervical lymphadenopathy. She was referred to hematology service due to a concern of lymphoma. Bone marrow biopsy was negative for lymphoma or leukemia. Cervical lymph node biopsy revealed diffuse effacement of nodal architecture by necrotic containing mixed large transformed lymphocytes, crescentic histiocytes and apoptotic bodies in parafollicular and sinus areas (Figure 1). There was no granuloma, acute inflammation, hematoxylin body or malignancy. EBV-encoded RNA (EBER), acid-fast bacilli and fungal stain were negative. The histopathology was consistent with Kikuchi-Fujimoto disease. She was treated with a short-course of prednisone (0.5 mg/kg/day), which was rapidly tapered in 2 weeks. After steroid was initiated, fever and lymphadenopathy were completely resolved. Over the several years course, she has had several episodes of fever and cervical lymphadenopathy requiring

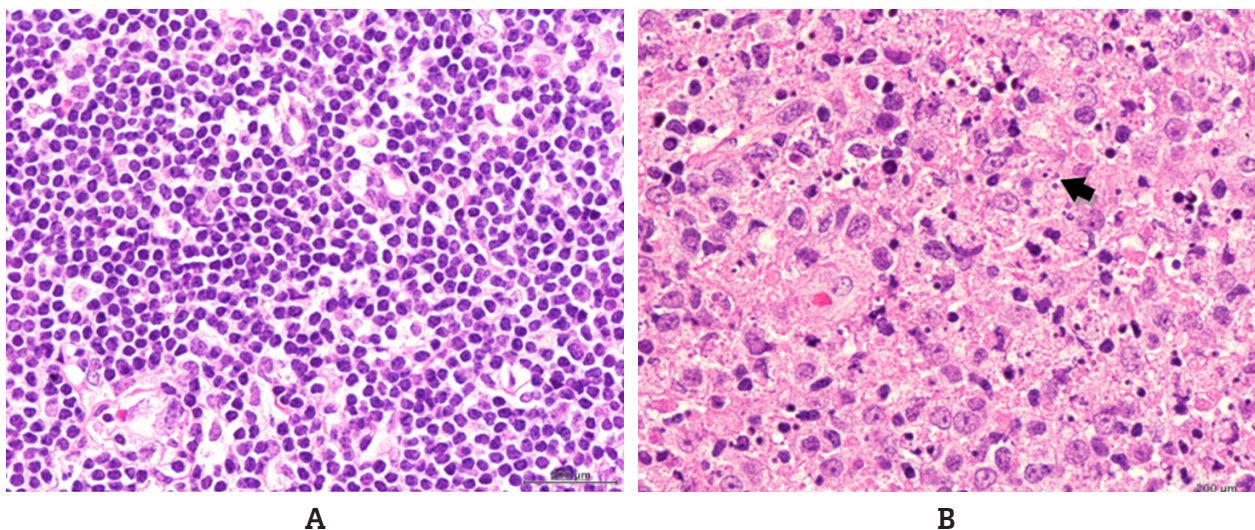


Figure 1 A light microscope shows diffuse effacement of nodal architecture by necrotic containing mixed large transformed lymphocytes, histiocytes and apoptotic body (arrow)

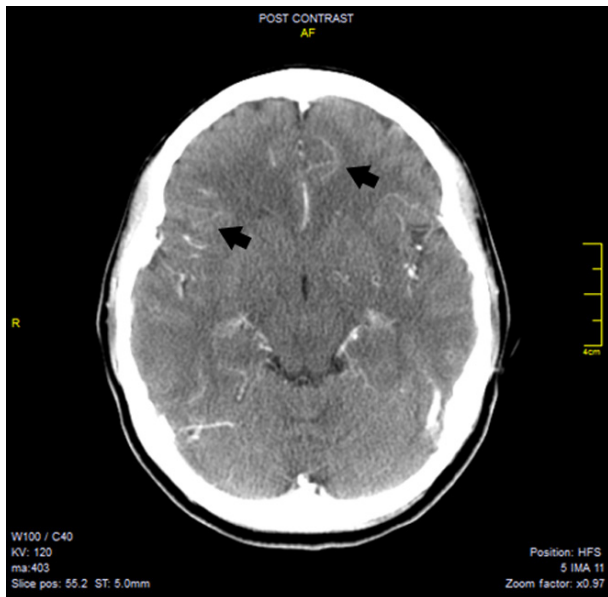


Figure 2 CT brain with contrast shows diffuse leptomeningeal enhancement predominantly at paramedian and bilateral frontal area (arrows)

intermittent courses of systemic corticosteroid. In 2011, she presented with an episode of fever, severe headache and ataxia. CT brain showed diffuse leptomeningeal enhancement with no brain parenchymal abnormality or hydrocephalus (Figure 2). Lumbar puncture for cerebrospinal fluid (CSF) analysis showed CSF lymphocyte

pleocytosis (WBC 310 cells/mL with neutrophils 12% and mononuclear cells 84%), elevated protein (176 mg/dL) and low glucose (56 mg/dL). PCR for tuberculosis and cryptococcal antigen were negative. CSF studies for HSV, CMV, and HHV-6 PCR were negative. She was started on dexamethasone 4 mg every 8 hours with rapid dose tapering over 3-week course. She responded promptly to the treatment and all symptoms subsided. She had been off steroid until August 2014, when she presented to the clinic with a low-grade fever, dyspnea on exertion, dry cough and hypoxia. Oxygen saturation at room air was 90%. Chest X-ray showed no active pulmonary infiltration. She was initially treated with a 5-day course of azithromycin for possible upper respiratory tract infection, however, her symptoms did not show significant improvement. High-resolution CT chest (Figure 3) showed evidence of diffuse ground glass opacity with scattered subpleural nodular opacities at both upper lobes and lower lobes measured up to 2.9 mm in size. There were also ill-defined nodular opacities at pre-vascular region and sub-centimeter mediastinal lymph nodes at bilateral lower paratracheal

and right hilar regions. The finding was consistent with interstitial pneumonitis. Sputum AFB, culture and PCR were negative. Fungal wright stain, culture, PCP antigen and galactomannan were all negative. Systemic corticosteroid was started at 1 mg/kg/day of prednisolone. Fever, respiratory symptoms and hypoxia resolved after steroid initiation and prednisolone was slowly tapered without recurrence of the

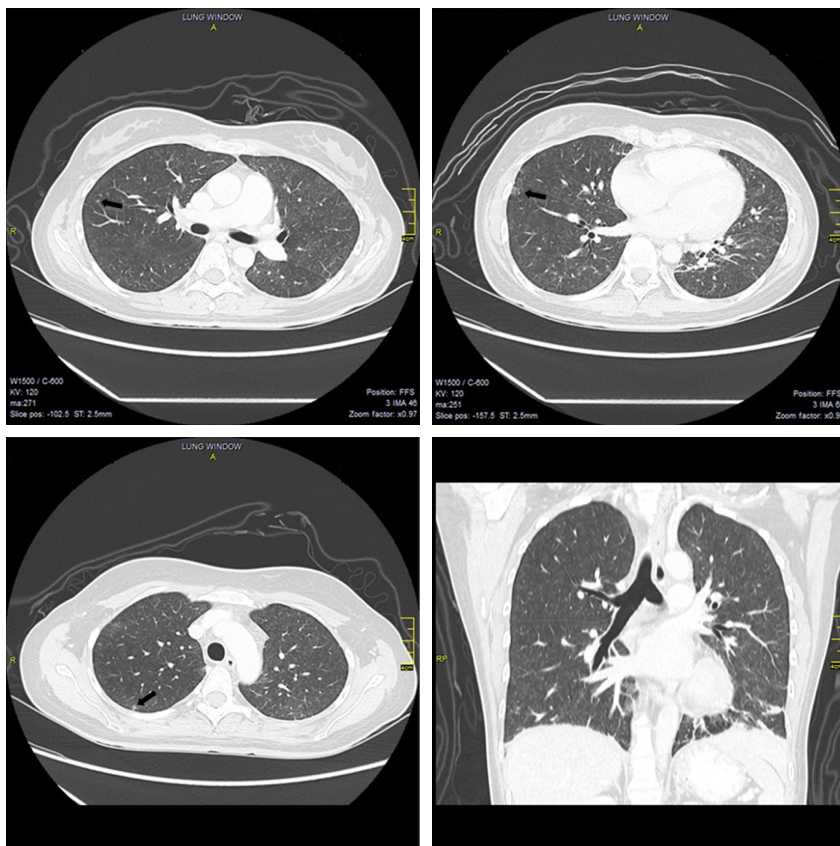


Figure 3 CT chest shows diffuse reticulonodular and ground glass opacity both lung predominantly lower lung area. Arrows demonstrate interstitial and alveolar nodules.

symptoms. Follow-up chest radiography returned to normal. Interestingly, she has been relatively asymptomatic since this pulmonary event in 2014 with no recurrent lymphadenopathy or any respiratory symptoms.

Discussion

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare condition which was first described in 1972 by Dr. Kikuchi and Dr. Fujimoto^{1,2}. KFD is characterized by subacute fever with localized lymphadenopathy, mostly in the cervical region. The pathogenesis of KFD is poorly understood but is thought to be associated with viral infection process i.e. Epstein-Barr virus, human herpes virus, parvovirus, HIV, etc. Autoimmune process such as systemic lupus erythematosus, rheumatoid arthritis, Still's disease or Sjogren's syndrome, etc, is another potential plausible etiology³. KFD is usually seen in young female patients with male to female ratio vary between 1:1.2 and 1:4. Common presentations of KFD are fever and localized lymphadenopathy. Cervical lymphadenopathy is the most typical involved area, however, lymphadenopathy can be found in any sites. Due to its clinical pictures, patients can present to hematologists masquerading as the diagnosis of lymphoma. Other symptoms include rashes, arthralgia/arthritis, constitutional symptoms, or abdominal fullness due to hepatosplenomegaly. In some rare instances, patients may present with unusual presentations such as aseptic meningitis, uveitis, and hepatitis. Our patient had extranodal diseases including aseptic meningitis and recent evidence of respiratory insufficiency, of which CT thorax showed finding consistent with interstitial pneumonitis. Lung involvement is an extremely uncommon manifestation of KFD^{4,6}. There were only a few case reports describing pulmonary symptoms in KFD. Most reported cases presented with interstitial lung process including cryptogenic organizing pneumonia and interstitial pneumonitis^{4,5}. Wong C, et al. reported a case of KFD who presented with pulmonary hemor-

rhage syndrome concurrent with the diagnosis of SLE⁶. Diagnosis of KFD requires histopathology mostly from lymph node biopsy. Biopsy is recommended not only to establish the diagnosis but also to exclude malignant process i.e. lymphoma or metastatic cancer. Pathology of lymph node in KFD varies upon particular phases of KFD but typically reveals variable degree of paracortical necrotic foci accompanied with a histiocytic cellular infiltrate and abundant karyorrhectic debris⁷. In difficult cases, immunophenotypic studies may be helpful in distinguishing KFD from non-Hodgkin lymphoma.

The natural course of KFD is benign and typically self-remitting process. Patients' symptoms usually spontaneously resolved within 1-4 months, however, recurrence was reported⁸⁻¹⁰. Although most patients do not require any treatment, in more symptomatic cases, systemic corticosteroid treatment is warranted¹¹. Patients typically respond well to therapy. Our patient had prompt response to systemic steroid resulted in complete resolution of fever, pulmonary symptoms and hypoxia. Follow-up chest radiography showed resolution of ground glass and interstitial nodules. Her steroid dose has been slowly tapered down.

In summary, we report a rare manifestation of KFD presenting as interstitial lung disease. Clinicians should be aware of lung involvement in KFD to promptly diagnose and provide proper treatment to the patients.

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