CASE REPORT

Kikuchi-Fujimoto disease: an unusual presentation of meningitis in a returning traveller

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SUMMARY

A 19-year-old, previously healthy woman developed a pruritic erythematous maculopapular rash on her bilateral palms and wrists, right-sided tender cervical lymphadenopathy and nightly fevers and headaches 5 days after returning from a 1-month trip to Cambodia. She presented 2 weeks after her trip due to ongoing nightly fevers to a maximum of 38.8°C. She was given empiric doxycycline for possible rickettsial disease, though an extensive infectious workup returned without positive findings. Lumbar puncture was performed on hospital day 4, and spinal fluid analysis was consistent with aseptic meningitis. On hospital day 5, core biopsy and fine-needle aspiration were performed on the largest anterior cervical lymph node. Her fever curve gradually improved, and she was discharged on hospital day 6. Results of the lymph node biopsy were finalized 5 days after discharge and were compatible with Kikuchi's lymphadenitis. Symptoms had completely resolved on follow-up with infectious disease and rheumatology.

BACKGROUND

When a returning traveller presents with fever and lymphadenopathy, early diagnosis and treatment are essential. Infectious diseases top the differential, but other causes should be considered, even those not usually associated with travel. Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotising lymphadenitis, is a rare clinical condition that can be difficult to diagnose due to its lack of specific signs, symptoms and serological markers.¹ The most interesting presenting feature in this case was the aseptic meningitis, which narrowed the differential slightly but was also found to have a rare association with KFD. Furthermore, evaluation and management in this setting can confer a substantial cost to the patient, both monetarily and emotionally, given the inherent uncertainty surrounding a diagnosis and the length of hospital stay. Early lymph node biopsy is necessary to diagnose KFD.

CASE PRESENTATION

A 19-year-old Caucasian woman developed fever, headache and a pruritic erythematous maculopapular rash on her bilateral palms and wrists 5 days after returning from a 1-month trip to Cambodia where she travelled to remote villages on behalf of a local non-governmental organisation. She presented to the hospital 2 weeks after her trip due to ongoing nightly fevers to a maximum of 38.8°C and associated chills, headache, night sweats,

light-headedness, nausea and myalgia. The headaches were not associated with any confusion or altered GCS. On admission, she was found to have right-sided tender submandibular lymphadenopathy with one particularly large lymph node. Her rash had mostly resolved. She denied illness during her stay in Cambodia, took prophylactic atovaquone-proguanil as directed and was vaccinated for tetanus and typhoid prior to leaving. She did swim in the Gulf of Thailand and suffered a laceration to her left great toe, since healed, after striking a rock.

She had a medical history of atopic dermatitis, mild intermittent asthma and seasonal allergies. She reported no prior surgeries. Family history was significant for asthma and hypertension in paternal and maternal grandmothers. She was an undergraduate student and denied alcohol use, tobacco use or illicit drug use.

INVESTIGATIONS

White blood cell (WBC) count $6.06 \times 10^9/\text{L}$ with increased atypical lymphocytes.

Haemoglobin 10.7 g/dL (previously 13) with a mean corpuscular volume of 87.

Negative

HIV 1/2, human T-lymphotropic virus (HTLV) 1/2, Epstein-Barr virus (EBV), cytomegalovirus (CMV), QuantiFERON Gold Tuberculosis, three thick and thin blood smears collected 12 hours apart, blood cultures collected with each fever, dengue IgG/IgM, chikungunya IgG/IgM, leptospira IgM, strongyloides IgG, Zika PCR, rapid plasma reagin, Lyme, ELISA and western blot analyses, stool ova and parasite and antinuclear antibody.

Positive

Lumbar puncture completed and spinal fluid analysis consistent with aseptic meningitis: opening pressure 25.5 mm H₂O, 8 WBCs with 94% lymphocytes in tube 1, 6 WBCs with 91% lymphocytes in tube 4, normal glucose and protein.

Ultrasound-guided core-needle biopsy of submandibular lymph node with bacterial, fungal and acid-fast bacilli culture/stain along with cytology: necrotising lymphadenitis consistent with Kikuchi's disease.

Serum IgE elevated at 2732.

DIFFERENTIAL DIAGNOSIS

Malaria, specifically *Plasmodium falciparum*, topped the differential given nightly fevers,

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Figure 1 Low-power image (40x) of a lymph node involved by necrotising granulomatous inflammation.

headache and new anaemia within 2 weeks of returning from Cambodia. Filariasis is another mosquito-borne illness endemic to Cambodia that can present with nightly fevers, though the predominant symptom is lymphedema. Other mosquito-borne pathogens were considered, including chikungunya virus despite a lack of arthralgia, dengue virus despite a normal platelet count and Zika virus despite our patient's prominent lymphadenopathy. Blood cultures were obtained to rule out typhoid fever despite recent vaccination. Given water exposure, schistosomiasis was considered, and stool ova and parasite sample were obtained. Leptospirosis was believed less likely given normal liver function tests and a lack of conjunctivitis. Testing was conducted for more common aetiologies of cervical lymphadenopathy, fever and rash such as HIV, human T-lymphotropic virus, Epstein-Barr virus, cytomegalovirus, Lyme disease, ehrlichiosis and Rocky Mountain spotted fever. The palmar rash raised concern for enterovirus, coxsackievirus and syphilis. *Mycobacterium tuberculosis*, endemic to Cambodia, was considered but thought much less likely. Given ongoing fevers and headache during hospital stay, lumbar puncture was obtained to assess for viral meningitis.

Figure 2 High-power image (400x) shows viable plasmacytoid dendritic cells with interspersed apoptotic cells and nuclear debris (karyorrhectic debris). There is an absence of neutrophils and eosinophils.

Finally, malignant causes such as lymphoproliferative disease and carcinoma along with autoimmune conditions such as systemic lupus erythematosus were considered given ongoing undifferentiated fever. A lymph node biopsy, along with culture and cytology, was obtained.

TREATMENT

Supportive care, including normal saline and acetaminophen, was given as needed. Empiric doxycycline was started to cover rickettsial disease given ongoing symptoms.

OUTCOME AND FOLLOW-UP

The patient was discharged on hospital day 6 after her symptoms gradually improved, although she continued to experience low-grade nightly fevers. The cervical lymph node biopsy resulted 5 days after discharge and was consistent with Kikuchi's lymphadenitis. Doxycycline was discontinued. Corticosteroids were considered, but symptoms had completely resolved on 1-week clinic follow-up with infectious disease and rheumatology.

Patient's perspective

Overall, I had a good experience at the hospital. I believe that my doctors did a good job of testing for many different ailments in a relatively short period of time. They were very thorough. I believe that all of the tests that they conducted were very necessary, from blood tests to the spinal tap, to the lymph node biopsy. I also appreciate that the testing was not only focused on testing for a large variety of illnesses, but that it also included repetitive testing to ensure that there were no glaring errors in previous testing. I think all of the tests done were very important to understanding the problem at hand. However, when I was no longer having high fevers, it was suggested that I be discharged from the hospital as I did not really have any tests for major illnesses coming back positive. I was then diagnosed with Kikuchi's disease. I never really understood what it was, and it seemed to be a bit of a catch-all with no clear-cut definition of what constitutes Kikuchi's and what differentiates it from other illnesses. I would suggest further research on the disease and how it manifests itself. Additionally, I believe that all patients who develop symptoms similar to myself should undergo testing with the same rigour (perhaps even more testing for a broader array of illnesses) as what I went through when in the hospital. Again, I believe that my doctors were wonderful and tried to figure out what the illness was to the best of their abilities, but I think more research is necessary to figure out what exactly Kikuchi's is.

Learning points

- Kikuchi-Fujimoto disease (KFD) should be considered in all patients with fever and lymphadenopathy, even in the setting of recent travel.
- Suspicion for KFD should be increased in young women with mild disease and typical symptoms, but aseptic meningitis should also raise suspicion in the appropriate clinical setting.
- Early lymph node biopsy is essential for diagnosis of KFD.

DISCUSSION

KFD, or histiocytic necrotising lymphadenitis, is a rare, self-limiting disease of unknown aetiology occurring mostly in young Asian women.¹ It generally presents with mild though persistent fever and lymphadenopathy, usually cervical.¹ Diagnosis is based on histopathology (paracortical necrosis, numerous macrophages containing karyorrhectic debris and peripheral nuclei, sparse neutrophils and plasma cells; figures 1 and 2), which is required to differentiate from less-benign disorders such as lymphoma, systemic lupus erythematosus (SLE) and infectious lymphadenopathies.^{1,2} The prevailing aetiological theory involves a viral autoimmune mechanism, inducing a hyperimmune lymphadenitis given an apparent association with SLE, which at times is diagnosed prior to, concomitantly, or years after the diagnosis of KFD.^{3,4} Although the true incidence of concurrent disease is estimated at 13%, surveillance at 6-month intervals is recommended.^{3,5} Reported cases have linked KFD with many viruses, including EBV, HHV 6, HHV 8, parvovirus B19, CMV, varicella zoster virus (VZV), dengue virus, HIV and HTLV-1.⁶ The patient in this case presented with the usual symptoms but also demonstrated less commonly associated aseptic meningitis, rash and night sweats. A retrospective study of 195 patients with KFD found that headache occurred in 16.9%, night sweats in 5.6% and rash in only 4.1%.¹ Aseptic meningitis is such a rare presentation for KFD that it can confuse workups.⁶ Yang *et al* described a case of a patient presenting with aseptic meningitis in which it took 9 hospital days before lymphadenopathy was discovered and the eventual diagnosis of KFD was made by histopathology.⁴ As aseptic meningitis is often of viral cause, there may be a joint aetiology of both the meningeal disease and KFD. Furthermore, almost all reported cases of KFD presenting with aseptic meningitis have been in Asia, which is especially interesting given this patient's recent travel to Cambodia.⁴ Treatment is supportive, though case series have found corticosteroids necessary for patients with lingering symptoms in approximately 16% of cases.^{5,7} Although most likely an incidental finding given

the patient's known atopy, elevated IgE levels can occur with eosinophilia in Kimura disease, another rare cause of benign lymphadenopathy.⁸ The wide range of atypical features, rarity of disease and variance in epidemiology all contribute to the difficulty in diagnosing KFD.

Contributors NDT and ASP contributed equally to this manuscript. Together, we represented the primary care team for this patient and contributed to the planning, conduct and reporting of this manuscript. Ex authorship: NDT and ASP.

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