CASE REPORT

Relapsing fevers and lymphadenopathy in a young woman

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SUMMARY

A 23-year-old woman presented to the emergency department with severe occipital headache, nausea and fever. She was treated with intravenous antibiotics for suspected meningitis. After a brief period of response, her symptoms relapsed and remained refractory despite continuing intravenous antibiotics for 10 days leading to referral to our centre. Physical examination was significant for tender right cervical lymph node. Initial tests included pancytopenia, elevated C reactive protein, lactate dehydrogenase and unremarkable cerebrospinal fluid. Extensive infectious and rheumatology work-up was negative. Massive posterior cervical, axillary and inguinal lymphadenopathy was revealed on imaging. Excisional biopsy of the deep cervical lymph node showed histiocytic necrotising lymphadenitis suggesting a diagnosis of Kikuchi disease. Her course was complicated by acute renal failure. Her symptoms resolved in about a week with supportive treatment along with improvement in pancytopenia and renal function. She had two additional self-limited recurrences in the next 3 months and remains symptom free thereafter.

BACKGROUND

Kikuchi disease is a rare, poorly understood condition affecting young women. Although the disease has a benign self-limited course, it mimics more sinister and common causes such as lymphoma. Patients often go through a prolonged, extensive work-up with delay in diagnosis, which can lead to unnecessary and potentially harmful treatments as well as financial and psychological comorbidity. In this report, we wish to highlight the diagnostic challenge presented by this condition.

CASE PRESENTATION

A 23-year-old Caucasian woman, with no significant medical history, presented to her local emergency department with a sudden onset of severe occipital headache, neck pain, nausea and photophobia. Physical examination revealed a temperature of 38.6°C and nuchal rigidity without any other meningeal signs. Her white cell count was $16.3 \times 10^9/L$, with a neutrophil predominance. Lumbar puncture revealed normal cell count, protein, glucose and opening pressure although Gram stain showed Gram-positive cocci. Owing to concern for *Streptococcus pneumoniae* meningitis, she was started on ceftriaxone, vancomycin, and prednisone. After 24 h, her symptoms improved. Although her blood cultures and cerebrospinal fluid (CSF) cultures were negative, she completed 10 days of outpatient intravenous ceftriaxone and

vancomycin. On the day her antibiotics were completed, she presented to our emergency department with a sudden onset of fever, rigors, severe occipital headache, neck pain, upper and lower back pain, photophobia, nausea and intermittent bilateral hand and right foot numbness.

On arrival, she had a temperature of 38.6°C with otherwise stable vital signs. Pertinent examination findings included neck tenderness without rigidity or meningeal signs and a 1 cm right posterior cervical lymph node.

INVESTIGATIONS

The following workup was unrevealing: CSF and blood cultures; CSF PCR for herpes simplex virus (HSV), varicella zoster virus, enterovirus and West Nile virus; serologies for Epstein-Barr virus (EBV), cytomegalovirus, HIV and tick-borne illnesses; anti-nuclear antigen, complements and antibodies to extractable nuclear antigens. She had a normal erythrocyte sedimentation rate with a mildly elevated C reactive protein and lactate dehydrogenase. A significant drop in her blood cell counts across all lines was noted.

Owing to neck tenderness and concern for brain abscess, an MRI of the head and neck was obtained, which revealed massive bilateral posterior cervical and retropharyngeal lymphadenopathy (figure 1). Further imaging with a CT of the chest, abdomen and pelvis showed bilateral axillary and inguinal lymphadenopathy.

Figure 1 MRI (axial, T2) of the cervical spine (C3) showing massive posterior cervical lymphadenopathy (arrows). A, anterior; R, right; L, left.

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DIFFERENTIAL DIAGNOSIS

A core needle biopsy of a cervical lymph node was non-diagnostic. An excisional biopsy revealed paracortical lymphoid hyperplasia with reactive immunoblasts and foci of necrotising lymphadenitis (figure 2). In situ hybridisation studies were negative for EBV-infected or HSV-infected cells, and Grocott's methenamine silver and acid-fast bacilli stains were negative for organisms. Bacterial and fungal cultures of the lymph node tissue were negative.

The differential diagnosis of diffuse lymphadenopathy and fever in a young patient is broad. The excisional biopsy and clinical workup effectively ruled out infectious aetiologies of lymphadenopathy: bacterial, viral, mycobacterial and fungal. Additionally there was no evidence for lymphoma, metastatic disease, squamous cell cancer, other malignancy or lymphoproliferative disorder. There also was no evidence for sarcoidosis, systemic lupus erythematosus (SLE), amyloidosis, chronic granulomatous diseases, Castleman's syndrome or adult-onset Still's disease. Based on the patient's classic clinical and pathological findings, a diagnosis of Kikuchi disease was made.

TREATMENT

Once the diagnosis was confirmed in our patient, antibiotics were stopped. The patient was managed symptomatically with acetaminophen and opioids for head, neck and back pain.

Figure 2 Histopathological features in the lymph node biopsy. (A) Low-power photomicrograph (H&E, ×40) of excisional lymph node biopsy demonstrating paracortical lymphoid hyperplasia (left) and focal necrosis (right). Immunoperoxidase stains (not shown) demonstrated scattered aggregates of small CD20-positive B cells and scattered small CD3-positive T cells. (B) Higher magnification (H&E, ×200) demonstrating paracortical lymphoid hyperplasia (left) and focal necrosis (right). The interface includes histiocytes with faintly eosinophilic and bubbly cytoplasm, plasmacytoid monocytes and reactive immunoblasts with prominent central nucleoli. The necrotic area contains karyorrhectic and eosinophilic granular debris.

OUTCOME AND FOLLOW-UP

In the 3 months following hospital discharge, the patient had two additional episodes of neck pain and headache with fevers. These episodes resolved without intervention. Six months after her initial presentation, the patient was symptom free.

DISCUSSION

Kikuchi disease, also known as Kikuchi-Fujimoto disease or histiocytic necrotising lymphadenitis, is a rare, poorly understood benign condition affecting young individuals under the age of 30, with more than three of four cases seen in women.^{1 2} In a systematic review compiling 244 cases reported worldwide between 1991 and 2005,² all patients had lymphadenopathy; most commonly of cervical nodes (posterior triangle). The affected lymph nodes were tender in half the cases.³ Rash with histological features of leukoclastic vasculitis and interface dermatitis⁴ were seen in 10–30% of cases.² Pancytopenias occurred in a few patients.² While severe headache and fever was common, aseptic meningitis was observed in a few cases.^{2 5} One group reported aseptic meningitis with lymphocytic or monocytic CSF pleocytosis in 10% of their cohort of 41 patients seen over a 20-year time frame.⁵ In our patient, CSF did not show pleocytosis or other features of meningitis despite initial suspicion.

Diagnosis of Kikuchi disease is made based on well-characterised histopathology features.^{6–8} However, there are occasional reports of biopsies being read as Hodgkin's lymphoma.^{7 8} Somewhat similar histological features can also be seen in SLE.^{7–9} Therefore, a diagnosis of Kikuchi disease based on histopathology can be challenging and requires careful interpretation in the context of clinical features.^{2 7 8 10}

Most patients, as in this case, go through extensive diagnostic evaluation.² Delay in diagnosis can lead to unnecessary and potentially harmful treatments, as well as financial and psychological comorbidity.² Our patient's hospitalisation was complicated by an episode of acute renal failure secondary to biopsy-proven acute tubular necrosis. Although this was presumed secondary to her antibiotics, there has been one previous case report of acute renal failure associated with Kikuchi disease.¹¹

Kikuchi disease has a benign, self-limited course in most patients with resolution of symptoms in 1–4 months.² Recurrences are rare in Kikuchi disease but have been reported.² The role of steroids or immunosuppressive therapy for treatment of Kikuchi disease is unclear. Most patients show spontaneous resolution with supportive management; however, death from Kikuchi disease occurred in 2.1% of 244 cases.² These were due to abrupt heart failure in a pregnant patient, pulmonary haemorrhage, haemophagocytic syndrome and pulmonary complications in the post-transplant setting. While SLE was seen in 13% cases, on longitudinal follow-up, only 2% Kikuchi disease patients developed SLE.² Patients with cutaneous manifestations seem to have much a higher association with SLE^{12 13} and this subset may warrant careful follow-up.

Learning points

- ▶ Kikuchi disease is a rare, benign disease presenting with fever and lymphadenopathy classically in young women.
- ▶ Diagnosis is made through typical findings on lymph node biopsy, and often can be challenging.
- ▶ There is no known effective treatment and symptoms usually resolve within 4 months of presentation.

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Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Bosch X, Guilabert A. Kikuchi-Fujimoto disease. *Orphanet J Rare Dis* 2006;1:18.
- 2 Kucukardali Y, Solmazgul E, Kunter E, *et al*. Kikuchi-Fujimoto disease: analysis of 244 cases. *Clin Rheumatol* 2007;26:50–4.
- 3 Chuang CH, Yan DC, Chiu CH, *et al*. Clinical and laboratory manifestations of Kikuchi's disease in children and differences between patients with and without prolonged fever. *Pediatr Infect Dis J* 2005;24:551–4.
- 4 Spies J, Foucar K, Thompson CT, *et al*. The histopathology of cutaneous lesions of Kikuchi's disease (necrotizing lymphadenitis): a report of five cases. *Am J Surg Pathol* 1999;23:1040–7.
- 5 Sato Y, Kuno H, Oizumi K. Histiocytic necrotizing lymphadenitis (Kikuchi's disease) with aseptic meningitis. *J Neurol Sci* 1999;163:187–91.
- 6 Tsang WY, Chan JK, Ng CS. Kikuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. *Am J Surg Pathol* 1994;18:219–31.
- 7 Kuo TT. Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology and DNA ploidy. *Am J Surg Pathol* 1995;19:798–809.
- 8 Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol* 1988;5:329–45.
- 9 Yilmaz M, Camci C, Sari I, *et al*. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) mimicking systemic lupus erythematosus: a review of two cases. *Lupus* 2006;15:384–7.
- 10 Lin HC, Su CY, Huang CC, *et al*. Kikuchi's disease: a review and analysis of 61 cases. *Otolaryngol Head Neck Surg* 2003;128:650–3.
- 11 Silva AF, Focaccia R, Oliveira AC, *et al*. Kikuchi-Fujimoto disease: an unusual association with acute renal failure. *Braz J Infect Dis* 2010;14:621–7.
- 12 Paradelo S, Lorenzo J, Martinez-Gomez W, *et al*. Interface dermatitis in skin lesions of Kikuchi-Fujimoto's disease: a histopathological marker of evolution into systemic lupus erythematosus?. *Lupus* 2008;17:1127–35.
- 13 Kim SK, Kang MS, Yoon BY, *et al*. Histiocytic necrotizing lymphadenitis in the context of systemic lupus erythematosus (SLE): is histiocytic necrotizing lymphadenitis in SLE associated with skin lesions? *Lupus* 2011;20:809–19.

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