

Kikuchi's disease: an important cause of cervical lymphadenopathy

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ABSTRACT – Kikuchi's disease is a form of necrotising lymphadenitis typically presenting in young women with lymphadenopathy. A case of Kikuchi's disease is reported in order to highlight the diagnostic confusion that is often associated with the condition. The possibility of the disease should be taken into account in any patient presenting with unexplained lymphadenopathy, and consideration of the diagnosis is particularly important before the introduction of potentially inappropriate drug therapy.

Introduction

Kikuchi's disease is a rare, self-limiting lymphadenitis predominantly occurring in young women and typically presenting with fever, cervical lymphadenopathy, and flu-like symptoms. It was first reported in Japan in 1972 by Kikuchi and Fujimoto independently.^{1,2} Although it has been reported worldwide it is most commonly seen in Asia³ and is rare in the UK. This scarcity increases the possibility of misdiagnosis when a patient presents with typical symptoms in the UK. We report a case of Kikuchi's disease causing fever and cervical lymphadenopathy that led to diagnostic confusion on first presentation. In order to remind clinicians about the salient features of the disease and the diagnostic dilemmas associated with it, we present a literature review, focusing on the disease's diagnostic criteria, histopathological changes and likely prognosis.

Case report

A 30-year-old South Asian female presented with a 10-week history of fever, night sweats and severe joint pains. She had been on holiday to Turkey four months previously. Initially she also suffered from diarrhoea, anorexia and headaches. She denied any history of weight loss. Examination revealed marked localised cervical lymphadenopathy, with a lymph node mass in the submandibular region measuring 2 × 2 cm. There was no associated organomegaly. She had been treated with a course of antibiotics six weeks previously for the lymphadenopathy, but there had been no response. She had been treated with a course of anti-tuberculous chemotherapy five years

previously for similar symptoms, and her mother had suffered from tuberculosis (TB) in the past.

A definitive diagnosis had not been made at this stage, but other conditions, such as infectious mononucleosis and systemic lupus erythematosus (SLE), were being considered. The only abnormalities on serum laboratory studies were a raised C-reactive protein (CRP) of 45 mg/l, and an erythrocyte sedimentation rate (ESR) of 88 mm/h. Renal, liver and thyroid function tests, as well as full blood count, were all normal. Rheumatological and hepatitis serology, angiotensin converting enzyme level, infectious mononucleosis screen, toxoplasma IgM and HIV antibody levels were also normal. However, she did have high levels of immunoglobulins IgA (5.3 g/l), IgM (4.4 g/l) and IgG (19.1 g/l).

She subsequently underwent excision biopsy of the cervical lymph node mass. This revealed a cellular picture with focal areas of necrosis containing karyorrhectic nuclear debris, scattered fibrin deposits and large collections of CD68 and CD163 positive plasmacytoid monocytes and phagocytic histiocytes containing 'crescentic' nuclei. There was no evidence of malignancy. The histological appearances were those of Kikuchi's lymphadenitis. As this is a self-limiting disease, no specific treatment was initiated. On review one month later, a marked improvement in the cervical lymphadenopathy was noted, although she did still complain of flu-like symptoms and malaise. Further review at three months confirmed a full recovery.

Epidemiology and natural history

Kikuchi's disease is a form of histiocytic necrotising lymphadenitis with characteristic histological features. It classically affects young females, with a typical female to male ratio of 3–4:1.⁴ It is a rare condition, and the true incidence is unknown. However, it is probably under-reported, and has been implicated in 6% of all pathologically abnormal lymph nodes.⁵ A large UK series highlighted the ongoing difficulty in recognising Kikuchi's disease by British pathologists.⁶ Knowledge of the disease is important as it may both clinically and pathologically mimic other conditions causing lymphadenopathy, particularly SLE, TB and lymphoma. Kikuchi's is a self-limiting disease and an

incorrect diagnosis may result in the administration of inappropriate and potentially toxic drug therapy.⁷

Aetiology and presentation

The aetiology of Kikuchi's disease is unresolved. Various infectious aetiologies, including toxoplasma, *Yersinia enterocolitica*, human herpes virus 6 and 8 and Epstein-Barr virus, have been postulated but these remain contentious. The disease typically affects young adults but has been reported in ages ranging from 19 months to 75 years.⁵ It has a predilection for the cervical lymph nodes, seen in 70–98% of cases, but may affect the axillary, intrathoracic, abdominal or pelvic lymph nodes.⁷ Dorfman and Berry⁸ found lymph nodes involved by Kikuchi's disease are usually less than 3 cm in size, a finding also seen in our case. Less common manifestations include weight loss, night sweats, nausea, vomiting, rashes and splenomegaly.⁹

Diagnosis and differential diagnosis

There are no specific diagnostic laboratory investigations available for detecting Kikuchi's disease,¹⁰ although negative tests are essential to exclude other differentials, for example:

- malignant lymphoma (Hodgkin's disease)
- SLE
- TB
- toxoplasmosis
- metastatic carcinoma
- cat scratch disease
- infectious mononucleosis
- AIDS.

Decreased peripheral blood leukocyte counts are seen in approximately 25–58% of patients, whereas 2–5% develop a leukocytosis;¹¹ few patients show an elevated ESR and CRP.⁴

Definitive diagnosis, therefore, is based on characteristic pathological findings, together with exclusion on histological grounds of conditions that mimic the disease, such as lymphoma which is incorrectly diagnosed in 30% of cases of Kikuchi's disease.⁸ Classical pathological findings in Kikuchi's include patchy areas of necrosis in the cortical and paracortical areas of the enlarged lymph node, together with nuclear debris or extensive karyorrhexis.⁹ Cellular histiocytic and immunoblastic proliferations seen in Kikuchi's may be mistaken for the atypical lymphocytes seen in lymphoma. Similarly, SLE may mimic Kikuchi's disease on histological grounds. In fact, an association between the two conditions has been suggested,⁸ although the true diagnosis of SLE is favoured by the presence of haematoxylin bodies or by large numbers of plasma cells surrounding necrotic foci.⁷

Treatment and prognosis

The majority of cases of Kikuchi's disease spontaneously resolve within one to four months.⁷ The treatment consequently is

Box 1. Key features of Kikuchi's disease.

- Commonly affects young Asian females
- Prodromal malaise, fatigue, and myalgia
- Fever is a prominent symptom
- Usually causes cervical lymphadenopathy
- Is a self-limiting illness
- Treatment usually symptomatic only
- Follow-up advised to detect recurrence or complications

symptomatic with non-steroidal anti-inflammatory drugs.¹² In more complicated cases, such as patients with recurrent episodes or prolonged symptoms, more aggressive management with systemic steroids has been required.¹³ Hydroxychloroquine has also shown some benefit in treating the disease.¹⁴ In common with other authors, we found no benefit of antibiotics.

A small number of fatalities due to Kikuchi's disease have been reported, with the causes of death including pulmonary haemorrhage and heart failure,¹⁵ as well as graft failure following renal, liver, and pancreatic transplants.¹⁶ Numerous studies have shown an association of Kikuchi's with a wide spectrum of autoimmune diseases, including Hashimoto's thyroiditis, polymyositis, mixed connective tissue disease, Still's disease and the antiphospholipid syndrome.^{17,18} Furthermore, other studies have described associations with infective disorders such as human T-lymphotropic virus (HTLV-1) and HIV.¹⁹

Of note in our patient's case was the anti-tuberculous therapy she had received five years previously. It may be that this was the first manifestation of Kikuchi's, which went unrecognised. Lin *et al*²⁰ found a number of their Kikuchi patients had a past history of TB, and suggest the possibility of a resultant transient immune reaction having some relationship with the subsequent development of Kikuchi's disease.

Kuo²¹ reported that although Kikuchi's is essentially a self-limiting illness, there is a 3% risk of recurrence. Recurrences usually occur within a few weeks of the first episode;²² however, they have been reported as late as 19 years after initial presentation.²³ Follow-up is advisable due to this small risk of recurrence. In addition, follow-up has been recommended due to the associated risk of developing SLE⁸ or lymphoma.²⁴

Key points (Box 1)

Kikuchi's disease is a rare but important cause of lymphadenopathy, which may present in a patient of any age and may affect a range of lymph node regions. It should be considered in the differential diagnosis of any patient presenting with unexplained lymphadenopathy, or with other non-specific symptoms such as fever and weight loss. Consideration of the diagnosis is particularly important before the institution of potentially inappropriate drug therapy, and to ensure patients are observed in order to detect recurrence or associated conditions such as SLE and lymphoma.

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