Severe Kikuchi’s disease responsive to immune modulation


ABSTRACT
Kikuchi’s disease, although an uncommon entity, has been increasingly reported since it was first discovered in 1972. The most common manifestation of Kikuchi’s disease, cervical lymphadenopathy, has no clinically distinguishable features. Therefore, a diagnosis of Kikuchi’s disease has largely been based on clinical suspicion and histopathological confirmation. We present a 15-year-old Chinese girl with severe Kikuchi’s disease, whose relapsing course was only responsive to high-dose steroids and intravenous immunoglobulin therapy.

Keywords: cervical lymphadenopathy, intravenous immunoglobulin, necrotising lymphadenitis, Kikuchi’s disease

INTRODUCTION
Kikuchi’s disease, although an uncommon entity, has been reported in increasing prevalence since its discovery in 1972. This is a clinicopathological condition characterised by histiocytic necrotising lymphadenitis, most commonly involving the cervical lymph nodes, and is associated with fever. It usually occurs in young adults with a female predilection, and is seldom reported in children. This illness typically runs a benign and self-limiting course.

CASE REPORT
The patient is a 15-year-old Chinese girl who was admitted to our hospital with prolonged high fever (maximum temperature of 40°C) for 11 days and gradual left neck swelling of six days duration. There were no upper respiratory tract symptoms, rash or joint pains. There were no associated constitutional symptoms and no prior history of tuberculosis exposure or contact history with cats. The symptoms did not abate despite a four-day course of oral amoxicillin prior to admission.

The physical examination revealed a firm, tender and non-fluctuant left cervical lymph node measuring 1 cm x 2 cm and multiple small right cervical lymph nodes. A Bacille Calmette-Guérin scar was present on the left deltoid. There were no rash, other enlarged lymph nodes or organomegaly noted on examination.

Blood counts showed a white blood cell count of 5.59–8.86 x 10⁹/L. The differential counts were normal with no blasts cells seen in the peripheral blood film. Acute phase reactants were elevated, while the blood and urine cultures were negative. Ultrasonography of the neck revealed enlarged posterior triangle lymph nodes with no evidence of abscess formation. The chest and lateral neck radiographs were normal. The screenings for autoimmune disease and Epstein-Barr Virus (EBV) infection were negative. The initial impression was cervical lymphadenitis, and she was started on intravenous penicillin. However, her fever and lymphadenopathy persisted in spite of the treatment with intravenous ceftriaxone and cloxacillin, bringing the total duration of illness to almost one month. The antibiotics prescribed are an appropriate first-line therapy for cervical lymphadenitis to cover for Gram-positive organisms. She subsequently developed a rash which consisted of pustular lesions over the face and limbs; however, there was no fluid which could be swabbed for culture. She also complained of arthralgia of the elbows and knees, accompanied by malaise, lethargy and a loss of appetite.

The cervical lymph nodes continued to enlarge bilaterally, with the largest reaching a diameter of 2 cm. There were no axillary or inguinal swellings, ulcers or joint swellings. The abdominal examination revealed mild hepatosplenomegaly. Serial blood tests during hospitalisation revealed a gradual leucopenia of 2.43 x 10⁹ cells per litre, with an absolute neutrophil count of 1.68 x 10⁹ and an elevated lactate dehydrogenase (LDH) exceeding 1,000 U/L. An extensive workup was performed to exclude non-infectious causes. The possibilities included autoimmune diseases, such as Still’s disease and systemic lupus erythematosus (SLE), malignancies such as lymphoma, and haematological conditions such as haemophagocytic syndrome.

Blood investigations carried out included SLE screening (anti-nuclear antibody, anti-double-stranded DNA, Complement 3 and 4 levels), anti-neutrophil cytoplasmic antibody, anti-extractable nuclear antigen panel, anti-smooth muscle antibody, anti-
lymphadenopathy, with minimal change limiting in progression

The rash also recurred

These histopathological findings were consistent with the diagnosis of Kikuchi’s disease. She was started on prednisolone (1 mg/kg/day) for symptomatic Kikuchi’s disease. The fever responded favourably, but there was no reduction in the size of the cervical lymph nodes. Attempts to taper steroid therapy resulted in a recurrence of fever, cutaneous rash and constitutional symptoms. Despite being on high-dose prednisolone for one month, the cervical lymph nodes increased in size and were accompanied by new lymph node enlargements in the cervical and inguinal areas. The enlarged cervical lymph nodes resulted in compressive symptoms of bilateral periorbital oedema and nasal swelling with congestion. The rash also recurred on the left cheek (Fig. 3). The progression of the signs and symptoms was unusual in Kikuchi’s disease, which is usually a benign, self-limiting condition. This necessitated further evaluation.

A repeat CT of the neck, thorax and abdomen demonstrated multiple bilateral diffuse cervical lymphadenopathy, with minimal change of the previously-enlarged mediastinal lymph nodes. A repeat biopsy of the cervical lymph nodes revealed a necrotising lesion with atypical cytotoxic NK/T-cell response. Immunostains showed a CD3+ T-cell population, with more CD8+ lymphocytes compared to CD4+. The CD8+ T-cells would unlikely play a prominent cellular role in lupus or tuberculosis. Detailed microbial studies carried out on the lymphoid tissues were negative for acid-fast bacillus (AFB) and other organisms. The lymph node biopsy specimen was negative for AFB smear and culture, as well as tuberculosis molecular studies. Toxoplasma immunoglobulin (IgG), cytomegalovirus (CMV), DNA, EBV polymerase chain reaction and human herpes virus 6 serology studies were negative. The patient was diagnosed with severe Kikuchi’s disease. Immunosuppressive therapy was started, as her debilitating symptoms had not abated even with high-dose steroid treatment. In addition to the constitutional symptoms of loss of weight and appetite, the patient also experienced pain over the neck region due to the enlarged cervical lymph nodes. There was also an apparent psychosocial impact on the child due to the prolonged course of her illness, the extensive workup and the protracted hospitalisation.

She was continued on prednisolone and administered a trial of immunosuppressive medicines. She did not respond to mycophenolate mofetil, and this was stopped after 12 days. There was some clinical improvement with the addition of ciprofloxacin. Intravenous methylprednisolone 300 mg (7.5 mg/kg) was administered daily over three days, followed by a dose of intravenous IgG 15 mg (0.4 mg/kg). A good clinical response was
obtained. Within a few days, there was a progressive decrease and an eventual disappearance of the enlarged lymph nodes, as well as a resolution of the rash and other constitutional symptoms. Intravenous immunoglobin (IVIG) and intravenous methylprednisolone therapies were repeated one month later with continued good response. There was an initial plan to administer a course of intravenous methylprednisolone and IgG monthly for a duration of six months, similar to the treatment for SLE. However, the patient demonstrated an almost complete clinical response to the first two doses, and there was no requirement to administer another course. She was maintained on low-dose steroids and ciprofloxacin, which was stopped after three months. She remains well eight months after cessation of all therapies.

**DISCUSSION**

The diagnosis of Kikuchi’s disease has largely been based on clinical suspicion and histopathological confirmation. Although there has been increased awareness of the disease since it was reported independently in 1972 by Kikuchi and Fujimoto, the origin of Kikuchi’s disease remains unknown. A demographical study for Kikuchi’s disease has been demonstrated in Asian patients. A case series on adult patients in Singapore showed similar findings compared to previous reports. However, there is no publication on paediatric patients or on patients with severe Kikuchi’s disease in Singapore.

The most common manifestation of Kikuchi’s disease, cervical lymphadenopathy, has no clinically distinguishable feature. Neck masses are frequently encountered in children, often posing a diagnostic challenge. The numerous causes of infection-related cervical lymphadenopathy include viral (EBV, CMV, human immunodeficiency virus, adenovirus), bacterial (Staphylococcus Aureus, Group A Streptococcus, Mycobacterium tuberculosis, Cat scratch disease, anaerobic bacteria), fungal (Candida, Aspergillus) and parasitic (toxoplasmosis) causes. Besides the abovementioned microbial causes, it is important to exclude diseases, such as malignancies (Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, leukaemia, metastatic disease, neuroblastoma) and autoimmune conditions (SLE, haemophagocytic syndrome, Kawasaki disease). Despite advances in modern technology, the diagnosis of Kikuchi’s disease is still based on clinical suspicion and histopathological confirmation. In retrospect, there were some clinical features in our patient which have been reported in association with Kikuchi’s disease: leucopenia, elevated acute phase reactants and LDH. The pathological features of Kikuchi’s disease, as described by Gleeson et al, include lymph node necrosis with karyorrhexis surrounded by histiocytes without granuloma formation, and the absence of neutrophilic or plasma cell infiltration. Kikuchi’s disease has a myriad of less common clinical presentations, such as axillary and mesenteric lymphadenopathy, splenomegaly, cutaneous rash, arthralgia, aseptic meningitis, bone marrow haemophagocytosis and interstitial lung disease. The cutaneous lesions include erythematous macules, papules, plaques and nodules. No pathognomonic pattern has been reported, although certain case series reported a more severe course when there was cutaneous involvement, as was seen in our patient.

Kikuchi’s disease has a reported association with several illnesses, including SLE and lymphoma. There was therefore the need to perform extensive investigations in our patient to exclude synchronous pathology. The course of our patient was atypical, as Kikuchi’s disease usually resolves spontaneously within months. Patients with severe or persistent symptoms usually respond to corticosteroids. Immunosuppressive therapy has also been recommended for complicated cases with increased LDH and raised serum antinuclear antibody titres, in order to prevent a fatal outcome. There was some improvement in the patient’s symptoms after steroids were started, but attempts at tapering the dosage led to a flare-up each time. In fact, consistent with the features of severe disease, her signs and symptoms worsened despite the high-dose steroids.
The pathogenesis of Kikuchi’s disease remains unknown, although some authors have hypothesised that this syndrome may reflect a self-limited autoimmune condition induced by virus-infected transformed lymphocytes. Kikuchi’s disease may represent an exuberant T-cell mediated immune response in a genetically susceptible individual to a variety of non-specific stimuli.\(^{10}\) Ohshima et al have demonstrated that apoptotic cell death may play a role in the pathogenesis of the disease – proliferating cytotoxic CD8+ T-cells participating in the apoptotic process via the Fas and perforin pathways.\(^{11}\) Therefore, immunosuppressive medications have been used in the treatment of severe Kikuchi’s disease. Mycophenolate mofetil was chosen for a more targeted T-cell suppression, which was unfortunately not effective in our patient. Other drugs that have been used include IVIG\(^{12}\) and ciprofloxacin.\(^{13}\) The role of IVIG in Kikuchi’s disease is still unknown, but with its nonspecific anti-inflammatory effects, it may be effective in conditions where no autoantibody has been demonstrated. Additionally, the modulation of T-cell-dependent inflammation has also been described. Previous documented success with the latter suggests the possibility of a microbial aetologic factor. Fortunately, this treatment regime was used with success in our patient.

Long-term follow-up studies of paediatric patients have shown that a significant proportion developed symptoms months to years later.\(^{14}\) Although their conditions were highly variable, this could be explained by the presence of an autoimmune process. The risk of evolution into an autoimmune syndrome in children with Kikuchi’s disease appears to be present, and long-term follow-up is thus recommended.

REFERENCES