Kikuchi’s Disease - A Rare Cause of Lymphadenopathy and Fever

Sukhjot Kaur*, Rajesh Mahajan**, Narender Pal Jain***, Neena Sood****, Sandeep Chhabra†

Abstract
Kikuchi’s disease is a rare, benign, self-limited disorder, characterised clinically by fever and tender regional lymphadenopathy. It has been reported worldwide and is particularly common in people of Asian descent. The cause of Kikuchi’s disease is unknown. It predominantly affects young females and can closely mimic several infectious and immunological conditions. Histopathologic features of lymph nodes in Kikuchi’s disease are characteristic and permit differentiation of this benign condition from lymphomas, systemic lupus erythematosus and infectious lymphadenopathies. We report a female patient presenting with fever and tender cervical lymphadenopathy. She was being treated for tubercular lymphadenitis and was referred after she developed a transient hepatitis and a skin rash following treatment with anti-tubercular drugs. An excisional biopsy of the lymph node revealed histiocytic necrotising lymphadenitis, consistent with Kikuchi’s disease. A brief review of the pathogenesis and differential diagnosis of Kikuchi’s disease is presented.

Introduction
Kikuchi’s disease or histiocytic necrotising lymphadenitis is an uncommon, benign and self-limited condition of unknown aetiology that was initially described in Japan.1,2 Kikuchi’s disease is known to have a worldwide distribution with a higher prevalence among Japanese and other Asian people. It mainly affects young adults and is clinically characterised by tender regional lymphadenopathy, fever, and occasional systemic involvement. The lymphadenitis in Kikuchi’s disease reveals characteristic histopathologic features of coagulative necrosis and karyorrhectic debris.3 Differential diagnosis includes lymphoma and lymphadenitis associated with systemic lupus erythematosus (SLE), and certain infectious aetiologies, which share similar clinicomorphologic features.4 We report a female patient presenting with prolonged fever and tender cervical lymphadenopathy, in which the diagnosis of Kikuchi’s disease was based on characteristic histopathologic findings in the lymph nodes. She was initially diagnosed as lymph node tuberculosis and developed transient hepatitis and a skin rash following anti-tubercular therapy. Kikuchi’s disease is a rare and possibly an under-diagnosed condition, with an excellent prognosis. We provide a brief review of literature with special emphasis on the differential diagnosis of histiocytic necrotising lymphadenitis.

Case Report
A 21-year old female presented with fever, malaise, anorexia, and a neck swelling of 12 weeks duration. She had also noticed a mildly pruritic, erythematous rash on her face, trunk and extremities since the past 10 days. Her other symptoms included headache, nausea, vomiting and sore throat. There was no history of a cough, chest pain or joint symptoms. She had been well until the onset of her current illness. Personal and family history was unremarkable. Fine needle aspiration cytology from the cervical lymph node done elsewhere showed necrotic debris, and lymphoid tissue with histiocytic collections admixed with few neutrophils. Her medications included antitubercular drugs (Rifampicin 450 mg/day, Isoniazid 300 mg/day, Ethambutol 800 mg/day and Pyrazinamide 1500 mg/day) started from a different centre, which she was taking for the past 20 days. Examination revealed a temperature of 38.9°C, pulse 108
beats per minute, and blood pressure of 110/70 mm Hg. Right cervical lymphadenopathy was identified. There were multiple, tender, mobile lymph nodes in the right posterior cervical and submandibular regions, with the largest node measuring approximately 3 cm x 4 cm. There were no lymph nodes elsewhere and she had no hepatosplenomegaly. On cutaneous examination a widespread, faintly erythematous, blanchable macular rash was appreciated on face, neck, trunk and extremities. The rest of the clinical examination was unremarkable.

Laboratory work up revealed a haemoglobin of 9.4 g/dl (reference range 13-17 g/dl), white blood cell count of 6.7 x 10^3/µl (reference range 4-10 x 10^3/µl), platelet count of 354 x 10^3/µL (reference range 150-410 x 10^3/µl), aspartate aminotransferase 214 U/L (reference range 0-40 U/L), alanine aminotransferase 135 U/L (reference range 0-41 U/L), and alkaline phosphatase of 85 U/L (reference range 40-129 U/L). Inflammatory markers were elevated with C-reactive protein 175.9 mg/L (reference range 0-6 mg/L), ferritin 837 ng/L (reference range 30-400 ng/L), and lactate dehydrogenase 585 U/L (reference range 240-480 U/L). Patient had normal values of urea, creatinine, urinalysis and blood and urine cultures. Antinuclear factor, double stranded DNA and anti-neutrophil cytoplasmic antibody were negative. Serology for Epstein-Barr virus, hepatitis B and C, and HIV was also negative. Chest X-ray was normal and Mantoux test showed no induration or erythema at 48 hours. Ultrasound abdomen did not reveal any abnormality. Bone marrow aspiration and a trephine biopsy showed normocellular marrow with myeloid prominence and reduced bone marrow iron stores. There was no evidence of lymphoma or non-caseating granulomas.

Excisional biopsy of the cervical lymph node was performed and a histopathologic examination revealed an effaced nodal architecture with foci of necrosis containing karyorrhectic debris, and an infiltrate of abundant histiocytes and lymphocytes (Figure 1). The histiocytes had a clear cytoplasm and round nuclei. A few plasma cells were also identified in the section (Figure 2). Neutrophils, atypical cells, Reed Sternberg cells or granulomas were not identified in any section. Stains and cultures for bacteria, fungi and mycobacteria were negative. These findings were consistent with a histological diagnosis of histiocytic necrotising lymphadenitis.

Based on a clinico-pathologic correlation, a diagnosis of Kikuchi’s disease with drug induced hepatitis and macular rash was made. Anti-tubercular therapy was withdrawn and patient was treated with mometasone cream 0.1% daily and oral hydroxyzine 25 mg twice daily for 2 weeks. Her temperature and the skin eruption settled after 2 weeks and hepatic enzyme levels reached normal limits within the next 3 weeks. The patient remains well 12 months after the diagnosis of Kikuchi’s disease.

Discussion

Kikuchi’s disease also known as histiocytic necrotising lymphadenitis was originally reported in young Japanese females in 1972, by Kikuchi and Fujimoto and colleagues. The classic findings of Kikuchi’s disease are lymphadenopathy and fever. Kikuchi’s disease affects all ethnic groups with a higher prevalence among the Japanese and other Asian people. A search of literature revealed less than 20 cases from India, following the first case reported in 1998 by Mathews et al.

Most of the patients are young adults, below the age of 40 years. In general, a female preponderance has been reported with a female to male ratio of 4:1. The onset of Kikuchi’s disease is usually acute or subacute with fever and regional lymphadenopathy which is mostly cervical; in a previously healthy young adult. Enlarged lymph nodes range from 0.5 to 4 cm in size.
and are tender and painful. Other anatomic sites of lymphadenopathy are involved in 2% to 40% of patients. Involvement of mediastinal, peritoneal and retroperitoneal regions is uncommon. Less frequent symptoms such as fatigue, arthralgia, joint pains, nausea, vomiting, anorexia, and sore throat have been reported in 2-7% of patients. Weight loss and night sweats, though rare, have also been observed.6

Extra-nodal involvement in Kikuchi’s disease is rare and has been documented in skin, bone marrow, myocardium and central nervous system.3,4 Cutaneous manifestations, mostly non-specific and variable in nature, have been reported in 16-40% of patients with Kikuchi’s disease.7 In a recent review the most common manifestation was a rash, followed by erythematous macules and patches, erythematous papules and plaques and erythematous macules and papules.7 Apart from these, malar erythema, oral ulcers, pruritus, alopecia, photosensitivity, conjunctival injection and scaling have also been observed in a smaller number of patients. Hepatosplenomegaly is relatively common; while neurologic involvement has been documented in form of isolated case reports of aseptic meningitis, acute cerebellar ataxia, and raised intracranial tension secondary to cerebral venous obstruction.6 Systemic symptoms are found more frequently in patients with extra-nodal involvement.

Various laboratory abnormalities that have been reported include leucopenia, elevated erythrocyte sedimentation rate, anaemia, elevated aminotransferases, elevated lactate dehydrogenase, thrombocytopenia and mild leucopenia. Anti nuclear antibody (ANA) is positive in about 7% of patients.6,7

Diagnosis of Kikuchi’s disease is based on histopathologic examination of an excision biopsy of affected lymph nodes.1,2 Characteristic histopathologic features include irregular paracortical areas of coagulative necrosis, with abundant karyorrhectic debris which can distort the nodal architecture and a large number of histiocytes at the margin of the necrotic area. Karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes, but also immunoblasts and small and large lymphocytes. Neutrophils and eosinophils are significantly absent and plasma cells are absent or scarce.3,4 A predominance of CD8+ cells over CD4+ cells among the T cell infiltrate is noted.5 The histiocytes express histiocytic-associated antigens such as myeloperoxidase, lysozyme and CD68.5

The histologic differential diagnosis of Kikuchi’s disease includes lymphadenitis associated with systemic lupus erythematosus, lymphoid malignancies, infections like tuberculosis, infectious mononucleosis, syphilis and rarely sarcoidosis and adenocarcinoma. The course and treatment of Kikuchi’s disease differs dramatically from these disorders, hence they should be excluded before a diagnosis of Kikuchi’s disease is made.

Systemic lupus erythematosus (SLE) presents the most challenging disorder from which it has to be differentiated. SLE lymphadenitis demonstrates aggregates of degenerated nuclear debris, degenerated nuclear material in walls of blood vessels, prominent reactive hyperplasia, abundant plasma cells, and capsular or pericapsular inflammation.5 Features that favour Kikuchi’s disease include predominance of CD8+ cells, absence of neutrophils, and a relative paucity of plasma cells.6 A careful evaluation of patient’s history, examination and anti nuclear antibodies can be helpful in difficult cases.6

Kikuchi’s disease can also be mistaken for malignant lymphoma, especially T-cell non Hodgkin’s lymphoma, due to presence of numerous atypical monocytes and immunoblasts.6,9 Classic Hodgkin lymphoma could cause necrosis and have histiocytic infiltrate, but presence of large Reed Sternberg cells that stain with CD30 or CD15, and numerous eosinophils, as well as neutrophils makes its recognition easier. The large cells observed in Kikuchi’s disease are positive for CD68 and myeloperoxidase (MPO), while they are negative for CD3, CD20, which excludes the possibility of lymphomas.9 The T-cell lymphomas are characterised by CD4 positivity while CD8 positive T-cells are present in Kikuchi’s disease. In difficult cases, Immunohistochemical and flow cytometric analysis can be useful to rule out malignant lymphoma.6 Positive immunostaining by monoclonal antibody Ki-M1 P1 is seen in Kikuchi’s disease but not in malignant lymphoma. In plasmacytoid T-cell leukaemia, proliferative plasmacytoid cells do not express myeloperoxidase, while in Kikuchi’s disease histiocytic component is MPO positive. Rarely Kikuchi’s disease may be associated with histiocytes resembling signet ring cells and a diagnosis of metastatic adenocarcinoma can be considered. The latter however has atypical nuclei and they contain mucin rather than cellular debris.

Several infectious aetiologies can also mimic Kikuchi’s disease histologically. In contrast to Kikuchi’s disease, viral lymphadenitis has less prominent histiocytic infiltrates, more neutrophils, more plasma cells and predominant CD4+ cells.3,6 Diagnosis of infectious mononucleosis can be made by characteristic clinical, haematologic and serologic findings.6 Necrotising granulomatous lymphadenitis of tuberculosis, leprosy, histoplasmosis, and cat scratch disease display proliferations of epithelioid cells, giant cells, and granuloma formation.6 Necrotising lymphadenitis in syphilis is usually accompanied by perivascular plasma cell infiltrates. These infectious agents could also be suggested by appropriate
serologic tests or can be detected by molecular diagnostic studies."Sarcoidosis is characterised by histologic evidence of epithelioid cell granulomas in an appropriate clinical situation.

The aetiology of Kikuchi’s disease is unknown, although a viral, genetic and an auto-immune hypothesis have been proposed. Several infectious agents have been implicated, including Epstein-Barr virus, human herpes virus 6, human immunodeficiency virus, HTLV 1, herpes simplex virus, hepatitis B, dengue virus, parvovirus B 19, Yersinia enterocolitica, Bartonella, Brucella and Toxoplasma organisms. Out of these, Epstein Barr virus has been most consistently studied, and serologic evidence of acute infection with EBV has been reported. Attempts have been made by several investigators for detection of EBV in the tissues by polymerase chain reaction (PCR), in-situ hybridisation (ISH), and detection of DNA, RNA and proteins by immunohistochemistry. It has also been hypothesised that Kikuchi’s disease might represent an exuberant T-cell mediated hyper-response to certain antigenic stimuli in genetically susceptible individuals. Some studies have shown that primary proliferative cells are CD8+ lymphocytes, which induce target cell apoptosis and also undergo apoptosis themselves, accounting for the characteristic necrosis and nuclear debris seen in Kikuchi’s disease. Another hypothesis that has been proposed is that Kikuchi’s disease might represent a SLE-like, autoimmune-type lymphadenitis, triggered by viruses or other infectious agents.

Association between Kikuchi’s disease and SLE has been reported, with some patients of Kikuchi’s disease developing a full blown SLE. Kikuchi’s disease can also precede or coincide with the diagnosis of SLE, and SLE should always be excluded in patients presenting with necrotising lymphadenitis. It is recommended to perform ANA screening at the time of diagnosis, and the patients with Kikuchi’s disease should also have a follow up evaluation for SLE.

Kikuchi’s disease typically is self-limited, usually resolving within one to four months. A low recurrence rate of 3% to 4% has been reported. Treatment is supportive, with analgesics, anti-pyretics and rest. Other therapies such as corticosteroids, hydroxychloroquine, methotrexate, and intravenous immunoglobulin have been used for severe cases.

Kikuchi’s disease with multisystem involvement and adverse reaction to drugs has been reported rarely before. Transient fulminant hepatic failure developed following anti-tuberculous therapy in a patient who also had severe systemic features. Our patient had received anti-tubercular therapy from another centre with a diagnosis of tuberculous lymphadenitis. Raised transaminases and a maculopapular skin rash that developed after anti-tubercular therapy resolved promptly on withdrawal of the drugs. The presence of fever and cervical lymphadenopathy particularly in a young adult in a developing nation like India, often leads to an initial diagnosis of tuberculosis or even lymphoma. Fourteen of 28 cases in Kikuchi’s series and seven of 12 in Fujimoto series had received an initial label of tubercular lymphadenitis. Tuberculosis remains a major differential diagnosis especially in a developing country like India.

The importance of this report is that although Kikuchi’s disease is well recognised by pathologists, rheumatologists and dermatologists, it is not a well known entity by general medical physicians. Awareness of this benign disorder by clinicians might help prevent misdiagnosis and inappropriate treatment. The course and treatment of Kikuchi’s disease differs dramatically from that of lymphoma, tuberculosis and SLE. Recognition of Kikuchi’s disease is thus crucial and it merits active consideration especially in young patients with cervical lymphadenopathy and fever.

References