Kikuchi's disease is a rare, benign, self-limiting disorder characterized by fever and lymphadenopathy. Kikuchi's disease has a varied presentation from being just a benign self-limiting lymphadenopathy to having systemic involvement and some patients have also been reported to develop autoimmune disorder. This enigmatic disease of unknown aetiology could easily be mistaken for several infective and autoimmune disorders which it resembles. Since a definitive diagnosis can only be made by lymph node biopsy and symptoms are non-specific Kikuchi's disease should be kept in mind as a differential diagnosis in a patient of PUO with lymphadenopathy. We report cases of two patients who were being treated for months as PUO with parotitis and lymphadenopathy before being diagnosed with Kikuchi's disease after lymph node biopsy and both patients were also seropositive for antinuclear antibodies.

INTRODUCTION
Kikuchi's disease or Kikuchi Fujimoto disease or histiocytic necrotizing lymphadenopathy was first described in 1972 as lymphadenitis with focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris. Kikuchi's disease is frequently found in East Asian countries. No definite aetiology of Kikuchi's disease is known despite autoimmune and infection factors being suggested. The diagnostic hallmark is histological findings from lymph nodes. Patients are usually young and seek medical care because of acute tender cervical lymphadenopathy and fever. We report two male patients, one of them was diagnosed with Kikuchi's disease at our hospital while the other patient had already been diagnosed and treated for Kikuchi's disease elsewhere several years back but presented to us with arthritis involving arteries of both upper limbs. Both patients, after lymph node biopsy, had histologically and immunohistochemically proven Kikuchi's disease but also had seropositivity for antinuclear antibodies.

CASE REPORT
Case 1:
A 25-year-old male presented to us with fever, preauricular swelling bilaterally of 1 month duration, yellowish discolouration of eyes since 1 week and had bleeding from gums and lips since last 2-3 days. Other symptoms included vomiting, weight loss and anorexia. There was no history of rashes, cough or joint pain. There was no history of tuberculosis or jaundice in the past and family history was unremarkable. Before coming to us he was admitted at a hospital where he was being treated with mumps and FNAC of parotid gland done there showed chronic inflammation of salivary gland with no malignant cells or granuloma. On examination he was afebrile, pulse 86 beats per minute, blood pressure of 120/70 mmHg. He had pallor, icterus and was bleeding from his lips. He had multiple small non tender mobile lymph nodes in left posterior cervical region, with the largest node measuring around 1.5 cm x 1 cm along with bilaterally enlarged axillary lymph nodes. There were also few small nodules in bilateral lower lobes of lung.

Because of the increased INR, lymph node biopsy could not be done and the patient was given symptomatic treatment along with vitamin K injections. Meanwhile he continued to have fever and his general condition was deteriorating along with increase in parotid swelling. In view of his deteriorating condition, previous FNAC showing no evidence of granuloma and the reports available till then it was decided to treat the patient with steroids to which the patient responded dramatically with clinical improvement within 2-3 days. Once INR normalized, axillary lymph node biopsy was done which had features of necrotizing lymphadenitis on histopathological examination with no evidence of lymphomatous involvement and no acid fast bacilli could be demonstrated on ZN staining. For confirmation immunohistochemistry was done which showed histological picture of necrotizing lymphadenitis of Kikuchi-fujimoto type.

The patient was discharged on oral steroids and was asymptomatic on follow up. His autoimmune profile was also repeated on follow-up to rule out any chance of false positive results during the previous admission, but it again was positive for RNP/Sm(++) and Anti Sm(-) antibodies.

Case 2:
A 29-year-old male patient came to us with complaints of painful swelling in pulp of both hands of 1 week duration along with bluish discolouration of eyes since last 3-4 days. He had no other significant complaints and there was no history of fever, dyspnoea, trauma, diabetes, hypertension, cardiacl illness or similar episodes in the past. He was a non-smoker and non-alcoholic. His symptoms used to get aggravated on exposure to cold and pain was somewhat relieved by keeping his hands warm but the bluish discolouration was persistent.

He gave history that two years back he suffered from fever, swelling in parotid region along with nodules in neck for 4 months before being diagnosed with Kikuchi's disease. His previous medical records

ABSTRACT
Kikuchi's disease, Lymphadenopathy, PUO, Autoimmune, SLE, ANA

KEYWORDS
Kikuchi's disease, Lymphadenopathy, PUO, Autoimmune, SLE, ANA
Involvement of mediastinal, peritoneal, retroperitoneal region is common and less frequent symptoms include weight loss, nausea, vomiting, sore throat, night sweats. It should be mentioned that systemic symptoms are found more frequently when extranodal involvement is present. Extranasal involvement is rare but skin, bone marrow, myocardium, central nervous system have been reported. A variety of dermatological patterns have been observed including rashes; nodules; erythematous, crusted papules; scattered, indurated, erythematous lesions; erythema multiforme; and erythematous maculopapular eruptions, all affecting face and upper body. A few patients have had generalized lymphadenopathy and hepatitisplenomegaly as initial presentation. Kikuchi's disease also has been reported as a cause of prolonged fever of unknown origin. Neurological involvement has been documented in form of isolated case reports of aseptic meningitis, acute cerebellar ataxia and increased intracranial tension secondary to central venous obstruction.

There is much speculation about the cause of Kikuchi's disease; a viral or autoimmune cause has been suggested. It is thought to be a nonspecific exuberant T cell mediated immune response in a genetically susceptible individual to a variety of nonspecific stimuli. Mycobacterium Szulgai, yersinia and toxoplasma have been implicated. More recently there have been growing evidence of role of EBV as well as other virus (HHV6,HHV8, Parvovirus B19,HHV and HTLV) in pathogenesis of Kikuchi's disease. However many independent studies have failed to identify the presence of these infectious agents in case of Kikuchi's lymphadenopathy. Some HLA class II genes are more frequent in patient with Kikuchi's disease. In particular, the incidence of DPA*0101 and DPBI*0202 alleles is significantly higher in patients with Kikuchi's disease than a healthy control subject. These genes are extremely rare or absent among Caucasians but relatively common among Asian people. This might provide an admissible explanation about the above mentioned epidemiological pattern.

Laboratory investigation revealed haemoglobin of 14 gm/dl (reference range 10.5-17 gm/dl), white blood cell count of 9.55 x 10^9/l (reference range 4.1-11 x 10^9/l), platelet count 166 x 10^9/l (reference range 150-450 x 10^9/l), ESR 08 mm/hr (reference range 0-22 mm/hr), CRP 0.5 mg/dl (reference range 0-1 mg/dl), creatinine 0.7mg/dl (reference range 0.8-1.3 mg/dl), aspartate aminotransferase 21 U/L (reference range 5-35 U/L), alanine aminotransferase 27 U/L (reference range 21-72 U/L), total bilirubin 0.4mg/dl (reference range 0.2-1.3 mg/dl), alkaline phosphatase 92 U/L (reference range 45-115 U/L), Antiphospholipid and antineutrophil cytoplasmic and dsDNA antibodies were negative. Antinuclear antibodies were positive for Anti Sc1 70(++).. X-Ray chest and X Ray cervical spine was normal. Arterial Doppler of upper limb showed decreased velocity and flow in left axillary artery, reduced flow and velocity with thickened wall of both radial arteries at wrist along with reduced flow in digital arteries. Steroids were continued and patient was also given cilastazol. Symptoms started improving after 3-4 days following which patient was discharged.

**DISCUSSION**

Kikuchi's disease was first described in Japan in 1972 by Dr. Masahiro Kikuchi as a case of lymphadenitis characterised by focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris in the Japanese Journal of the Haematological Society. In the same month, Dr. Fujimoto presented a similar case in a separate Japanese journal. Kikuchi Fujimoto disease is known to have a worldwide distribution with higher prevalence among Japanese and other Asiatic population. It is scarcely known in the western hemisphere. In fact, the first description of this disorder outside Asia was made by Pilew and colleagues in 1982 with Kikuchi as co-author. In general the disease affects young adults (mean age 20-30 years). Although earlier reported to be a female predominant illness with Female:Male ratio of 4:1, recent reports suggest that actual ratio is closer to 1:1. Very few cases of Kikuchi's disease have been reported in India following the first case reported in 1998 by Mathew et al.

Onset of Kikuchi's disease is acute or subacute evolving over a period of 2-3 weeks and lasting for 1 to 4 months with possible recurrence rate of 3%-4%. Tender lymphadenopathy with fever is the most common presentation. Lymph node size ranges from 0.5-4cm. Generalized lymphadenopathy have been reported in 1%-22% of cases. Involvement of mediastinal, peritoneal, retroperitoneal region is uncommon and less frequent symptoms include weight loss, nausea, vomiting, sore throat, night sweats. It should be mentioned that systemic symptoms are found more frequently when extranodal involvement is present. Extranasal involvement is rare but skin, bone marrow, myocardium, central nervous system have been reported. A variety of dermatological patterns have been observed including rashes; nodules; erythematous, crusted papules; scattered, indurated, erythematous lesions; erythema multiforme; and erythematous maculopapular eruptions, all affecting face and upper body. A few patients have had generalized lymphadenopathy and hepatitisplenomegaly as initial presentation. Kikuchi's disease also has been reported as a cause of prolonged fever of unknown origin. Neurological involvement has been documented in form of isolated case reports of aseptic meningitis, acute cerebellar ataxia and increased intracranial tension secondary to central venous obstruction.

Imamura and co-workers hypothesized that Kikuchi's disease might reflect a self limiting Systemic Lupus Erythematosus(SLE) like autoimmune condition induced by virus infected transformed lymphocytes. Yet the results of serologic studies testing ANA, Rheumatoid factor and other immunological parameters consistently have been negative in these patients providing no support for an autoimmune nature. Nevertheless the association between Kikuchi's disease and SLE have been reported with frequency probably greater than that expected by chance alone. The diagnosis of Kikuchi's disease can precede, post date or coincide with the diagnosis of SLE. With regard to this topic, in 2003, Hu and co-workers reported a clinicopathologic analysis of 18 cases of Kikuchi's disease plus SLE and tried to classify the relationship between the conditions. They concluded that Kikuchi's disease is not related to SLE and that Kikuchi's disease like lymphadenitis coexisting with SLE should be regarded as a lupus lymphadenitis on the basis of several histologic criteria. Nevertheless 6 cases of pre SLE or post SLE necrotizing lymphadenitis were found to be true Kikuchi's disease. In addition to SLE other autoimmune condition and manifestations such as antiphospholipid syndrome, polyarthritis, systemic juvenile idiopathic arthritis, bilateral uveitis, arthritis, cutaneous necrotizing arteritis, idiopathic arthritis, uveitis, arthritis, cutaneous necrotizing arteritis and antiphospholipid syndrome, polyarthritis, systemic juvenile idiopathic arthritis, bilateral uveitis, arthritis, cutaneous necrotizing arteritis and antiphospholipid syndrome. More recently there have been growing evidence of role of EBV as well as other virus (HHV6,HHV8, Parvovirus B19,HHV and HTLV) in pathogenesis of Kikuchi's disease. However many independent studies have failed to identify the presence of these infectious agents in case of Kikuchi's lymphadenopathy. Some HLA class II genes are more frequent in patient with Kikuchi's disease. In particular, the incidence of DPA*0101 and DPBI*0202 alleles is significantly higher in patients with Kikuchi's disease than a healthy control subject. These genes are extremely rare or absent among Caucasians but relatively common among Asiatic people. This might provide an admissible explanation about the above mentioned epidemiological pattern.

**DIAGNOSIS**

- **Differential diagnosis includes - SLE**
- **Lymphomas**
- **Tuberculosis**
- **Infectious mononucleosis**
- **Syphilis**
- **Sarcoidosis**

- **Laboratory investigations** – Mild granulocytopenia observed in 20%-25% cases. Leukocytosis in 2%-5% cases. A t y p i c a l lymphocytosis in 25%-31% cases. ESR and CRP may be elevated. Increased LDH suggests hepatic involvement.

- **Imaging studies** – diagnostic imaging studies can confirm the
presence of enlarged lymph node in affected areas but they cannot specifically confirm the diagnosis of Kikuchi’s disease.

- **Laboratory procedures** - FNAC: definitive diagnosis can only be made by tissue examination. Cytological examination by FNAC can suggest the diagnosis of Kikuchi’s disease when supported by typical clinical findings but in general it is less useful than excisional lymph node biopsy. In a retrospective study of 44 patients FNAC achieved an accuracy of 56.25%. Characteristic cytological findings include crescentic histiocytes, plasmacytoid monocytes, macrophages and immunoblasts (predominantly T cells).

- **Excisional lymph node biopsy**: histological findings consistent with Kikuchi’s disease include:
  1. Paracortical necrosis which may be patchy or confluent, the degree of necrosis varying considerably from one case to another.
  2. In the presence of granulation tissue, histiocytes and macrophages containing phagocytized debris from degenerated lymphocytes are seen.
  3. Other cells include lymphocytes, plasmacytoid monocytes, macrophages and immunoblasts (predominantly T cells).

Histiocytes and plasmacytoid monocytes make the most distinctive cell types found within karyorrhectic foci. In fact it has been considered that the earliest recognizable foci and minimum diagnostic criteria of Kikuchi’s disease are para-cortical clusters of plasmacytoid monocytes with interspersed karyorrhexis and crescentic histiocytes.

Kuo proposed the following three histological stages:

- Proliferative - initial phase consisting basically of various histiocytes, plasmacytoid, monocytes and a variable number of lymphoid cells with karyorrhectic nuclear fragments and eosinophilic apoptotic debris.
- Necrotizing - extensive necrosis that may destroy the normal architecture of lymph node.
- Xanthomatosus - predominance of foamy histiocytes regardless of the presence or absence of necrosis.

The most common type is the necrotizing type, accounting for slightly more than half the cases. The histological type might represent different stages of the disease or might reflect differences in cause or host reaction. It is thought that Kikuchi’s disease begins as proliferative, progresses to necrotizing and finally resolves into xanthomatosus. However, sequential biopsy specimens were not available in study by Kuo to verify the postulated concept. Also data on duration of disease did not correlate with progression of three histological types.

- **Immunohistochemical features**: predominance of T cells with very few B cells with predominance of CD8+ cells over CD4+. The histiocytes express histiocyte associated antigens such as lysozyme, MPO and CD68. They also express CD4 and CD74 and are positively stained by macrophage mononuclear antibody Ki-MIP.

- **Distinguishing Kikuchi’s disease from Lymphoma**: The numerous atypical monocytes and T cell immunoblast observed in Kikuchi’s disease with a histiocytic pattern. Finally the presence of large number of plasma cells with reoccurrence of symptoms as was evident in both our cases.

- **Distinguishing Kikuchi’s disease from SLE**: Kikuchi’s disease and SLE have similar histopathological appearance. Features that can be seen in SLE associated lymphadenitis but not in Kikuchi’s disease include Hematoxylin bodies, believed to represent degenerated nucleoli that have reacted with antimullerian antibodies, and the Azzopardi phenomenon (i.e. encrustation of blood vessel wall with nuclear material). These striking features might not be identified in every case of SLE associated lymphadenitis, however, and the diagnosis cannot always be ruled out on histological grounds alone. Nevertheless even though this information is little about lupus associated lymphadenitis, its immunophenotype seems to be virtually identical to that of Kikuchi’s disease including CD68+/MPO+ histiocytic pattern. Finally the presence of large number of plasma cells in a given lymph node with features resembling those of Kikuchi’s disease favours SLE associated lymphadenitis over Kikuchi’s disease.

Most patients of kikuchi’s disease can be managed by supportive therapy, such as analgesics and anti-inflammatory medication. Use of steroid has been recommended in severe and persisting symptoms and recurrences. There are reports of excellent responses to hydroxychloroquine, immunoglobulins, and minocycline.

**REFERENCES**


