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KIKUCHI'S DISEASE - *A COMPREHENSIVE REVIEW WITH CASE REPORT OF TWO PATIENTS OF KIKUCHI'S DISEASE WITH AUTOIMMUNE DISORDER.*

General Medicine

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ABSTRACT

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 withparotitis and lymphadenopathy before being diagnosed with Kikuchi's disease after Lymph node biopsyand both patients were also seropositive for Antinuclear antibodies.

KEYWORDS

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

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. [1] 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'sdisease elsewhere few years back but presented to us with arteritis 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 25year 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. He was completely asymptomatic until his symptoms started appearing and 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 treatedas 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. He also had tender hepatomegaly while rest of the clinical examination was unremarkable.

Laboratory work up revealed a haemoglobin of 11.9 gm/dl (reference range 10.5-17 mg/dl) , white blood cell count of 5.61 x 10^3 /µl (reference range 4-11.5 x 10^3 /µl) , platelet count of 90 x 10^3 /µl (reference range 150-450 x 10^3/µl), aspartate aminotransferase 1795 U/L (reference range 17-59 U/L), alanine aminotransferase of 329 U/L (reference range 21-72 U/L), alkaline phosphatise 1311U/L (reference range 45-115 U/L) , total bilirubin 4.9mg/dl(reference range 0.2-1.3mg/dl), direct bilirubin 3.2mg/dl (reference range 0.0-0.3mg/dl) , indirect bilirubin 1.7mg/dl (reference range 0.2-1.0mg/dl) , creatinine 0.5mg/dl (reference range 0.8-1.3 mg/dl), angiotensin converting enzyme 123.6 U/L (reference range 8-52 U/L) , International normalized ratio(INR) of 2.15 (reference range 0.8-1.1). HIV, hepatitis B, hepatitis C serology and anti-neutrophil cytoplasmic antibody and dsDNA antibody were negative. Keeping an autoimmune aetiology in mind his antinuclear antibody profile was sent which was positive for Anti RNP/Sm (+++) and Anti Sm(+) antibodies.

Ultrasonography scan of abdomen showed hepatomegaly with multiple mesenteric and iliac lymphadenopathy.HRCT chest revealed enlarged necrotic lymph nodes in subcarinal region with enlarged bilateral axillary and left cervical 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 histologicalpicture of necrotizing lymphadenitis of Kikuchi-fujimoto type.

The patient was discharged on oral steroids and was asymptomatic on follow up. His autoimmune profile wasalso 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(+++) , Sm(+++) , Ro-52 recombinant(++) 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 in the pulp of index and middle finger of right hand since the last 3-4 days. He had no other significant complaints and there was no history of fever, dyspnoea, trauma,diabetes, hypertension, cardiac illnessor 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

showed that he had been suffering from fever, bilateral parotitis along with cervical and submandibular lymphadenopathy. Hisblood investigations done at that time were normal except for persistent leukopenia. Antinuclear antibodies, ds DNA antibody, HIV serology and Mantoux was negative. CT scan of chest revealed nodular lesion in left upper lobe, enlarged level II, III, IV lymph nodes bilaterally along with a enlarged parotid gland and few pretracheal, paratracheal and subcarinal lymph node. FNAC of submandibular gland had features of sialoadenitis and FNAC of parotid gland showed presence of reactive lymphoid tissue. His Bone marrow biopsy revealed hypocellular, normoblastic marrow with no evidence of granuloma or malignancy. Lymph node biopsy showed large areas of necrosis surrounded by karryohectic debris in cortex and paracortex with presence of lymphocytes, plasmacytoid and large mononuclear cells. Overall histology was in favour of Kikuchi fujimoto disease. Patient had been treated with steroids and his symptoms resolved for sometime but they kept recurring on and off for about a year when he was again admitted at another hospital where the repeated lymph node biopsy still showed features of necrotizing lymphadenopathy. Immunohistochemistry of biopsy sample was again in favour of Kikuchi's disease. He was then treated with intravenous immunoglobulins for five days. He was asymptomatic thereafter till around two months before presenting to us when he again developed enlargement of submandibular gland for which he was treated with steroids following which lymphadenopathy resolved. He was still taking prednisolone 40 mg OD when he came to us with his complaints.

On examination he was afebrile, pulse rate of 74 beats per minute, respiratory rate of 21 per minute and blood pressure of 110/90 mm Hg. He had no lymphadenopathy but had cyanosis involving the index and middle finger of right hand. Radial pulse was palpable bilaterally along with all other peripheral pulses. His systemic examination was unremarkable except for mild splenomegaly.

Laboratory investigation revealed haemoglobin of 14 gm/dl (reference range 10.5-17 gm/dl), white blood cell count of 9.55 x 10^3/µl (reference range 4-11 x 10^3/µl) , platelet count 166 x 10^3/µl (reference range 150-450 x 10^3/µl) , 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 17-59 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), Direct bilirubin 0.1mg/dl (reference range 0.0-0.3 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 Scl 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.[1] In the same month, Dr. Fujimoto presented a similar case in a separate Japanese journal.[2] Kikuchi Fujimoto disease is known to have a worldwide distribution with higher prevalence among Japanese and other Asiatic population.[3] 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.[4]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.[3] Very few cases of Kikuchi's disease have been reported in India following the first case reported in 1998 by Mathew et al.[5]

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%.[3] 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.[6] Involvement of mediastinal, peritoneal, retroperitoneal region is uncommon and less frequent symptoms include weight loss, nausea, vomiting, sore throat, night sweats.[7] It should be mentioned that systemic symptoms are found more frequently when extranodal involvement is present.Extranodal involvement is rare but skin, bone marrow, myocardium, central nervous system have been reported.[8] 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.[9] A few patients have had generalized lymphadenopathy and hepatosplenomegaly as initial presentation. Kikuchi's disease also has been reported as a cause of prolonged fever of unknown origin. [10] 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.[11]

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,HIV 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 DPA1*01 and DPB1*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.[12]

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.[13] 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.[6] 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.[14] 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.[15] In addition to SLE other autoimmune condition and manifestations such as antiphospholipid syndrome, polymyositis, systemic juvenile idiopathic arthritis, bilateral uveitis, arthritis, cutaneous necrotizing vasculitis and pulmonary haemorrhage have been linked to Kikuchi's disease.[16-22]Furthermore, some fatal cases, which had been reported as Kikuchi's disease, were found to be related to potentially life threatening autoimmune conditions.[22,23]Bernado et al did a follow up of 20 confirmed cases of Kikuchi's disease till 10 years and found that 9 of them (all women) developed autoimmune disease (4-SLE, 2-sjogren's, 1-thyroiditis, 1-SLE like and 1- antiphospholipid antibodies).[24]

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. Atypical lymphocytes in 25%-31% cases.[3] ESR and CRP may be elevated. Increased LDH suggests hepatic involvement.
- Anti-nuclear antibodies is positive in about 7%.[3]
- **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 evaluation. 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%.[25] Characteristic cytological findings include cresentric histiocytes, plasmacytoid, monocytes and extracellular debris.

- **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. Histiocytes, crescent shaped nuclei, karryohexis, histiocytesand macrophages containing phagocytozed debris from degenerated lymphocytes are seen.
3. Other cells include lymphocytes, plasmacytoid monocytes, macrophages and immunoblast (predominantly T cells)

Histiocytes and palsmacytoid monocytes make the most distinctive cell types found within karryohectic foci. In fact it has been considered that the earliest recognizable foci and minimum diagnostic criteria of Kikuchi's disease are paracortical clusters of plasmacytoid monocytes with interspaced karryohexis and cresentric histiocytes.[26]

Kuo proposed the following three histological stages:[27]

- *Proliferative* :- initial phase consisting basically of various histiocytes, plasmacytoid, monocytes and a variable number of lymphoid cells with karryohectic nuclear fragments and eosinophilic apoptotic debris.
- *Necrotizing*:- extensive necrosis that may destroy the normal architecture of lymph node.
- *Xanthomatous*:-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 histiological 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 xanthomatous. 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.[27]

- **Immunohistochemical features:-** predominance of T cells with very few B cells with predominance of CD8+ cells over CD4+ cells. The histiocytes express histiocyte associated antigens such as lysozyme, MPO and CD68. They also express CD4 and CD74 and are positively stained by pan macrophage monoclonal antibody Ki-M1P.[3]

- **Distinguishing Kikuchi's disease from Lymphoma :-**

The numerous atypical monocytes and T cell immunoblast observed in Kikuchi's disease may lead to an erroneous diagnosis of lymphoma especially high grade lymphoma. However lymphoma typically features cytological atypia and monomorphic cells.Features of Kikuchi's disease that may help prevent its misdiagnosis as malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rate and absence of Reed Sternberg cells. Immunohis tochemical stains are helpful in distinguishing Kikuchi's disease from lymphomas. The large cells are negative for CD3, CD20 which excludes the possibility of lymphoma and they are positive for CD68 which demonstrates their histiocytic feature. Positive immunostaining results by monoclonal antibody Ki-M1P are seen in Kikuchi's disease but not in malignant lymphoma.

- **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 Hemotoxylin bodies, believed to represent degenerated nuclei that have reacted with antinuclear antibodies, and the Azzopardi phenomenon (i.e. encrustation of blood vessel wall with nuclear material).[3] 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.[26] Nevertheless even though there is little information in literature about lupus associated lymphadenitis, its immunophenotype seems to be virtually identical to that of Kikuchi's disease including CD68+/MPO+ histiocytic pattern.[28] 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.[29]

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. [30]There are reports of excellent responses to hydroxychloroquine[31-32], immunoglobulins[33] , and minocycline.[34]

CONCLUSION

Kikuchi's disease is said to be a benign self limiting rare disease of unknown aetiology but as more and more cases are being diagnosed and reported various disease manifestations of this disease are being known. It can easily be misdiagnosed, as clinically it mimics lymphoma, tuberculosis or SLE and also because of little general awareness about the disease. Awareness of this disorder not only among clinicians but also pathologists might help prevent misdiagnosis and inappropriate treatment. Kikuchi's disease must be considered among the differential diagnosis in a patient of fever of unknown origin with lymphadenopathy. These patients should also be investigated for autoimmune disorder and need regular follow up as they might develop autoimmune disorder later on and also have reoccurrence of symptoms as was evident in both our cases.

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