International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(1): January-February 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Case Report……!!!**

Received: 05-01-2016; Revised: 09-01-2016; Accepted: 10-01-2016

KIKUCHI-FUJIMOTO DISEASE IN A 17 YEARS OLD GIRL: A CASE REPORT AND REVIEW OF THE LITERATURE

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Keywords:

Cervical lymphadenopathy, excision biopsy, Kikuchi-Fujimoto disease

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ABSTRACT

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis is a rare, benign and self-limited disease of unknown etiology, predominantly affecting younger people. We report the case of KFD in a young girl who presented with fever and tender cervical lymphadenopathy.It masquerades diseases like lymphoma, adenocarcinoma and tuberculosis. The clinicians as well as pathologists must, therefore, be aware of this disease so as to prevent misdiagnosis and inappropriate treatment.

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis (HNL), is an enigmatic, benign self-limiting entity of unknown etiology and is associated with fever with lymphadenopathy and systemic symptoms [1].Identification of characteristic microscopic findings in lymph node biopsy specimen: paracortical geographic necrosis with karyorrhectic apoptotic fragments; some ingested by the histiocytes, immunoblasts, plasmacytoid monocytes, large and small lymphocytes of predominantly CD 8+ type and absence of neutrophils, ensures the differentiation of this disease from other types of necrotizing lymphadenitis, especially systemic lupus erythematosus, pyogenic infections and lymphomas [2].Complete pathophysiological knowledge is still elusive, however, immunological response to unidentified antigenic stimuli and autoimmune apoptotic pathology are thought to be primarily involved [3,4]. We describe a case of KFD in a young girl who presented with fever associated with neck masses.

CASE PRESENTATION

A 17 years old girl presented with two weeks history of fever which was moderate to high grade (101 to 103^0 F), intermittent, associated with chills and rigors. It used to subside with intake of antipyretics. One week after the onset of fever she noticed painful lumps on both sides of her neck, more prominent on the left side. She gave no history suggestive of pulmonary tuberculosis or any contact with any case of tuberculosis. There was no history of rash, mouth ulcers, drug intake or any dental complaint. She also gave no family history suggestive of autoimmune or lymphoproliferative disorders.

She was febrile at the time of admission to our hospital. There were multiple palpable lymph nodes in her neck, more prominent in the left posterior triangle. They were 2 to 3 cm in size, non-matted, discrete, tender and mobile.

During the course of disease, her hemoglobin was 10.3 g/100 ml, ESR was raised to 50 mm fall in 1^{st} hour (Wintrobe's method), Total Leucocyte Count was 3800/cu mm with absolute neutrophil and lymphocyte counts of 2,300and 1,000 cells/μL respectively. She had a haematocrit of 30 % and red cell indices were within normal limits. Viral screening tests for HIV I and II, hepatitis B and hepatitis C were negative.Biochemical profile revealed raised LDH, SGOT and SGPT at 880 U/L, 260 IU/L and 212 IU/L respectively. Anti Nuclear Antibody (ANA) and Anti ds DNA were negative. Ultrasound scan of the neck showed enlarged hypoechoic lymph nodes, more prominent in the left posterior triangle. Chest X-ray revealed no abnormality.

She underwent excision biopsy of one of the lymph nodes in the left posterior triangle, and the same was submitted for histopathological evaluation.Microscopic examination showed extensive irregular areas of coagulative necrosis, especially in the paracortical regions, surrounded by histiocytes and activated lymphoid cells (Figure 1). There was abundance of karyorrhectic apoptotic fragments, some ingested by the histiocytes (Figure 2). Neutrophils and eosinophils were conspicuously absent, and so were multinucleate giant cells or epitheloid cell granulomas as well. A histopathological diagnosis of Kikuchi-Fujimoto necrotizing lymphadenitis was given. She was managed with NSAIDs, which resulted in complete resolution of her symptoms along with regression of cervical lymphadenopathy. She was discharged after 30 days of in-hospital stay and was symptom-free during subsequent follow-ups in this hospital.

Figure 1: Confluent areas of necrosis in the expanded paracortex of the lymph node. Haematoxylin and Eosin staining x 4 Magnification

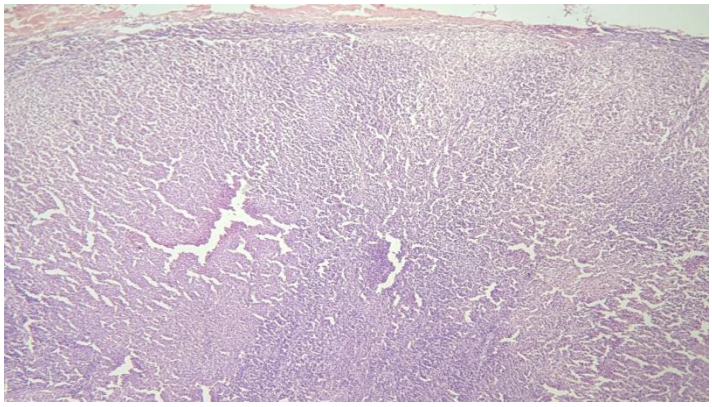
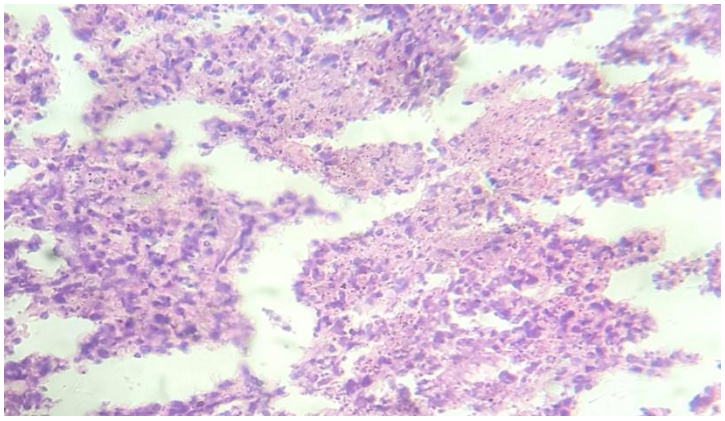


Figure 2: Area of histiocytic infiltrate showing abundance of karyorrhectic debris. Absence of neutrophils is evident. Haematoxylin and Eosin staining x 10 Magnification



DISCUSSION

KFD was first described in 1972 by Dr Masahiro Kikuchi, in the Japanese journal of haematological society, as a case of lymphadenitis with focal reticular cells proliferation associated with abundant histiocytes and nuclear debris [5]. In about the same period, Fujimoto et al also reported a similar case of cervical subacute necrotizing lymphadenitis, as a new clinicopathologic entity, in the journal Naika [6]. The disease has been most commonly reported among the Japanese and East Asian populations. However, the cases were first reported in North America and Europe in 1982 [7] and since then the disease has been reported worldwide [8-15]. Young adults under 30 years of age are predominantly affected with a slight female preponderance [16]. The etiopathogenesis of this enigmatic disease remains obscure. A wide range of viruses like parvovirus B19 [17], hepatitis B virus [18], Epstein-barr virus [19], Human Immunodeficiency Virus [20] and human T-lymphotropic virus type 1 [21,22] have been implicated but subsequent studies have not been able to confirm their role. Other infectious agents to be inconclusively implicated are Yersinia enterocolita [23] and Toxoplasma gondii [24,25].

The immunological basis of KFD has been extensively researched. Cases of KFD have been found to be associated with systemic lupus erythematosus [26], Hashimoto thyroiditis [27] and Still's disease [28].DNA typing of HLA class II genes in Japanese patients by Tanaka et al revealed a significantly more frequent occurrence of DPA1*01 and DPB1*0202 allele in KFD patients [29]. It has been postulated that a variety of microbial, neoplastic and physiochemical agents like pacemaker implants [30] and silicone breast implants [31] might be acting as a trigger, initiating T-cell mediated hyperimmune response in genetically susceptible host. It has been demonstrated conclusively by immunohistochemistry that the predominant proliferating cell in the affected lymph nodes are the CD8+ T cells [32].T-immunoblasts in these lymph nodes have been shown expressing markers of activation as well as proliferation-associated nuclear antigen Ki-67 [33]. CD8+ T cells have been postulated to be effector as well as target cells of apoptotic process by Fas and perforin pathways [34,35]. Clinically KFD may mimic lymphomas, tuberculosis, SLE, infectious mononucleosis and herpes. Menasce et al in a series of 25 cases of KFD have brought out the diagnostic dilemma faced by the medical fraternity and reported that these cases are still being misdiagnosed as lymphomas [36].Cervical lymphadenopathy is the commonest presentation, with location in the posterior triangle in approximately 88.5%. Approximately

59 % of cases have painful lymphadenopathy [37]. Patients may have signs and symptoms like fever, malaise, anorexia, skin rash, splenomegaly and weight loss [38,39].

Laboratory evaluation may reveal non-specific haematological features like raised ESR, increased CRP levels, anaemia, and mild neutropenia [40]. In some cases, serum lactate dehydrogenase (LDH) and aminotransferases are found to be raised [41]. In our case serum levels of these enzymes were indeed found to be raised; serum LDH: 880 U/L, SGOT: 260 IU/L and SGPT: 212 IU/L. Limitation of cytological diagnosis by FNAC was brought about by Tong et al, who reported an overall accuracy of 56.3 % [42]. However, features on FNAC, like presence of phagocytic histiocytes having peripherally placed crescentic nuclei and medium-sized plasmacytoid dendritic cells with eccentrically placed nuclei may aid in cytological diagnosis [43].

Currently, KFD is diagnosed on the basis of histopathological evaluation of lymph node biopsy specimens. Characteristic microscopic findings include irregular areas of coagulative necrosis partially effacing the architecture, with abundant karyorrhectic debris in the paracortical zone and abundant histiocytes of different types at the periphery of the necrotic areas [44]. The types of histiocytes seen are tingible body macrophages, foamy histiocytes and non-phagocytic (crescentic) histiocytes. Plasmacytoid dendritic cells tend to cluster, especially at the margins of the necrotic foci. The karyorrhectic areas are composed of histiocytes, immunoblasts, and small and large lymphocytes. Reactive atypia may be seen in the immunoblasts and the pathologist must guard against misdiagnosis as lymphoma [45,46]. Absence of neutrophils and eosinophils with scarce or absent plasma cells is of diagnostic importance [47]. Thrombosed vessels may be present at the periphery of the necrotic areas. In majority of cases reactive lymphoid follicles are seen. Based on the histopathological features, Kuo et al [48] proposed classification of KFD into 3 stages, namely, proliferative, necrotizing and xanthomatous. Proliferative stage is characterized by presence of plasmacytoid monocytes, histiocytes and lymphoid cells with karyorrhectic fragments and apoptotic debris. Presence of coagulative necrosis in the lymph node characterizes necrotizing stage. The disease will be classified into xanthomatous stage based on predominance of foamy histiocytes irrespective of presence or absence of necrosis.

KFD is self-limiting, generally resolving spontaneously within 4 months, although a recurrence rate of 3 % to 4 % has been reported [49]. There is no specific treatment of KFD and supportive treatment is all that is usually required. NSAIDs may be used for fever and painful lymph nodes. In cases of severe extranodal involvement or generalized disease, use of

corticosteroids has been recommended [50]. Because of pathogenic association of KFD with SLE, patients should be followed-up to monitor development of SLE at a later date [51].

CONCLUSION

KFD is rare, but it should be considered in the differential diagnosis of tender cervical lymphadenopathy, especially in young adults. Its histopathological differentiation from diseases like lymphomas and tuberculosis, which it masquerades, assumes importance in order to avoidexpensive, unnecessary and inappropriate investigations and treatment as exemplified in this case.

ACKNOWLEDGEMENT

We are sincerely thankful to Dr (Brigadier) K Kapur, Commandant of Military Hospital Allahabad for his continued support and guidance in this case report.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding publication of this case report.

AUTHORS' CONTRIBUTIONS

The final manuscript was read and approved by all the authors.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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