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Pyrexia of unknown origin and cervical lymphadenopathy: Kikuchi Fujimoto disease; a diagnostic challenge

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Abstract

One of the rarest cause of pyrexia of unknown origin is Kikuchi Fujimoto disease. It is usually associated with cervical lymphadenopathy and generalized symptoms such as body aches, loss of appetite and chills and rigors. These nonspecific symptoms make the diagnosis difficult.

This is the case series of six patients admitted to the hospital with nonspecific complaints suffering through the Kikuchi Fujimoto disease.

Keywords

cervical lymphadenopathy; kikuchi fujimoto disease; head & neck surgery.

Abbreviations

KFD: Kikuchi Fujimoto Disease; EBV: Epstein Bar Virus; HIV: Human Immuno Deficiency Virus; CMV: Cyto Megalo Virus; HPV: Human Papilloma Virus

Introduction

Fever with cervical lymphadenopathy after a negative sepsis workup often directs towards a more sinister differential diagnosis and treating physician must consider atypical pathologies in such difficult cases. Histiocytic necrotizing lymphadenitis or Kikuchi Fujimoto disease is one of these atypical pathologies which has come up in literature in past few decades.

This benign, self- limiting disease of unknown origin was first identified in Japan almost simultaneously in 1972 by Kikuchi and Fujimoto [1,2], who described it in Japanese descent with females being more commonly affected (4:1) [3]. It is uncommon in the western population, patients usually belong to Asian ethnic group and present with unilateral cervical lymphadenopathy and high-gradefever associated with nonspecific symptoms such as chills, rigors, malaise, generalized body pain, loss of appetite, upper respiratory tract infection and others. This wide array of generalized symptoms poses a diagnostic challenge to the treating physician [4].

We present our case series of 6 patients admitted to our hospital with similar complaints.

Case Series

A total of 6 patients were referred to the Department of Otolaryngology-Head & Neck Surgery at Armed Forces Hospital Southern Region KSA. This was over the period of 10 years (2007-2017). There were 2 males and 4 females in our series and 5 of them were referred to ENT via outpatient clinic while one was in-patient referral. The onset of disease was almost same in all patients with a history of high-grade fever and simultaneous tender cervical lymphadenopathy. Fever was different in almost every patient and it was either continuous or intermittent with occasional spikes reaching up to 101-103 F but no definitive pattern could be identified. Almost all the patients complained of generalized body aches, myalgia's and fatigue along with the loss of appetite but only one female patient also complained of small joint pain (fingers, wrist, and ankles). All patients gave a history of initial flu-like symptoms followed by high-grade fever with tender cervical lymphadenopathy. All the patients were young adults and had insignificant prior medical or surgical history. Since patients were referred from medical specialty; these patients already had undergone extensive workup for pyrexia of unknown origin and were already been treated with different empirical broad-spectrum antibiotics. While in most of them the referral to ENT was purely intended for biopsy of neck node.

ENT examination along with laryngo-pharyngoscopy was unremarkable in all of the patients and no source of infection could be identified. Neck examination revealed multiple, tender, mobile, soft nodes along levels III, IV and V, largest was >3cm but none more than 3.5cm. Nodes were bilateral in 1 one patient while in rest of the patient's lymphadenopathy was unilateral. Rest of general examination was unremarkable with non-palpable liver and spleen.

An extensive lab worksup to rule out infectious causes was already undertaken by referring physicians. Laboratory reports revealed neutropenia, with raised ESR ranging from 30-50mm/hr. Neutropenia resolved usually in 2-3 weeks duration after the acute phase was over while the ESR took more than 8 weeks to come to normal levels. Post Operatively patient was started on I/V Steroids, broad spectrum I/V antibiotics; (Ceftriaxone, Augmentin, Clindamycin, Flagyl) according to surgeons preferences and regular analgesia, antipyretic and cold sponges when necessary.

All the patients underwent a CT scan of Head and neck with I/V contrast prior to planning for neck node biopsy. Biopsy in all the cases was in usual fashion with excision of the largest palpable node.

All the patients were discharged upon the satisfactory improvement of condition with regular follow-up. The lymphadenopathy disappeared in most of the patients in 8-12 weeks duration. Table 1 shows important variables in all 6 patients. Only one patient had a recurrence after 2 years of initial presentation and on recurrence, the lymphadenopathy occurred on the same site. But condition improved after few weeks of treatment and bed rest.

The histopathology of neck node showed (Figure 1) para-cortical non-neutrophilic karyorrhexis, and fibrin deposits. Phagocytic histiocytes and plasmacytoid monocytes were present at the periphery of the necrotic zone. Rare plasma cells without follicular hyperplasia or nuclear atypia were seen.

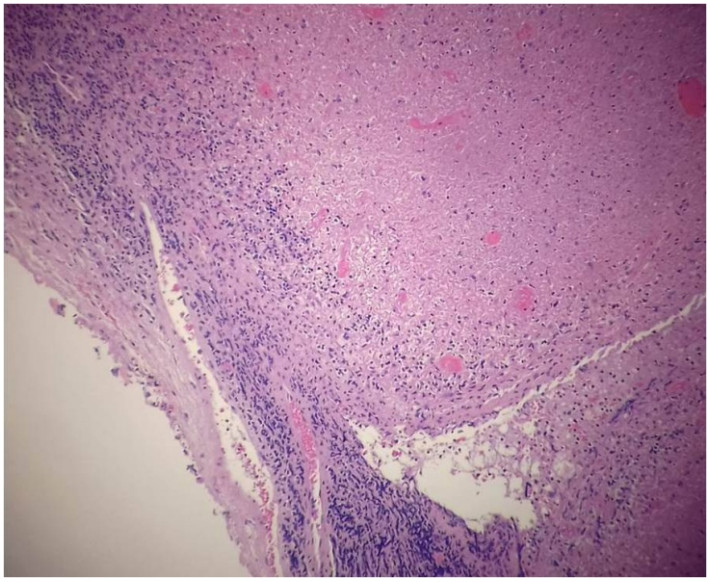

Figure 1: Hematoxylin and eosin stain, original magnification × 200

S.No.	Gender	Age (Yrs)	Lymphadenopathy (Neck)	Largest Size (Neck Node in cm)	Neck Level	Generalize Symptoms*	Neutropenia	ESR	Recurrence
1	Male	36	B/L	2.5	IV, V	Yes	Yes	38	No
2	Female	22	Left	2.00	V	Yes	Yes	41	No
3	Male	21	Right	3.1	III, IV, V	Yes	Yes	35	No
4	Female	25	Right	2.8	V	Yes	Yes	44	No
5	Female	34	Left	3.2	IV,V	Yes	Yes	32	Yes
6	Female	17	Right	2.9	V	Yes	Yes	53	No

Table 1: *Symptoms such as chills, rigors, malaise, generalized body pain, loss of appetite, upper respiratory tract infection and others

Discussion

The incidence of KFD in our national literature is sparse. KFD is a disease presenting with most common symptoms but yet remains one of the most commonly missed disease and still controversial in literature; this is due to the fact that no definitive history, sign,and symptoms or clinical test or examination has been attributed to this disease and neck node biopsy for identification of this pathology remains gold standard [4]. Similarly in our patients who underwent extensive septic workup which included EBV, CMV, HIV, Syphilis, Toxoplasmosis, Brucellosis and Tuberculosis to identifythe cause of pyrexia and lymphadenopathy and finally after all negative workup a decision to perform excision neck node biopsy was undertaken. Etiology for Kikuchi Fujimoto disease remains unknown till this date and a long list of causative organisms have been identified in literature such as EBV, HPV 6 & 8, HIV, Toxoplasma, Parvovirus, Para influenza, Paramyxoviruses, Brucella and Yersinia Enterocolitica [5,6]. A strong association with SLE has been shown in literature as well [4,7]. Usual clinical manifestation is that of a young female of Asian descent with acute onset of fever and lymphadenopathy [3,4,7]. Recent literature has shown male dominance in the pediatric population; in our case series, 2 adult males presented with

The lymph nodes are usually Less than or equal to 3cm, unilateral and occur in 30 to 50 % of patients. Our patients also fall into the similar description whereas there was one patient with bilateral lymphadenopathy. This lymphadenopathy is almost always associated with a fever which could be high or low grade while leukopenia is a prominent feature in 50 % of cases [3]. Extranodal KFD is much rare but has been reported in skin, eye, bone marrow and affecting liverfunction [9].

The diagnosis is mainly histopathological and may mimic SLE but could be differentiated from other infective causes of lymphadenopathy by the presence of gross necrotic foci with histiocytic infiltrate around the paracortical area while neutrophils are characteristically not seen [3,5,10]. Histology findings depend on the phase of differentiation; proliferative phase may mimic lymphoma with T and B blast cells while necrotic phase exhibiting foci of necrosis with histiocytes. Immunohistochemical stains will be positive for CD68 plasmacytoid monocytes and histiocytes with predominantly CD8 T lymphocytes [5].

When it comes to distinguishing this disease with another inflammatory lymphadenopathy such as Kawasaki disease the key histopathologic criteria is the absences of neutrophils. The histopathologic features of Kawasaki disease in the lymph node can include multiple foci of necrosis associated with mixed inflammatory infiltrate in the marginal zone composed of neutrophils (lacking in Kikuchi disease) and macrophages [11] In addition to the presence of fibrin thrombi of the small blood vessels and absence of nuclear atypia helps to rule out other differential diagnosis like lymphoma [12] while The lymphoma can be also excluded with the aid of the immuno-histo-chemical studies [13].

KFD is self-limiting and usually resolves in 1-4 months with lymphadenopathy resolving 1-6 months post-diagnosis. Treatment is usually symptomatic with treatment arsenal including analgesics antipyretics, nonsteroidal inflammatory or corticosteroids and IV immunoglobulins reserved for severe forms of KFD [3,5]. The follow-up is usually for several years and the recurrence is seen in 3-4% of cases [14] similarly we had one case of recurrence as well.

Conclusion

KFD is a diagnostic dilemma and should be suspected and not only restricted to young female patients with pyrexia of unknown origin and lymphadenopathy after all septic workup is negative and before labeling a patient towards more sinister differential such as lymphoma.

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