Kukuchi-Fujimito disease

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ABSTRACT

Objective: Kukuchi-Fujimito disease is a rare, benign and self limiting condition, which usually presents with lymphadenopathy or fever of an unknown etiology, or both. Its rarity, as well as the similarity of its clinical features to other more common conditions, contribute to overlooking it in the differential diagnosis of patients presenting with lymphadenopathy or fever of an unknown etiology.

Methods: The study was carried out at Qatif Central Hospital, Qatif, Kingdom of Saudi Arabia. All lymph node excisional biopsies received in the histopathology laboratory between 1989 and 1999 were evaluated and those diagnosed as Kukuchi-Fujimito disease were reviewed for clinical data and histological findings.

Results: A total of 6 cases were diagnosed as Kukuchi-Fujimito disease out of 390 lymph node biopsies. All patients were young with an average age of 21.5 years and equal sex distribution. Enlarged cervical lymph nodes with or without fever were the most familiar presenting symptoms. Anemia and leukopenia were observed in 3 patients. There was no recurrence of the lymphadenopathy over a peroid of 1-12 years follow up.

Conclusion: Kukuchi-Fujimito disease although rare should be included in the differential diagnosis of patients presenting with lymphadenopathy as well as fever of an unknown origin. To obviate unnecessary investigations and therapeutic trials, these patients should undergo early lymph node biopsy which must be interpreted by an experienced pathologist.

Keywords: Kukuchi-Fujimito disease, lymphadenopathy, fever of an unknown origin.

Saudi Med J 2002; Vol. 23 (4): 405-408

In 1972, Kukuchi and Fujimito, 2 Japanese pathologists independently described a benign, self limiting disease characterized by histocytic necrotizing lymphadenitis which now bears their names.[1,2] Initially all reports concerning Kukuchi-Fujimito disease (KFD) were confined to Japan, but subsequently it has been reported from other countries in Europe, America, Asia and recently from the Kingdom of Saudi Arabia (KSA).[3-9] Kukuchi-Fujimito disease usually presents with mild lymph node enlargement or fever of an unknown origin, but due to its rarity it is usually not included in the differential diagnosis of these patients, and although its pathological features are distinct, not uncommonly it is confused with lymphoma necessitating sometimes unnecessary diagnostic evaluation and inappropriate administration of treatment.[7] To obviate this, both physicians and pathologists should be aware of this disease, which must be included in the differential diagnosis of patients presenting with lymphadenopathy or fever of unknown etiology. This is a report of 6 cases of KFD highlighting their clinical features and aspects of diagnosis. The literature on this subject is also reviewed.

Methods. Over a period of 10 years between December 1989 through to November 1999, 390 patients had lymph node biopsy as part of their diagnostic evaluation Qatif Central Hospital, Qatif,

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Received 15th September 2001. Accepted for publication in final form 18th November 2001.

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Kingdom of Saudi Arabia, (KSA) and 6 were found to have KFD. The medical records of these patients were reviewed for age at presentation, sex, clinical features, diagnosis, treatment and outcome. Their paraffin blocks were resectioned and stained with Hematoxylin and Eosin (H&E), Periodic Acid Schiff (PAS), reticulin, and Ziel-Neelsen stains (ZN) and examined by one pathologist.

Results. Out of 390 lymph node biopsies examined, 6 patients were found to have histocytic necrotizing lymphadenitis forming 1.5% of all biopsies. Their demographic and clinical features are shown in **Table 1.** There were 3 males and 3 females and all were Saudi nationals. Their ages ranged between 15 and 32 years (mean 21.5 years). They all presented with cervical lymphadenopathy, which was painful in only one. Five of them were febrile. Two patients had weight loss and one had dry cough, nausea, vomiting and night sweat. One patients (patient 2 in **Table 1**) was diagnosed during her pregnancy, which ended by delivery of a normal healthy baby. Patient one was investigated several times for fever of an unknown origin before he was referred to our hospital. Their physical examination revealed no abnormalities apart from cervical lymphadenopathy which was bilateral in 50%, but the right group of lymph nodes were larger and in one 3rd of them and the posterior cervical group of lymph nodes were affected. In this group, the possibility of posterior cervical lymphadenopathy caused by toxoplasmosis was excluded histologically. Five of our patients had extensive febrile work up including full septic screen, complete blood count (CBC), Widal test, Brucella serological studies, peripheral films for malaria, Mantoux test but all of them were negative. Two patients had transient leukopenia at presentation (white blood count (WBC) $1.4x10^9$/l and $2.3x10^9$/l) but their mean WBC, hemoglobin (Hb), and Platelets were $3.4x10^9$/l, 118g/l, and $248x10^9$/l. Erythrocyte sedimentation rate was raised in 3 patients, normal in 2 and borderline in one. The liver enzymes were significantly deranged in only one patient (Patient one in **Table 2).** This patient had Hb of 95 g/l, a positive Coombs' test and his antinuclear antibodies (ANA) was 1:160 while the other autoimmune antibodies were negative. All the other patients had normal liver enzymes and their autoimmune profile was negative as shown in **Table 2.** All patients underwent cervical lymph node biopsy under general anesthesia.

Histological findings. The lymph node sizes ranged from 1.5-2.5cm with no specific gross findings. All lymph nodes showed intact architecture, which was best, demonstrated by reticulin stain except in one (patient 4) where large areas of necrosis were seen with loss of reticulin network in some areas. Patchy necrotic foci with karyorrhectic debri as well as absence of granulocytes were seen in all lymph nodes accompanied by focal immunoblastic reaction. The overall pattern was not suspicious of lymphoma, although ideal immunohistochemical confirmation is preferred, however this facility was not available. Residual lymphoid follicles were seen in 4 patients, and in 3 patients there was an increase in histocytes both in sinuses and interfollicular regions. Neither Acid-Fast Bacilli nor fungal organisms were demonstrated on special stains. **(Figure 1).**

Table 1 - Clinical features.

Clinical Details	Patient 1	Patient 2*	Patient 3	Patient 4	Patient 5	Patient 6
Age	15	27	18	21	32	16
Sex	M	F	F	M	M	F
Fever	Yes	Yes	No	Yes	Yes	Yes
Cervical adenopathy	Yes	Yes	Yes	Yes	Yes	Yes
Painful	No	No	No	No	No	Yes
Other lymph node	No	No	No	No	No	No

* pregnant at time of diagnosis, F - female, M - male

Discussion. Kukuchi-Fujimoto disease (necrotizing lymphadenitis) is a very rare clinicopathological entity of unknown etiology. The fact that it was originally described by 2 pathologists and the final diagnosis is a histopathological one resulted in most reports being published in pathology journals stressing the typical histopathological features without much emphasis on the clinical aspects of the disease. This, as well as its rarity and the similarity of its clinical features to other more common diseases contributed to overlooking it in the differential diagnosis of patients presenting with lymphadenopathy with or without fever. In fact, in the majority of cases the diagnosis of KFD usually comes as a total surprise on histological examination. Although KFD is an uncommon cause of fever of unknown origin as well as lymphadenopathy, and in order to obviate unnecessary investigations and treatment, awareness of this among physicians needs to be emphasized. The exact etiology of KFD is not known but the consensus now is that it is an immune response to a variety of infectious and environmental stimuli namely viruses including Ebstien-Barr virus, Herpes virus-6 and parainfluenza virus as well as parasites such as toxoplasmosis.[12-14] Systemic lupus erythromatosis (SLE); which sometimes may be

Table 2 - Laboratory Data.

Laboratory Data	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
White blood count x 10^9/l	2.3	5.8	4.7	3.4	2.7	1.4
Hemoglobin g/l	95	118	116	139	118	120
Platelet x 10^9/l	193	410	323	238	161	164
Erythrocyte sedimentation rate mm/1st H	78	130	8	5	123	32
Alanine aminotransferase (30-65)	863	23	10	29	34	27
Aspartate transaminase (15-37)	1106	10	25	37	35	12
Lactate dehydrogenase (100-190)	2358	164	170	145	201	197
AlkPh (52-136)	274	87	67	74	89	103
Culture	-ve	-ve	N/D	-ve	-ve	-ve
Antinuclear antibodies	+ve 1:160	-ve	N/D	-ve	-ve	N/D
Anti deoxyribonucleic acid	-ve	-ve	N/D	-ve	-ve	N/D
Coombs' Test	+ve	N/D	N/D	N/D	N/D	N/D
Malaria	-ve	-ve	N/D	-ve	-ve	N/D
Widal	-ve	-ve	N/D	-ve	-ve	N/D
Toxoplasmosis	-ve	N/D	N/D	N/D	N/D	N/D

N/D - not done
-ve - negative, +ve - positive
Alk Ph - alkaline phosphatase

clinically and histologically indistinguishable from KFD, can precede; accompany or more commonly follow KFD.[15] The incidence of KFD is not known and this is usually reported in relation to lymph node biopsies which is variable ranging from 0.54% to 5.7%. In a pathological study from Taiwan KFD was seen in 5.7% of abnormal lymph nodes.[16] Two studies from the KSA one from the central province and another from the eastern province reported KFD in 1.2% out of 1884 lymph nodes and in 0.54% out of 920 lymph nodes.[8,9] Although our series is small we found KFD in 1.5% of 390 lymph nodes. Originally described in Japan, KFD now appears worldwide, and due to increasing awareness regarding the disease among physicians, the incidence is actually rising. Kukuchi-Fujimito disease has been reported in children as well as elderly patients with an age range between 11-80 years, but the majority of patients are young adults less than 30 years of age and earlier reports quoted a marked female predominance,[7] but now most series report an equal distribution between males and females or slightly females predominance.[15] Clinically patients with KFD typically present with localized, moderately enlarged lymphadenopathy and although this can affect any group of lymph nodes, cervical lymph nodes are the most commonly involved in more than 70% of patients.[15] Lymph node involvement may be painful and sometimes generalized and associated with splenomegaly. Fever is another presenting symptom in 30% to 70% of cases, and many of these patients are actually admitted to hospital due to pyrexia of unknown origin. This was the case in 5 of our patients who were febrile on admission to the hospital. Other less common manifestations includes weight loss, night sweat, chills, skin rash and vomiting. Laboratory investigations may show leukopenia, which is reported, in approximately 50% of patients.[15] Erythrocyte sedimentation rate, although not specific has been reported to be greater than 60mm/first hour in up to 70% of patients.[15] Half of our patients had elevated ESR and leukopenia (WBC < $3x10^9$/l) was seen in 3 of our patients. The transaminases and lactate dehydrogenase may be increased in some patients, but this is usually mild and transient. Autoimmune studies are usually negative, and the results are valuable in excluding other diseases. The possibility of SLE must be kept in mind as some of these patients have been reported to develop SLE as well.[15,17] The diagnosis of KFD

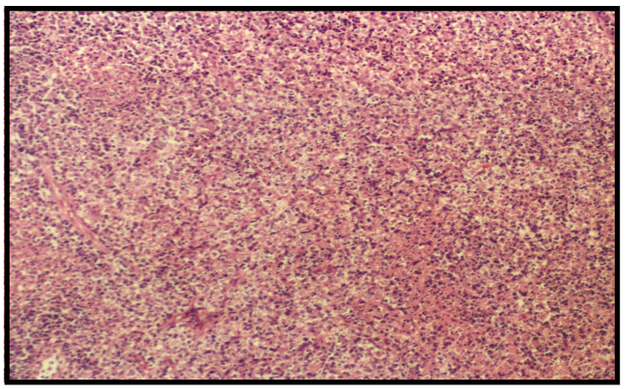

Figure 1 - High power view demonstrating immunoblasts, karyorrhexis, and lack of neurophils and plasma cells (25x).

depends totally on histology of the excised lymph nodes, which is characterized by necrosis and preservation of nodal architecture. The extent of necrosis is variable ranging from 5% to 95% of the node and this is characteristically associated with marked karyorrhexis, histocytic infiltrate and absence of granulocytes.[1,2] Special stains for acid-fast bacilli and fungi are usually negative. Systemic lupus erythomatosus is a common inflammatory condition most commonly confused with KFD and at times difficult to distinguish histologically, but the presence of large numbers of plasma cells surrounding the necrotic foci, or the presence of hemotoxylin bodies as well as positive serological studies should establish the diagnosis of SLE. Malignant lymphoma is another serious disease that is commonly confused with KFD.[18] The fact that 30% of 108 lymph nodes reviewed by Dorfman and Berry[7] were initially misdiagnosed as malignant lymphoma should alert the pathologists who are unfamiliar with KFD. This diagnostic confusion resulted in some patients receiving unnecessary investigations and treatment in the form of antibiotics, steroids, antitubercolus drugs and chemotherapy.[15,19] Kukuchi-Fujimito disease is fortunately a benign, self limiting disease, and the exact etiology is not known, there is no effective therapy for KFD. All our patients survived and are well over a follow-up period ranging from 6 months to 10 years. None of them developed SLE including the patient who has positive ANA on presentation.

In conclusion, KFD although rare should be included in the differential diagnosis of patients presenting with lymphadenopathy as well as fever of an unknown origin, and to obviate unnecessary investigations and therapeutic trials, these patients should undergo early lymph node biopsy which must be interpreted by an experienced pathologist.

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