Case report

A case of Kikuchi-Fujimoto's disease in a 31 year old Saudi female patient with lupus nephritis

Ekhlas Bardisi 1, Hani Almoallim 1, Hassan Sayadi 3
1 Medical Intern, Department of Medicine, King Faisal Specialist Hospital & Research center (KFSH&RC), Jeddah,
1 Medical College, Umm Al-Qura University, Makkah, Saudi Arabia, Consultant Rheumatologist, KFSH&RC, Jeddah
3 Consultant Pathologist, KFSH&RC, Jeddah

Correspondence :
Dr. Hani Almoallim
Associate Professor, Medical College, Umm Alqura University
P.O. Box 1821, Jeddah 21441, Saudi Arabia
hanialmoallim@hotmail.com

الاشكال المتعددة لجين الجلوتاثيون س – ترانسفيريز ومخاطر الإصابة بسرطان قولون المستقيم في السعوديين

د. الاخلاص البرديسي 1، د. هاني معلم 2، د. حسن الصيادي 3
متدرب الطبية، قسم الطب ومستشفى الملك فيصل التخصصي ومركز الأبحاث (مستشفى الملك فيصل التخصصي)، جدة [1]، كلية الطب، جامعة أم القرى، مكة المكرمة، المملكة العربية السعودية، أمراض الروماتيزم استشاري، مستشفى الملك فيصل التخصصي بجدة[2] ، علم الأمراض استشاري، مستشفى الملك فيصل التخصصي بجدة [3].

الملخص

يعتبر مرض كاكوشـــي فيوجيموتو مرضـــاً نادراً ينتهي تلقائياً مع علاقة موثقة بمرض الذئبة الحمراء الحمامي الجهازي. نحن نوثق هنا في هذا التقرير حالة من هذا المرض بناء على خزعة أخذت من غدة لمفاوية من إمرأة ســـعودية عمرها ٣١ عاماً مع تشخيص سابق بإلتهاب الذئبة الحمامية الكلوي من الدرجة الرابعة. لقد ظهر المرض لديها بحرارة وإنتفاخ في الغدد اللمفاوية الباطية مع قلة كريات الدم البيضاوية. لقد أخذت المريضة مضادات حيوية وريدية ولكن المريضة تحسنت بصورة تلقائية

ABSTRACT

Background:
Kikuchi-Fujimoto's disease (KFD) is a rare benign self-limited disease with reported relation to systemic lupus erythematosus (SLE). We report a case of KFD based on a lymph node biopsy in a 31 year old Saudi female patient with an established diagnosis of stage IV lupus nephritis. She presented with fever, axillary lymphadenopathy, and neutropenia. Intravenous antibiotic was considered as a case of febrile neutropenia. The patient recovered spontaneously.

Keywords:

INTRODUCTION

Kikuchi-Fujimoto's disease (KFD) or histiocytic necrotizing lymphadenitis is a benign, self-limited disease of unknown etiology that affects mainly young women. It presents with localized lymphadenopathy, predominantly in the cervical region, less commonly axillary and mesenteric lymphadenopathy accompanied by fever and leukopenia in up to 50% of the cases [1, 2]. KFD has been reported in association with systemic lupus erythematosus (SLE) [1-4]; the relation between KFD and SLE is not yet completely understood and remains complex. SLE may be present before, at the same time, or after the clinical appearance of KFD [1, 2, 5]. We described a case of KFD in a 31 year old Saudi female patient with an established diagnosis of stage IV lupus nephritis.

CASE REPORT

We reported a 31 year old Saudi female patient who is a known case of SLE diagnosed 16 years ago (1994). She presented at that time with fever, easy fatigability, arthralgia and generalized bodyache. Investigations revealed 2+ proteins in the urine; speckled ANA (titer 1:1160), positive anti-ds-DNA antibodies at 347 IU/ml (normal range 0 – 18 IU/mL), positive anti-Sm/RNP, anti-SSA/Ro antibodies as well as low complement levels (C3, C4). She was started on prednisolone, hydroxychloroquine, azothioprine and calcium and vitamin D. She was regularly followed in our center since 2001. The patient was evaluated in 2007 due to nephrotic range proteinurea of more than 6g/24 hour. Laboratory investigations revealed speckled ANA pattern (titer 1:2640), positive anti-DNA at 813 IU/ml and hypocomplementemia with negative anti-phospholipids antibodies titer. Renal biopsy in February 2007 was characterized by stage IV lupus nephritis. The condition was treated with mycophenolate mofetil (1 gram orally twice a day), tapering dose of prednisolone, hydroxychloroquine and calcium and vitamin D supplements. Proteinurea initially regressed to 1.65 g/day but with poor medical compliance, this, unfortunately, resulted in flare up of her disease.

In August 2008, repeated renal biopsy again showed class IV lupus nephritis with membranous component. She was treated with six doses of cyclophosphamide from September 2008 to February 2009. She was maintained afterwords on azothioprine and hydroxychloroquine.

Due to persistent leukopenia (WBC 1.5 x 109/L) azothioprine was discontinued in outpatient rheumatology clinic in her follow up visit in April 2010. She was admitted to the hospital in May 2010 with 1-week history of high grade fever (39-40°C) and persistent leukopenia despite stopping azothioprine. Her fever was continuous with minimal response to antipyretics. It was associated with sweats, chills, and rigors. There was no history suggestive of any source of infection. She denied history of joint pains and swellings. There was no history of alopecia, mouth or genital ulcers, malar rash or skin rash and no history of weight loss or loss of appetite.

On physical examination, she was in general good condition but with temperature of 39.1°C, blood pressure of 121/63 mmHg, heart rate of 88 beat/min and respiratory rate of 20 breath/min, O2 saturation 98% on room air. She had tender, right axillary lymphadenopathy. Cardiovascular, respiratory and abdominal examinations

were unremarkable. There were no signs of arthritis.

The laboratory investigations showed WBC of 1.52 x 109/L, hemoglobin of 100 g/l, platelets of 161,000 /mm3, absolute neutrophilic count (ANC) of 0.69 x 103/µL, dropped to below 0.50 x 103/µL and lymphocytes of 44.4%, erythrocyte sedimentation rate (ESR) of 47 mm/h, C-reactive protein(CRP) of 36.1 mg/l. Renal and hepatic profiles were normal. Urinalysis was normal except of 2+ protein that was similar to previous findings. All cultures including blood and urine were all negative. Serological tests for Brucella, cytomegalovirus (CMV), Epstein - Barr virus (EBV), malaria, hepatitis A, B, C, were all negative. ANA was positive and also Anti-ds- DNA was 39.3 IU/ml with normal complement level C3 of 1.2 g/l and C4 of 0.16 g/l. CT of chest, abdomen and pelvis showed no evidence of fluid collection with hepatosplenomegaly and significant bilateral axillary lymphadenopathy more on the right. Right axillary lymph node excisional biopsy was done and showed histiocytic necrotizing lymphadenitis consistent with KFD {figure 1, 2, 3}.

The patient was treated as a case of febrile neutropenia with intravenous antibiotics for 7 days. Her symptoms, signs including WBC count improved spontaneously. She was discharged in good condition on plaquenil, calcium, and vitamin D. She developed post operative wound infection; abscess was drained at site of axillary lymph node biopsy with daily dressing. Her WBC count reached 2.38 x 109/L two weeks after discharge at time of outpatient follow up visit. This count continued to improve and reached 4.0 x 109/L a month later. She was put back on azothioprine with normal WBC count for 9 months after initial presentation.

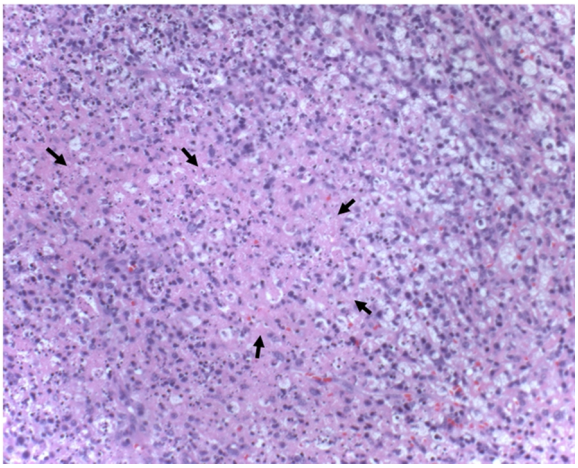

Figure 1: It shows an area of patchy necrosis (arrows) with increased number of histiocytes in the paracortical regions (hematoxylin-eosin, original magnification x 200).

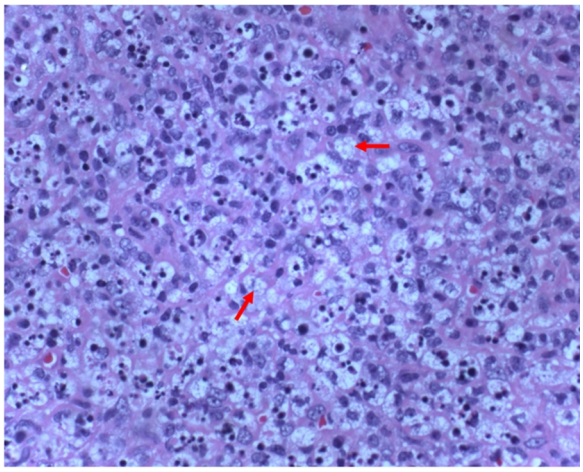

Figure 2: high power view of an expanded paracortical area showing numerous histiocytes (arrows), many of which are necrotic (hematoxylin-eosin, original magnification x 400).

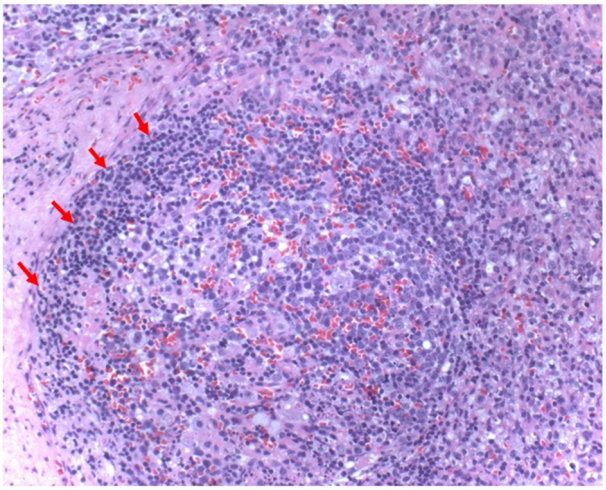

Figure 3: this slide shows only rare residual lymphoid follicles (arrows) with reactive germinal center are seen (hematoxylin-eosin, original magnification x 200).

DISCUSSION

KFD or histiocytic necrotizing lymphadenitis, was originally described in Japan in 1972 by Kikuchi [6] and Fujimoto et al. [7]. It has been reported in several countries since then [8] including Saudi Arabia [9] but predominantly in Asia.

It often affects young adult women [9, 13-15]. Pathogenesis of this disease is still not fully understood. It is proposed that the primary event may be the activation of T lymphocytes and histiocytes. Proliferating T cells enter the cycle of apoptosis, which may form the areas of necrosis in lymph nodes and then the cellular debris is removed by histiocytes [5, 16, 17]. Certain microorganisms (EBV, herpes human 6 virus, Toxoplasma, parvovirus B19, CMV, Brucella, Yersinia enterocolitica and parainfluenza virus) have been suggested as the causative agents of the disease, initiating a hyper- immune response of the T cells and histiocytes to the infectious agents. However, none of these possibilities have been definitively proven [5, 12, 17]. An autoimmune origin has also been suggested due to a number of cases in which SLE was diagnosed previously, simultaneously or after KFD, demonstrating a strong association [1, 2]. I In most of the cases the diagnosis of KFD was made before or at the same time of the diagnosis of SLE, Hoever, In our case the diagnosis of KFD was made years after the diagnosis of SLE. It is also noted that our patient received prolonged courses of immunosuppressant medications including mycophenolate mofetil, and later 6 cycles of cyclophosphamide, she was then placed on azothioprine and hydroxychloroquine. Can we consider the prolonged use of immunosuppressant medications a risk factor for KFD in a well established SLE with lupus nephritis? This is a concern that might be raised; however, there is no literature suggestive of this observation. It clearly warrants further evaluation.

Clinically, a unilateral cervical lymphadenopathy in KFD is observed [10, 13, 15, 16], but enlargement of lymph nodes in other regions may also be seen, sometimes in the form of generalized lymphadenopathy [10, 11, 14]. The affected lymph nodes vary in size from 0.5 to 7 cm of diameter [14] and may be tender or painful [13, 14, 16, 17]. The other, most common clinical symptoms of this disease are low-grade fever [10, 14-17], arthralgia and variety of skin rashes that usually precede lymphadenopathy [10, 13]. However, non-specific symptoms, e.g. weakness, night sweats, weight loss, diarrhea, anorexia, chills, nausea, vomiting, chest and abdominal pain have also been reported [10, 13, 16]. Sometimes splenomegaly and hepatomegaly are encountered [10, 13] like what we encountered in the case presented here.

Laboratory findings are not specific including elevated ESR, leukopenia with mild lymphocytosis and atypical lymphocytes [10, 13-17]. Moreover, in less than 5% of cases leukocytosis is found [11, 14].

The disease is generally diagnosed on the basis of an excisional biopsy of affected lymph nodes. Characteristic histopathological findings of KFD include irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas [2]. The karyorrhectic foci are formed by various cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent, and plasma cells are either absent or scarce. The pathological findings in our case include abnormal nodal architecture; there is extensive expansion of the paracortical regions with numerous histiocytes, many of which are necrotic and contain nuclear debris. In addition, there are patchy areas of necrosis; also there are several reactive lymphocytes and immunoblasts with occasional plasma cells in the paracortical regions.

KFD tends to resolve spontaneously within 1 week to 3 years [15, 16] but it may also recur in about 3% of cases [11, 13, 14]. In the cases in which KFD was diagnosed after or concomitantly with SLE, an obvious tendency was observed to adopt the use of corticosteroids, associated or not with hydroxychloroquine, as a standard treatment [5, 12]. On the other hand, when KFD is diagnosed before SLE, it is considered a clinically isolated entity and generally there is no need for treatment due to its benign and self-limited nature, with spontaneous resolution in weeks or months [3, 4, 18], our patient was treated as a case of febrile neutropenia with intravenous antibiotics for 7 days. Her symptoms, signs, and WBC count improved spontaneously.

In conclusion, although KFD is a self-limited condition, it can rarely be associated with SLE. We described a case of SLE with stage IV lupus nephritis that developed clinically and pathologically new clinical and pathological findings that was explained by KFD. Supportive measures were considered, and the disease resolved spontaneously. Is the prolonged use of immunosuppressant medications a risk factor for KFD in SLE patients?

REFERENCES

1. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M. Kikuchi-Fujimoto Disease: analysis of 244 cases. Clin Rheumatol. 2007 Jan;26(1):50-4.
2. Santana A, Lessa B, Galrão L, Lima I, Santiago M. Kikuchi-Fujimoto's disease associated with systemic lupus erythematosus: case report and review of the literature. Clin Rheumatol. 2005 Feb;24(1):60-3.
3. Litwin MD, Kirkham B, Henderson DR, Milazzo SC. Histiocytic necrotising lymphadenitis in systemic lupus erythematosus. Ann Rheum Dis. 1992 Jun;51(6):805-7.
4. El-Ramahi KM, Karrar A, Ali MA. Kikuchi disease and its association with systemic lupus erythematosus. Lupus. 1994 Oct;3(5):409-11.

5. Martínez-Vázquez C, Hughes G, Bordon J, Alonso-Alonso J, Anibarro-Garcia A, Redondo-Martínez E, Touza-Rey F. Histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto's disease, associated with systemic lupus erythemotosus. QJM. 1997 Aug;90(8): 531-3.
6. Kikuchi M.Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: a clinicopathological study. Acta Hematol Jpn 1972; 35: 379-80 .
7. Fujimoto Y, Kojima Y, Yamaguchi K. cervical sub acute necrotizing lymphadenitis. Naika1972. 20:920–7
8. Dorfman RF, Berry GJ.Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol. 1988 Nov;5(4):329-45.
9. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M. Kikuchi-Fujimoto Disease: analysis of 244 cases. Clin Rheumatol. 2007 Jan;26(1):50-4.
10. Adhikari RC, Sayami G, Lee MC, Basnet RB, Shrestha PK, Shrestha HG. Kikuchi-Fujimoto disease in Nepal: a study of 6 cases. Arch Pathol Lab Med. 2003 Oct;127(10):1345-8.
11. Snow RL, Ferry JA. Case 5-1997—a 24-year-old woman with cervical lymphadenopathy, fever, and leukopenia. N Engl J Med. 1997 Feb 13;336(7):492-9.
12. Danowski A, Bica B, Baptista R, Nentzinsky W, Azavedo MN. Linfadenite de Kikuchi associada ao lupus eritematososisteˆ mico. Rev Bras Reumatol 2003 43:58–61
13. Charalabopoulos K, Papalimneou V, Charalabopoulos A, Chaidos A, Bai M, Bourantas K, Agnantis N. Kikuchi-Fujimoto disease in Greece. A study of four cases and review of the literature. In Vivo. 2002 Sep-Oct;16(5):311-6.
14. Kuo TT. Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology, and DNA ploidy. Am J Surg Pathol. 1995 Jul;19(7):798-809
15. Tumiati B, Bellelli A, Portioli I, Prandi S. Kikuchi's disease in systemic lupus erythematosus: an independent or dependent event? Clin Rheumatol. 1991 Mar;10(1):90-3.
16. Papaioannou G, Speletas M, Kaloutsi V, Pavlitou-Tsiontsi A. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) associated with antiphospholipid syndrome: case report and literature review. Ann Hematol. 2002 Dec;81(12):732-5 .
17. Menasce LP, Banerjee SS, Edmondson D, Harris M. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease): continuing diagnostic difficulties. Histopathology. 1998 Sep;33(3):248-54.
18. Vilá LM, Mayor AM, Silvestrini IE. Therapeutic response and long-term follow-up in a systemic lupus erythematosus patient presenting with Kikuchi's disease. Lupus. 2001;10(2):126-8.