Case Report:

Familial Kikuchi-Fujimoto disease

J. Krishnappa,[1] D. Bharath Reddy,[1] P.J. Harsha,[1] C.S.B. Prasad[2]

Departments of [1]Paediatrics, [2]Pathology, Sri Devraj Urs Medical College, Kolar

ABSTRACT

Kikuchi-Fujimoto disease (KFD) is a rare, self-limiting disease of unknown aetiology presenting with cervical lymphadenopathy, fever, vomiting, weight loss, night sweats and chills. Familial occurrence of KFD is reported very rarely in literature. We report two cases from the same family presenting with KFD. The two non-twin sisters presented with symptoms of fever, cervical lymphadenopathy, weight loss, nausea, vomiting, night sweats and chills 6 months apart. The elder sibling with KFD also manifested mononeuritis multiplex. Laboratory evaluation revealed raised erythrocyte sedimentation rate, C-reactive protein levels and leucopenia. Anti-nuclear antibody and anti-double stranded deoxyribonucleic acid antibody were negative. Histopathological findings were suggestive of Kikuchi -Fujimoto's disease. The patients responded well to oral corticosteroid treatment.

Key words: *Kikuchi-Fujimoto disease, Necrotizing lymphadenitis, Immunohistochemistry, Familial*

Krishnappa J, Bharath Reddy D, Harsha PJ, Prasad CSB. Familial Kikuchi-Fujimoto disease. J Clin Sci Res 2015;4:40-4. DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.13.077.

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) first described from Japan has now been reported in most regions of the world. The median age at presentation is 30 years. Most patients are young adults, but the disease can occur at any age. There is female predilection with male: female ratio ranging from 1:3 to 1:4.[1] Familial occurrence of KFD has been reported rarely in literature.[1,2] We describe familial occurrence of KFD in two siblings.

CASE REPORTS

Case 1

A 17-year-old girl, presented with history of progressive cervical lymphadenopathy of 2 months duration associated with fever, night sweats, poor appetite and loss of weight. Two weeks after the onset of symptoms, the patient developed burning pain of both feet and inability to walk. On examination she had bilateral submandibular and upper deep cervical lymphadenopathy. Examination of mental status and cranial nerves were normal. Nutrition, tone, power and deep tendon reflexes of both the upper limbs were normal. Power, tone and deep tendon reflexes were decreased in both the lower limbs. Plantars were flexor on both the sides. Laboratory investigations (Table 1) revealed leucopenia, anaemia, thrombocytosis, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Anti-nuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies were negative. Magnetic resonance imaging (MRI) of brain showed acute ischaemic lesion in left thalamus, left para-ventricular deep white matter and right lateral margins of superior pons. Nerve conduction study findings were suggestive of mononeuritis multiplex. Biopsy of the sural nerve revealed necrotizing vasculitic neuropathy. Lymph node biopsy showed multiple areas of histiocytic aggregates showing necrosis and karyorrhexis with preserved architecture. The child was treated

Received: January 0, 2013; Accepted: June 16, 2014.

Corresponding author: Dr J. Krishnappa, Associate Professor, Department of Paediatrics, Sri Devraj Urs Medical College, Kolar, India.
e-mail: drjkgowda@gmail.com

Online access
http://svimstpt.ap.nic.in/jcsr/jan-mar15_files/1cr15.pdf
DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.13.077

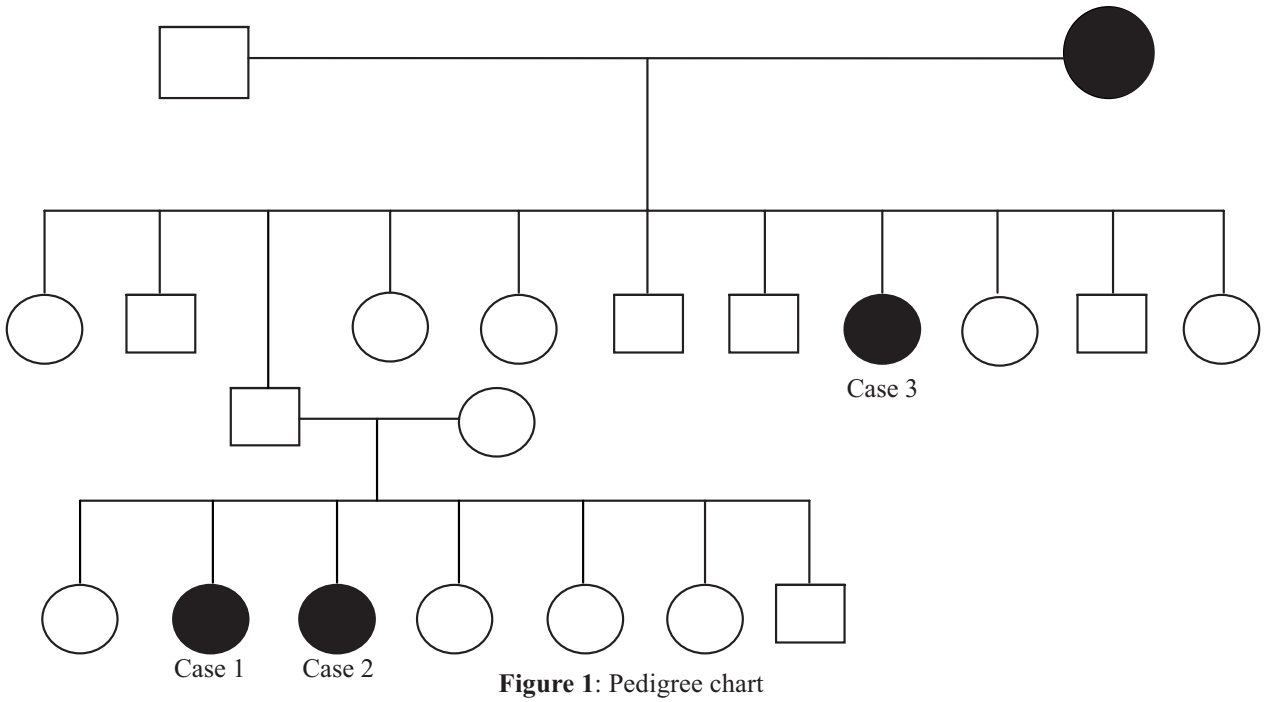

Figure 1: Pedigree chart

with intravenous (IV) methyl prednisolone 30 mg/kg for 3 days followed by 1 mg/kg of oral prednisolone for 4 weeks and tapered over 2 weeks. She responded well to the treatment.

Case 2

Six months later, the younger sibling of case 1 (Figure 1), who was a 15-year-old girl presented with a history of fever and bilateral neck swellings of two-and-a half months duration. She also gave a history of chills, night sweats, nausea, vomiting, anorexia and weight loss. Physical examination revealed pallor and significant peripheral lymphadenopathy. Rest of the physical examination was unremarkable. Laboratory investigations (Table 1) revealed anaemia, leucopenia, raised ESR and CRP.

Table 1: Laboratory investigations

Tests	Case 1	Case 2
Haemoglobin (g/dL)	8.5	6.2
Total counts (/mm^3)	2200	1600
Differential Counts (%)		
Neutrophils	49	57
Lymphocytes	37	38
Monocytes	07	03
Absolute eosinophil count	132	160
Platelet count (× 100,000/mm^3)	2.4	2.2
ESR	95	110
C-reactive protein (mg/L)	45	64
Serum electrolytes	Normal	Normal
Liver function tests	Normal	Normal
Peripheral blood smear for malarial parasite	Negative	Negative
Mantoux test (5 TU)	Negative	Negative
Chest radiograph	Normal	Normal
Anti-nuclear antibody	Negative	Negative
Anti- dsDNA	Negative	Negative

ESR = erythrocyte sedimentation rate (mm at the end of the first hour)
TU = tuberculin units; ds-DNA = double stranded deoxy ribonucleic acid

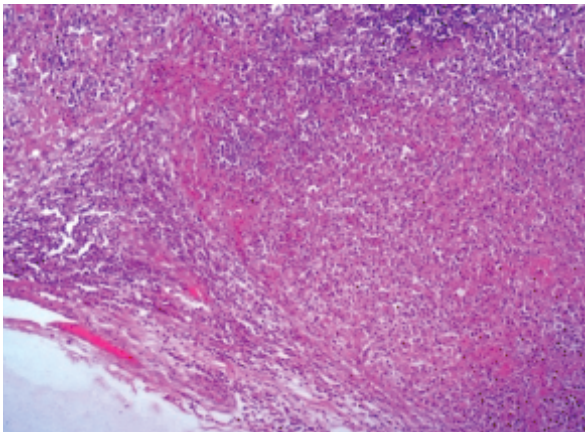

Figure 2: Lymph node biopsy (Case 2). Photomicrograph showing wide areas of necrosis with few preserved follicles and karyorrhexis (Haematoxylin and eosin, · 100)

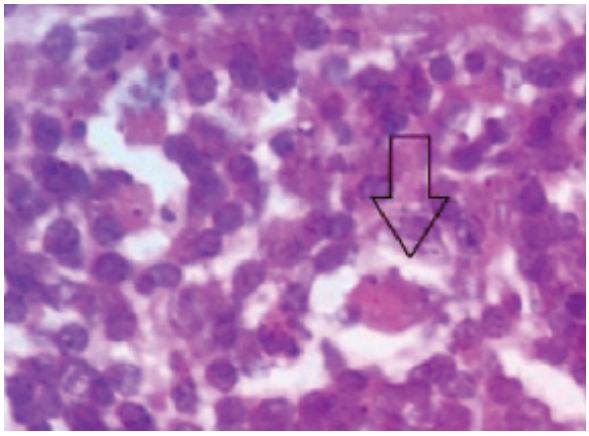

Figure 3: Photomicrograph Lymph node biopsy (Case 2) showing the presence of histiocytes with engulfed eosinophilic debris (arrow) (Haematoxylin and eosin, · 450)

Mantoux test [5 tuberculin units (TU)] was negative. Renal function tests were within normal limits. Chest radiograph and abdominal ultrasonography were normal. ANA and anti-dsDNA were negative. Lymph node biopsy (Figures 2 and 3) revealed areas of necrosis and karyorrhexis suggestive of KFD. The child was treated with oral prednisolone 1 mg/kg for 2 weeks. On follow-up, tenderness and the size of the lymph nodes were reduced. Both patients are on regular follow-up.

Case 3, the paternal aunt of Cases 1 and 2 (Figure 1) aged 30 years had similar clinical features of bilateral neck swelling, fever and loss of weight 2 years ago. She was evaluated for the above clinical features by a general physician. Investigations revealed anaemia, leucopenia and a raised ESR. Chest radiograph was normal. Mantoux test (5 TU) was negative. Lymph node biopsy was inconclusive. The patient was empirically treated with anti-tuberculosis treatment for 6 months. She improved symptomatically after 2 months.

A detailed family history revealed that the 60-year-old grandmother of Cases 1 and 2, (who is also mother of Case 3) had similar complaints of neck swelling with fever during early fourth decade of life for which she had received treatment from a general physician following which symptoms resolved over a period of 3 months. The details of the treatment were not available.

DISCUSSION

KFD is a unique form of self-limiting disease of unknown aetiology presenting with cervical lymphadenopathy, fever and sometimes accompanied by weight loss, nausea, vomiting, fatigue, chills, night sweats and abdominal pain. KFD mainly affects young women between 30 to 40 years. It has seldom been reported in persons aged less than 16 years and has very rarely been reported among those less than 10 years of age.[3] Both of our patients were women aged between 15 to 17 years. The other women in this family had a similar illness at about 30 years of age.

KFD is commonly reported in females of Japanese and Asian origin.[4] Viral and post viral hyperimmune reactions have been proposed to explain the aetiology.[3] Some studies proposed autoimmune mechanisms which may result in the primary event of T-lymphocyte and histiocyte activation leading to proliferation, apoptosis and necrosis.[4] Our patients presented with cervical lymphadenopathy, fever, weight loss, night sweats and fatigue of two-and-half months duration. Some KFD case studies indicate initial presentation as pyrexia of unknown origin (PUO) and subsequent development of lymphadenopathy.[4,5] Hence

KFD should be one of the differential diagnoses for PUO. The common site of lymphadenopathy reported is in posterior cervical lymphadenopathy as was seen in our patients.

There are few reported instances of familial KFD.[1,2] In one report[1] KFD was documented in two human leucocyte antigen (HLA) identical non-twin sisters living in same environment, presenting two years apart at same age with cervical lymphadenopathy, poor dental hygiene and periodontal disease.[1] Another study[2] reported familial occurrence of KFD in two HLA-identical non-twin sisters, not living in same environment, presenting 10 years apart with cervical lymphadenopathy; they had no evidence of recent infection or connective tissue disease.[2] Our patients living in the same environment presented with PUO and cervical lymphadenopathy six months apart. Case 1 had mononeuritis multiplex in addition to above features. Aunt and grandmother of the patients also had history of fever with cervical lymphadenopathy.

Neurological impairment like aseptic meningitis, mononeuritis multiplex, hemiparesis, cerebellar ataxia, nystagmus and photophobia are rarely described in patients with KFD.[6] Case 1 had weakness and burning sensation of both limbs following the common features of KFD. Nerve conduction studies and nerve biopsy were suggestive of peripheral polyneuropathy. A 17-year-old Asian boy who presented with peripheral neuropathy that was confirmed on nerve conduction studies was diagnosed to have KFD and responded well to oral corticosteroid treatment.[6] Case 1 was treated with i.v. methyl prednisolone initially and then with oral corticosteroids.

Elevated ESR, CRP and leucopenia were observed in our patient. Around 25% of patients with KFD manifest atypical lymphocytes and leukopenia is evident in 16.6%-58.3%.[8] Chest radiograph was normal in both of our patients. Chest radiograph and computed tomography help in localizing other diagnoses like tuberculosis or malignancy.[8] In 30% of KFD patients histopathological features have been interpreted as malignant lymphoma, and it is important to differentiate these two conditions is crucial.[10] The histopathological features are patchy circumscribed areas of eosinophilic necrosis in the cortex, para-cortical region with significant karyorrhexis and fragmentation of nuclear debris distributed in an irregular pattern throughout the necrotic area. Also absence of granulocytes and paucity of plasma cells and presence of plasmacytoid monocytes and immunoblasts is a feature.[10] Tuberculosis, lymphoma, systemic lupus erythematosus, (SLE), Kawasaki disease and infectious mononucleosis are considered in the differential diagnosis.

Clinically KFD may mimic SLE or lymphoma as both the diseases can present with lymphadenopathy and fever. The skin lesions of KFD can resemble those seen in SLE. KFD and SLE share some common clinical, pathological and ultra-structural features which require careful histopathological examination.[11] KFD and SLE affects young women and can precede and follow or coincide each other. Studies have reported the rate of association between KFD and SLE as 1.3%-7% in general population requiring the need for follow-up of KFD patients for progression to SLE.[11] KFD is a self-limiting disease with spontaneous resolution in most of the cases within 6 months. Though no specific treatment is available for KFD, non-steroidal anti-inflammatory drugs, corticosteroids and IV immunoglobulin have all been used; The recurrence rate ranges from 3%-4%.[1,2,11]

The diagnosis of KFD should be considered in the differential diagnosis in young females of Asian origin presenting with fever and cervical lymphadenopathy. Histopathology of lymph nodes help in confirming the diagnosis. Patients with KFD must be monitored for progression to SLE.

REFERENCES

1. Stasiuk A, Teschke S, Williams GJ, Seftel MD. Kikuchi-Fujimoto disease: lymphadenopathy in siblings. CMAJ 2011;183:E58-60.
2. Amir ARA, Amr SS, Sheikh SS. Kikuchi-Fujimoto disease: report of familial occurrence in two human-leukocyte antigen in identical non-twin sisters. J Intern Med 2002;252:79-83.
3. 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;19:798-809.
4. Tsang WY, Chan JK, Ng CS. Kikuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. Am J Surg Pathol 1994;18:219-31.
5. Mohan A, Harikrishna J, Prabath Kumar D, Dinesh Kumar N, Radhika K, Phaneendra BV. Kikuchi-Fujimoto disease presenting as pyrexia of unknown origin. J Clin Sci Res 2014;3:2-6.
6. Avkan-Oguz V, Yapar N, Ozakbas S, Demir-Onder K, Aktas E, Alp-Cavus S, et al. A case of fever of unknown origin: coexistence of Kikuchi-Fujimoto disease and acute disseminated encephalomyelitis (ADEM). Intern Med 2010;49:1823-6.
7. Justice EA, Warfield AT, Winer JB, Rankin EC. Late recurrence of Kikuchi-Fujimoto disease in a young male complicated by sensory neuropathy. Clin Exp Rheumatol 2010;28:587-8.
8. Turner RR, Martin J, Dorfman RF. Necrotising lymphadenitis. A study of 30 cases. Am J Surg Pathol 1983;7:115-23.
9. Na DG, Chung TS, Byun HS, Kim HD, Ko YH, Yoon JH. Kikuchi disease: CT and MR findings. AJNR Am J Neuroradiol 1997;18:1729-32.
10. Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol 1988;5:329-45.
11. Lin HC, Su CY, Huang CC, Hwang CF, Chien CY. Kikuchi's disease: a review and analysis of 61 cases. Otoralyngol Head Neck Surg 2003;128:650-3.