Kikuchi-Fujimoto's disease: case report and review

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Abstract

Kikuchi-Fujimoto's disease is a rare, benign and self-limited disorder. It is characterized by regional cervical lymphadenopathy with tenderness, usually accompanied by symptoms such as fever, sweats, nausea, vomiting, sore throat and cutaneous manifestations. Its aetiology is unknown. A definitive diagnosis can only be made histologically on lymph node biopsy tissue. In this study, we report a case of Kikuchi-Fujimoto's disease in a Greek child and present a review of the literature.

Key words: Kikuchi-Fujimoto's disease, children, lymphadenopathy.

Introduction

Kikuchi-Fujimoto's disease (KFD) was first described independently in 1972 by Kikuchi [1] and Fujimoto et al. in Japan [2]. Kikuchi-Fujimoto's disease has a worldwide distribution from Japan to the United States including Europe, the Middle East and South America. Kikuchi-Fujimoto's disease has a higher prevalence among Japanese and other Asiatic individuals and only isolated cases have been reported in Europe [1-5]. This difference of distribution among Japanese and European people recently led to the hypothesis that it might be due to a genetic factor, corresponding to an allele of the histo-compatibility HLA class II system detected with a statistically significant frequency in the DNA of Japanese patients presenting the disease [3]. Kikuchi-Fujimoto's disease occurs most often in adults younger than 40 years of age and is less common in the paediatric age. Song et al. reported the first case in a paediatric patient in 1990 [6].

The aetiology of KFD is not known. Several infectious agents have been suggested such as *Yersinia enterocolitis*, *Toxoplasma gondii*, EBV and other *Herpes* viruses, but none have been confirmed [3-5, 7]. Also, it has been hypothesized that KFD may reflect a self-limited autoimmune condition induced by virus-infected transformed lymphocytes [8, 9]. Some case reports have linked KFD to systemic lupus erythematosus (SLE), and patients whose symptoms were attributed to KFD went on to develop SLE. The most common clinical manifestation is painful cervical lymphadenopathy and fever [3, 10]. Other manifestations include axillary and mesenteric lymphadenopathy, splenomegaly, parotid gland enlargement, cutaneous rash, arthralgias, myalgias, aseptic meningitis, bone marrow

haemophagocytosis and intestinal lung disease [3-10]. The clinical presentation of KFD is very similar to malignant lymphoma, tuberculosis and SLE [3, 7, 9]. As has been described, KFD has a course of non-specific signs, symptoms and laboratory findings. It is a self-limited, benign form of histiocytic necrotizing lymphadenitis and always runs a benign course and resolves in several weeks to months. The mechanism of cell death involved in KFD has not been extensively studied. It has been hypothesized that apoptotic cell death may play a role in the pathogenesis of the disease [3]. Disease recurrence is unusual.

Case report

An 11-year-old boy was admitted to the hospital because of a two-week history of right cervical lymph node enlargement associated with slight fever, rigors, night sweats but in good general condition. On physical examination, the patient had a temperature of 38.5°C and a 4 × 5 cm right cervical mass that was tender to palpation, warm, firm and unmovable. There was no systemic lymphadenopathy. He had already been treated for apparent bacterial lymphadenitis with amoxycillin/clavulanate and fucidine without reduction of the lymph node volume. Clinical history did not reveal any travel, exposure to animals, insect bites or contact with infection. Clinical examination showed splenomegaly. The examination of other systems was normal.

The laboratory findings on admission during hospitalisation and after surgical excisional biopsy are shown in Table I.

Cultures of blood for microorganisms were repeatedly negative. Serology titres for *Epstein-Barr virus* (EBV), *Cytomegalovirus* (CMV), *Parvovirus B19*, Coxsackie, *Bartonella henselae*, *Borrelia, Mycoplasma, Toxoplasma, Adenovirus* and *Brucella* were negative. Serology titres for circulating immunocomplexes, antinuclear antibodies, antibodies to extractable nuclear antigens and double-strand DNA, rheumatoid factor, antineu-trophil cytoplasmic antibodies and complement levels were normal. A Mantoux test was negative after 48 and 72 h. Chest X-ray was normal but abdominal ultrasonography showed mild spleno-megaly.

Neck ultrasound showed multiple lymph nodes measuring up to 2 cm on the right neck with normal structure and no evidence of abscess formation. Some of the nodes were round.

Due to the persistence of fever and swelling for 19 days, an excisional biopsy of the lymph nodes was decided. The lymph node biopsy demonstrated plasmacytoid monocytes, crescentic histiocytes and activated lymphoid cells with abundant nuclear dust and with focal necrosis. The characteristic absence of polymorphonucleates, together with the presence of a proliferation of plasmacytoid monocytes mixed with the necrosis in the paracortical site, prompted the definition of the lesion as histiocytic necrotising subacute lymphadenitis diagnostic of Kikuchi-Fujimoto's disease. The patient became afebrile two days after lymph node excision. During an 8-month follow-up period the patient remained in good general condition and no relapse was observed.

Table I. Laboratory findings at admission and during hospitalisation

	Reference range	Admission	5th day	12th day	19th day	21st day (2 days after excisional biopsy)
WBC [mm³]	4000-9000	3180	2800	2600	2200	5060
Hb [gr/dl]	13-15	13.1	11.7	11.5	10.8	10.3
PLT [mm³]	150 000-400 000	141 000	153 000	181 000	197 000	267 000
ESR [mm/hour]	0-12	37	63	73	94	90
LDH [u/l]	100-440	498	622	670	720	499
CRP [mg/dl]	0-0.5	2.3	3.2	7.52	9.5	1.8
PCT [ng/ml]	0-0.1	3	0.9	0.3	0.3	0.1
SGOT [u/l]	7-40	35	44	75	82	56
SGPT [u/l]	1-35	32	40	72	95	60
IGG [mg/dl]	700-1500	803				
IGM [mg/dl]	40-180	92				
IGA [mg/dl]	40-120	192				
IGE [IU/ml]	100-120	863				
Body temperature [°C]		38.5/8 H	38.8/8 H	39.5/6 H	39.5/4 H	36.3 all day

Discussion

The clinical symptoms are non-specific and for this reason, in paediatric patients the diagnosis of KFD is often missed. Kikuchi-Fujimoto's disease generally includes cervical lymphadenopathy, as in our patient, while generalized lymphadenopathy is very rare [3]. Lymph node size has been found to range from 0.5 to 4 cm, but it may reach 5 to 6 cm and rarely more than 6 cm. In addition to lymphadenopathy, patients may have fever with a combination of other associated symptoms consisting of chills, sweats, general malaise, night sweats, nausea, vomiting, diarrhoea, weight loss, fatigue, headache, mouth ulcers, arthralgias, myalgias, hepatomegaly, and/or splenomegaly [1-3, 10]. Patients with KFD may also have cutaneous manifestations [8]. Our patient had painful cervical lymphadenopathy, fever and splenomegaly at admission and later he presented chills, sweats, nausea and hepatomegaly.

Kikuchi-Fujimoto's disease is generally diagnosed on the basis of an excisional biopsy of affected lymph nodes. Histological features allow KFD to be distinguished from other diseases. The pathological features of KFD include lymph node necrosis with karyorrhexis surrounded by histiocytes, without granuloma and neutrophil infiltration, as in our patient (Figures 1, 2) [3, 8].

No specific diagnostic laboratory tests are available. Leukopenia, neutropenia, lymphocytosis, anaemia, abnormal liver enzyme levels, an elevated level of lactate dehydrogenase, an elevated sedimentation rate, a relatively low value of CRP and elevated values of immunoglobulins G and E have been reported, as in our patient [3, 4-6]. Autoimmune evaluation (including antiphospholipid and ANA, antibodies to extractable nuclear antigens and double-stranded DNA, RF, ANCA) and immunohistochemistry was helpful in identifying the characteristic histiocytic nature of the cells. In our patient, this was achieved by the use of CD68 together with CD4 monoclonal antibodies in the biopsy specimen, which are indicators verifying the histiocytic nature of the cells (Figures 1, 2).

Computed or ultrasonographic tomographic and magnetic resonance imaging do not yield features that distinguish KFD from other diseases which predominantly involve lymph nodes as in our patient (Figures 3, 4).

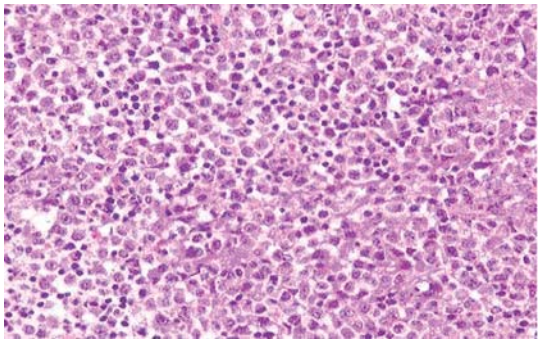

Figure 1. Biopsy specimen, colouring of haematoxylin-eosin. The picture shows the degradation of the lymph gland architecture and the extensive histiocyte agglomerations

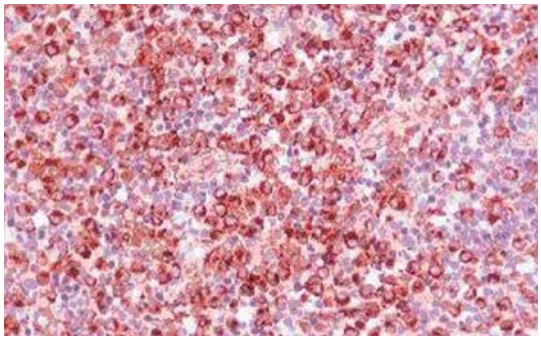

Figure 2. Biopsy specimen, immunohistochemical colouring with the CD68 indicator verifying the histiocytic nature of the cells

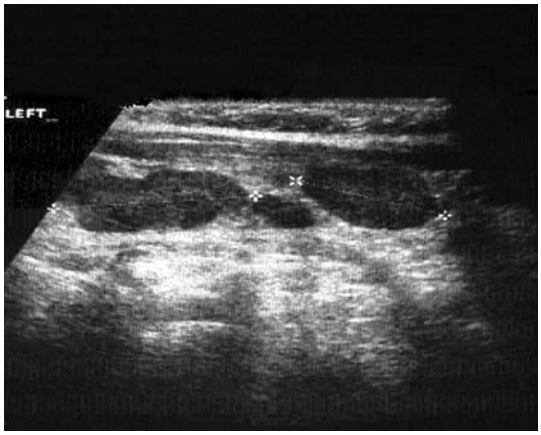

Figure 3. Neck ultrasound depicting enlarged lymph nodes

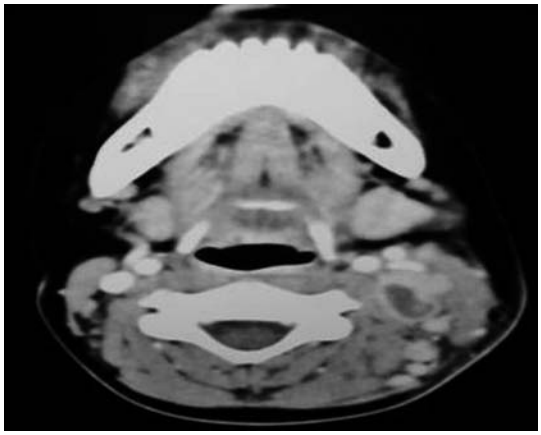

Figure 4. Neck CT scan depicting a block of neck lymph nodes with central necrosis

The differential diagnosis of this disease includes tuberculosis, SLE, sarcoidosis, Kawasaki disease and lymphoma [6-9].

Kikuchi-Fujimoto's disease is usually a benign and self-limited disease lasting from 1 to 6 months. A low recurrence rate, 3-4% of cases, has been described and it may occur as late as 8 to 16 years after the initial diagnosis. In a few patients, SLE may occur some years later [6-9].

During an 8-month follow-up period our patient remained in good general condition and no relapse was observed. The follow-up is continued.

There is no specific treatment for KFD. Analgesics-antipyretics and nonsteroidal anti-inflammatory drugs may be used to alleviate lymph node tenderness and fever. Cervical lymphadenopathy appears to resolve spontaneously 1-6 months after definite diagnosis [3-6, 8].

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