CASE BASED REVIEWS

Kikuchi-Fujimoto disease – a case report of a paediatric patient

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ABSTRACT

Kikuchi-Fujimoto disease is usually a self-limited cause of lymphadenitis. It is a prevalent disease amongst Asian individuals, but rare in other parts of the world. It affects especially young women, with limited cases described in children.

Kikuchi-Fujimoto disease is characterized by focal and tender lymphadenopathy, mostly cervical, accompanied by fever and, less commonly, systemic manifestations. This disease is seldom associated with systemic lupus erythematosus.

Herein we describe the case of a previously healthy 7-year-old male patient, who presented with prolonged fever (13 days), rash, polyarthritis, cervical lymphadenopathy, hepatosplenomegaly, leucocytosis and markedly elevated inflammatory markers. No changes were seen on the echocardiogram. Antinuclear antibodies were not identified and complement levels were normal. Differential diagnosis included systemic juvenile idiopathic arthritis, infectious diseases and malignancy. Bone marrow aspiration and bone biopsy were normal. The cervical node biopsy was diagnostic for Kikuchi-Fujimoto disease. Oral prednisolone (2mg/kg/day) was started with notorious clinical response. After one year of follow up, the patient is without medication and remains asymptomatic.

This case report shows the often-convoluted course of Kikuchi-Fujimoto disease and diagnostic dilemmas clinicians face when dealing with atypical presentations.

Keywords: Fever of unknown origin; Kikuchi-Fujimoto disease; Children; Lymphadenopathy.

INTRODUCTION

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, was first described in Japan in 1972[1,2]. It is a prevalent disease amongst Asian individuals, but rarely reported in other parts of the world. It mainly affects young women and is seldom diagnosed in paediatric patients[3].

Kikuchi-Fujimoto disease is classically characterized by focal and tender lymphadenopathy, mostly cervical, accompanied by fever and less commonly, systemic manifestations[3–7]. The latter includes fatigue, weight loss, night sweats, arthralgia and rash. Rarely, hepatosplenomegaly and neurological symptoms may be present[3–7]. Laboratory findings may include high inflammatory markers levels (erythrocyte sedimentation rate [ESR] and C reactive protein [CRP]) and mild cytopenias (anaemia and leukopenia)[3,6,8].

Kikuchi-Fujimoto disease usually represents a challenging diagnosis since the initial signs and symptoms are often nonspecific. Differential diagnosis includes infections, malignancy, autoimmune and autoinflammatory diseases.

No therapeutic guidelines exist and most patients do well with anti-inflammatory drugs. Corticosteroids and other immunomodulatory drugs may be useful, particularly in recurrences and severe cases[3,9,10].

Prognosis is excellent, although some patients may recur and a minority go on to develop immune-mediated diseases, mainly systemic lupus erythematosus[3,5,11].

CASE DESCRIPTION

A previously healthy, 7-year-old boy, of Ukrainian descend, presented, five months prior to admission, with a non-tender right posterior cervical adenopathy without other symptoms. His family doctor ordered a cervical ultrasound that documented bilateral lymphadenopathy, with the largest node (1 cm) in the aforesaid location. He remained asymptomatic for five months, after which he developed a daily fever (maximum axillary temperature of 39ºC), accompanied by fatigue, anorexia, odynophagia and a non-pruritic erythematous rash distributed over his face, torso and limbs that worsened with fever. The patient mentioned an irregular contact with a non-do-

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Table I. Laboratory data (A) and other results (B).

A	Local hospital			Tertiary hospital center				
Parameter (Blood)	**D1**	**D4**	**D5**	**D9**	**D11**	**D15**	**2 months**	**Reference range**
Hemoglobin (g/dl)	11.3	11.6	10.8	11	9.5	11.6	12.5	11.5-15.5
Leucocyte count/µL	13 300	18 400	14.500	14.480	7.680	39.980	10.200	5.000-13 000
Neutrophils/µL	10.746	14.720	12.223	12.235	5.775	32.064	6.630	2.0-8.0
Lymphocytes/µL	1 277	-	-	1 100	1 398	5 437	2 346	1.0-5.0
Platelet count/µL	257.000	250.000	356.000	294.000	248.000	891.000	311.000	180.000-400.000
CRP (mg/dl)	12.3	18.3	14,5	-	8.06	5.18	0.3	<0.5
ESR (mm/1st h)	-	35	92	50	28	53	15	<20
LDH (U/L)	243	279	-	-	427	440	-	100-250
Ferritin (ng/ml)	-	-	-	11.122	8.644	1.617	65.9	7-84
Triglycerides (mg/dl)	-	-	-	157	117	264	-	-
Fibrinogen (mg/dl)	-	-	-	-	248	326	-	-
ALT (U/L)	13	11	9	12	13	34	-	13-53
AST (U/L)	23	28	44	48	38	32	-	0-32
C3 (mg/dl)	-	-	-	186	-	-	-	-
C4 (mg/dl)	-	-	-	39	-	-	-	-

B	Other investigations	Result
	Myelogram and bone biopsy	Normal
	Peripheral blood smear	Normal
	Serum Protein electrophoresis	Normal
	Urinalysis	Normal
Immunology		
	Anti-nuclear ab	Negative
	Anti-dsDNA ab	Negative
Microbiology		
	Blood culture	Negative
	Urine culture	Negative
	Oropharyngeal culture	Negative
	Influenza A/B (nasopharyngeal RT-PCR)	Negative
	Monospot	Negative
	Cytomegalovirus	IgG+/IgM-
	Parvovirus B19	IgG+/IgM-
	Epstein Barr virus	Anti-VCA Ab IgG+ Anti-VCA Ab IgM- Anti-EBNA Ab IgG+
	Coxsackie (A7, A9, A16, A24 and B)	IgG+/IgM-
	Echovirus 7	IgG+/IgM-
	HIV 1,2 (Ab)	Negative
	Mycoplasma Pneumoniae	IgG+/IgM-
	Salmonela (TO, TH, AH, BH, Widal)	Negative
	Brucella	Negative
	Bartonella henselae	IgG-/IgM-
	Toxoplasma	IgG-/IgM-
	Interferon Gama Release Assay	Negative

ab – antibody, ALT- alanine aminotransferase, AST – aspartate transaminase, CRP – C reactive protein, CK – creatine kinase, ESR – erythrocyte sedimentation rate; LDH – lactate dehydrogenase.

mestic cat. His household contacts were asymptomatic and no relevant prior family history was documented. No recent travelling occurred. He denied headaches or other neurologic symptoms, as well as respiratory or gastrointestinal complaints. Prior history of weight loss, night sweats, recurrent skin lesions, oral/nasal ulcers, or prior evidence of arthritis was also denied.

On the third day of symptoms he was evaluated at his local hospital emergency department and was discharged home with symptomatic treatment. Three days later, he returned due to persistence of fever and a new onset limping. On physical examination, the patient was febrile, maintained the previously described rash and had right ankle arthritis. Oropharynx was clear. Bilateral cervical adenopathies were palpable, without hepatosplenomegaly. The remaining of his physical examination was unremarkable. His initial blood work (Table I) documented an elevation of inflammatory markers and he was admitted for investigation. The following days, the patient developed polyarthritis with large and small joint involvement (right ankle, both wrists and two interphalangeal joints), and the fever and rash persisted. Echocardiogram and EKG were normal. Chest X-ray was normal, as well as several laboratorial studies (Table I). Nonetheless, he maintained persistently elevated inflammatory markers (leucocytes 18 400/ul, CRP 18.3 mg/dl and ESR 92 mm/h). Microbiological studies included a negative monospot test, throat swab culture and influenza screen, as well as negative serology of acute infection for Cytomegalovirus, Epstein-Barr virus, Coxsackie virus and Echovirus. Blood culture was also negative. Antinuclear antibodies were negative and C3 and C4 levels were normal. Antiphospholipid antibodies were also negative. After seven days of admission, the fever persisted and he was transferred to a tertiary hospital for continued investigation.

On admission, he was febrile, ill-appearing and thin, maintaining the previously described maculopapular rash and polyarthritis (Figure 1). The patient did not show bone pain and was able to bear weight. Cervical adenopathies were noted, with a large and tender node on the right spinal group (2 cm). The remaining of his physical examination was normal. He was started on oral ibuprofen (30mg/kg/day).

On the course of his stay there was an additive joint involvement (Figure 1), with marked systemic symptoms, including high fever with 2 to 3 spikes per day and a poor response to antipyretics. Serial blood evaluation documented slight anaemia and persistent inflammatory markers elevation (Table I), including a maximum ferritin level of 11 122 ng/ml. Homogenous hepatosplenomegaly and mesenteric and ileocolic adenopathies were identified by abdominal ultrasound. Infectious causes were broadly excluded, including tuberculosis, with a negative Interferon Gama Release Assay. The peripheral blood film, bone marrow aspirate and bone biopsy were normal.

An excisional cervical lymph node biopsy was performed. The pathology exam showed nodal paracortical expansion resulting in general architecture derangement, presence of T lymphocytes in different maturing stages, histiocytes and areas of necrosis and intense karyorrhexis (Figure 2). No granulomas or neutrophil infiltration were found and no microorganisms were detected. These findings supported the diagnosis of Kikuchi-Fujimoto disease.

Following the biopsy, the patient was started on oral prednisolone (2mg/kg/day) due to marked systemic symptoms. After the first dose, he remained afebrile,

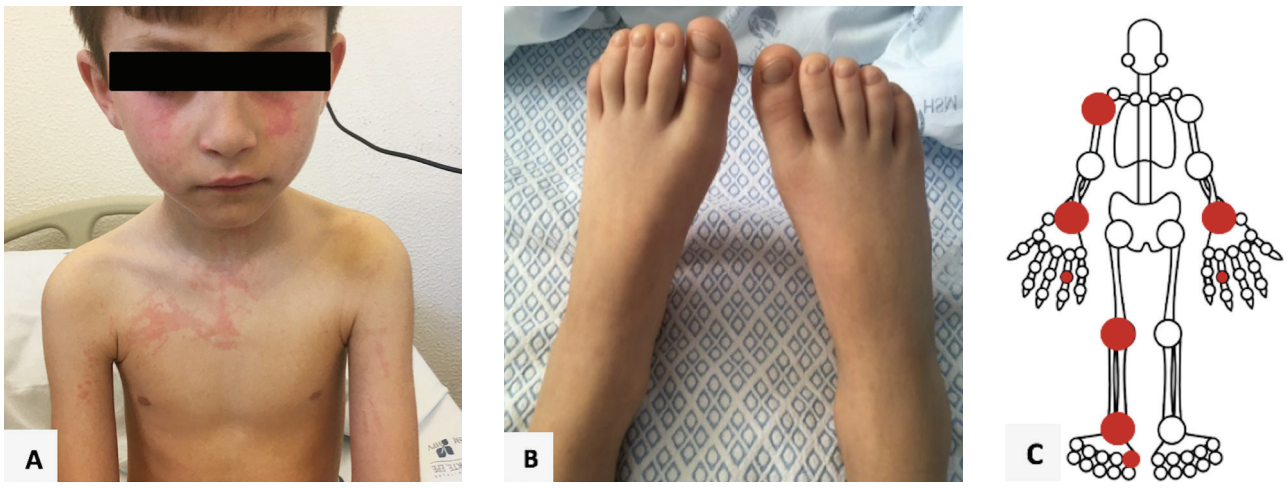

Figure 1. Physical findings. (A) The patient presented ill-appearing and thin with an erythematous, evanescent maculopapular rash on periorbital area, face, thorax and upper limbs. (B) Right ankle arthritis and mild erythematous rash on both feet. (C) Affected joints during the course of the disease - asymmetric polyarticular joint involvement, including large and small joints, with a total of eight joints.

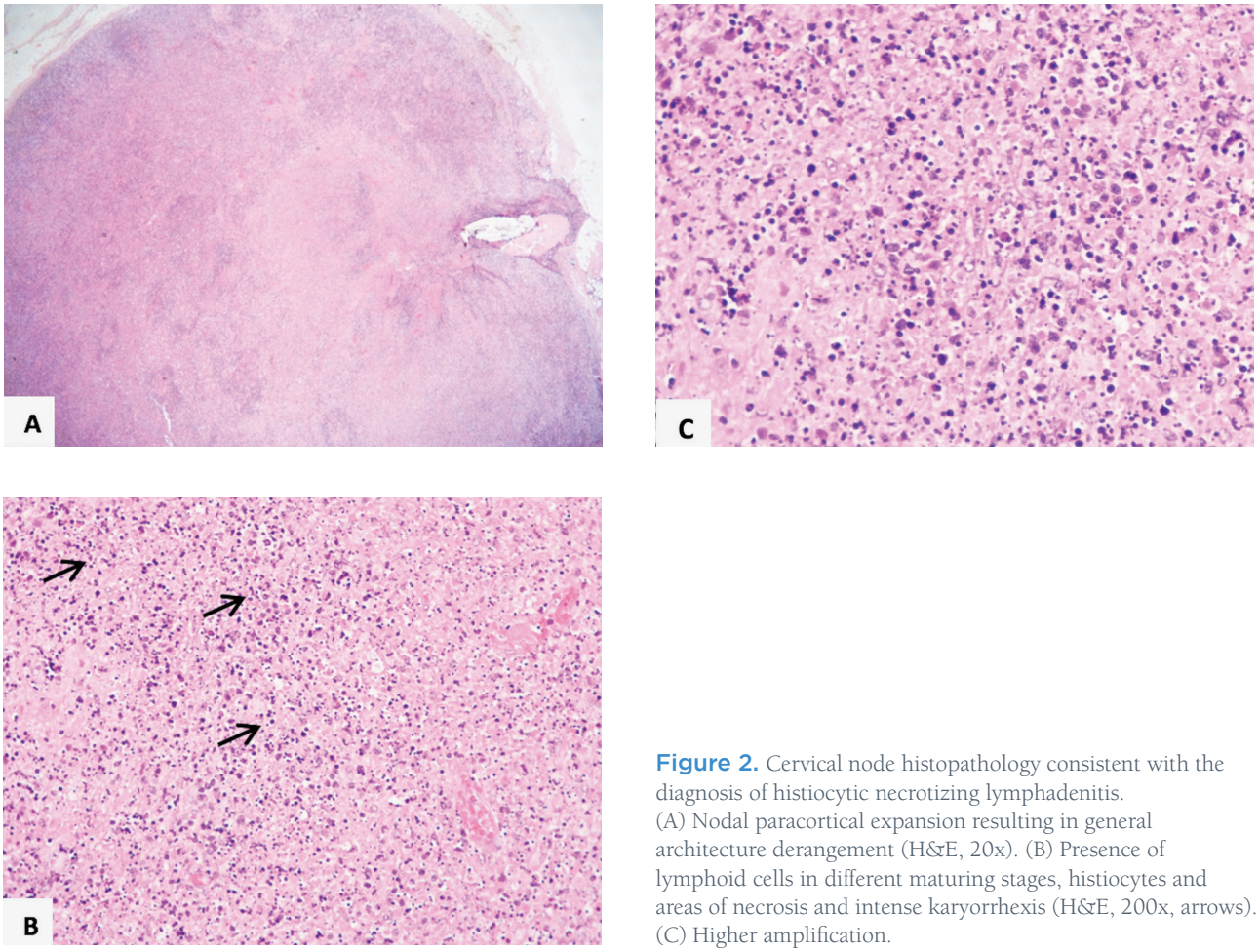

Figure 2. Cervical node histopathology consistent with the diagnosis of histiocytic necrotizing lymphadenitis. (A) Nodal paracortical expansion resulting in general architecture derangement (H&E, 20x). (B) Presence of lymphoid cells in different maturing stages, histiocytes and areas of necrosis and intense karyorrhexis (H&E, 200x, arrows). (C) Higher amplification.

with progressive clinical and laboratorial improvement. Prednisolone was then tapered (1 mg/kg/day) and on the ninth day the patient was discharged home asymptomatic, maintaining oral prednisolone. He was regularly followed on the paediatric rheumatology clinic and corticosteroids were progressively decreased over the course of four months. After one year of follow-up, the patient remains asymptomatic, with no articular damage, and without anti-nuclear antibodies.

DISCUSSION

Kikuchi-Fujimoto disease is a rare and usually self-limited cause of lymphadenitis. Due to its unspecific and frequently mild manifestations, it is likely under-diagnosed. This disease has a high prevalence in young Asian females, although there have been some reports across the world in different age groups and ethnicities[3-4]. Nevertheless, patients younger than 10 years of age have rarely been described[3].

Previous reports in children indicate that the main clinical manifestation is unilateral lymphadenopathy, generally tender, with the majority of cases involving the posterior cervical region. Most patients present with fever, lasting on average one to two weeks. However, a paediatric study with 86 patients showed that 45% of cases presented with prolonged fever[5]. The same study documented that 42% had at least two constitutional symptoms (among fatigue, weight loss, night sweats, and myalgia), and 28% had at least three symptoms other than fever at the time of diagnosis. Rash, odynophagia and hepatosplenomegaly are rare in all series, including adults. The most common hematologic finding is leukopenia. In some cases, atypical lymphocytes can be detected in peripheral blood smears and infrequently, patients may present with anaemia or thrombocytopenia. ESR is usually elevated and CRP may also be mildly elevated[3,5,6,8,10,11]. As compared to adults, male paediatric patients seem to be more frequently diagnosed (male to female ratio 1.4:1) and present with more tender and localized lymphadenopathy. Fever and rash are also more frequently found[11].

Our patient had an atypical presentation for Kikuchi-Fujimoto disease with marked systemic symptoms, polyarthritis, rash, hepatosplenomegaly, intraperitoneal

adenopathy and also marked elevation of acute-phase reactants.

Kikuchi-Fujimoto disease may be frequently mistaken for other clinical entities involving typically three main groups: infections, malignancy and auto-immune/auto-inflammatory diseases.

Infectious agents often comprise viruses and intracellular microbes, including Mycobacterium spp and Bartonella-henselae. Viral infections were broadly excluded in our patient, as well as Tuberculous adenitis. The latter was considered given the presence of bilateral adenopathy with systemic symptoms. However, the interferon gamma release assay was negative as well as the culture result and Ziehl-Neelsen coloration from his node biopsy. Cat-scratch disease was also considered due to the patient's contact with a non-domestic cat, however given the negative serology and the node's histology and culture this aetiology was also excluded.

Malignancy, most frequently lymphoma, may be confused with Kikuchi-Fujimoto disease. Despite lymphadenopathy, hepatosplenomegaly, acute leucocytosis and marked systemic symptoms, our patient's cervical node and bone marrow aspirate and biopsy excluded this entity. Furthermore, the patient presented with an additive non-remitting polyarthritis, did not show bone pain in locations away from affected joints or refusal to bear weight, and did not present with severe persistent cytopenia, which are usually red flags for a lymphoproliferative disease.

Finally, auto-immune/auto-inflammatory diseases may also present similarly to Kikuchi-Fujimoto disease. In this setting, juvenile systemic lupus erythematous (jSLE) and systemic juvenile idiopathic arthritis (sJIA) were considered. In the former case, the presence of systemic symptoms accompanied by rash and polyarthritis could point towards this aetiology, however given the negative anti-nuclear antibodies and normal complement levels, this diagnosis was excluded. sJIA is always a diagnosis of exclusion. The most frequent manifestations are intermittent daily fevers, arthritis and an evanescent rash, often accompanied by hepatosplenomegaly and lymphadenopathy. The patient presented with all these manifestations. The diagnosis of Kikuchi-Fujimoto disease was only possible due to characteristic findings on the cervical node pathology.

Macrophage activation syndrome was also highly considered. In fact, our patient presented with numerous clinical and laboratorial signs of excessive immune activation, including high and prolonged fever, hepatosplenomegaly and high ferritin. His maximum Hscore was 214 on the eleventh day of admission, providing a probability of 93-96% for this syndrome[12]. A few reports have also described an association between Kikuchi-Fujimoto disease and macrophage activation syndrome[13,14]. In fact, both entities seem to be associated with abnormal histiocyte activation and inflammatory cytokines such as interleukin (IL)-1, and IL-6 and tumor necrosis factor-α[15]. Since there are no disease-specific clinical manifestations or laboratory abnormalities and many of the symptoms may overlap between the two entities, a lymph node biopsy is mandatory for diagnosis of Kikuchi-Fujimoto disease. Recently, a 15-year-old Italian girl with sJIA and previous episodes of macrophage activation syndrome, who was being treated with anakinra for two years, developed Kikuchi-Fujimoto disease and a new episode of macrophage activation syndrome[14]. This patient carries the Ala91Val mutation in the perforin gene, which increases the risk for macrophage activation syndrome. Defects in perforin-mediated killing prolong the synapse time between T lymphocytes and target cells, contributing to persistent lymphocyte activation and, consequently, massive production of proinflammatory cytokines, including IFNy, which activates macrophages[16]. Further work needs to be done to better determine the immunologic mechanisms behind Kikuchi-Fujimoto disease and to understand the rare association between this disease and macrophage activation syndrome.

Open excisional lymph node biopsy is the definitive diagnostic test for Kikuchi-Fujimoto disease. Although it does not have pathognomonic findings, the diagnosis is usually established on the basis of node's morphologic evaluation from pathology samples[5,17].

In fact, it proved to be a fundamental exam to establish a final diagnosis in this patient, as it provided more specific findings that helped to differentiate Kikuchi Fujimoto disease from sJIA. In Kikuchi Fujimoto disease, characteristic findings include areas of necrosis with karyorrhectic nuclear debris and large accumulation of histiocytes in the periphery, with classic absence of neutrophils and absent/scarce plasmocytes[4,17,18]. In sJIA, lymph node biopsy usually only shows benign reactive hyperplasia. Our patient's histology findings included the presence of histiocytes and areas of necrosis and intense karyorrhexis, supporting the diagnosis of Kikuchi Fujimoto disease.

In certain circumstances, it may also be difficult to distinguish Kikuchi Fujimoto disease from lymphoma or SLE adenitis. Moreover, the diagnosis of SLE can precede, coincide or follow the diagnosis of Kikuchi-Fujimoto disease. Fortunately, some pathologic features also help distinguishing these two entities. Considering lupus adenitis, some clues are the presence of hematoxylin bodies and plasmocytes. Conversely, in Kikuchi-Fujimoto disease, histiocytes usually have crescent-shaped nuclei and phagocytosed debris, which also help differentiating it from other lymphadenopathies such as tuberculosis or lymphoma. In Kikuchi-Fujimoto disease there is a predominance of T cells, with preponderance of CD8+ over CD4+ cells. Intense CD8+ cell apoptosis occurs in

necrotic foci of the lymph nodes and histiocytes express myeloperoxidase and CD68[4,17,18]. Besides diagnostic purposes, excisional biopsy results in symptom resolution in virtually all cases.

There is no specific treatment nor validated guidelines for Kikuchi-Fujimoto disease. Treatment is mainly symptomatic, including analgesia, antipyretics and anti-inflammatory drugs. Corticosteroids are often reserved for patients with prolonged or severe presentations, as well as recurrences[4]. Some reports also show benefits of hydroxychloroquine use[9]. Finally, there are some case reports of intravenous immunoglobulin use with a good outcome[19].

Following diagnosis, patients commonly have an excellent prognosis, although a small proportion may experience recurrence[5,20]. Although rare, there are some reports of patients developing SLE later on, which accentuates the importance of appropriate referral for close monitoring after recovery. Some authors also suggest that these children should be monitored closely as they are at a higher risk of macrophage activation system in the future[14].

This case report shows the often-convoluted course of Kikuchi-Fujimoto disease. Definitive diagnosis is challenging and usually requires an invasive open lymph node biopsy.

This case report emphasizes the importance of considering this entity in the differential diagnosis of patients with lymphadenopathy and systemic symptoms. Awareness of this disorder might help prevent misdiagnosis and inappropriate, time-consuming and expensive treatment and interventions.

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