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Kikuchi-Fujimoto disease: pediatric case report

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Abstract

The Kikuchi-Fujimoto disease is a rare disease that occurs mostly in young adults, although some cases have been reported in children. It is usually characterized by fever and cervical lymphadenopathy. The etiology of the disease remains unknown. Its course is usually benign and self-limited. It has special histopathological features that allow the differential diagnosis with other entities, which from a clinical point of view can be very complicated. We report a 9 years 11 months old girl with lymphadenopathy and fever with five months evolution, which is the longest evolution among the cases reviewed by the authors in world literature. Given that the presentation of this disease in children is very rare, we estimate that the knowledge of this disease is relevant and pediatricians must consider it in the differential diagnosis of fever of unknown origin in children.

Introduction

The Kikuchi-Fujimoto disease also called necrotizing histiocytic lymphadenitis is an entity described first in 1972 in Japan almost simultaneously by Kikuchi and Fujimoto [1]. First descriptions of the disease were made in young women and mainly in eastern countries. However, in literature, there are descriptions of the disease in all other continents [2],[3],[4],[5]. Pediatrics cases reports can also be found [5],[6],[7]however, the disease is not very prevalent in this age group.

This entity is characterized by the presence of lymphadenopathy, usually of cervical location, and fever [8]; a fact that poses a very wide differential diagnosis which includes infectious, autoimmune diseases and neoplasms. The etiology of the Kikuchi-Fujimoto disease is still unknown, although different hypotheses have been presented [8]. In spite of reported lethal cases and others in which systemic lupus erythematosus developed [9], the course of the disease, in most cases, is benign and it spontaneously resolves in a few weeks. The Kikuchi-Fujimoto disease has special histopathological characteristics, almost unique, which help much during the differential diagnosis with other more severe entities [10]. Therefore, biopsy is essential for diagnosis.

Although we have identified, in international literature search, two series of pediatric patients [1],[11], most of the reports of this disease refer to young adults' cases. In Peru, Arias-Stella *et al.* reported the two first Kikuchi-Fujimoto disease cases in adults in 1996 [12]. Since then, we have not found reports in our country and even less related to pediatric ages.

We present a 9 years 11 months old girl case, diagnosed and attended at Dos de Mayo National Hospital in Lima, Peru. The patient presented cervical lymphadenopathy and 5-month evolution fever, in addition to other systemic symptoms. This time of illness is the longest among the cases found, after the review of world literature made by the authors.

Knowledge about this disease and its appearance in pediatric ages by pediatricians will enrich the differential diagnosis of children with prolonged fever and lymphadenopathy.

Clinical case

Female patient, 9 years 11 months old, from an urban district in the city of Lima, without major personal antecedents. She was admitted at the Pediatric Service of Dos de Mayo National Hospital, Lima, Peru; with a five-month illness, characterized by fever treated at home using

paracetamol, with a progressive and wavy course. Gradually, other symptoms were added as myalgia, arthralgia, hyporexia and weight loss. Two months before service admittance, she presented a diarrheal episode for which she received sulfometoxazol/trimetroprim, getting better at the seventh day. However, fever and other previously described symptoms persisted. One month before admittance, symptoms were more intense and for that reason, the girl was carried to the emergency service in our hospital.

At service admittance moderate general state, malnutrition and pale skin were observed. Weight and height indexes for the age corresponded to exacerbation of chronic malnutrition. During the initial clinical evaluation, she had fever (38°C). Lymphadenopathy was palpated in the posterior cervical chain with diameters bigger than 1.5 cm, mobile and painless. Additionally, liver was palpated 2 cm below the right costal margin. While no objective alterations in joints were observed, range of movement was limited due to pain. The rest of the exam was normal.

Laboratory exams showed pancytopenia: anemia (hemoglobin: 8.2 g/dl and hematocrit: 24.1%), leukopenia (leukocytes: 2 630 X mm^3, without left deviation and the presence of 5% activated leukocytes) and thrombocytopenia (platelets: 112 000 x mm^3). C-reactive protein 2 mg/L, sedimentation rate 90 mm/h, total protein 8.1 g/dl, albumin 3.6 g/dl, globulin 4.5 g/dl, DHL 1081 U/L, serum ferritin 335 µg/dl. The rest of biochemical exams were within normal range, including liver and kidney tests.

Serological tests for toxoplasmosis, brucellosis, viral hepatitis, typhoid fever, cytomegalovirus infection, Epstein-Barr virus, herpes and HLTV-1 were negative. The blood cultures, urocultures and staining by Ziehl Neelsen for mycobacteria in sputum, urine and feces were also negative, as well as sensibility test with purified protein derivative (or PPD) and thoracic X-ray. Antinuclear antibodies had a mottled pattern and were positive in a dilution of 1:40.

We made a right cervical lymph node biopsy of excisional type, obtaining a cervical ganglion of 1.6 cm diameter and other smaller. We made a histological sample staining with hematoxylin-eosin and we noted the presence of paracortical necrosis with lymphocytic infiltrate, presence of histocytes and signs of karyorrhexis. This histopathological finding established the definitive diagnosis of the disease.

We must mention that at this point we had initiated empirical treatment, prior to biopsy, with ceftriaxone in an 80 mg/kg/day dose without obtaining any therapeutic response. Once the previously mentioned biopsy was made, and having initiated the treatment with prednisone in a 1 mg/kg/day, fever and other symptoms decreased. The cortico-therapy remained ten days. The patient was discharged and remained in ambulatory monitoring.

Discussion

The Kikuchi-Fujimoto disease or necrotizing histiocytic lymphadenitis is an infrequent entity at pediatric ages. It was described in 1972 almost in simultaneously by Kikuchi and Fujimoto in Japan [1]. From this moment, many cases have been presented in different parts of the world, although Asian continent is still the place where more cases are reported [3]. In Peru, Arias-Stella *et al*. reported in 1996 the two first cases of the disease in adult patients [12].

The disease is more frequent in young people, younger than 40 years old [8] and predilection is observed for female adults [10]. The report of cases in pediatric ages is much less frequent and they are generally unitary. In a 12 children series, the average age at the moment of diagnosis was 11.3 years old, with a range from six to fifteen years and predominance of males [1]. In another 13 children series, there were eight boys and five girls [11].

The case we are now reporting occurred in a 9 years 11 months old female patient, being the first pediatric case reported of the Kikuchi-Fujimoto disease in Peru.

The disease etiology remains unknown so far. Many hypotheses have been raised. Some authors argue that the disease can be caused by a hyper-response of the immune system, induced by some mainly viral infection. Diverse microbial agents have been involved [8], among them: Epstein-Barr virus, herpes 6, herpes 8, HIV, parvovirus, influenza, *Toxoplasma Gondii*, Yersenia enterocolitica, *Brucella sp* and *Bartonella henselae* [13]. This idea emerged because in some patients there was a positive serology for some of these germs, but the presence of antigens in the lymph node tissue has not been demonstrated by PCR methodology (polymerase chain reaction). Yet this hypothesis is based in some particularities of the disease, which presume the viral cause [14]:

a. Clinical manifestations:

- Upper airway acute respiratory infection prodromal.
- Atypical lymphocytes in blood.
- Lack of response to antibiotics.

b. Histopathological presentation:

- Immunoblasts proliferation.
- Localized necrotic areas.
- T-lymphocyte predominance.
- Paracortex expansion.

Other authors endorse the possibility that the Kikuchi-Fujimoto disease could be an entity of autoimmune origin. This opinion is based in observations with electronic microscopy which show the presence of tubular reticular structures in the cytoplasm of lymphocytes [15]. This phenomenon is observed in some autoimmune diseases as systemic lupus erythematosus and others. In this regard, it has been informed that some patients who suffer the Kikuchi-Fujimoto disease have later developed systemic

lupus erythematosus[9] and juvenile rheumatoid arthritis [16]. This fact, as the striking similarities between the histopathological image of lymphadenitis due to systemic lupus erythematosus and the one produced in the Kikuchi-Fujimoto disease [9] have led to the suggestion that this last one is really a frustrated systemic lupus erythematosus[10].

Finally, recent reports indicate that Kikuchi-Fujimoto disease would develop in genetically predisposed people [6]. Due to this reason, researchers are studying two genes of HLA class II: DPA*01 and DPB1*0202. All of them related to the Kikuchi-Fujimoto disease, present more frequently in Asian people [1].

In our patient, we ordered serological studies and blood cultures that did not demonstrate positivity for any of the following infectious diseases: tuberculosis, cytomegalovirus infection, Epstein-Barr virus, HTLV-I, toxoplasmosis hepatotrophic virus infection, *Bartonella hensaleae*, brucellosis and typhoid fever.

The clinical picture is characterized by an acute or subacute onset of lymphadenopathy, generally of cervical (56-98%) [8], axillary and inguinal predominance. Most of the cases are unilateral (88.5%), slightly painful and with a dimension between 0.5 to 4 cm diameter [10]. This description of cervical lymphadenopathy in adults is the same as the one found in two of the most important pediatric series found in the literature [1],[11]. In the case of our patient, we observed lymphadenopathy of the right posterior cervical chain with the same characteristics mentioned in international reports.

Fever is another characteristic symptom, which usually lasts many days, even weeks. In one of the pediatric series, it is reported that total duration of fever has an average of 19.5 days with a range from nine to 75 days[1]. Our patient had an estimated fever time of five months until diagnosis, which constitutes the longest reported in literature.

Other described symptoms are fatigue (7%), arthralgia (7%), skin rash (10%-30%) [2] and hepatosplenomegaly (3%) [8]. Systemic symptoms can be observed: night sweats, nausea, vomits, diarrhea and weight loss. In our case, the girl presented myalgia, arthralgia, decay, hyporexia, weight loss and hepatosplenomegaly. This description is compatible with the one found in world literature.

In the laboratory tests it can be usually observed leukopenia (43%), sedimentation rate increase (40%), anemia (23%), DHL, AST, ALT increase and presence of atypical lymphocytes among 25 to 31% of cases. These data are relevant for adult and pediatric ages [1],[8],[11]. We found leukopenia, anemia, thrombocytopenia and sedimentation rate increase. It is interesting to mention that in the two reviewed pediatric series they describe relatively low C-reactive protein values [1],[11], which we also observed in our patient. Isolated cases of aseptic meningitis [17],[18] and pancytopenia [5] have been reported; in addition to the simultaneous presentation of Kikuchi-Fujimoto and hemophagocytic syndrome [19] and including, two isolated cases of unexpected death [20],[21].

The Kikuchi-Fujimoto disease diagnosis is possible through the biopsy of the compromised ganglion(s). In literature it is described both the biopsy by fine-needle aspiration [3] and the ganglion excisional biopsy. However, most authors prefer the last procedure due to its best yield. In addition, it has been reported that fever decreases after the ganglion removal. This would be due to the removal of the focus which originates the inflammatory process. Thus, the excisional biopsy would have, in addition to its diagnostic importance, therapeutic effects [1],[10]. In our patient, the ganglion removal for a biopsy resulted in fever resolution.

The Kikuchi-Fujimoto disease histopathological characteristics are quite specific and they are described as:
a) Focus areas of paracortical necrosis.
b) Abundant karyorrhectic nuclear remains.
c) Polymorphous cell population and fibrin deposits.
d) Apoptosis with destroyed cells remains. This is the most characteristic finding.
e) Intense phagocytic activity.
f) Neutrophils and plasmatic cells absence. It is also a basic diagnosis criterion [22].

Some authors have presented three developmental phases of the disease regarding to its histopathological characteristics with relevant importance for the differential diagnosis of this disease. The first phase is the proliferative one, in which it is observed intense inflammatory activity with low karyorrhexis display. Diseases which share this pattern and in which the differential diagnosis must be made in this clinical stage are cat scratch disease, typhoid fever, tuberculosis, tularemia, primary syphilis and venereal lynphogranuloma. The second phase is the necrotic one, with intense apoptosis with karyorrhectical characteristics and irregular cellularity, with high degree necrotic lymphomas and Hodgkin lymphoma as differential diagnosis. The third phase is the organizational one [2],[8],[10],[22].

The biopsy practiced to the patient of our report, reported classic characteristics of the Kikuchi-Fujimoto disease and dismissed the possibility of malignancy and other specific processes like tuberculosis. Given the previously mentioned description and what was observed in the patient histological preparations, we can state that our girl was in the necrotic histological phase at the moment of diagnosis.

The disease has a progressive course with a very favorable prognosis [1],[8],[10], reporting isolated lethal cases [20],[21]. Fever usually resolves spontaneously in some weeks [1],[8],[10]. In literature, it can be found the association of this disease with some more serious entities as systemic lupus erythematosus [9], juvenile rheumatoid arthritis [16], organizational cryptogenic pneumonia [23]. In the *Wang* series, it was reported that high titles of antinuclear antibodies in children with Kikuchi-Fujimoto

disease, were associated to a longer and more complicated course [11].

Our patient showed suggesting clinical features of systemic lupus erythematosus as probable diagnosis: weight loss, prolonged fever, arthralgia, pancytopenia and antinuclear antibodies mottled pattern. However, the necessary criteria were not completed to diagnose systemic lupus erythematosus. In addition, the ganglion excision, the fever decrease and the remission in the general state led us to think that our patient definitive diagnosis was the Kikuchi-Fujimoto disease. However, due to the description in literature regarding the possible association of Kikuchi-Fujimoto disease and systemic lupus erythematosus, we have decided a close following of the girl in order to detect any signal of change in the course of the disease which would be compatible with systemic lupus erythematosus or juvenile rheumatoid arthritis, as it is recommended in the literature [2].

The relapse possibility of the Kikuchi-Fujimoto disease is close to 4% [24], while the period between the first episode and the relapse could extend up to 12 years [25].
Most of the cases do not need treatment, however in cases in which there are systemic symptoms and a mayor compromise of the general state it could be used systemic corticosteroids with a good result, although there is no consensus about its real effectiveness [1],[8],[10]. In the *Kyung-Yil* pediatric series, three of the 12 reported patients received corticosteroid treatment [1]. Our patient was prescribed prednisone 1 mg/kg/day for 10 days. We cannot determine in this moment if the prescribed corticosteroids were relevant in the patient recovery due to the ganglion removal also performed, that as we have mentioned before, is related to fever drop and patient recovery.

Conclusions

The Kikuchi-Fujimoto disease is unusual at pediatric ages, and it is characterized by lymphadenopathy, usually of cervical location and prolonged fever. The differential diagnosis is very wide and it includes infectious, autoimmune and neoplastic diseases. The lymph node excisional biopsy is essential for the definitive diagnosis, due to the disease showing almost unique histopathological characteristics as karyorrhexis, paracortical necrosis, intense phagocytic activity and absence of neutrophils, and plasmatic cells. The evolution of the disease is usually benign and autolimited, although the resolution can be accelerated with the extraction of the affected ganglion. Cases of evolution towards systemic lupus erythematosus and others towards the recurrence have been described. We have made the first report of a pediatric case of the Kikuchi-Fujimoto disease in Peru.

Notes

From the editor

This article was originally submitted in Spanish and was translated into English by the authors. The Journal has not copyedited this version.

Conflicts of Interests

The authors have completed the conflicts of interests declaration form from the ICMJE, and declare not having any conflict of interests with the matter dealt herein. Forms can be requested to the responsible author or the editorial direction of the *Journal*.

Ethical aspects

The *Journal* has evidence that the tutor of the pediatric patient subject of this study signed the consent form for publishing this article

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