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CASE REPORT

Patient with recurrent Kikuchi-Fujimoto disease associated with adult Still desease

Paciente con enfermedad de Kikuchi-Fujimoto recurrente y enfermedad de Still del adulto asociada

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Sumary

We report a patient with Kikuchi-Fujimoto disease (KFD) with a history of a similar process thirty years earlier. She concurrently presented clinical and analytical manifestations of adult Still's disease (AOSD).

Key words: Recurrent Kikuchi-Fujimoto disease, Adult Still's disease.

Resumen

Presentamos una paciente con enfermedad de Kikuchi-Fujimoto (EKF) con antecedentes de un proceso semejante treinta años antes. De forma concurrente presentaba manifestaciones clínicas y analíticas de enfermedad de Still del adulto.

Palabras clave: Enfermedad de Kikuchi-Fujimoto recurrente. Enfermedad de Still del adulto.

Case report

A 51-year-old woman diagnosed with Kikuchi-Fujimoto disease (KFD) by biopsy 30 years ago that progressed satisfactorily with nonsteroidal anti-inflammatory drug (NSAID) treatment. She was admitted to our department with a 2-month intermittent history of acute spiking fever (40ºC) and profuse sweating, without a clear focus. She also presented progressive pain and swelling in the left axilla, wrists, metacarpophalangeal joints and shoulders.

The general physical examination was normal, except for the palpation of lymphadenopathy in the left axilla and neck as well as inflammation signs in both hands and shoulders. Repeated blood and urine microbiological studies tested negative and so did the infectious serology and autoimmunity screenings. General blood tests revealed an anemia of inflammation (9,5g/dl), leukocytosis (15,7x10^9 L) with neutrophilia (98%) and lymphopenia (2%). The acute phase reactants were high: VSG 77, PCR 114. The rise of ferritin level up to 3135 ng/ml was striking. The rest of blood and urine determinations were normal except for a slight increase in liver enzymes.

Mantoux test was negative.
Chest X-Ray didn't show any significative alteration.
Echocardiography was normal.

A positron emission tomography-computed tomography (PET/CT) (**Figure 1**) revealed metabolically active disease in the lymph nodes especially in the supra-diaphragmatic area and left axilla. Lymph node biopsy (**Figure 2**) shows necrotic area, phagocytic histiocytes, dendritic cells, eosinophilic granular material and karyorrhectic debris. Immunohistochemistry showed CD3, CD4, CD8-positive T cells with CD68 histocytes. Mixed with lymphoid areas of smalls cells with blasts and absence of neutrophils or plasma cells. These findings correspond to a histiocytic necrotizing lymphadenitis compatible with KFD.

Given the poor response to the initial treatment with ibuprofen 600 mg every 8 hours, a new treatment was initiated with daily prednisone 30 mg combined with weekly methotrexate 12,5 mg and supplementary folic acid. The fever quickly resolved and there was an obvious improvement of the articular affectation and general condition.

Figure 1: PET/CT imagen.

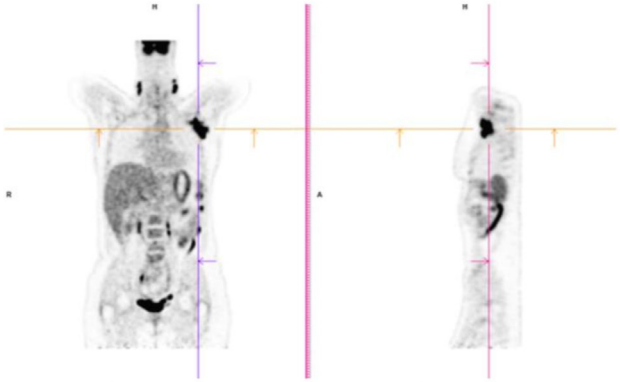
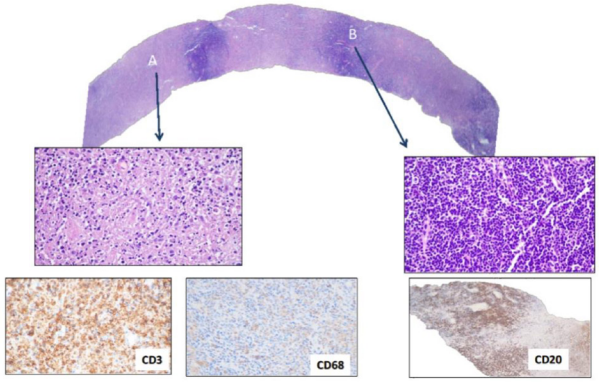


Figure 2: Lymph node biopsy. Histiocytic necrotizing lymphadenitis.



Discussion

Although Kikuchi-Fujimoto disease (KFD) and adult Still's disease (AOSD) were described during the 1970s, the number of published cases of both pathological processes is very scarce. Its simultaneous presentation (overlap syndrome) is exceptional and provokes varied manifestations[1,2].

The case we are reporting is exceptional given that the patient had already suffered from KFD 30 years earlier. It was thought that the recurrence of this disease was below 5%, however an important revision made in 13 French hospitals[3] proved a relapse in 21,3% of the cases, in a timeframe of 1 to 11,5 months, in contrast with other described cases which presented a gap of up to 8 years[4]. Consequently, it is remarkable that our patient suffered KFD thirty years later which also was associated with AOSD symptoms.

This overlapping is to be expected given that both diseases have an idiopathic inflammatory origin. The most accepted theory is that both KFD and AOSD are the result of an abnormal immune response to several infections, especially viral ones (Epstein- Barr Virus, herpesvirus 6, parvovirus B19, cytomegalovirus). The prevalence of KFD seen in young Asian women is related to haplotypes of the HLA (human leukocyte antigens) system, however more cases have been diagnosed in other races and geographic regions[1,3].

The key sign for KFD is adenopathy, cervical lymph nodes are the most affected (92%) followed by axillary nodes (50%), even though half of the patients can present polyadenopathies. Along with mild fever (62%), sweating and asthenia and weigh loss in almost the totality of the patients. A non-specific and brief exanthema can appear (21%) as well as hepatosplenomegaly in very few cases (10%).

In the analysis, acute phase reactants and hepatic enzymes slightly increase in half of the patients and in some cases lymphopenia and thrombopenia can appear. Given that there are no pathognomonic clinical or analytical findings, the diagnosis should be based in an affected lymph node biopsy[3].

A 18F-FDG PET/CT could be useful for a differential diagnosis with a lymphoproliferative syndrome[5].

The KFD is a self-limited disease in 61,5% of the cases. If the symptoms are severe the treatment of choice is corticosteroids, in high doses initially (0,5 mg/kg) with progressive reduction according to the patient's response. There were cases that demanded the prescription of hydroxychloroquine or methotrexate in order to lower the steroids dose[3,4].

Unlike KFD, AOSD is more frequent, with an incidence of 0,16 for every 100.000 people and an average age of 25. It presents a bimodal distribution with one peak of incidence between 15-25 and another one between 36-46 years old. Amongst many published case series there is no proof of it being a female predominant disease[6].

The clinical and analytical manifestations of AOSD clearly differ from KFD[6,7,8]. The onset is acute with fever spikes of 39ºC, in 21% of the cases the temperature remains slightly elevated. The most common skin manifestation is an evanescent salmon-pink maculopapular rash that appears with the fever spikes. Its incidence ranges from 51-87% of the cases and sometimes can be misconceived as an allergic reaction. The joint involvement is present in 94% of the patients. Its described as polyarticular, migratory and symmetric, affecting knees, ankles and small articulations. Myalgia is also frequent (56-84%). In approximately half of the patients soft

Table I: Yamaguchi et al. criteria. Diagnosis is made when there are 5 or more criteria which include at least 2 major criteria.

MAJOR CRITERIA	MINOR CRITERIA
Arthralgia lasting 2 weeks or longer	Sore throat
Fever of 39ºC or higher lasting 1 week or longer	Lymphadenoapthy and/or splenomegaly
Typical rash	Liver dysfunction
Leukocytosis >10.000 including 80% or more of granulocytes test	Negative Rheumatoid Factor (RF) and negative Antinuclear antibody (ANA)

and mobile adenomegalies can be found, located in the cervical, submaxillary, supraclavicular and inguinal areas. Hepatosplenomegaly with slight liver biochemical alteration is less frequent. Pulmonary infiltrates and minor pleural effusion can occasionally appear. Exceptionally perimyocarditis can appear too.

The analytical study in 80-90% of the patients with AOSD presents an anemia of inflammation that can be intense in patients with severe disease. Thrombocytosis is usual and precedes and goes with inflammatory flares. Leukocytosis with neutrophilia is very common. Ferritin levels above 1000ng/L are considered to be a very characteristic feature of this disease with a sensibility of 80% and a specificity of 41%[9]. We have to underline the negativity of antinuclear and anti-citrullinated peptide antibodies. The result of the lymph node biopsy is unspecific as well as the imaging studies. The exclusion of differential diagnoses is essential in this rheumatic process, especially regarding infectious diseases. To make diagnosis easier several criteria have been published, amongst them the Yamaguchi et al. criteria[6] (**Table I**) which are considered to be the ones with a higher degree of sensibility (95,5%). The latter increases even more when ferritin levels are very high[9].

The AOSD treatment is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs), although corticosteroids are necessary in 12% of the cases. In order to reduce the steroids dose, hydroxychloroquine, methotrexate, azathioprine and lastly anti-TNF agents have been used, even though there are no controlled trials of it[9].

In our patient, recurrent KFD diagnosis is unquestionable given the characteristic findings from the lymph node biopsies carried out during each episode.

The AOSD comorbidity is obvious given that it meets the Yamaguchi criteria, as well as the remarkable elevation of acute phase reactants and the strikingly high ferritin level.

Ethical approval

Patient's consent has been obtained before writing this manuscript.

Declaration of interest

The authors have no conflicts of interest to declare

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