BILATERAL PLEURAL EFFUSION AND INTERSTITIAL LUNG DISEASE AS UNUSUAL MANIFESTATIONS OF KIKUCHI-FUJIMOTO DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Kikuchi-Fujimoto’s Disease (KFD), also called Histiocytic Necrotizing Lymphadenitis, is a rare, idiopathic and self-limited condition usually characterized by cervical lymphadenopathy and fever. While initially described in young Asian women, it clearly also occurs in men and worldwide. Aetiology is unknown, although a viral or autoimmune pathogenesis has been suggested. Differential diagnosis includes mainly malignant lymphoma, tuberculous lymphadenitis and Systemic Lupus Erythematosus (SLE), so early diagnosis is crucial. We present a 32-year-old man, on treatment for iatrogenic hypothyroidism, histologically diagnosed with KFD and who developed bilateral pleural effusion and interstitial lung disease; both of them resolved with prednisone, and after two years of following up he remains asymptomatic and without evidence of any other associated disease. To the best of our knowledge this is the first case of isolated KFD with pleuropulmonary involvement.

Keywords: Kikuchi. Fujimoto. Histiocytic Necrotizing Lymphadenitis. Pleural. Pulmonary. Hypothyroidism.
INTRODUCTION
Kikuchi-Fujimoto’s disease (KFD), or Histiocytic Necrotizing Lymphadenitis, was first described in Japan in 1972 as a self-limiting disease mostly affecting the cervical lymph nodes of young individuals, mainly females\(^1\). In 1982 the first cases of KFD were reported in North America and Europe\(^2\) and the disease is now reported worldwide. Although the aethiology is unknown, it has been suggested to be an apoptopic process mediated mainly by CD8-positive T lymphocytes, and viral or autoimmune etiology is believed to be causative factors\(^1,\,^3\). Occasionally it may co-exist with autoimmune diseases, mostly Systemic Lupus Erythematous (SLE)\(^3,\,^4\). Enlargement of cervical lymph nodes, fever and leukopenia are the most prominent symptoms, although several other clinical manifestations have been reported\(^1,\,^3\). We report the first case of isolated KFD with interstitial lung disease and bilateral pleural effusion, which also improved quickly with oral prednisone.

CASE REPORT
A 32-year-old Caucasian man, with past history of hyperthyroidism six months before due to toxic multinodular goiter, treated with radioactive iodine developing iatrogenic hypothyroidism and on initiated substitutive treatment, was admitted due to continuous fever (39-40ºC), malaise, and painful cervical lymphadenopathies of 2 weeks’ duration. Laboratory findings were as follows: haematocrit 34%, haemoglobin 12 gr/dl, leukocyte count 3,400/mm3, platelet count 246000/mm3, erythrocyte sedimentation rate 63 mm/h, alanine transaminase (ALT) 176 IU/L,
aspartate aminotransferase 89 IU/L, alkaline phosphatase 176 IU/L and gamma-glutamyl transpeptidase (GGT) 657 IU/L; serum lactic dehydrogenase (LDH) 1896 IU/ml, Thyroid-stimulating hormone (TSH) 73 mU/L and thyroxine (T4) 0.25 µg/dl. Blood cultures as well as serologic tests for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Rubella, *Toxoplasma*, Parvovirus B19, *Yersinia enterocolítica, Salmonella and Brucella* were found to be negative. Serum antinuclear antibody (ANA) and rheumatoid factor were also negative. On admission, chest X-ray and computed tomography of the neck, thorax and abdomen only revealed multiple cervical and one mediastinal lymphadenopathies, with both lung fields clear (Figure 1). During the first week after admission the patient got worse, with high grade daily fever, increasing size of cervical lymphadenopaties, axillary bilateral lymphadenopathies developed and he referred mild dyspnea on exertion, with absence of breath sounds in both lung bases on physical examination. A second computed tomography of the thorax revealed extensive axillary, mediastinal and hilar bilateral lymphadenopathies, interstitial infiltrate in both lungs and bilateral pleural effusion (Figure 2). Cervical lymph node biopsy revealed necrotizing lymphadenitis with areas of histiocytic infiltrate, prominent necrosis, abundant non-neutrophilic karyorrhexis, few plasma cells and no neutrophils, consistent with KFD. Stains and tissue cultures for bacteria, fungi and mycobacteria were negative. Prednisone therapy was started at 1 mg/Kg/day with rapid improvement: he became afebrile on third day, cervical and axillary swelling and tenderness began to decrease, dyspnea disappeared and respiratory auscultation normalized. Daily dose of thyroxine was slowly increased
by the endocrinologist. Prior to discharge, chest X-ray revealed normal. Tapering doses of prednisone were prescribed during subsequent two months; all biochemical and haematological parameters normalized except for TSH, which reached normal values four months later. After follow-up appointments for two years the patient is asymptomatic, physical examination and chest X-ray is absolutely normal and serum antinuclear antibodies remain negative.

DISCUSSION
KFD is a benign disease with usual spontaneous resolution between 1 and 4 months, affects all ethnic groups and is more common in young women (in a proportion of 4:1 for women), manifests as localized lymphadenopathy, usually in the cervical region, and is commonly associated with fever and leukopenia\(^1,5\). The aetiology of KFD remains obscure: a viral pathogenesis is thought to be the most likely candidate due to its self-limiting clinical course and the lack of neutrophilic response\(^6,7\). It has been reported in association with Epstein-Barr virus, Human Herpesvirus, Human Herpesvirus 8, HIV, HTLV1, Dengue virus, Parvovirus B19, *Yersinia enterocolítica*, *Bartonella*, *Brucella*, *Entamoeba histolytica* and *Toxoplasma*\(^7,8,9\). On the other hand, an autoimmune origin has also been suggested due to electron microscopic studies that have identified tubular reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes in patients with KFD, which have also been noted within lymphocytes and endothelial cells of patients with Systemic Lupus Erythematosus and other autoimmune disorders, so it is possible that KFD may represent an exuberant T-cell mediated self-limited
immune response to a variety of non-specific stimuli in genetically susceptible individuals\textsuperscript{10}.

The differential diagnosis of lymph node enlargement in patients with the clinical course of KFD includes mainly tuberculous and other infectious lymphadenitis, and malignant lymphoma\textsuperscript{4}. The diagnosis is confirmed by biopsy of the lymph node, whose histopathology reveals necrotizing lymphadenitis restricted to the cortical and paracortical areas, with partial or complete loss of follicular architecture, marked karyorrhexis, and absence of neutrophils, granulomatous reaction or lymphoma cells\textsuperscript{5}. Most of the cases of KFD improve within a six-month period\textsuperscript{3}, and different recurrence rate from 4 to 27\% have been reported\textsuperscript{11,12,13}.

Kikuchi-Fujimoto disease has been rarely described in association with simultaneous SLE\textsuperscript{4,5}, Sjögren syndrome\textsuperscript{14}, antiphospholipid syndrome\textsuperscript{4,15}, relapsing polychondritis\textsuperscript{16} or even autoimmune hepatitis\textsuperscript{17}. On the other hand, unusual manifestations of isolated KFD include axillary and mesenteric lymphadenopathy, splenomegaly, parotid gland enlargement, cutaneous rash, arthralgias, myalgias, aseptic meningitis, bone marrow haemophagocytosis and liver dysfunction\textsuperscript{3}. Occasional patients with arthritis\textsuperscript{18,19} or bilateral panuveitis\textsuperscript{20} have also been reported. Although KFD, as a systemic disorder, could theoretically be associated with interstitial lung disease\textsuperscript{21}, pulmonary involvement has only been described previously in patients who developed SLE\textsuperscript{4}, in a patient in whom KFD was associated with polymyositis and intensive immunosuppressive treatment\textsuperscript{22}, in another patient who died of pulmonary haemorrhage in whom KFD was the only etiological factor objectived upon postmortem examination\textsuperscript{3}, in three patients who developed the disease after transplantation and died of respiratory failure probably
because of a reason other than KFD in author’s opinion\(^3\), and recently one case of KFD associated with cryptogenic organizing pneumonia has been reported\(^{23}\). To the best of our knowledge, this is the first documented case of isolated KFD with pleuropulmonary involvement due to interstitial lung infiltrate and pleural effusion, both of them bilateral and with rapid improvement and resolution with oral prednisone. We must take into account the simultaneous hypothyroidism of the patient and be aware of its possible clinical co-expression, but its presence several months before the development of the KFD and even after the clinical and analytical resolution of the latter, the absence of other clinical symptoms related to thyroxine deficiency and the rapid development and improvement of the pleuropulmonary manifestations with prednisone suggest an inflammatory rather than an endocrine etiology.

In conclusion, pleuropulmonary involvement in patients with KFD has been seldom reported. We describe a patient with an isolated KFD in whom bilateral pleural effusion and interstitial lung pattern developed. Clinical and radiological response to prednisone were excellent.

**Disclosures:**

Conflicts of interest:

REFERENCES
