

# Kikuchi-Fujimoto disease: an unusual association with acute renal failure

## ABSTRACT

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis of unknown etio-pathogenesis, is a self-limited disease which frequently appears as feverish lymphadenomegaly, thus creating the need for differential diagnosis with lymphoma, systemic lupus erythematosus (SLE), infectious mononucleosis, cat-scratch disease, and toxoplasmosis with lymphonodal impairment. However, there are cases in which it may evolve with complications such as aseptic meningitis, cerebellar ataxia, and aseptic myocarditis. We are presenting a case of a 24-year-old man who had an initial picture of arthralgia, evening fever and adenomegaly. Kikuchi disease was diagnosed through lymph node biopsy with immunohistochemistry and evolves with severe systemic manifestations, such as pericarditis with cardiac tamponade, pneumonitis, hepatitis, and acute kidney failure - the latter has not been reported in literature yet. There was significant improvement of the clinical picture with prednisone.

Keywords: Kikuchi-Fujimoto disease; histiocytic necrotizing lymphadenitis; acute renal failure.

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## INTRODUCTION

Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, was described in Japan, in 1972, by Kikuchi and Fujimoto<sup>1,2</sup> simultaneously. It is a frequently self-limited entity, and for that reason it is not often diagnosed. It most usually affects women up to 30 years old. Most cases resolve within six months.<sup>3</sup> The most common symptoms are lymphadenomegaly, fever, rash, fatigue, and arthralgia,<sup>3</sup> but there are reports of cases with severe systemic manifestations, such as aseptic meningitis, cerebellar ataxia, and aseptic myocarditis.<sup>4</sup> The histologic findings includes areas of coagulation necrosis with abundant karyorrhexis debris. The latter consists of different types of histiocytes, plasmocytes, monocytes, immunoblasts, and small and large lymphocytes. There is abundant predominance of T lymphocyte with prevalent CD8+ in relation to CD4+.<sup>11</sup> This disease's pathogenesis is unknown, with autoimmune and viral factors implied. It is essential to establish a differential diagnosis with lymphoma, systemic lupus erythematosus (SLE), infectious mononucleosis, cat-scratch disease, and toxoplasmosis with lymphonodal impairment.<sup>3</sup>

The authors report a case with severe systemic manifestations, such as hepatosplenomegaly, pneumonia, pericardial effusion with cardiac tamponade, sepsis, and acute renal failure. The latter has not been reported in literature yet.

## CASE REPORT

Male patient, 24-years-old, black, born in Piauí, coming from Bertioga, SP. He was accepted at *Santa Casa de Misericórdia* de Santos with a history of evening fever for 46 days at 38°C, arthralgia in major articulations, myalgia, weight loss of 10 kg, anemia, hepatosplenomegaly of 5 cm and adenomegaly of fibroelastic consistence, 1 to 2 cm long, in inguinal, axillary, and posterior cervical chains, as well as jaundice +/++++. The neck computerized tomography observed multiple neck lymph nodes of 1.5 cm in submentonian and posterior cervical chains. The abdominal ultrasound showed mild hepatomegaly and moderate splenomegaly. Results of the blood count were: leukocytes 53,900 mm<sup>3</sup>, platelets 131,000/mm<sup>3</sup>, red blood cell 3,47 million/mm<sup>3</sup>, hemoglobin 7.67 g/dL, hematocrit 24.7%, aspartate aminotransferase (AST) 1,208 U/L,

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alanine aminotransferase (ALT) 844 U/L, indirect bilirubin (IB): 0.38 mg/dL, direct bilirubin (DB): 1.75 mg/dL, total bilirubin (TB): 2.13 mg/dL, gamma glutamyl transferase (GGT) 542 U/L, as shown in Table 1. For the investigation of fever of infectious origin, brucellosis,

**Table 1. Laboratory from the first hospitalization**

|                                  |                               |
|----------------------------------|-------------------------------|
| Red blood cell                   | 3,470 million/mm <sup>3</sup> |
| Hemoglobin                       | 7.67 g/dL                     |
| Hematocrit                       | 24.7%                         |
| Leukocytes                       | 53,900/mm <sup>3</sup>        |
| Platelets                        | 131,000/mm <sup>3</sup>       |
| AST (aspartate aminotransferase) | 1,208 u/L                     |
| ALT (alanine aminotransferase)   | 844 u/L                       |
| Total bilirubin                  | 2.13 mg/dL                    |
| Direct bilirubin                 | 1.75 mg/dL                    |
| Indirect bilirubin               | 0.38 mg/dL                    |
| Gamma glutamyl transferase       | 542 U/L                       |

leptospirosis, toxoplasmosis, HTLV1, HTLV2, and viral hepatitis types A, B, C were investigated, and ELISA method was used for all research; for mononucleosis, another two samples were collected, and the method used was Hoff and Bauer; for leishmaniasis and paracoccidioidomycosis the technique of complement fixation reaction was used; for Chagas disease, immunofluorescence was used; for cytomegalovirus, chemiluminescence was used. All results were negative. When researching HIV (human immunodeficiency virus) 1 and 2, at least two samples were collected at different times with microparticle enzyme immunoassay (MEIA), and all were negative. PPD (Purified Protein Derivative of tubercle bacilli) was non-reactive, as shown in Table 2. Lymph node biopsy revealed diffuse proliferation of histiocytic cells with mature

**Table 2. Search for the infectious agent**

|   |              |                                  |
|---|--------------|----------------------------------|
| Brucellosis                                     | Non-reactive | Enzyme immunoassay               |
| Leptospirosis                                   | Non-reactive | Enzyme immunoassay               |
| Toxoplasmosis                                   | Non-reactive | Enzyme immunoassay               |
| HTLV-1, HTLV-2                                  | Non-reactive | Enzyme immunoassay               |
| Viral hepatitis types A, B, C                   | Non-reactive | Enzyme immunoassay               |
| Mononucleosis - two samples                     | Non-reactive | Monotest Hoff-Bauer              |
| Leishmaniasis                                   | Non-reactive | Complement fixation reaction     |
| Paracoccidioidomycosis                          | Non-reactive | Complement fixation reaction     |
| Chagas disease                                  | Non-reactive | Immunofluorescence               |
| Cytomegalovirus                                 | Non-reactive | Chemiluminescence                |
| HIV 1 e 2 - two samples with a 3-month-interval | Non-reactive | Microparticle enzyme immunoassay |
| PPD   | Non-reactive |                                  |

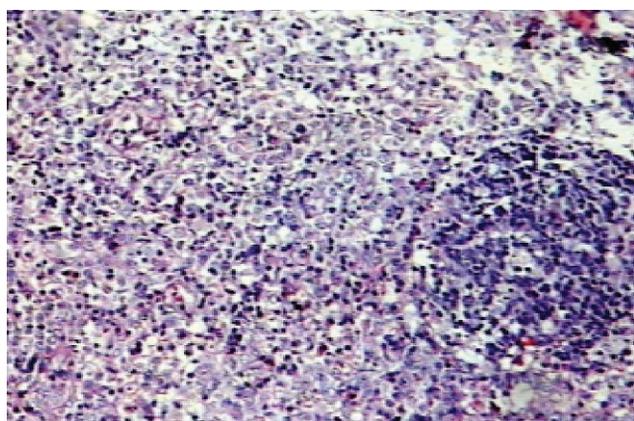
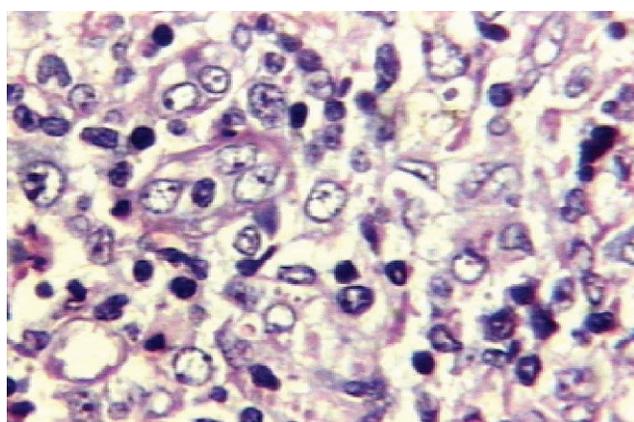
lymphocytes. Several histiocytic cells showed enlarged nucleus with prominent nucleolus. The diagnosis of Hodgkin's lymphoma was excluded by the absence of Reed-Steinberg cell and by immunohistochemical examination (negativity of immunoexpression for marker CD30).

The histochemical exam of the lymphonodal tissue has demonstrated an interfollicular histiocytic and lymphoid proliferation with focuses of reactive pattern apoptosis, which is coherent with the proliferative phase of histiocytic necrotizing lymphadenitis, also known as Kikuchi-Fujimoto disease. The material was assessed by another pathologist, who confirmed the diagnosis of Kikuchi-Fujimoto disease through an immunohistochemical analysis. Besides the polyclonal aspect, the finding of lymphocyte CD30 expression was discovered to be occasional, with B lymphocyte (CD20) islands, preserved lymphoid follicle, and a number of histiocytes (CD68) diffusely distributed (Table 3 and Figures 1 and 2).

In the evolution, the patient showed intense dyspnea, and the echocardiogram revealed pericardial effusion with cardiac tamponade, which was drained and underwent to a biopsy. The anatomopathological examination resulted in a mild, non-specific, chronic pericarditis. With remission of symptoms, the patient was discharged from hospital three months later. After 75 days, he was readmitted into the Service of Infectious Diseases, presenting pneumonia and evolution of fever to sepsis. He had fever, hepatosplenomegaly, arthralgia, hyperchromic macula-papular skin lesions, blurred vision, oral candidiasis, and inguinal and axillary adenomegaly of fibroelastic consistence, fixed and tenderness. Blood count: leukocytes 18,000 mm<sup>3</sup>, platelets 277,000/mm<sup>3</sup>, hemoglobin 11.6 g/dL, hematocrit 35%, red blood cell 4,95 million/mm<sup>3</sup>. Lactic dehydrogenase (LDH) 942U/L, alkaline phosphatase (AP) 72 UI, AST 107 U/L, ALT 69 U/L, GGT 33 U/L, creatinine 0.8 mg/dL, BUN 24 mg/dL, potassium (K) 4.9 mEq/L, sodium (Na) 140 mEq/L, albumin 3.2 g/dL, as shown in Table 4. In the investigation of autoimmune

**Table 3. Results of the examinations through lymph node tissue histochemistry**

| Antigen  | Result                                     |
|--|--|
| Antigen ki-67 (clone MIB-1)                          | Positive (++/+++)<br>in follicular areas   |
| CD30 (clone Ber-H2)                                  | Negative                                   |
| Epithelial membrane antigen (EMA)                    | Focal positive in permeate [R1] plasmocyte |
| Leukocyte common antigen (LCA-CD45)                  | Positive                                   |
| CD15 (granulocyte associated antigen)                | Negative                                   |
| Oncoprotein Bcl-2                                    | Negative follicular areas                  |
| CD3 (monoclonal antibody - T lymphocyte marker)      | Positive interfollicular lymphoid cells    |
| CD20 (monoclonal antibody L26 - B lymphocyte marker) | Positive in follicular lymphoid cells      |

**Figure 1:** Lymph node slice presenting preserved lymphoid follicle, surrounded by numerous histiocytes. (HE stain, 100X).**Figure 2:** Presence of numerous histiocyte cells, with vesicular nucleus, and some degenerating cells. Small and medium-sized lymphocytes can also be observed. (HE stain, 400X).

disease, antinuclear factor (ANF), anti-native DNA, anti-SSA/Ro, RNP - antigen extracted from nucleus, anti-SM (anti-smith), anti-endomysial, SSB (La) - antigen extracted from nucleus; all were non-reactive. Total complement 385 mg/dL, complement C3 175 mg/dL, complement C4 43.9 mg/dL, as it is shown in Table 5. Cell immunity was evaluated at CD4 = 250 cells/mm<sup>3</sup>, CD8 = 2,340 mm<sup>3</sup>, as shown in Table 6. The abdominal ultrasound showed hepatosplenomegaly.

**Table 4. Laboratory from the second hospitalization**

|                |                               |
|----------------|-------------------------------|
| Red blood cell | 4,950 million/mm <sup>3</sup> |
| Hemoglobin     | 11.6g/dL                      |
| Hematocrit     | 35%                           |
| Leukocytes     | 18,000/mm <sup>3</sup>        |
| Platelets      | 277,000/mm <sup>3</sup>       |
| LDH            | 942 U/L                       |
| AP             | 72 UI                         |
| AST            | 107 U/L                       |
| ALT            | 69 U/L                        |
| GGT            | 33 U/L                        |
| Creatinine     | 0.8 mg/dL                     |
| BUN            | 24 mg/dL                      |
| K              | 4.0 mEq/L                     |
| Na             | 140 mEq/L                     |
| Albumin        | 3.2 g/dL                      |

**Table 5. Investigation of autoimmune disease**

|   |              |
|---|--------------|
| Anti-nuclear factor (ANF)                 | Non-reactant |
| Anti-native DNA                           | Non-reactant |
| Anti-SSA/RO                               | Non-reactant |
| RNP - antigen extracted from nucleus      | Non-reactant |
| Anti-SM                                   | Non-reactant |
| Anti-endomysial                           | Non-reactant |
| SSB (La) - antigen extracted from nucleus | Non-reactant |
| Total complement                          | 385 mg/dL    |
| Complement C3                             | 175 mg/dL    |
| Complement C4                             | 43,9 mg/dL   |

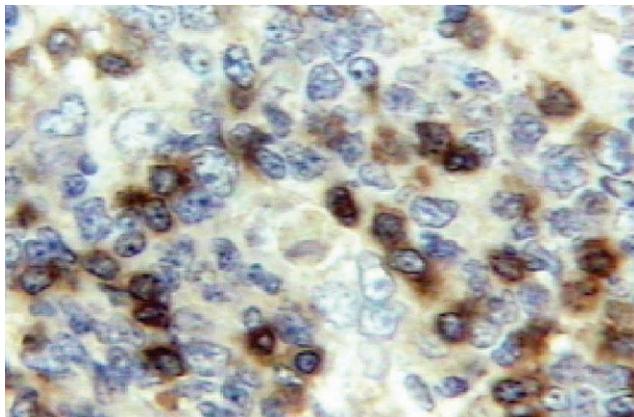
**Table 6. Evaluation of cell immunity**

|     |                             |
|-----|-----------------------------|
| CD4 | 250 cells/mm <sup>3</sup>   |
| CD8 | 2,340 cells/mm <sup>3</sup> |

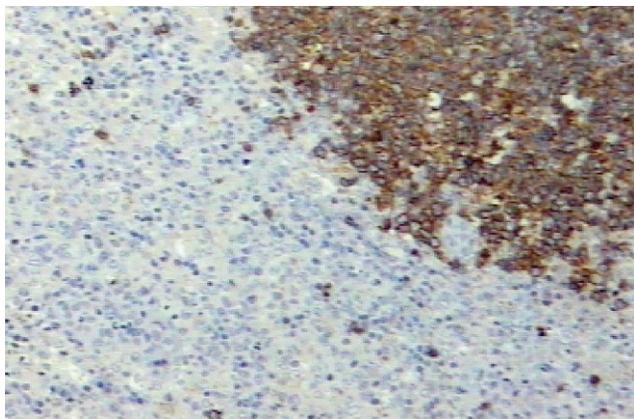
All tests were performed at Laboratório da Santa Casa de Misericórdia de Santos (Figures 3, 4 and 5).

An antibiotic therapy for lung focus was initiated with moxifloxacin (400 mg/day for three days), with no improvement. The patient evolved for lung focused sepsis, and the medication was changed for cefepime (4 g/day) and vancomycin (2 g/day).

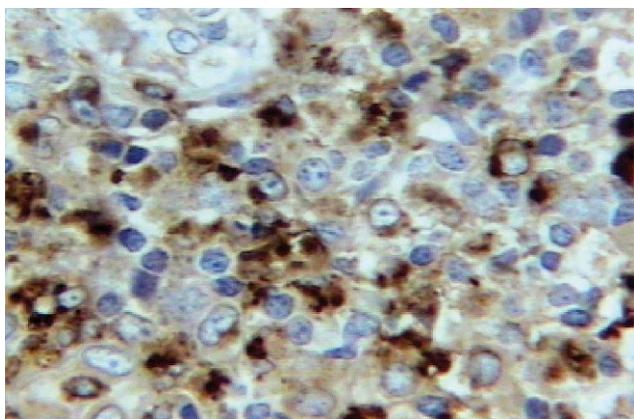
**Figure 3:** Immunohistochemical examination. Nuclear immunoexpression in lymphoid cells from paracortical area. (CD3, 400X).



**Figure 4:** Immunohistochemical examination. Immunoexpression of B lymphocyte in the lymphoid follicle (CD20, 100X).



**Figure 5:** Lymph node immunohistochemical examination. Great expression in histiocyte cells present on the display (CD68, 400X).



Considering Kikuchi-Fujimoto disease as the pathological basis, the use of non-hormonal anti-inflammatory piroxicam (40 mg/day for five days) was initiated. There was no response to the anti-inflammatory, and although the patient remained severely ill, renal function remained preserved (creatinine 0.8 mg/dL; urea 34 mg/dL). Due to the case's severity, a treatment with prednisone (60 mg/day for 15 days) was adopted, having good clinical response. Once the corticosteroid dose started to be reducing (20 mg of prednisone/day), the patient worsened and evolved to acute renal failure, with serum levels of creatinine at 72 mg/dL; BUN 231 mg/dL; Na 141 mEq/L; and K 6.1 mEq/L. On the ultrasound scan, the kidneys appeared to have acute parenchymatous nephropathy. Four sessions of hemodialysis were performed.

With prednisone's dose as it was previously (60 mg/day), the patient had excellent improvement with a regression of the syndrome. After 64 days of outpatient treatment, he was discharged from the hospital, keeping the corticoid therapy. As he evolved, renal and liver biopsy revealed: tubular degenerative change, and mild chronic hepatic inflammatory activity, eliminating the diagnosis of autoimmune hepatitis. Currently the patient maintains proteinuria of 0.27 g/24 h, and therefore receives captopril (25 mg/day), and prednisone (20 mg/day). The patient has had the disease inactive for three years.

## DISCUSSION

Historically, it has been reported that KFD affects women more than men in a ratio of approximately four to one.<sup>1</sup> Recent reports seem to indicate that the female preponderance was overemphasized in the past, and that the actual ratio is closer to 1:1.5. And KFD has been reported to have occurred in a parent and a child.<sup>6</sup>

This disease's pathogenesis is still unknown. Several etiologies have been reported. Cases of KFD have been described as being associated with infections by Epstein-Barr virus, cytomegalovirus, herpes simplex type 6 and 8, HTLV-1, HIV, parvovirus type B, parainfluenza, paramyxovirus, Toxoplasma, *Yersinia enterocolitica*, brucellosis, the mumps virus, *Mycobacterium szulgai* and *Bartonella henselae*.

The hypothesis of a casual relation between viral infectious agents and KFD is coherent due to a raise found in the levels of interferon alpha and 2-5 oligoadenilate synthetase.<sup>1</sup> There are also reports of raise in the serum level of interferon gamma and interleukin-6 in patients with KFD. However, the attempts to identify a specific etiologic agent through culture, serology, polymerase chain reaction (PCR), and hybridization techniques have all failed.<sup>1,7</sup> A strong autoimmune component of the disease, which has been observed<sup>2</sup> and is also our case, could be related to the etiology. Thus all the cultures and serologies are negative, and through remission of the disease with high dose of corticosteroids. In the case in study, cell immune deficiency has been reported due to low counting of lymphocyte

CD4 (CD4 = 250 cells/mm<sup>3</sup>). The existence of lymphocyte and histiocyte cells suggests hyperimmune lymphadenitis reactive to several infectious, irritative, toxic, and neoplastic factors.<sup>2</sup> A change in cell immunity (T lymphocyte) with delayed hypersensitivity to some antigens was also observed. There are reports on the association of Kikuchi-Fujimoto disease with systemic lupus erythematosus (SLE), Still's disease, Hashimoto's thyroiditis, subacute lymphocyte thyroiditis, silicone implants, hepatic transplant,<sup>1</sup> polymyositis, and rheumatoid arthritis.<sup>7</sup> In our case, the antibodies present in the autoimmune diseases' diagnosis were negative. What can also be discarded is lupus nephritis, since the tubular lesion seen in this patient's optical microscopy (OM) is non-specific, and none deposits suggesting lupus nephritis, were found in the immunofluorescence, nor a glomerular lesion in the OM.

Clinical manifestations of KFD frequently occur as acute or subacute forms, which last for periods of 2 to 3 weeks. The most common form of presentation is lymphadenopathy, primary cervical (74% to 90% of the cases) or supraclavicular. Adenopathies typically measure less than 3 cm in diameter, present a firm consistency and are sometimes painful upon palpation. Generalized lymphadenopathy occurs in a minority (5%) of cases.<sup>8</sup>

The disease courses with fever from 30% to 50% of cases, usually of low-grade, associated with symptoms of upper respiratory tract. Symptoms such as weight loss, nausea, vomiting, sore throat, and night sweat are not common, and when they occur, they are related to extranodal involvement.<sup>5,6,7,9</sup> Recurrence of the disease is about 3% of cases in a period of 12 to 18 years after the first episode.

Because of this, long-term follow-up evaluation should be performed due to disease recurrence and to the possibility of SLE (systemic lupus erythematosus) development.<sup>8</sup>

There are atypical systemic manifestations such as panuveitis with impairment of visual acuity,<sup>10</sup> arthritis,<sup>11</sup> four cases of aseptic meningitis, amigdalitis<sup>12</sup> and cryptogenic organizing pneumonia.<sup>13</sup> Mortality is rarely found in KFD, but there have been three cases due to the disease, such as a 38-year-old woman with acute heart failure, in whose necropsy multiple focuses of cardiac necrosis were found; there has been another case of a 19-month-old child who died of febrile syndrome, and whose necropsy revealed a clinical picture compatible with extranodal and nodal KFD;<sup>14</sup> finally, there has been a case of KFD death in a patient who had received a transplant.<sup>12</sup>

The definitive diagnosis of KFD is made through lymph node excision biopsy and histologic examination. There are several classic histologic features of KFD. The affected lymph nodes have patchy necrotizing regions (the degree of necrosis varies widely among patients), mainly in the paracortical areas. They often contain well-circumscribed areas of eosinophilic fibrinoid material with a substantial degree of karyorrhexis. Transformed lymphocytes (immunoblasts) may surround the necrotic areas, creating a characteristic mottled appearance at

low magnification. Nuclear debris is evenly scattered throughout the necrotic areas and is associated with atypical mononuclear cells, which may be macrophages phagocytosing the debris.<sup>14</sup> It has been reported that the lesional cells extended into the perinodal fibroadipose tissue.<sup>15</sup> The histological change in KFD has been classified into three stages: an early proliferative stage, an intermediate phagocytic stage, and a full-blown post necrotic or xanthomatous stage. During the proliferative stage, CD116 and CD11c positive histiocytes predominant are accompanied by numerous atypical lymphocytes, which are primarily CD4+ T helper cells. In contrast, CD8+ suppressor T lymphocytes are the most predominant cells in the post-necrotic stage.<sup>16</sup> In a retrospective study of 1,724 lymph node biopsy samples, KFD was found in 36 cases.<sup>17</sup>

As reported in the literature, the lymph nodes immunohistochemistry were characterized by numerous CD20-positive B-cell displayed in primary and secondary reactive lymphoid follicles, often surrounded by prominent B-cell rich mantle zones. In contrast, most cells within the necrotizing foci were large CD68-positive phagocytic macrophages and plasmacytoid dendritic cells, with scattered medium to large CD3-positive T-cells, and relatively few scattered medium to large CD20-positive B-cells.<sup>18</sup>

Radiographic findings specific to KFD have not been established, and reports of KFD in the medical literature have largely focused on the disease pathology. Chest radiography should be included in the diagnostic evaluation to eliminate the possibility of malignancy or tuberculosis. CT and ultrasonography scans are common and often helpful before obtaining a biopsy specimen. Ultrasonography scan frequently shows lymph nodes with a hypoechoic center and a hyperechoic rim.<sup>11,12</sup> CT findings generally mimic those of lymphoma; however, lymph nodes in patients with KFD are not as large as those in patients with lymphoma. There are no specific assays available to confirm the diagnosis of KFD.<sup>14</sup>

The radiographic diagnosis of KFD is broad and includes Hodgkin and non-Hodgkin disease, metastatic tumor, tuberculosis, nontuberculous mycobacterial infection, SLE, human immunodeficiency virus infection, infectious mononucleosis, cat-scratch disease, mucocutaneous lymph node syndrome (Kawasaki disease), and toxoplasmosis. In one series, 29% of patients with KFD were initially misdiagnosed as having Hodgkin or non-Hodgkin disease.<sup>14</sup>

The differential diagnosis of a slow-growing neck mass is broad and includes malignant lymphoma, systemic lupus erythematosus (SLE), Hodgkin disease, toxoplasmosis, metastatic carcinoma, infectious mononucleosis, acquired immunodeficiency syndrome, cat-scratch disease, and angioimmunoblastic lymphadenopathy.<sup>14</sup> KFD is different from lymphoma, especially in early stages, in which there are few necrosis zones and also immunoblasts originating among nuclear debris. Immunophenotyping constitutes a process valuable for distinguishing these two entities.<sup>19</sup>

There are some characteristics, such as gender and age, as well as histological alterations, that KFD and SLE have in common, some authors considering the former to be a lupus-like syndrome. It has been proposed that KFD is a manifestation of, or evolves to, SLE, justifying the surveillance of KFD patients using immunological studies such as ANF (antinuclear factor) testing. Patients can present positivity for ANF, anti ribonucleoprotein, anti-DNA and lupus anticoagulant. Other autoimmune conditions, such as antiphospholipid antibody syndrome, polymyositis, Still's disease, uveitis, scleroderma, thyroiditis, pulmonary hemorrhage and interstitial lung disease, can be associated with KFD.<sup>8</sup>

KFD and lymph nodal tuberculosis (LTB) are commonly mistaken. There are cases in the literature described with LTB diagnosis before the anatomopathological examination.<sup>12</sup> There is also another case in which the patient received treatment for Wegener's granulomatosis.<sup>8</sup> That is why the etiologic diagnosis is important, in order to avoid long and expensive treatment.

There is no effective treatment. Patients with more severe or persistent symptoms have been treated with corticosteroids.<sup>8</sup> In our case, corticoid therapy with prednisone has had significant importance, for it revealed transitory relation with symptom reduction. With the remission of prednisone, the patient has shown a worse KFD picture and has presented an atypical systemic manifestation, which has not been reported in the literature for this disease: acute kidney failure (AKF). Because suspicion that AKF had relation to the disease was arisen, immunosuppressant doses were retaken, thus immediately improving KFD and leading to remission of nephropathy, revealing it to be dependent on prednisone dosage. The new attempt of reducing the doses of corticoid therapy had success. For the authors, remains the impression that the AKF appeared in a moment when KFD had stronger symptoms and when adequate treatment of Kikuchi disease reduced kidney failure. All this leads us to thinking that besides turbidity, arthralgia, myalgia, pericarditis, and hepatitis, acute kidney failure is another manifestation of the disease.

In conclusion, KFD usually occurs as acute or subacute, with auto limited evolution; an important differential diagnosis must be done with lymphoma, which was the main differential diagnosis in the case reported. Although it might still be related to autoimmune disease, so far there has not been a report of renal failure in literature. With that being said, nephropathy associated with HIV can be discarded, since the patient is HIV-negative and no typical lesion has been identified. Despite the patient having presented a series of irregularities during the disease's evolution, the possibility of interstitial nephritis induced by drugs has not been confirmed, since that was not evident in the renal biopsy. However, the patient's lesion was non-specific, and although it was atypical, it could have been induced by drugs, by any irregularity, or it could even have

resulted from Kikuchi-Fujimoto disease itself. The disease induced by drugs usually evolves in a benign way, with extranodal impairment and severe systemic manifestations, which were found in our patient. For the cases in which there is no auto limited evolution, it may be necessary to have corticoid therapy in immunosuppressant dosage, depending on how severe it is. Such strategy was successfully adopted in the case under study.

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