Kikuchi-Fujimoto's disease and systemic lupus erythematosus

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ABSTRACT

The case study of Kikuchi-Fujimoto’s disease or histiocytic necrotizing lymphadenitis is described in a previously healthy 20-year-old man with concomitant diagnosis of systemic lupus erythematosus and hemophagocytosis. Kikuchi-Fujimoto’s disease is a rare idiopathic condition, more often found in young women with weight loss, fever and lymphadenopathy. The diagnosis is established with base on the histopathology and immunohistochemistry data. The association with lupus may be incidental and the coexistence of infections or hemophagocytosis might be considered a risk factor of poor prognosis. Nevertheless, in the case herein reported, the patient was successfully managed with prednisone and azathioprine. Case studies may enhance the suspicion index about rare conditions in primary health care.

Descriptors. Kikuchi-Fujimoto’s disease; histiocytic necrotizing lymphadenitis; immunohistochemistry; systemic lupus erythematosus.
INTRODUCTION

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare benign idiopathic condition more common in young women, manifested by weight loss, fever, cervical lymphadenopathies, and leukopenia. The first description of this entity was made in 1972, and the differential diagnosis should involve lymphatic malignancies, connective tissue diseases, and infections by mycobacteria, bacteria, protozoans, or virus. Systemic lupus erythematosus (SLE) may be associated with KFD, and hemophagocytosis developing in this clinical scenery might lead to poor outcomes. The SLE diagnosis can be attained before, simultaneously, or after the diagnosis of KFD. The KFD diagnosis must be based on histopathology and immunohistochemistry data; whereas hemophagocytosis should be characterized by the presence of erythrocytes, platelets, leukocytes, or fragments of these cells inside the cytoplasm of the activated macrophages. The main challenges related to KFD diagnosis involve lymphomas and SLE lymphadenitis. KFD treatment includes AINEs, corticosteroids, and hydroxychloroquine.

CASE REPORT

A previously healthy 20-year-old man had been presenting with asthenia, neck pain, and difficulty to perform lateral head movements for a month. In the last two weeks, he noticed morning stiffness, pain, edema and hyperemia in the distal phalanges of the hands. He also had lower-limb myalgia, nasal lesions with bleeding, and reddish and violet plaques on the extensor surface of the upper limbs, in addition to weight loss of six kilograms in 30 days. Hand plain radiographs showed no changes in soft tissue, bone or articular structures. Laboratory tests revealed anemia, leukopenia with lymphocytosis, proteinuria, and increased myoglobin (table 1) levels. He was discharged to the outpatient clinic using NSAIDs. Three days after discharge he was hospitalized with headache, neck pain and vomiting. He was pale (4+), dehydrated (2 +), febrile (38.2° C), and hypotensive (70/40 mmHg); BMI was 21.3 kg/m², and he showed movement restriction in the cervical spine, without signs of meningitis. The cerebrospinal fluid (CSF) evaluation revealed no abnormalities. The patient underwent volume expansion and ceftriaxone was administered; then, he was referred for control in the ICU. Computed tomography (CT) of the skull and cervical spine, with and without contrast, showed a retropharyngeal abscess measuring 7cm (Figure 1A), which was drained. Biopsy was performed in the lymph nodes of the left jugular and carotid chains that showed

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<tr>
<th>Parameters (normal ranges)</th>
<th>D1</th>
<th>D30</th>
<th>D60</th>
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<tbody>
<tr>
<td>Red cells (4.5-6.1 x 10¹²/L)</td>
<td>3.64</td>
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<td>Hemoglobin (13-18 g/dL)</td>
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<td>Hematocrit (42-52%)</td>
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<td>Leukocytes (4-10 x 10⁹/L)</td>
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<td>6045</td>
<td>5806</td>
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<tr>
<td>Platelets (140-450 x 10⁹/L)</td>
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<td>243</td>
<td>224</td>
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<tr>
<td>Sodium (135-145 mmol/L)</td>
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<td>144</td>
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<tr>
<td>Potassium (3.5-5.5 mmol/L)</td>
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<td>4.2</td>
<td>3.7</td>
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<td>Urea (10-50 mg/dL)</td>
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<td>39.9</td>
<td>23.9</td>
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<tr>
<td>Creatinine (0.7-1.3 mg/dL)</td>
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<td>0.94</td>
<td>0.95</td>
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<td>ESR (&lt;10mm/1ʰ)</td>
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<td>68</td>
<td>67</td>
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<tr>
<td>C-Reactive protein (&gt;0.5mg/dL)</td>
<td>2.0</td>
<td>0.6</td>
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areas of necrosis and abscesses; and the antibiotic therapy was changed to cover infection by anaerobes. Control CT images showed reduction of the retropharyngeal abscess, and bilaterally enlarged lymph nodes with central areas of necrosis (Figure 1B). The patient developed episodes of chills and weight loss of 10 kg during the hospitalization. The hypothesis of lymphoproliferative disease (lymphoma) with B symptoms was then raised. A biopsy study of cervical lymph nodes showed reactive lymphoid hyperplasia, characterized by a predominant follicular pattern with enlarged follicles and prominent germinal centers and mantle zones; lymph mononuclear infiltrate permeated by polymorphonuclear cells and leukocytoclasis; septal fibrosis around nodules and germinal centers; in addition to numerous tingible body macrophages. Vasculitis, hematoxylin bodies, plasmocytes, atypical polylobated or lacunar cells, and parasites were absent. The immunohistochemistry evaluation evidenced CD20+, CD3+, CD10+, CD15+, and CD30+ in activated lymph nodes (Figure 2); in addition to BCL2- and TDT-, and absence of MUM-1 in histiocytes. The PET-CT images showed inflammatory or infectious lymph nodes with low SUV and no lymph node larger than 2 cm. Malignant

Figure 1. Computed tomography (CT) showing inflammatory changes in the right tonsil, extending to the retropharyngeal space (9.2 x 3.2 x 1.4 cm, and approximately 22 ml); the right posterolateral area of the neck had densification of soft tissues; the lymph nodes appeared enlarged with central necrosis (the largest one with 0.8 cm in the smallest diameter).
lymphoproliferative disease was then discarded. He was again hospitalized with head and cervical pains, without visual disturbances or meningeal signs; CSF analysis was normal. The serological tests revealed hepatitis B-HBsAg: negative; hepatitis B-anti-HBc IgM: negative; hepatitis C-anti-HCV: negative; HIV 1 and HIV 2: negative; cytomegalovirus IgM: negative; toxoplasmosis IgM: negative; rubella IgM: negative; Epstein Barr (IgG): positive; Epstein-Barr (IgM): negative; antistreptolysin O: positive; VDRL: negative; anti-Treponema pallidum: negative; and FTA-ABS IgG: negative. The images of magnetic resonance and angioresonance of the skull showed no abnormalities. The 24-hour proteinuria was normal; ANA titer was 1:640 (homogeneous nuclear pattern) and anti-dsDNA 1:320; protein electrophoresis showed high gamma globulin; the direct Coombs test was positive; C3: 62.92 (normal: 90-180) and C4: 9.76 (normal: 10-40); anti-Ro, anti-La, anti-Sm, anti-RNP, anti-cardiolipin IgA, IgG and IgM, lupus anticoagulant, LKM-1, and anti-mitochondria were normal. His clinical course evolved with arthralgia, malar rash, serositis, leukopenia, lymphopenia, and immune hemolytic anemia; in addition to above mentioned positive rheumatologic markers. Therefore, the definitive diagnosis of SLE could be established in accordance with the ACR criteria; whereas the SLE-disease activity index-2000 (SLEDAI-2K) was estimated at 13 on that occasion. Due to hydroxychloroquine contraindication (flat macula with change in pigmentation, and brightness in fovea), the patient received prednisone (1mg/ kg daily) and azathioprine (2mg/ kg daily) with good clinical response. Asymptomatic, he has been under specialized outpatient follow-up to date.

DISCUSSION

KFD is a rare benign condition of unclear etiopathogenesis, limited clinical course and uncommon recurrences, and usually associated with infectious or autoimmune diseases. Because the clinical and pathological features of KFD can mimic diverse benign and malignant entities, it may constitute diagnostic challenges, mainly for primary health care workers. The diagnosis of KFD is based on lymph node histopathology showing necrotic areas surrounded by histiocytes and plasmocytes, with apoptotic bodies and nuclear dust, and absence of neutrophils and eosinophils. Except for vasculitis and hematoxylin bodies, several morphological characteristics of KFD may be observed in the lymphadenitis of SLE. Possible diagnostic pitfalls should be always considered based on the
high frequency of association with SLE, which may manifest before, concomitantly or after the diagnosis of KFD. Therefore, immunohistochemistry evaluation is mandatory to establish the definitive diagnoses. In this patient with KFD and SLE, the immunohistochemistry evaluation performed in lymph node samples revealed the following findings: CD30+, CD20+, CD15+, CD10+, and CD3+. Interestingly, immunohistochemistry studies in lymph nodes of patients with KFD and SLE showed more frequently: CD68+, CD123+, CD4+, and CD8+ T predominance. Similar analysis revealed CD30+ and CD45+ in a patient with isolated lymphadenitis due to SLE. Immunostaining often shows CD68+, CD45+; CD43+, and CD8+ T cells in KFD lymph nodes, but some studies suggest that CD30+ may be consistent with this diagnosis. As commented by Vassallo et al. about a patient with KFD and HIV+, damages to the immune system caused by SLE may play a role in the increased number of CD30+ macrophages. Worthy of note, this young woman had tonsillitis associated with lymphadenopathies in the cervical region with areas of necrosis, in addition to the positive Epstein Barr IgG test. From a clinical standpoint, the main differential diagnoses were lymphomas and SLE lymphadenitis. The initial concern was Hodgkin’s lymphoma, which can be associated with CD30+, CD45+, CD43+, CD20+, CD15+, CD3+, as well as to previous EBV infection. The authors found different rates of EBV DNA positivity among the groups, as follows: 18/30 (60%) in KFD; 9/10 (90%) in RLH without SLE; and 2/2 (100%) in RLH plus SLE. The immunohistochemistry pattern that was disclosed in KFD lymph nodes was CD68+, CD20+, CD3+, and CD8+. In this case, the evaluation showed mixed KFD and SLE features. Hydroxychloroquine is a good option for both diseases, but was contraindicated in this case, and the patient was successfully controlled with prednisone and azathioprine.

**CONCLUSION**

The differential diagnosis of cervical lymphadenitis should include KFD; and the possible association with connective tissue diseases must be ruled out because of their role in outcomes. SLE lymphoma and lymphadenitis are among the main alternative hypotheses to be ruled out. The earlier the correct diagnosis is established, the better the final prognosis will be. Despite of the inherent weaknesses of a single-case study, this report may increase the awareness about still unsuspected, misdiagnosed, underdiagnosed or underreported uncommon conditions.

**REFERENCES**