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Case report

Kikuchi-Fujimoto disease prior to childhood-systemic lupus erythematosus diagnosis

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) is a self-limiting histiocytic necrotizing lymphadenitis of unknown origin. Of note, KFD was infrequently reported in adult systemic lupus erythematosus (SLE), with rare occurrence in childhood-SLE (C-SLE) patients. To our knowledge, the prevalence of KFD in the paediatric lupus population was not studied. Therefore, in a period of 29 consecutive years, 5,682 patients were followed at our institution and 289 (5%) met the American College of Rheumatology classification criteria for SLE, one had isolated KFD (0.03) and only one had KFD associated to C-SLE diagnoses, which case was reported herein. A 12 year-old female patient had high fever, fatigue and cervical and axillary lymphadenopathy. The antinuclear antibodies (ANA) were negative, with positive IgM and IgG herpes simplex virus type 1 and type 2 serologies. Fluorine-18-fluoro-deoxy-glucose positron emission tomography/computed tomography (PET/CT) imaging demonstrated diffuse lymphadenopathy. The axillary lymph node biopsy showed necrotizing lymphadenitis with histiocytes, without lymphoproliferative disease, compatible with KFD. After 30 days, she presented spontaneous regression and no therapy was required. Nine months later, she developed malar rash, photosensitivity, oral ulcers, lymphopenia and ANA 1:320 (homogeneous nuclear pattern). At that moment the *Systemic Lupus Erythematosus Disease Activity Index 2000* (SLEDAI-2K) score was 10 and she was treated with prednisone (1.0 mg/kg/day) and hidroxychloroquine showing progressive improvement of hers signs and symptoms. In conclusion, KFD is a benign and rare disease in our paediatric lupus population. We also would like to reinforce the relevance of autoimmune diseases diagnosis during the follow-up of patients with KFD.

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Doença de Kikuchi-Fujimoto antes do diagnóstico de lúpus eritematoso sistêmico juvenil

Palavras-chave:
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RESUMO

A doença de Kikuchi-Fujimoto (DKF) é uma linfadenite necrosante histiocítica autolimitante de origem desconhecida. É digno de nota que a DKF era apenas pouco frequentemente comunicada em pacientes com lúpus eritematoso sistêmico (LES), com rara ocorrência em pacientes com LES juvenil (LESJ). Até onde vai nosso conhecimento, ainda não foi estudada a prevalência de DKF na população pediátrica lúpica. Assim, em um período de 29 anos consecutivos, 5.682 pacientes foram acompanhados em nossa instituição e 289 (5%) satisfaziam os critérios de classificação do American College of Rheumatology para LES; um sofria DKF isolado (0,03%) e apenas um padecia de DKF associada a diagnósticos de LESJ; este caso foi descrito no presente artigo. Uma jovem com 12 anos de idade apresentava-se com febre alta, fadiga e linfadenopatia cervical e axilar. Os anticorpos antinucleares (ANA) estavam negativos, com imunologia positiva para IgM e IgG antivírus do herpes simples tipos 1 e 2. As imagens obtidas por tomografia por emissão de pósitrons com flúor-18-fluoro-desoxi-glicose/tomografia computadorizada (PET/TC) demonstraram linfadenopatia difusa. A biópsia dos linfonodos axilares demonstrou linfadenite necrosante com presença de histiócitos, sem doença linfoproliferativa, compatível com DKF. Transcorridos 30 dias, a paciente apresentou regressão espontânea, não havendo necessidade de tratamento. Nove meses depois, a paciente exibia erupção malar, fotossensibilidade, úlceras orais, linfopenia e ANA 1:320 (padrão nuclear homogêneo). Nessa ocasião, a aplicação do *Systemic Lupus Erythematosus Disease Activity Index 2000* (SLEDAI-2K) (Índice de Atividade de Doença/LES 2000) teve um escore igual a 10, e a jovem foi tratada com prednisona (1,0 mg/kg/dia) e hidroxicloroquina, demonstrando melhora progressiva dos sinais e sintomas. Em conclusão, DKF é doença benigna e rara em nossa população lúpica pediátrica. Também queremos enfatizar a relevância do diagnóstico de doenças autoimunes durante o acompanhamento de pacientes com DKF.

Introduction

Kikuchi or Kikuchi-Fujimoto disease (KFD) is a self-limiting histiocytic necrotizing lymphadenitis of unknown origins.[1–6] The most common clinical manifestations of this disease are localized or diffused painful lymphadenopathy with concomitant fever and fatigue. This systemic disorder may be associated with infectious diseases, neoplasia and autoimmune rheumatic diseases, especially systemic lupus erythematosus (SLE).[4]

Of note, KFD was infrequently reported in adult SLE,[1–6] with rare cases in childhood-SLE (C-SLE).[7–9] However, to our knowledge, the prevalence of KFD in pediatric lupus population has not been studied.

Therefore, from January 1983 to May 2012, 5,682 patients were followed at our Pediatric Rheumatology Unit, and 289 (5%) of them met the American College of Rheumatology (ACR) classification criteria for SLE.[10] Of the total population, two had KFD (0.03%). From these KFD patients, only one had KFD associated to C-SLE (0.02 of total population, 0.3 of C-SLE population), and this case was reported herein.

Case report

A 12-year-old female patient had high graduated fever (over 39 °C) daily, fatigue, and painful cervical and axillar lymph nodes enlargement (diameter of 1.0-2.0 cm, fibroelastic). At that moment, the laboratory findings showed hemoglobin 11.2 g/dL, white blood cell count (WBC) 4,700/mm^3 (80% neutrophils, 15% lymphocytes and 5% monocytes) and platelets 198,000/mm^3. C-reactive protein (CRP) was 224.8 mg/dL (normal range < 5.0), and erythrocyte sedimentation rate (ESR) was 57 mm/1st hour. The antinuclear antibodies (ANA) were negative, C3 was 135 mg/dL (normal range 79-152), C4 23 mg/dL (normal range 16-38) and urinalysis showed granular casts. IgM and IgG herpes simplex virus type 1 and type 2 serologies were positive. The other serologic tests: hepatitis virus A, hepatitis virus B, hepatitis virus C, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus were negative. Fluorine-18-fluoro-deoxy-glucose positron emission tomography/computed tomography (PET/CT) imaging demonstrated diffuse lymphadenopathy with large conglomerate of lymph nodes in abdominal cavity that involved perihepatic, peripancreatic and right iliac regions (4.0 cm of diameter), multiple bilateral axillary lymph nodes (1.6 cm of diameter) and a single cervical lymph node (1.0 cm of diameter). The axillar lymph node biopsy showed necrotizing lymphadenitis with histiocytes, without lymphoproliferative diseases, compatible with KFD. After 30 days, she presented spontaneous regression and no therapy was required. No recurrence of KDF was also observed. Nine months later, she developed malar rash, photosensitivity, oral ulcers, alopecia, and arthralgia on the knees. She presented only cervical

lymph nodes (1.0 cm of diameter) without swelling and painless. The laboratory findings showed hemoglobin 13.1 g/dL, WBC 7,100/mm^3 (77% neutrophils, 16% lymphocytes, 1% eosinophils and 6% monocytes) and platelets 264,000/mm^3. CRP was 5.4 mg/dL, ESR 35 mm/1st hour, C3 154 mg/dL and C4 24 mg/dL. Immunological tests showed antinuclear antibodies ANA 1:320 (homogeneous nuclear pattern), positive anti-Ro antibodies and negative anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, IgG and IgM anticardiolipin and anti-La antibodies. Urinalysis demonstrated leukocytes 20,000/mL and erythrocytes 2,000/mL, urea 26 mg/dL, creatinine 0.81 mg/dL and proteinuria 0.057 g/24 h. Therefore, the diagnosis of C-SLE was confirmed according to ACR classification criteria.[10] At this moment the *Systemic Lupus Erythematosus Disease Activity Index 2000* (SLEDAI-2K) score was 10, and she was treated with prednisone (1.0 mg/kg/day) and hydroxychloroquine sulphate (6.0 mg/kg/day) showing progressive improvement of hers signs and symptoms.

Discussion

KFD was infrequently described in our pediatric rheumatology service, and the histiocytic necrotizing lymphadenitis was rarely diagnosed in C-SLE population, particularly prior to lupus diagnosis.

This disease occurs most commonly in young females,[2,4,5,7,11] and the main clinical manifestations of KFD in pediatric and adult populations are cervical lymphadenopathy, usually painful, associated to fever and constitutional symptoms,[1,2,4,6,7] as observed in our patient. Interestingly, the cervical lymphadenopathy in KFD is generally unilateral (79%) and generalized lymphadenomegaly, as evidenced in the present case, was rarely reported (5%).[4]

Of note, the diagnosis was confirmed by lymph nodes biopsy showing necrotizing histiocytic lymphadenitis.[3–6] This procedure is also required to evaluate the possibility of comorbidities, especially infectious, lymphoproliferative, autoimmune and hemaphagocytic diseases.[4] Herpes virus type 1 and type 2 infections may have triggered KFD in the current case, however we did not repeat these virus serologies confirming the primary infection. In addition, one study did not observe any association of this infection with KFD.[12]

The laboratory exams are almost unchanged at KFD diagnosis, except elevated ESR and CRP levels,[11] as also observed herein. One relevant point assessed in our patient was the PET/CT imaging findings. Our patient had diffuse adenopathy that was not observed in the physical examination. Indeed, this imaging has a high sensitivity and specificity for occult adenomegaly,[13] and may help to identify the reticuloendotelial system involvement. Moreover, the combination of PET and CT might be a promising noninvasive diagnostic tool, especially in children with fever of unknown origin. This radiologic examination allows for localizing the inflammation site more accurately.[14]

KFD has been infrequently reported with autoimmune diseases, especially SLE, mixed connective tissue disease, anti-phospholipid syndrome, thyroiditis, polymyositis, scleroderma, autoimmune hepatitis and Still's disease,[4] and rarely associated with C-SLE.[7–9] KFD was reported in 4%[7] to 13% in SLE population.[4] Importantly, KFD occurred mainly simultaneously to SLE diagnosis,[4] in contrast of the present case. Additionally, our patient had negative autoantibodies at KFD diagnostic, thus suggesting separated condition of C-SLE. Conversely, other authors suggest that KFD and SLE had overlap manifestations with the same histologic findings and autoimmune mecanisms.[9] Moreover, adenopathy occurred frequently in our active C-SLE patients, mainly at beginning of the disease.[15,16]

It is important to emphasize that most of cases of isolated KFD are self-limited, with good outcome and no treatment is required, as demonstrated here. In fact, KFD symptoms and signs may regress in a period of six months without any therapy.[7]

In conclusion, KFD was a benign and rare disease associated with pediatric lupus population. Our study reinforces the relevance of autoimmune diseases diagnosis during the follow-up of patients with KFD.

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Conflicts of interest

The authors declare no conflicts of interest.

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