REVISTA BRASILEIRA DE REUMATOLOGIA

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Case report

Multicentric Castleman disease not associated with HHV-8 and HIV viruses

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ARTICLE INFO

Article history:
Received on 29 May 2012
Accepted on 18 May 2013

Keywords:
Castleman's disease
B lymphocytes
Anaemia
Interleukin-6
Inflammation
Autoimmune

ABSTRACT

Castleman's disease (CD) is a polyclonal lymphoproliferative disorder also known as giant nodular hyperplasia or angiofollicular lymph node hyperplasia. It is a rare disease often associated to human immunodeficiency virus (HIV) and human herpes virus 8 (HHV-8). Histopathological findings in Castleman's disease suggest an exaggerated response to antigenic stimuli seen in other diseases associated with immune activation, such as rheumatoid arthritis. An important aspect of its pathogenesis is the autonomous production of interleukin-6 (IL-6). In this disease, the clinical manifestations are associated to IL-6 serum levels, and surgical removal of the compromised lymph nodes or use of anti-IL-6 antibodies can slow down the symptoms. We describe a multicentric Castleman's disease in a young woman not associated to HHV-8 virus infection or immunosuppression. A short review of the literature follows the description of this clinical case.

Doença de Castleman multicêntrica não associada aos vírus HHV-8 e HIV

Palavras-chave:
Doença de Castleman
Linfócitos B
Anemia
Interleucina-6
Inflamação
Autoimune

RESUMO

A doença de Castleman (DC) é uma desordem linfoproliferativa policlonal, também conhecida como hiperplasia nodular gigante ou hiperplasia angiofolicular linfoide. Esta é uma doença rara que está frequentemente associada ao vírus da imunodeficiência humana (HIV) e ao herpes vírus 8 (HHV-8). Os achados histopatológicos encontrados na DC sugerem uma intensa resposta aos estímulos antigênicos observada em várias doenças associadas com ativação imune, como a artrite reumatoide. Um fator importante implicado na patogênese da DC é a produção autônoma da interleucina-6 (IL-6). Nessa doença, as manifestações clínicas estão relacionadas aos níveis de IL-6, e a remoção cirúrgica dos linfonodos acometidos ou a utilização de anticorpos anti-IL-6 fazem regredir os sintomas. Descrevemos um caso da DC multicêntrica em uma mulher jovem, não associada à in-

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0482-5004/$ - see front matter.
http://dx.doi.org/10.1016/j.rbr.2013.05.004

fecção pelo vírus HHV-8 ou à imunossupressão. Uma breve revisão da literatura se segue à descrição do caso clínico.

Introduction

The lymphoid angiofollicular hyperplasia or Castleman's disease (CD) was described in 1956 by Benjamin Castleman, who identified a number of patients with solitary and hyperplasic mediastinal lymph nodes containing follicles with interfollicular vascular proliferation.[1] After the discovery of herpes virus associated with Kaposi's sarcoma (HHV-8) in HIV-positive patients and its identification in patients with CD, there was a real breakthrough in the understanding of disease pathogenesis.[2]

CD is a rare disease and there are no reliable estimates of its incidence in the population. There are two clinical syndromes: unicentric and multicentric. In the unicentric form, only one lymph node is affected, usually in the mediastinum, and the patient is clinically asymptomatic. In the multicentric form, the patient can present various clinical symptoms including anaemia, fatigue, anorexia, night sweats, weight loss, fever and hepatosplenomegaly.[3]

The multicentric form is often associated with HHV-8 and HIV-1 viruses. In HIV-positive patients, the disease tends to be more aggressive, with intense constitutional symptoms, splenomegaly, generalized lymphadenopathy, pancytopenia, interstitial pneumonitis and increased incidence of Kaposi sarcoma.[4] In the multicentric form, associated or not with HHV-8, there is an overproduction of IL-6 and a polyclonal proliferation of B lymphocytes.

These changes stimulate the onset of autoimmune manifestations, including POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, and this complicates the diagnosis during the clinical investigation of a connective tissue disease. By histological analysis of lymph nodes, DC is classified in three forms: hyaline-vascular variant, plasmacytic variant, and a variant associated with HHV-8.

The hyaline-vascular form is characterized by separate follicles, with expansion of the mantle zone and presence of small lymphocytes forming concentric rings that surround the germinal center, which presents intense vascularization. The vascular proliferation also occurs among the follicles and there is often perivascular hyalinization.

In the plasmacytic form, a disruption of lymph node architecture can be observed, with variable germinal center hyperplasia, expansion of the mantle zone and marked plasmacytosis. In the unicentric form, the hyaline-vascular variant constitutes the most common histologic pattern, and in the multicentric form the most frequent histologic pattern is the plasmacytic variant, which can be associated or not to HHV-8 and to HIV-1.[5]

The clinical and laboratory features of the two Castleman's disease syndromes are compared in Table 1.

Case report

A woman, 31 years-old, dentist, sought medical attention due to complaints of fatigue, weakness and pallor occurring for over two years. Previous CBCs showed hypochromic microcytic anaemia, detected since 1995. At that time, the patient showed hemoglobin 9.4 g/dL and hematocrit 30%, maintaining similar levels throughout the years. Due to the detected anaemia, the patient sought the Haematology Service, where obtaining a definitive diagnosis was not possible.

As the patient had, in addition to anaemia, a positive test for antinuclear antibody (ANA) and tests showing evidence of inflammatory activity, she was referred to the Rheumatology Department in search of a possible autoimmune disease that could justify the clinical and laboratory findings.

On physical examination at admission, the patient was in good general condition, except for a slight pallor of mucous membranes. BP=110×70, afebrile and speaking clearly. Lungs without adventitious sounds and a rhythmic heart without murmurs. Ganglia, liver and spleen were not palpable.

The initial laboratory workup showed hypochromic microcytic anaemia with normal WBC and platelets. Serum iron and transferrin saturation were low.

Subsequent tests to clarify the cause of anaemia were negative, including: reticulocyte count, hemoglobin electrophoresis, sickling test, erythrocyte resistance to hypotonic solutions, coagulogram, folic acid, vitamin B12, glucose 6-phosphate dehydrogenase (G6PD), ceruloplasmin and aminolevulinic acid. All hormone levels were within normal limits. The protein electrophoresis study showed an increase in α, β and γ globulin fractions. At the first evaluation, the following results were obtained: Erythrocyte Sedimentation Rate (ESR) 63 mm/h,

Table 1 – Characteristics of Castleman disease variants

	Unicentric	Multicentric
Clinical picture	Single asymptomatic mass	Generalized lymphadenopathy, hepatosplenomegaly, fever
Laboratory abnormalities	Uncommon	Anaemia, hypergammaglobulinemia, ↑ESR
Age group	15-30 years	50-65 years
Gender	Men, in 60%	Same
Histopathologic pattern	Hialinovascular (90%)	Plasmacytic or mixed (90%)
HHV-8	Rare	Present in all patients HIV+ Present in 50% of patients HIV–

ESR – Erythrocyte Sedimentation Rate, HHV-8 – Herpes Virus 8, HIV – Human Immunodeficiency Virus

C Reactive Protein (CRP) 19.2 mg/dL (Reference Value [RV] up to 0.5 mg/dL), Complement fraction 3 (C3) 186 mg/dL (RV 90-189 mg/dL) and total complement 426 mg/dL (RV 170-330 mg/dL).

Autoantibodies tests, including anti-Ro/SSA, anti-La/SSB, anti-native DNA, anti-Sm, anti-RNP, antineutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor, were negative, with ANA 1/80 positive with a fine speckled pattern. The serology for HIV, toxoplasmosis, Epstein-Barr virus and HHV-8 was negative. Tests for anti-HBs and anti-herpes simplex virus (HSV) were positive and our patient reported an episode of oral herpes involvement and a previous vaccination against hepatitis B. The study of tumour markers was negative. Examinations of urine, faeces and cervical secretion showed no changes.

Thoracic radiographs and pelvic ultrasound showed no changes. An ultrasonography study of the abdomen revealed solid nodules: the smaller in the splenic hilum, measuring 2.8 × 1.6cm, and the larger anterior to the left kidney and lateral to the tail of the pancreas, measuring 7.0 × 4.1 × 4.0cm.

The myelogram showed normocellular granulocytic, erythrocytic and megakaryocytic series, medullary iron ++ (RV ++/+++), sideroblasts 5% (RV 30%), and ring sideroblasts absent – findings consistent with microcytic anaemia of chronic inflammation.

A magnetic nuclear resonance study of the abdomen showed multiple oval nodular images in the splenic hilum with 1-3cm in diameter, not impregnated by the ferric contrast, and a solid mass of well-defined contours located medially to the inferior pole of the spleen, measuring approximately 6.0 × 4.5 × 4.5cm. The gallium-67 scintigraphy showed anomalous and intense hyperconcentration of the radiotracer in the topography of a solid mass at the lower pole of the spleen.

An ultrasound-guided fine needle aspiration (FNA) biopsy of an abdominal lymph node revealed cytological findings consistent with typical mature lymphoid and myeloid cells, which could correspond to an accessory spleen or to myeloid metaplasia. A bone marrow biopsy revealed hypocellular granulocytic, erythrocytic and megakaryocytic series and no granulomas, necrosis, amyloid or abnormal cells.

A videolaparoscopic surgery was performed with a biopsy of enlarged retrogastric lymph nodes and spleen chain. The pathologic examination of the specimens was consistent with the diagnosis of Castleman's disease (plasmacytic variant) (Fig. 1).

In the case described, the patient was initially treated with corticosteroids, with no clinical response. On that occasion, tocilizumab (an anti-IL-6 receptor antibody) was not available for use in our country. Due to the chronic and persistent inflammation, the patient developed renal amyloidosis, progressing to chronic renal failure. After a prolonged period on dialysis, the patient underwent renal transplantation and currently remains clinically well.

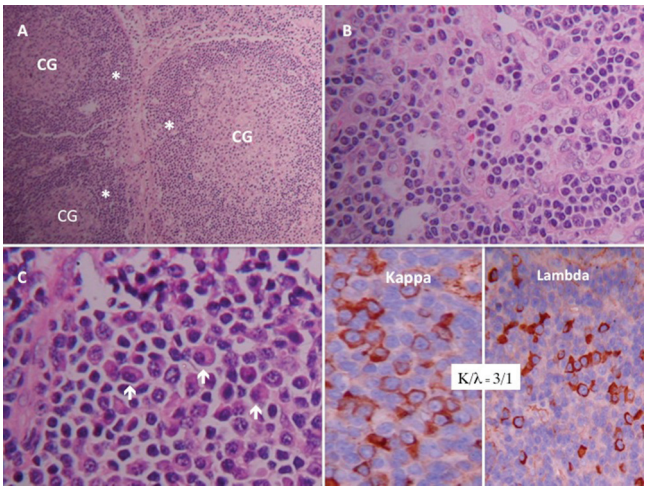

Fig. 1 – Abdominal lymph node biopsy showed histological findings consistent with Castleman's disease, plasmacytic variant. A) Lymphoid follicular hyperplasia with prominent germinal centers, B) Paracortical proliferated blood vessels with plump endotelial cells, C) Numerous expressing kappa and lambda immunoglobulin light chains.

Discussion

In this paper, we describe the case of a young female patient with symptoms of fatigue on exertion, hypochromic microcytic anaemia, tests of inflammatory activity persistently high and a positive ANA test. In principle, these findings could be consequent to a number of diseases, including SLE, and this was the reason for the referral of our patient to the Department of Rheumatology.

Only after the completion of imaging studies (ultrasonography, MRI and scintigraphy), our diagnostic reasoning suggested lymphoproliferative or infectious disorders that could justify the laboratory changes and also the presence of multiple intra-abdominal nodules. Despite all clinical investigation, the diagnosis of CD was obtained only after the biopsy of abdominal nodes by videolaparoscopy, followed by histopathological and immunohistochemical analysis.

The clinical and laboratory data of this patient can be explained by the biological actions of IL-6 overproduction including anaemia and an increase of immunoglobulins and high inflammatory activity tests. Furthermore, IL-6 can induce the formation of autoantibodies, thus justifying the positive ANA test.[6] During the evolution of the clinical case, we could not obtain a value for serum IL-6 because this test was not yet standardized in our country.

The systemic involvement and the plasmacytic histological presentation allowed us to classify our patient in CD's multicentric form. The connective tissue diseases and the multicentric form of CD share many pathophysiological characteristics, and this may cause diagnostic difficulties. A review of the presence of autoimmune diseases concomitant to DC revealed an association with RA, Sjogren's syndrome, myasthenia gravis, SLE/polymyositis overlap syndrome, mixed connective tissue disease and SLE.[7]

The rheumatologist should consider the investigation of a solitary DC or of DC in association with a connective tissue disease when his/her patient has additional clinical features not expected in his/her disease development, a persistence of symptoms and of constitutional signs unusual for a connective tissue disease, lymphadenomegaly on physical examination or on imaging studies, or if unexpected difficulties arise during his/her treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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