ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Autoimmune hemolytic anemia in multicentric Castleman's disease: case report

Anemia hemolítica autoimune na doença de Castleman multicêntrica: relato de caso

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ABSTRACT

Castleman disease is a rare lymphoproliferative disorder that can manifest as localized masses or as multicentric disease. Multicentric Castleman disease is characterized by generalized adenopathies, visceromegaly, autoimmune manifestations, and recurrent infections. This article presents the case report of a patient with multicentric Castleman's disease and autoimmune hemolytic anemia by warm antibodies. Effective response was obtained with systemic corticotherapy and tocilizumab.

Keywords: Castleman Disease, autoimmune hemolytic anemia, monoclonal antibodies.

RESUMO

A doença de Castleman é um distúrbio linfoproliferativo raro, podendo se manifestar sob a forma de massas localizadas ou como doença multicêntrica. A doença de Castleman multicêntrica é caracterizada por adenopatias generalizadas, visceromegalias, manifestações autoimunes e infecções recorrentes. Este artigo apresenta o relato de caso de anemia hemolítica autoimune por anticorpos quentes em paciente com doença de Castleman multicêntrica. Resposta eficaz foi obtida com uso de corticoterapia sistêmica e tocilizumabe.

Descritores: Hiperplasia do linfonodo gigante, anemia hemolítica autoimune, anticorpos monoclonais.

Introduction

First described in 1954 by Castleman and Towne,[1] Castleman disease (CD) is a rare polyclonal lymphoproliferative disorder of B lymphocytes and plasma cells, which may manifest as unicentric or multicentric disease.[2]

Histopathology

CD can be subdivided into two main histopathological forms: hyaline-vascular variant and plasma cell variant.[3] The mixed variant has elements of both variants, and is present in approximately 10% of cases. There is also the plasmablastic subvariant, associated with infection by HHV-8 (human herpes virus type 8) and HIV (human immunodeficiency virus), with risk of progression to plasmablastic monoclonal lymphoma.

Histologically, the classic hyaline-vascular variant is characterized by distortion of the lymph node architecture. An increase in the number of lymphoid follicles is observed, with variation in size and shape. One of the lesions identified is follicular atresia, with lymphocytes from the mantle zone arranged in layers around the follicular center (onion skin appearance). There is deposition of hyaline material in the germinal centers, highlighted by the periodic acid Schiff (PAS) reaction. Vascular alterations, such as sclerosis of the vessels that penetrate the follicles, give rise to lesions known as lollipop follicles.[4]

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The histopathological features of the plasma cell variant show differences in the HHV-8 negative and HHV-8 positive forms. HHV-8 negative cases show an increase in the number of aggregated mature plasma cells, mainly in the interfollicular areas. Vascular proliferation in the paracortical region is prominent. The follicles are hyperplastic or normal. In HHV-8 positive forms, there is expansion of the interfollicular zone by immature and mature plasma cells, with a variable degree of atypia. In addition, there is less distinction in the boundary between the mantle zone and the interfollicular region. The mixed variant, histologically, shows an overlap of the two variants; hyaline-vascular and plasma cells.[5]

Unicentric Castleman's disease (UCD) is commonly associated with the hyaline-vascular variant, corresponding to approximately 70% of cases. It is characterized by localized lymph node enlargement, usually in the mediastinum or abdomen, in oligo or asymptomatic patients, in which the resection of the affected lymph node results in the cure of the disease.[6]

Multicentric Castleman disease (MCD) is commonly associated with the plasma cell variant, accounting for approximately 10-20% of cases. It is characterized by diffuse lymph node enlargement and moderate to severe systemic symptoms, including fever, night sweats, weakness, anorexia and weight loss. Clinical features also include hepatosplenomegaly, ascites, pericardial effusion, pleural effusion, and skin rash. Laboratory abnormalities include anemia of chronic disease, thrombocytopenia, hypoalbuminemia, polyclonal hypergammaglobulinemia, increased ESR (erythrocyte sedimentation rate), C-reactive protein, IL-6 (interleukin 6), and VEGF (vascular endothelial growth factor).

Etiology

DCM can be associated with HHV-8 infection, with or without HIV co-infection, in up to 50% of cases. More rarely, it may also be associated with POEMS syndrome (paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes). In the other half of the cases, DCM is considered idiopathic.[7]

The etiology of idiopathic DCM is uncertain, and its theories include: pathological autoantibodies or mutations in the regulation of the innate immune system (autoimmune/autoinflammatory hypothesis); presence of a small population of neoplastic cells (paraneoplastic hypothesis); or the presence of some other unidentified virus (viral hypothesis).[8] A severe variant of idiopathic DCM known as TAFRO syndrome has also been described, which includes thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly in its clinical aspects.[9]

It is also known that the overproduction of pro-inflammatory interleukins, especially IL-6, is implicated in the pathophysiology of the disease.

DCM also presents with recurrent infections, including opportunistic ones, and autoimmune manifestations. However, the occurrence of autoimmune hemolytic anemia is rare, and six cases have been described to date, as far as the authors of this report are aware.[10-15]

Interleukin-6 and Tocilizumab

IL-6 is a pro-inflammatory cytokine that induces the differentiation and proliferation of T and B lymphocytes, is involved in the synthesis of acute phase proteins, in the stimulation of hematopoiesis and hepcidin production and in the development of constitutional symptoms present in various inflammatory diseases. In CD, hyperplastic lymph nodes with infiltration of plasma cells have a constitutionally increased production of IL-6.[16]

In order to confirm the involvement of IL-6 in the pathophysiology of CD, in 1986[17] a study was carried out with two patients affected by CD (one in the multicentric form and the other unicentric). Both underwent resection of the largest affected lymph node chain – in the case of UCD, the only one affected. The culture of the supernatant from the resected lymph nodes confirmed the production of IL-6. It was also observed that the patient with UCD showed complete remission of symptoms after the procedure, while the patient with DCM maintained high serum levels of IL-6 and persistence of symptoms.

Yoshizaki et al., in a 1989 study, also demonstrated an association between IL-6 levels, lymph node hyperplasia, hypergammaglobulinemia, C-reactive protein levels and clinical abnormalities in CD.[18]

In this way, studies followed looking for effective anti-IL-6 therapies in the treatment of the disease. The first drug to show promising results was developed in Japan, in the form of an anti-IL-6 receptor monoclonal antibody: tocilizumab. Initially developed for the

treatment of rheumatoid arthritis in the late 1990s, tocilizumab was also approved for clinical studies in CD and juvenile idiopathic arthritis in the early 21st century.

The first studies with the administration of tocilizumab in patients with DCM also took place in Japan[19,20] and demonstrated reversal of inflammatory parameters, resolution of constitutional symptoms and reduction of lymphadenopathy levels. The results were maintained after three years of continuous use of the medication, and it also allowed the weaning of systemic corticosteroid therapy in part of the patients who had started it concomitantly.

Since then, tocilizumab has become an important therapy to be considered in patients with idiopathic DCM. However, in view of its uncertain etiology and the severe multisystem involvement of the disease, a definitive cure has not yet been discovered, and the prognosis of the disease remains unfavorable.

Case report

A 25-year-old male patient was admitted in August 2020 to the Hospital de Clínicas da UNICAMP with headache for 6 days associated with dyspnea on exertion, greenish vomiting, inappetence and jaundice. He denied fever, respiratory symptoms, changes in bowel or urinary habits, including acholic stools or choluria, recent travel, insect bites, and ingestion of suspicious foods or medications.

Patient with idiopathic multicentric Castelman disease, whose diagnosis was confirmed in 2006 through mesenteric lymph node biopsy. During the previous course of the disease, it manifested with a chronic inflammatory condition – marked by recurrent periods of fever, weight loss, adynamia and anorexia – recurrent opportunistic infections and immune-mediated complications, such as glomerulonephritis and cardiomyopathy.

Next, the histological sections of the mesenteric lymph node resected in 2006 show distortion of the lymph node architecture, with expansion of the paracortical region due to an increase in the number of mature plasma cells (Figure 1), associated with prominent vascularization (Figure 2). Follicular hyperplasia is identified, but with regressed germinal centers, some with an “onion skin” appearance (Figure 3).

The immunohistochemical study shows positive CD20 on B lymphocytes in regressive follicles, CD3

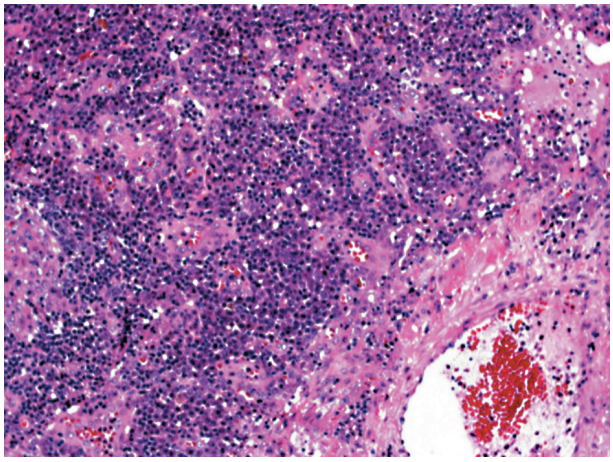

Figure 1
Evident increase in the number of plasma cells causing expansion of the paracortical lymph node zone (H&E, 100x)

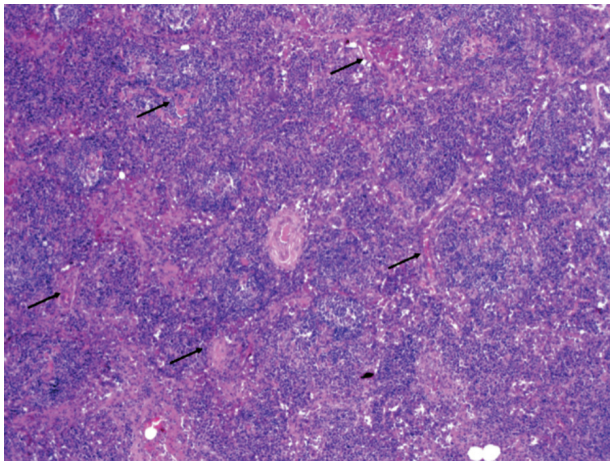

Figure 2
Prominent interfollicular vascularization (arrows). Note moderate distortion of lymph node architecture (H&E, 40x)

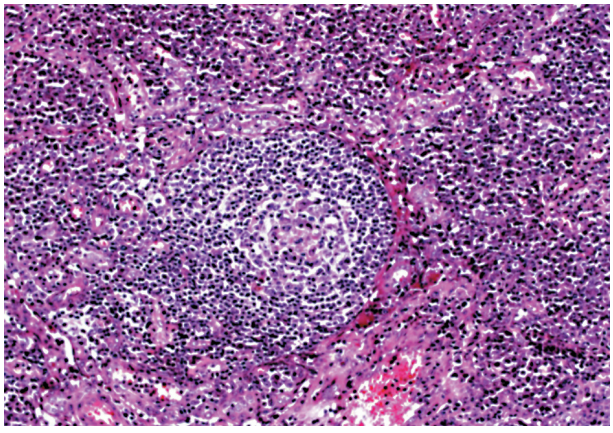

Figure 3
Lymphoid follicle regression in the cortical zone (H&E, 100x)

positive on interfollicular T lymphocytes, positive kappa and lambda in frequent plasma cells in a polyclonal pattern (Figure 4). CD30, HHV8 markers and in situ hybridization were negative. Thus, the immunohistochemical study confirmed the diagnosis of Castleman's disease, a mixed histopathological variant.

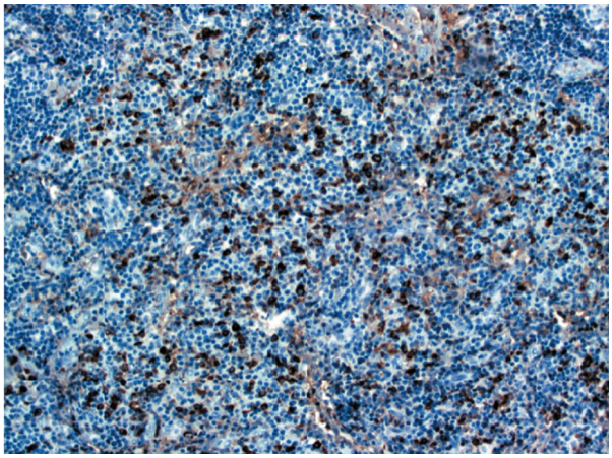

Figure 4
Prominent increase in plasma cells in the paracortical zone (immunohistochemical reaction for lambda light chain, 100x)

On current physical examination, he presented with cutaneous-mucosal pallor, mild jaundice and mild tachycardia, without hepatomegaly or splenomegaly. Laboratory tests showed hemoglobin 3.4 g/dL, mean corpuscular volume (MCV) 83.1 fl, platelets 1,064,000 µL, haptoglobin 32.6 mg/dL, total reticulocytes 176,000/mm^3, LDH 372 U/L, indirect bilirubin 1.18 mg/dL, positive direct antiglobulin test (IgG 1+, C3d 3+) and positive eluate, with the presence of IgG class autoantibodies without defined specificity. In the peripheral blood smear, no schizocytes or other abnormal forms of red blood cells were found.

Hepatitis A, hepatitis B, hepatitis C, syphilis and HIV serologies were negative. Urine I negative for hemoglobinuria. Total abdomen ultrasound without abnormalities. Also, triglycerides 156 mg/dL, ferritin 7540 ng/mL, fibrinogen > 900 mg/dL and C-reactive protein 300 mg/L. AST, ALT, amylase, lipase, cryoagglutinins, albumin and coagulogram were normal.

Altered laboratory tests on admission are shown in Table 1.

Based on the above data, the diagnosis of warm antibody autoimmune hemolytic anemia was defined. Initially, a unit of packed red blood cells was transfused, with no significant increase in hemoglobin levels (3.4 g/dL to 4.3 g/dL). After diagnostic confirmation, treatment was initiated with systemic corticosteroid therapy (methylprednisolone 4 mg/kg/day) and, two days later, tocilizumab 4 mg/kg single dose.

On the first day after tocilizumab administration, a progressive increase in hemoglobin levels was observed, with normalization of levels on the eighth day. Normalization of LDH, bilirubin and haptoglobin levels was also observed. Progressive weaning of corticosteroids was started from the seventh day.

The response to the administered treatment is represented in Figures 5 and 6.

The patient maintained regular returns after hospital discharge, with monthly administration of tocilizumab 8 mg/kg in monotherapy, with a sustained response to date.

Discussion

The existence of a close relationship between autoimmunity and lymphoproliferative diseases is known, and is based on the pathophysiology of proliferation, transformation and self-reactivity of B21 lymphocytes. It is inherent in any B lymphocyte to produce low-affinity antibodies against self-antigens, which are eliminated by immunoregulatory mechanisms as soon as they are recognized. However, in lymphoproliferative diseases, mutations in the germ line, the high proliferative activity of B lymphocytes and the defect in the apoptosis mechanism lead to dysregulation of the immune system and the generation of autoantibodies.

The lymphoproliferative diseases that are most associated with autoimmune diseases are: multiple myeloma, monoclonal gammopathy of undetermined significance, non-Hodgkin's lymphoma and chronic lymphoid leukemia. In the latter, the occurrence of autoimmune hemolytic anemia occurs in up to 20-25% of patients during the course of the disease.[22]

Autoimmune diseases have already been reported in patients with idiopathic DCM, such as systemic lupus erythematosus and hemophagocytic lymphohistiocytosis.[23] However, reports of autoimmune hemolytic anemia are rare.

Among the systemic signs and symptoms present in DCM, anemia is almost always present, usually with the typical characteristics of anemia of chronic disease.[24] The pathogenesis of anemia of

Table 1
Laboratory tests on admission

Laboratory exam	Results obtained	Reference values
Lactic dehydrogenase (LDH)	372 U/L	140 to 271 U/L
Total bilirubin	1.91 mg/dL	0.3 to 1.2 mg/dL
Indirect bilirubin	1.18 mg/dL	0.1 to 1 mg/dL
Haptogloblin	32.6 mg/dL	30 to 230 mg/dL
Hemoglobin	3.4 g/dL	14 to 18 g/dL
Hematocrit	12.3%	41 to 52%
Mean corpuscular volume (MCV)	83.1 fL	80 to 99 fL
Mean corpuscular hemoglobin (MCH)	23 page	27-32 pages
Platelets	1064 x 10^3 µL	150 to 400 x 10^3 µL
Reticulocytes (absolute)	176 x 10^3/mm^3	50 to 100 x 10^3/mm^3
Reticulocytes (percentage)	11.93%	0.5 to 2.5%
Ferritin	7540 ng/mL	30 to 500 ng/mL
Fibrinogen	> 900 mg/dL	175 to 400 mg/dL
C-reactive protein	300 mg/L	> 3 mg/L
Interleukin-6 (IL-6)	72.75 pg/mL	< 6.4 pgmL

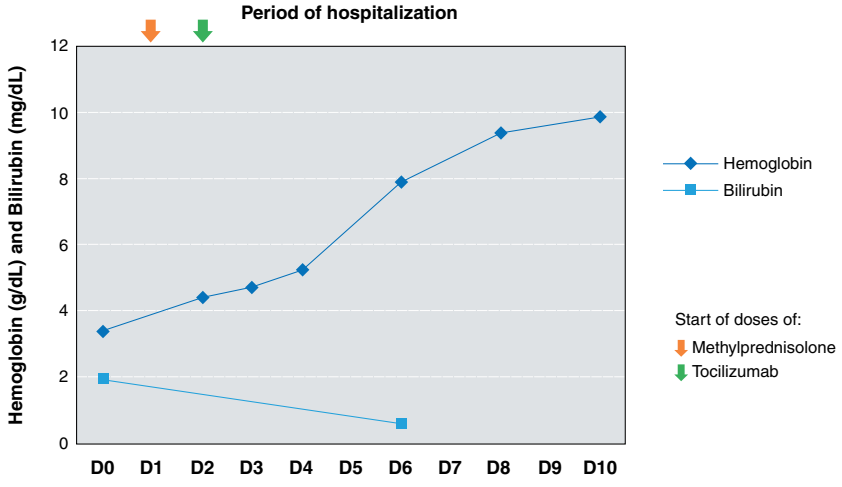

Figure 5
Treatment response

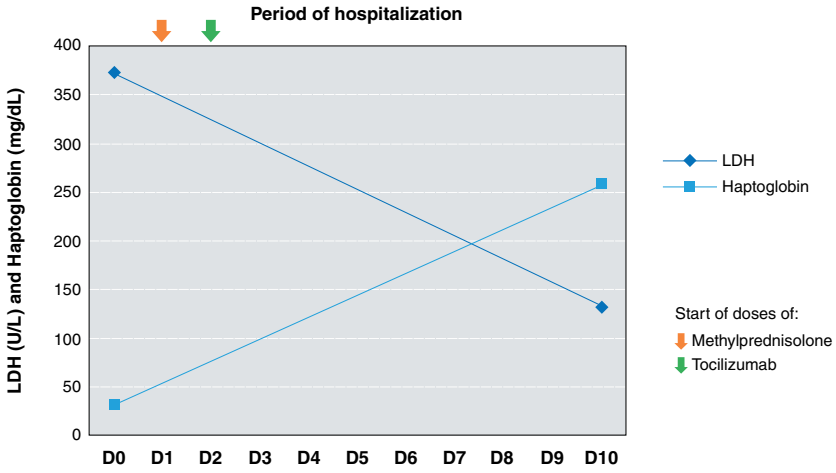

Figure 6
Treatment response

chronic disease in these patients involves the same determinants as other inflammatory diseases, with the additional mechanism of IL-6, which has inhibitory activity on erythropoiesis. However, it is possible that IL-6 overproduction itself may be involved in the pathophysiology of autoimmune hemolytic anemia (AIHA) by stimulating the generation and differentiation of plasma cells.

For over 20 years, experimental models of autoimmunity induction, such as collagen-induced arthritis and antigen-induced arthritis, have used IL-6.[25] Also in patients with DCM and AHAI, studies show increased levels of IL-6, as well as IL-4, IL-10, IL-13, IL-17 and IL-21.[26] In addition, the presence of T helper 2 (Th2), regulatory T (Treg) and T helper 17 (Th17) cells suggest their association with disease activity.[27] Th2 cells secrete IL-6, IL-4, IL-10, IL-13 and TGF-β, cytokines that stimulate the production of antibodies by B lymphocytes, while IL-6 induces the differentiation of Th17 cells, amplifying the response proinflammatory and autoimmune.[28,29]

So far, only one study has reported success in the treatment of AIHA in CD with the use of tocilizumab,[30] while a more recent study in 2019 showed partial success. In this study, Tabata S. et al. report the case of a patient with idiopathic DCM with AIHA, with initial treatment with tocilizumab 8 mg/kg every two weeks for a total of 6 doses. However, after the second dose of medication, anti-tocilizumab antibodies were detected in the patient's serum, with a consequent decrease in the effectiveness of the treatment. However, it is observed that there was a late introduction of corticosteroid therapy at an immunosuppressive dose in this patient (six days after starting tocilizumab).

Our study allowed the use of tocilizumab at a dose of 4 mg/kg, as it also associated methylprednisolone at a dose of 4 mg/kg. This association not only made it possible to reduce the dose of tocilizumab, which makes the treatment more affordable, but also prevented the possible emergence of antibodies against the drug. However, it is worth mentioning that the high dose of corticosteroids, even if followed by complete weaning, brought as a side effect to the patient in this study moderate acne and lack of glycemic control. It is possible to assume that the dose of 1-2 mg/kg would also have an immunosuppressive effect, but would be accompanied by fewer side effects.

Tocilizumab was approved in Japan for the treatment of idiopathic DCM in 2005, but due to the lack of randomized controlled studies, it was not approved in the United States, where in 2014 another similar drug was approved, called siltuximab, an anti-IL-6 monoclonal antibody. Althoughconsideredcurrently the treatment of choice, only 34% of patients responded to siltuximab therapy. Half of the non-responders had low serum levels of IL-6.[31]

The signaling pathways involved in the pathogenesis of idiopathic DCM are not yet fully understood, and other therapies involving pathways consequent to IL-6 activation have also been studied.

Conclusion

New therapeutic options for idiopathic DCM have emerged and have shown promising results. Because it is a rare disease, of uncertain etiology and with a wide variety of clinical manifestations, idiopathic DCM is still a major challenge for the scientific community and remains the subject of study. However, it is known that IL-6 plays a fundamental role in the pathophysiology of the disease, and the inclusion of anti-IL-6 and anti-IL-6 receptor monoclonal antibodies in the list of treatment radically changed the prognosis of these patients.

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