Case Report

Castleman's disease accompanied by pleural effusion*

Doença de Castleman associada a derrame pleural

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Abstract

Castleman's disease is a rare disorder of the lymphoid tissue. We report the case of a female patient with bilateral otosclerosis, no respiratory symptoms, and pleural effusion discovered as an incidental finding on a chest X-ray. Computed tomography of the chest revealed a mediastinal mass. The biopsy findings demonstrated that it was a plasmacytic variant of Castleman's disease. The patient underwent mediastinal mass resection. This resulted in near-total resolution of the effusion, which remained as a small loculation within the left pleural space.

Keywords: Giant lymph node hyperplasia; Pleural effusion; Case reports.

Resumo

A doença de Castleman é uma rara afecção do tecido linfóide. Relatamos o caso de uma paciente do sexo feminino com otosclerose bilateral, sem sintomas respiratórios e com achado incidental de derrame pleural esquerdo em uma radiografia de tórax. A tomografia computadorizada de tórax revelou uma massa mediastinal. A biópsia demonstrou tratar-se de variante plasmocitária da doença de Castleman. A paciente foi submetida à ressecção da massa mediastinal. Houve regressão do derrame, o qual persistiu como pequena loculação no espaço pleural esquerdo.

Descritores: Hiperplasia do linfonodo gigante; Derrame pleural; Relatos de casos.

Introduction

Castleman's disease (CD) is a rare disorder of the lymphoid tissue, of unknown etiology, characterized by massive lymph node enlargement, anemia, and hypergammaglobulinemia. The disease was initially described by Castleman,[1] in 1954, as benign mediastinal lymph node hyperplasia, histologically similar to a thymoma,[2] of unknown cause. Since then, it has been described using a wide variety of terms: giant lymph node hyperplasia[3]; angiomatous lymphoid hamartoma; angiofollicular lymph node hyperplasia; follicular lymphoma[4]; and, more rarely, Castleman's lymphoma.[5] Although it has been identified at other anatomical sites, including the neck (14%), pelvis (4%), and axilla (2%),[5,6] CD is most frequently found in the mediastinum (67% of cases). There is no gender predominance. It affects patients of different ages, having been described in adolescents and in patients up to the seventh decade of life.[7,8]

Clinically, it can manifest as localized masses. The hyaline-vascular variant accounts for most cases (80%), and such patients are frequently asymptomatic, whereas the plasmacytic variant is less common (20%), and patients with the latter form can present systemic symptoms, such as asthenia, weight loss, and lymph node enlargement. Less frequently, CD manifests as a multicentric or systemic disease (predominance of the plasmacytic variant) accompanied by more pronounced symptoms: systemic involvement of the peripheral lymphoid tissue, hepatosplenomegaly, fever, and night sweats.[6,9-11]

The definitive diagnosis is established through anatomopathological examination and immunohistochemical profiling. Curative surgical treatment can be used for localized forms, whereas chemotherapy and corticosteroids can be used to treat systemic forms.[9] The prognosis depends on

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the form and on the histological variant. The have been reports of rare cases in which the localized form evolved to tumors similar to Hodgkin's lymphoma or vascular neoplasms resembling Kaposi's sarcoma. The multicentric forms, however, have a poor prognosis, a mortality rate of 50%, and a mean survival of 26 months.[10]

Since CD is an uncommon entity and has features similar to those of malignant tumors (such as lymphoma), as well as of infectious diseases (such as tuberculosis and mononucleosis), it is difficult to diagnose, which makes the presentation of this case relevant.

Case report

A 45-year-old female patient (married and a dressmaker) without respiratory symptoms was admitted to undergo stapedectomy due to otosclerosis (she had a 4-year history of buzzing in the ears and bilateral conductive hearing loss). The surgery was postponed due to the incidental finding of left pleural effusion on a preoperative chest X-ray (Figure 1).

The physical examination revealed that the patient presented good general health status (lymph nodes were not palpable). The left inferoposterior third of the chest was rigid, with absent breath sounds upon auscultation. Pleural fluid testing (thoracocentesis) revealed the following: 25% neutrophils; 70% lymphocytes; 5% macrophages; few erythrocytes; absence of neoplastic cells; glucose, 102 mg/dL; total proteins, 5.5 g/dL; lactate dehydrogenase, 264 U/L; and pH, 7.45. No acid-fast bacilli were found in the direct examination of the pleural fluid, and a culture was negative for *Mycobacterium tuberculosis*. A pleural biopsy revealed chronic nonspecific pleuritis with mild fibrosis. The induration diameter on the purified protein derivative skin test was 30 mm, and the serology was negative for HIV-1 and HIV-2. In view of the diagnosis of probable pleural tuberculosis, treatment with regimen I (rifampicin, isoniazid, and pyrazinamide) was instituted. After 6 months of treatment, there was no resolution of the left pleural effusion volume, although the patient remained free of respiratory complaints. Computed tomography of the chest revealed a left anterior mediastinal mass with well-defined borders near the heart, with areas of intense contrast uptake (Figure 2), in addition to the left pleural effusion.

The patient underwent excision of the lymph node and mediastinal mass, which were brownish, firm and pliable. The histopathological study of these specimens (Figure 3) revealed lymphoid tissue consisting of small cells in follicular arrangements, sometimes concentrically arranged, sometimes presenting previously reactive germinal centers and hyalinization of vessel walls; among such follicles, there were numerous cells identifiable as plasmacytes. The immunohistochemical study revealed the following: positivity for CD45 (LCA) and CD20 (Pan B) in the follicle cells; positivity for CD3 (Pan T) in the interfollicular area; positivity for CD45 (LCA) and Bcl-2 in the mantle cells; positivity for CD68 in

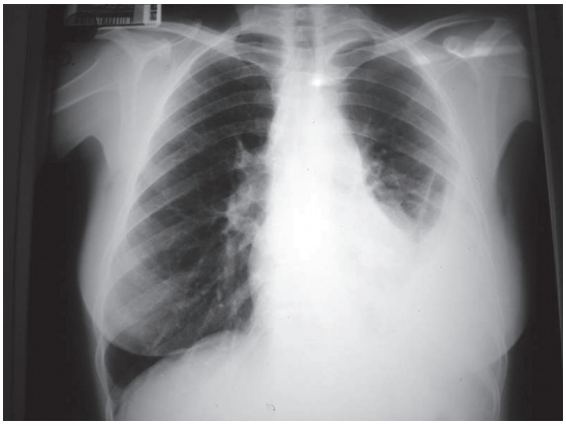

Figure 1 - Anteroposterior chest X-ray revealing left pleural effusion.

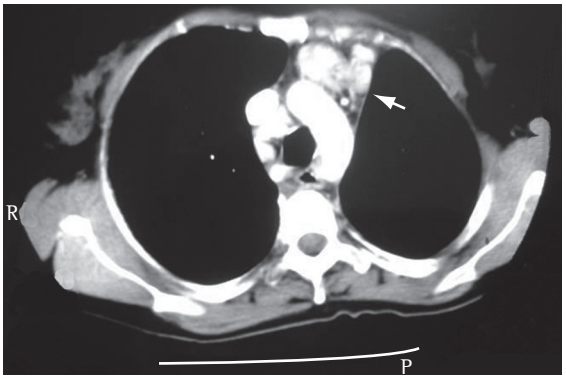

Figure 2 - Computed tomography of the chest revealing an anterior mediastinal mass (arrow) with well-defined borders and areas of intense contrast uptake projecting to the left.

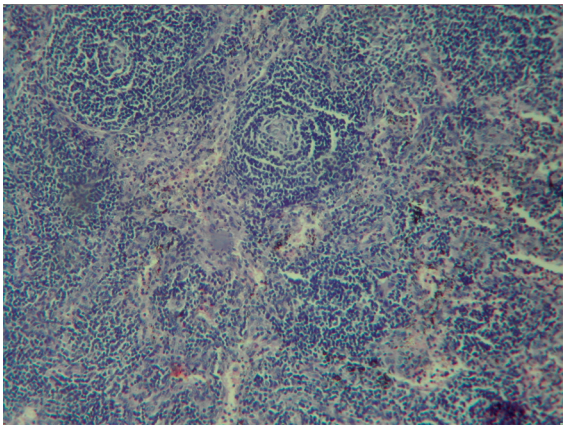

Figure 3 - Follicles with lymphocytes arranged in an onion bulb formation; plasmacytosis seen among the follicles (H&E ×10).

the macrophages and dendritic cells; and absence of AE1/AE3 expression.

The results favored a diagnosis of reactive hyperplasia, consistent with the morphologic diagnosis of CD (localized form, plasmacytic variant) accompanied by pleural effusion.

Discussion

A diagnosis of CD is considered rare.[11] In the general population, its prevalence has not been established. In the United States, the prevalence of CD has been estimated to be between 30,000 and 100,000 cases, based on the number of cases of lymph node enlargement of initially unknown etiology treated at oncological centers and later diagnosed as CD.[11] Only a few cases have been reported in Brazil.[12-14]

The etiology of CD is unknown. However, there is evidence suggesting the participation of viral infections, notably those caused by human herpes virus 8 and Epstein-Barr virus. Some authors suggest that those agents induce the B lymphocyte population present in the (cortical) mantle area of lymph nodes to produce interleukin-6 (IL-6), and that, conversely, vascular endothelial growth factor gives rise to the proliferation of B lymphocytes and the vascular alterations seen in CD.[11] The extensive vascularization seen in CD supports the possibility that vascular endothelial growth factor participates in the physiopathology of the disease. The plasmacytic variant in the multicentric form of the disease is most frequently found in combination with HIV/human herpes virus 8 co-infection and Kaposi's sarcoma, which seems to support the hypothesis of a viral etiology.[9] The increased IL-6 expression by viral antigens of human herpes virus 8 seems to be responsible for the constitutional symptoms seen in the multicentric form and for the poorer prognosis.[9,11]

The clinical presentation of CD is quite varied, including patients who are asymptomatic or have mild lymphadenopathy and patients who have recurrent episodes of diffuse lymphadenopathy and severe systemic symptoms. In the hyaline-vascular variant of the localized form, lymph node enlargement can be observed in the mediastinum, neck, abdomen or axilla, and can even be extrapulmonary (between lung lobes).[14] The symptoms, which can result from compression effects, vary according to the site involved, and CD can be an incidental finding in imaging studies in asymptomatic patients. In such cases, the diagnosis is established through lymph node resection and biopsy.[10] Among the localized forms of presentation, the presence of a mediastinal mass in the plasmacytic variant is less common (20%).

The case presented here has unusual clinical aspects. The initial clinical sign was left pleural effusion, discovered on a chest X-ray performed for the preoperative evaluation of otorhinolaryngological surgery. Despite the pleural involvement, the patient was asymptomatic and presented a normal hematological profile (hemoglobin: 12.1; hematocrit: 37.4%). According to the literature, most cases of the plasmacytic variant, even in the localized form, present constitutional symptoms: anemia and increased erythrocyte sedimentation rate; fever; adynamia; and night sweats.[11] However, this was not observed in our patient, and it should be noted that she tested negative for HIV.

The differential diagnosis of CD should include infectious diseases, such as tuberculosis, toxoplasmosis, cytomegalovirus, mononucleosis, cat scratch disease, and HIV. Sarcoidosis should also be included. In addition, some neoplastic diseases, such as thymoma, neurofibroma, cervical lipoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma, as well as lymph node metastasis, should always be considered during the investigation.[9]

It should be borne in mind that, in the case reported here, this rare disease presented clinical aspects that were even more unusual. Initially, in view of the high prevalence of tuberculosis in Brazil and the purified protein derivative skin test status (strong reactor), we hypothesized that the etiology of the pleural effusion was tuberculous. However, neither the examination of the pleural fluid nor the biopsy findings confirmed this diagnosis. In addition, specific treatment did not result in resolution of the effusion. A computed tomography scan of the chest revealed a mediastinal mass. The histopathological and immunohistochemical findings for the sample confirmed the diagnosis of CD. In cases of CD, pleural masses have been described,[15] as has massive pleural effusion,[16] the latter being an unusual form. The review of the present case suggests that the pleural effusion was an unexpected form of presentation of CD. The fact that other lymphoproliferative disorders (such as primary effusion lymphoma) and tuberculosis, both of which affect the pleural cavity, were ruled out supports this supposition.[17,18] One interesting finding in the present case was the bilateral conductive hearing impairment due to otosclerosis. The determining factors of otosclerosis are not well established. Various etiopathogenic hypotheses have been proposed, and the principal ones consider immunological, viral infectious, and genetic factors, including the identification of the gene implicated (OTSC1-3).[19] The cause of the bilateral otosclerosis presented by the patient was not identified. Could there be a relationship between otosclerosis and CD? To date, there is no evidence in the literature that otosclerosis is linked to disorders of the lymphoid tissue. However, in principle, we cannot rule out the possibility that there are concurrent risk factors for the two conditions.

In its localized, hyaline variant form, CD is nearly always cured after surgical resection. In the case of the plasmacytic variant, some patients require complementary postoperative treatment for the resolution of persistent systemic symptoms. In its multicentric form, however, the treatment is controversial, involving chemotherapy (cyclophosphamide, vincristine, and doxorubicin), immunomodulators (corticosteroids, interferon-α, retinoic acid, and thalidomide), monoclonal antibodies (anti-IL-6 and rituximab), and antiviral therapy (ganciclovir, foscarnet, and cidofovir).[6,11]

The patient underwent excision of the mediastinal mass and the affected small mediastinal nodes without presenting any complications. There was partial resolution of the pleural effusion, a small volume of which remained loculated within the left pleural space. Throughout the investigation period, the patient presented good general health status and no respiratory symptoms. No complementary treatment was instituted. The patient remained under clinical follow-up treatment at our facility.

In conclusion, CD, albeit rare, should be considered in the differential diagnosis of lymph node enlargement, particularly in cases of mediastinal lymph node enlargement. Pleural effusion can be a form of presentation of the disease. Surgical treatment is curative in most cases.

References

1. Castleman B, Towne VW. Case Records of the Massachusetts General Hospital. Case 40001: Hyperplasia of mediastinal lymph nodes. N Engl J Med. 1954;250(1):26-30.
2. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer. 1956;9(4):822-30.
3. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer. 1972;29(3):670-83.
4. Harrison EG Jr, Bernatz PE. Angiofollicular mediastinal lymph-node hyperplasia resembling thymoma. Arch Pathol. 1963;75:284-92.
5. Frizzera G, Banks PM, Massarelli G, Rosai J. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease. Pathological findings in 15 patients. Am J Surg Pathol. 1983;7(3):211-31.
6. Peterson BA, Frizzera G. Multicentric Castleman's disease. Semin Oncol. 1993;20(6):636-47.
7. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer. 1972;29(3):670-83.
8. Herrada J, Cabanillas F, Rice L, Manning J, Pugh W. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med. 1998;128(8):657-62.
9. Dham A, Peterson BA. Castleman disease. Curr Opin Hematol. 2007;14(4):354-9.
10. Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. Hum Pathol. 1985;16(2):162-72.
11. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol. 2005;129(1):3-17.
12. Marques CD, Nunes PS, Duarte AL, Cavalcanti FS. Doença de Castleman mimetizando doença de Still do adulto. Rev Bras Reumatol. 2005;45(5):331-4.

13. Oliveira CV, Gonçalves CE, Almeida VF, Oliveira AM, Pimenta FC. Doença de Castleman localizada abdominal. Rev Bras Hematol Hemoter. 2005;27(2):133-7.
14. Krawczun GA, Garcia CM, Ito K, Ferreira Filho OF, Thomson JC. Castleman disease or angiofollicular hyperplasia as a solitary pulmonary nodule: case report J. Bras. Pneumol. 2007;33(2):226-8.
15. Ko SF, Ng SH, Hsieh MJ, Lin JW, Huang CC, Lee TY, et al. Castleman disease of the pleura: experience with eight surgically proven cases. Ann Thorac Surg. 2003;76(1):219-24.
16. Reynolds SP, Gibbs AR, Weeks R, Adams H, Davies BH. Massive pleural effusion: an unusual presentation of Castleman's disease. Eur Respir J. 1992;5(9):1150-3.
17. Antonângelo L, Vargas FV, Teixeira LR, Vaz MA, Sales MM, Moreira LC, et al. Primary effusion lymphoma in an immunocompetent patient. J. Bras. Pneumol. 2005;31(6):563-6.
18. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis. 2002;2(6):344-52.
19. Niedermeyer HP, Arnold W. Etiopathogenesis of otosclerosis. ORL J Otorhinolaryngol Relat Spec. 2002;64(2):114-9.