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CASE REPORTS

CASTLEMAN DISEASE. A RARE DIAGNOSIS IN CHILDHOOD

DOENÇA DE CASTLEMAN. UM DIAGNÓSTICO RARO NA INFÂNCIA

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ABSTRACT

Introduction: Castleman Disease (CD) is a rare polyclonal lymphoproliferative disorder characterized by massive growth of lymphoid tissue. The most common sites of disease are the chest, abdomen, neck, and axilla. Excisional biopsy is mandatory for diagnosis, and complete surgical resection the gold-standard treatment in unicentric CD.

Case report: A ten-year-old girl was observed at the Emergency Department with sore throat and fever. Oropharynx examination revealed inflamed tonsils, with no exudates. Enlarged lymphadenopathy was palpable in the right supraclavicular fossa. Ultrasound revealed right supraclavicular lymphadenopathy with loss of adipose hilum and histopathologic assessment established CD diagnosis.

Discussion/Conclusion: Lymphadenopathy is a common presentation in children, usually benign and self-limited. But it may also be a sign of underlying malignancy. Any lymphadenopathy in the supraclavicular fossa is worrisome and requires prompt investigation. CD diagnosis may be challenging, due its rare nature in childhood and nonspecific symptoms.

Keywords: Castleman disease; childhood; lymphadenopathy

RESUMO

Introdução: A doença de Castleman (DC) é um distúrbio linfoproliferativo policlonal raro caracterizado por crescimento anormal de tecido linfóide. Os locais mais comummente afetados são o tórax, abdómen, pescoço e axila. A biópsia excisional é mandatória para o diagnóstico e a resseção cirúrgica é o tratamento de eleição na forma unicêntrica.

Caso clínico: Uma criança de dez anos de idade, do sexo feminino, foi observada no Serviço de Urgência por odinofagia e febre. Ao exame físico, apresentava rubor amigdalino sem exsudados e adenomegalia palpável na região supraclavicular direita. A ecografia cervical confirmou linfoadenopatia com perda do centro adiposo e o exame histopatológico foi compatível com DC.

Discussão/Conclusão: As adenomegalias são uma apresentação comum na infância e geralmente benignas e auto-limitadas. Contudo, poderão ser um sinal de neoplasia. Uma adenopatia na região supraclavicular é preocupante e requer investigação atempada. O diagnóstico de DC é desafiante, devido à sua raridade em idade pediátrica e sintomas inespecíficos.

Palavras-chave: adenopatia; doença de Castleman; infância

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INTRODUCTION

First described in 1954 and better classified by Benjamin Castleman in 1956, Castleman Disease (CD) is a polyclonal lymphoproliferative disorder characterized by massive growth of lymphoid tissue, with several different characteristic histopathologic variants.[1,2] Although rare in the pediatric population, its exact prevalence remains unknown.[3] The pathogenesis of CD is poorly understood, although reaction to a chronic viral antigenic stimulation has been proposed as possible underlying etiology.[3,4] Talat *et al* reported a slightly increased incidence of CD in female patients in the early decades of life and in male patients in the second half of life.[5] However, Rabinowitz *et al* showed that, in pediatric populations, the male-to-female ratio was approximately 1:1.[3] Early literature on CD was based on a very limited number of cases and the condition was traditionally classified by its centricity as unicentric CD (UCD) – usually one lymph node or a single lymph node region affected – or multicentric CD – two or more lymph nodal groups affected.[2,5] However, the more recent classification system categorizes CD based on histopathologic findings in hyaline vascular CD, plasma cell CD, mixed variant (with features of both previous variants), and plasmablastic variant (with plasma cell features and plasmablasts).[2,3] Recently, three entities emerged in CD classification, with multicentric CD further subdivided in human herpesvirus-8 (HHV8)-positive or HHV8-negative according to presence or absence of HHV8 infection, and UCD remaining a single entity.[2] Patients diagnosed with UCD are commonly asymptomatic or display signs or symptoms related to compression of adjacent structures.[4] CD may occur anywhere in the lymphatic system, but in pediatric age the most commonly affected sites are the chest, followed by the abdomen, neck, and axilla.[3] The outcome is not influenced by location of the affected lymphadenopathy.[1] Although useful for excluding other diagnoses far more common in childhood, blood analyses and imaging findings are not helpful for diagnosing CD.[3] An excisional biopsy of the most abnormal lymph node is mandatory to diagnose CD by histopathologic review.[4] Complete surgical resection of the affected lymph node is considered the gold-standard treatment in UCD, with recurrences occasionally reported.[4] Some case reports document gradual spontaneous improvement to even complete remission without treatment.[1] In the pediatric population, CD often holds favorable prognosis, particularly in cases of hyaline-vascular CD subtype.[3]

CASE REPORT

A ten-year-old Caucasian girl was observed at the pediatric Emergency Department (ED) with complaints of recent-onset sore throat and fever. Medical history was unremarkable, except for recurrent tonsillitis and a history of suspected penicillin allergy. Her two-year-old sibling had been diagnosed with acute viral tonsillitis three days earlier. The girl's general appearance was good. Oropharynx examination revealed inflamed tonsils with no exudate. The girl presented five lymph nodes bilaterally on the neck (the largest with 2–2.5 cm), with no tenderness on palpation or overlying erythema. Additionally, an enlarged lymph node with rubbery consistency measuring 2 cm in diameter was palpable in the right supraclavicular fossa. No other significant lymphadenopathy was identified. The girl had no respiratory distress and pulmonary auscultation was normal. The abdomen was soft, with normal bowel sounds, non-palpable liver and spleen, and no abdominal masses. No recent travel abroad, previous medication history, animal exposure (namely cats), or tuberculosis contact were reported. The girl had complete routine immunisation vaccine schedule. Initial laboratory data included complete blood count, with white cell count of 12.500/µL (68.3% neutrophils, 22.4% lymphocytes, and 8.8% monocytes), hemoglobin of 13.1 g/dL, hematocrit of 37.5%, and platelet count of 184.000/µL. Erythrocyte sedimentation rate was 22 mm/h, C-reactive protein was 33.5 mg/L, and lactate dehydrogenase and uric acid levels were normal for age. Rapid antigen test in the oropharynx to detect group A streptococcal infection was negative. Serological tests for Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* were negative for IgM antibodies, and human immunodeficiency virus was also negative. No mediastinal enlargement was detected in chest radiograph. Cervical ultrasound showed numerous lymph nodes in the anterior cervical area bilaterally (the largest with 45x13 mm in diameter) and a right supraclavicular lymphadenopathy (with 18x9 mm in diameter), suggestive of reactive lymph node. Abdominal ultrasound revealed splenomegaly with 12.2 cm of diameter (normal range, 6.8–11.4 cm).

Considering bacterial lymphadenitis as the most probable diagnosis, an empiric course with azithromycin (10 mg/kg once daily, 7 days) was prescribed. One week later, the patient was afebrile and asymptomatic, but still maintained a palpable supraclavicular lymph node with similar size. A new cervical ultrasound showed persistent adenopathy with loss of adipose hilum. The patient was referred to the pediatric Oncology Unit for lymph node fine-needle aspiration (FNA) biopsy. Smears showed a polymorphic population of lymphocytes, immunoblasts, and lymphohistiocytic aggregates, suggestive of reactive lymphadenitis. Four weeks later, as no lymph node size regression was observed, an excisional biopsy was performed. Histopathologic assessment showed occasional vascular proliferation and hyalinization of vessel walls and germinal centres traversed by penetrating vessels, and expansion of the mantle zones with lymphocytes arranged in layers. The lymphatic follicle contained more than one germinal centre (2 to 3) and immunohistochemistry study (CD20, CD3, CD10, Bcl-2, CD21, Kappa, and Lambda) was not compatible with malignancy. These features confirmed CD hyaline-vascular subtype diagnosis. Whole-body 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) scan excluded other hypermetabolic lesions. The child was diagnosed with UCD and, after six months of follow-up, she was asymptomatic, with no palpable lymphadenopathies, and normal abdominal ultrasound.

DISCUSSION/CONCLUSIONS

The lymphatic system is an important component of the immune system and lymphadenopathy is a common presentation in children seeking medical support. In the pediatric population, lymphadenopathies are usually secondary to a benign and self-limiting infection.[9] Either viral or bacterial infections may lead to localized lymphocyte and macrophage responses, causing lymph node swelling.[6] However, they may occasionally indicate presence of more serious underlying conditions.[10] A palpable lymph node in the supraclavicular fossa is worrisome and requires further investigation, as it is often associated with malignancy in children. Right supraclavicular adenopathy is linked to mediastinal cancer, whereas left supraclavicular suggests intra-abdominal cancer.[11] Castleman disease, or angiofollicular lymph node hyperplasia, comprises a diverse group of lymphoproliferative disorders.[4] CD diagnosis is challenging, as patients are commonly asymptomatic and therefore underdiagnosed or misdiagnosed. Although rarely, these patients may develop systemic symptoms or signs – including night sweats, fever, weight loss, fatigue, enlarged liver or spleen, or skin findings as violaceous papules – or symptoms related to compression of adjacent structures (as the airway or vessels) by the enlarging mass.[4] Laboratory tests are often unremarkable in UCD patients, although they may occasionally exhibit blood workup abnormalities, such as elevated inflammatory parameters, anemia, thrombocytopenia or thrombocytosis, renal dysfunction, or polyclonal hypergammaglobulinemia.[4] Nonspecific lymphoid hyperplasia is a common finding in FNA biopsy. While useful in excluding other diagnoses, FNA unlikely establishes CD diagnosis.[3]

Excisional biopsy of the lymph node is the gold-standard procedure, since it is both diagnostic and therapeutic and complete surgical resection is the only significant predictor of survival.[4] Lymphadenopathy location may prevent a safe surgical procedure if the mass is adjacent to a main bronchus or major blood vessels. In these cases, as removal might be life threatening, some authors recommend embolization or using rituximab to convert the lymph node into a resectable mass.[4] Usually, death due to UCD is a rare event and life expectancy after CD diagnosis remains unchanged.

In the present case, the patient sought medical support due to fever and sore throat. Recent symptom onset and oropharynx examination findings suggested viral infection as the most likely diagnosis, enhanced by a history of contact with viral tonsillitis of the sibling. However, detailed physical examination enabled detection of a lymph node in the supraclavicular fossa. Presence of fever and characteristics of this adenopathy prompted further investigation. Initial findings in neck ultrasound and chest radiograph suggested a benign disorder. Laboratory tests showed elevated inflammatory parameters, common in the setting of tonsillitis infection. Considering a possible bacterial lymphadenitis, the child was discharged from the ED with antibiotic prescription. Since the most common organisms implicated are *Staphylococcus aureus* and group A streptococcus, first-line empiric treatment should be an association of penicillin-like antibiotic and beta-lactamase inhibitor or first- or second-generation cephalosporin. However, due to suspicion of penicillin allergy, a macrolide was prescribed. Despite general condition recovery and symptom resolution, persistence of the abnormal lymph node in the supraclavicular fossa, combined with new ultrasound findings, prompted referral for biopsy in the Oncology Unit. FNA results suggested reactive lymphoid hyperplasia, a common and inconclusive finding, and reasoned for a wait-and-see approach. The observation of stable findings one month later argued in favor of excisional biopsy, and histopathologic assessment established CD diagnosis.

After complete lymphadenopathy surgical removal, the child was assessed for systemic involvement. 18F-FDG PET scan excluded additionally affected lymph nodes, confirming the surgical procedure effectiveness. Although complete removal of affected lymphadenopathies is associated with low recurrence rates, long term follow-up of these patients is still mandatory.

Because CD is an uncommon entity in childhood and may be associated with nonspecific symptoms, it is often underdiagnosed or misdiagnosed as infectious or inflammatory disease, a more common entity in pediatric age.[3]

REFERENCES

1. Farruggia P, Trizzino A, Scibetta N, Cecchetto G, Guerrieri P, D'Amore ESG, *et al*. Castleman's disease in childhood: report of three cases and review of the literature. Italian Journal of Pediatrics. 2011; 37:50.
2. Sopfe J, Endres A, Campbell K, Hayes K, Trout AT, Liang X, *et al*. Castleman disease in pediatrics: Insights on presentation, treatment, and outcomes from a two-site retrospective cohort study. Pediatr Blood Cancer. 2019; e27613.
3. Rabinowitz MR, Levi J, Conard K, Shah UK. Castleman disease in the pediatric neck: A literature review. Otolaryngol Head Neck Surg. 2013; 148:1028-36.
4. Fajgenbaum DC. Unicentric Castleman Disease. UpToDate 2019.
5. Talat N, Schulte KM. Castleman's Disease: Systematic Analysis of 416 Patients from the Literature. The Oncologist. 2011; 16:1316-24.
6. Nguyen T. Approach to lymphadenopathy. November 2011. Available at: https://learn.pediatrics.ubc.ca.
7. Friedmann A. Evaluation and Management of Lymphadenopathy in Children. Pediatrics in Review. 2008; 29:53-60.
8. Gow KW. Pediatric Lymph Node Disorders. Medscape 2019.
9. Weinstock M, Patel N, Smith L. Pediatric Cervical Lymphadenopathy. Pediatrics in Review. 2018; 39:433-43.
10. King D, Ramachandra J, Yeomanson D. Arch Dis Child Educ Pract Ed 2014; 99:101–110.
11. McClain K. Peripheral lymphadenopathy in children: Etiology. UpToDate 2019.

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