Castleman Disease Presenting in the Neck: A Report of 3 Cases and a Literature Review

ACEF 1,2 Peng Jiang
EF 1,2 Zheng-hui Huang
BD 1,2 Wei-ying Liu
ABG 1 Hong-guang Pan

Corresponding Author: Hong-guang Pan, e-mail: 1481717890@qq.com

Financial support: None declared
Conflict of interest: None declared

Case series
Patients: Male, 8-year-old • Male, 5-year-old • Female, 10-year-old
Final Diagnosis: Castleman disease
Symptoms: Neck masses
Clinical Procedure: —
Specialty: Otolaryngology

Objective: Rare disease
Background: Castleman’s disease (CD) is a reactive lymph node hyperplasia initially identified by Castleman in 1956. CD predominantly affects individuals 20-50 years of age, with low incidence in children. This case report describes 3 cases of CD treated in our hospital and reviews the relevant literature. The purpose of this case report was to enhance clinical understanding and treatment of CD in the head and neck in children.

Case Reports: To enhance clinical understanding and improve treatment of CD in the head and neck region in children, we present the cases of 3 patients who were admitted to the hospital, primarily presenting with a neck mass. Preoperatively, the patients collectively exhibited non-specific findings. Surgical interventions were performed with Cases 1 and 3 undergoing left functional (radical) neck lymph node dissection, in contrast to Case 2, in which bilateral functional (radical) neck lymph node dissection was executed. Pathological examination confirmed the diagnosis of CD in each of the 3 patients. Following surgery, a follow-up period ranging from 3 months to 1 year revealed that all patients had successfully recovered, with no recurrence.

Conclusions: Castleman disease is a rare disease in children and difficult clinical diagnosis. Some patients with unicentric Castleman disease (UCD) can be treated with surgery, and those with multicentric Castleman disease (MCD) need chemotherapy, but at present there is no widely accepted treatment plan.

Keywords: Lymphadenopathy • Multi-centric Castleman’s Disease • Neck • Pediatrics

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/943214
Introduction
Castleman disease (CD) is a reactive lymph node disease of unknown cause, which is relatively rare in clinical practice. It is mainly characterized by significant enlargement of the lymph nodes, which can be accompanied by systemic symptoms, and in severe cases it can involve multiple systems throughout the body. The incidence of this disease is about 1 in 50,000, with males and females having similar incidence rates [1]. It can be divided into hyaline-vascular type, plasma cell type, and mixed type based on pathological characteristics [2]. Of these, the hyaline-vascular type is the most common, accounting for 80% to 90%; the plasma cell type is less common, accounting for 8-9%; and the mixed type combines features of the previous 2 types. Furthermore, based on the range of lymph node involvement, it can be categorized into unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD). UCD is more localized in lesion, more common in young people, often asymptomatic, typically presents as single or localized lymph node enlargement, most common in the mediastinal lymph nodes, followed by cervical, axillary, and abdominal lymph nodes, and generally has a better prognosis. MCD often involves multiple lymph nodes and regions, tends to occur at older ages, has more prominent systemic symptoms (such as fever and hepatosplenomegaly), and has a poorer prognosis [3,4]. Here, we report 3 cases of CD treated in our hospital and review the relevant literature to enhance clinical understanding and treatment of this disease.

Case Reports
Case 1
Five years ago, a left neck lump was discovered in a boy now age 8 years 10 months. The lump had grown larger in the past 2 months, so he was admitted to the hospital in January 2023 for further treatment. Upon specialized physical examination, a 7×8 cm lump could be palpated in the left neck, which had no redness, swelling, or tenderness, with normal mobility, slightly hard texture, clear boundaries, and adhesion to the surrounding area. Laboratory tests, including red blood cells, white blood cells, platelets, coagulation, and liver and kidney function, showed no significant abnormalities. Neck ultrasound showed multiple hypoechoic masses in the deep surface of the left sternocleidomastoid muscle and supraclavicular fossa, with no obvious fluid accumulation echo in the periphery. The largest was 4.9×2.4 cm, with clear boundaries, regular shape, and uneven internal echo. Band-like hyperechoic signals were observed internally, without obvious hypoechoic areas or calcification. No obvious abnormalities were observed in the surrounding soft-tissue echo. Neck magnetic resonance imaging (MRI) showed an irregular lobulated lesion in the left neck-left thoracic cavity, with uneven signal intensity in the mass, predominantly low signal on T1WI, and high signal on T2WI. Scattered low signal areas were seen internaly on T1WI and T2WI, with visible vascular flow voids passing through. The lesion was located behind the left sternocleidomastoid muscle, on the outer side of the left neck vascular sheath, extending downward to the left thoracic cavity and anterior mediastinum (approximately at the level above the left brachiocephalic vein). The mass had clear boundaries, with a maximum cross-sectional size of 68×71×28 mm (superior-inferior×left-right-anterior-posterior). After enhancement, the mass showed uneven enhancement, with visible small enhanced vascular shadows entering the lesion. The adjacent left jugular vein and carotid artery were compressed, with no apparent filling defect. No clear abnormal signals or enhancements were observed near the clavicle. No clear abnormal signals or enhancements were observed in the adjacent muscles. No apparent enlarged lymph nodes were observed (Figure 1A, 1B). Ultrasound-guided lymph node puncture examination (Tru-Cut) showed enlarged lymph nodes, reduced central germinal centers, increased small blood vessels in the interior, partial glassy degeneration, and small lymphocyte proliferation in the capsule area arranged in concentric circles. Results of postoperative tissue pathology showed a 5.5×3.4×2.6 cm mass in the left neck, appearing to be gray-red tissue, with a gray-white appearance on the cut surface. The surgical method was left neck functional (radical) neck lymph node dissection. Based on the patient's medical history and immunohistochemistry results, the pathological type was considered to be the hyaline-vascular type of CD, and the clinical classification was UCD. The patient was followed up for 3 months after surgery, with no evidence of local recurrence or distant metastasis as long-term complications.

Case 2
A 5-year-old boy was discovered to have bilateral neck masses over 1 year ago. He was admitted to the hospital in May 2022 for further treatment. Physical examination revealed palpable masses along the anterior border of the bilateral sternocleidomastoid muscle, with the largest measuring 4×1 cm on the left side, located at the upper 1/3 of the sternocleidomastoid muscle, and the largest measuring 4×1.5 cm on the right side, also located at the upper 1/3 of the sternocleidomastoid muscle. The masses were mildly tender, with normal skin temperature, no apparent fluctuation, and no signs of skin breakdown. Results of laboratory tests showed that red blood cells, white blood cells, and platelets were normal. The white blood cell count was 13.51×10^9/L. The absolute neutrophil count was 10.38×10^9/L (76.9%). Liver and kidney function, coagulation profile, and Epstein-Barr virus (EBV) screening were all normal. Tumor markers (serum) showed no abnormalities. Results of superficial lymph node and abdominal ultrasound...
revealed enlarged lymph nodes in the bilateral neck region and diffuse hepatomegaly, with the liver extending 3.2 cm below the right rib. CT and MRI were not performed before operation. The surgical method was bilateral functional (radical) neck lymph node dissection. Results of ultrasound-guided lymph node puncture examination (Tru-Cut) revealed preserved lymph node architecture with lymphoid hyperplasia, primarily characterized by increased lymphoid follicles. Some lymphoid follicles had small germinal centers and eosinophilic material, forming a ring-like distribution in the paracortex. Blood vessel infiltration was observed in some individual lymphoid follicles. Regarding past medical history, the patient was diagnosed with asthma 1 year ago. Based on the patient’s medical history and immunohistochemical results, the pathological type of this case was presumed to be the hyaline-vascular type of CD, clinically classified as UCD. The patient has been followed up for 1 year postoperatively, with no evidence of local recurrence or distant metastasis.

**Case 3**

A 10-year-old girl was discovered to have a left neck mass, which had persisted for over 6 months. She was admitted to the hospital in July 2021 for further treatment. Results of laboratory tests showed that red blood cells, white blood cells, platelets, liver and kidney function, and coagulation function were normal. Findings from superficial lymph node and abdominal ultrasound suggested multiple enlarged lymph nodes with increased echogenicity in the deep aspect of the left neck (level IV), with the largest measuring 4.9×3.0 cm. No obvious enlarged lymph nodes were found in the right neck. Neck CT revealed an oval-shaped lesion behind the sternocleidomastoid muscle in the left neck (level Vb), measuring 30×49×44 mm (anteroposterior×left-right×superior-inferior). No liquefaction necrosis or calcification was observed, and the border was relatively clear. Multiple enlarged lymph nodes were seen around the lesion, with no definite signs of fusion. The adjacent fat planes were clear. Results of neck magnetic resonance imaging (MRI) showed an oval-shaped lesion behind the sternocleidomastoid muscle in the left neck (level Vb), with a similar size to the previous findings (30×50×53 mm). The lesion had homogeneous signal intensity on plain scans, low signal intensity on T1-weighted images, high signal intensity on T2-weighted images.
images, and moderate enhancement on contrast-enhanced scans. The enhancement of the margin was greater than that of the central portion. The surrounding fat planes remained clear. Multiple slightly enlarged lymph nodes were observed in the left neck, left supraclavicular fossa, and upper mediastinum, with no signs of fusion. The enhancement pattern was similar to that of the lesion. The left common carotid artery and internal jugular vein were compressed and displaced anteriorly, with narrowing of their lumen (Figure 2). Results from ultrasound-guided lymph node puncture examination (TrueCut) showed concentric proliferation of lymphoid follicles surrounding the germinal center, vascularization of the germinal center, partial atrophy of the germinal center, proliferation of blood vessels between follicles, and hyalinization of blood vessel walls. Immunohistochemistry showed positive staining for CD38 (scattered individual cells), CD3, CD19 (follicular), and CD21, and negative staining for CD30. The patient in this case was considered to have the histopathological type of transparent vascular type Castleman disease, with a clinical classification of unicentric Castleman’s disease (UCD). The patient was followed up for 1 year after surgery, with no local recurrence or distant metastasis.

**Discussion**

**Clinical Presentation**

Castleman disease (CD), a reactive lymph node hyperplasia, was first identified by Castleman et al in 1956 [5]. The exact cause is still uncertain, but it is commonly linked to the cytokine interleukin-6 (IL-6), human herpes virus 8 (HHV-8), and human immunodeficiency virus (HIV) infection [6,7]. The disease occurs in people aged 20 to 50 years, and the incidence in children is very low. Parez suggested that Castleman disease in children differs from that in adults in that it is less polycentric and is usually characterized by a triad of anemia, hyperimmunoglobulinemia, and developmental disorders [8]. The primary clinical characteristic is a significant enlargement of the lymph nodes, potentially accompanied by systemic symptoms, and in severe cases, multiple bodily systems can be affected. Based on clinical symptoms, it can be categorized into UCD and MCD. UCD usually exhibits no symptoms, with a few cases showing isolated swollen lymph nodes and systemic symptoms like fever, night sweats, weight loss, and anemia. MCD typically presents with swollen lymph nodes throughout the body, enlarged liver and spleen, and systemic symptoms. Laboratory tests usually show that patients with UCD and MCD have systemic inflammation, anemia, elevated IL-6, and hypoalbuminemia [9]. Among the 3 cases of Castleman disease in this study, all had painless neck lumps. One case showed increased white blood cells and neutrophils in laboratory tests, with no other specific manifestations. Therefore, the clinical manifestations of the disease are non-specific, a definitive diagnosis requires intraoperative pathological biopsy, and treatment is then based on the pathological classification.

**Diagnosis and Differentiation**

The clinical presentations of CD are non-specific, with enlarged lymph nodes as the main feature [10], possibly accompanied by systemic symptoms. A definitive diagnosis is challenging through only clinical presentations and imaging studies. Pathological lymph node biopsy is the criterion standard for diagnosing CD, meaning a confirmed diagnosis of CD must have pathology support [11]. The diagnosis is then categorized based on clinical presentations and pathology. Before a confirmed diagnosis, various other potential diseases need to be eliminated. Castleman disease, also known as angiofollicular lymph node hyperplasia, requires the exclusion of other diseases causing lymph node hyperplasia initially. These include malignant tumors (eg, lymphoma, plasmacytoma, and POEMS syndrome) [12], infectious diseases (eg, HIV, tuberculosis, syphilis, EB virus infection), and autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis). For examination of neck masses, ultrasound indicates clear boundaries, rich blood supply, and low echo. Different clinical types correspond to different CT presentations. CT plain scan indicates the mass has a uniform density and clear boundaries. Significant enhancement in enhanced scans suggests UCD. MRI exhibits uniform T1, slightly long T2 signals, with a typical feature of tortuously dilated blood vessels within or at the edge of the lesion [13,14]. Moreover, 18F-FDG-PET/CT is crucial in detecting swollen lymph nodes throughout the body, particularly for differentiating MCD [15].

**Treatment and Prognosis**

The treatment plan for Castleman disease depends on the clinical and pathological classification. For UCD, surgery is often the first choice, and if UCD can be completely removed, the prognosis is good, with a 10-year overall survival rate exceeding 95%. Postoperative recurrence is rare [3,4]. In contrast, for MCD, due to its extensive involvement, recurrence is common after surgery, making drug therapy (including chemotherapy and immunotherapy) the first choice. According to the literature [11,16], for those positive for HHV-8, the treatment protocol is based on rituximab (monoclonal anti-CD20 antibody). Treatment of idiopathic MCD includes rituximab±prednisone, the TCP regimen (thalidomide+cyclophosphamide+prednisone), the RCV regimen (rituximab+cyclophosphamide+vincristine), or rituximab±prednisone. For recurrent and refractory MCD, hematopoietic stem cell transplantation can be considered. In this study, the 3 patients were preliminarily diagnosed with neck masses in outpatient clinics based on their clinical manifestations. In adult otolaryngology clinics, patients presenting neck
masses often require the clinician to exclude nasopharyngeal cancer accompanied by cervical lymph node metastasis; hence, the need for nasopharyngoscopy to inspect the formation of any neoplasm in the pharyngeal recess. However, for children presenting with neck masses, given the extremely low incidence, nasopharyngeal cancer with cervical lymph node metastasis is not initially considered. In this study, all 3 patients had non-specific preoperative examination results. However, 1 was diagnosed as CD by postoperative pathology without any imaging examination. Preoperative examination can only clarify the scope of tumor invasion, which is an important reference for choosing the surgical method. In addition, for both children and adults, the decision of treatment depends on the pathology classification; for example, for UCD patients with different conditions the ultimate goal of treatment is to achieve a resectable mass. For MCD, the specific treatment method is still inconclusive and requires further research.

Conclusions

Although imaging and laboratory tests for CD are non-specific, they are essential to rule out other diseases and prepare for surgery. Castleman disease is relatively rare and easy to be misdiagnosed clinically, with multiple lymph node enlargement and even compression. In the diagnosis of CD, minimally invasive techniques such as ultrasound-guided lymph node biopsy (Tru-Cut) can be used before surgery. Finally, the appropriate treatment plan is selected according to the classification.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

7. Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008;112(10):3959-64
15. Han EJ, O JH, Jung SE, et al. FDG PET/CT findings of Castleman disease assessed by histologic subtypes and compared with laboratory findings. Diagnostics (Basel). 2020;10(12):998

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)