

Castleman's disease mimicking a parotid gland tumor: report of a case and review of the literature

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Abstract. – Castleman's disease (giant lymph node hyperplasia, angiofollicular hyperplasia, lymphoid hamartoma, benign giant lymphoma), is a quite rare and complex disease of lymphoid tissue that causes progressive lymph node enlargement, typically presenting as a solitary mediastinal mass. It was first described by Castleman et al in 1956. The head and neck regions are the second, less common site for this lesion. The preoperative diagnosis is very often extremely difficult and the routine investigations are often inconclusive. A multicentric extension of this disease shows poorer prognosis compared to the unifocal

Histologically, three types do exist: the hyaline-vascular type, the plasma cell type and the mixed type. The etiology and pathogenesis is still unclear. In the literature, to our knowledge, only 112 cases have been reported involving head and neck, and only 22, including our own, interesting the parotid gland. In this report we describe a rare singular of Castleman's disease presenting as a tumor of the inferior pole of the parotid gland extending in the submandibular region, in a 35-year-old woman. The patient undergone a surgical treatment and, therefore, the mass was successfully totally removed.

Key Words:

Castleman's disease, Angiofollicular hyperplasia, Benign giant lymphoma, Head and neck.

chronic antigenic stimulation, excessive production of interleukin-6 by the involved lymph node has been considered also, and there are several clinical observations that it may be also associated to chronic inflammatory process, viral infections as Epstein-Barr, Kaposi's sarcoma, Herpes Virus, immunological disturbance and neoplastic formation. The disease can have unicentric or multicentric locations and in most of cases is asymptomatic, or compressive symptoms can be described due to the size. The multicentric cases present with poly-lymphadenopathy and multi-organ involvement, therefore, is associated to systemic symptoms. Hystologically three different types have been described: the hyaline vascular type, the plasma cell type, and the mixed type. A plasmablastic variant, recently observed, is associated to Human herpes Virus 8 (HHV8) and Human Immunodeficiency Virus (HIV) and is extremely aggressive^{2,3}. The location of this disease within the parotid gland is very rare and very few cases have been reported to date. The diagnosis can be possible only by histological examination and the radiological exams are not exhaustive. The optimal treatment of the unicentric variant can be surgery alone, the multicentric variants, because of their heterogeneity and complex spectrum of disease, can be sometimes extremely difficult to treat.

Introduction

Castleman's disease is an uncommon benign lymphoproliferative disorder that is characterized by hypervascular lymphoid hyperplasia¹. The head and neck compartments represent the second site of location, being the mediastinum the most common region involved. Its etiopathology is still unknown, but some hypothesis have been suggested in recent years, it can be the result of a

Case Report

A 35-year-old woman with a swelling in the right submandibular lodge, was observed in our Department on February 2006. The patient had undergone a right superficial parotidectomy, with preservation of the facial nerve, in another Center on July 1987 because of a neof ormation of the parotid gland diagnosed as benign limphoepithelial tumor at histological sections. She had no

systemic symptoms but only a not aesthetical swelling in the right submandibular area and a scar of the previous surgery, a classic Redon parotid approach (Figure 1). Physical examination of the neck regions, showed that the mass was located in close proximity of the right submandibular gland. Its dimensions were 4 × 3 cm, and it was mobile and nonpulsatile, with a rubbery firm consistency and well defined borders. Computed Tomography of the neck confirmed the presence of a well-circumscribed ovoid mass, approximately 4 cm in maximum diameter, located in the inferior portion of the right parotid gland, and developing antero-inferiorly, in contact with the submandibular gland, mimicking a possible pleomorphic adenoma (Figures 2a, b). Fine-needle aspiration biopsy revealed a mixed population of lymphoid cells, a specific reactive hyperplasia, and no evidence of malignant cells. The patient underwent total excision of the tumor. In order to directly approach the lesion, the skin incision was performed in the submandibular region. The mass had developed in between the inferior pole of the parotid and submandibular glands, tightly adherent to, and arising from



Figure 1. Lateral view of the patient: the previous Redon scar is appreciable.

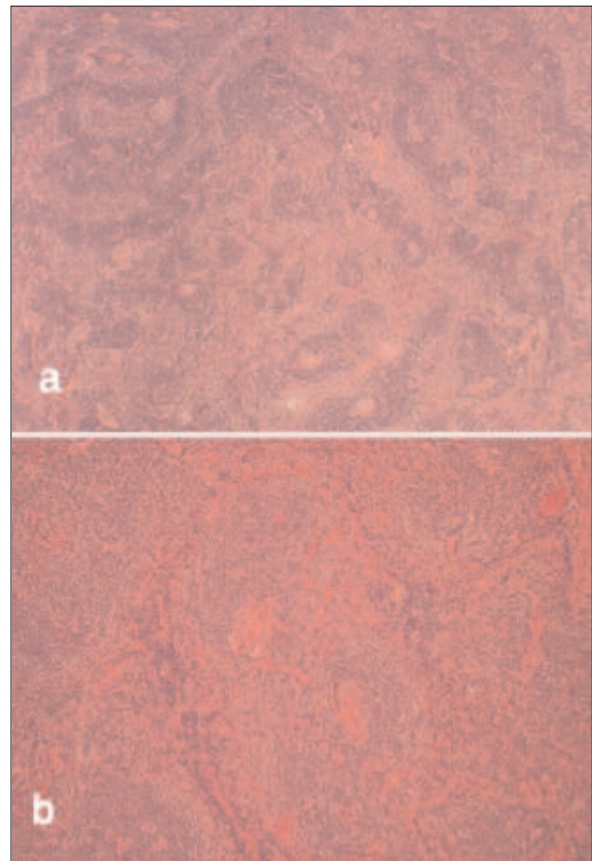


Figure 2. Preoperative CT of patient: **a**, The red arrow indicates the tumour mass; the black arrow indicates the submandibular gland. It is evident the space between the tumour and the gland. **b**, The red arrow shows the posterior and upper portion of the tumour mass in relationship with the parotid gland tissue.

the parenchyma of the parotid gland, without an evident cleavage plan, and in contact with the posterior pole of the submandibular gland, being clearly separated by a cleavage plan (Figures 3a, 3b). The histopathological examination was in favour of a hyaline vascular type of giant lymph node hyperplasia (Figures 4a, 4b). At a recent follow-up the patient is still disease free.

Discussion

Castleman's disease was first described by Castleman et al in 1956 in 13 cases involving a type of mediastinal mass, describing it as a localised mediastinal lymph node hyperplasia resembling thymoma¹. Until 2001 only 60 cases involving head and neck had been described⁴. After extensive review of the literature, to our

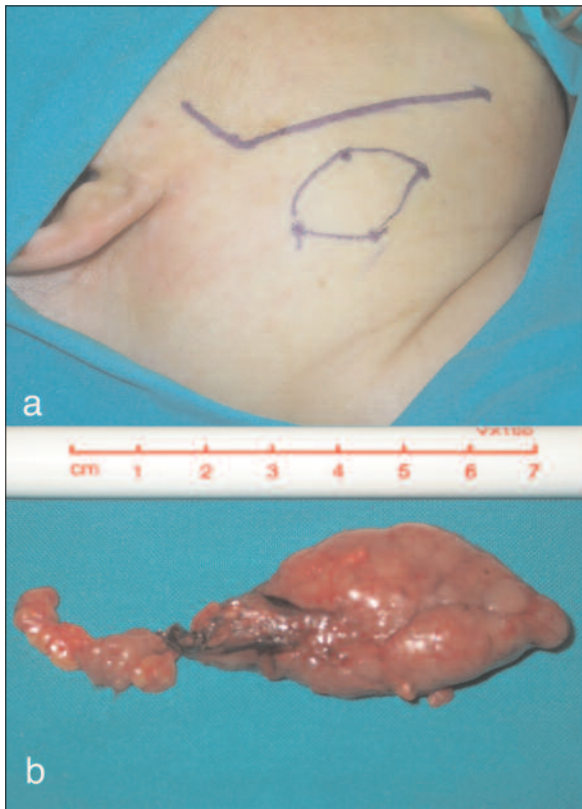


Figure 3. *a*, Skin marker painting the inferior border of the mandible and the tumour mass. *b*, Specimen: the removed mass measures 6 × 4 cm.

knowledge, 112 cases involving head and neck have been described to date in the pertinent literature^{1,4-33} and only 22 cases, including our own, involving the parotid gland^{4,21,25,31,32,34-44}. It can occur at any age but most of cases are adolescents and young adults between 15 and 35 years of age, with no sex predilection. The aetiology and the pathogenesis of Castleman's disease is poorly understood and remains to be established. It has been supposed that this disease can be the result of a chronic antigenic stimulation, possibly viral. An excessive production of interleukin-6 by the involved lymph node can be implicated in the pathogenesis of this disease, because of its hematopoietic and angiogenic effects. The disease usually arises as a solitary mass, commonly found in the mediastinum (60%), neck (14%), retroperitoneum (11%), or maxilla (4%)^{45,46}. Within the neck the Castleman's disease usually presents as an asymptomatic solitary mass located deep to the sternocleidomastoid muscle. In our case the lesion was located superficially, mimicking a parotid gland tumor.

The hyaline vascular type is the most common type of this disease (80-90%), and is characterised by large fibrous masses and proliferation of small hyalinized lymphoid follicles surrounded by a dense cellular matrix of small lymphoid cells with marked interfollicular vascular proliferation^{35,36,46}; small vessels in the perivascular area are mixed with intersperses areas of plasma cells; the vessels show hyalinisation of their walls and are surrounded by sheets of lymphocytes with an "onion skin" appearance.

Clinically this type presents as an asymptomatic enlarging mass. The plasma cell type occurs uncommonly and is histologically represented by sheets of mature plasma cells in the interfollicular tissue with small areas of hyaline^{17,20,36}. This type is very often associated to constitutional and systemic symptoms such as fatigue,

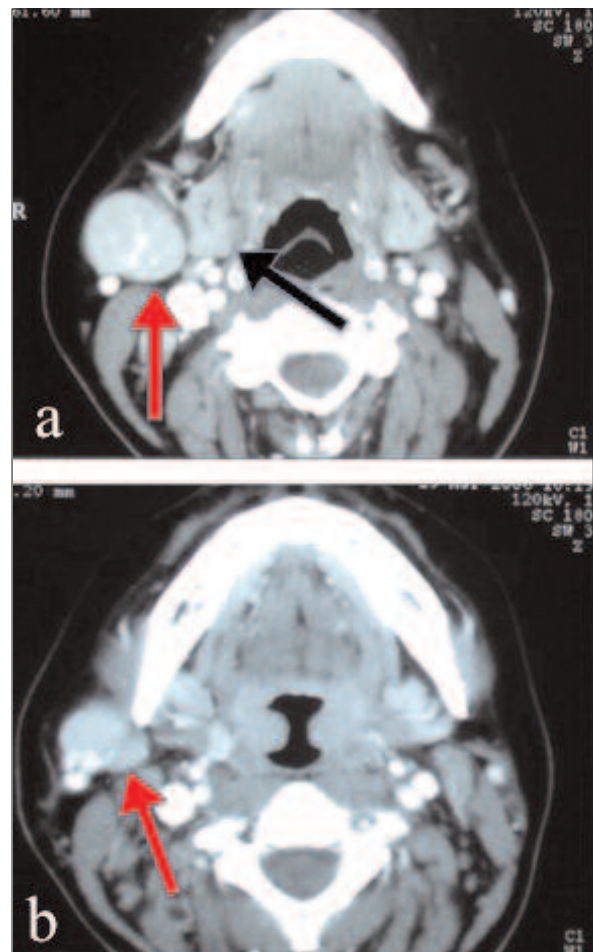


Figure 4. *a*, 20 × magnification: Castleman's disease associated with marked vascular proliferation in the interfollicular tissue. *b*, 40 ×: Higher magnification shows follicles often radially penetrated by a blood vessel (lollipop follicle)

sweats, systemic haematological abnormalities like anaemia, hypoalbuminaemia, hypergammaglobulinaemia, leukocytosis, elevated sedimentation rate, because this type can show polylimphadenopathy and multi-organ involvement. It may be associated to chronic inflammatory process, viral infections as Epstein-Barr, Kaposi's sarcoma, Herpes Virus, immunological disturbance and neoplastic formation. It has been hypothesized that the plasma cell type is the earlier, more active stage of the process and the hyaline vascular type represents the final phase²⁵. The mixed type is represented by elements of both the hyaline vascular and plasma cell types and could be an intermediate variant. Recently the plasma-blastic multicentric Castleman's disease variant has been classified, because of its aggressiveness and the constant association to Human Herpes Virus-8 (HHV-8) and Human Immunodeficiency Virus (HIV)^{2,3,14,47}. Clinically the disease can be classified as unicentric, if a single node or localized groups of nodes are involved, and there are no general symptoms or symptoms are due only to local compression, and multicentric, with involvement of several lymph-node stations and organs³². All the cases reported in the literature with parotid region involvement showed increasing swelling of the gland and no other general symptoms; only a case has been described with bilateral parotid involvement⁴². In our case it is interesting to note that the patient was operated on nineteen years before, because of a tumor of the parotid gland diagnosed as a lymphoepithelial tumor, obviously misdiagnosed and not correlated to Castleman's disease. The records of the patient describe the surgery as a total removal of the tumor; perhaps the previous surgery was not a real total removal, and we have not studied the postoperative CT because the patient lost it, or at time of the first surgery another lesion, located more inferiorly, was not identified or, moreover, our case is a recurrence. The hyaline vascular type, which is the most common type, usually present unicentrically and affects men and women equally, the median age is 40-50 years. The levels I, IV and V in the neck are more commonly involved, the parotid area and nasopharynx are extremely rarely involved. The plasma cell type is more commonly multicentric than unicentric. The less frequent unicentric variant of plasma cell type is associated with systemic symptoms and abnormal laboratory findings. The common symptoms are fever, night sweats, malaise, splenomegaly, anaemia, cytope-

nia, bone marrow plasmacytosis. The plasma cell type is considered to be a serious risk for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) and lymphoma. The multicentric variant is a systemic disease presenting with disseminated lymphadenopathy, hepatosplenomegaly, nephritic disease and constitutional symptoms^{34,48}. It is often associated to malignancies including Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma and POEMS syndrome. The prognosis is poor with a median range of survival between 14 and 30 months. The Human Herpes Virus-8 associated multicentric plasma cell variant, also called plasmablastic variant, a newly established subtype, is typical of immunodepressed individuals, especially HIV positive patients, is extremely aggressive, and the prognosis is very poor and the survival time of patients is some weeks⁴⁹.

The high grade of difficulty in the diagnosis is related to a paucity of signs and symptoms in the unicentric variants, and to the absence of diagnostic specific markers and to the ability of Castleman's disease to mimic other neoplasms of the head and neck, therefore the diagnosis is a real challenge. Giant lymph node hyperplasia can be confused with other neoplasms of the head and neck, such as branchial cleft cyst, hemangioma, lymphangioma, dermoid cyst, teratoma, thyroglossal duct cyst, thyroid pyramidal lobe, adenopathy, lipoma, lymphoma, sarcoma, metastatic nodes. Indeed Denenberg and Levine described Castleman's disease as "the lymphoma impostor"¹¹.

The laboratory tests can be helpful in the differential diagnosis but are always inconclusive. The computed tomography (CT) scans usually show a well circumscribed homogeneous soft tissue mass with variable contrast enhancement depending on the injection rate and volume of contrast media; the hyaline vascular type enhance more than the plasma cell type due to its greater vascularity. The CT is not diagnostic because other pathologies, such as lymphoma, tuberculosis, metastatic thyroid carcinoma, Kaposi's sarcoma, show the same features. Nevertheless, it has been recently suggested that the presence of a non-enhanced stellar scar within the center of the mass, due to dense fibrous tissue, could be a diagnostic clue²¹. On Magnetic Resonance (MR) Castleman's disease shows a linear hypointense signal in a stellate or arborizing pattern, especially on T2-weighted se-

quences, due to perivascular lamellar fibrosis or sinus histiocytes and radial fibrosis; these peculiar features have been considered an important diagnostic clue of this pathology²¹.

Surgical excision is the treatment of choice for this pathology in the head and neck with a 100% control rate for the hyaline vascular type, and because of the histopathologic examination, excision is both diagnostic and therapeutic with no recurrences in the unicentric variants. The multicentric disease is much more complex to treat; chemotherapy with cyclophosphamide and prednisolone and also radiotherapy have been suggested⁵⁰, but considering the rarity of the disease and the small number of cases described in the literature further studies are needed.

Conclusions

Castleman's disease is a heterogeneous disorder that can represent a continuous spectrum of disease or several different diseases all together; clinically it might be asymptomatic or could be lethal, the final diagnosis can be made by histopathological evaluation, therefore the treatment has to be surgery, that appears to be curative in local lesions; in inoperable or systemic variants the treatment is radiation therapy and chemotherapy.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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