Case Report

Castleman's disease

Himanshu Srivastava[1], Dulganti Santosh Reddy[1], Shreyas N Shah[2], Vandana Shah[2]

[1]Department of Oral and Maxillofacial Pathology and Microbiology, Aditya Dental College, Beed, Maharashtra, [2]Department of Oral and Maxillofacial Pathology and Microbiology, K.M. Shah Dental College and Hospital, Sumandeep Vidyapeeth, Vadodara, Gujarat, India

Abstract

Castleman's disease, a type of lymph node hyperplasia, usually occurs in the mediastinum and rarely presents in the cervical region as an asymptomatic solitary mass. Clinically, they are of two types-solitary and multi-centric. Most of the solitary types are asymptomatic with no associated symptoms, whereas the multi-centric type is associated with systemic symptoms and has a poor prognosis. Histologically, they can be classified as–Hyaline vascular, plasma cell, transitional and stromal rich type. We report a case of Castleman's disease involving the submandibular lymph node in a 75-year-old male patient whose definitive diagnosis was made only on histological examination. Isolated Castleman's disease of the submandibular node is rare and a thorough clinical and histological examination is necessary to rule out the systemic form of the disease and other diseases with manifestations as a cervical lymph node enlargement.

Keywords: Angiolymphoid hyperplasia, Castleman's disease, cervical lymphadenopathy

Address for correspondence: Dr. Himanshu Srivastava, Department of Oral and Maxillofacial Pathology and Microbiology, Aditya Dental College, Beed, Maharashtra, India.
E-mail: himanshu.srivastava97@gmail.com

Submitted: 03-Jul-2020, **Revised:** 01-Sep-2020, **Accepted:** 05-Sep-2020, **Published:** 09-Jan-2021

INTRODUCTION

Castleman's disease is an uncommon benign lymphoproliferative disorder characterized by hyper-vascular lymphoid hyperplasia. It has no sex predilection, and the age of presentation ranges from 5 years to 70 years.[1] It occurs in any area of the body where lymph nodes are found, such as mesentery, axilla, groin, lung, pelvis and the retroperitoneum.[2] It has also been reported in the tongue, palate, lymph nodes within parotid gland parenchyma,[3,4] and capsule. The mediastinum is the most common site of occurrence followed by head-neck region. Isolated Castleman's disease in the neck is rare. Sometimes, cervical lymph node enlargement may be the only clinical presentation of this disease.

Castleman's disease is usually limited to one site (solitary), or rarely may involve several sites (multi-centric). The solitary lesions are usually asymptomatic, and most often are discovered incidentally as an asymptomatic mass.[5] They become symptomatic when the adjacent structures are compressed by the enlarged lymph node. The multi-centric variant is widespread and aggressive and involves lymphadenopathy in several sites with splenomegaly. This variant is sometimes associated with human immunodeficiency virus (HIV) infection.[6] Furthermore, Kaposi sarcoma appears to have a significantly increased incidence in the multicentric form of Castleman's disease.[7]

Castleman's disease often presents a diagnostic challenge because of the paucity of signs and symptoms, and its tendency to mimic neoplasms. Patients present with an asymptomatic mass and rarely with vague systemic symptoms such as fatigue, fever and sweats. Diagnostic tests like complete blood count, blood chemistry,

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.JOMFP_283_20

How to cite this article: Srivastava H, Reddy DS, Shah SN, Shah V. Castleman's disease. J Oral Maxillofac Pathol 2020;24:593.

Mantoux test, chest X-ray and fine-needle aspiration cytology help to rule out other conditions like infections, tuberculous lymphadenopathy, metastatic lesions, salivary gland neoplasms, lymphoma, Kaposi sarcoma and Kimura disease. Definitive diagnosis is made only on histopathological examination.[4]

We herewith report a case of Castleman's disease in a 75-year-old patient involving sub-mandibular lymph node, for its rarity.

CASE REPORT

A 75-year-old male patient presented with a swelling in the left half of the lower jaw for the past 2 years. History reveals trauma in the lower jaw region 2½ years back.

On clinical examination, extra orally, there were two swellings in the sub-mandibular region positioned anteriorly and posteriorly. Anteriorly placed swelling measured about 3 cm × 4 cm firm and nontender, immobile with ill-defined margins and normal skin overlying it. Posteriorly placed swelling measured about 3 cm × 3 cm, nontender, and firm to hard in consistency. On systemic examination, there were no palpable axillary and inguinal lymph nodes. The intra-oral examination was noncontributory. A provisional diagnosis of nonspecific lymphadenopathy was made based on the clinical findings.

All routine clinical laboratory investigation, including Mantoux test and chest radiograph, were normal. Ultrasonographic examination of the abdomen was normal, and the submandibular region revealed two lymph nodes with internal echoes [Figure 1]. Anterior node was fixed and the posterior node was mobile with no evidence of increased vascularity. The ultra-sonographic findings were suggestive of chronic inflammatory pathology.

The nodes were surgically removed, and on histopathological examination showed varied features. The anteriorly placed submandibular node showed lymph node architecture with multiple lymphoid follicles of varying sizes [Figure 2]. The inter-follicular areas showed vascular proliferation and an absence of sinuses with a variable number of plasma cells and immunoblasts. Vessels with hyalinized walls and proliferating endothelial cells surrounded by concentric layers of lymphocytes (onion skin pattern) were seen [Figure 3]. The posteriorly placed submandibular node showed loss of lymph node architecture. Residual lymphoid aggregates were separated by thick bundles of collagen fibers. Small capillaries were seen both within the residual lymphoid aggregates and in the fibrous connective tissue [Figure 4].

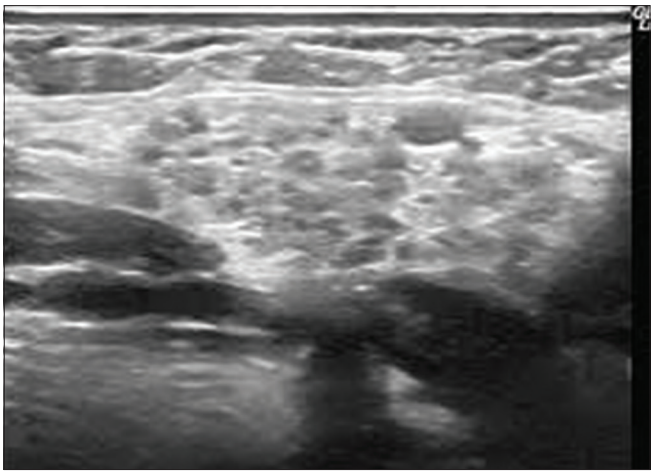

Figure 1: Ultrasonography pictures of the sub- mandibular region

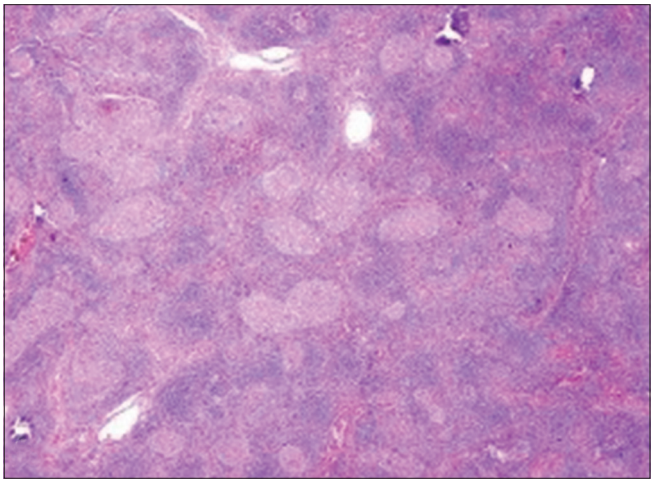

Figure 2: Microscopic appearance of the lymph node (H&E, ×40, original magnification)

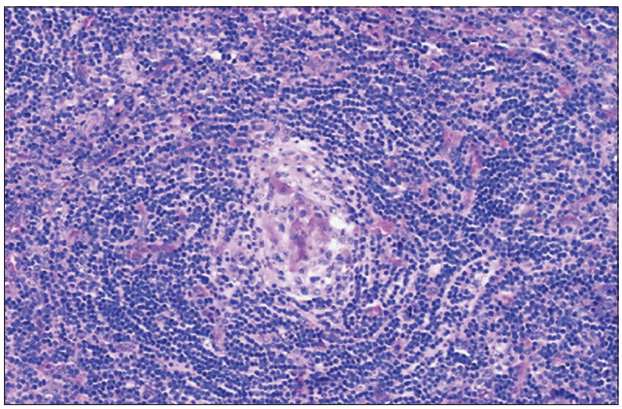

Figure 3: Vessels with hyalinized walls and proliferating endothelial cells surrounded by concentric layers of lymphocytes (onion skin pattern)

Based on the clinical and histopathological findings, the case was diagnosed as Castle man's disease.

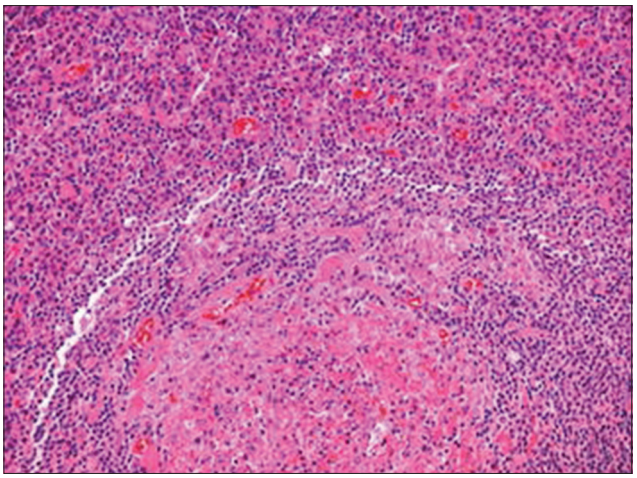

Figure 4: Small capillaries were seen both within the residual lymphoid aggregates and in the fibrous connective tissue

DISCUSSION

Benjamin Castle man and associates in 1954 described the condition as a benign reactive lymph node hyperplasia[8] and defined it as the distinct clinco-pathological entity under the title localized mediastinal lymphnode hyperplasia resembling thymoma. The condition had often been confused with thymoma not only because of the common mediastinum localization of the abnormal lymphoid tissue but because of the similarity of the altered germinal centers within the lymphoid aggregates to Hassall's corpuscles. It has been since known by different names including lymphoid hamartoma, benign giant cell lymphoma, giant lymph node hyperplasia and angio-follicular lymph node hyperplasia.[9] The pathogenesis of Castleman's disease is complex. Some speculate that this disease represents a reactive hyperplastic response to some antigenic stimulus (virus) while others consider it to be a lymphoid hamartoma. However, investigations have shown no evidence of any infectious disease.[10] The role of interleukin (IL-6) was suggested by the finding of increased IL-6 production by germinal centers in angio-follicular hyperplasia.[11] Serum IL-6 also appears to correlate with systemic manifestations of Castleman's disease.[12]

Clinically, this disease can be divided into two types, solitary and multi-centric. Ninety percent of the cases are localized type, usually affecting a single lymph node. Patients are usually asymptomatic unless the enlarged lymph node compresses adjacent structures. Only 3% of patients will have systemic manifestations such as fever, sweats, fatigue and abnormal hematologic findings such as anemia and hypergamma globulinemia. The multi-centric type is less common, affecting only 9% of cases and may manifest usually as lymph node enlargement. However, 50% of these patients have systemic manifestations such as fatigue, fever, splenomegaly and abnormal hematologic findings such as anemia, elevated erythrocyte sedimentation rate, leukocytosis, hypo-albuminemia and elevate alkaline phosphatase. Patients with multi-centric type have a progressive course, complicated by infection, Kaposi sarcoma or lymphoma[7,13] and HIV infection looms large in these patients. Epstein-Barr (EB) virus and Kaposi sarcoma attenuated human herpesvirus (HHV-8) has been demonstrated in many cases. In this type, death usually occurs by superadded infection due to severe immunosuppression.[14] In the present case, the patient had cervical lymphadenopathy without any systemic manifestations. All the clinical and laboratory investigations were within normal limits suggesting the solitary type of Castle man's disease.[15,16]

Histologically, Castleman's disease can be of 4 type, namely hyaline vascular type, plasma cell type, transitional type and stromal type.[17] The classic histological findings include hypo-cellular lymphoid follicles of varying sizes, atrophic germinal centers with eosinophilia material and small vessels. Mantle zone lymphocyte show characteristic material and small vessels. Mantle zone lymphocytes show characteristic concentric onion skinning around the atrophic germinal centers. Hyaline vascular type is the most common type and is characterized by abnormal small follicles and intermolecular vascularity, consisting of a network of small capillaries with thickened hyalinized walls radially penetration the germinal centers from the with thickened hyalinized walls radially penetrating the germinal centers from the per follicular tissue.[18] Plasma cell type id characterized by solid sheets of plasma cells in the intermolecular area. The follicles are usually larger and the prominent intermolecular capillary network characteristic of the hyaline vascular type is usually lacking in the plasma cell type.[19] Transitional type has intermediate histological features between hyaline vascular type and plasma cell type. The stromal rich type has enlarged intermolecular zones.[20]

Some degree of hyaline change of the fibrous connective tissue of the lymph nodes is usual in the lymph nodes of older people. Sclerosis or hyalinization is also a common finding following long-standing nonspecific low-grade inflammation and in association with certain neoplastic processes such as nodular sclerosing Hodgkin's disease.[21] Sometimes extensive hyalinization may affect greater part of the lymph node, converting it into a hard mass of tissue with no hint to the underlying cause. In some of these cases the general architectural pattern may still be preserved; in others, is the complete obliteration of lymph node structures with only a few lymphoid follicles

remaining together with a scattering of lymphocytes and few plasma cells.[22]

Interpretation of the histopathology and subtype distinction in CD should be performed in concert with the clinical presentation and evaluation of laboratory tests for inflammatory cytokines, especially IL6, and serologic and molecular tests for HHV8, HIV and other viruses, including EB virus and cytomegalovirus. Clinical and serologic exclusion of autoimmune disorders, connective tissue diseases, rheumatoid arthritis and other similar entities is required prior to attributing the morphologic changes to CD, especially in cases of multicentric CD.[23,24]

IL6 plays a central role in the pathophysiology of CD [Figure 5]. IL6 can form a heterodimer with the soluble IL6R a, which subsequently binds to the gp130 signaling complex at the cell surface, resulting in activation of the Janus kinase/signal transducer and activator of transcription signaling pathway.[25] Alternatively, IL6 binds to the IL6R a that is already bound to gp130. Serum IL6 levels in CD can be much higher than in any other disorder, including Hodgkin lymphoma, nonHodgkin lymphoma, rheumatoid syndromes and multiple myeloma.[26] Excess IL6 induces a pro-inflammatory syndrome that leads to severe constitutional symptoms, with the elevation of acute-phase reactants. IL6 also induces the secretion of VEGF, which can be found in the supernatant of cultured cells derived from CD lymph nodes.[27] Increased VEGF expression is present in the interfollicular areas of lymph nodes, and some patients have elevated systemic VEGF levels.[28] Excess VEGF explains the increased angiogenesis and vascularization that are present in CD lymph nodes.[29]

Autoimmune phenomena, such as cytopenias, are thought to arise due to IL6-induced immune dysregulation. IL6 is a potent growth and survival factor for B-lymphocytes and plasma cells, and it is at least partially responsible for lymph node hyperplasia in CD.[30]

Pathogenesis, by acting as a promoter of the terminal B-cell differentiation and by stimulation of plasma cell proliferation and production of immunglobulins [Figure 6].[24,31] Furthermore, by stimulating the production of acute-phase proteins, IL-6 is responsible for part of the clinical manifestations.[32] VEGF has been strongly related to the secretion of IL-6[2,33] and acts by promoting cellular survival and angiogenesis. The increased production of VEGF has been strongly related to the manifestations of POEMS syndrome.[22,34] HHV-8 uses the same signaling pathway, due to the presence of a human IL-6 mimic.[35]

In the present case, the node from the anterior submandibular region with concentric perivascular hyalinization represents hyaline vascular variant of Castle man's disease. The node from the posterior sub-mandibular region with loss of lymph node architecture and extensive fibrosis may be age related.

The histological differential diagnosis includes a range of lymphoid follicular proliferation like reactive follicular hyperplasia, follicular lymphomas, nodular sclerosing variant of Hodgkin's lymphoma[12] and HIV-associated lymphadenopathy. In reactive follicular hyperplasia, there is preservation of nodal architecture and follicles are prominently seen in the cortical portion of the lymph-node. The individual follicles show marked variation in size and shape and there is no infiltration of the capsule and peri-capsular fat. In follicular lymphomas, there is complete effacement of normal architecture with even distribution of follicles throughout cortex and medulla. The individual follicles show nil or moderate variation in size and there is marked infiltration of capsule and per capsular fat. In HIV associated lymphadenopathy,[18] the germinal centers

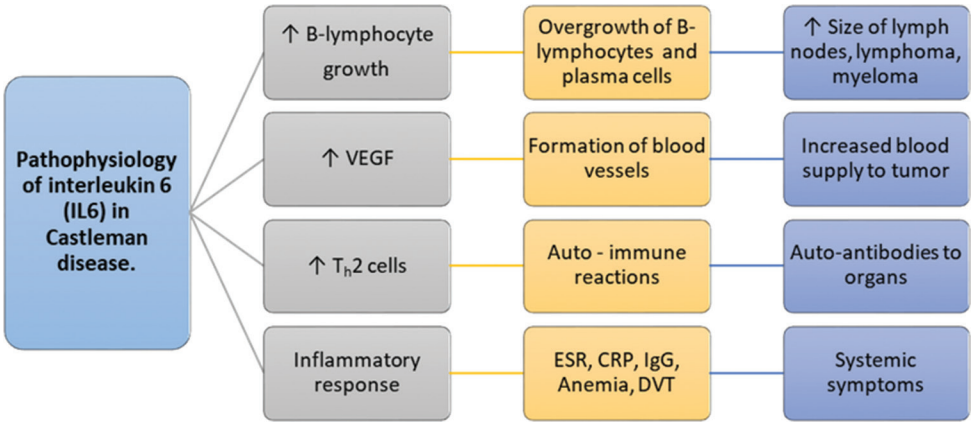

Figure 5: Pathophysiology of interleukin 6 in Castleman disease. Excess interleukin 6 in Castleman disease patients results in increased B-lymphocyte growth, lymph node vascularity and inflammatory response. Autoimmune phenomena may also be present

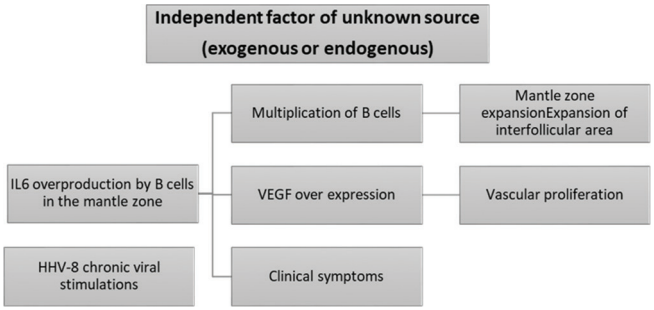

Figure 6: Schematic representation of the pathogenesis of the disease

are greatly expanded and bizarrely shaped with areas of hemorrhage and necrosis. In our present case, follicles were seen in cortical areas and are of varied sizes with no capsular invasion, thus ruling out follicular lymphoma. Negative Elisa ruled out HIV associated lymphadenopathy, thus ruling out the nodular sclerosing variant of Hodgkin's lymphoma.[36]

It is also speculated that the different histologic types represent different chronologic phases of the same disease resulting from changing host responses.[2] There is also conjecture that the plasma cell type represents a more active and aggressive phase of the disease and that the hyaline–vascular type represents a letter, more indolent stage. Correlating clinical and histological features, it is suggested that plasma cell type of Castleman's disease has a greater tendency to present as multiple rather than solitary neck masses[37] and is more likely to be associated with constitutional symptoms.[2,38]

Management of Castleman disease

There have been no published randomized clinical trials regarding the management of CD. Most of the literature is confined to small series or case reports, and it is difficult to make firm recommendations. The preferred management of unicentric CD is complete surgical excision, which is curative in approximately 95% of patients. Early interventions in the treatment of CD were iterations of standard therapy for lymphoproliferative diseases, including surgical excision, cytoreductive chemotherapy and radiation therapy [Figure 7].[39]

The treatment of choice for both the hyaline vascular and plasma cell type is surgical excision of the involved lymph nodes. Localized Castleman's disease has an excellent prognosis with surgical resection.[40] Generalized disease has a poor prognosis and requires chemotherapy and radiotherapy in addition to surgery though radiation therapy used in the past was not successful. Kaposi sarcoma and nonHodgkin's lymphoma appears to have significantly increased incidence in the metacentric from of Cattleman's

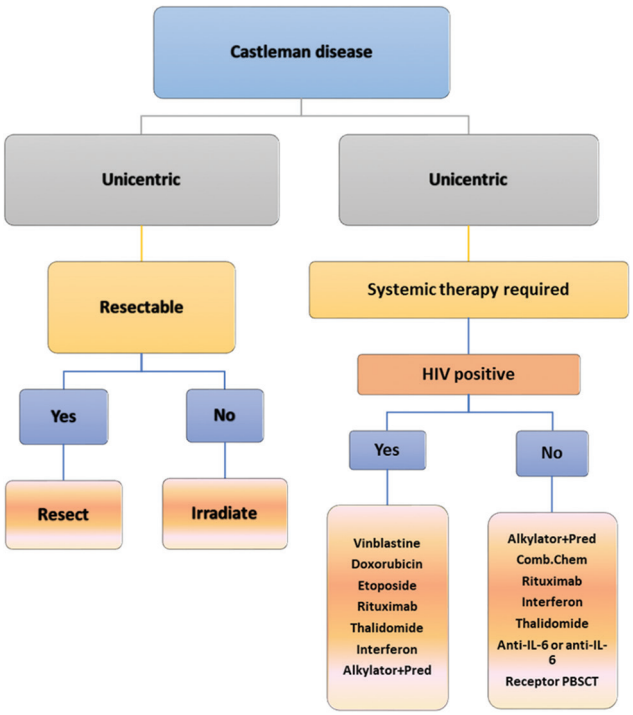

Figure 7: Schematic presentation of the treatment plan in Castleman disease. Pred: Prednisolone, Comb. Chem: Combined chemotherapy

disease.[41,42] Recurrences are rare in the hyaline vascular type though a study reported 12.5% recurrences in the hyaline vascular type[43] and follow-up is required in plasma cell type lesion.[44]

CONCLUSIONS

We presented Castleman disease cases, with emphasis on the clinical aspects, pathology findings used for the diagnosis. To the best knowledge it is the best case with CD presented so far in India, focused on the clinical-pathological findings. Our data are consistent with the ones presented in the literature. We strongly believe that by understanding the pathogenesis of the precursor lesions we will gain a better understanding of the pathways that lead to neoplasia and that Castleman disease is a very interesting "natural experiment" illustrating the progression from chronic antigen stimulation to reactive lymphoid hyperplasia and finally to overt lymphoid neoplasia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financials support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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