*Original Article*

# Onion Castle: A Rare Presentation in a Rare Case

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**Abstract:** Castleman's disease (CD) is an uncommon and heterogeneous lymphoproliferative condition that was first reported by Benjamin Castleman in the year 1956. It is also referred to as angiofollicular or giant lymph node hyperplasia. The cervical and abdominal regions are the next most common sites of involvement, after the mediastinum, which causes the most cases. Inflammatory and autoimmune states, as well as viral infections like human immunodeficiency virus (HIV) and human herpesvirus type 8 (HHV-8), are the primary contributors to the etiopathogenesis of the condition. Regardless of gender, the majority of individuals affected are between the ages of 30 and 50. The clinical presentation is not specific, and there are no biomarkers or definite radiological findings to support the diagnosis. According to the findings of a histology and immunohistochemistry research, the diagnosis is considered to be definitive. Castleman disease, also called angiofollicular lymph node hyperplasia encompasses several distinct lymphoproliferative disorders. It has two expansion types, namely unicentric and multicentric, which play a major role in determining therapy. It is a rare condition occurring in 1 in 100 000 patients and may occur in various locations but frequently occurs in the posterior mediastinum. It is uncommon in the pediatric population with no substantial reported percentage found in the submandibular area, thus a rare presentation in a rare case.

**Keywords:** Angiofollicular, Castleman Disease, Lymphoproliferative

## 1. INTRODUCTION

Castleman's disease (CD) is a rare and heterogeneous lymphoproliferative disorder described by Benjamin Castleman in 1956 [1], also known as angiofollicular or giant lymph node hyperplasia. The most prevalent site of involvement is the mediastinum, followed by the cervical and abdominal regions [2]. The etiopathogenesis is mainly related to inflammatory and autoimmune states, as well as viral infections such as human immunodeficiency virus (HIV) and human herpesvirus type 8 (HHV-8) [3]. It mainly affects patients aged between 30 and 50, regardless of gender. The clinical presentation is non-specific and there are no biomarkers or definitive radiological findings for the diagnosis, which is established by a histopathology and immunohistochemistry study [4]. CD is classified according to its distribution in the human body, manifesting as a localized (unicentric) or disseminated form, involving more than one anatomical site (multicentric). It is also divided by histological pattern into four main types: hyaline vascular, plasma cell, transitional type and stromal type [4,5]. The unicentric form typically manifests as isolated lymph node enlargement with no evident systemic symptoms, often diagnosed as an incidentaloma on imaging. On the other hand, the multicentric form is characterized by generalized lymph node growth, constitutional symptoms, anemia, thrombocytopenia, elevated PCR and visceromegaly, usually with a clinical course that is more aggressive [4,5]. The presentation as a localized retroperitoneal mass has several differential diagnoses with entities such as sarcoma, lipoma,

 

lymphoma and paraganglioma, all of which have variable prognosis [4-7]. 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, 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 [8]. In a case presenting as lymphadenopathy, although usually caused by benign conditions, it causes an alarm to clinicians to look for other serious conditions, and this is where strong support from pathologists will come to play. As of 2021, only one reported case of castleman disease was published in the Philippine literature. It is an uncommon lymphoproliferative disorder characterized by enlarged hyperplastic lymph nodes (s). It presents most commonly in the fourth decade of life with site predilection to the mediastinal area [1]. A more common yet more serious condition, lymphoma, share the same presentation as with Castleman. This is why a careful examination and cost efficient use of the ancillary tests are needed to pinpoint this mimicker. This is the journey of a 17 year old male in finding the truth hidden in an extraordinary castle.

## 2. CASE REPORT

A 17-year-old male student presented with a history of a slowly enlarging mass in his left submandibular area for 7 months which started as pustule. The patient was initially self-medicated with unrecalled topical ointment but with no relief of symptoms. 4 months prior to admission, patient underwent a neck ultrasound and was initially diagnosed with a second branchial cleft cyst. A fine needle biopsy was also done only revealing acute and chronic inflammation on smears. The mass persists with a notable gradual increase in size necessitating subsequent follow-up clinic visits. The painless swelling was gradually increasing in size. There was no history of constitutional symptoms like fever, weight loss and night sweats. There was no history of pain in the throat, dysphagia, dyspnea change of voice and exposure to tuberculosis either. General examination of the patient was normal. Neck examination showed a firm, nonwarm, non-tender, non-reducible swelling, in the submandibular region of neck on the left side measuring 6x5 cm in its greatest dimension which was freely mobile in all directions. There was no movement on deglutition or protrusion of tongue. There were no generalized lymphadenopathies, hepatomegaly or splenomegaly. All Hematological, Serological and Biochemical investigations were within normal limit. Fine needle aspiration cytology (FNAC) was advised by the clinicians and patient referred to cytopathology laboratory. FNAC was performed with all precautions after taking consent [5-11]. In the interim, He was generally asymptomatic with just occasional dysphagia and discomfort around the mass. His past medical and social history was unremarkable. Family history of breast cancer on his maternal grandmother was only reported. The physical examination revealed a 6x5 cm, solid, nontender, non- erythematous mass at the left submandibular area. The rest of the physical examination was unremarkable. A CT scan was done revealing a well-defined lesion in the left lateral neck anteromedial to the sternocleidomastoid and lateral to the jugular and carotid vessels compressing the internal jugular vein. It has a soft tissue density and homogenous post-contrast enhancement consistent with an enlarged lymph node. There are also small-sized to slightly enlarged lymph nodes seen in the rest of the neck on both sides, thus lymphoma was considered. Laboratory diagnosis revealed slight anemia with a hemoglobin of 128 g/L and an elevated creatinine of 1.31 mg/dl.An excisional biopsy revealed an ovoid, tan brown to dark brown rubbery tissue measuring 5x4x2 cm with a tan white homogenous soft cut surface. Microscopic evaluation revealed follicular hyperplasia with varying sizes and shape with the germinal centers showing mixed small and large lymphocytes. There is also “onion skinning” noted in the mantle cell layer. Because of this histomorphologic characteristics, a diagnosis of atypical lymphoid proliferation was made, in which

 

lymphoma particularly mantle cell lymphoma is still a differential. Immunohistochemical stains were suggested for a definitive diagnosis. Further evaluation revealed positivity in CD3 which stains T cells, CD20 for B cells, CD30 and PAX5 for immunoblasts, and BCL2 staining B cells in the mantle cell layer and T cells in the interfollicular areas. These immunohistochemical stain panels suggested a possible diagnosis of Castleman disease and rule out lymphoma. Another set of Immunohistochemical stains were requested which showed positivity in MUM1 confirming the diagnosis. The patient had an uneventful follow visits and now lives a normal teenage life, free from fears and anxiety.

## 3. CASE DISCUSSION

Castleman disease also called angiofollicular lymphoid hyperplasia, Giant lymph node hyperplasia, lymphoid hamartoma, and benign lymphoma was first described in 1956 in a group of patients with solitary hyperplastic mediastinal lymph nodes with small germinal center resembling hassle corpuscles of the thymus by Benjamin Cattleman. It is a rare lymphoproliferative disorder occurring in 1 out of 100 000 patients which can develop anywhere in the lymphatic system with a median age to be at 43 years and with a slight female predilection [9]. Castleman disease is divided into three classifications namely:

- Hyaline vascular, the most common at around 90%,
- Plasma cell group, which can be accompanied by systemic symptoms like fever, night sweat, and weight loss.
- Mixed variety.

All of these types can manifest clinically as either unicentric or in a multicentric pattern. The hyaline vascular type usually manifests as a unicentric involving a single site of lymph node commonly on the abdomen, peripheral lymph nodes, and mediastinum while the plasma cell type is multicentric with associated systemic manifestations that include, anemia, fever, hypergammaglobulinemia, hypoalbuminemia, and an association with a syndrome known as POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin pigmentation). The systemic symptoms are thought primarily caused by an elevated IL-6 [10].

### 3.1 Etiologies

Possible etiologies of Castleman disease include viral, autoimmune, and neoplastic processes. Familial cases have been reported although rare though genomic sequencing has not been performed to identify mutations [11].

### 3.2 Clinical and Histopathologic Features

Unicentric Castleman disease (UCD) presents as an enlarged lymph node and has features of hyaline-vascular variant. They exhibit follicular and interfollicular changes. The follicles may be increased in density but appear atretic. An “onion-like” appearance can be appreciated caused by concentrically arranged lymphocytes in the mantle zone with a zone of small, mature lymphocytes with condensed chromatin and minimal cytoplasm. In a unicentric hyaline-vascular variant, sinuses are absent [12]. In multicentric Castleman disease (MCD), it is characterized as diffuse lymphadenopathy or at minimum, lymphadenopathy that involves more than one lymph node region. There are two common patterns seen microscopically for multicentric CD, these are hypervascular and plasmacytic variants. The key difference between the multicentric hyaline variant from unicentric is the retention of nodal sinuses in the former. The plasmacytic variant is the most common variant seen in multicentric CD and is characterized by the prominence of interfollicular plasma cells with the lymph node as they present as sheets located between lymph node follicles. These patients also have systemic inflammatory symptoms

 

with generalized lymphadenopathy, hepatosplenomegaly, cytopenias, and organ dysfunction. Multicentric Castleman disease is further subclassified according to the presence of Human Herpes Virus-8

- HHV-8 associated MCD
- HHV-8 negative/idiopathic MCD

### 3.3 Laboratory Studies

Laboratory diagnosis is usually normal in patients with UCD. Some parameters that can be abnormal include elevated C - reactive protein, Anemia, Thrombocytopenia, hypoalbuminemia, renal dysfunction, and polyclonal hypergammaglobulinemia [13].

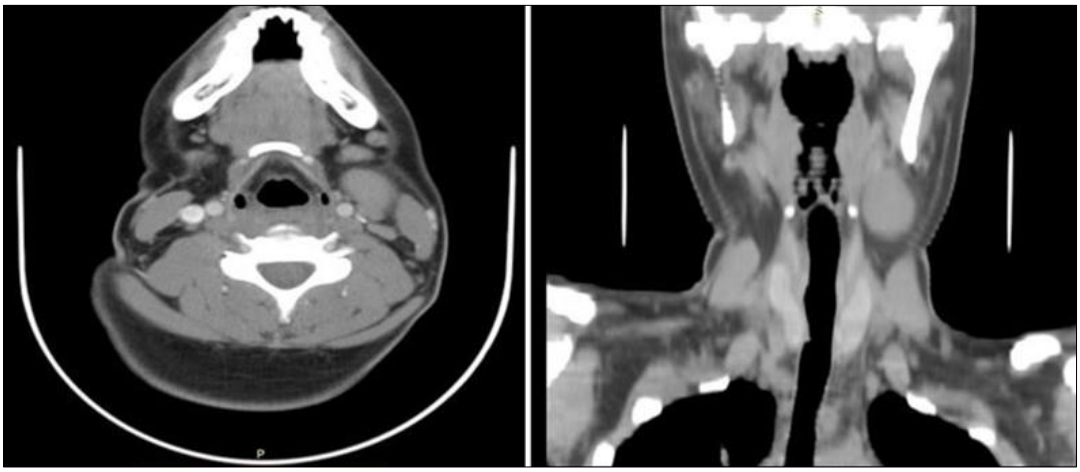

**Figure 01:** CT-Scan image showing a homogenous left submandibular mass

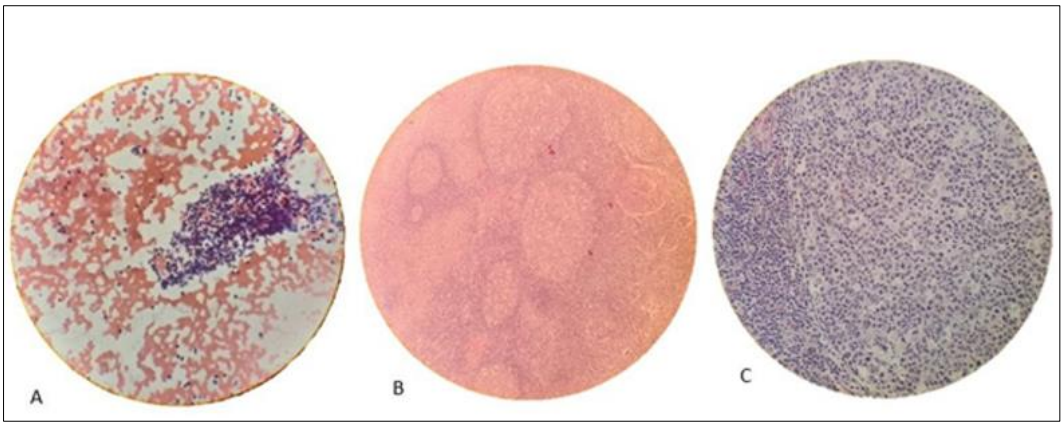


**Figure 02:** Photomicrographs of the submandibular mass. A) Fine needle Biopsy showing and chronic inflammatory cells. B) Low power shows lymph node replaced by follicles. C) High power shows a follicle consisting of small lymphocytes with suggestion of sclerotic center.

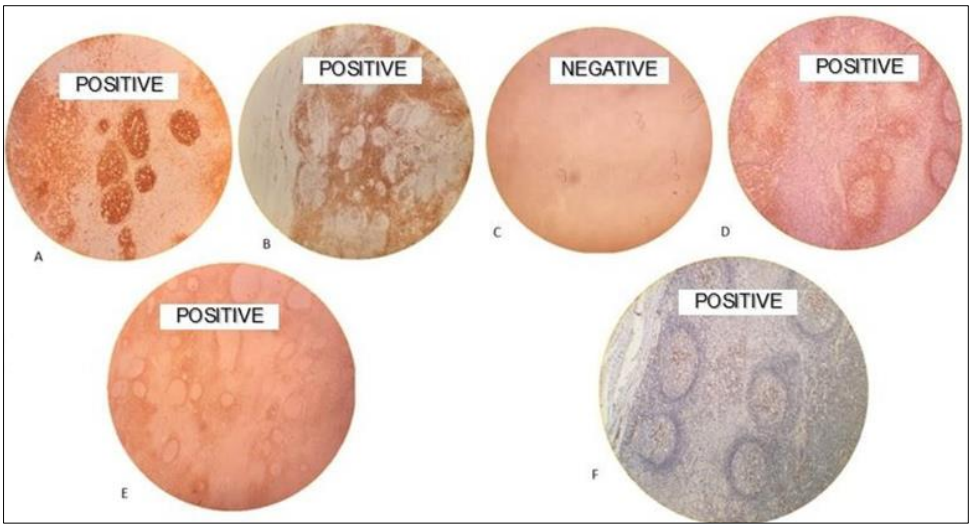


**Figure 03:** Immunohistochemical stain Reaction, A) CD20, B) CD3, C) CD30, D) PAX-5, E) BCL2, F) MUM1

## 4. MANAGEMENT

Unicentric and multicentric Castleman disease require a different therapeutic approach. Resection is the gold standard of treatment in unicentric disease while it is critical to distinguish patients with HHV-8 associated Multicentric Castleman from those negative [14]. Systemic therapies are required for the management of Multicentric Castleman disease. Rituximab monotherapy is the mainstay therapy; however, anti-Interleukin 6 agents are emerging. The management also requires careful attention to infections, concomitant malignancies, and associated syndromes.

## 5. SUMMARY

Castleman disease is a rare disorder that mimics other serious disease entities. It is still a diagnostic challenge and requires histopathologic evaluation. This case report represents an uncommon presentation of Castleman Disease, which may be misdiagnosed as lymphoma thus emphasizing the role of histopathological evaluation in avoiding costly medical workups and unnecessary treatments.

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