CASE REPORT

Castleman Disease: A Rare and Intriguing Malady: A Case Series

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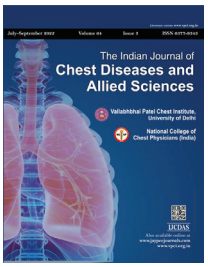

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Abstract

Castleman disease (CD), first described by Benjamin Castleman as angiofollicular mediastinal lymph–node hyperplasia, is a rare benign lymphoproliferative disorder with varied modes of presentation. Its common presentation within the mediastinum misleads the clinician and merits special attention since it is essentially a diagnosis of exclusion. We are sharing our experience with three patients, within a relatively short period of 2 years. All three presented with a mediastinal mass, however, each of them came with an entirely different clinical scenario and diagnosis. All three were successfully operated and Castleman disease [hyaline–vascular (HV) type] was diagnosed only after the final histopathology.

Keywords: Castleman disease, Hyaline vascular, Mediastinal mass, Unicentric.

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Abbreviation used in this Article

CD = Castleman disease; HV = Hyaline–vascular; UCD = Unicentric Castleman disease; MCD = Multicentric Castleman disease; HHV-8 = Human herpesvirus 8; POEMS = Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; iMCD = Idiopathic MCD; IgG4 = Immunoglobulin; CECT = Contrast-enhanced computed tomography; MRI = Magnetic resonance imaging; FDG–PET = Fluorodeoxyglucose–positron emission tomography; PET-CT = Positron emission tomography–computed tomography; FDG = Fluorodeoxyglucose; VATS = Video-assisted thoracic surgery.

Introduction

Castleman disease is an unusual non-malignant lymphoproliferative disorder that typically presents as mediastinal masses. It was first described by Castleman et al. as a localized mass of mediastinal lymphoid follicles in 1954. It is a disease with an estimated incidence of approximately 25 cases per million person-years.[1] Owing to the rarity of this disease and resemblances with the more common benign or malignant mediastinal tumors, it is mostly a diagnosis of exclusion. We report three patients with CD, encountered within just 2 years in our department, who presented to us in completely different clinical scenarios, and all three patients were successfully operated on. The challenges faced to reach the final diagnosis make each case unique and worth sharing.

Materials and Methods

The clinical data were collected from medical records of three patients (referred to as patient 1, 2, and 3 hereafter) who were diagnosed with unicentric Castleman disease (UCD) in 2019 and 2020 in our institute. The clinical presentation and working diagnosis in each of our cases were different (Table 1). Patient 1 (Fig. 1) and patient 2 (Fig. 2) came to our OPD with tissue diagnosis of adenocarcinoma and thymoma respectively, which was done elsewhere, while patient 3 (Fig. 3) was provisionally diagnosed as a neurogenic tumor based on imaging. The cases went through a formal multidisciplinary tumor board prior to planning for surgery. All three underwent necessary imaging for further characterization of the lesion and preoperative planning (Table 1). Patient 3 was reviewed by the neurosurgical team for the requirement of any possible intraoperative intervention, and the same was ruled out.

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Results

Surgical approaches were chosen after thorough review of imaging and each of them underwent complete excision (Table 1). Patient 1 experienced postoperative chylothorax which was managed with thoracoscopic chyle duct ligation. Patient 2 required conversion to median sternotomy. Histopathology and immunohistochemistry (performed on all three) confirmed the diagnosis of the HV variant of CD in all three patients (Figs 1 to 3).

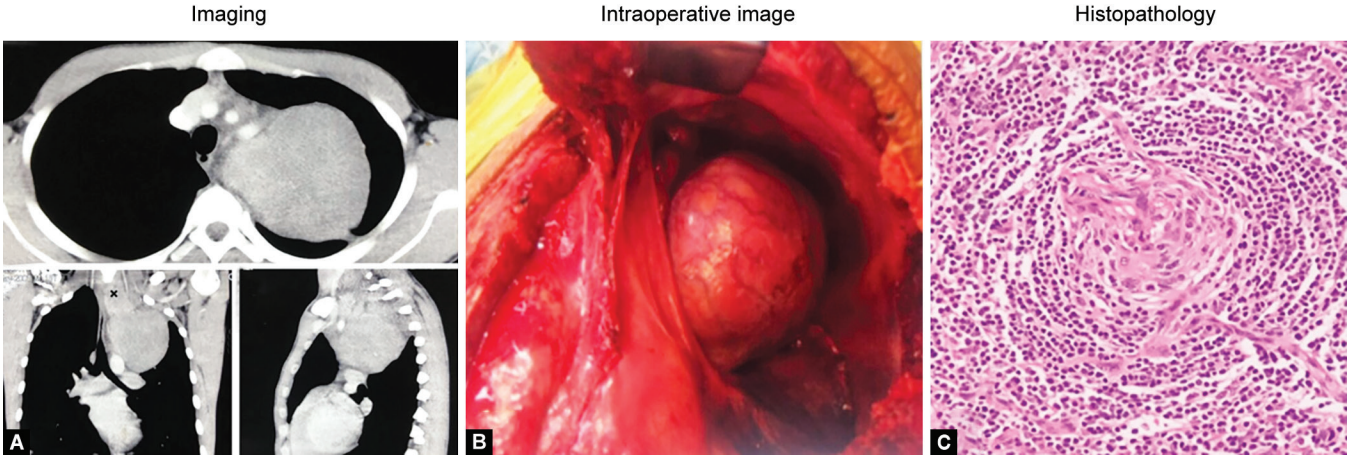
Discussion

The CD is a heterogeneous group of lymphoproliferative disorders with common histopathological features known for its ubiquitous presence in various anatomical locations. Clinically, it is classified into UCD involving a single region of lymph nodes, and multicentric Castleman disease (MCD) variety which involves multiple stations. Unicentric Castleman disease is more common than MCD and has

Table 1: Description of clinical, radiological, intraoperative and histopathological findings of each patient

	Patient 1	*Patient 2*	*Patient 3*
Age/Gender	19/Male	27/Male	47/Male
Symptom	Prolonged hoarseness; recurrent oral ulcers	Frontal chest pain; exertional dyspnea	Chest pain; palpitations
Clinical findings	Clubbing; mild bowing of left vocal cord; reduced left apical air entry	Unquantified weight loss; loss of appetite	Multiple subcutaneous swellings; uncontrolled; hypertension
Initial diagnosis	Adenocarcinoma (biopsy done and reported elsewhere)	Thymoma – confirmed on immunohistochemistry (biopsy done and reported elsewhere)	Suspicion of schwannoma vs neurogenic tumor vs pheochromocytoma (biopsy not done)
Imaging	PET–CT: Heterogeneous, mildly FDG-avid (Fig. 1)	MRI thorax: Well-defined, lesion T2 hyperintense. (Fig. 2)	MRI thorax: Well-defined lesion, mildly hyperintense on T2 and hypointense on T1 images (Fig. 3)
Size	9.2 cm × 9 cm × 10.0 cm	5.6 cm × 5 cm × 4.8 cm	5 cm × 5.5 cm × 5.6 cm
Location	Left superior paravertebral region, extending into the left supraclavicular region (Fig. 1)	Anterior mediastinum, anterior and left lateral to aortic arch (Fig. 2)	Left posterior mediastinal mass, extending from the level of D4–D7 vertebra (Fig. 3)
Additional imaging features	No significant mediastinal lymph node enlargement	Indentation upon the aortic arch and left second rib	Extension into the D6/D7 intervertebral foramen, with widened foramina
Approach	Left sternothoracotomy with supraclavicular extension	Uniportal VATS – Left chest approach; converted to median sternotomy	Uniportal VATS – Left chest approach
Intraoperative findings	Well-encapsulated mass (Fig. 1)	Well-encapsulated mass, firm to hard in consistency (Fig. 2)	Well-encapsulated mass firm in consistency (Fig. 3)
Intraoperative challenges	Closely associated with subclavian vessels on its superficial aspect and brachial plexus roots on its deeper aspect	Dense vascular adhesions to retrosternal area and difficulty in manipulation of mass which required conversion	Extension into widened intervertebral foramen of D6/D7. Dense adhesions to the descending aorta and left lower lobe (required parenchymal wedge resection)

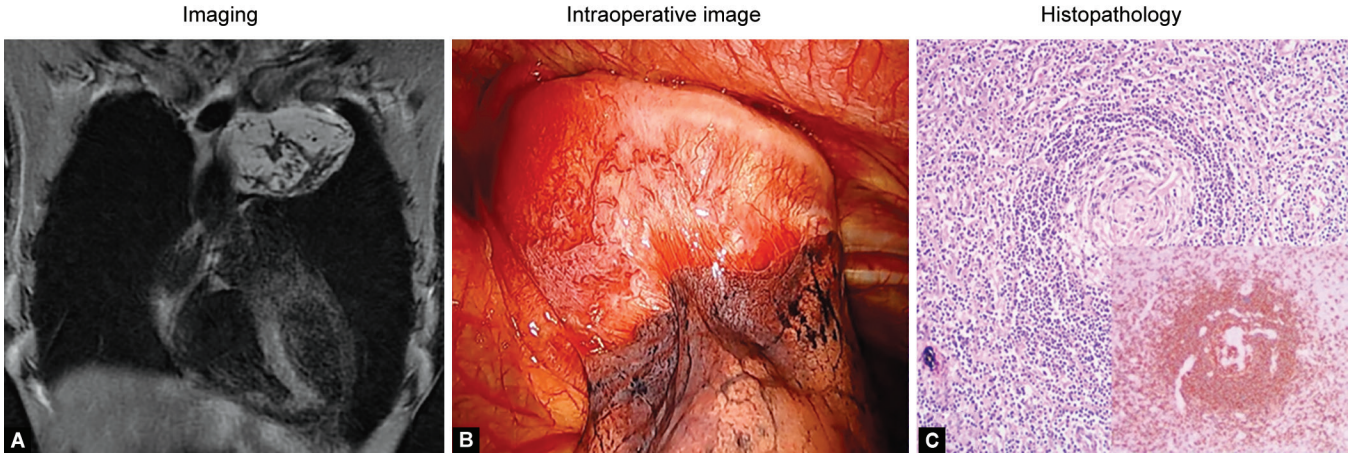
PET-CT, positron emission tomography–computerized tomography (fusion images); FDG, fluorodeoxyglucose – 18 (radiolabeled); MRI, magnetic resonance imaging; VATS, video-assisted thoracic surgery



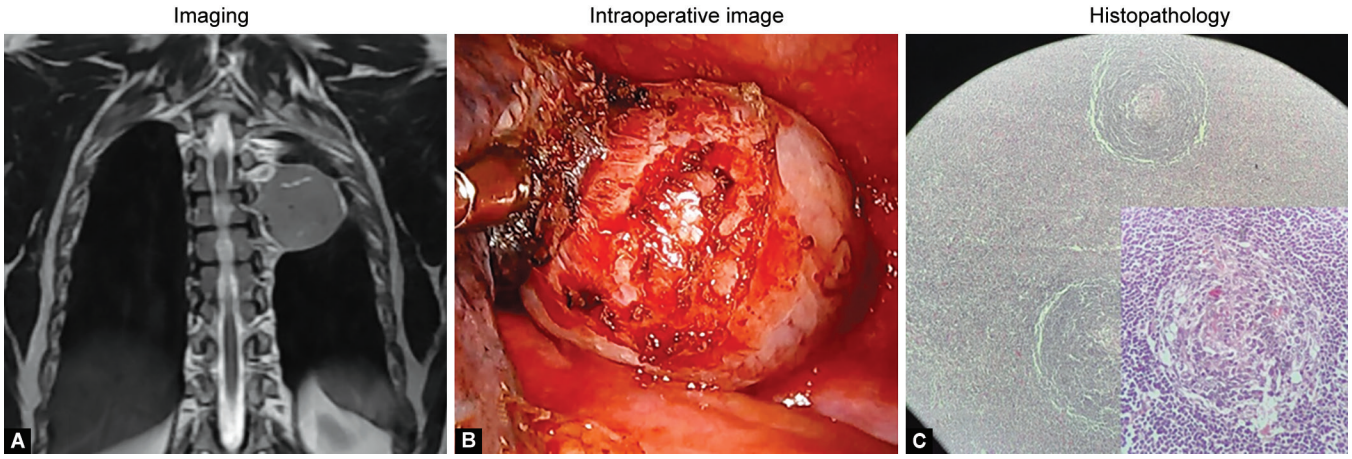
Figs 1A to C: Patient 1. (A) A CECT-chest image depicting the mass in the left posterosuperior mediastinum with extension into the neck (symbol "x" seen in the coronal section in the bottom left corner); (B) The mediastinal mass in the left posterosuperior mediastinum extending into the neck, in close proximity to the brachial plexus roots and left subclavian vessels; (C) Histopathological examination showed preserved lymph node architecture with a capsule, perivascular hyalinization

been reported in younger individuals, although both can occur in any age group.[1] Multicentric Castleman disease is further divided into the following three subgroups: Human herpesvirus 8 (HHV-8)-associated MCD; polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)-associated MCD; and idiopathic MCD (iMCD).[2]

The challenge lies in differentiating amongst these four subgroups while establishing the diagnosis, as there is a significant



Figs 2A to C: Patient 2. (A) The T2-weighted magnetic resonance imaging (T2W-MRI)—chest image depicting the mass in the anterior mediastinum with extension into left hemithorax, measuring 5.6 cm × 5 cm × 4.8 cm, located anterior and lateral to the aortic arch, causing indentation; (B) Intraoperative (left thoracoscopic view) showing a well-encapsulated mass with dense adhesions to the left lung on the posterolateral aspect and pericardium on its medial aspect; (C) Histopathological examination showed mantle zones are thickened with lymphocytes arranged in layers ("onion skin" appearance) with atretic germinal centers traversed by penetrating vessels ("lollipop follicles"), and (inset) cells took up immunostain for CD20



Figs 3A to C: Patient 3. (A) An MR-T2-weighted image shows a left paravertebral mass extending from T4–T7 level, measuring with a small component extending into left neural foramina at T6–T7 level; (B) Intraoperative (thoracoscopic view) of the lesion overlying the descending aorta and with adhesions to the lower lobe of left lung; (C) Histopathological microphotograph showed widely spaced follicular germinal centers and interfollicular vascular proliferation with (inset) perivascular hyalinization

overlap in clinical characteristics. The treatment options and prognosis vary for each of them. Furthermore, diseases such as lymphomas, immunoglobulin G4 (IgG4)-related disease, Kaposi's sarcoma, and various tumors show clinicopathological resemblance to CD.[2] Patients with UCD can be asymptomatic and are discovered incidentally on imaging for other medical conditions. Others may present with symptoms related to a "mass-effect" on surrounding structures. The most common location of UCD is the mediastinum, followed by the neck, abdomen, and retroperitoneum.[1] Mediastinal CD merits special attention due to the variable presentations and misleading diagnoses. Investigations commonly used to localize and characterize the disease are contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI). The argument against these imaging modalities is that they cannot differentiate between reactive hyperplasia and pathological nodal enlargement, nor can they differentiate from alternative diagnoses with similar presentations such as autoimmune, malignant, or infectious disorders.[3] Fluorodeoxyglucose–positron emission tomography (FDG–PET) has the joint functionality of defining the lesion, the extent of the disease (staging), other involved lymph nodes, as well as detecting their metabolic activity, especially if they otherwise appear normal in size on CT or MRI. It also assists in definitive diagnosis by targeting the active lymph nodes for biopsy. Its role in monitoring response to treatment has been found to be promising in several series.[4]

Tissue diagnosis with histological confirmation forms the basis for a definitive diagnosis. The histopathologic classification distinguishes CD into HV, plasma cell, and mixed types.[5] Also, FNAC can give an insight, but complete excisional biopsy alone provides the final confirmation. Unicentric Castleman disease commonly shows HV (~90%) pathology, while only a few demonstrate plasma cell picture (~10%). The HV variant is characterized by hyalinized atretic follicles with lymphodepletion and relative hypervascularity. The concentrically arranged mantle-zone cells and penetrating vessels impart an "onion-skin" and "lollipop" appearance, respectively.[5]

Unicentric Castleman disease can present in various clinical scenarios and can have misleading alternative diagnoses. They may be occasionally associated with disorders such as paraneoplastic pemphigus, lymphomas, and follicular dendritic cell sarcoma.[6]

Reports on treatment for UCD are limited to case reports and small case series. In a systematic review of a large cohort of 404 published cases, Talat et al. studied the role of surgery in CD beyond diagnosis. For a unifocal lesion, complete resection remains the gold standard, as it provides both diagnostic confirmation and is curative. If complete resection is not possible, debulking can be considered to reduce local symptoms.[7] It eliminates any associated systemic symptoms and achieves complete control in conditions such as pemphigus.[7] The associated residual smaller "satellite" lymph nodes may involute after surgery.[8] The CD lesions are known to be hypervascular and embolization might have a role as a preoperative procedure.[9] Interestingly, the following two "grey zones" exist in UCD: Patients with oligocentric CD and those with plasma cell variants; the latter behaves more like MCD, which influences the choice between treatment options. For these patients, complete surgical resection may be mutilating, and especially in asymptomatic patients, a wait-and-watch policy can be adopted.[10] In a retrospective study of 71 cases of UCD, medical reduction therapy with agents such as rituximab, cyclophosphamide, or tocilizumab, either as a stand-alone treatment or in preparation for surgery showed a response rate of around 50%.[10] The role of radiotherapy is mainly limited to inoperable or residual lesions; however, the ability to achieve complete resolution solely with radiotherapy has been reported in less than half of the patients.[11] Recurrence after complete surgical resection is exceedingly rare and it was reported in one case of mediastinal UCD 14 years after complete resection.[12]

Conclusion

The present series highlights the diagnostic dilemma caused by the same pathology, wherein all three patients, encountered within a relatively short span of two years, presented with a different initial clinicoradiological picture, and only after surgical resection the final histopathology revealed this rare entity. Hence, a high index of suspicion is paramount; only a complete resection is the most definitive therapy and a histopathological study of the entire lesion can confirm the diagnosis. Adjuvant radiotherapy or chemotherapy has a role only in limited cases. Thorough radiological imaging is necessary, if not done preoperatively, to confirm the extent of the disease and also to follow up for recurrences.

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