

## Original Research Article

## Castleman Disease: A Clinicopathological Analysis of 18 Cases

Namrata Rao<sup>1</sup>, Varun Kumar Singh<sup>2</sup>, Pavithra P<sup>3</sup>, Rashmi Shetty<sup>4</sup>, Nikitha Valerina Kairanna<sup>5</sup>

<sup>1,2,4</sup>Assistant Professor, <sup>3</sup>Associate Professor, Department of Pathology, Melaka Manipal Medical College, Manipal 576104, Karnataka, India. <sup>5</sup>Assistant Professor, Department of Pathology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India.

**Corresponding Author:**

**Pavithra P**, Associate Professor, Department of Pathology, Melaka Manipal Medical College, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India.

E-mail: pavithra.p@manipal.edu

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**Abstract**

**Introduction:** Castleman disease (CD) is a benign uncommon lymphoproliferative disorder requiring a high index of suspicion. Based on the clinical features and lymph node involvement, they can be categorized into unicentric (UCD) and multicentric (MCD) types. The rarity of this entity and infrequency of diagnosis accounts for the incomplete knowledge of this disease.

**Materials and Methods:** This is a retrospective eight year study conducted in the department of pathology, cases of CD reported on histopathology were retrieved. The age, sex, clinical features site involved and the histopathological type, laboratory findings was noted and analysed.

**Results:** Eighteen cases of CD were reported on histopathology over a period of 8 years. Majority were adults in the age group 30-50 years. There was no sex predilection. Majority of the patients (77.7%) showed features of UCD and four cases showed features of MCD. Most of these patients were asymptomatic and presented with painless lymph node enlargement. Patients with MCD had anaemia, hypoalbuminaemia and raised ESR levels. The commonest site of involvement was cervical lymph node. Among the cases of CD, 14 cases were of hyaline vascular type, 2 cases were of plasma cell type and 2 cases were of mixed type.

**Conclusion:** CD is a rare entity with a wide spectrum of benign and malignant mimics. Since the presentation is non-specific and CD is usually not suspected clinically, histopathology is the gold standard for diagnosis.

**Keywords:** Castleman; Hyaline-Vascular; Multicentric, Plasma-cell; Unicentric.

**Introduction**

Castleman disease (CD) is a benign uncommon lymphoproliferative disorder requiring a high index of suspicion. CD is also referred to as angiofollicular hyperplasia and giant lymph node hyperplasia.<sup>1</sup> Based on the clinical features and lymph node involvement, they can be categorized into unicentric (UCD) and multicentric (MCD) types, with multicentric having systemic involvement.

On histopathology the three types include-hyaline vascular type (HV), plasma cell type and mixed type. The rarity of this entity and infrequency of diagnosis accounts for the incomplete knowledge of this disease. Hence information regarding this lesion is limited to case studies and reviews of literature. The age distribution, sex predilection, site of involvement and histopathological features are discussed in detail in order to provide clarity of a lesser explored entity.



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**Materials and Methods**

This is a retrospective eight-year study conducted in the department of pathology of a tertiary hospital. Cases of CD reported on histopathology in the previous eight years were retrieved from the laboratory information system. All histopathology slides were stained with Haematoxylin and Eosin. The age, sex, clinical features, site involved and the histopathological type was noted and analysed. The laboratory findings such as hemoglobin, ESR, albumin levels, gamma globulin levels, LDH were analysed in the cases for which the data was available.

*Inclusion criteria:* Cases of CD reported on histopathology

*Exclusion criteria:* Other neoplastic and non-neoplastic lesions of the lymph node.

**Results**

Eighteen cases of CD were reported on histopathology over a period of 8 years. The age distribution of the above cases is shown in Fig. 1A. Majority were adults in the age group 30-50 years. There was no gender predilection with 9 cases of each.

In this study, majority of the patients (77.7%) showed features of UCD and four cases showed features of MCD. Most of these patients were asymptomatic and presented with painless lymph node enlargement. Three patients having omental, retroperitoneal and mesenteric mass presented with pain abdomen. Two other cases having mesenteric and retroperitoneal mass were detected incidentally during radiological examination. Patient with mediastinal mass presented with chest pain and breathlessness. The site of involvement of

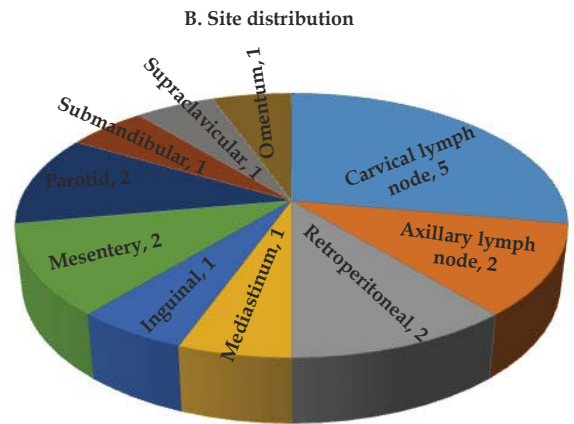
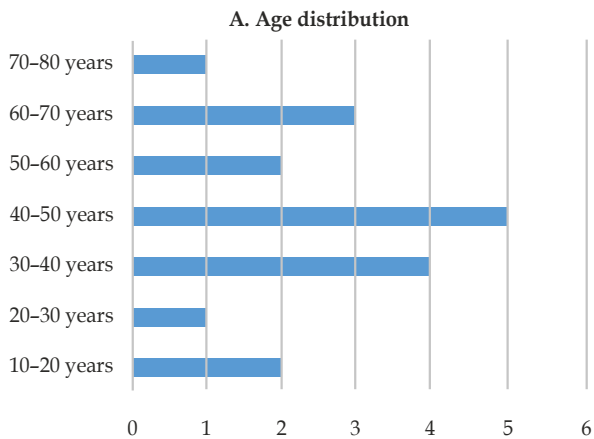
all cases of CD is shown in Fig. 1B. The commonest site of involvement was cervical lymph node. Pre-operatively CD was not suspected in any of the cases.

On gross examination, all the lesions had a tan cut surface devoid of hemorrhage and necrosis. Among the cases of CD, 14 cases were of hyaline vascular type, two cases were of plasma cell type and two cases were of mixed type. Hyaline vascular CD predominantly showed vascular proliferation and hyalinization, atretic germinal centers with penetrating vessels and onion skinning of mantle zone (lollipop follicles), and frequent twinning of germinal centers (Fig. 2). Plasma cell CD shows hyperplastic follicles with inter-follicular sheets of mature plasma cells (Fig. 3). A mixed type shows a pattern comprising of varying proportions of the former two. The site of involvement of mixed type was submandibular lymph node and cervical lymph node. Plasma cell type was seen in inguinal lymph node and as a mass in the mesentery. Both the patients with plasma cell type were negative for retroviral disease.

Comparison of features of UCD and MCD in shown in Table 1. Details of the four MCD cases are summarized in Table 2.

**Table 1:** Comparison of UCD and MCD.

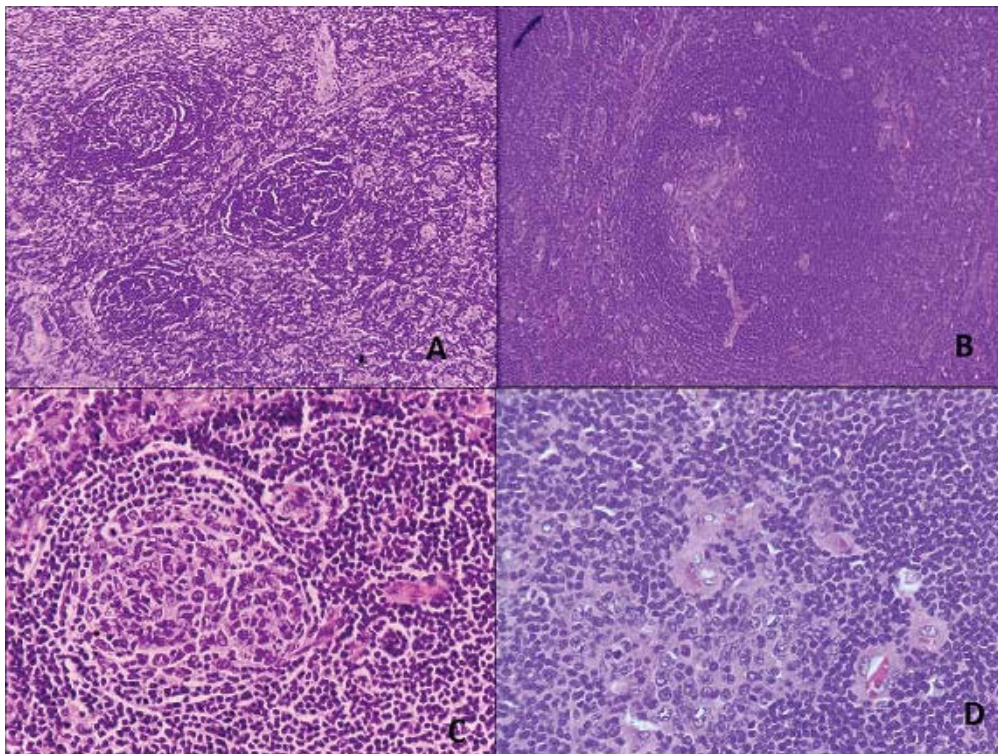
	UCD	MCD
Number of cases	14	4
Age (in years)	Median age 42	Median age 47
Sex	6-male 9-female	4-male
ESR	Normal	Increased
Haemoglobin	Normal	Low (4-8g/dl)
HIV status	Negative	Positive in 1 case
Histological type	Hyaline vascular	11
	Plasma cell type	1
	Mixed	2
		3
		1
		0



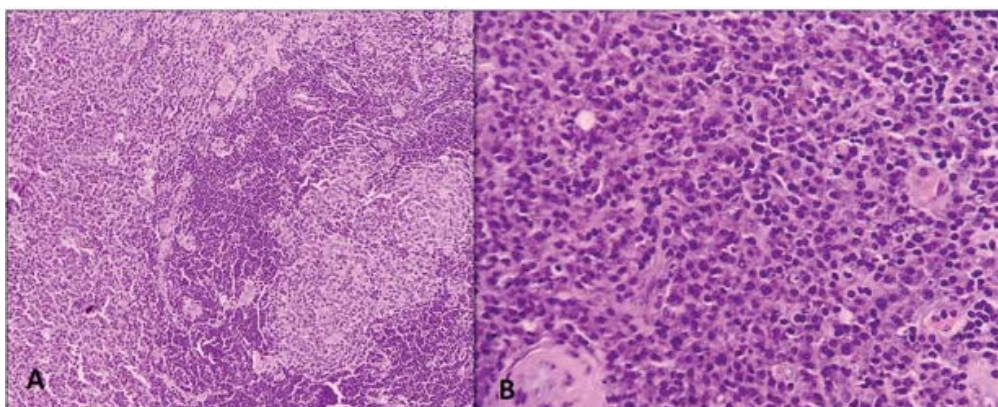
**Fig. 1.** Age and Site distribution of Castleman disease.

**Table 2:** Details of cases of MCD.

MCD	Age (in years)	ESR mm/hour	Hemoglobin g/dl	S. Albumin	HIV Status	Histopathological Type	Site of Lymph Node Biopsy	Other Associated Features
Case 1	48	80	6.5	2.8	+	Hyaline vascular	Cervical	Hepatosplenomegaly, pancytopenia, fever
Case 2	66	64	7.3	3.0	-	Hyaline vascular	Axillary	Myeloproliferative neoplasm, hypergammaglobulinemia
Case 3	46	100	9.7	2.9	-	Hyaline vascular	Supraclavicular	Plasmacytoma with multiple lymph node enlargement
Case 4	45	>140	4.8	3.2	-	Plasma cell	Inguinal	Cold agglutinins and presence of multiple lymph nodes



**Fig. 2:** Hyaline vascular type CD with interfollicular vascular proliferation (A, H&E, 50x), follicles with atretic centres, onion skinning of mantle zone lymphocytes and traversing vessels (B, H&E, 50x). Fusion of mantle zones forming follicles with more than one germinal centers (C, H&E, 100x) and vascular proliferation with prominent perivascular hyalinisation (D, H&E, 200x).



**Fig. 3:** Plasma cell type CD shows a preserved lymph node architecture with hyperplastic germinal centres in the lymphoid follicles (A, H&E, 100x) with mature plasma cell proliferation in the inter-follicular region (B, H&E, 200x). The Plasma cells are generally polytypic.

## Discussion

CD was first described by Dr. Castleman in 1956 which was retroperitoneal in location.<sup>2</sup> Similar lesions are described in other locations. Mediastinum (60%), retroperitoneum (11%), and axilla (4 %) are the sites commonly involved.<sup>1</sup> In this study the most common site was cervical lymph node with 5 cases followed by axillary lymph node, retroperitoneum, mesentery and parotid with 2 cases each. One case of castleman in mediastinum was reported. The patients can be asymptomatic or can present with systemic symptoms like fever, anorexia, weight loss, night sweats and cytopenias. The lesions can be unicentric/multicentric and can be nodal/extranodal (multiorgan involvement). Unicentric castleman disease usually affect young adults and present with solitary lesion while multicentric ones affect elderly and present with multiple lesions associated with systemic symptoms. MCD cases associated with HIV, HHV8 infections have an aggressive clinical course. Patients with multicentric lesions have the following laboratory abnormalities-anemia, decreased albumin, hypergammaglobulinemia, elevated erythrocyte sedimentation rate, interleukin (IL)-6, and C-reactive protein.<sup>3</sup> CD commonly involves adults less than 30 years with no sex predilection.<sup>4,5</sup> In this study it is seen involving all the age groups with maximum number of cases between 40-50 years of age indicating that castleman can affect any age group. There was no sex predilection with male: female ratio being 1:1. Patients affected by MCD were elderly as compared to those having UCD. Majority of patients with UCD presented with painless enlargement of lymph node. However patients with MCD had other associated features as shown in Table 4. In addition these patients had low hemoglobin, raised ESR and low albumin levels. These findings are consistent with the findings seen in the previous studies.

Microscopically CD can be of three types-hyaline vascular type, plasma cell type and mixed type with hyaline vascular type accounting for over 90% of cases.<sup>6</sup> Hyaline vascular type is characterized by hyalinization of vascular wall with vascular proliferation. Hyalinised vessels are seen traversing the germinal center of the lymphoid follicle. The mantle zones are thickened with concentric arrangement of lymphocytes also referred to as onion skin arrangement. Fusion of mantle zones may be seen. Hyalinised vascular proliferation is seen in the interfollicular areas. Proliferation of dysplastic follicular dendritic cells

may be seen in the germinal center in few cases, the significance of which, in the pathogenesis of CD remains unknown.<sup>1,7</sup> This finding was seen in one case, in the present study. The plasma cell type is characterized by sheets of plasma cells between the reactive follicles.<sup>8</sup> Mixed type of CD have overlapping features of hyaline vascular type and plasma cell type. In this study, the characteristic histopathological features was observed in all the cases as described above. Hyaline vascular type commonly present as solitary/unicentric lesions and plasma cell type usually is multicentric involving HIV positive individuals. However deviations is both the cases has been observed. In the present study majority of the patients of UCD (78.5%) and MCD (75%) had hyaline vascular type of CD and HIV positive status was seen in only one patient with MCD.

The differential diagnosis of CD can include neoplastic and non-neoplastic conditions. Importance lies in excluding the other differentials before considering a diagnosis of CD. The differential diagnosis to be considered based on microscopic pattern is listed in Table 3.<sup>9</sup>

The aetiopathogenesis of CD is unclear, although it is believed to be due to defects in immunoregulation. In HIV positive patients having plasma cell type CD, HHV-8 causes upregulation of viral IL-6 and VEGF causing CD.<sup>3</sup> However in HIV negative individuals it is believed then certain unknown factors cause increase in the level of IL-6 with causes lymphovascular proliferation and inflammatory effects. The IL-6 stimulates the liver to produce hepcidin which inhibits iron absorption resulting in anaemia of chronic disease.<sup>10,11</sup>

The mode of treatment for unicentric lesions is complete surgical resection. In cases of incomplete

**Table 3:** Differential diagnosis of CD.

Microscopic feature	Differential diagnosis
<b>Hyaline vascular type</b>	
Prominent nodular pattern	Follicular lymphoma
Conspicuous mantle zone	Mantle hyperplasia, mantle cell lymphoma
Prominence of dendritic cells	Autoimmune disease, Kikuchi lymphadenitis
Hyalinisation/hypervascularity	Thymoma, rheumatoid arthritis
<b>Plasma cell type</b>	
Plasma cells between follicles	Plasmablastic lymphoma, Plasmacytoma, Lymphoplasmacytic lymphoma
Hyperplasia of follicles	Follicular lymphoma, Reactive lymphadenitis

resection, radiotherapy can be given. Multicentric lesion require a combination of chemotherapy and steroids.<sup>12</sup> According to a study done by Zhang et al, independent factors which determine prognosis include hypoalbuminaemia, splenomegaly and older age. It is therefore vital to completely evaluate the patient with MCD for laboratory abnormalities.

### Conclusion

CD is a rare entity with a wide spectrum of benign and malignant mimics. Since the presentation is non-specific and CD is usually not suspected clinically, histopathology is the gold standard for diagnosis. Importance lies in identifying these subtle microscopic features, in order to avoid a misdiagnosis.

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