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Original Research Paper

Pathology

RETROSPECTIVE STUDY OF CASTLEMAN DISEASE IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Castleman Disease (CD) is a rare, heterogeneous group of lymphoproliferative disorders. Unicentric Castleman Disease (UCCD) is a localized disease, with little or no systemic symptoms. It may be an incidental radiological finding or detected while investigating for a symptomatic lymph node mass. Surgery is the primary treatment and has good long-term prognosis. Multicentric Castleman Disease (MCCD) is a more serious systemic condition, often associated with constitutional symptoms. There are various types of multicentric CD including HHV8-associated, idiopathic and a subset of cases that arise in association with POEMS syndrome. Therapy is required for most patients with multicentric CD. As evidenced, the designation Castleman disease encompasses a heterogeneous group of diseases of varied pathogenesis and require different therapies. **Aim:** To have an accountant of occurrence of CD in a tertiary care centre and to study the clinical and histopathological features and categorize them as unicentric and multicentric tumors. **Objective:** To determine the frequency and pattern of CD. **Materials And Methods:** This study is a retrospective analysis of 8 cases of Castleman disease over a period of 12 years from June 2010 to June 2022. **Results:** All cases were unicentric. One case was locally extensive. The clinical symptoms were related mostly to compression effects. 7 cases were of Hyaline vascular type and one was Plasma cell variant. **Conclusion:** CD is misdiagnosed due to absence of specific clinical symptoms. It should be included in differential diagnosis when evaluating lymph node hyperplasia. The progression from chronic antigen stimulation to reactive lymphoid hyperplasia and then to overt lymphoid neoplasia can be illustrated by the Castleman disease.

KEYWORDS : Castleman disease, Human Herpes virus 8, Immunohistochemistry.

INTRODUCTION

Castleman disease (CD) is a rare non-malignant chronic lymphoproliferative disease [1]. CD was described by Dr.Benjamin Castleman in 1954 and later in 1956 as a hyperplastic process involving mediastinal lymph nodes. Various synonyms include Giant lymph node hyperplasia, Angiomatous lymphoid hamartoma, Angiofollicular hyperplasia [2,3]. Three pathological variants of CD have been recognized : Hyaline vascular type, Plasma cell and HHV-8 associated multicentric CD [3,4]. Depending on the extent of lymph node involvement and clinical profile, CD has been categorized into unicentric (UCD) and multicentric (MCD) forms [5,6]. UCD usually presents in young adults with localized masses (mediastinum being the most common site) and is rarely associated with systemic symptoms. In contrast, MCD commonly affects the elderly (age 60 and older), presents with generalized lymphadenopathy and multi-organ involvement, and is usually associated with systemic features. Disease associations include the POEMS syndrome (Polyneuropathy,

Organomegaly, Endocrinopathies, M-Protein, and Skin changes), Kaposi sarcoma, Pemphigus, Refractory anemia, nephrotic syndrome, amyloidosis [7,8,9]. Associations with lymphoid malignancies have been described and these include: Diffuse large B-Cell lymphoma, mantle cell lymphoma, peripheral T-Cell lymphoma and lympho plasmacytic lymphoma, follicular lymphoma [10].

The prognosis is dependent on disease type. The localized form has an excellent prognosis following excision or radiotherapy, but the multicentric form frequently requires systemic therapy [3,4].

In this study, eight instances are presented from a clinical and pathological standpoint. The clinical presentation and histology were highlighted. Specific details are offered regarding the use of immunohistochemistry (IHC) in the final diagnosis.

Patients :

All the patients with biopsy proven CD diagnosed at ASRAMS and patients referred from periphery over a period of 12 years were reviewed for analysis.

METHODS:

Specimens were obtained by surgery and the processing was routinely performed (fixation in 10% formalin and paraffin embedding). The manufacturer's instructions were followed while applying immunohistochemical stains, wherever necessary.

Methodology:

The current study was a retrospective study conducted in the Department of Pathology, at Alluri Sitarama Raju Academy of Medical Sciences, a tertiary care center, which caters to the patients attending and referred from periphery. History, radiology findings, FNAC and histopathology reports were collected and data was analyzed.

Inclusion Criteria:

All biopsy proven cases in adult age group.

Exclusion Criteria:

Inadequate tissue samples are excluded.Ethical approval was obtained from ethics and institutional review committee of the hospital with the approval number : IEC/ASR/APPROVAL/38/2021.

RESULTS:

During 12 year study, a total of 8 Castleman disease diagnosed formed the study group. Due to the rarity of disease, limited number of cases were included. The disease was Unicentric in all the cases.

Mean age was 33.5 years with female : male ratio of 6:2 . Symptoms were related mostly to compression effects. One case showed hematological abnormalities. Mean tumor size was 5.5cm. One case was locally extensive.

Gross aspect was represented by grey white to grey brown solid tumors and cut surface showed a homogenously solid mass with grey white and grey brown areas, a typical of multinodular appearance was present in most of the cases. Seven cases were pathologically classified as the Hyaline vascular type of Castleman disease and one was classified as Plasma cell type.

Immunohistochemical stains were performed in few cases which confirmed the normal distribution of B and T cell compartments (CD3, CD20) and showed the distribution of blood vessels (CD 31, CD34). CD 21 and CD 23 revealed the follicular dendritic cells in germinal centers and in the interfollicular area.

CD 138 revealed plasma cells. BCL2 and Cyclin D1 staining pattern were used to exclude follicular cell lymphoma and mantle cell lymphoma.

S No	Age	Sex	Complaints	Location	Size	Observation
1	22	F	Oligomenorrhea	Retroperitoneal region	6.3x5.2 cms	Solid mass in left inguinal region with its epicenter towards retroperitoneal region
2	31	F	Abdominal pain	Mesentry	5x4 cms	Chronic refractory Anemia associated
3	28	F	Nodule on palpation	Above right clavicle	4x5 cm	-
4	17	M	Mass on palpation	Left lateral cervical region	4.5x3cms	-
5	32	F	Pain in right flank	Right retroperitoneal region	5x8cm	Mass completely surrounded the external iliac vein and right vena cava
6	53	M	-	-	-	Specimen and slide Submitted for second opinion.
7	39	F	-	-	-	Referred from periphery
8	37	F	Lymphadenopathy	Mediastinum	5x5 cms	Solid mass in the mediastinum.

Summary Of Histology Findings:

Sno	Disease type	Architectural effacement	Mantle zone expansion	Aspect of follicles	Dysplastic follicular dendritic cells	Interfollicular space
1	Hyaline vascular CD	Yes	Present	Atrophied follicles, Hyaline capillaries penetrating the follicles,lollipop follicles	Present	Vascular proliferation
2	Hyaline vascular CD	Yes	Present	Large reactive/ atrophic follicles, Onion-ring arrangement, Hyaline capillaries penetrating the follicles	No	Vascular proliferation with high endothelial cells
3	Hyaline vascular CD	Yes	Present	Atrophied follicles, Hyaline capillaries penetrating the follicles,Lollipop follicles,Fibrosis of germinal centers	Present	Expanded, Spindle cells present, Vascular proliferation
4	Hyaline vascular CD	yes	Present	Atrophied follicles, Hyaline capillaries penetrating the follicles.	Present	Vascular proliferation
5	Hyaline vascular CD	Yes	Present (focal)	Atrophied follicles, Hyaline capillaries penetrating the follicles	No	Vascular proliferation
6	Plasma cell CD	Yes/ extension beyond capsule	Present	Atrophic/Focal fragmentation, Plasma cells with Russell bodies	No	Plasma cells with vascular proliferation
7	Hyaline vascular CD	Yes	Present	Atrophied follicles, Hyaline capillaries penetrating the follicles	Present	Vascular proliferation
8	Hyaline vascular CD	Yes	Present	Atrophied follicles, Hyaline capillaries penetrating the follicles	Present	Vascular proliferation

Immunohistochemical Profile Of Cases :

Patient no	Immunohistochemistry Profile
1	-
2	Cd20 (Predominant in follicular areas, scattered cells in interfollicular area), CD21 (highlights the follicular dendritic cells in germinal center), CD10 and BCL-6 were expressed in germinal center, CD 3 (predominant in interfollicular area)
3	Cd20 (Predominant in follicular areas, scattered cells in interfollicular area),CD3 (predominant in interfollicular area), CD34 (interfollicular capillaries),CD21 (follicular dendritic cell hyperplasia). Isolated cells were positive for CD 30.

4	-
5	-
6	CD 38 (Plasma cells), CD68, TCL-1 (Clusters of plasmacytoid monocytes in interfollicular region),
7	-
8	-

DISCUSSION:

The cases were classified as hyaline vascular (87.5%) and plasma cell (12.5%) variants. Despite the small number of cases, the percentage distribution of cases is similar with the data in literature [4]. The typical age of the hyaline vascular type was 28.2 years, which is significantly younger than the patients with the plasma cell variant, and is in line with the data from literature [3,4].

The following criteria formed the basis for the pathology findings: Vascular proliferation of hyalinized capillaries extending into the germinal centre, diffuse effacement of normal lymph node histology, proliferation of abnormal lymphoid follicles with expanded mantle zone and expansion of the interfollicular area for the hyaline vascular type [11].

Following were the criteria for the plasma cell variant: Hyperplastic lymphoid follicles, active germinal centers, interfollicular sheets of plasma cells, plasmacytoid monocytes and polyclonal immunoglobulins [11].

Fig:1 shows retroperitoneal solid mass with external surface nodular grey brown areas and cut section showing homogenous grey white to grey brown areas.

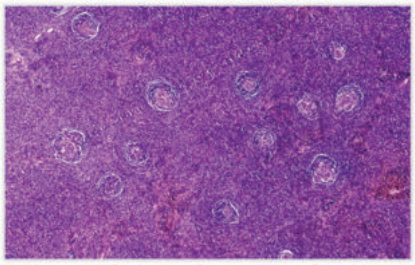

Fig 2 shows histopathological image of Castleman disease showing lymphoid follicles in "Onion ring arrangements".

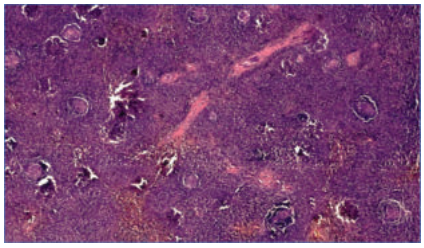

Fig 3 histological features of Castleman disease, hyalinized blood vessels in the interfollicular regions.

The differential diagnosis for Hyaline vascular variant are Toxoplasma lymphadenitis, Mantle cell lymphoma, follicular lymphoma, thymoma, follicular hyperplasia. For the Plasma cell variant, the systemic IgG4-related lymphadenopathy was strongly taken into consideration [11,12]. Although some publications classify the disease as a lymphoproliferative disorder, the histological feature strongly suggests a persistent reactive process. B and T cell compartment preservation is a helpful diagnostic indicator. The hypothesis that the disease is caused by chronic inflammatory processes that are endogenous or virally driven and are mediated by Interleukin-6 is supported by evidence regarding the disease's pathophysiology (IL-6) [3,4,13].

By acting as a promoter of terminal B cell differentiation, by stimulating plasma cell proliferation, and by increasing the production of immunoglobulins, interleukin-6 has been directly linked to the pathogenesis. Also, by stimulating the production of acute phase proteins, IL-6 is responsible for part of the clinical manifestations [14]. VEGF has been strongly related to the secretion of IL-6 and acts by promoting cellular survival and angiogenesis. The increased production of VEGF has been strongly related to the manifestations of POEMS syndrome [3,14] . HHV-8 uses the same signalling pathway, due to the presence of a human IL-6 mimic [15].

However, drugs targeting the IL-6 pathway, such as the anti-interleukin-6 receptor monoclonal antibody tocilizumab, although with proven efficiency in most cases, have failed to control the symptoms in a small number of cases suggesting an alternative pathway [15]. Other important molecules that have been noted to be elevated include interferon alpha, IL1, IL5, TNF, epidermal growth factor, and interferon alpha [3,4].

Although the human immunodeficiency virus (HIV) is also involved in the pathogenesis, its significance is overshadowed by the immunodeficiency status that HIV causes, which in turn favours HHV-8 infection. Clonal rearrangements in the immunoglobulins and T-cell receptor have not always been described [4], and they appear to have a minor impact on the pathogenesis.

CONCLUSION :

This study presented a series of Castleman disease, with emphasis on clinical aspects, pathology findings and extensive description of immunohistochemical stains used for the diagnosis. The data is in concordance with other studies in the literature. CD is rare and often misdiagnosed due to absence of specific clinical symptoms. CD should be included in differential diagnosis when evaluating lymph node hyperplasia. The progression from chronic antigen stimulation to reactive lymphoid hyperplasia and then to overt lymphoid neoplasia can be illustrated by Castleman disease, which is a very interesting "natural experiment." We firmly believe that by understanding the pathogenesis of the precursor lesions, we will better understand the pathways that lead to neoplasia.

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