

CASTLEMAN DISEASE. A REPORT OF SIX CASES.

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Abstract

Background and aims: Castleman’s disease is a rare disorder situated at the boundary between reactive and neoplastic conditions. The pathogenesis is a subject of debate and the limited number of cases renders the study of the disease difficult.

In our paper we present a series of six cases of Castleman disease with emphasis on the clinical presentation, pathology examination and the use of immunohistochemistry in the final diagnosis of the cases.

Patients and method: The classification of the disease was based on clinical, imaging and pathological assessment. Specimens were obtained by surgical excision and were routinely processed for the pathology examination.

Results: All cases were unicentric disease. Two cases were locally extensive. The clinical symptoms were related mostly to compression effects. Five cases were of the hyaline-vascular type and one was included in the plasma cell variant. One case showed angiomatoid differentiation.

Conclusions: We strongly believe that by understanding the pathogenesis of the precursor lesions we will gain 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.

Keywords: Giant lymph node hyperplasia, Interleukin-6, Herpesvirus 8, Human, Immunohistochemistry

Background and aims

The gathering of new evidence in the field of lymphoproliferative disorders has brought to attention entities considered benign or of uncertain malignant

potential. Castleman’s disease (CD) is included in this wide and poorly defined category. Described by Dr. Benjamin Castleman in 1954 and later in 1956 as a hyperplastic process involving mediastinal lymph nodes, the disease was most often mistaken for a thymoma and the clinical course was thought initially to be benign [1]. The disease has been granted many synonyms (angiofollicular lymph

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node hyperplasia, giant cell lymph node hyperplasia, follicular lymphoreticuloma, lymphoid hamartoma [2,3], perhaps due to the lack of evidence regarding the pathogenesis. Chronic viral stimulation, especially Herpes virus 8 (HHV-8, Kaposi sarcoma virus) infection, the IL-6 signaling cascade, angiogenesis and clonal rearrangements play a role in the pathogenesis of CD [4].

CD is rare and exact statistical data are missing [3]. In the simplest way the disease can be classified as localized (unicentric) or multicentric based on the clinical presentation and imaging examination [5,6]. Microscopically the disease has two main types: the hyaline vascular type and the plasma cell type [7]. The localized form is clinically silent and is associated commonly with the hyaline vascular type [3]. The multicentric disease is associated with general symptoms (fatigue, fever) and nonspecific laboratory findings (increased sedimentation rates, hypoalbuminemia, anemia etc) [4,8]. The rarity of the disease also influences the therapeutic approach, no unique therapeutic regimens being unanimously accepted [3,9,10,11,12]. Disease associations include the POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin changes) [13,14], Kaposi sarcoma, pemphigus, refractory anemia, nephrotic

syndrome, amyloidosis [15,16,17]. Associations with lymphoid malignancies have been described and these include: diffuse large- B cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and lymphoplasmacytic lymphoma, follicular lymphoma [18].

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

We present in this paper a series of six cases, from a clinical and pathological perspective. Emphasis was placed on the clinical presentation and histology. Detailed information are presented regarding the use of immunohistochemistry (IHC) in the final diagnosis of the case.

Patients and method

The tumors were classified as unicentric by clinical and imaging criteria. Specimens were obtained by surgery and the processing was routinely performed (fixation in formalin 10% and paraffin embedding). Immunohistochemical stains were performed following the manufactures specifications. One case was referred to our department from an external source and information was

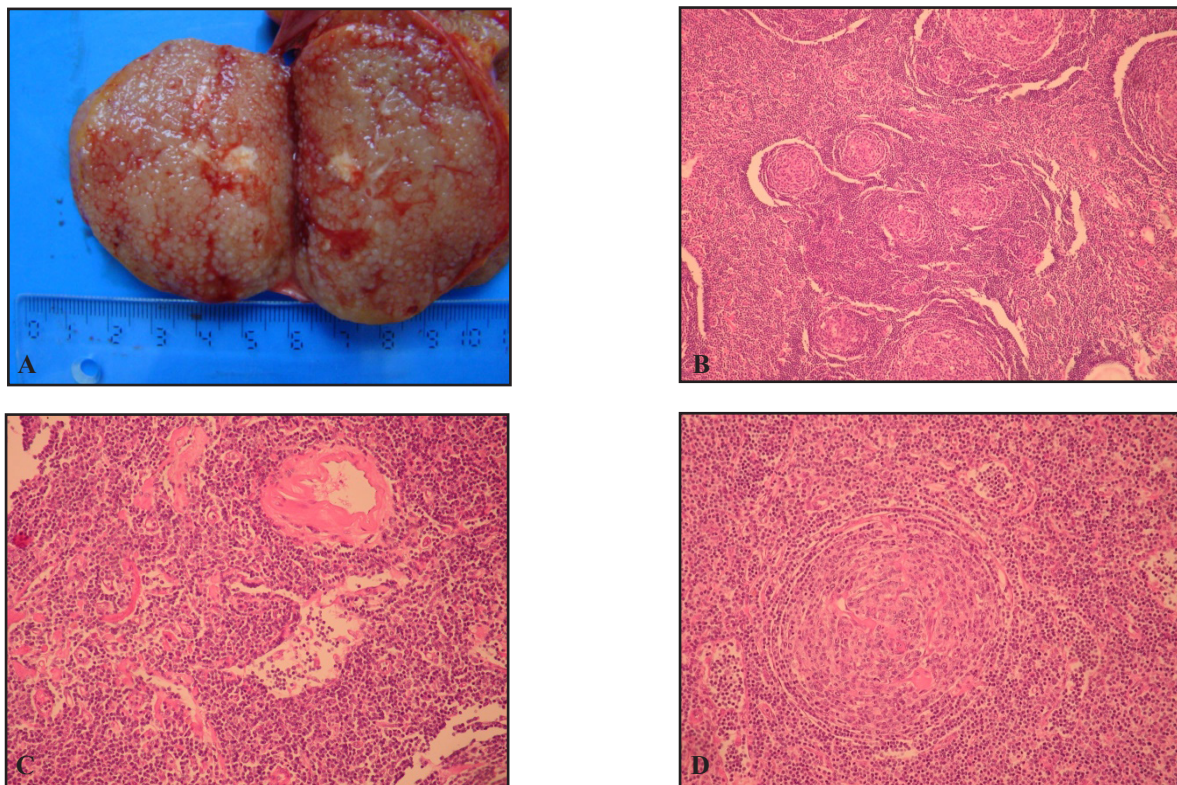


Figure 1. Gross and microscopic aspect of Castleman disease hyaline vascular type. **A.** Cut section of lymph node with micronodular pattern **B.** Follicular hyperplasia replacing the normal architecture (large reactive follicles middle upper and lower part and atrophic follicles in the center); **C.** Thick walled-hyaline small diameter blood vessels. **D.** Lymphoid follicle with “onionskin” pattern and hyaline capillaries.

Case Reports

Table I. Clinical features of cases

Patient Number	Age	Sex	Initial complaints/ Cause(s) of discovery	Location	Size (cm)	Observations
1	31	F	Palpation of nodule	Above the right clavicle	5/4/2.5	-
2	28	F	Abdominal pain	Mesentery	7/5/5.5	Chronic refractory anemia associated
3	17	M	Palpation of nodule	Left lateral cervical area	4.5/3/2.3	-
4	31	F	Pain in the right flank and back	Right retroperitoneal area	5/8	Tumor surrounded completely the external iliac vein, partially the right the inferior vena cava and displaced the right ureter and right adnexa
5	37	M	-	-	-	Submitted from an external pathology department
6	57	F	Abdominal pain/ Intestinal transit disturbances/Rectal haemorrhage	Mesentery of sigmoid colon	3/2	Tumor infiltrated the colonic layers

limited.

Results

The disease was unicentric in all cases. The mean age was 33.5 years, with female: male ratio of 4:2. Symptoms were related mostly to the compression effects.

One case showed other hematological abnormalities. Mean tumor size was of 5.5 cm. Two case (cases 3 and 6) were locally extensive.

Gross aspect was represented by gray white tumors, with variable delimitation and on cut surface a typical multinodular appearance was present in most

Table II. Summary of the histology findings

Patient Number	Disease type	Architectural effacement	Mantle zone expansion	Aspect of follicles	Dysplastic follicular dendritic cells	Interfollicular space
1	Hyaline vascular CD	Yes	Yes	Atrophic Hyaline capillaries penetrating follicles	Yes	Vascular proliferation
2	Hyaline vascular CD	Yes	Yes (focal)	Large, reactive/Atrophic Hyaline capillaries penetrating follicles Plasma cells	No	Vascular proliferation Plasma cells
3	Hyaline vascular CD	Yes/Extension beyond capsule	Yes	Atrophic/Focal fragmentation Hyaline capillaries penetrating follicle	Yes	Vascular proliferation with high endothelial cells
4	Hyaline vascular CD	Yes	Yes (focal)	Atrophic Hyaline capillaries penetrating follicles	No	Expanded Spindle cells Vascular proliferation
5	Hyaline vascular CD	Yes/Extension beyond capsule	Yes	Atrophic Hyaline capillaries penetrating follicles Fibrosis of germinal centers	No	Expanded Spindle cells Vascular proliferation Rare plasma cell and eosinophils
6	Plasma cell CD	Yes/Extension beyond capsule	Yes	Atrophic/Focal fragmentation Plasma cells with Russell bodies	No	Plasma cells with Russell bodies Vascular proliferation

Table III. Immunohistochemical (IHC) profile of cases

Patient Number	IHC profile
1	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area), CD31 highlight interfollicular capillaries some extending to the germinal center, CD23 and S100 positive on the dendritic follicular areas, AE1/AE3 negative.
2	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area), CD21 highlight follicular dendritic cell hyperplasia limited to the germinal center, CD10 and BCL-6 were expressed in the germinal center, CD4 and CD4 variable positivity in the interfollicular area, CyclinD1 excluded a mantle cell lymphoma; isolated cells were positive for CD30 in the germinal center and close vicinity, but negative for CD15. Ki-67 was high only in the germinal centers.
3	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area), CD34 highlight interfollicular capillaries some extending to the germinal center; CD21 highlight follicular dendritic cell hyperplasia; Isolated cells were positive for CD30; B cells express κ and λ chains
4	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area); CD21 positive on follicular dendritic cells and negative on the spindle cells in the interfollicular area; SMA-positive on spindle cells showing myoid differentiation; KI-67 low on spindle in the interfollicular.
5	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area); CD21 and CD23 positive on follicular dendritic cells and negative on the spindle cells in the interfollicular; Spindle cells are negative for S100, CD1a, LCA, CD31; CD30 positive/CD15 negative cells are present in reduced number in the germinal center and its close vicinity; Ki-67 low in the interfollicular area
6	CD20 (predominant in follicular areas, scattered cells in interfollicular area), CD3 (predominant in interfollicular area); CD23 highlighted the follicular dendritic cell are; BCL-2 staining pattern excluded a follicular lymphoma; Ki-67 had low values on the interfollicular area; Cyclin D1 excluded a mantle cell lymphoma

cases. Five cases were pathologically classified as the hyaline vascular type of Castleman's disease and one was classified as the plasma cell type. One case (case 4) showed angiomatous proliferation and another showed only focal changes suggestive for this particular subtype (case 5). Immunohistochemical stains confirmed the normal distribution of B and T cell compartments (CD3, CD20) and showed the distribution of blood vessels (CD31, CD34). CD21 and CD23 revealed the follicular dendritic cells in the germinal centers and in the interfollicular area. CD138 revealed plasma cells. BCL2 and Cyclin D1 staining pattern were used to exclude follicular respectively mantle cell lymphoma.

Discussion

The cases were classified as hyaline vascular (83.3%) and plasma cell variants (16.7%). Although the number of cases is low, the percentage distribution of cases is similar to the data in literature [4]. The mean age for the hyaline vascular type was 28.2 years, much younger than the patient with the plasma cell variant (number 6), also consistent with data from the literature [3,4].

The pathology findings were based on the following criteria: diffuse effacement of normal lymph node histology, proliferation of abnormal lymphoid follicles with expanded mantle zone, vascular proliferation of hyalinized capillaries extending into the germinal center, expansion of the interfollicular area for the hyaline vascular type [19]. The arguments for angiomatous differentiation were

represented by spindle cell proliferation and reactivity for smooth muscle actin (SMA) [20]. For the plasma cell variant the criteria were as follows: hyperplastic lymphoid follicles, active germinal centers, interfollicular sheets of plasma cells, plasmacytoid monocytes and polyclonal immunoglobulins [19].

In the differential diagnosis we included follicular lymphoma and mantle cell lymphoma for the hyaline type. In the case of the spindle cells variant the main differential diagnosis was the dendritic cell sarcoma. For the plasma cell variant the systemic IgG4-related lymphadenopathy was strongly taken in consideration.

The histological aspect is highly suggestive of a chronic reactive process although some authors include the disease in the lymphoproliferative disorders category [4]. Preservation of B and T cell compartments is a useful clue in establishing the diagnosis. Evidence regarding the pathogenesis of the disease are supporting the idea of a viral driven/endogenous driven chronic inflammatory processes mediated by Interleukin-6 (IL-6) [3,4,21].

Interleukin-6 has been clearly linked to the pathogenesis, by acting as a promoter of the terminal B cell differentiation and by stimulation of plasma cell proliferation and production of immunoglobulins [4,21]. Also, by stimulating the production of acute phase proteins, IL-6 is responsible for part of the clinical manifestations [21]. VEGF has been strongly related to the secretion of IL-6 [3] and acts by promoting cellular survival and angiogenesis. The increased production of VEGF has been

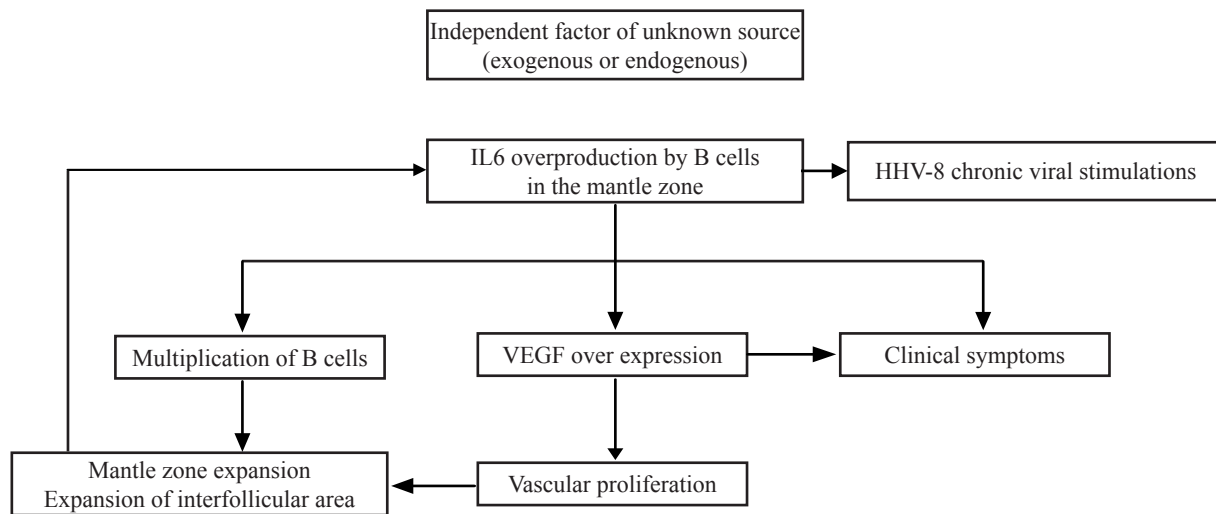


Figure 2. Schematic representation of the pathogenesis of the disease [4].

strongly related to the manifestations of POEMS syndrome [3,22]. HHV-8 uses the same signaling pathway, due to the presence of a human IL-6 mimic [23].

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 [3] suggesting an alternative pathway [24]. IL1, IL5, TNF, epidermal growth factor and interferon alpha [3,4] are other preeminent molecules that have been reported as elevated. The human immunodeficiency virus (HIV) is also involved in the pathogenesis, but its role is secondary to the immunodeficiency status for which it is responsible, which in turn favors the infection with HHV-8 [3]. Clonal rearrangements in the T-cell receptor and immunoglobulins have not been constantly described [4] and they seem to play a minor role in the pathogenesis.

Conclusions:

We presented a series of Castleman disease cases, with emphasis on the clinical aspects, pathology findings and extensive description of the IHC stains used for the diagnosis. To our best knowledge it is the only series of cases with CD presented so far in Romania, focused on the clinical-pathological findings. Our data are consistent with the ones presented in literature. We strongly believe that by understanding the pathogenesis of the precursor lesions we will gain 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.

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