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Castleman Disease Lymphadenopathy in The Era of HIV. Pitfalls in Diagnosis and Their Avoidance.

Chaithra GV, Debarshi Saha*, Beshwant Chowdary, and Nirupama M.

Department of Pathology, Kasturba Medical College, Mangalore. Manipal University, Mangalore 575001, Karnataka, India.

ABSTRACT

Castleman disease and HIV-lymphadenitis share similar morphologies, but they can be identified separately. We retrospectively studied 16 cases diagnosed as Castleman disease over a seven-year-period. Four HIV-infected patients (two men and women) with lymphadenitis and 10 Castleman disease cases were obtained. All patients with Castleman disease had unicentric disease except one with multicentric variety. All had characteristic follicular morphologies and four of them also had interfollicular changes. The HIV-lymphadenites showed similar follicular morphologies except for conspicuous concentric ringing in the broadened mantle zone. Additionally, in the interfollicular region, plasmacytoid cells were found. None of the Castleman disease recurred after surgery, except the multicentric case who continue to suffer and is currently being treated with chemotherapy. The remaining two cases were one each of follicular lymphoma and follicular hyperplasia. Castleman disease is a well-defined lymphadenopathy characterized by small follicles, diminished sinuses, broadened mantle zones with concentric ringing of lymphocytes around hyalinized germinal centers composed of follilcular dendritic cells. HIV-lymphadenitis progresses from follicular hyperplasia to a hyalinized, fibrotic node with sclerotic germinal centers, plasma cells and marked angiogenesis. In spite of numerous similarities, pathologists should not confuse one with the other because treatment implications are grave. A thorough clinical history aids in diagnosis.

Keywords: Castleman disease lymphadenopathy, HIV-lymphadenitis, Plasmacytoid cells, Mantle zone, Sclerosis, Hyalinization.

Corresponding author

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INTRODUCTION

Lymphadenopathy is defined as lymph node swelling ≥1cm. The exceptions limiting size are the epitrochlear (≥0.5cm) and inguinal region (≥1.5cm). Lymphadenopathy in ≥2 different locations if not neighboring each other, persevering for ≥3months may be termed as persistent generalized lymphadenopathy (PGL), if stable [1]. In the present times, in these cases, HIV infection has to be ruled out [1].

Castleman disease (CD) is a rare cause of non-neoplastic lymphadenopathy. Some authors consider Castleman disease to consist of four histological subtypes viz. the hyaline vascular (HV-CD), the plasma cell (PC-CD), the HHV-8 associated CD and the multicentric CD – not otherwise specified (Multicentric CD, NOS). Of these, the latter three share similar histological characteristics, except that the HHV-8 associated CD is etiologically entailed to immunosuppression or human immunodeficiency virus (HIV) infection [2]. The HV-CD usually involves a single lymph node or a lymph node region and the PC-CD, ≥2 non-contiguous lymph node regions i.e. multicentric with PGL [3].

Three patterns of HIV lymphadenitis are observed viz. grades 1, 2 and 3 also termed patterns A, B and C respectively. These patterns emerge from a follicular hyperplasia with folliculolysis (Grade 1/ pattern A) progressing to depletion of lymphoid population with influx of plasma cells and proliferation of vessels between the follicles (Grade 2/ pattern B) culminating in burnt-out follicles with fibrosed germinal centers and marked vascular hyperplasia in the interfollicular region [4,5].

The total number of Castleman diseases that have been reported over the past seven years exceeds expectation of rarity. In this study, we attempted to search out the confounders of HIV-lymphadenitis that may have misled the reporting pathologist to conclude CD, wherein it was not.

MATERIALS AND METHODS

Study design

The current study is retrospective wherein archived hematoxylin and eosin (H&E) stained, paraffin embedded routine histopathology sections of 16 cases diagnosed with CD from January 2009 to April 2016 were retrieved and studied. The clinical details including age, gender and lymph nodes involved were revised from the case files. Particular attention was given to note PGL. History of concomitant disease or immunodeficiency was noted.

Study methods

Histological features in cortical, paracortical regions, within and outside the lymphoid follicles were studied in the lymph nodes. The follicles were evaluated with regard to their distribution, size and germinal center characteristics. Vascular hyperplasia, sclerosis and presence of plasma cells were other attributes examined in the interfollicular region.

The major histological criteria used for diagnosis of CD and HIV-associated lymphadenopathy [5,6]

HV-CD

Lymphocyte depleted small follicles
Diminished sinuses
Onion-skin like mantle zone lymphocytes
Vascular hyperplasia with sclerotic blood vessels
Mitoses not pronounced

PC-CD

May share similar features
Sinuses patent
Sheets of plasma cells between follicles

Follicular hyperplasia with intact germinal centers
HIV lymphadenopathy

Pattern A (grade 1)

Hyperplastic coalesced follicles
Disruption of germinal centers by mantle zone lymphocytes
Interfollicular monocytoid cells

Pattern B (grade 2)

Shrinkage of germinal centers with lymphoid depletion
Plasma cells with angiogenesis in interfollicular region

Pattern C (grade 3)

Sclerosed germinal centers
Sclerosed arterioles
Further lymphoid depletion with increase of plasma cells

RESULTS AND OBSERVATION

Of the sixteen cases evaluated, only ten fulfilled the strict histologic criteria of CD and were of hyaline vascular subtype. There were eight females and two males. The patients presented within the gamut of 17-61 years of age, the median being 31.5 and the mean, 35.6 years. The commonest location of lymphadenopathy was cervical (4 cases) followed by intrabdominal that included two in the retroperitoneal region and one, a subhepatic lymphnode. Of the cervical lymphadenopathy, the upper cervical group involving the submandibular region was usually involved. The sole case of mediastinal lymphadenopathy was found in a 61-year-old male, while the other male had cervical lymphadenopathy. All cases but one were unicentric. The multicentric presentation was noted in a nineteen-year-old female with bilateral cervical lymphadenopathy and massive ascites, anemia and raised erythrocyte sedimentation rate (ESR).

Follicular irregularities were noted in six cases, stromal abnormalities in two and aberrations in both regions of the lymph node were noted in two cases. The follicular abnormalities are listed in Tab. 1. Shrunken germinal centers (GCs) (Fig. 1a and 1d) with diminished lymphocytes and concentric ringing of mantle zone lymphoid cells were seen in all the 10 cases (Fig. 1b). Angiogenesis with sclerosed blood vessels in GC were seen in most cases (Fig. 1c).

Tingible body macrophages were inconspicuous in the germinal centers of the follicles. The 'lollipop lesion' (small germinal center surrounded by thick mantle of small lymphoid cells in concentric rings pierced by a sclerotic vessel) (Fig. 1e) was seen in two cases. Twinning of germinal centers was noted in two cases (Fig. 1f). The changes in interfollicular region are summarized in Tab. 2.

The interfollicular region had increased vascularity in all cases and hyalinized vessels only in the stroma rich variant, the lymph nodes of which were surrounded by thickened capsule. The interfollicular region was populated by small lymphocytes with plasmacytoid cell admixture in two and eosinophils in none of the cases.

There were four cases of HIV-associated lymphadenitis reported as CD. The follicular changes are similar to that of CD except that the much broadened mantles with concentric ringing of small lymphoid cells were not discernible. Also, in contrast to that of CD, marked follicular hyperplasia was noted in parts of lymph node with folliculolysis and tingible body macrophages (Fig. 2a). Vascular hyperplasia with sclerosis (Fig. 2b), hyalinized GCs (Fig. 2c) and twinning of GCs (Fig. 2d) were the common features. The interfollicular region had an abundance of plasmacytoid and monocytoid cells (Fig. 2e), a feature sparingly shared among the two entities.

These patients were all undergoing antiretroviral therapy (ART) with three drugs. Their CD4 counts were between 330 and 360/ cu. mm and were supposed to be in the WHO stage 1 disease. At the time of diagnosis, they were free from pulmonary Tuberculosis (TB). Their lymphadenopathy was chiefly observed in the cervical

region. They also had barely palpable lymph node enlargement in axilla except a woman who fulfilled the criteria of PGL. The clinical suspicions were TB lymphadenitis with/without pulmonary TB and atypical lymphoproliferative disorder. Human herpes virus 8 (HHV-8) induced multicentric CD could not be clinically excluded. Since the facility to perform immunohistochemistry (IHC) with HHV-8 latency-associated nuclear antigen-1 antibody is not available, serum tests to detect HHV-8 were advised to exclude the possibility of infection. Immunofluorescence assay and ELISA tests on the serum of these patients returned negative, thereby ruling out any active HHV-8 infection. All the four patients were in their 40s with equal gender ratio, the youngest being a man at 41 and the oldest, a woman at 49 years. Follow-up on the lymph nodes with recommendation for repeat excision biopsy should there be any increase in the lymph node size, especially rapidly, was advised.

The remaining two cases were a case each of follicular lymphoma and diagnosed on IHC and follicular hyperplasia.

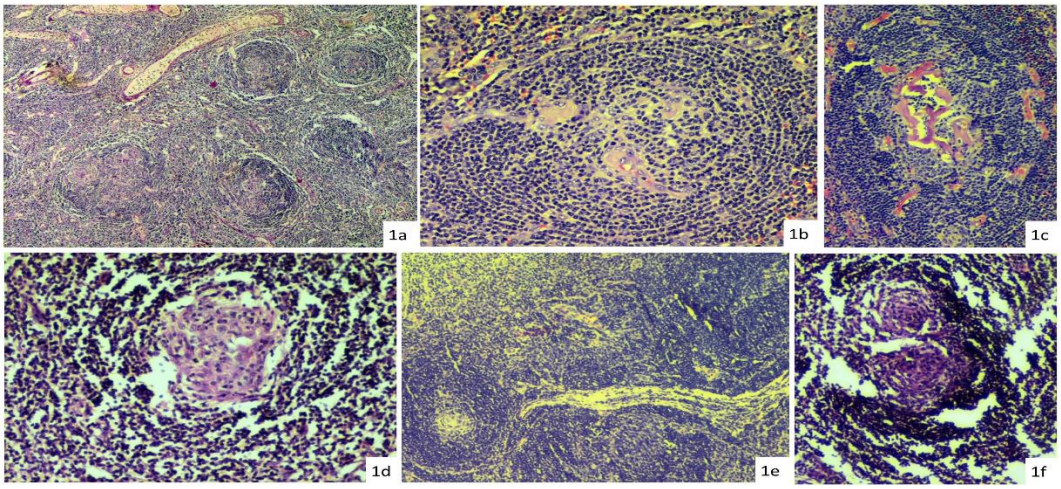

Figure 1: Features of Castleman lymphadenopathy

Fig 1a: small follicles effacing lymph node architecture (X40; H&E)
Fig 1b: broadened mantle zone with concentric ringing of small lymphoid cells (X400: H&E)
Fig 1c: vascular hyperplasia and sclerosed arterioles in germinal centers and interfollicular region (X100; H&E)
Fig 1d: atrophic germinal centers composed of follicular dendritic cells (X100; H&E)
Fig 1e: sclerosed artery piercing a follicle – lollipop lesion (X40: H&E)
Fig 1f: twinning of germinal centers (X100: H&E)

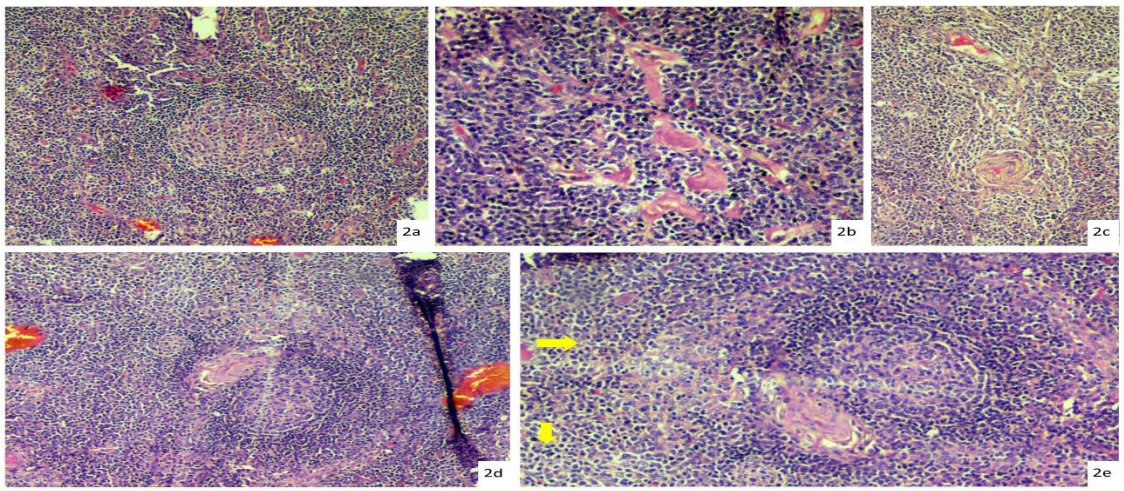

Figure 2: Features of HIV-lymphadenitis

Fig 2a: small germinal center with tingible body macrophages inside and outside the germinal center – folliculolysis. (X100, H&E)
Fig 2b: sclerosed arterioles in germinal center (X400, H&E)
Fig 2c: small, sclerosed germinal center (X100, H&E)
Fig 2d: double (twinning of) germinal centers, one of which is hyalinized (X100, H&E)

Fig 2e: plasmacytoid cells in interfollicular region (X100, H&E)

Table 1: Follicular changes in CD

Follicular changes	Frequency
Attenuated GCs with dwindling lymphocytes and FDC predominance	10
Angiogenesis and hyalinized blood vessels in GC	8
Partially effaced architecture with follicles both in cortex and medulla (Fig. 1a)	7
Mantle zone expansion with concentric ringing of lymphocytes	10
Double GCs	2

GCs – germinal centers, FDC – follicular dendritic cell

Table 2. Interfollicular changes in CD

Interfollicular changes	Frequency
Increased vascularity	10
Few hyalinized blood vessels	6
Plasmacytoid cells	3
Thickened capsule	2

Table 3: Differences between CD and HIV-lymphadenitis.

HIV lymphadenitis	CD (HV-CD)
Follicular hyperplasia.	Numerous small follicles, frequently in the medulla.
Tingible body macrophages.	Absent/ minimal.
Focal concentric ringing may be present but never surrounds the GC totally.	Broad mantle zone with concentric ringing (Fig. 1b).
Lollipop lesions absent.	Lollipop lesions present.
Plasma cells may be present in interfollicular region, but plasmablasts absent. Plasmacytoid monocytes in interfollicular region absent.	Plasma cells and plasmablasts present in interfollicular region in PC-CD. IHC with CD123, bcl11a, CD2AP stains plasmacytoid monocytes.
Sinuses patent filled with histiocytes	Sinuses absent/ greatly diminished. Subcapsular sinuses may be patent in Multicentric/ PC-CD.

DISCUSSION

Castleman disease was originally described in mediastinal/ thoracic lymph nodes. However, other lymph node regions may be involved. The first case description fitted with that of HV-CD variant. Later, other types i.e. the multicentric, PC-CD and the HHV-8 associated types were also incorporated. Thus, CD became a morphologic diagnosis encompassing disease entities that have similar pathogenesis and related etiologies [3,7].

The most commonly encountered CD type is the HV-CD, accounting for 80-90% of the cases [5]. Clinical presentation in fourth decade with impartial gender predilection is the norm. Localized mass, thoracic lymph node presentation, unapparent clinical signs and symptoms are other common characteristics of this disease. In the present study, the mean and median ages found are in fact in the fourth decade (30s) but with a female predilection, Males:Females = 2:8.

On histology, the follicular changes of HV-CD shows numerous small follicles both in cortex and the medulla. The mantle zone is broadened by concentric ringing of lymphoid cells. The GC is largely replaced by FDCs, some of which may be enlarged. Vascular proliferation with hyalinization is commonly seen but may not be diffuse. A sclerosed arteriole piercing the atrophied GC may be seen (lollipop lesion) [2,6,8]. All these features were encountered in various degrees in all the reviewed HV-CD cases. The interfollicular region stands witness to increased high endothelial venules lined by plump endothelial cells and some showing hyalinization. The background cell population is often polymorphous comprising of small lymphocytes, plasma cells, plasmacytoid monocytes and eosinophils [6]. In the current study, eosinophils were completely absent, plasmacytoid cells were few to be found and small lymphocytes filled the interfollicular region. The origin of the plasmacytoid cells could not be discerned vis-à-vis plasma cells or monocytes. This required IHC with CD123, CD2AP, bcl11a that are not available with us [8]. Again, it may not be urgently required as there were no morphologic inkling of progression to dendritic cell sarcomas or vascular tumors. Though association of HV-CD with vascular tumors is

anecdotal, with dendritic cell sarcomas is well established [2,6]. Furthermore, progression to lymphomas are well documented in PC-CD/ HHV-8 associated CD, but not with HV-CD.[2] Excision of the affected node usually cures HV-CD [6].

HIV-associated lymphadenopathy shows non-specific morphological characteristics. These may be graded into three patterns viz. patterns A, B and C corresponding to Grades 1, 2 and 3. Evidence of other infections or neoplasms being absent, these grades approximate to the stage of the disease i.e. grade 3 or pattern C commonly corresponds to progression from mere HIV infection to frank AIDS. Longevity of the patient also correlates significantly with the grades, the highest grade corresponding to lowest survival. The highlights of morphology include marked follicular hyperplasia at the outset. Few tingible body macrophages may be seen outside the GC. This progresses to lymphocyte depletion with interfollicular and intrafollicular angiogenesis with hyalinization. Influx of plasma cells in the interfollicular region is noted. With progression, fibrosis sets in the interfollicular region with marked vascular hyperplasia. The GCs become totally atrophic and sclerotic showing few follicular dendritic cells (FDCs). Scattered plasma cells are noted. Frequently, these patterns are not isolated but combined [4,5]. All the four HIV-lymphadenites in the current study demonstrated these features in varying degrees. When sclerosis starts to set in, a CD like appearance may be imparted [4]. This may have led to misdiagnosis of CD in these cases. Thus, we propose differences between HIV-lymphadenitis and CD shown in Tab. 3.

The similarities are however, i. Twinning of GCs, ii. Small, hyalinized GCs, iii. Vascular hyperplasia, iv. Sclerotic blood vessels and v. Plasmacytoid cells in the interfollicular region.

If at all CD should be suspected in HIV-positive patient, HHV-8 infection has to be ruled out. In the tissue sections of the lymph node, it may be done by IHC with HHV-8 associated latency-associated nuclear antigen-1. [4] HHV-8 infection may also be confirmed by serological test of whole virion ELISA and lytic IFA, currently deemed very sensitive. Alternatively, polymerase chain reaction (PCR) to detect HHV-8 DNA was also found to be very reliable [9].

The crux of the situation lies in the treatment of each of these entities or a situation where HIV infection is complicated by concomitant CD. If surgical option is not amenable, radiotherapy can be given in unicentric CD [3]. Multicentric/ PC-CD require detection of HHV-8 and excluding simultaneous HIV infection. A combination chemotherapy using Rituximab and etoposide along with ART is advocated, if HIV-positive. Nonetheless, antiherpesvirus agents though logically required, failed to match the remission rate of rituximab. Foscarnet and ganciclovir/ valganciclovir showed some promise. Antibody to IL-6 receptor, Tocilizumab was tried in Multicentric CD in HIV-negative patients achieving good remission rate. IL-6, either secreted from the host or derived from HHV-8 virus leads to Multicentric/ PC-CD. The efficacy of Toclizumab on HIV-positive patients is currently not available [10].

Hence, it is of utmost importance that CD be ruled out in HIV-positive patients. Additionally, HIV-lymphadenitis should not be diagnosed of CD due to huge difference in the treatment implications.

CONCLUSIONS

CD is a well-defined lymphadenopathy characterized by small follicles that at least partially efface the lymph node architecture, also diminishing the sinuses greatly. Broadened mantle zones with concentric ringing of lymphocytes around hyalinized GCs composed of FDCs are typical and reproducible features of HV-CD. In contrast, HIV-lymphadenitis progresses from follicular hyperplasia to a hyalinized, fibrotic node with sclerotic GCs, plasma cells and marked angiogenesis. Vascular hyperplasia and sclerosed blood vessels may be seen in both. Since CD in HIV-positive patients entails considering HHV-8 infection and thereby, grave therapeutic implication, HV-CD has to be distinguished from HIV-lymphadenitis. In spite of numerous similarities, one should not be confounded as HV-CD is clearly defined histologic entity. A thorough clinical history aids in diagnosis.

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