

The Immunophenotypic Patterns of Follicle Centre and Mantle Zone in Castleman's Disease

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ABSTRACT

Background: Castleman's disease is an uncommon disease and the histopathogenesis is poorly understood. This study aims to investigate their clinicopathological and immunophenotypic profile.

Materials and Methods: Castleman's disease was reconfirmed in biopsy tissue from 10 patients in a period of 17 years. Immunohistochemical staining was performed on the archival materials, with antibodies to lymphoid antigens and oncogene products, Bcl-6 and Bcl-2. Six reactive hyperplastic lymph nodes and three tonsils were used for comparative study of the phenotypic expression.

Result: There were three cases of plasma-cell and seven of hyaline-vascular variant. The ages of patients ranged from eight to 60 years (median 30 years). The three patients with plasma-cell variant were older, all females. Two of the plasma-cell variant had multicentric lesions associated with systemic disease. All patients with hyaline-vascular variant had localised disease. Atrophic follicle centres were present in all the diagnostic tissue of both subtypes, with loss of Bcl-6 follicular centre B-cells and presence of relatively few CD57 T-cells. These follicle centres stained strongly with anti-CD21. In the mantle zone, CD5 expression was observed in only two cases and Bcl-2 expression similar to reactive follicles was present in six.

Conclusion: Loss of Bcl-6 B-cells in the atrophic follicle centres, characteristic CD21 network patterns, low rate of CD5 and Bcl-2 expression in the mantle-zone lymphocytes are present in both variants of Castleman's disease, differ distinctly from reactive follicles. The phenotypic similarity in these two variants suggests possibility of closely related pathogeneses.

Keywords: Castleman's disease, hyaline-vascular, phenotype, plasma-cell type

Singapore Med J 2003 Vol 44(4):185-191

INTRODUCTION

Castleman's disease, first described in 1954 by Castleman and colleagues is also known as angiofollicular hyperplasia and many other names such as lymph node hamartoma, angiomatoid lymphoid hamartoma, giant lymph node hyperplasia⁽¹⁾. It is an uncommon lymphoproliferative disorder that can present at any age, commonly with lymph node enlargement clinically⁽¹⁾. Two histomorphological variants had been described, the hyaline vascular and plasma cell types⁽²⁾. The histopathology of hyaline-vascular subtype show increased vascularity, numerous follicles with poorly formed germinal centres and the rims of small lymphocytes are arranged in an orderly concentric "onion-skin" array. In the plasma cell type, there are predominance of plasma cells in the interfollicular area⁽¹⁻³⁾. Here, the follicle centres may appear larger, with a deposition of an amorphous acidophilic material that probably contains fibrin and immune complexes in the centre⁽²⁾. Despite good documentation of these distinguishing morphological features, the issue of the histopathogenesis remains unresolved. There have been suggestions that these lesions may be caused by chronic antigenic stimulation, possibly due to viral infection^(1,3,4), and still others have proposed origin from a vascular hamartoma^(1,3-5). Nonetheless, it is possible that the pathogenesis of these two variants may differ, to account for the differences observed in the histological appearance, and clinical manifestations in some instances. The plasma cell variant appear to be more closely related to some form of abnormal immune reaction⁽³⁾, whereas, hyaline-vascular type can represent developmental growth disturbance based on the histomorphology^(1,5). Recently, deregulated production of IL-6 has been implicated in the pathogenesis of plasma cell subtype, especially those presented with systemic disease⁽⁶⁻⁹⁾.

Classically, distinction between Castleman's disease and other lymphoid pathology is based on histomorphological appearance⁽³⁾. However, immunophenotyping may play an important role in

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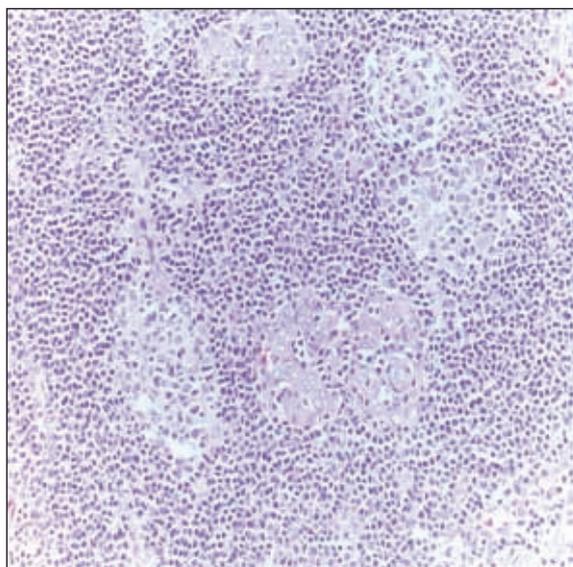
Table I. Primary antibodies and antigen retrieval methods used.

Antibody	Antigen	Dilution	Source	Antigen Retrieval Method
Polyclonal CD3	CD3	1:75	Dako, Denmark	MW, Citrate buffer pH 6.0
NCL-CD5/54/B4	CD5	1:50	Novocastra, UK	MW, EDTA pH 8.0
L 26	CD20	1:500	Dako, Denmark	MW, Citrate buffer pH 6.0
IF8	CD21	1:100	Dako, Denmark	Trypsin, (0.1% in 0.1% calcium chloride, pH7.8)
NCL-CD23-1B12	CD23	1:50	Novocastra, UK	MW, Citrate buffer pH 6.0
Leu 7	CD57	1:50	Becton-Dickinson, USA	MW, Citrate buffer pH 6.0
Anti Bcl-2	Bcl-2	1:50	Dako, Denmark	MW, Citrate buffer pH 6.0
Anti Bcl-6	Bcl-6	1:50	Dako, Denmark	MW, Citrate buffer pH 6.0

Abbreviation: MW; microwave

Table II. Clinical and demographic pattern, morphological variants and immunophenotype in Castleman's disease.

No.	Age/ Gender	Site of LN	Other Nodes	Variant	Follicle Centres				Mantle		EBER Status
					CD21	CD23	CD57	Bcl6	CD5	Bcl2	
1	8/f	Left cervical L	-	HV	+	+	+	Some +	-	+	-
2	18/f	Unspecified	-	HV	+	+	+	-	-	+/-	-
3	24/f	Retroperitoneal	-	HV	+	-	+	-	-	+/-	-
4	28/m	Hilar	-	HV	+	-	+	-		+	Few + lymphocytes
5	29/f	Right inguinal	-	HV	+	-	+	-	-	+/-	-
7	38/m	Right submandibular	-	HV	+	-	+	-	-	+/-	-
8	53/m	Left supraclavicular	-	HV	+	-	+	-	+	+	Few + lymphocytes
5	31/f	Left cervical	-	PC	+	+	+	Some +	+	+/- +	Few + lymphocytes
9	53/f	Left cervical	Multiple cervical supraclavicular	PC	+	+	+	Some +		+	Few + lymphocytes
10	60/f	Right axillary	Cervical	PC	+	++	+	Some +	-	+	Few + lymphocytes

**Fig. 1** Hyaline-vascular type Castleman's disease: large nodule with expanded mantle zone containing a few atrophic hyaline-vascular follicle centres. H&E X550.

making the distinction^(3,4). This study aims to study the clinicopathological patterns and the immunophenotypic profile of Castleman's disease diagnosed in a group of Asian patients.

MATERIALS AND METHODS

The archival material of all cases diagnosed as Castleman's disease was retrieved from the surgical biopsy files for a period of 17 years from January 1982 to December 1998. The tissues were all formalin-fixed and paraffin-embedded. Histology sections stained with haematoxylin and eosin (H&E) were reviewed by the pathologists for confirmation of diagnosis, and sub-classified into the hyaline-vascular and plasma-cell variants. Ten cases were reconfirmed as Castleman's disease. The demographic data of these patients and their clinical information were extracted from the patients' case records. Six cases of hyperplastic reactive lymph nodes and

three of chronic tonsillitis with reactive follicular hyperplasia were randomly retrieved from the files within the same period for a comparative study of the immunohistological profile.

Immunohistochemistry

Serial 4 μ sections were stained immunohistochemically using a panel of antibodies to lymphoid antigens, CD3, CD5, CD20, CD21, CD23, CD57 and oncogenes, Bcl-2 and Bcl-6 (Table I). A standard avidin-biotin complex (ABC) method was performed using the kit from Dako (Denmark). Antigen retrieval steps either with microwave pre-treatment or trypsin digestion were carried out depending on the antibodies.

In-situ hybridisation

All the cases were probed for the presence of EBV by RNA (EBER) *in-situ* hybridisation (ISH) with the fluorothiocynate labelled peptide nucleic acid (PNA) probes (Y5200, Dako, Denmark). Visualisation was achieved after using anti-fluorothiocynate labelled with substrate NBT/BCIP (Nitro blue tetrazolium choride/5-Bromo-4-chloro-3-indolyl phosphate). A known EBV-positive nasopharyngeal carcinoma section was used as an external control.

RESULTS

Clinical Profile

All 10 patients presented the disease in the lymph nodes. Three patients had plasma cell variant and seven had hyaline-vascular type pathology in their biopsies (Table II). The ages of these patients ranged from eight to 60 years with a median of 30 years. Patients with plasma cell variant were older, and all were females. There were three males and four females in the hyaline-vascular group. All patients with hyaline-vascular pathology had localised disease. Two of the three patients with plasma cell variant had multicentric lesions. One of them developed POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) five years after the initial diagnosis of Castleman's disease (Case 9), the other had elevated ESR, hypergammaglobulinaemia and hypoalbuminaemia at presentation (Case 10). The unicentric plasma cell variant lesion was discovered incidentally during investigation for the complaint of diminished hearing. Both patients with multicentric systemic disease were alive during their last follow-up assessment, 10 years and one year (Case 9 and 10 respectively) after the initial diagnosis. Unfortunately Case 10 was later lost to follow-up assessment. All the other

patients were alive and well during their last clinical assessment, ranging from one to three years after the diagnosis, before they were discharged from follow-up clinics. The HIV status of these patients were not known.

Histopathology

In the hyaline vascular subtype, the inter-follicular region was prominently vascular, haemangioendothelioma-like. All cases showed numerous follicular structures in the lymph nodes. The mantle rim was expanded, composed of small lymphocytes. In some instances there was formation of large nodules containing several atrophic centres of varying size, giving a "moth-eaten" appearance (Fig. 1). One case showed in addition some follicles with expanded reactive follicle centres (Case 1). In the three cases of plasma-cell type, the follicle centres showed a range of sizes. Some were atrophic but the majority were expanded, reminiscent of reactive follicle centres. Two cases showed associated presence of classical hyaline-vascular follicles with "onion-skin" arrays of lymphocytes and inter-follicular vascular pattern in focal areas (Case 9 and 10). The presence of prominent enlarged polyploid follicular dendrite reticulum cells (FDRC) were seen in the follicles; it has been previously reported as follicular dendritic cell dysplasia. All the cases showed follicular dendritic cell dysplasia of varying degree irrespective of the variant. The hyperplastic reactive lymph nodes and chronic tonsillitis cases used as controls showed presence of large secondary follicles with prominent follicle centres. The follicles demonstrated distinct segregation between their light-staining centrocytic areas from their dark-staining centroblastic zones.

Immunophenotypic pattern

The atrophic follicular centres in all these cases irrespective of the variants showed absence of Bcl-6 follicular centre B-cells (Fig. 2a). Small numbers of CD57-positive T cells were present, often located at the edge of the follicle centres (Fig. 2b). The reactive follicles present in Cases 1, 8, 9 and 10 (Table II) contained comparatively larger numbers of Bcl-6 and CD57-positive cells. On the other hand, the germinal centres of reactive lymph nodes (six cases) and tonsils (three cases) showed a presence of large numbers of Bcl-6-expressing follicle centre cells (Fig. 2c) and some were rosetted by CD57-positive cells (Fig. 2d). In all cases, immunohistochemic staining with antibody to CD21 showed small, tight follicular dendritic cell (FDC) networks (Fig. 3a), and in some instances

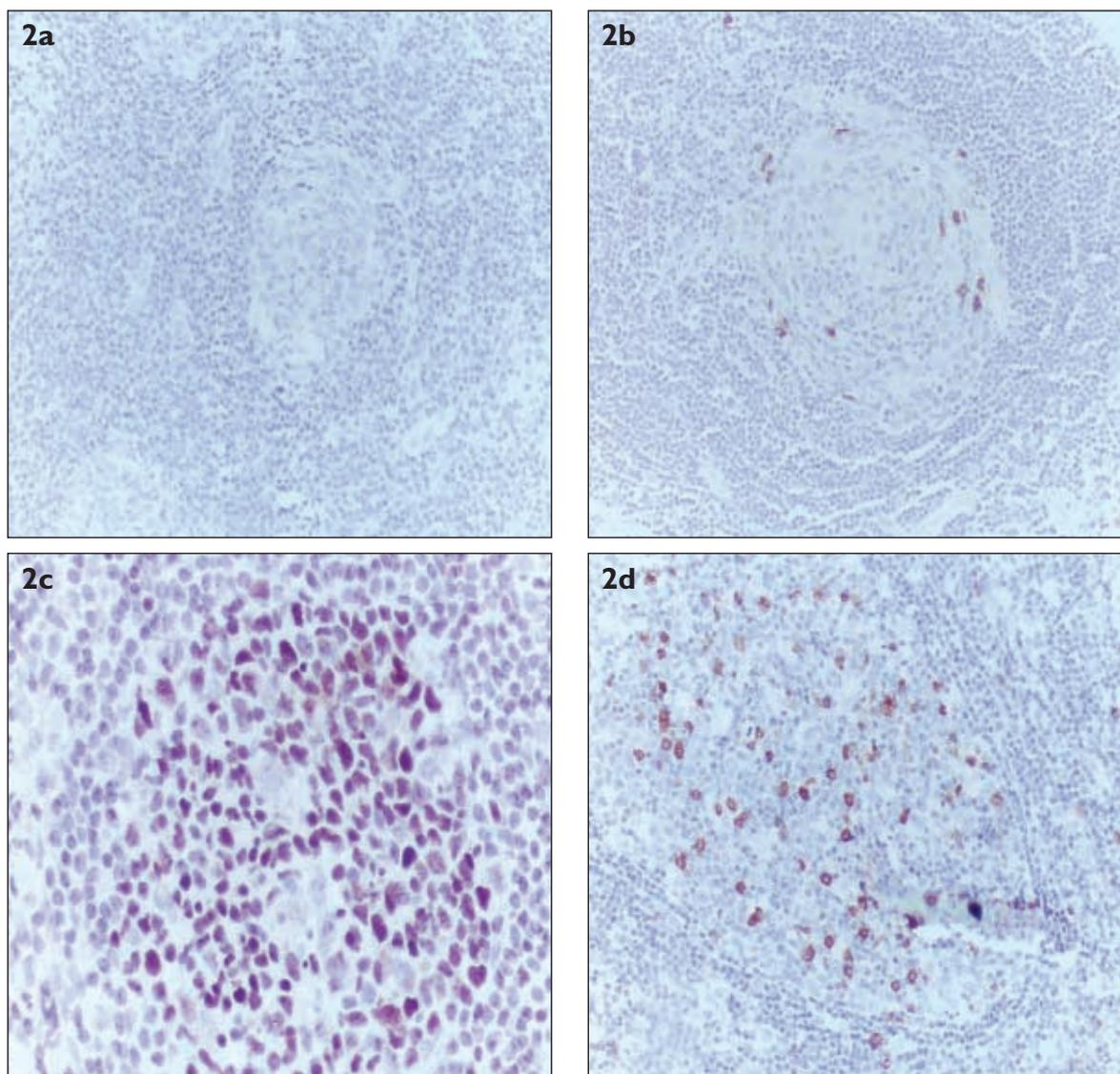


Fig. 2a: Hyaline-vascular type Castleman's disease: loss of Bcl-6 follicle centre B-cells. Anti-Bcl-6 immunoperoxidase stain X550.
2b: Hyaline-vascular type Castleman's disease: small numbers of CD57-positive cells at the edge of follicle centre. Anti-CD57 immunoperoxidase stain X550.
2c: Tonsil: large numbers of Bcl-6 positive germinal centre cells. Anti-Bcl-6 immunoperoxidase stain X550.
2d: Reactive lymph node: follicle centre shows the presence of large number of CD57-positive cells. Anti-CD57 immunoperoxidase stain X550.

expanded, disrupted networks extending out from the atrophic centres were present (Fig. 3b). There was no FDC proliferation present in the interfollicular region in any of the hyaline-vascular cases. In contrast, the follicular dendritic cells in reactive follicles of lymph nodes and tonsils formed large, well-defined, circular meshworks enveloping the follicular centre cells (Fig. 3c). Only five cases showed presence of CD23-positive FDC networks in the follicle centres, in two cases being of hyaline-vascular variant and three cases of plasma-cell type. Disrupted CD23 networks were observed in these five cases (Fig. 3d). In contrast, all the follicular centres in the reactive lymph nodes and tonsils showed strong CD23 expression (Fig. 3e).

The small lymphocytes forming the mantle zone expressed CD20 strongly in all cases. However, weak CD5 expression was found only in two cases. The remaining eight cases had no CD5 expression in their mantle zone of B-cells. Evenly strong Bcl-2 expression similar to the mantle-zone of reactive follicles was observed in six cases, the remaining four showing a smaller proportion of positive cells, with a tendency towards negative expression in the inner mantle (Fig. 3f). There was no variant predilection for negative expression of CD5, but a tendency for small numbers of lymphocytes to express Bcl-2 weakly was seen in cases of the hyaline-vascular variant (Table II). In contrast, the mantle zone lymphocytes of reactive lymph nodes and tonsils showed consistently strong expression of CD5 and Bcl-2.

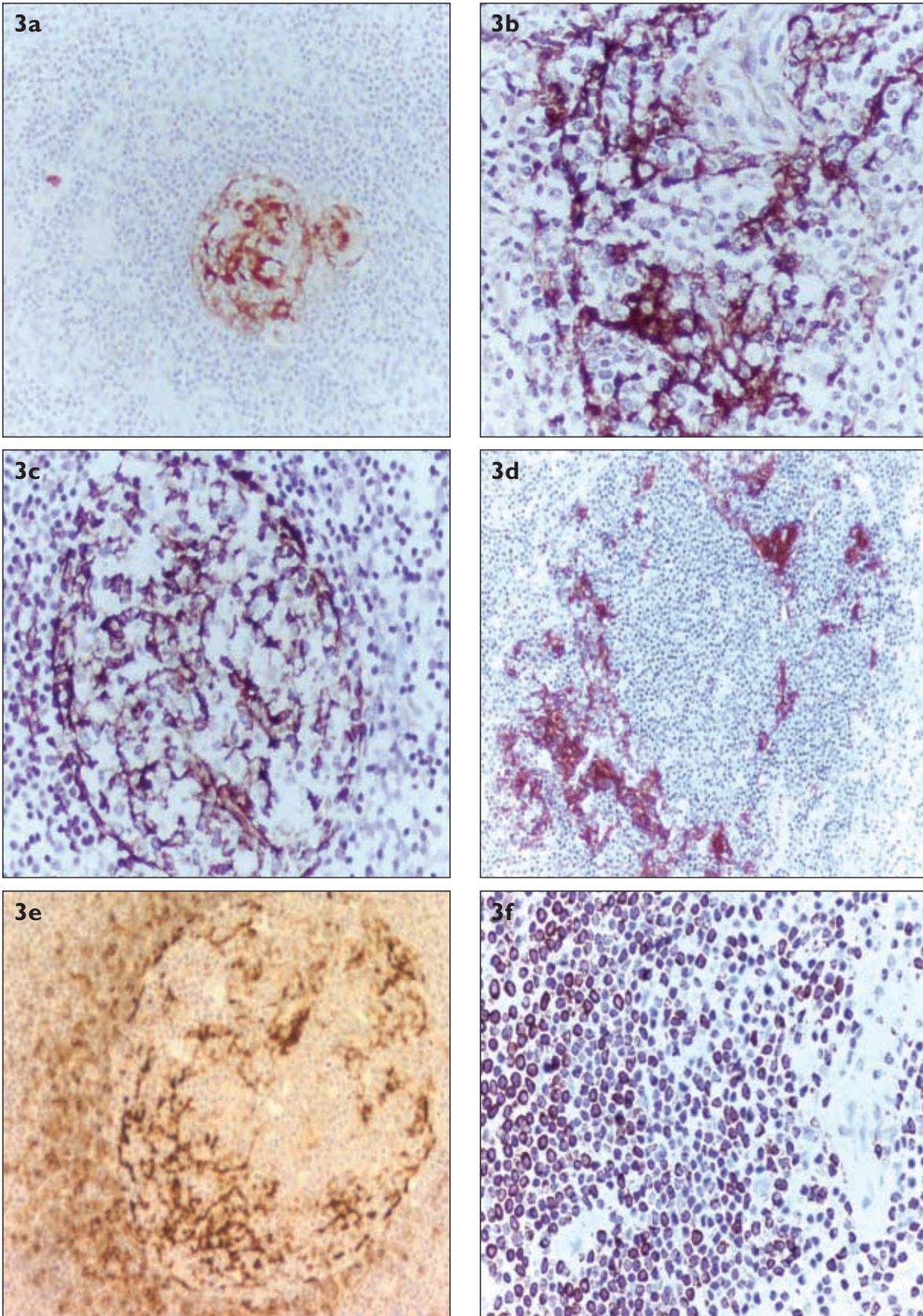


Fig. 3a: Hyaline-vascular type Castleman's disease: tight follicle dendritic cell (FDC) network. Anti-CD21 immunoperoxidase stain X550.
 3b: Plasma-cell variant Castlaman's disease: expanded and disrupted FDC network. Anti-CD21 immunoperoxidase stain X550.
 3c: Reactive lymph node: well-defined circular FDC network. Anti-CD21 immunoperoxidase stain X550.
 3d: Plasma cell variant Castleman's disease: disrupted and diminished follicular dendritic CD23 expression. Anti-CD23 immunoperoxidase stain X200.
 3e: Reactive lymph node: CD23-positive FDC network. Anti-CD23 immunoperoxidase stain X150.
 3f: Plasma-cell variant Castleman's disease: lack of Bcl-2 expression in the inner rim of mantle-zone lymphocytes. Anti-Bcl-2 immunoperoxidase stain X550.

Status of EBV

Five cases showed very few randomly scattered small lymphocytes expressing EBER in their nuclei, including all three cases of the plasma-cell type and two of the hyaline-vascular variant.

DISCUSSION

Castleman's disease is an uncommon condition. Only 10 cases were diagnosed during a period of 17 years, from a total of 152,490 surgical biopsies reported in the corresponding period. All our patients presented with disease in the lymph nodes, with one case involving the hilar node from spleen whereas other studies reported common localisation of the disease in the mediastinum^(1,2,4), in particular, cases with the hyaline-vascular variant. In our series, two of the three patients with the plasma-cell variant had multicentric disease associated with systemic symptoms' which is similar to previous observations of the propensity of this disease to do so^(1,2,5,6). Although previous studies have suggested relatively poor prognosis⁽¹⁾, with median survival ranging from 24 to 33 months, one of our patients had a prolonged survival of 10 years from the time of initial diagnosis. We also investigated the possible role of EBV in the pathogenesis of Castleman's disease, and concur with other investigators that EBV does not play an important pathogenetic role, in contrast to human herpes virus 8 (HHV 8)^(10,11).

The characteristic CD21-positive FDC networks as described previously^(4,5) were demonstrated in all our cases irrespective of the histological variant, which differed from the findings of Nguyen et al⁽⁵⁾. These authors noted the characteristic patterns only in their hyaline vascular subtype, while a normal reactive pattern was found in their cases of the plasma cell variant. Hence, our observation supports the possibility that both variants are closely related. None of our seven cases of hyaline vascular variant and those reported by Nguyen et al⁽⁵⁾ showed follicular dendritic cell overgrowth as described by Lin et al⁽⁴⁾. One may thus conclude that this is an uncommon occurrence, in comparison with FDC dysplasia which is frequently associated with Castleman's disease. Interestingly, there have been some reports of rare FDC sarcomas associated with Castleman's disease⁽¹²⁻¹⁴⁾, which raise the possibility that there may be a spectrum of lesions, differing in their degree of proliferation and biological behaviour.

The absence of Bcl-6 follicular centre B-cells and scarcity of CD57-cells in the atrophic follicle centres was a distinctive feature. It has been reported

previously that many of the follicles in the hyaline vascular variant have a cellular composition reminiscent of primary follicles and consistently lack "natural killer" (Leu7+/CD57+) cells^(5,15). However, a more logical possibility is that the intrafollicular CD57+ cells in the germinal centre of reactive follicles might represent a subset of T-helper cells that co-express CD3, CD4 and CD57, playing an important role in the regulation of immunoglobulin production by B cells^(16,17) and that these cells are diminished in the atrophic follicles of Castleman's disease.

These alterations were seen in the germinal centres of all our cases, irrespective of the underlying pathological variant. Our cases also lacked consistent presence of a CD23-positive FDC subset in the follicular centre. In normal reactive follicular structure, a high level of CD23 expression has been reported within a discrete subset of follicular dendritic cells (FDC) localised mainly in the apical light and peripheral mantle zones⁽¹⁸⁾. FDC networks play an important role in trapping antigen and presenting these antigens on their surfaces for recognition by B lymphocytes. The antigen receptors in the latter bind the displayed antigens for further development of the germinal centre. Studies have shown that high levels of soluble CD23 promote B cell activation' and further encourage the development of germinal centre B cells by preventing apoptosis⁽¹⁹⁾. Loss of CD57+ intrafollicular T-helper cells and absence of the CD23-positive subset of follicular dendritic cells may therefore be responsible for the atrophic state of the follicle centres in some cases of Castleman's disease, as cases which have expanded follicle centres show increased numbers of these cells, similar to reactive follicles.

Interestingly, the loss of Bcl-6 gene expression was reported to be associated with systemic inflammatory disease that suggests loss of repressive control of Th-2 dependent responses⁽²⁰⁾. Such manifestations have been reported to occur in systemic Castleman's disease⁽²¹⁾. Activated Th-2 cells secrete large amounts of IL-4, IL-5, IL-6 and IL-13 in the absence of Bcl-6 protein⁽²²⁾, and this may explain the reported elevated level of IL-6 observed in the plasma-cell variant of Castleman's disease⁽⁶⁻⁹⁾. Bcl-6 protein has been identified as an obligatory regulator of germinal centre formation and differentiation^(20,22), therefore loss of Bcl-6 gene expression can lead to a specific defect in germinal centre formation. Whether or not there is defective Bcl-6 gene expression in cases of Castleman's disease to account for the poorly formed follicle centres or the elevation of IL-6 in some of the reported cases in the literature is not immediately evident, and is beyond the scope of this study.

CD5 expression in the mantle zone of small lymphocytes was observed in only 20% of our cases (Table II). CD5 positivity in “mantle zone” lymphocytes was reported earlier in the plasma cell variant by Hall et al⁽²³⁾ (commentary by Isaacson⁽²⁴⁾), and later in both the variants by Menke et al⁽³⁾. These CD5-positive B-lymphocytes were found to be immunophenotypically aberrant⁽³⁾, identified as Ly-1 B lymphocyte subsets^(25,26). Subsequently, it was recognised that CD5-negative “mantle zone” B lymphocytes occurred in Castleman’s disease, and they may originate from Ly-1 sister B lymphocytes⁽³⁾. Hence, both CD5 positive and CD5 negative “mantle zone” B-cells can be present in Castleman’s disease, as observed in our series. The reason for the tendency towards weaker and diminished Bcl-2 expression by the mantle-zone lymphocytes is not clear. This observation had not been previously noted or studied before.

In conclusion, we found distinctive patterns of FDC networks, diminished or absent CD57-positive and Bcl-6-positive cells in the atrophic follicle centres, frequent absence of CD5 and variable Bcl-2 expression in the mantle zone lymphocytes in both variants of Castleman’s disease. These similarities suggest that the two variants may be closely related histogenetically. Castleman’s disease being an uncommon condition and infrequently diagnosed in surgical biopsies, this phenotypic profile can be helpful in identifying of this unusual reactive lymphoid lesion in difficult situations.

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