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ORIGINAL ARTICLE

Cytological features of Castleman disease: a review

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Introduction Castleman disease (CD) is a benign lymphoproliferative disorder with hyaline vascular (HVCD), plasma cell (PC-CD), and mixed subtypes. Only HVCD lymph node cytomorphology has been described, mainly as case reports. We reviewed all CD subtypes. To the best of our knowledge, our case series is the largest and most comprehensive yet published.

Materials and methods We searched our institution's database for histologically confirmed CD cytology cases (fine needle aspiration, touch preps) for the past 23 years. Two independent pathologists evaluated cytomorphology. We then reviewed touch preps from 6 histologically confirmed, non-CD reactive lymph node excisions.

Results 8 patients (5 women, 3 men) had the following subtypes: HVCD (5 patients), PC-CD (2), and mixed (1). All cases had a heterogenous background population composed predominantly of small lymphocytes with single and clustered follicular dendritic cells (FDCs). The FDCs had delicate pale cytoplasm with indistinct borders showing lymphocyte emperipolesis. They were often binucleated or multinucleated with fine chromatin, regular nuclear borders, large nuclei, and small nucleoli. HVCD cases had traversing, frequently hyalinized capillaries. PC-CD cases had increased plasma cells, including binucleate forms, and tingible body macrophages with fewer FDC clusters. Human herpes virus-8 immunostain was negative in all cases. Non-specific follicular hyperplasia cases had abundant tingible body macrophages, rare hyalinized capillaries, and no lymphocyte emperipolesis.

Conclusions CD is distinguished by background lymphocytes and cohesive FDC clusters with lymphocyte emperipolesis. HVCD has traversing, hyalinized capillaries and PC-CD has increased plasma cells and tingible body macrophages. Knowledge of these features can prevent a lymphoma misdiagnosis.

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Introduction

Castleman disease (CD), or angiofollicular lymph node hyperplasia, is a benign lymphoproliferative disorder that can occur in a single lymph node (unicentric) or in multiple lymph nodes (multicentric) associated with systemic disease. The most common histologic subtype, hyaline vascular Castleman disease (HVCD), is characterized by germinal centers surrounded by concentric rings of mantle zone lymphocytes and a hyalinized vascular proliferation between follicles. HVCD patients typically present in the third or fourth decade with a localized thoracic mass and no systemic symptoms. The plasma cell subtype of Castleman disease (PC-CD) is characterized by paracortical plasmacytosis and plasmablasts in the mantle zone and paracortex. These patients usually present with multicentric disease and systemic symptoms such as fever, night sweats, and splenomegaly. PC-CD is associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein disorder, and skin changes). Mixed cases have hyaline-vascular type follicles with increased plasma cells. Immunosuppressed patients, especially with human immunodeficiency virus (HIV) infection, can develop multicentric CD due to human herpes virus-8 (HHV-8) superinfection.[1] Unfortunately, cytomorphology is poorly understood, posing problems for fine needle aspiration (FNA) and intraoperative frozen section diagnosis of CD. Cytologic descriptions of CD exist mainly as case reports. The largest case series is 3 HVCD cases,[2] and all cases were initially misdiagnosed on FNA. The cytomorphology of PC-CD has only been described in a cerebrospinal fluid specimen,[3] and lymph node cytology has not been previously reported. To the best of our knowledge, our case series is the largest and most comprehensive yet published.

Materials and methods

We searched our institution's database for histologically confirmed cases of CD for the past 23 years (November 1992-May 2015). A total of 15 cases were found, 8 of which had available cytologic material for review (2 FNAs and 6 touch preps prepared at the time of frozen section). Surgical excisions in all 8 cases were performed. All 6 surgical specimens were received fresh and touch preps and/or smears were prepared and stained with Diff-Quik stain (Dade Behring, Newark, Dela.). Smears from the 2 FNA cases were stained with Diff-Quik, and in 1 case, ThinPrep (Hologic Inc., Marlborough, Mass.) smears were prepared and stained with Papanicolaou stain. Cell blocks and histologic sections were made and stained with hematoxylin and eosin. Immunohistochemical stains were performed on formalin-fixed, paraffin-embedded sections. Cytomorphology was evaluated by 2 independent pathologists who were blinded to the final histologic diagnosis. We then evaluated cytomorphology of touch preps from 6 histologically confirmed non-CD, reactive lymph node excisions.

Results

Relevant clinical findings are summarized in Table 1. The 8 patients (5 women, 3 men) had a mean age of 40 years (range: 29-63 years). The patients presented with masses in the following locations: thorax/mediastinal lymph nodes (3), neck lymph nodes (2), abdominal/pelvic lymph nodes (2), and parotid gland (1). Half of the patients (4 of 8) were serologically tested for HIV, and all were negative. The histologically confirmed subtypes were hyaline vascular (5), plasma cell (2), and mixed (1). One PC-CD patient had a history of drug-induced lupus and the other was immunosuppressed after renal transplant.

Two of the 8 cases were sampled by FNA. Intraoperative cytology with touch preps was performed in the remaining 6 cases. Grossly, the lymph nodes had a diffuse tan cut surface (Fig. 1D).

Cytomorphology

All cases were cellular specimens with a dyshesive heterogenous background population composed predominantly of small, mature lymphocytes (Fig. 1A-B). Eosinophils and neutrophils were not prominent. Follicular dendritic cells (FDCs) were present in clusters and as single binucleated cells with large nuclei and distinct nucleoli. They had ample, delicate pale cytoplasm with frequent streaking and indistinct cytoplasmic borders. Some of these cells contained mature cytoplasmic lymphocytes (emperipolesis phenomenon) (Fig. 1B). The cytoplasm was sky blue on Diff-Quik stains and green-blue on Papanicolaou stains. Nuclei usually had fine, even chromatin, regular nuclear borders, and small nucleoli. Few FDCs had indented nuclei or nuclear grooves. Only 2 cases, both HVCD, had coarse chromatin. The chromatin had a clumped appearance in one case and the chromatin in the other case resembled wrinkled tissue paper. Naked nuclei were present in almost all cases (7 of 8).

HVCD cases had traversing, mostly hyalinized capillaries (Fig. 1A) and large tissue fragments. Few plasma cells and tingible body macrophages were observed. All cases had multinucleated FDCs, and most of these cells showed lymphocyte emperipolesis (3 of 5 cases).

In the PC-CD cases, fewer FDC clusters were present. Both cases had increased mature plasma cells, including binucleate forms (Fig. 2A), and one case had plasmablasts. All had tingible body macrophages. One case had hyalinized capillaries. The other case showed multinucleated FDCs with lymphocyte emperipolesis (Fig. 2A inset).

The mixed case showed a background heterogenous lymphoid population composed mainly of small, mature lymphocytes with large tissue fragments. Traversing capillaries were not present, but both lymphocyte emperipolesis and multinucleated FDCs were observed. Plasma cells were not increased. Lymphocytes were arranged around follicular centers in a whirled pattern, reminiscent of the concentric lymphocyte arrangement seen in histologic sections.

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