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Case Report

Cytology of Castleman's disease (hyaline-vascular type) masquerading as Hodgkin's lymphoma

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Abstract: Castleman disease (CD) is a rare benign disorder presents as a lymph nodal mass in mediastinum, cervical, axillary or abdomen. Due to the presence of dysplastic dendritic cell in a background mature lymphocyte and plasma cell, it mimics Hodgkin disease (HD). Synchronous and metachronous occurrence in HD and CD can also occur. An 11-year-old male presented with cervical lymphadenopathy (3.5 × 3.5 cm). Fine needle aspiration shows atypical binucleate cell in a background of small lymphocytes, a diagnosis of Hodgkin disease is suggested. Excisional biopsy showed classical features of Hyaline vascular Castleman disease. Careful cytological evaluation and clinical correlation is required for definitive diagnosis.

Keywords: Castleman's disease, Hodgkin's lymphoma, hyaline vascular, lymphadenitis, fine needle aspiration cytology

Introduction

Castleman disease (CD) is benign hyperplastic lymphadenopathy mimicking malignancy, first reported in 1956 by Benjamin Castleman [1]. It is also known as angiomatous lymphoid hamartoma, angiofollicular hyperplasia, giant lymph node hyperplasia, and follicular lymphoreticuloma. The exact prevalence of CD is not known but is estimated to be 21-25 cases per million per year [2]. It presents as mass lesion in body cavities (e.g., abdomen, pelvis, thoracic cavity) and mimics malignancies [3]. CD involves lymph nodes of the mediastinum, cervical, axillary, or abdominal localization [4, 5]. It occurs in diverse clinicopathological forms and, based upon sites of clinical involvement, can be unicentric (UCD; 90%) or multicentric (MCD).

Histopathologically, most cases of UCD show hyaline vascular (HV) morphology, and MCDs are a plasma cell (PC) variant; mixed variants were also seen. The diagnosis of CD is based on histological features. The HV type showed concentric arrangement of mantle zone cells around the germinal center. Dysplastic dendritic cells, along with hyalinized vessels, are seen in the regress germinal center. The PC variant does not have specific findings. There is marked expansion of the paracortical zone, which shows sheets of plasma cell [6, 7]. This feature can be seen in many other conditions, such as autoimmune diseases (SLE, rheumatoid arthritis), IgG4-related disease, and HIV infection. All of these potential causes should be excluded before diagnosing PC-variant CD. After diagnosis of CD is established, cases should be screened for human herpes virus 8 (HHV8), and for the presence of multifocal lesion by computerized tomography or magnetic resonance imaging. The diagnosis is then further classified into UCD or MCD. Idiopathic MCD (iMCD) is determined according to the international consensus on CD for diagnosis of iMCD by Fajgenbaum et al. [7, 8].

The association of CD and lymphoma can be synchronous mostly with Hodgkin lymphoma (HL) or metachronous (with HL or large B-cell lymphoma) [9]. It may be syndromic, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), or TAFRO syndrome. The other associated diseases include paraneoplastic pemphigus, plasma cell dyscrasia, and Kaposi's sarcoma [10]. Due to presence of binucleate dysplastic dendritic cells in

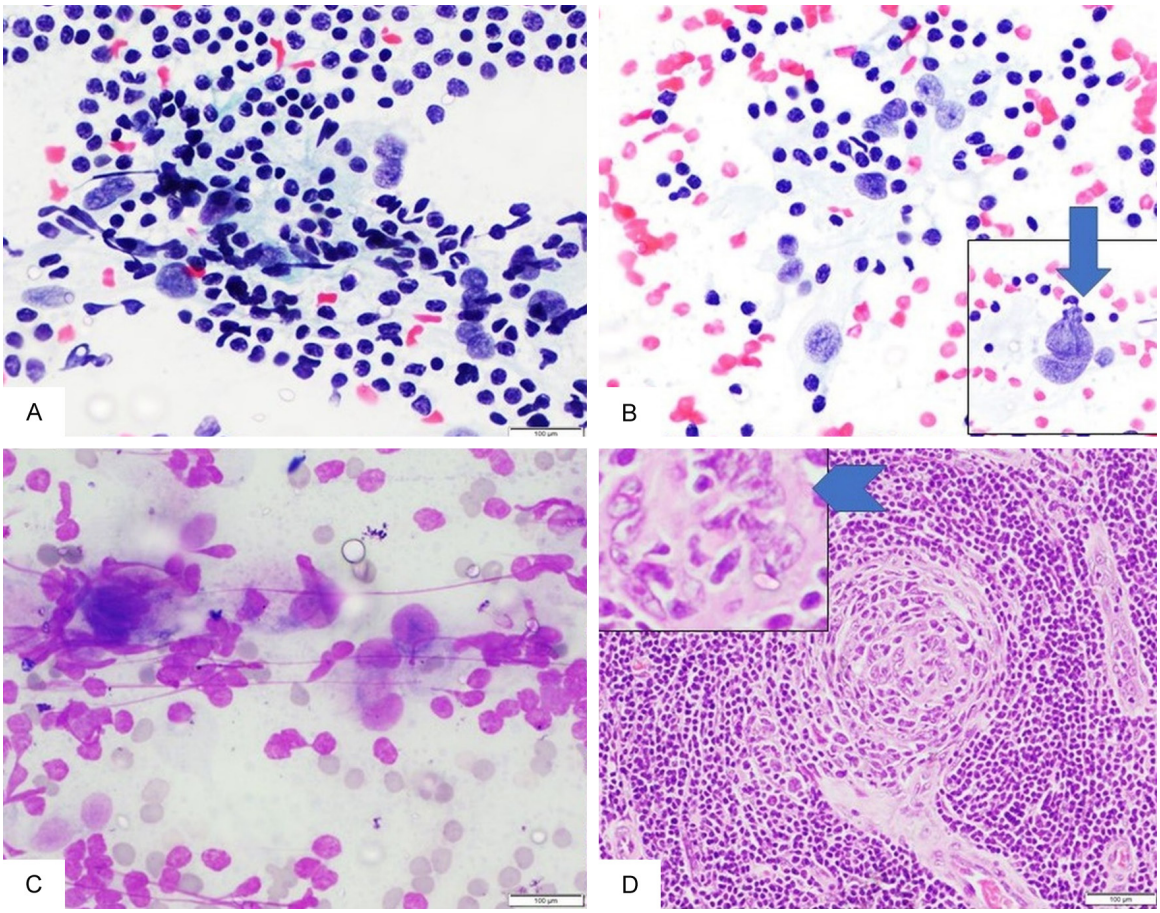

Figure 1. Fine-needle aspiration cytology and histopathological findings of lesion tissues. A: Right cervical lymph node shows lymphoid cells with all stages of maturation along with large oval to round cell with one to two nuclei (Pap × 100); B: The large atypical cells have coarse chromatin with appearance of wrinkled tissue paper (PAP × 200); C: Large atypical mononucleated and binucleated cells with conspicuous nucleoli (MGG × 400); D: Excision biopsy shows large follicles with marked vascular proliferation and hyalinisation of the germinal centre and onion skinning appearance (H&E × 200).

the background of mature PCs and lymphocytes, CD mimics morphologically HL in fine-needle aspiration cytology (FNAC). Here, we report a case of CD cytomorphologically mimicking HL and confirmed histopathologically as CD.

Case presentation

An 11-year-old male presented with an enlarged right-side cervical lymph node (3.5 × 3.5 cm), which has been reported to be firm in consistency and non-tender for the past 2 years. There was no other systemic manifestation. FNAC from the mass showed a reactive lymphoid population with an excess of mature lymphocytes. Additionally, there were large atypical mononuclear and binucleated cells with large nuclei and distinct small nucleoli. These cells are form loose clusters. Capillaries and eosinophils were not seen (**Figure 1A-C**). Based on the cytological findings, HL was suggested. In view of suspicion of Hodgkin lymphoma on FNAC, an excisional biopsy of mass was done for confirmation of diagnosis. Hodgkin lymphoma of histology show polymorphous population of cells comprising mature lymphocyte, eosinophil, plasma cell with interspersed neoplastic Reed Sternberg (RS)/Hodgkin cell. RS cell also can be seen in many other benign and malignant conditions. The lymphnodal architecture and the inflammatory milieu is required for diagnosis. So, biopsy confirmation is required for treatment. The patient undergone excisional biopsy the mass. As the mass is 3 cm in maximum dimension complete excision of the mass was done. Excisional biopsy of the cervical lymph node showed large follicles with marked follicu-

lar dendritic cell proliferation and hyalinized vessel in the germinal center. Lymphocytes surround the follicle, mimicking onion skin (**Figure 1D**). The HV variant of CD was diagnosed based on histomorphological features. After diagnosis the Castleman disease, no further treatment was given as the index case was Unicentric and patient was asymptomatic.

The patient remained disease-free until the last follow-up at 24 months.

Discussion

Castleman disease is an atypical lymphoproliferative disorder with features intermediate between benign and malignancy. The exact aetiology is unknown, but the two suggested hypothesis is autoimmune and viral aetiology. All the organs can be involved by Castleman disease. The most common presentation is lymphadenopathy. The extranodal sites include the head and neck region (e.g., parotid, larynx), retroperitoneal organ (e.g., pancreas), and meninges [3-5]. Among the histological types of CD, the HV variant is more prevalent than the PC variant and is mostly asymptomatic. The HV variant affects younger populations and has a benign clinical course. Unlike HV, the PC variant predominates in older populations, has a multifocal presentation, and has systemic manifestations such as fever and anemia [3-5].

Recognition of CD in cytology smears is often difficult, and only a few case reports are available. The cytological features of CD include marked proliferation of dendritic cells. The cells are usually binucleated, with prominent nuclei and distinct small nucleoli. The cells have a moderate amount of cytoplasm, and their borders are not distinguishable. Papanicolaou staining shows the cells to have a bluish-green appearance. Mallick et al. proposed criteria for diagnosis of CD on FNAC and suggested dysplastic changes in dendritic cells, a prominent feature of CD [11]. Few cases show multinucleated follicular dendritic cells. The background population mostly depends upon the type of CD; small lymphocytes in cases of the CD-HV subtype and predominantly plasma cell in the CD-PC subtype. Binucleated and abnormal forms of plasma cell can be seen. Mostly, the plasma cells are polyclonal, but light chain restriction cannot rule out the possibility of CD [12]. Unlike HL, eosinophils and Reed-Sternberg cells are not seen. Many authors have described the presence of traversing capillaries in the FNA smear in the CD-HV variant; however, this is not a constant feature in all cases; its presence will support the diagnosis [11, 13]. In the index case, our smear does not have prominent capillaries. Malzone et al. describe the imaging findings of a hypervascular mass with a well-delineated margin, which is hypoechogenic [14].

The differential diagnosis depends upon the location. As the most common site of CD is the mediastinum and retroperitoneum, the differential diagnoses include HL. Mostly, CD mimics HL due to presence of binucleated dendritic cells with prominent nucleoli in a background of mature lymphocytes and plasma cells. However, the nucleoli of the Reed-Sternberg cells are larger than the dendritic cell, which has minimal nucleoli. The dendritic cells have moderate cytoplasm with indistinct cytoplasmic borders. The presence of eosinophils in the background favors the diagnosis of HD. Immunocytochemistry (CD30- and CD15-positivity) is undoubtedly useful for diagnosis. But in our view, without cell block, immunocytochemistry may not always prove helpful. Castleman disease-like features may be seen in other lymphomas, but it presents in the focal area.

A review by Lyapichev et al. showed that most CD cases (76%) associated with HL are of the PC variant, followed by the mixed variant. The HLs are of interfollicular variant (62%), followed by the nodular sclerosis variant (22%) [9, 15]. Rarely, thymoma (if the mass is located in the mediastinum) is the differential diagnosis, but the background cells show a mixture of mature and immature T cells, and the epithelial cells are smaller than dendritic cells. The mass in the salivary gland may be confused with Warthin's tumor. The dirty background of Warthin's tumor and radiologically confirmed, well-defined cystic lesions help corroborate the diagnosis. The other common differential diagnosis incudes small B-cell lymphoma, due to presence of mature lymphocytes in the background. The presence of capillaries will favour CD. Immunocytochemistry and flowcytometry will be helpful to rule out the possibility of non-HL.

The treatment of CD depends upon the type of CD: UCD or MCD. The UCD type, usually of HV

type on histology, can be managed by surgical excision; the recurrence rate is very low. In case of incomplete excision, a single agent, rituximab (375 mg/m^2). Other treatments for unresectable cases include vascular ablation or radiotherapy. UCD has excellent prognosis; 94% of cases have a 10-year survival [16-18].

Multicentric CD is usually of PC variant or, rarely, of mixed variant. The treatment depends upon further the etiology. Based on clinical features, laboratory findings, and HHV positivity on histopathology, MCD can be classified as HHV8-MCD or non-HHV MCD. Among the non HHV type, it may be associated with the syndromes TARFO or POEMS. If all the etiology excluded, it classifies as idiopathic MCD (iMCD). Rituximab (375 mg/m^2 weekly for 4 weeks) is the choice for treating HHV8-MCD [18, 19]. In severe refractory cases, the addition of etoposide (100 mg/m^2) weekly should be helpful [17]. MCD associated with POEMS disease should be treated for plasma cell dyscrasia, which includes therapy for multiple myeloma followed by stem cell transplant. Treatment of iMCD follows the international consensus, CDCN, and on the severity. The non-severe case treated with monoclonal antibodies against IL6 (siltuximab) ± oral steroids [8]. Rituximab combined with thalidomide can be used along with steroids in non-severe cases. In aggressive cases, siltuximab with parenteral steroids is the preferred choice. Combination chemotherapy RCHOP or RCVP are alternatives to monoclonal antibody therapy [18].

Conclusion

Binucleated dysplastic dendritic cells in a background of mature lymphocytes and plasma cell on FNA smear closely mimics HL. Histopathological examination should be done to confirm diagnosis prior to treatment. Castleman disease should be kept as a differential diagnosis of all localized or multicentric lymphadenopathy, especially in asymptomatic patients. Though cytological features are well described, diagnosis based solely on cytopathology should be avoided. In cases with a high index of suspicion on cytopathology, histopathological examination is encouraged to prevent misdiagnosis.

Disclosure of conflict of interest

None.

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References

[1] Castleman B, Iverson L and Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956; 9: 822-30.

[2] Munshi N, Mehra M, van de Velde H, Desai A, Potluri R and Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. Leuk Lymphoma 2015; 56: 1252-60.

[3] Talat N and Schulte KM. Castleman's disease: systematic analysis of 416 patients from the literature. Oncologist 2011; 16: 1316-24.

[4] Keller AR, Hochholzer L and Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972; 29: 670-83.

[5] Singh A, Purkait S, Mallick S, Ramteke P, Das CK, Gogia A, Sharma MC and Kumar L. Clinicopathological profile of Castleman's disease in Indian population: experience from a tertiary care center. Indian J Hematol Blood Transfus 2020; 36: 254-259.

[6] Wu D, Lim MS and Jaffe ES. Pathology of Castleman disease. Hematol Oncol Clin North Am 2018; 32: 37-52.

[7] van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, Munshi N, and Schey S, Streetly M, Pierson SK, Partridge HL, Mukherjee S, Shilling D, Stone K, Greenway A, Ruth J, Lechowicz MJ, Chandrakasan S, Jayanthan R, Jaffe ES, Leitch H, Pemmaraju N, Chadburn A, Lim MS, Elenitoba-Johnson KS, Krymskaya V, Goodman A, Hoffmann C, Zinzani PL, Ferrero S, Terriou L, Sato Y, Simpson D, Wong R, Rossi JF, Nasta S, Yoshizaki K, Kurzrock R, Uldrick TS, Casper C, Oksenhendler E and Fajgenbaum DC. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018; 132: 2115-2124.

[8] Mohtaram A, Afif M, Sghiri T, Rami A, Latib R, Kettani F, Ben Ameur El Youbi M, Boutayeb S, Kebdani T, Benjaafar N, Aaribi I and Errihani H. Coexistence of Hodgkin's lymphoma and Castleman's disease: a case report with successful response to chemotherapy and radiotherapy. Case Rep Oncol Med 2013; 2013: 487205.

[9] Larroche C, Cacoub P, Soulier J, Oksenhendler E, Clauvel JP, Piette JC and Raphael M. Castleman's disease and lymphoma: report of eight cases in HIV-negative patients and literature review. Am J Hematol 2002; 69: 119-26.

[10] Mallik MK, Kapila K, Das DK, Haji BE and Anim JT. Cytomorphology of hyaline-vascular Castleman's disease: a diagnostic challenge. Cytopathology 2007; 18: 168-74.
[11] Murro D, Agab M, Brickman A, Loew J and Gattuso P. Cytological features of Castleman disease: a review. J Am Soc Cytopathol 2016; 5: 100-106.
[12] Meyer L, Gibbons D, Ashfaq R, Vuitch F and Saboorian MH. Fine-needle aspiration findings in Castleman's disease. Diagn Cytopathol 1999; 21: 57-60.
[13] Malzone MG, Campanile AC, Sanna V, Ionna F, Longo F, De Chiara A, Setola SV, Botti G and Fulciniti F. Castleman's disease of a submandibular mass diagnosed on Fine Needle Cytology: report of a case with histopathological, immunocytochemical and imaging correlations. Intractable Rare Dis Res 2016; 5: 36-41.
[14] Lyapichev KA, You MJ, Vega F, Solis LM and Medeiros LJ. Classic Hodgkin lymphoma and Castleman disease: an entity appears to be emerging. Virchows Arch 2020; 477: 437-444.
[15] Robert JH, Sgourdos G, Kritikos N, Didier D and Terraz S. Preoperative embolization of hypervascular Castleman's disease of the mediastinum. Cardiovasc Intervent Radiol 2008; 31: 186-8.
[16] Safford SD, Lagoo AS and Mahaffey SA. Preoperative embolization as an adjunct to the operative management of mediastinal Castleman disease. J Pediatr Surg 2003; 38: E21-3.
[17] Lomas OC, Streetly M, Pratt G, Cavet J, Royston D, Schey S and Ramasamy K; British Society for Haematology (BSH) Committee. The management of Castleman disease. Br J Haematol 2021; 195: 328-337.
[18] Powles T, Stebbing J, Montoto S, Nelson M, Gazzard B, Orkin C, Webb A and Bower M. Rituximab as retreatment for rituximab pretreated HIV-associated multicentric Castleman disease. Blood 2007; 110: 4132-3.
[19] Bower M, Newsom-Davis T, Naresh K, Merchant S, Lee B, Gazzard B, Stebbing J and Nelson M. Clinical features and outcome in HIV-associated multicentric Castleman's disease. J Clin Oncol 2011; 29: 2481-6.