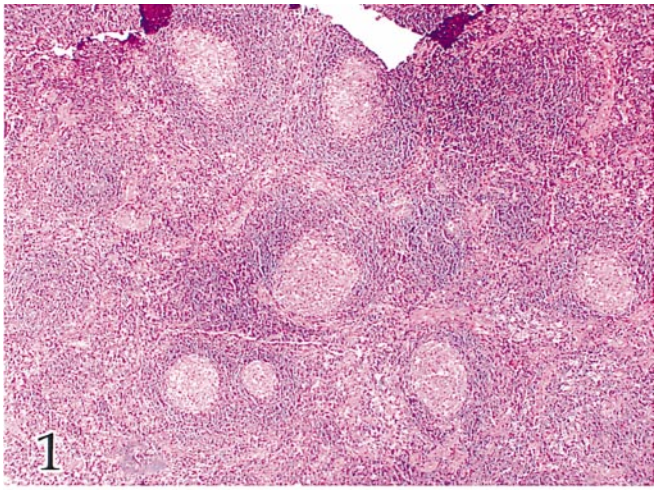
A 53-Year-Old White Man With Right-Sided Supraclavicular Lymphadenopathy

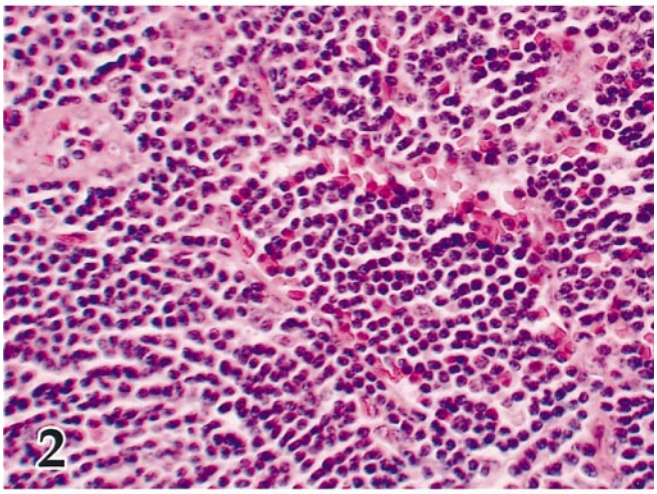
Stacie L. Roshong-Denk, MD, MSBS; Summer L. Bohman, BS; Robert L. Booth, MD

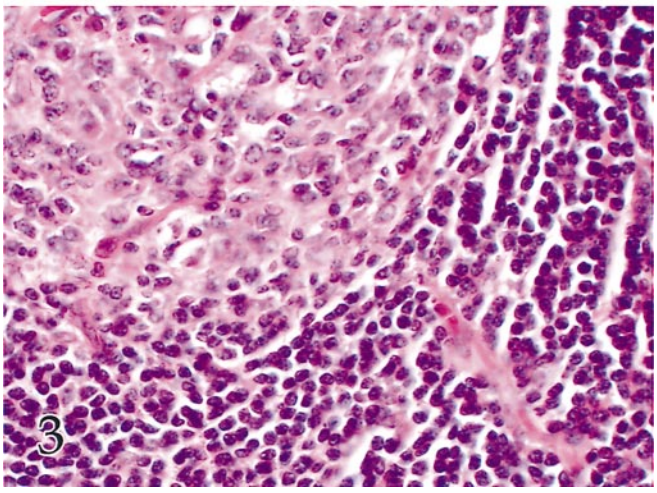
A 53-year-old white man with a history of hypothyroidism, hypertension, asthma, and obstructive sleep apnea presented to the clinic with right-sided supraclavicular lymphadenopathy that had been enlarging for 3 months. The lymphadenopathy was associated with a dull and constant ache, and hurt when he lifted heavy objects. The patient was fatigued, but he did not have weight loss, fever, or night sweats. Chest radiographs were normal. A biopsy of the mass was performed.

The biopsy consisted of a multinodular soft tissue mass that measured 3.8 × 1.9 × 1.2 cm. Touch preparations showed clusters of small lymphocytes and macrophages. Flow cytometry did not detect a monoclonal cell population. Microscopic examination of the hematoxylin-eosin–stained sections showed lymph node hyperplasia with concentric mantle zones (Figure 1) and prominent vascular proliferation within the interfollicular zones (Figure 2). Hyperplastic germinal centers were identified; however, others were atrophic and hyalinized. Moreover, there was a targetoid alignment of lymphocytes in the mantle zone of the hyalinized follicles with an occasional capillary penetrating radially into the germinal centers (Figure 3). We found no evidence of metastatic disease.

What is your diagnosis?







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From the Department of Pathology, Medical College of Ohio, Toledo.

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Corresponding author: Robert L. Booth, MD, Department of Pathology, Medical College of Ohio, School of Medicine, 3000 Arlington Ave, Toledo, OH 43614-2598 (e-mail: rbooth@mco.edu).

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Pathologic Diagnosis: Hyaline-Vascular Variant of Castleman Lymphadenopathy

Castleman disease (CD), also called angiofollicular or giant lymph node hyperplasia and angiomatous lymphoid hamartoma, was first described by Castleman et al[1] in 1956 in a report of cases of solitary masses in the mediastinum. There are 2 distinct histologic patterns, namely, the hyaline-vascular and plasma cell variants. Clinically, CD is either unicentric (localized) or multicentric. The multicentric type is associated with human herpesvirus 8 (HHV-8) infection and is more common in patients infected with human immunodeficiency virus (HIV).[2] The pathogenesis is complex. The prognosis for unicentric CD is good; however, it is unpredictable in the multicentric type.

The hyaline-vascular variant comprises 90% of cases and presents as a unicentric lymphadenopathy involving the mediastinum.[3] Symptoms, if present, are due to mass effect. Microscopically, an increased number of small lymphoid follicles, many of which are hyalinized, and vascular proliferation of the interfollicular zones are evident. The lymph node sinuses are inapparent. Frequently, a capillary penetrates the follicle, imparting a ''lollipop'' appearance. Lymphocyte alignment in the mantle zone gives a targetoid or stadium-seating appearance. The pathogenesis of this variant is thought to be a disorder of stromal cells, which might explain why the hyaline-vascular variant can evolve into mesenchymal tumors.[4] Dysplastic or atypical follicular dendritic cells (FDCs) have frequently been described in the hyaline-vascular variant, yet their role in the pathogenesis of CD is unclear.

The hyaline-vascular variant of CD has also been associated with FDC sarcoma, angiomyoid proliferative lesions, vascular tumors, and inflammatory myofibroblastic tumor.[5] In support of this association, Cokelaere et al[5] described the presence of a clonal proliferation of FDCs that expressed an intragenic high mobility group protein I-C (*HMGI-C*) gene rearrangement involving the long arm of chromosome 12. This gene encodes proteins that facilitate transcription by altering the stereospecific DNA enhancer and promoter sequences to enable efficient transcription.[5] Deregulation of *HMGI-C* is important in the development of mesenchymal tumors. Moreover, Sun et al,[6] using complementary DNA microarray analysis, found that epidermal growth factor receptor transcripts are up-regulated in FDC sarcoma, as well as in FDCs of CD, but not in FDCs of reactive germinal centers or in those associated with lymphomas. Furthermore, increased epidermal growth factor receptor expression in the hyaline-vascular variant of CD was correlated with FDC dysplasia, an increased number of regressed follicles, and stromal overgrowth.[6] These data suggest that a clonal proliferation of FDCs may explain the stromal overgrowths and neoplasms that are associated with the hyaline-vascular variant of CD. In most cases, complete surgical removal or radiotherapy is curative.

The plasma cell type tends to be multicentric and is associated with systemic disease. Fever, fatigue, night sweats, and weight loss are usually present.[3] The physical findings coupled with constitutional symptoms may mimic a lymphoma rather than a benign process. Microscopically, follicular hyperplasia with large active germinal centers is characteristic; however, involuted, atrophic, or hyalinized follicles may coexist.[7] Regardless of follicle type, the plasma cell variant differs from the hyaline-vascular type by the presence of a diffuse plasma cell infiltrate within the interfollicular and medullary areas, and hypergammaglobulinemia is common. Moreover, this variant is associated with elevated interleukin 6 (IL-6) levels that are believed to play a role in the pathogenesis of this form of CD.[4] The high levels of IL-6 may also explain the systemic symptoms associated with this variant. The plasma cell variant is more aggressive than the hyaline-vascular type and is treated with combination chemotherapy. This variant may progress to lymphoma, owing to the constitutive expression of IL-6.[4]

The multicentric form of CD is morphologically identical to the plasma cell variant. Although this type of CD is most common in individuals infected with HIV, reports of this disease have also been described in patients who have undergone renal transplantation or received immunosuppression therapy, such as cyclosporin A.[8] The multicentric form is associated with HHV-8 infection. Fever, hepatosplenomegaly, peripheral lymphadenopathy, edema, and pulmonary symptoms, as well as secondary tumors related to HHV-8 infection (eg, Kaposi sarcoma, non-Hodgkin lymphoma, or plasmablastic lymphoma) are common, especially with coexisting HIV disease.[2] Like the plasma cell variant, the pathogenesis of multicentric disease stems from high levels of IL-6; however, it is virally mediated.[4] Human herpesvirus 8 encodes a viral IL-6 (v-IL-6), which induces endogenous human IL-6 production.[4] Multicentric disease follows an aggressive course in patients with HIV and may represent a medical emergency.[2] Treatment includes chemotherapy, and the HHV-8 viral load is monitored in conjunction with chemotherapy to assess the effectiveness of treatment.

The etiology of CD is unknown. It has been hypothesized that the 2 variants may represent a continuum of the same disease, that is, the plasma cell variant evolving into the hyaline-vascular variant; however, most investigators consider the 2 variants to be distinct entities.[4] Interestingly, Menke et al[7] found an aberrant immunophenotypical population of mantle zone B lymphocytes in all the variants of CD.

References

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer.* 1956;9:822–830.
2. Aoki Y, Tosato G. Pathogenesis and manifestations of human herpesvirus-8-associated disorders. *Semin Hematol.* 2003;40:143–153.
3. Ioachim HL, Ratech H. Castleman lymphadenopathy. In: *Ioachim's Lymph Node Pathology.* 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002: 246–253.
4. van den Berge M, Pauwels P, Jakimowicz JJ, Creemers CJ. Hyaline vascular Castleman's disease: a case report and brief review of the literature. *Neth J Med.* 2002;60:444–447.
5. Cokelaere K, Debiec-Rychter M, De Wolf-Peeters C, Hagemeijer A, Sciot R. Hyaline vascular Castleman's disease with HMGIC rearrangement in follicular dendritic cells. *Am J Surg Pathol.* 2002;26:662–669.
6. Sun X, Chang K, Abruzzo LV, Lai R, Younes A, Jones D. Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease. *Hum Pathol.* 2003;34:835–840.
7. Menke DM, Tiemann M, Camoriano JK, et al. Diagnosis of Castleman's disease by identification of an immunophenotypically aberrant population of mantle zone B lymphocytes in paraffin-embedded lymph node biopsies. *Am J Clin Pathol.* 1996;105:268–276.
8. Bollen J, Polstra A, Van Der Kuyl A, et al. Multicentric Castleman's disease and Kaposi's sarcoma in a cyclosporin treated, HIV-1 negative patient: case report. *BMC Blood Disord.* 2003;3:3.