Peripheral T-Cell Lymphoma With Extensive Dendritic Cell Network Mimicking Follicular Dendritic Cell Tumor

A Case Report With Pathologic, Immunophenotypic, and Molecular Findings

Cindi R. Starkey, MD, PhD,1 Ayumi I. Corn, MD,1 Richard S. Porensky, MD,2 David Viswanatha, MD,1 and Carla S. Wilson, MD, PhD1

Key Words: Hematopathology; Peripheral T-cell lymphoma; Follicular dendritic cell network

DOI: 10.1309/Q1YKAU1XXENQNVQ

Abstract

Peripheral T-cell lymphoma (PTCL) with a nodular pattern of growth is uncommon and may be misdiagnosed initially as a B-cell lymphoma or reactive process. We report a case of a rapidly growing PTCL with a distinctly nodular pattern in an axillary lymph node from an 89-year-old man. Immunohistochemical stains for CD21, CD23, and CD35 highlighted an extensive dendritic cell network that imparted the nodular appearance and, in addition, was associated intimately with the neoplastic cells. The neoplastic cells otherwise had an immunophenotype similar to previously reported cases of PTCL with a nodular pattern and germinal center origin (CD3+, CD4+, CD5+, bcl-6+, CD31+, subset CD10+, subset CXCL13+, and subset CD79a+). Molecular studies confirm a clonal T-cell receptor γ gene rearrangement. This case emphasizes unusual morphologic features in a PTCL that may be mistaken for follicular lymphoma or a tumor of follicular dendritic cell origin.

The World Health Organization classification places mature T-cell neoplasms that do not have morphologic or immunophenotypic features of a well-defined entity into the category of peripheral T-cell lymphoma (PTCL), unspecified.1 This has become the most common type of mature T-cell lymphoma diagnosed in Western countries, accounting for half of PTCLs and 3.7% of non-Hodgkin lymphomas. Although PTCL typically shows a diffuse pattern of infiltration, rare cases of PTCL with a nodular pattern of growth have been described that vary in cytologic appearance.2-8 These cases have been included most commonly in the category of PTCL, unspecified.8 With their frequent helper T-cell immunophenotype, expression of germinal center–related antigens (CD10, CD79a, bcl-6, and CXCL13), and dendritic cell markers, they alternatively may represent a variant of angioimmunoblastic T-cell lymphoma (AITL). We report the case of an 89-year-old man with a PTCL demonstrating a nodular pattern of growth and a more prominent follicular dendritic cell (FDC) network than previously described for this type of lymphoma. The prominent staining with dendritic cell markers, including CD21, CD23, and CD35, initially raised concern for involvement by an FDC tumor, but additional immunohistochemical stains and identification of a monoclonal T-cell receptor γ (TCRγ) gene rearrangement confirmed an underlying neoplastic T-cell process.

Report of a Case

An 89-year-old man in declining health owing to severe chronic obstructive pulmonary disease saw his physician because of increasingly prominent bilateral axillary and cervical
lymphadenopathy. His medical history was significant for multiple basal cell and squamous cell carcinomas, melanoma, and renal cell carcinoma, for which he underwent a nephrectomy in 1989.

The physical examination revealed an extensive, scaly, excoriated, pruritic rash involving the head and trunk. A large nonhealing open wound of the scalp and a skull defect were present, secondary to recent excision of a squamous cell carcinoma. Laboratory data included a normal serum globulin level of 2.7 g/dL (reference range, 2.3-3.8 g/dL) and normal quantitative immunoglobulin and complement levels. Serial computed tomography scans demonstrated extensive lymphadenopathy involving the neck, mediastinum, and bilateral axilla. No hepatosplenomegaly was observed. The largest left axillary lymph node, measuring $5.0 \times 3.0 \times 2.0$ cm, was excised for evaluation. Morphologic, immunohistochemical, and molecular analyses on this lymph node specimen confirmed a diagnosis of a PTCL, as detailed in the following sections.

Owing to the patient’s poor overall health, he declined further staging procedures and elected not to receive therapy. The patient died approximately 3 weeks after diagnosis.

**Pathologic Findings**

Microscopic examination of the lymph node showed complete effacement of the normal architecture by irregular, pale pink, back-to-back nodules, which merged to form a serpiginous pattern in many areas [Image 1A]. The nodules consisted predominantly of intermediate to large cells with round to irregular nuclear contours, vesiculated chromatin, and 1 or 2 prominent nucleoli [Image 1B]. The cells had abundant eosinophilic to clear cytoplasm and indistinct cell borders. Intermixed were small lymphocytes, spindled cells, and frequent eosinophils. No increase in plasma cells was noted. The nodules had no germinal center formation and were devoid of mantle zones, with only minor collections of small lymphocytes in the internodular areas. High endothelial venules were not prominent and were localized primarily between the nodules, with no evidence of tumor angiocentricity or angiodestruction. The lymphomatous infiltrate extended through the lymph node capsule into the surrounding adipose tissue.

Immunohistochemical stains showed that the neoplastic cells were positive for CD3, CD4, CD5, CD45RO, CD45, and bcl-6, with significant subsets positive for CD10, CXCL13, and CD31 [Image 2]. A minority of cells showed coexpression of CD79a. The tumor cells were negative for CD8, CD15, CD20, CD30, CD57, CD68, CD138, anaplastic lymphoma kinase-1 (ALK-1), desmin, epithelial membrane antigen, keratin AE1/AE3, HMB-45, myeloperoxidase, and S-100. Ki-67 demonstrated positivity in up to 30% of lymphoma cells. The nodular proliferation was associated with an extensive FDC network that was brightly positive for CD21, CD23, and CD35 [Image 3A]. The FDC network intricately involved each nodule and defined its borders, without extending into the uninvolved internodular areas. Although the FDC network encircled the majority of cells within the nodules, clusters and linear arrays of malignant cells outside the FDC network were clearly negative for CD21, CD23, and CD35 (Image 3A, inset). In situ hybridization for Epstein-Barr virus (Epstein-Barr virus–encoded RNA) was positive in scattered B cells (Image 2B, inset) and [Image 3B].
Evaluation for clonality of the TCRγ and immunoglobulin heavy chain genes was performed by using the polymerase chain reaction (PCR) technique with post-PCR analysis performed by fluorescent capillary electrophoresis on an ABI 3100 Bioanalyzer (Applied Biosystems, Foster City, CA). This analysis revealed a clonal TCRγ gene rearrangement and no clonal rearrangement of immunoglobulin heavy chain genes.

Discussion

We describe an 89-year-old man with a PTCL showing a distinctly nodular growth pattern in association with an extensive FDC network resembling an FDC neoplasm. Immunohistochemical evaluation revealed the neoplastic cells to be of T-cell immunophenotype and positive for CD3, CD4, CD5, CD45RO, and bcl-6, with subsets positive for CD10, CD31, CXCL13, and CD79a. This immunophenotypic profile denotes a neoplasm of the germinal-center T-helper cell type and is similar to the immunophenotype reported for PTCLs with a nodular pattern. Molecular studies confirmed the clonal nature of this T-cell tumor.

PTCL most commonly exhibits a diffuse pattern of infiltration, whereas lymphomas with a nodular growth pattern are more commonly B-cell processes. PTCL with a nodular or follicular growth pattern has been described; however, to our knowledge, there are only 25 reported cases in the literature.

Image 2A, Lymphoma cells are CD4+ (original magnification ×200). B, Lymphoma cells are negative for CD20 (original magnification ×200). Inset, Epstein-Barr virus (EBV) in situ hybridization (EBV-encoded RNA, blue) and CD20 (brown) costaining demonstrates scattered EBV+ B cells localized primarily between tumor nodules (original magnification ×400). C, The majority of lymphoma cells are bcl-6+ (original magnification ×200). D, A subset of lymphoma cells are CXCL13+ (original magnification ×100).
Many reported PTCLs with a nodular pattern initially were misdiagnosed as follicular hyperplasia, atypical lymphoid infiltrate, or B-cell lymphomas, including follicular and marginal zone.3,6-8 Often, the cytologic features are most similar to those of follicular lymphoma, with a mixture of small and large neoplastic cells.2,3 This was not seen in our case. FDC networks associated with the nodular pattern of PTCL are described in many of the previously reported cases2,3,5 but not in all.4,6

Our case is unusual owing to the prominence of the FDC network that intertwined with and encircled many of the lymphoma cells within the loosely formed nodules, raising concern for a neoplastic FDC process. FDC neoplasms are rare and consist primarily of spindled cells, which are positive for CD21, CD23, and CD35 and variably positive for CD68 and S-100.1,9 The majority of neoplastic cells in our case did not have the characteristic spindled appearance of an FDC tumor, and, although the FDC markers (CD21, CD23, and CD35) seemed to be associated closely with the neoplastic infiltrate, clusters of malignant cells within and particularly along the periphery of the nodules were clearly negative for these markers. In addition, CD68 and S-100 were negative. A more extensive immunohistochemical evaluation established the correct diagnosis.

PTCL with a nodular pattern has been speculated to arise from germinal-center helper T cells with the unusual nodular growth pattern possibly relating to the capacity of these T cells to induce follicular structures. An alternative hypothesis by Jiang et al2 is that expression of CD31 on the neoplastic T cells promotes selective infiltration of lymphoid follicles by this type of lymphoma through patent perifollicular sinuses. Regardless of the source or manner of growth, the cellular expression of unusual activation and adhesion molecules undoubtedly has a role in the close association and interaction of lymphoma cells with FDCs in these tumors, giving rise to the nodular appearance.

Gene expression profiles of T-cell lymphoma link the chemokine CXCL13 to germinal-center T-helper cells.10 Expression of CXCL13 in PTCLs is regarded by some investigators to improve distinction between PTCL, unspecified and AITL.11,12 One downstream effect of CXCL13 is the stimulation and proliferation of FDCs, prominently observed in this case, but also a hallmark of AITL (particularly pattern III). Therefore, these uncommon lymphomas are likely a variant of AITL, although a number of clinical and morphologic features of our case are unusual for this diagnosis. Our lymphoma did not show the distinct arborizing networks of high endothelial venules, the extension of FDCs into and surrounding vascular structures in interfollicular areas, or the polymorphous infiltrate with frequent plasmacytosis more characteristic of AITL.13 A monoclonal B-cell population has been described in a subset of AITLs,13 and this was excluded by molecular studies in the present case. Large networks of desmin-positive reticulum cells, a consistent finding in AITL, also were not observed.14 The FDC network in our case was restricted to and defined the neoplastic T-cell infiltration, sparing uninvolved intermodal areas. Finally, the patient did not

!!Image 3!! A, CD23 highlights the striking proliferation of follicular dendritic cells (original magnification ×20). Inset, CD23 is intimately associated with the lymphoma cells, although small clusters are notably CD23– (original magnification ×400). B, CD21 highlights the extensive dendritic cell network that defines nodules of tumor cells. Epstein-Barr virus (EBV) in situ hybridization (EBV-encoded RNA, blue) and CD21 (brown) demonstrates scattered EBV+ cells, localized primarily between tumor cell nodules, without coexpression of CD21 (original magnification ×200).
have hepatosplenomegaly or hypergammaglobulinemia, which are clinical findings seen in a majority of patients with AITL.\textsuperscript{13}

We report on a unique case of PTCL with a nodular pattern of growth and extensive FDC proliferation, mimicking an FDC tumor. This case demonstrates the importance of considering a diagnosis of PTCL in lesions with a nodular pattern of growth, particularly in light of different treatment modalities for T-cell, B-cell, and dendritic cell processes.

From the Departments of Pathology, 1University of New Mexico Health Sciences Center, Albuquerque, and 2Maine Medical Center, Portland.

Address reprint requests to Dr Wilson: Dept of Pathology, University of New Mexico Health Sciences Center, MSC08 4640, University of New Mexico, Albuquerque, NM 87131.

Acknowledgments: We thank Michael Grady for technical assistance with images and Ahmet Dogan, MD, PhD, for performance and help with interpretation of CXCL13 immunohistochemical analysis.

References


