Primary T-Cell–Rich B-Cell Lymphoma of the Ethmoid Sinus

A Case Report With 5 Years of Follow-up

Jun Wang, MD; Nora C. J. Sun, MD; Sanford M. Weinstein, MD; Rinaldo Canalis, MD

The term T-cell–rich B-cell lymphoma (TCRBCL) was introduced in 1988 by Ramsay and associates to describe an unique variant of large B-cell non-Hodgkin lymphoma (NHL) that displayed morphologic features similar to peripheral T-cell lymphoma (PTCL) and Hodgkin disease.1,2 Histologic differentiation of TCRBCL from other lymphoproliferative diseases can be difficult.3,4 Early diagnosis of this entity is important to ensure proper treatment.5 Most patients with TCRBCL present with nodal disease, although primary extranodal involvement also occurs.1,2 The common primary extranodal sites include liver, soft tissue, dura, bone, stomach, intestine, bone marrow, and others.1,5,6 We describe here a case of primary TCRBCL of the ethmoid sinus in a 51-year-old man who had an excellent response to combined chemotherapy and radiotherapy.

REPORT OF A CASE

A 51-year-old man presented with a 3-month history of purulent nasal discharge with blurred and diminished vision of the right eye. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the head revealed a right ethmoid sinus mass that extended into the right superior nasal cavity, middle meatus, nasal septum, sphenoid wing, nasopharynx, and the right and left medial orbital wall (Figure 1, A). The tumor also extended posteriorly along the base of the cranial vault, destroying the pterygoid plates inferiorly and the clinoid process superiorly. An ethmoid sinus biopsy specimen was obtained. A diagnosis of TCRBCL was rendered based on morphologic and immunohistochemical findings (see “Pathologic Findings”). Staging procedures, including detailed head and neck examination, body CT scan, and bone marrow examination, were undertaken. No evidence of lymphomatous involvement was identified outside the ethmoid sinus.

The patient initially underwent 25 sessions of conventional fractionated radiation therapy with a total dose of 45 Gy over 36 elapsed days. Follow-up MRI showed resolution of the ethmoid mass 5 months later. Six months after radiotherapy, however, the lymphoma relapsed in the ethmoid sinus. Combined chemotherapy consisting of 6 courses of standard CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone) and additional 25 sessions of 45 Gy of fractionated radiation treatment were administered. Repeated head CT and MRI scans showed complete resolution of the ethmoid mass (Figure 1, B). The patient has been followed up every 6 months for more than 5 years with periodic head CT scans. He remains well without clinical or radiologic evidence of recurrence or disseminated lymphoma.

PATHOLOGIC FINDINGS

The biopsy specimen showed multiple tiny fragments of respiratory epithelial-lined mucosa and underlying stroma that were heavily infiltrated by numerous lymphoid cells, histiocytes, occasional plasma cells, and neutrophils with marked fibroblastic response and capillary proliferation (Figure 2). The predominant population of the lymphoid cells was small lymphocytes with folded or irregular nuclei, clumped chromatin, and an indiscernible amount of cytoplasm. Admixed with these small lymphocytes were scattered large lymphocytes. The large cells had oval, highly folded or multilobulated nuclei containing coarse, stippled chromatin and 1 or several prominent nucleoli. Occasional large lymphocytes resembled Reed-Sternberg (RS) variants. It was estimated that the large cells constituted less than 20% of all nucleated cells. Mitotic figures were infrequently noted.

Cell marker study by an immunoperoxidase method revealed that the large lymphoid cells expressed CD45, CD20, and MB2 (Figure 3, A). They were nonreactive with anti-CD3, anti-CD4, anti-CD43, and anti-CD45RO, respectively (Figure 3, B). The large cells were also negative for...
CD15, CD30, \( \lambda \) and \( \kappa \) light chains, lysozyme, vimentin, cytokeratin, and latent membrane protein 1 (LMP-1) for Epstein-Barr virus (EBV). In addition, in situ hybridization failed to detect EBV-encoded messenger RNA (EBER). The small lymphocytes in the background expressed T-cell markers CD3, CD43, CD45RO, and CD4. The diagnosis of TCRBCL of the ethmoid sinus was established.

**COMMENT**

The characteristics of TCRBCL, ie, a diffuse large B-cell lymphoma with a predominant population of reactive small T cells and a variable number of histiocytes morphologically resembling PTCLs, were originally recognized by Jaffe and colleagues in 1984. These authors proposed the term *pseudo T-cell lymphoma*. In 1988, Ramsay and associates delineated the lesion on morphologic, immunologic, and genetic grounds and introduced the term *T-cell–rich B-cell lymphoma*. Currently, TCRBCL is considered as a variant of diffuse large B-cell lymphoma. The neoplastic large B-cells constitute less than 20% to 25% of the total cellular population scattered among a prominent component of reactive T lymphocytes and variable numbers of histiocytes, including epithelioid cells and occasional eosinophils in the background. Stromal fibrosis and hypervascularization may also be present. The T-cell component, by definition, must be greater than 50% at minimum. The neoplastic B lymphocytes display a heterogeneous spectrum of morphology, including centroblasts, immunoblasts, multilobated, multinucleated, RS-like cells (especially the lymphocytic and histiocytic [L&H] variants of RS cells), as well as large cleaved cells and large noncleaved cells. In many instances, 2 or 3 morphologic types of tumor cells are often present in the same lesion.

The difficulty in reaching a correct diagnosis of TCRBCL is well illustrated in a large series study in which the initial diagnosis of 36 (82%) of 44 patients with TCRBCL was incorrect. It has been repeatedly stated that immunohistochemical stain on paraffin sections provides the best adjunct to morphologic diagnosis. It should also be pointed out that TCRBCL may occur concurrently with or evolving from a follicular lymphoma or lymphocyte-predominant Hodgkin disease (LPHD), nodular type. Adequate sampling, careful histologic examination, and ancillary studies such as immunophenotypic or genotypic studies are essential to reach a correct diagnosis.

The B-cell clonality can usually be demonstrated by immunologic or molecular methods in TCRBCL. Immunophenotypically, the neoplastic B cells stain uniformly positive for most B-cell markers, such as CD20, CD45RA, CD79a, MB1, MB2, CDw75, and CD74, but they are negative for T-cell markers, myelomonocytic marker CD15, and activating marker CD30. The small T cells are immunophenotypically normal reactive T lymphocytes. Genetically, the majority of cases show immunoglobulin heavy-chain gene rearrangement in the neoplastic B cells as demonstrated by polymerase chain reaction and/or Southern blot techniques. Occasionally, light-chain gene rearrangement can be demonstrated as well, whereas the T cells usually showed germline (no T-cell receptor [TCR] gene rearrangement). On the contrary, the spectrum of neoplastic T cells in PTCL displays gene rearrangement with 1 or more TCR genes. It should be noted that an occasional PTCL may contain clusters of reactive

**Figure 1.** A, T1-weighted postgadolinium coronal magnetic resonance (MR) image shows an ethmoid sinus mass (arrow), which extends into the adjacent nasal cavity, orbital wall, and the base of cranial vault. B, T1-weighted postgadolinium coronal MR image shows complete regression of the tumor after combined chemotherapy and radiotherapy.
Figure 2. Ethmoid sinus biopsy specimen shows a heavy lymphohistiocytic infiltration of the sinus mucosa by scattered large neoplastic lymphoid cells (arrows) admixed with numerous small lymphocytes and scattered histiocytes (hematoxylin-eosin, original magnification ×430).

Figure 3. A, Immunohistochemical stain shows strong positivity of large neoplastic lymphoid cells for B-cell marker CD20 (L26). B, These large neoplastic cells were negative for T-cell marker CD3 (arrows), but the small lymphocytes were positive for the T-cell marker (both A and B, avidin-biotin complex immunostain, original magnification ×430).

polyclonal B immunoblasts. Since the morphology of the neoplastic cells in TCRBCL resembles RS cells, especially L&H variants of RS cells, differential diagnosis between TCRBCL and LPHD is necessary. As stated earlier, the neoplastic cells in TCRBCL usually express pan B-cell markers with monoclonal immunoglobulin expression, which may be demonstrated by immunohistochemical or molecular methods. They are usually negative for CD30 and CD15 immunostains, while the neoplastic cells in Hodgkin disease frequently express CD30 and CD15. Although L&H variants usually display a positive staining for CD45 and CD20 but negative staining for CD15, the relatively high content (>30%) of CD57+ T lymphocytes and their rosettelike arrangement around the neoplastic (RS) cells are typically seen in LPHD.

Clinically, most patients with TCRBCL present with nodal disease involving various sites of the body. Splenomegaly is common, and many patients are in an advanced disease stage at the time of diagnosis. Bone marrow involvement, which occurs in 20% to 62% of cases, is more frequent than in other large B-cell lymphomas. Extranodal presentations and atypical manifestations can also occur. Nasopharynx has been occasionally cited as an initial site of presentation in a few cases with TCRBCL; however, to our knowledge, ethmoid sinus has never been mentioned in any of the reports. Non-Hodgkin lymphomas of the sinonasal tract are uncommon and account for only 1.5% of all NHLs in the United States and 0.18% at the Kiel Lymph Node Registry. Some NHLs of the sinonasal tract are associated with EBV, and EBV has been demonstrated in some cases of TCRBCL with most patients having nodal presentations. It is interesting to note that EBV was not detected in the present case either by immunohistochemistry (LMP-1) or molecular method (EBER).

Although a uniform agreement has not been reached whether TCRBCL is a distinct entity or simply a unusual variant of large B-cell lymphoma with a prominent T-cell...
component, TCRBCL is classified with large B-cell lymphoma as proposed by the International Lymphoma Group (REAL Classification) and the classification being finalized by the World Health Organization. One has to be aware that TCRBCL frequently mimics PTCL or LPHD morphologically, and it may coexist with one of these lesions, but it behaves and responds to therapy like a conventional diffuse large B-cell lymphoma. Patients treated as having aggressive lymphomas have a very good response rate, even those with advanced-stage disease.

The case presented is, to our knowledge, the first primary ethmoidal TCRBCL reported. The correct diagnosis was made on the basis of morphology and immunophenotyping. Combined chemotherapy and radiotherapy resulted in complete resolution of the lesion and a long-term remission of more than 5 years. Differentiation of TCRBCL from T-cell NHL and Hodgkin disease is critical in this aggressive lymphoma, and it should be treated in the same manner as an aggressive NHL.

References