Cytokeratin-Positive, CD45-Negative Primary Centroblastic Lymphoma of the Adrenal Gland
A Potential for a Diagnostic Pitfall

Ludvik R. Donner, MD, PhD; Frank E. Mott, MD; Isaac Tafur, MD

We report a case of cytokeratin-positive, CD45-negative primary polymorphic centroblastic lymphoma of the adrenal gland. Additional immunostaining, which demonstrated positivity for CD20 and κ light chain, as well as detection of the monoclonal rearrangement of the immunoglobulin heavy chain gene, helped to establish the diagnosis of lymphoma and to rule out an initially favored diagnosis of poorly differentiated carcinoma.

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Primary adrenal lymphoma is a rare disease of unknown incidence; over 70 cases have been reported during the past 40 years. More than 70% of the patients present with bilateral adrenal masses, and 50% of them have varying degrees of adrenal hypofunction. The lymphomas are usually of diffuse large B-cell type, either centroblastic or immunoblastic. We have seen 3 cases of primary adrenal diffuse large B-cell lymphoma in our clinic during the past 25 years. One case was diagnostically difficult and is described in this article.

REPORT OF A CASE

A 76-year-old Mexican man presented with right upper abdominal mass, fever, and night sweats. Abdominal ultrasound and computed tomography revealed a 10-cm heterogeneous mass between the liver and the right kidney (Figure 1). The right adrenal gland could not be seen on computed tomography scans. The tumor was resected with a portion of the adherent liver except for a 3-cm portion of the tumor that was adherent to the inferior vena cava. No gross adenopathy was noted during surgery. The results of a computed tomography of the chest, abdomen, and pelvis performed after surgery as well as the results of a bone marrow biopsy were negative. The patient received 3 cycles of cyclophosphamide-doxorubicin-vincristine-prednisone chemotherapy. He developed para-aortic and retroperitoneal adenopathy that led to bowel obstruction, and he died 6 months after diagnosis.

MATERIALS AND METHODS

We performed immunohistochemical stains for cytokeratin (AE1/AE3, Cell Marque, Austin, Tex; CAM5.2, Becton Dickinson, San Jose, Calif; cytokeratins 5/6, Zymed, San Francisco, Calif; cytokeratin 7, Dako Corporation, Carpinteria, Calif; cytokeratin 20, Dako; 34BE12, Enzo, New York, NY), CD3, CD20, CD30, CD45RO, CD68, κ light chain, λ light chain, myeloperoxidase, epithelial membrane antigen, neuron-specific enolase, synaptophysin, S100 protein, HMB-45 (Dako), and chromogranin A (Cell Marque) on a TechMate 500 with a ChemMate Secondary Detection Kit–Peroxidase/DAB (Ventana Medical Systems, Tucson, Ariz). The histologic sections were pretreated by steaming in citrate buffer solution (Target Retrieval Solution, Dako) for 30 minutes at 99°C.

The monoclonal antibodies AE1/AE3 (working concentration, 0.4 μg of protein/mL) were applied for 25 minutes at room temperature. The immunostaining was repeated twice, each time with identical results.

The ultrastructural study was performed on glutaraldehyde-fixed tissue. Primers VFr3 and JH6A (Oligos Etc, Inc, Wilsonville, Ore) were used for polymerase chain reaction.

RESULTS

Gross and Microscopic Findings
The tumor was a rubbery, lobulated, tan, centrally necrotic mass weighing 812 g and measuring 14 × 14 × 13...
cm. A 5-cm remnant of the adrenal gland was attached to the tumor’s surface. Microscopically, the tumor was composed of centroblasts and immunoblasts and was divided by delicate fibrous bands containing lymphocytes and plasma cells (Figure 2).

**Immunohistochemical Findings**

Approximately 50% of the tumor cells displayed distinct immunoreactivity for cytokeratin when stained by AE1/AE3, but not by CAM5.2; 34βE12; and anticytokeratins 5/6, 7, or 20. The cells were also positive for CD20 and κ and negative for CD3, CD30, CD45, CD45RO, and CD68, λ, myeloperoxidase, epithelial membrane antigen, chromogranin A, neuron-specific enolase, synaptophysin, S100 protein, and HMB-45 (Figure 3).

**Ultrastructural Findings**

The nuclei were round, with mildly undulating contours, marginated chromatin, and large nucleoli. No nuclear pockets were present. The cytoplasm contained many mitochondria, prominent Golgi apparatus, numerous polyribosomes, moderate endoplasmic reticulum, a few lipid droplets, and, focally, intermediate filaments. The cell membranes were straight and did not contain any cell junctions (Figure 4).

**Molecular Biologic Findings**

Monoclonal rearrangement of the immunoglobulin heavy chain gene was identified by polymerase chain reaction (data not shown).

**COMMENT**

The positivity of the tumor cells for cytokeratin and their negativity for CD45 led us initially to favor a diagnosis of poorly differentiated adrenal cortical carcinoma. Although ultrastructural features of the tumor favored lymphoma, one had to bear in mind that a third of adrenal cortical carcinomas do not show convincing evidence of steroid-cell differentiation, their amount of intracytoplasmic lipid can be scanty, and their intercellular junctions can be sparse. Additional immunostaining that revealed positivity for CD20 and light chain κ and demonstration of monoclonal immunoglobulin heavy chain gene rearrangement helped us to establish the diagnosis of lymphoma with certainty. The lymphoma was classified as a diffuse large B-cell type according to the World Health Organization classification and as a polymorphic centroblastic according to the updated Kiel classification.

Since the initial description of a cytokeratin-positive diffuse large cell lymphoma of the stomach, only a handful of lymphomas expressing this marker have been reported.
Immunoreactivity for cytokeratin was detected in 27% of anaplastic large cell lymphomas of T-cell type, whereas the other 52 lymphomas of different types and lineages were negative for this marker.\(^6\) Following the study by Gustmann et al., cytokeratin was detected in 3 extranodal and 1 nodal anaplastic large cell lymphomas,\(^7\)–\(^10\) and only 5 diffuse large B-cell lymphomas,\(^11\) all, as in our case, extranodal. Expression of cytokeratin was not described in previously studied cases of primary adrenal lymphomas, and our other 2 cases were negative for this marker. According to the manufacturer’s data, the anticytokeratin cocktail AE1/AE3 detects 6 different cytokeratins (cytokeratins 2, 3, 4, 15, 16, and 19) that are not detectable by other anticytokeratin antibodies used in our study. One or more of these cytokeratins are likely to be expressed in our tumor.

Although CD45 is expressed in 95% of B-cell and T-cell lymphomas, this marker was not expressed in our case. A few of the cytokeratin-positive lymphomas also did not express CD45.\(^6\)–\(^8\),\(^11\) This rare, highly anomalous, and diagnostically confusing immunophenotype led to misclassification of several cytokeratin-positive, CD45-negative tumors as carcinomas rather than lymphomas. Pathologists must be aware of this phenomenon to avoid diagnostic errors.

References