Anaplastic Large-Cell Lymphoma With Aberrant Expression of Multiple Cytokeratins Masquerading As Metastatic Carcinoma of Unknown Primary

Case Report

A 52-year-old woman without a significant past medical history presented to her primary care physician in July 2011 for evaluation of a large, nontender, firm, fixed left inguinal mass. A computed tomography (CT) scan of the abdomen and pelvis confirmed bulky left inguinal adenopathy measuring up to 5.6 cm and numerous left iliac nodes measuring up to 4.7 cm, but was otherwise negative. An excisional left inguinal lymph node biopsy showed a neoplasm with anaplastic morphology. The tumor cells formed cohesive clusters that were centered in the subcapsular spaces and near sinuses with extension into the paracortex (Fig 1A). On high-power examination, the tumor cells were pleomorphic, with vesicular chromatin and prominent to inconspicuous nucleoli (Fig 1B). Immunohistochemistry showed that the tumor cells were positive for CD30 and the cytokeratins epithelial membrane antigen (EMA), intercellular adhesion molecule 5 (CAM5.2), and OSCAR (Figs 1C through 1E). Focal positive staining for cytokeratins AE1/AE3 was also noted. CD45, CD15, S100, CD2, CD3, CD5, CD7, CD10, CD19, CD20, anaplastic lymphoma kinase (ALK1), cytokeratin 7 (CK7), CK20, thyroid transcription factor 1, granzyme B, T-cell intracellular antigen, synaptophysin, and chromogranin were negative. T- and B-cell receptor gene rearrangement studies were negative. A pathologic diagnosis: “consistent with metastatic poorly differentiated carcinoma,” was rendered by the initial institution after review and concurrence by pathologists at a National Cancer Institute–designated cancer center.

Evaluation for a primary site of carcinoma included a negative upper endoscopy, colonoscopy, mammogram, and gynecologic exam. CA-125 and carcinoembryonic antigen were normal. The patient developed low-grade fevers, abdominal discomfort, and a diffuse, dry, flaky maculopapular pruritic rash. She received one cycle of carboplatin and Taxol (Bristol-Myers Squibb, Princeton, NJ) on October 14, 2011, for presumed carcinoma of unknown primary (CUP). A repeat CT scan on November 2, 2011, showed progression of her abdominal and pelvic adenopathy when compared with a CT scan from October 13, 2011. She was empirically treated with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, completing six cycles in February 2012, with a marked decrease in the bulky adenopathy.

In January 2012, a sample from her initial biopsy was sent for a CancerType ID gene test (bioTheranostics, San Diego, CA) for molecular classification; this test measures and integrates the expression of 92 genes to distinguish 28 tumor types and 50 subtypes. On the basis of the gene expression profiling, there was a 96% chance that the primary malignancy was lymphoma.

The patient’s bulky pelvic adenopathy recurred less than a month after completion of cyclophosphamide, doxorubicin, vincristine, and prednisone treatment. Positron emission tomography CT scanning showed additional new lesions involving the mediastinum, midesophagus, and bones. She developed daily fevers, drenching sweats, and increasing weakness, and her weight decreased by 30 pounds. A new right inguinal lymph node biopsy in April 2012 showed similar morphologic and immunohistochemical findings as her previous biopsy, although more numerous tumor cells were seen in this subsequent biopsy. The differential diagnosis on the repeat biopsy included classical Hodgkin lymphoma (cHL), anaplastic large-cell lymphoma (ALCL), and metastatic, poorly differentiated carcinoma. Numerous atypical mitoses and apoptotic figures were seen along with necrosis. Additional immunostains showed that the tumor cells also expressed CD4, CD33, CAM5.2, and Wilms’ tumor 1, but were negative for a large panel of antibodies including ALK1, paired box gene-5, and other T-cell antigens (CD1, CD2, CD3, CD5, CD7, and CD8). T-cell receptor (TCR) gamma rearrangement studies showed a biclonal TCR rearrangement (Fig 1F). The molecular results, the morphologic, and the immunophenotype were most consistent with an anaplastic lymphoma kinase (ALK)–negative ALCL with aberrant cytokeratin expression. The patient began treatment with the CD30-targeted antibody-drug conjugate brentuximab vedotin; however, she died less than 1 week after treatment initiation.

Discussion

To our knowledge, this is the first case of ALCL with this unique cytokeratin immunoprofile to be reported in the English language medical literature. Lymph node involvement by a malignancy with pleomorphic morphology can be challenging to diagnose when the cells have an overlapping immunoprofile, given that many metastases can involve nodal sites. ALCL is a type of non-Hodgkin T-cell lymphoma that can involve lymph nodes and uniformly expresses CD30. It was first recognized by Stein et al in 1985, who described 45 cases with CD30 (Ki-1 antigen) expression and prominent sinusoidal invasion that had previously been diagnosed as malignant histiocytosis or anaplastic carcinoma. ALK-negative ALCL is a subtype of ALCL that is a T- or null-cell phenotype and lacks ALK1 protein expression/ALK translocation. The majority of ALCLs shows a clonal rearrangement of the TCR gamma and beta chain genes, irrespective of whether or not they express T-cell antigens.2

The differential diagnosis of ALCL includes cHL, metastatic carcinoma, melanoma, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), other malignant lymphomas, histiocytic sarcoma, and embryonal carcinoma. Evaluation of the expression of epithelial markers such as cytokeratin AE1, CAM5.2, EMA, and OSCAR is routinely used to identify poorly differentiated carcinoma.4 Some early studies showed that some cytokeratins, such as AE1, are specific...
and helpful in distinguishing carcinoma from lymphoma and melanoma. However, subsequent studies showed rare and limited expression of cytokeratins in B-cell lymphomas, cHL, PTCL-NOS, and even plasma-cell myeloma. One study of 18 cases of ALCL showed staining in 11% of cases with CK2 (an antibody specific for keratin 18) and 28% of cases with KL1 (a pan keratin). In some situations, ALK-negative ALCL diagnosis can be challenging when CD45 and other T-cell antigens are not expressed and other markers, such as myeloid antigens (CD33), are present that can cause concern for a myeloid sarcoma or other malignancies. One large study that analyzed 866 cases of lymphoma and leukemia showed rare expression of CK8, CK5/6, and CK22 in 1.5% of cases (n = 13); these included 0.4% of cHLs (one of 230), 0.6% of diffuse large B-cell lymphomas (two of 326), and 4% of PTCL-NOS (one of 27). A larger number of ALCLs show positivity for EMA, and EMA has been reported more frequently in ALK-positive than ALK-negative ALCL (83% v 43%); thus, the use of EMA alone to distinguish between ALCL and metastatic carcinoma should be avoided.

Another diagnostic difficulty is that other nonlymphoid lesions can show expression of CD30, a cell membrane protein of the tumor necrosis factor receptor family, including embryonal carcinomas, osteogenic sarcomas, mesotheliomas, seminomas, Ewing sarcoma, salivary gland carcinomas, and rare lymphoepithelial carcinomas. In some situations, other ancillary studies such as electron microscopy have helped to distinguish a carcinoma from a cytokeratin-positive lymphoma by showing the characteristic electron microscopy features of epithelial differentiation, such as tonofibrils and desmosomes.

CUP is a clinically recognized disorder that accounts for 3% to 5% of all malignant epithelial tumors. In the last several years, molecular assays have become important in determining the tissue of
TuDung T. Nguyen, Friederike H. Kreisel, John L. Frater, and Nancy L. Bartlett
Washington University School of Medicine, St Louis, MO

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

REFERENCES
DOI: 10.1200/JCO.2012.46.7910; published online ahead of print at www.jco.org on June 17, 2013

origin. These molecular assays include gene expression profiling (GEP) microarrays, microRNA quantitative reverse-transcriptase polymerase chain reaction assays, and other reverse-transcriptase polymerase chain reaction assays. Tissue of origin determination is clinically important because it can allow a specific type of therapy to be given on the basis of the identification of the primary of tissue of origin, which may improve survival. However, currently, the role of molecular platform testing in clinical practice is unknown. Sites of involvement of CUP can include liver, lung, peritoneal cavity, lymph nodes, and bones. Several clinical features for CUP are characterized: short history with symptoms and signs associated with the metastatic sites, early metastasis in the absence of a primary tumor, aggressive clinical course, unpredictable metastatic patterns, and a third of patients can demonstrate involvement of three or more organs at the time of diagnosis.

In summary, a comprehensive clinicopathologic work-up that includes repeat biopsy and molecular testing with GEP in conjunction with T- or B-cell receptor gene rearrangement studies may help to differentiate a rare cytokeratin-positive lymphoma from a metastatic carcinoma if a case with an unusual immunoprofile should be encountered in clinical practice. Our case also demonstrates the utility of continued clinical vigilance, repeat B- or T-cell receptor gene rearrangement studies, and multiple biopsies in the evaluation of these rare cytokeratin-positive lymphomas.