of unknown primary site (CUP). CUP accounts for approximately 2% of all new cancer diagnoses in the United States, with 31,860 new cases anticipated in 2013. CUPs are heterogeneous with a highly variable clinical presentation and prognosis. Although the primary site rarely becomes evident during the course of the disease, molecular profiling suggests that CUP is frequently a result of occult lung, kidney, bladder, or pancreaticobiliary cancer.

Clinical Presentation

Most patients with CUP have nonspecific complaints. Constitutional symptoms such as anorexia, weight loss, and fatigue are typical of advanced disease and are commonly present at the time of diagnosis. Pain at the time of presentation is more variable but is frequently experienced by patients with bone metastasis. Less common presenting signs and symptoms include epidural spinal cord compression, hypercalcemia, isolated brain metastasis, ascites, and venous thromboembolic disease.

However, many patients have very few symptoms initially, such as progressive lymphadenopathy only. Occasionally, the diagnosis is arrived at incidentally, during evaluation for an unrelated condition.

Pathology

CUPs are categorized based on histologic evaluation. Most CUPs demonstrate adenocarcinoma histology. However, squamous cell carcinoma, neuroendocrine carcinoma, and poorly differentiated carcinoma are also commonly encountered. Poorly differentiated carcinoma must be distinguished from melanoma, lymphoma, and sarcoma, because the treatments differ by disease.

Immunohistochemistry may disclose the site of origin. For example, in the case of poorly differentiated tumors, the presence of S100 and HMB45 supports a diagnosis of melanoma, whereas CD45 supports a diagnosis of lymphoma. Chromogranin and synaptophysin suggest neuroendocrine differentiation. Cytokeratin 5 (CK5) and CK6 are strongly expressed by squamous cell carcinomas, whereas the expression pattern of CK7 and CK20 can limit the differential diagnosis of adenocarcinomas.

Molecular tumor profiling studies suggest that gene expression profiles can identify the primary site in 60% to 80% of patients. However, it remains unclear whether gene expression profiling improves patient outcomes.

Treatment and Prognosis

CUP confers a median survival time of 8 to 11 months. Therapy is almost always offered with palliative intent. Chemotherapy can mitigate cancer-related symptoms and improve overall survival. However, there are several clinical presentations for which the prognosis is more favorable and therapy can be curative. For example, a woman presenting with adenocarcinoma isolated to unilateral axillary lymph nodes should be evaluated and treated as for a locally advanced breast cancer, regardless of whether imaging investigations demonstrate a primary breast malignancy. Likewise, a patient with squamous cell carcinoma isolated to cervical lymph nodes at presentation should receive therapy for locally advanced head and neck cancer, again regardless of whether a primary lesion can be identified. In both these circumstances, therapy may prove curative. Another clinical scenario for which specific therapy is beneficial is that of a young man with a poorly differentiated midline tumor: A favorable response to a chemotherapy regimen for germ cell cancers may be beneficial.

Assays that provide a molecular tumor profile, which may more accurately identify the primary site than standard clinicopathologic variables, are currently available.

For a deeper discussion on this topic, please see Chapters 190, "Head and Neck Cancer," 202, "Sarcomas of Soft Tissue and Bone, and Other Neoplasms of Connective Tissues," 203, "Melanoma and Nonmelanoma Skin Cancers," and 204, "Cancer of Unknown Primary Origin," in Goldman-Cecil Medicine, *25th Edition.*

SUGGESTED READINGS

Chapman PB, Hauschild A, Robert C, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation, N Engl J Med 364:2507–2516, 2011.

Fletcher CDM, Unni KK, Mertens F: World Health Organization classification of tumors: pathology and genetics of tumors of soft tissue and bone, Lyon, 2002, IARC Press.

Hainsworth JD, Rubin MS, Spigel DR, et al: Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute, J Clin Oncol 31:217–223, 2012.

Rajendra R, Pollack SM, Jones RL: Management of gastrointestinal stromal tumors, Future Oncol 9:193–206, 2013.

Robert C, Thomas L, Bondarenko I, et al: Ipilimumab plus decarbazine for previously untreated metastatic melanoma, N Engl J Med 364:2517–2526, 2011.

Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013, CA Cancer J Clin 63:11–30, 2013.

Wisco OJ, Sober AJ: Prognostic factors for melanoma, Dermatol Clin 30:469–485, 2012.

Zandberg DP, Bhargava R, Badin S, et al: The role of human papillomavirus in nongenital cancers, CA Cancer J Clin 63:57–81, 2013.