Diagnostic Reasoning

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Diagnosis and Management of Leptomeningeal Disease

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Once considered the culmination of metastatic disease and a marker of the terminal end of a patient’s experience with cancer, leptomeningeal disease (LMD), also known as neoplastic meningitis and carcinomatous meningitis, has become an increasingly frequent complication of cancers (Bomgaars, Chamberlain, Poplack, & Blaney, 2002). LMD may even occur when a patient is in systemic remission. As patients live longer, leptomeningeal tissues increasingly play host to malignant cells, requiring clinicians to be alert for the signs and symptoms heralding their involvement. Research in the diagnosis and treatment of LMD is growing as prevalence rises. Although prognosis remains poor and treatment mostly is palliative, some patients are experiencing improved quality of life and length of survival with conscientious management of LMD and its symptoms.

Case Report

Ms. A is a 27-year-old woman who was diagnosed with right temporoparietal glioblastoma (GBM) in 2004. She underwent resection with placement of carmustine wafers followed by chemoradiation with concurrent temozolomide. In 2005, she had progression of her tumor and underwent a second resection with pathology consistent with GBM and radiation necrosis, followed by multiple chemotherapy regimens as the tumor continued to progress. In 2007, Ms. A was diagnosed with LMD and had an ommaya reservoir placed. She was treated with intrathecal topotecan from September 2007 to April 2008. She also received radiation to the lumbar spine for metastasis at L1 from September to October 2007. In addition, she received systemic treatment with 6-thioguanine, lomustine, capecitabine, and celecoxib from August 2007 to April 2008. Systemic therapy then was stopped because of bone marrow suppression, but she continued to receive topotecan intrathecally. In April 2008, Ms. A evidenced rising cerebral spinal fluid (CSF) protein higher than 200 mg/dl, indicating progressive disease, and topotecan was changed to methotrexate. She then experienced significant myelosuppression, so intrathecal chemotherapy was stopped on April 24, 2008. After bone marrow recovery, Ms. A was placed on protocol 2007-0931 with ANG1005, a peptide designed to cross the blood-brain barrier and release paclitaxel within the tumor (Angiochem, Inc., 2006). Protocol stopped on July 11, 2008, because of further disease progression. Ms. A began dose-dense temozolomide with sorafenib in August 2008, which she continues to date.

Prevalence

About 5% of all patients with cancer will develop LMD (Larson, Rubenstein, & McDermott, 2005). Although LMD can occur with any cancer, certain types carry a greater propensity, including breast cancer, small cell lung cancer, leukemia, non-Hodgkin lymphoma, and melanoma (Bomgaars et al., 2002; Pentheroudakis & Pavlidis, 2005). Solid tumors of the central nervous system (CNS) also may metastasize to the leptomeninges. Patients with low-grade intracranial tumors, such as pilocytic astrocytoma, are affected at a rate of 5%-10%, with higher levels related to progressive disease (Abel et al., 2006). A study by Sarker, Thirlwell, Nelson, Gazzard, and Bower (2003) examined LMD occurrence in AIDS-related non-Hodgkin lymphoma and found that 10% of patients in the study had evidence of LMD at presentation; patients with Burkitt lymphoma or disease involvement in the paraspinous and paranasal regions represented the greatest number of LMD cases.

About 25% of patients with small cell lung cancer and 5% of patients with breast cancer will develop LMD (McAllister, Ward, Schulman, & DeAngelis, 2002). Twenty-five percent of patients with metastatic melanoma also will develop LMD (Larson et al., 2005).

Pathophysiology

LMD occurs when malignant cells migrate from a primary site and infiltrate the meningeal membranes of the brain and spinal cord. Maroldi, Ambrosi, and Farina (2005) described the brain as a possible “sanctuary site” in which metastatic lesions grow and become troublesome clinically even though systemic disease may be in remission. Maroldi et al. postulated that the growth may occur because most systemic chemotherapy cannot penetrate the blood-brain barrier. Spread of malignant cells through the vascular system appears to be the most common route of infiltration. Tumor cells may seed brain parenchyma when in cerebral circulation.

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