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CASE REPORT | BILIARY

Treatment of Leptomeningeal Carcinomatosis in a Patient With Metastatic Cholangiocarcinoma

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Abstract

A 49-year-old woman with cholangiocarcinoma metastatic to the lungs presented with new-onset unrelenting headaches. A lumbar puncture revealed malignant cells consistent with leptomeningeal metastasis from her cholangiocarcinoma. Magnetic resonance imaging (MRI) of the brain revealed leptomeningeal enhancement. An intrathecal (IT) catheter was placed and IT chemotherapy was initiated with methotrexate. Her case is notable for the rarity of cholangiocarcinoma spread to the leptomeninges, the use of IT chemotherapy with cytologic and potentially symptomatic response, and a possible survival benefit in comparison to previously reported cases of leptomeningeal carcinomatosis secondary to cholangiocarcinoma.

Introduction

Cholangiocarcinoma is a malignancy of the epithelial lining of the intra- or extrahepatic biliary tree. The incidence of cholangiocarcinoma has been increasing over the past several decades with a concomitant increase in mortality rates. Risk factors for developing cholangiocarcinoma include primary sclerosing cholangitis, cirrhosis, and chronic hepatitis B and C infections. Patients present with painless jaundice, abdominal pain, weight loss, or abnormal liver function tests. Management depends on the extent of disease, but usually involves surgical resection. Advanced disease, including metastatic disease, may be amenable to systemic chemotherapy with gemcitabine and cisplatin.[1]

Case Report

A 49-year-old woman diagnosed with cholangiocarcinoma was treated with hepatic resection, radiation therapy, and low-dose gemcitabine followed by cisplatin and gemcitabine. She developed pulmonary metastases and was treated with oxaliplatin, irinotecan, methotrexate, 5-fluorouracil, and bevacizumab for progressive pulmonary metastases. Three years later, she developed severe, unrelenting headaches; lumbar puncture (LP) demonstrated malignant cells consistent with leptomeningeal metastasis (LM; Figure 1). Magnetic resonance imaging (MRI) of the brain revealed leptomeningeal enhancement in the posterior fossa (Figure 2). She underwent intraventricular catheter placement with initiation of intrathecal (IT) methotrexate. After 4 treatments, cerebrospinal fluid (CSF) cytology demonstrated a decreased cellular burden of disease, and after 8 treatments, cytology was negative for malignant infiltrate.

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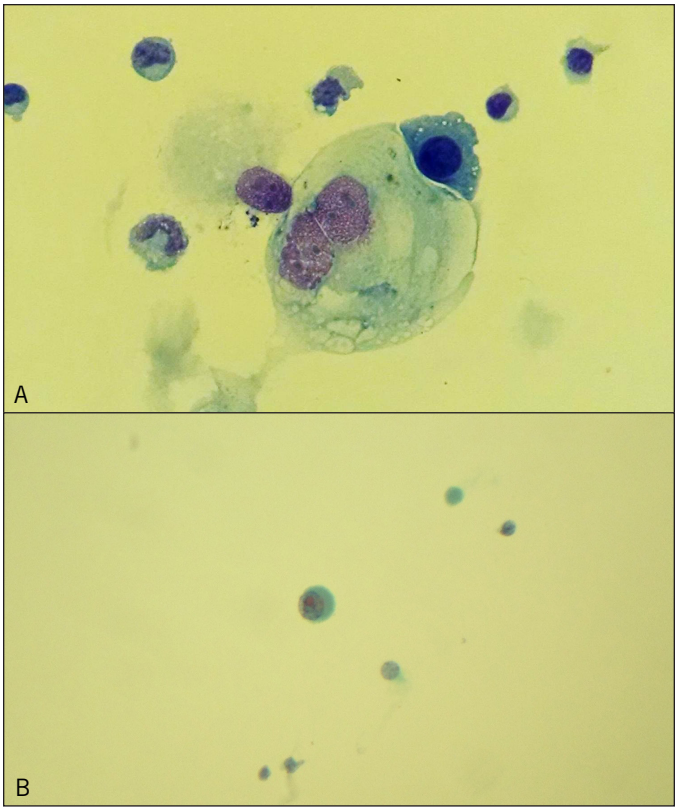

Figure 1. CSF fluid pathology with (A) large, atypical cells with irregular nuclei and (B) prominent cytoplasmic vacuoles consistent with adenocarcinoma (40x magnification).

Months later, she developed persistent nausea and vomiting. Her symptoms were temporized by serial CSF drainage. Repeat imaging showed stable leptomeningeal enhancement and repeat CSF cytology showed no malignant cells. IT methotrexate was continued. However, she then became intermittently somnolent and developed a new sensorineural hearing deficit. CSF cytology was repeated 1 month later and showed recurrent malignant infiltrate. Radionuclide cisternogram demonstrated normal CSF flow. Whole brain radiation therapy and high-dose intravenous dexamethasone was initiated. After completion of radiation, she continued to be somnolent and disoriented, and developed a new right facial droop and right pronator drift. Repeat LP showed atypical cells and follow-up imaging revealed extensive progression of LM with progressive hydrocephalus (Figure 2).

The patient became increasingly abulic, which intermittently improved with serial LPs. Repeat cisternogram demonstrated communicating hydrocephalus, and a ventriculoperitoneal shunt was placed. Despite short-lived improvement after the shunt, her mental status continued to deteriorate. She was transferred to hospice and died comfortably several days later.

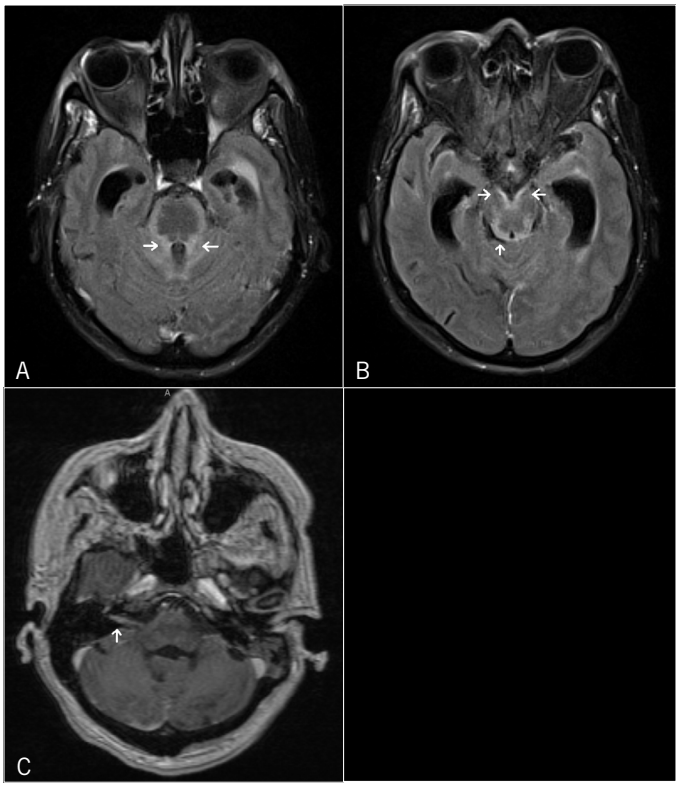

Figure 2. (A) Axial FLAIR MRI with striking symmetric intra-axial T2/FLAIR signal abnormalities on the surface of the brainstem, surrounding the fourth ventricle, and extending into the anterior portions of the cerebellar hemispheres. The fourth ventricle is mildly enlarged. (B) Leptomeningeal metastases involving multiple lower cranial nerves within the posterior fossa bilaterally. (C) Axial 3D multi-planar reconstruction (MPR) with enhancement of the right eighth cranial nerve demonstrating encasement by tumor.

Discussion

LM is rare, occurring in 1–8% of cancer patients in autopsy series.[2] Its incidence varies by histology, and it occurs most frequently in breast, lung, and hematopoietic malignancies; LM due to gastrointestinal cancer is uncommon, accounting for only 7% of cases.[2] There are only 4 cases of leptomeningeal carcinomatosis due to metastatic cholangiocarcinoma reported in the literature.[3–6]

The diagnosis of LM requires recognition of the clinical syndrome, which can include signs of elevated intracranial pressure (ICP), global or focal cerebral dysfunction, cranial neuropathies, or spinal radiculopathies. MRI with intravenous contrast identifies leptomeningeal enhancement in 76–100% of cases, and examination of the CSF reveals pleocytosis, elevated protein, or low glucose in 60–90% of cases.[2,7] A positive CSF cytology is diagnostic of LM, but sensitivity of a single CSF cytology is only 71%, so diagnosis often requires multiple CSF samples, or a combination of clinical, neuroimaging, and CSF features.[8] Prognosis of

LM is poor, and treatments are generally considered palliative. Although survival of 7–10 months has been reported in selected patients with chemotherapy-sensitive malignancies such as breast cancer and hematopoietic tumors, median survival in patients with aggressive cancers is 3–4 months.[2,7]

Treatment options include radiotherapy (especially those impeding normal CSF flow), systemic chemotherapy, and IT chemotherapy. Since the use of systemic chemotherapy is limited by central nervous system penetration of the drug, IT therapy is often considered the treatment of choice, provided that normal CSF flow is established. Methotrexate, cytarabine, and thiotepa have been approved for IT administration.[2] The main complications of IT treatment are chemical/aseptic meningitis (43%), myelosuppression (18%), and infectious meningitis (8%).[7]

This is the first report of a patient with metastatic cholangiocarcinoma and LM treated with IT chemotherapy, and the initial cytologic response to treatment with IT methotrexate is worth highlighting. The patient survived 4.5 months from the diagnosis of LM, similar to survival reported in other solid tumors treated with IT chemotherapy. Thus, consideration of IT chemotherapy in patients with this histology is warranted. Our case also highlights several management issues that occur in the treatment of LM, including the importance of serial evaluation of CSF flow and management of elevated ICP. The most important consideration in the management of these patients requires the cohesive efforts of a multidisciplinary medical team including gastroenterologists, medical oncology (including neuro-oncology), surgical oncology, and hospitalists at a tertiary care center.

Disclosures

Author contributions: All authors contributed equally to designing the study concept and to drafting and revising the manuscript for scientific accuracy and content. REA Jacobs is the article guarantor.

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The patient has passed away, but informed consent for this case report was obtained from her next of kin.

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