

Pemetrexed and Communicating Hydrocephalus

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ABSTRACT

Background: Pemetrexed (Alimta) is widely used in combination with platinum as a first-line treatment of mesothelioma and adenocarcinoma of the lung. It is also approved for use in the maintenance setting as a single agent after patient completion of 4 to 6 cycles of a platinum-based doublet regimen for non-small cell lung cancer. With the increasing use of pemetrexed and longer durations of therapy, unexpected cumulative toxicity or other toxicities are possible.

Case Report: We report a case of a patient receiving maintenance pemetrexed for advanced adenocarcinoma of the lung who developed communicating hydrocephalus.

Conclusion: We are not aware of any other reports of communicating hydrocephalus in association with pemetrexed therapy. As more patients routinely receive pemetrexed as maintenance therapy, the development of toxicities or unexpected diagnoses is possible and may be a consideration in the chronic management of such patients.

INTRODUCTION

Pemetrexed (Alimta) is widely used in combination with platinum as a first-line treatment of mesothelioma and adenocarcinoma of the lung. It is also approved for use in the maintenance setting as a single agent

after patient completion of 4 to 6 cycles of a platinum-based doublet regimen for non-small cell lung cancer. With the increasing use of pemetrexed and longer durations of therapy, unexpected cumulative toxicity or other toxicities are possible. We report a case of a patient receiving maintenance pemetrexed for advanced adenocarcinoma of the lung who developed communicating hydrocephalus.

CASE REPORT

A 40-year-old male in good health with no history of smoking presented with a 2- to 3-month history of cough. A computed tomography (CT) scan of the chest showed a centrally obstructing mass in the right middle lung. Bronchoscopy revealed a partially occlusive endobronchial lesion in the right middle lobe bronchus intermedius that was positive for poorly differentiated adenocarcinoma. A positron emission tomography scan showed hypermetabolic activity in the right lung mass and multiple metastatic lesions throughout the axial and appendicular skeletons. Epidermal growth factor receptor mutation status was intermediately positive.

The patient was enrolled in a clinical trial and received carboplatin, paclitaxel, and bevacizumab for 4 cycles, complicated by grade 1 peripheral neuropathy and thrombocytopenia, as well as grade 2 phlebitis and leucopenia. Otherwise the patient did not require any dosage modifications or delays. His follow-up CT scans showed partial response in the lung and stable osseous disease.

Per protocol, he was randomized to maintenance therapy with pemetrexed 500 mg/m² every 3 weeks. At cycle 13, he developed dizziness and grade 3 hypertension (blood pressure 190/104 mmHg). Serum creatinine doubled from 0.5 mg/dL to 1.1 mg/dL. Magnetic resonance imaging (MRI) of the brain was negative (Figure 1). Amlodipine was started for hypertension. Pemetrexed was withheld for 2 weeks and then resumed at full dose. At cycle 19, the patient's blood pressure again increased and was accompanied by complaints of fatigue, headache, nausea, vomiting, and visual disturbance. Serum creatinine increased to 1.8 mg/dL. Pemetrexed was reduced by 25% for the next cycle. Amlodipine was discontinued, and metoprolol and valsartan were

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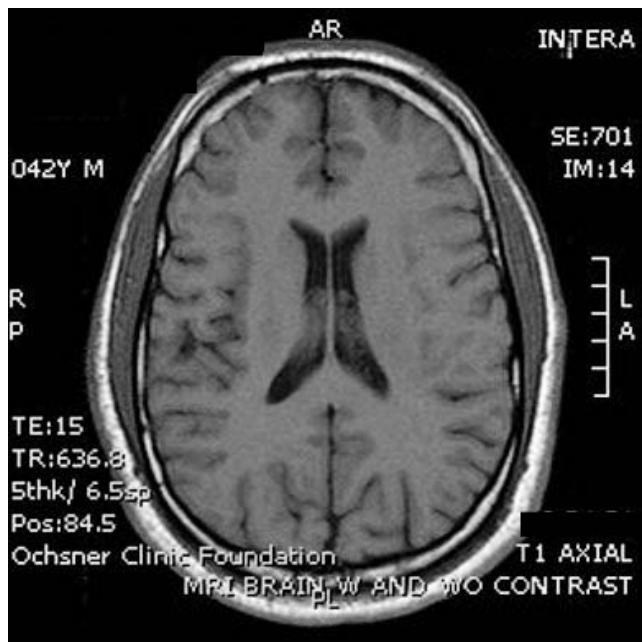


Figure 1. Normal magnetic resonance imaging at onset of neurologic symptoms in patient after 13 cycles of pemetrexed.

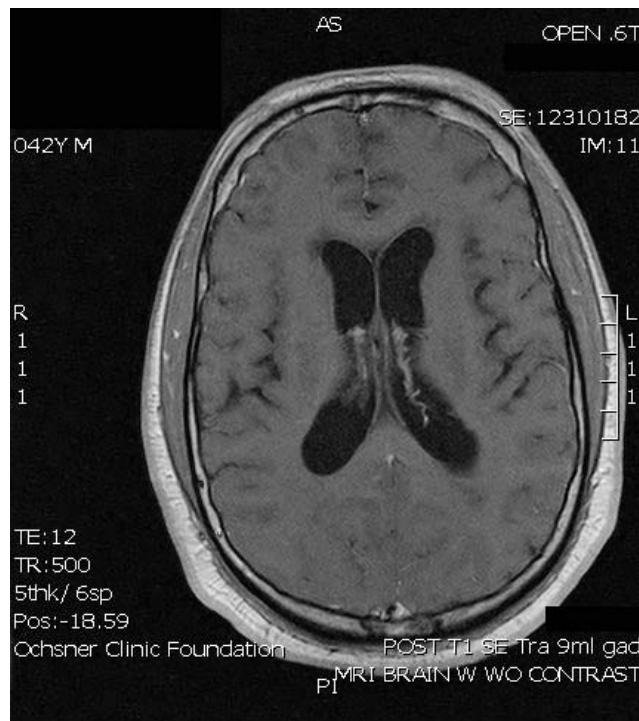


Figure 2. Magnetic resonance imaging showing development of hydrocephalus after 19 cycles of pemetrexed.

prescribed for hypertension. Another MRI of the brain showed interval enlargement of the ventricular system consistent with communicating hydrocephalus but with no evidence of metastatic lesions or meningeal carcinomatosis (Figure 2). Treatment with pemetrexed was discontinued, and the patient was removed from the clinical trial.

Serial lumbar punctures were performed a total of 4 times, with removal of 10-25 mL of cerebrospinal fluid (CSF) each time. The patient noted transient improvement of symptoms after each procedure. CSF cytology was repeatedly negative, and other studies—including cell count, protein, gram stain, bacterial and viral cultures, and West Nile virus serology—were all negative and/or normal on each procedure. Neurosurgical consultation was obtained, and a lumbar-peritoneal shunt was placed. The patient showed symptomatic improvement; follow-up brain MRI showed decreased ventricular enlargement. The patient was subsequently started on erlotinib.

DISCUSSION

Acquired hydrocephalus in adults is usually associated with central nervous system (CNS) infections or tumors, especially posterior fossa medulloblastomas, astrocytomas, and ependymomas. These conditions are associated with the obstructed flow of CSF through the ventricular system and impaired CSF

absorption.¹ CT or MRI typically shows ventricular dilation proximal to the level of obstruction.

Communicating hydrocephalus in adults is less common than in children, is often acquired, and is thought to be caused by impaired absorption of CSF. Imaging usually shows dilation of the entire ventricular system, including the fourth ventricle.^{2,3}

Regardless of the etiology, symptoms of hydrocephalus are the result of increased intracranial pressure (ICP) and can be nonspecific.⁴ Headache, vision disturbances, nausea and vomiting, anorexia with weight loss, lethargy, drowsiness, difficulty concentrating, behavioral changes, and hypertension are possible. Examination is often unremarkable, but hypertension and bradycardia may be present. Papilledema may be seen on fundoscopic examination, but other cranial nerve findings are not usually present unless the ICP is advanced, causing brain-stem pressure.

In a patient with cancer, especially with advanced-stage disease, the development of neurologic changes may indicate metastatic spread to the CNS, either in the form of meningeal carcinomatosis or lesions involving the brain parenchyma. Workup includes imaging of the brain with either CT or, preferably, MRI, followed by assessment of CSF cytology if no obvious etiology is visible on those studies. Other causes include bacterial or viral infections, hemorrhage, trauma, or, rarely, paraneoplastic phenomena.⁴

This patient presented initially with stage 4 adenocarcinoma of the lung, primarily with osseous metastases, nearly 18 months prior to the onset of symptoms that led to the diagnosis of communicating hydrocephalus. Serial lumbar punctures consistently showed clear and biochemically normal CSF with normal pressures. Cytology and infectious etiologies were negative. Hemorrhage was not evident, and no history of trauma existed. Symptoms improved with placement of a shunt and cessation of pemetrexed therapy.

Pemetrexed is a cytotoxic agent that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase. These enzymes are involved in folate metabolism and deoxyribonucleic acid synthesis. To date, pemetrexed has not been reported to cause or to be associated with communicating hydrocephalus. However, fetal hydrocephalus has been reported in rabbits exposed to methotrexate (a DHFR inhibitor)⁵ and in leukemic patients treated with induction regimens containing intrathecal methotrexate,⁶ although it is unclear in the latter case if the hydrocephalus was caused by the drug or by the infiltration of leukemic cells at the level of the arachnoid villi. A case of hydrocephalus has been reported in a breast cancer patient receiving 5-fluorouracil (a TS inhibitor); however, the patient also had brain metastases that were considered to be the more likely cause.⁷

CONCLUSION

We are not aware of any other reports of communicating hydrocephalus in association with pemetrexed therapy. As more patients routinely receive pemetrexed as maintenance therapy, the development of toxicities or unexpected diagnoses is possible and may be a consideration in the chronic management of such patients.

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