

CLINICAL VIGNETTE

Metastatic Glioblastoma Multiforme: A Case Report and Review of the Literature

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A 62-year-old female with no significant past medical history was brought to the emergency room by ambulance for new onset seizures. A CT brain stroke protocol revealed a lesion in the left temporal region, and MRI brain confirmed an intra-axial mass measuring 6.2 x 3.8 x 3.1 cm in the left posterior temporal to posterior parietal region with associated vasogenic edema. Blood counts and a comprehensive metabolic panel were within normal limits. CT chest, abdomen and pelvis was unremarkable.

The patient was seen by Neurosurgery and taken to the operating room for a left stereotactic guided partial craniotomy for maximal tumor resection. Surgical pathology confirmed a World Health Organization (WHO) grade 4 Glioblastoma Multiforme (GBM), 06-methylguanine-DNA-methyltransferase (MGMT) un-methylated, IDH1, IDH2 and BRAF wild type.

The patient completed adjuvant chemo-radiation with temozolomide and was placed on monthly temozolomide maintenance therapy. Surveillance MRI brain images obtained following chemo-radiation and every 2 cycles of monthly, maintenance temozolomide, were stable, without progressive disease.

After 5 cycles of maintenance temozolomide, the patient began complaining of progressive upper neck pain and fatigue. An MRI brain revealed progressive disease around the resection cavity with a new site of involvement in the temporal horn of the right lateral ventricle. MRI of the cervical spine identified extensive metastatic disease involving the vertebral bodies of C2 through C6, with extension of disease into the soft tissue of the prevertebral space around C2. Thereafter, an MRI of the thoracic and lumbar spine was obtained, in addition to a CT chest, abdomen and pelvis. Imaging noted metastatic disease throughout the lungs, liver and bone, without an unequivocal alternative primary as an explanation for these findings.

Given the question of a second primary, a CT guided biopsy of a 2.8 cm lytic lesion of the third lumbar vertebra was performed. Surgical pathology confirmed metastatic GBM. The histologic features and immunophenotype were similar to the prior tumor specimen obtained from her craniotomy tumor resection.

Discussion

The patient with GBM who underwent a maximal tumor resection followed by standard of care, concurrent, temozolomide

based chemo-radiation followed by monthly, maintenance temozolomide, was diagnosed only 6 months following her surgery with biopsy confirmed, metastatic GBM to bone, liver and lung. This demonstrates the importance for health care providers caring for patients with GBM to consider, the possibility of extra-cranial metastases. Timely detection and treatment of extra cranial metastases may improve overall quality of life.

GBM is the most common primary malignant tumor of the central nervous system in adults,¹ with an estimated incidence of 2-3 cases per 100,000 individuals. Standard treatment, which includes surgery, radiation and chemotherapy. Risk of loco-regional relapse is high, and median survival is limited, with a median overall survival of only 15 months.² Extra-cranial metastases of GBM are rare, affecting only 0.4 – 0.5% of all patients diagnosed with GBM.³ Metastases, when they do occur, are most commonly in the lungs and pleura (60%), regional lymph nodes (51%), and less commonly, the bone (31%) and liver (22%).⁴

The natural history of extra-cranial GBM is unknown. The small number of patients with extra-cranial metastases from GBM limits prospective research studies. One possible explanation for the lack of patients with extra-cranial metastatic disease is the limited overall survival of patients diagnosed with GBM. It is not entirely clear how GBM can escape the central nervous system, resulting in extra-cranial metastatic disease. Several theories include escape via vascular invasion, cranial nerve peri-neural spread, lymphatics, direct invasion or iatrogenic spread into soft tissue.⁵

While age and performance status remain important prognostic factors, the molecular genetics of the tumor itself can also aid in determining prognosis. Methylation of the 06-methylguanine-DNA methyltransferase (MGMT) promoter results in epigenetic silencing and loss of expression of the MGMT DNA repair protein, which is associated with an average survival of 48.9% at 2 years and 13.8% at 5 years. This is superior to survival of those with unmethylated MGMT, whose average survival rates are 14.8% and 8.3%, at 2 and 5 years.⁶ In individuals diagnosed with extra-cranial metastatic disease, the metastatic site influences survival expectations, with the lowest survival expectation in those harboring metastatic disease to the liver, with approximately 7-month median survival.⁷

There are currently no clinical trials providing information regarding the best way to treat patients with relapsed, progressive, metastatic GBM. Therapeutic intent is palliative in nature, with the systemic agents being the same drugs utilized in those being treated with loco-regionally progressive disease. Off of a clinical trial, most patients are treated with single agent lomustine or bevacizumab if they have progressed on temozolomide. In patients with a long treatment free interval following maintenance temozolomide after concurrent chemoradiotherapy, a return to temozolomide would be reasonable, most especially in those with MGMT promoter methylation. No single agent has been shown to be superior to another. The addition of bevacizumab to lomustine improved progression free survival, though not overall survival, while toxicities were higher with the combination regimen.⁸ Current research is looking at genotype directed therapies in patients with somatic mutations, using larotrectinib and entrectinib in those with fusions involving one of the neurotrophic receptor tyrosine kinase (NTRK) genes or dual BRAF and mitogen-activated protein kinase (MEK) inhibition in those with BRAF V600E alterations. In addition, checkpoint inhibition is also being evaluated to define the potential role of immunotherapy in GBM, though it is not clear at this time how, or where these agents may be positioned.

Our patient with MGMT and IDH1/2 wild type GBM had early and widespread metastatic extra-cranial disease progression. To date, we do not have clinicopathologic or biomarker data to help predict which patients will develop metastatic disease. Furthermore, the limited number of patients with extra cranial metastatic GBM prevents the development of prospective studies to help define which systemic therapies would be of particular benefit in this setting. Though rare, it is important for physicians who care for those with GBM to understand extra-cranial metastatic disease can occur. An argument exists for earlier diagnosis being associated with improved quality of life in the context of metastatic sites of involvement.

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