Case Report

We report the case of a 24-year-old African-American female with metastatic World Health Organization grade IV glioblastoma (GBM). Following treatment for her primary right frontal brain tumor, the patient presented with metastasis to the lung, liver, and ovary, demonstrating the first reported case of GBM metastasis to the ovary.

The patient presented with bifrontal headaches, drowsiness, and dizziness in September 2009. Magnetic resonance imaging scans demonstrated a 4.6 cm contrast enhancing right frontal mass with vasogenic edema. A right frontal craniotomy with stereotactic, volumetric gross total resection was performed. Upon pathologic examination, the specimen demonstrated anaplasia, necrosis, and high proliferative index (Ki-67 >50%), rendering it consistent with GBM diagnosis. Postoperatively, the patient experienced mild left-sided weakness.

The patient received radiation therapy (RT) targeting the resection cavity to 50.4 Gy, in 1.8 Gy/fraction, with a 10.8 Gy boost completed January 26, 2010 (cumulative dose, 61.2 Gy), with concurrent temozolomide (75 mg/m² daily). One month later, she began adjuvant temozolomide (140 mg/m²) in 5-day cycles every 28 days. Serial cranial magnetic resonance imaging scan follow-up was initiated 4 weeks after RT completion and continued at 8-week intervals thereafter. In the following months, the patient’s weakness, headaches, and dizziness improved.

In March 2011, she began experiencing right-sided chest pain and dyspnea. A contrast enhanced computed tomography (CT) scan of the thorax demonstrated a large right-sided pleural effusion, right lung atelectasis, and a 14 × 8 × 12 cm mass in the right lower lobe, with associated pleural nodules (Fig 1). Pathologic confirmation of metastatic GBM was established via ultrasound guided thoracentesis and needle biopsy of the mass. Microscopic examination of the tissue revealed small fragments of highly pleomorphic cellular tumor, vacuolated cytoplasm, and eosinophilic inclusions (Fig 2A-B). Giant and multinucleated forms were present. Mitotic figures were frequent and Ki-67 was >50%. The aspirated tumor cells stained positively for vimentin, p53, endothelial growth factor receptor (EGFR), and periodic acid-Schiff staining was negative for glial fibrillary acidic protein (GFAP), synaptophysin, S-100, AE1/AE3, CK7, CK20, TTF-1, and calretinin. Additional staining for ERCC1, Phosphatase and Tensin Homolog (PTEN), thymidylate synthase, and RRM1 were also negative. Overall tumor morphology and staining profile was consistent with the previous right frontal GBM. A
A tissue sample was sent for molecular profiling (TargetNow; Caris Life Sciences, Irving, TX), which demonstrated methylated-MGMT promoter status and PIK3CA wild-type. Given these data, particularly the immunohistochemical ERCC1 negativity, carboplatin was cited as a potentially effective agent. (See Fig. 2.)

At this point, a permanent central port and pleural catheter (CareFusion, San Diego, CA) were placed for effusion drainage. Palliative RT was also delivered via opposing anteroposterior/posteroanterior fields (10 MV beam) to a volume encompassing nearly the entire right hemithorax, to a total dose of 37.5 Gy in 2.5 Gy fractions. During RT, the patient subjectively felt less dyspneic and had a decreased fluid volume from each successive pleural catheter aspiration. Following completion of RT, treatment with carboplatin and bevacizumab was initiated and

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**Figure 1** Chest computed tomography scan with intravenous contrast demonstrating lung metastasis.

**Figure 2** Core biopsy demonstrating extracranial glioblastoma metastasis. (A) Hematoxylin and eosin stain, 400× magnification, demonstrating pleomorphic tumor cells with giant and multinucleate cell processes. (B) Periodic acid-Schiff stain, 400× positive staining for eosinophilic granular bodies. The sample stained positive for vimentin, featured a high Ki-67, was negative for all carcinoma markers (AE1/AE3, CK7, CK20, TTF-1) and was morphologically consistent with intracranial primary.

**Figure 3** Abdominal CT images with contrast demonstrating (A) liver metastasis and (B) ovarian metastasis with intrauterine device present. b, bladder; m, mass; o, ovary; u, uterus
continued for 15 cycles. Upon reimaging, both the lung lesion and surrounding pleural effusion displayed significant reductions in volume.

In December 2012, the patient reported severe abdominal pain. Abdominal CT revealed a hematocoric mass and subsequent biopsy confirmed GBM metastasis, prompting palliative cryoablation (Fig 3), but given clear signs of progression, systemic therapy was discontinued. In January 2013, the patient presented with lower right abdominal quadrant pain and vaginal bleeding. Chest and abdominal CT revealed ascites and a new ovarian mass measuring 7.0 × 5.3 cm (Fig 3). New lung consolidation, atelectasis, and worsening pleural effusion were also noted. The patient received palliative RT using a 4-field technique targeting the ovarian metastasis to 37.5 Gy. Additionally, she was treated with 1 cycle of nanoparticle albumin-bound-paclitaxel, after which only comfort measures were pursued. The patient died shortly thereafter, in February 2013.

Discussion

Gliomas originate from glial cells within the brain, including astrocytes (astrocytoma, 70% of cases); oligodendrocytes (oligodendroglioma, 20%-25% of cases); or a mixture of astrocytes, oligodendrocytes, and ependymal cells.1 GBM is the most aggressive and prevalent form of brain cancer, with mean survival of 15 months and a 10% 5-year survival.2 On autopsy, up to 20% of cases demonstrate spread of cancer cells to cerebrospinal fluid; however, only 2% of patients develop extracranial metastasis3 and 0.2% develop extraneural involvement.4 The most common sites of extracranial involvement include the pleura, lymph nodes, vertebral bodies, and liver, in order of likelihood,3 with an overall median time from metastatic diagnosis to death of 1.5 months.5 Disease spread to multiple organ systems, however, is extremely rare.

Most often extracranial GBM metastases are diagnosed within 24 months of a craniotomy for resection of the primary tumor,3 which may be a result of blood–brain barrier interruption.4 Other hypotheses for extracranial involvement suggest increased vascular permeability because of RT-induced inflammation, necrosis, and upregulation of nuclear transcription factors such as nuclear factor-κ, HIF-1α, and tumor necrosis factor-α.6 Alternatively, a possible immune evasion mechanism has been proposed, describing tumor induced myeloid production of natural killer group 2, member D, via increased lactate dehydrogenase 5, causing decreased natural killer cell responses.7

Forty months after initial diagnosis, this patient presented with a third extracranial site of metastasis: the ovary. Although examples of pelvic metastases following a ventriculoperitoneal shunt exist,8 there are no confirmed diagnoses of reproductive system metastasis with or without a shunt.

The Krukenberg tumor, named originally in 1854 to describe a primary ovarian malignancy, but later redefined as metastatic, is a signet ring cell tumor and comprises 1% to 2% of ovarian metastases.9 Signet ring cells are characterized by mucin-laden vacuoles with granular, eosinophilic cytoplasm and eccentrically located nuclei. Clinical diagnosis is determined by positive immunohistochemical stains for AE1/AE3 and negative stains for vimentin, synaptophysin, and inhibin.9 Typically, a Krukenberg tumor metastasizes from a gastric tumor (70%), with colorectal and breast as the next most common sites of origin9; however, it is possible for a glioblastoma with epithelial differentiation to contain signet ring cells.10 Biopsy results for this patient indicated vacuolated eosinophilic cells, staining positively for vimentin and negatively for AE1/AE3 and synaptophysin. Patients with Krukenberg tumors generally present with abdominal pain and distention and sometimes with slightly elevated β-hCG levels,11 as in this patient. Although not all pathologic criteria were met to classify this patient’s ovarian tumor as a Krukenberg, it bears strong resemblance to the description. To our knowledge, this marks the first reported case of GBM metastasis to the ovary, and, remarkably, in a patient without ventriculoperitoneal shunt.

References