Epithelioid Glioblastoma Presenting as Aphasia in a Young Adult with Ovarian Cancer: A Case Report

Megan M Finneran, MS, Joseph Georges. DO/PhD, Michael Kakareka, DO, Ryan Moncman, Miriam Enriquez, Alan Turtz, MD, Steven Yocom, DO, H. Warren Goldman, MD, James Barresse, MD
Cooper University Health Care, Camden, NJ

BACKGROUND

Epithelioid glioblastoma (eGBM), is a rare, recent addition to the World Health Organization's (WHO) classification of central nervous system (CNS) tumors. We describe a unique case of a young woman with a history of ovarian cancer presenting with expressive aphasia and a new left temporal brain lesion. Open biopsy provided a diagnosis of eGBM. Here, we discuss this unique case and a relevant literature review of eGBM.

Patient History, Examination and Imaging

29-year-old female with past medical history of breast fibroadenoma and ovarian juvenile-type granulosa cell tumor at age fourteen presented to the emergency room following two episodes of disorientation, global aphasia, left-sided facial and lower extremity numbness with paraesthesias. The patient did not lose consciousness but was somnolent after both episodes. The patient states she was able to continue with her work that day. Further history revealed the patient had experienced intermittent headaches during the prior two weeks. She denied trauma, seizure history, vision changes, gait instability or recent illness.

Patient had a left salpingo-oophorectomy at age fourteen. Routine follow-up scans for five years after her cancer diagnosis suggested remission. Her last menstrual period was two days prior to presentation. Social history revealed the patient never smoked and drank socially. She denied drug use. The patient worked in communications for a flooring company. Patient's mother had a known cerebral vascular abnormality and a maternal aunt that died of a brain aneurysm. The patient's father was diagnosed with rectal cancer at age 37 and died of T-cell lymphoma at age 47. Her paternal grandfather had colon and lung cancer at age 47 and died at age 50. Her maternal grandmother was diagnosed with multiple myeloma at age 78.

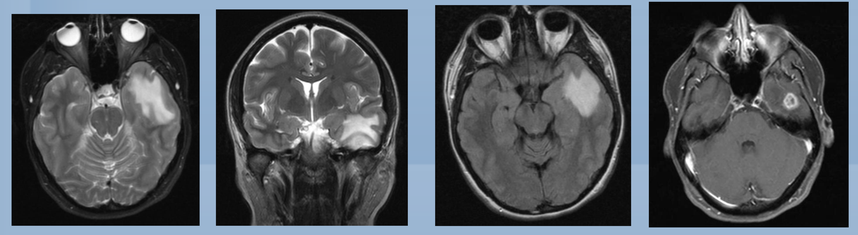
Physical Examination:

Alert and oriented to self, time and place with no focal neurologic deficits

Diagnostic imaging:

MRI brain with and without contrast demonstrated an intra-axial anterior left temporal lobe enhancing mass measuring 1.5cm in diameter. The lesion was isointense on T1-weighted images, hyperintense on T2-weighted images, showed ring enhancement on T1 with contrast and had perilesional hyperintensity on FLAIR sequence suggestive of vasogenic edema (Figure 1). CT chest, abdomen and pelvis were remarkable for a 1.4cmx2.2cm soft tissue density within the left breast consistent with a benign fibroadenoma. A transvaginal ultrasound was performed which demonstrated a left salpingo-oophorectomy and a right ovary that measured 4cmx2.8cmx3.7cm with slightly complex cysts that measured 2.1cmx1.5cmx2.2cm suggested to be a physiologic corpus luteal cyst.

Fig 1: Preoperative MRI



Hospital Course

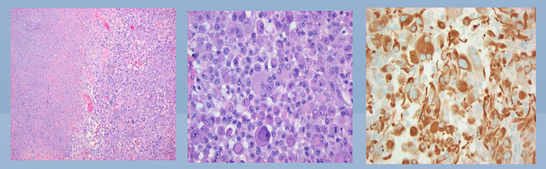
The patient was admitted to the oncology service with frequent neurological evaluations and started on dexamethasone 4mg every six hours and levitiracetam 500mg twice daily. Five days after admission, the patient underwent an image-guided left frontal-temporal craniotomy. A 4cm incision was marked traversing superiorly from the zygoma in order to access the anterior inferior temporal mass. Dura was opened in a cruciate fashion and the tumor was located using image guidance. On gross examination, the lesion was firm, well encapsulated and was removed *en bloc*. Tissue from this lesion was sent for frozen section and permanent pathology. Frozen section suggested a poorly differentiated malignant metastatic lesion of unknown primary origin. After maximal safe resection, hemostasis was obtained, dura was closed with duraform (DePuy Synthesis; Raynham, MA) and the bone flap was replaced. MRI post-operative day one suggested gross total resection.

The patient was observed overnight in the neuro-intensive care unit (NICU) with hourly neurologic examinations. Her pain was controlled with ice and Tylenol. On post-operative day one, the patient was neurologically intact, her foley catheter and arterial line were removed and she was transferred from the NICU to a general medical-surgical room. The patient was monitored for an additional 24 hours, remained medically stable and was discharged home on post-operative day two. She was prescribed a short steroid taper that would be re-evaluated on her first outpatient appointment seven days after surgery.

Pathological Findings

Histologic sections revealed tumor with large areas of necrosis and numerous mitotic figures (Figure 2A). The tumor cells consisted predominantly of pleomorphic epithelioid cells showing plump eosinophilic cytoplasm and sharp cell borders, mimicking a metastatic melanoma or carcinoma (Figure 2B). The morphologic features were inconsistent with an ovarian juvenile-type granulosa cell tumor. Immunohistochemisty showed that the tumor was positive for GFAP, supporting glial differentiation (Figure 2C). Immunostains for melanoma including SOX10, HMB45 and S100 were negative. An immunostain for p53 also showed diffuse positivity and INI-1 showed no loss of nuclear expression. Molecular analyses were also obtained and revealed no mutations in the IDH1 and IDH2 genes (wild-type) and in exon V600 of the BRAF gene. Mutations for EGFR variant III expression and MGMT promoter methylation were also negative. The overall findings were consistent with glioblastoma, in which the epithelioid type was supported by the cytologic features—namely the sharp cell borders and rounded nuclei—that imparted a more epithelioid, rather than glial, appearance.

Fig 2a,b,c: Pathological Images

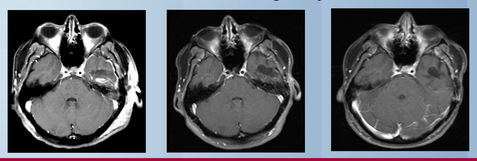


Histology. A) Areas of necrosis are appreciated under low magnification H&E staining (arrows)(40x). B) Epithelioid tumor cells showing plump eosinophilic cytoplasm and sharp cell borders, mimicking metastatic melanoma or carcinoma (400x). C) Tumor cells expressed GFAP by immunohistochemistry, supporting glial origin (400x).

Patient Outcome

The patient's steroid taper was completed on post-operative day 7. Four weeks after surgery, she underwent fractionated focal irradiation targeting the previous tumor bed in daily fractions of 2 Gy given 5 days per week for 6 weeks. She completed an MRI brain with and without contrast at 3 and 6 months postoperatively which showed no evidence of tumor recurrence (fig 3). Patient has since refused adjuvant temozolamide therapy and is currently seeking nutritional therapies. She has been seizure-free throughout her clinical course and remains neurologically intact.

Fig 3 Postoperative T1 post-contrast MRI. A) 24-hour postoperative MRI reveals gross total resection with a small posterior area of residual enhancement consistent with postoperative changes. B) 3-month and C) 6-month postoperative MRIs show T1 hypointensity in left temporal lobe without areas of residual or new enhancement



Discussion

The epithelioid type has been added to the classification of IDH-wildtype GBM but it is unique in its predilection for younger patients [5] and poorer prognosis. The poor prognosis may be in part due to an increased propensity for leptomeningeal dissemination [7]. Diagnosis of eGBM relies on a combination of radiologic, histologic and genetic analyses. Radiologic features of eGBM include areas of cystic necrosis with nodular enhancement, often accompanied by vasogenic edema, mass effect and midline shift [4]. Genetically, eGBM differs from traditional IDH-wildtype glioblastomas in that it often lacks identifiers such as EGFR amplification [5]. Histologically, differential diagnosis includes metastatic carcinoma, metastatic melanoma and pleomorphic xanthoastrocytoma [1,4]. Epithelioid GBM features large epithelioid cells with abundant eosinophilic cytoplasm, vesicular chromatin, multiple mitotic figures, fairly extensive necrosis and prominent nucleoli. The appearance of the nucleoli particularly may cause eGBM to be mistaken for metastatic melanoma during frozen section analysis. Its histology may also be mistaken for pleomorphic xanthoastrocytomas (PXA), a WHO grade II lesion, and its anaplastic subset (PXA-A) with shared characteristics of loosely cohesive cells with epithelial and glial markers [1]. Special stains assist in narrowing the differential as GBM is typically GFAP positive, S-100 protein positive, negative for HBM-45 and Melan-A.

Summary

Identification and diagnosis of glioblastoma is often straightforward, however eGBM can radiographically mimic a metastatic lesion. Thus the importance of tissue sampling is paramount when differentiating from suspected cases of metastasis. As unique classifications of GBM are investigated it is important to further evaluate brain masses using histologic stains and genetic analysis for early detection of eGBM. Due to its poor prognosis and predilection for leptomeningeal dissemination, early identification of this lesion is needed for appropriate care. Here, we discuss a 29-year-old female with past medical history of ovarian cancer presenting with receptive aphasia and radiographic evidence of a temporal lesion resembling metastatic disease. Frozen section of this lesion suggested a metastasis. However, final histological evaluation of this lesion revealed eGBM, a rare and newly classified subtype of GBM by the WHO classification.

References

1 Alexandrescu S, Korshunov A, Lai SH, Dabiri S, Patil S, Li R, Shih CS, Bonnin JM, Baker JA, Du E, Scharnhorst DW, Samuel D, Ellison DW, Perry A. Epithelioid glioblastomas and anaplastic epithelioid pleormphic xanthoastrocytomas-same entity or first cousins? Brain Pathol. 2016 Mar;26(2):215-23. PubMed PMID: 26238627.

2 Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun;364(26):2507-16. PubMed PMID: 21639808.

3 Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK. Epithelioid GBMs show a high percentage of BRAF V600E mutation. Am J Surg Pathol. 2013 May;37(5):685-98. PubMed PMID: 23552385.

4 Liebelt BD, Boghani Z, Takei H, Fung SH, Britz GW. Epithelioid glioblastoma presenting as massive intracerebral hemorrhage: case report and review of the literature. Surg Neurol Int. 2015 Mar;6(Suppl 2):S97-100. PubMed PMCID: PMC4392545

5 Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2006 May;131(6):803-20. PubMed PMID: 27157931.

6 Ohgaki H, Kleihues P (2013). The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013 Feb;19(4):764-72. PubMed PMID: 23209033.

7 Sugimoto K, Ideguchi M, Kimura T, Kajiwara K, Imoto H, Sadahiro H, Ishii A, Kawano H, Ikeda E, Suzuki M. Epithelioid/rhabdoid glioblastoma: a highly aggressive subtype of glioblastoma. Brain Tumor Pathol. 2016 Apr;33(2):137-46. PubMed PMID: 26667174.