Malignant epithelioid glioneuronal tumor with *BRAF V600E* mutation

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Malignant epithelioid glioneuronal tumors are rare, highly malignant tumors with glial and neuronal components. Very few cases of this variant of malignant glioneuronal tumors have been reported and their clinical presentation, imaging and prognosis remain poorly defined. A 19-year-old female presented to us with a new onset of a seizure disorder and was found to have a large right frontal mass with heterogeneous signal on Magnetic Resonance Imaging (MRI), surrounding edema, patchy enhancement and two small satellite lesions adjacent to mass inferiorly. The patient underwent a craniotomy for tumor resection and pathology revealed a very cellular high-grade malignant epithelioid cell tumor. Tumor cells staining strongly and diffusely for vimentin, S-100, Glial Fibrillary Acidic Protein (GFAP) and synaptophysin - leading to the diagnosis of malignant epithelioid glioneuronal tumor. Genotyping revealed a *BRAF V600E* mutation. Patient had stable disease until recurrence at 10 months post-operatively. Malignant epithelioid glioneuronal tumors are rare and aggressive tumors but *BRAF V600E* gene mutation inhibitors may help alter the course of these tumors.

Key Words: *Central nervous system; Glioneuronal tumors; Mutation; Brain tumors*

INTRODUCTION

Central Nervous System (CNS) glioneuronal tumors are neoplasms exhibiting both glial and neuronal differentiation and are relatively rare with an incidence of around 1-2 percent of all CNS neoplasms [1]. There are many different subtypes of glioneuronal tumors, most common gangliogliomа, central neurocytomas, paragangliomas, dysembryoplastic neuroepithelial tumors, and desmoplastic infantile astrocytoma/ gangliogliomas [1]. These are typically benign lesions, however with the latest immunohistochemical staining techniques, new malignant forms have recently been identified [1].

CASE REPORT

A 19-year-old female presented with new onset seizure. She was in good health other than a febrile seizure at 8 months of age but did have nausea and vomiting the week prior to seizure onset. She had a generalized tonic clonic seizure and a post ictal period with subsequent nausea and vomiting. She returned to baseline with no further seizures.

CT revealed a right frontal parasagittal hyperdense mass with mass effect. MRI of the brain revealed a parasagittal right frontal lobe 3.8 x 3.1 x 3.4 cm intra-axial mass with mild surrounding edema. The mass contained a central T2 hyperintense, non-enhancing cystic focus and areas that are T2 isointense to gray matter, with restricted diffusion, that enhanced with contrast administration (Figure 1). There were 2 small foci of enhancement immediately adjacent to the mass inferiorly measuring 9.4 mm and 6.6 mm each (Figure 1). The patient was started on anti-seizure medication and steroids and underwent a right frontal craniotomy with gross total resection of the mass (Figure 2).

Histo-pathology revealed a hypercellular high-grade malignant neoplasm with distinctly epithelioid tumor cells. The tumor cells showed a striking perivascular pattern of arrangement of tumor cells around blood vessels reminiscent of perivascular pseudorosettes in some areas and pseudopapillary arrangement of the tumor cells with multiple layers of tumor cells arranged around blood vessels without intervening solid sheets of tumor cells in others. The tumor cells had round nuclei and moderate amounts of clear or eosinophilic cytoplasm with small nucleoli.

Abundant mitotic figures including atypical mitoses were seen with focal necrosis and prominent vascular endothelial cells. The tumor was somewhat circumscribed from the neural parenchyma in some areas, but in other areas there was diffuse infiltration as well as extension along blood vessels in a perivascular manner (Figure 3).

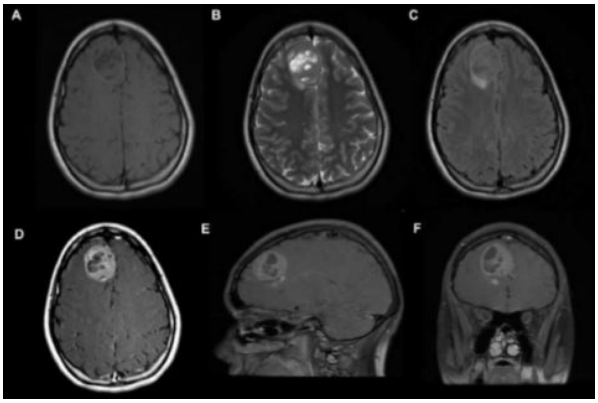

Figure 1) *MRI brain preoperative revealing (A) T1 mixed hypointense and isodense right frontal lesion. (B) T2 mixed hyperintense and isodense right frontal lesion. (C) FLAIR image with minimal edema. (D-F) MRI brain with contrast preoperatively with right frontal paramedian enhancing heterogeneous lesion with two satellite lesions inferior to the lesion*

Immunostaining showed that the tumor cells were strongly and diffusely positive with vimentin, S-100, GFAP and synaptophysin (Figure 3), with strong but patchy reactivity for neurofilament and for CAM-5.2. p53 nuclear staining was seen in less than 10% of the tumor cells; INI-1 staining was retained in the tumor cell nuclei and the Ki-67 labeling index was approximately 30% (Figure 3). Genotyping revealed a *BRAF V600E* gene mutation.

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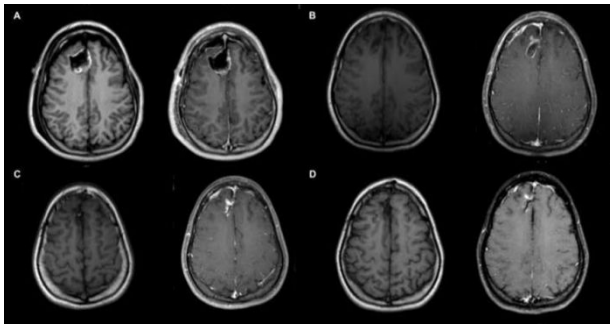

Figure 2) *(A) Immediate post-operative T1 noncontrast MRI (left) and contrasted study (right) with no residual enhancement noted. (B) 3-month post-op with some enhancement around the lateral anterior border of resection cavity, possible radiation vs. post-treatment reaction. (C) 6months post-op with stable enhancement along the lateral anterior resection cavity (D) 12months post-op with decreased enhancement at resection cavity*

The patient underwent 13 cycles of concomitant radiation and chemotherapy with temozolamide. The patient's images remained stable until 18 months post-operatively when recurrence was noted along the anterior resection bed. Repeat craniotomy and mass resection was completed and tumor genomics with BRAF inhibitor response were sent for analysis. The patient was started on the FDA approved dosing for BRAF targeted therapy of Dabrafenib 150 mg twice daily and Trametinib 2 mg daily.

DISCUSSION

Malignant glioneuronal tumors have malignant features in the neuronal, glial or both components [2]. Asides from anaplastic gangliogliomas, malignant glioneuronal tumors are rare though several variants have been reported recently [2]. Malignant epithelioid glioneuronal tumors are rare high-grade malignant glioneuronal tumors that express both glial and neuronal markers and show epithelioid morphology along with aggressive clinical behavior [3]. These tumors are not currently included in the most recent World Health Organization (WHO) classification of brain tumors. The most similar lesions that should be considered in the differential diagnosis are epithelioid glioblastomas, anaplastic pleomorphic xanthoastocytomas, and atypical teratoid rhabdoid tumors. Immunohistochemical staining can differentiate these tumors on pathology.

Only a handful of cases of malignant epithelial glioneuronal tumors have been reported in the literature though minimal details are available. All cases to date have been supratentorial in location with a predilection from frontal and parietal lobes. CT scans typically reveal a large hyperdense lesion, and MR imaging reveals a large heterogeneous mass with edema that enhances in some variance to contrast. In children, usually a solitary lesion is present but in adults multicentric lesions are common [1]. Grossly, these tumors tend to be well circumscribed and highly vascular with necrosis.

Pathology reveals large epithelioid cells with open chromatin and prominent nucleoli [1]. The cytoplasm is usually eosinophilic vacuolated, clear cell or xanthomatoid with defined borders [1]. On immunostaining, these tumors stain positive for glial makers, typically GFAP, vimentin, or S100, and neuronal markers, typically synaptophysin, Neu-N, chromogranin, neurofilament protein, or Microtubule Associated Protein 2 (MAP-2) [4]. Epithelioid glioblastomas and anaplastic pleomporphic xanthoastrocytomas typically lack immunoreactivity for neuronal markers and mutant IDH1 (R132H) immunoreactivity which can help differentiate these tumors [3].

All malignant epithelial glioneuronal tumors are positive for INI-1 protein expression, which is critical in excluding atypical teratoid/rhabdoid tumors where INI-1 is negative. Ki67 has increased proliferative activity in the anaplastic areas of the tumors and MIB-I shows variable but generally high labeling indices with up to 60% proliferation index [1]. Despite adjunctive therapy, death usually occurs within a year of diagnosis [1].

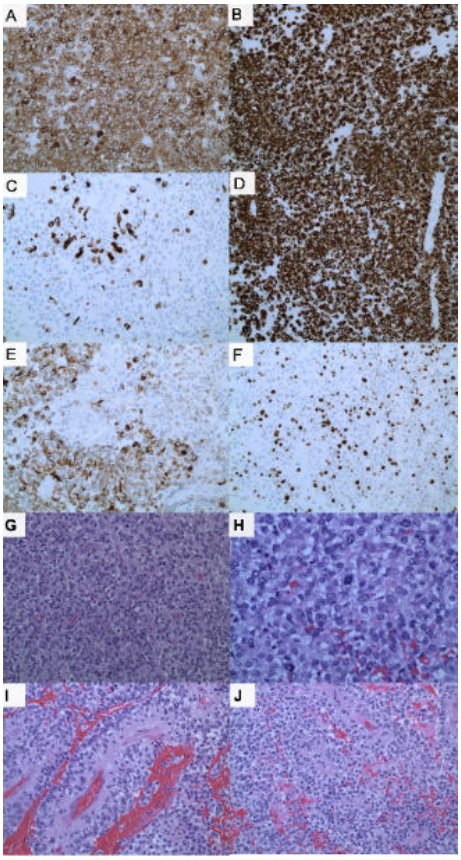

Figure 3) *Positive immunostains for (A) Synaptophysin, (B) Vimentin, (C) Neurofilament (NFP), (D) GFAP, (E) CAM 5.2 (keratin, epithelial marker), and (F) Ki67 (proliferation marker). (G-J) H and E images of the tumor showing a highly cellular tumor with distinct epithelioid tumor cells. The tumor cells show a striking perivascular pattern of arrangement of tumor cells around blood vessels. The tumor cells have round nuclei and moderate amounts of clear or eosinophilic cytoplasm*

CONCLUSION

The *BRAF V600E* gene mutation has been identified in many brain tumors most commonly pleomorphic xanthoastrocytomas and gangliogliomas; however multiple cases of glioneuronal tumors with this mutation have been identified. The *BRAF V600E* mutation has proven to be a negative prognostic factor in other neoplasms, and is also the target for novel therapeutic agents [5]. These tumors are very aggressive and cases in the literature all showed rapid progression and death within a year of diagnosis despite surgery, chemotherapy and radiation [1].

BRAF - inhibitor administration for the treatment of *BRAF V600E* mutation [5] positive malignant epithelioid glioneuronal tumors may be an option to help alter the course of these highly malignant neoplasms.

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