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 patient presented with her first generalized tonic clonic seizure and a post ictal period with subsequent nausea and vomiting. 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. Staining was retained in the tumor cell nuclei and the Ki-67 labeling index was approximately 30% (Figure 3). Genotyping revealed a *BRAF V600E* mutation.

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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Received: 19 February 2019, Accepted: 5 March 2019, Published: 21 March 2019

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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]. Aside 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 xanthoastrocytomas, 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 multcentric 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 markers, 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 pleomorphic 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-1 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].

**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.

**REFERENCES**

