Case Report

Malignant glioma-primitive neuroectodermal tumor recurring as PNET-like only subdural collection: Case report

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Abstract

**Background:** Histologic variants of conventional glioblastoma are rare clinical entities. In recent years, an aggressive variant termed malignant glioma with primitive neuroectodermal tumor components (MG-PNET) has been described in adults. In addition to the rarity of supratentorial primitive neuroectodermal tumors (sPNET) in adults, MG-PNET can present with unique radiographic features.

**Case Description:** We report the case of a 42-year-old male who presented with headaches and vision changes. Magnetic resonance imaging (MRI) of the brain revealed a large right frontal lesion. He underwent craniotomy with pathology demonstrating glioblastoma WHO grade IV, with primitive neuroectodermal tumor-like components (MG-PNET). Seven weeks later the patient represented with worsening headaches and left-hand weakness. MRI brain revealed a diffusion restricting subdural collection overlying the prior craniotomy site. Biopsy revealed PNET-like recurrence of the previously treated MG-PNET.

**Conclusion:** In addition to histologic deviation, MG-PNET can present with variable radiographic findings on MRI and a clinical course distinctive from traditional glioblastoma. The hypercellular nature of this lesion can present as a diffusion-restricting lesion.

**Key Words:** Diffusion-weighted MRI, glioblastoma, platinum-based chemotherapy, primitive neuroectodermal tumor, temozolomide

**INTRODUCTION**

Glioblastoma is an aggressive, high-grade glioma and is the most common primary malignant brain tumor in adults. Variants retaining foci of variable histology are recognized and are usually cited as single case reports. The etiology of these tumors with distinct areas of sarcoma or primitive neuroectodermal tumor (PNET) is unknown; existing literature suggest that discrete foci of cellularity arise in pre-existing glioma. Of interest, these lesions can present with radiographic features deviating from the contemporary glioblastoma on magnetic resonance imaging (MRI), thus pointing towards a variant form. A specific variant, malignant glioma with primitive neuroectodermal tumor components (MG-PNET), is exceptionally rare with...
paucity of knowledge regarding its clinical behavior, imaging characteristics, and prognosis.

Clinical behavior and treatment approach vary with the individual components of MG-PNET. Glioblastomas are glial neoplasms, staining briskly with glial fibrillary acidic protein (GFAP) and most often present in adulthood. Treatment consist of surgical resection followed by radiation therapy and chemotherapy with alkylating agents such as temozolomide. Craniospinal axis dissemination is rare. Treatment resistance is not uncommon and prognosis is dismal, although MGMT-methylation appears to denote a subgroup which can achieve durable disease control with conventional treatments.

In comparison, supratentorial PNETs (distinct from medulloblastoma) are predominately neuronal tumors, appearing as small round blue-cell tumors and staining for synaptophysin and neuron-specific enolase (NSE). These tumors primarily affect children, retain a high proliferation index, and have the potential for cerebrospinal fluid (CSF) dissemination. Interestingly, PNETs can show restricted diffusion on diffusion-weighted imaging (DWI). Treatment typically entails surgical resection and craniospinal radiation with platinum-based chemotherapy. Despite this more aggressive treatment, PNET retains a poor prognosis, similar to glioblastoma, yet response to treatment is more frequent and long-term survival is slightly better for PNET.

MG-PNET is difficult to diagnose radiographically due to their rarity, microscopic (as opposed to macroscopic) areas of neuronal tumor within the more dominant glial tumor, and lack of large studies. Prior work has reported the use of diffusion-weighted MRI in diagnosing suspected lesions as they have the potential to demonstrate reduced apparent diffusion coefficient (ADC) values in areas containing hypercellular foci, compared to conventional GBM. Here, we report a case of a MG-PNET, initially resected, recurring as PNET-only histology and presenting as diffusion restricted subdural collection on MRI.

**CASE REPORT**

A 40-year-old male presented with 2-week history of subjective headache, nausea, and blurry vision. MRI brain [Figure 1a] revealed a large right frontal lobe neoplasm consistent with high-grade glial neoplasm. Craniotomy was performed and postoperative imaging demonstrated gross total resection with marginal enhancement along the posterior margin of the surgical cavity thought to imply postoperative blood and hemostasis product [Figure 1b]. Pathology confirmed glioblastoma WHO grade IV with primitive neuroectodermal tumor-like components (MG-PNET) [Figure 2a-d]. Immunohistochemical staining demonstrated abundant GFAP immunoreactivity and frequent p53 nuclear staining. Fluorescence in-situ hybridization (FISH) analysis was negative for MYC rearrangement, but did confirm extra copies of the MYC region in 70% of the tumor nuclei. MIB-1 nuclear labeling approached 100% in solid component regions of the mass with abundant EGFR expression. 1p 19q were intact. Isocitrate dehydrogenase 1 (IDH1) was wild type, and unmethylated MGMT was observed.

Due to the PNET-like component of the tumor, MRI of the spinal axis was performed and was without evidence of drop metastasis. Subsequent treatment with radiation therapy and concurrent temozolomide chemotherapy was completed. Twelve weeks after the initial resection and post radiation therapy/temozolomide, surveillance MRI scan revealed multiple new enhancing foci within the left frontal lobe [Figure 1c]. Due to the MGMT unmethylated status and the areas of new enhancement, open resection was performed, with pathology demonstrating cortex and white matter with very mild hypercellularity; no obvious tumor was recognized [Figure 1d]. Chemotherapy was continued. Seven weeks later (and prior to his next planned MRI scan), the patient presented to the emergency department with acute onset of worsening headaches,
nausea, vomiting, and left-hand weakness. He proceeded to develop status epilepticus. MRI brain revealed a diffusion restricting subdural collection overlying the prior craniotomy site [Figure 3a-d]. Considering the possibility for empyema, the patient was taken to the operating room for evacuation with intraoperative inspection of the subdural space revealing a thick, gelatinous mass adherent to the pia mater and invading the brain parenchyma. Biopsy results demonstrated PNET-like only recurrence of the previously treated MG-PNET [Figure 4]. The small blue cell tumor component was histologically identical to the original MG-PNET tumor. Due to mixed-glia nature of the original tumor, biomarker molecular profiling was performed to assess the molecular characteristics of the tumor to determine chemotherapy sensitivity and provide targeted treatment. Considering that gliomas can exhibit multiple histologic and molecular subtypes with different clinical phenotypes and responsiveness to treatment, molecular profile testing provides the ability to evaluate tumor cell genetic characteristics and biomarkers. Specifically, molecular profiling evaluates gene amplification, deletion, and methylation-specific PCR to determine MGMT promoter methylation status and FISH for 1p and 19q deletion status. Though not routinely performed at our institution on gliomas demonstrating a homogenous histology, this study can be obtained and analyzed at an outside facility to assist in developing focused treatment regimens for mixed-gliomas. In our patient, Caris Life Sciences comprehensive molecular tumor profiling test was conducted and included analysis of DNA, RNA, and proteins utilizing immunohistochemistry, in-situ hybridization, next-generation sequencing, and pyrosequencing techniques. Based on molecular testing results, chemotherapeutic agents with potential or lack of benefit have been suggested in clinical trials. In our patient, biomarker results were positive for PTEN, TOP01, and TOP2A; chemotherapeutic agents with potential benefit included carboplatin, cisplatin, and irinotecan.

Because PNET is typically treated with platinum-based chemotherapy, studies confirmed MGMT unmethylated status and demonstrated potential sensitivity to platinum-based chemotherapy. In addition, biomarker results demonstrated topoisomerase activity. Given these findings and that PNET is traditionally treated with platinum-based chemotherapy, the patient was treated with salvage cisplatin and irinotecan. These agents were selected as cisplatin gains superior central nervous system penetration and irinotecan has been used in this setting on primary brain tumors. Given the toxicity associated with the selected regimen, a long discussion was held with the patient prior to initiating therapy. Initially, the patient responded well both clinically and radiographically to therapy; however, surveillance imaging at 8 weeks demonstrated significant tumor progression [Figure 5]. Following discussion, platinum-based chemotherapy was discontinued as the tumor demonstrated resistance, and salvage therapy with bevacizumab was undertaken. The patient continued to decline clinically and eventually succumbed to the disease burden 8 months following the initial diagnosis.

**DISCUSSION**

MG-PNET represents a rare histological variant of high-grade glioma. The reported overall frequency of PNET-like components appearing with glioblastoma has
been estimated in 1 out of 200 cases. The clinical behavior and treatment options remain the subject of patient reports and case series. Conventional glioblastoma treatment (radiation therapy, temozolomide, and surgical resection) is often implemented for its variants, including MG-PNET; however, in some patients this may not be adequate. Standard treatment for pediatric supratentorial PNET entails craniospinal axis radiation and platinum-based chemotherapy, which is more toxic than standard glioblastoma therapy and may not be any more effective in providing tumor control.

Due to the limited knowledge regarding radiographic features and clinical nature of GBM-PNET, these entities pose both diagnostic and therapeutic challenges.

Neurologic dysfunction in GBM-PNET is related to rapid tumor growth, peritumoral edema, and elevated intracranial pressure. Manifestations include headaches, nausea, vomiting, and seizures. Furthermore, focal neurological deficits including visual field defects, aphasia, extremity paresis, and facial nerve palsy may present depending on the anatomic location of the neoplasm. Our patient initially presented with headaches, nausea, and visual disturbances. Following presentation with subdural recurrence, signs and symptoms included headache, facial droop, left upper extremity paresis, and status epilepticus. Merely 6 weeks following subdural resection, imaging demonstrated diffuse recurrence with parenchymal infiltration. How quickly symptom onset occurs is a feature of the underlying aggressiveness of such lesions. Kim et al. reported Ki-67 index to be the most important prognostic factor in adults harboring PNET-like components. Their findings concluded that adult patients with Ki-67 index greater than 30% demonstrated poor outcome with a mean postoperative survival time of 8 months. This is similar to the median survival reported by Perry et al. (9.1 months). In our case, the Ki-67 index approached nearly 100% in some tumor regions and the patient died 8 months following the original tumor resection. Thus, evaluating the proliferation index of GBM-PNETs seems to provide prognostic value but further larger studies are warranted.

Even so, the genetic features and prognosis of adult PNET are still widely uncertain. It is known that pediatric PNETs associated with c-myc and N-myc gene amplifications are associated with a decreased survival. A review by Gessi et al. on supratentorial PNET occurrence in adults did not demonstrate amplification of c-myc/N-myc genes, thus indicating that PNET in adults may represent a specific subset of tumors. In our case, FISH analysis failed to demonstrated MYC rearrangement and MYCN and MYCC gene amplification was absent illustrating increased gene copying (3–5 copies) in 70% of the tumor cell nuclei. The significance of this finding is unknown but may point towards the aggressive tumor growth demonstrated in our patient (Figures postoperative to last MRI). Though it is not the focus of this article to...
discuss the underlying molecular abnormalities implicated in the behavior of GBM-PNET, it is not without doubt that these molecular disturbances contribute to the unique clinical and radiographic features of GBM-PNET.

The clinical features and behavior of GBM-PNET are variable, and the knowledge regarding its associated molecular markers is largely unknown. In a review of 53 patients of MG-PNET, Perry et al. concluded that the median age of diagnosis was 54 years ranging 21–80 years. This is in agreement with a median age of 51.5 years reported in the study by Song et al. Given the age range similar to secondary glioblastoma tumor occurrence, the hypothesis of PNET-like foci arising from a pre-existing malignant glioma is more consistent with GBM-PNET development. lp 1q co-deletions and IDH1 mutations are associated with secondary GBM and are known to confer improved prognosis. Song et al. concluded patients harboring IDH1 mutation showed prolonged survival as demonstrated by 2 patients with IDH1 mutation demonstrating survival at 15 and 31 months of follow-up compared to the median survival of 17 months in IDH1 wild type patients. However, following studies have failed to demonstrate such findings. In our patient, 1p/1q and 19p/19q ratios were normal (1.16 and 1.02, respectively); ratios less than 0.8 are consistent with deletion. In addition, IDH1 mutation was absent, which may have correlated with the more aggressive tumor nature encountered.

Aside from the difficulties in treating GBM-PNET, radiographic presentation varies considerably and imaging characteristics are not fully understood. Though there reports of PNET presenting as intracranial hemorrhage (ICH) are rare, this is the first writing of a co-deletion. Ali S, Joseph NM, Perry A, Barajas RF Jr, Cha S. Apparent diffusion coefficient in glioblastoma with PNET-like components, a GBM variant. J Neurooncol 2014;119:353-60. A 1p 19q co-deletion and IDH1 mutation demonstrating survival at 17 months compared to median survival of 15 months in IDH1 wild type patients. However, following studies have failed to demonstrate such findings. In our patient, 1p/1q and 19p/19q ratios were normal (1.16 and 1.02, respectively); ratios less than 0.8 are consistent with deletion. In addition, IDH1 mutation was absent, which may have correlated with the more aggressive tumor nature encountered.

There are no conflicts of interest.

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