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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 neuroectdoermal 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

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INTRODUCTION

Glioblastoma is an aggressive, high-grade glioma and is the most common primary malignant brain tumor in adults.[3,9-11] Variants retaining foci of variable histology are recognized and are usually cited as single case reports.[4,6,8] 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.[9] 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.[1,2,10] A specific variant, malignant glioma with primitive neuroectodermal tumor components (MG-PNET), is exceptionally rare with

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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.[3,9-11] 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.[9,10] Interestingly, PNETs can show restricted diffusion on diffusion-weighted imaging (DWI).[1] 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.[9]

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.

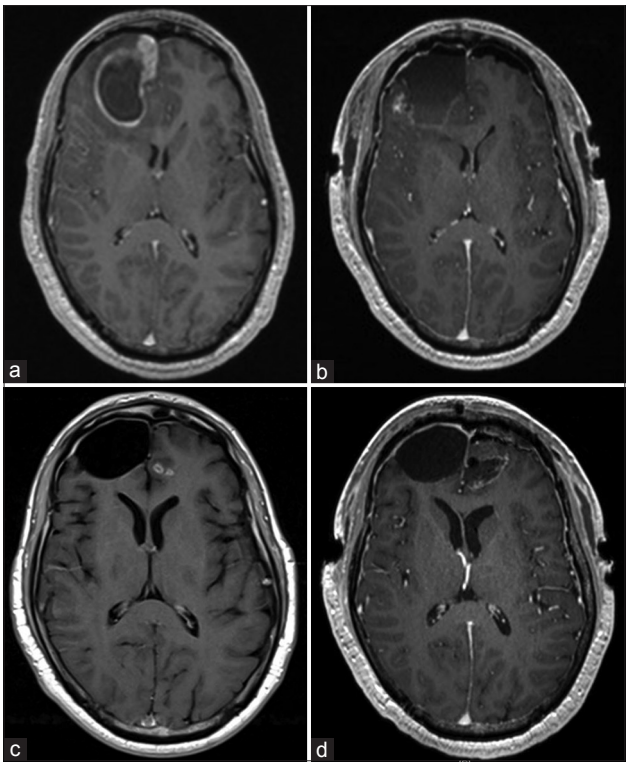

Figure 1: (a) MRI brain with contrast demonstrated 4.7 cm multiloculated rim enhancing cystic lesion with additional smaller projections invading the right frontal lobe with associated vasogenic edema and midline shift. (b) MRI brain with contrast demonstrating resection of right frontal mass with expected postoperative changes. (c) MRI brain with contrast demonstrating enhancing foci within left frontal lobe adjacent to prior surgical cavity. (d) MRI brain with contrast demonstrating resection of left frontal foci with expected postoperative changes

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,

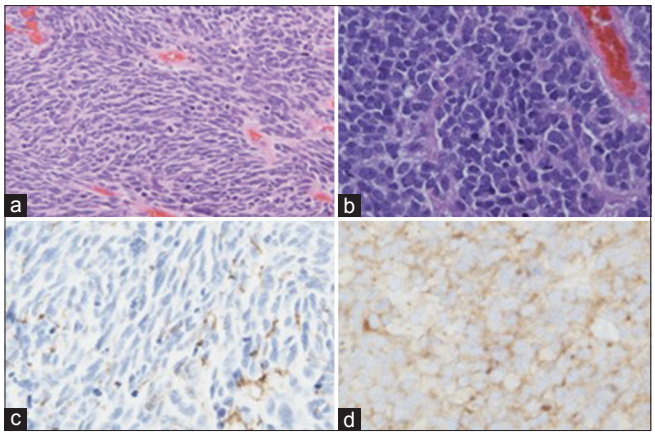

Figure 2: Histologic features of glioblastoma with PNET-like components. (a) Glioblastoma. (b) Small round blue cell component. (c) GFAP stain. (d) PNET-like components are strongly positive for synaptophysin

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-glial 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, TOPO1, and TOP2A; chemotherapeutic agents with potential benefit included carboplatin, cisplastin, and irinotecan.

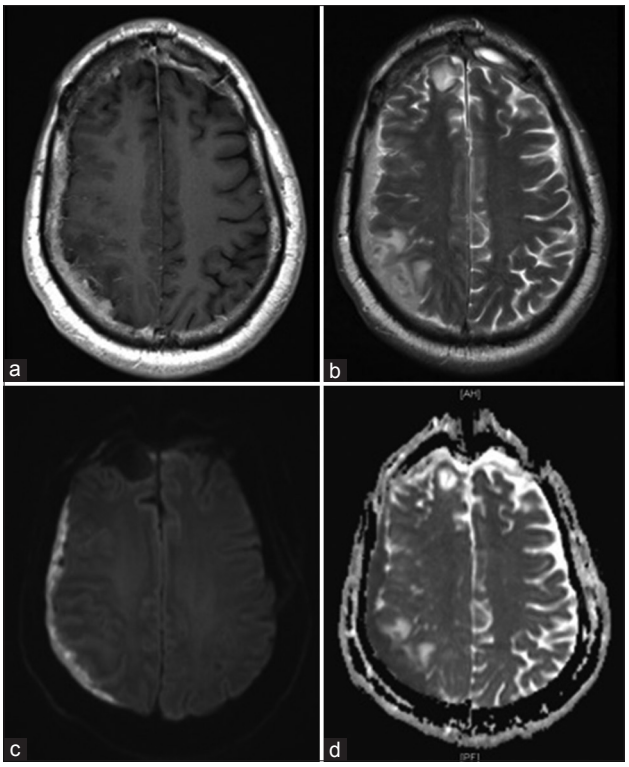

Figure 3: (a) MRI with contrast; (b) MRI T2WI; (c) DWI; (d) ADC. MRI Head demonstrating right frontoparietal subdural collection with associated vasogenic edema and restriction on DWI and ADC maps

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

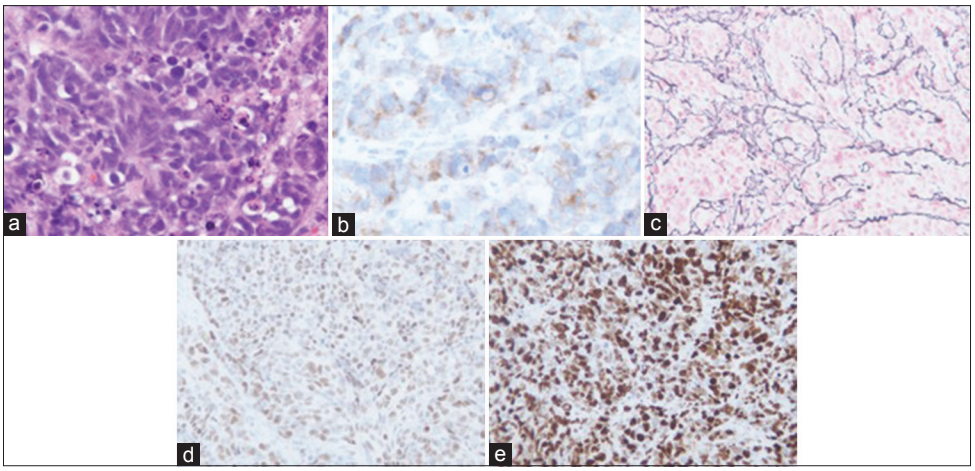

Figure 4: Histologic features of PNET-like subdural collection. (a) H and E stain. (b) Synaptophysin stain. (c) Reticulin stain. (d) p53 stain. (e) MIB-1 stain

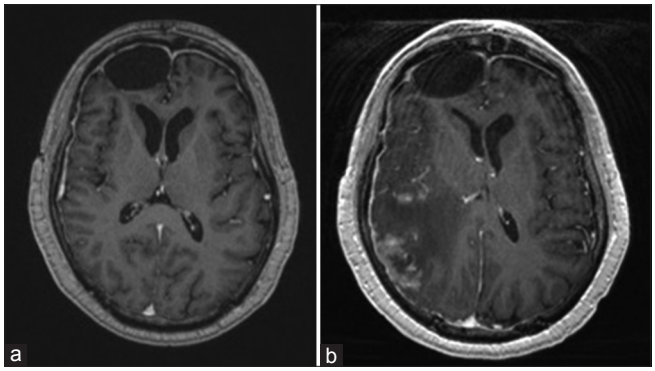

Figure 5: (a) MRI T1W with contrast four-weeks post-surgical evacuation of subdural collection and initiation of platinum-based chemotherapy demonstrating marked improvement. (b) MRIT1W with contrast eight-weeks following initiation platinum-based chemotherapy demonstrating marked progression of invasive tumor in the right parietal and posterior frontal lobes, extensive vasogenic edema extending to the atrium of the right lateral ventricle and midline shift

been estimated in 1 out of 200 cases.[9,10] 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.[3,9-11] 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.[9] 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.[7] 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).[9] 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.[5] 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.[9] This is in agreement with a median age of 51.5 years reported in the study by Song *et al*.[10] 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.[9] 1p 19q 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.[10] 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,[8] this is the first writing of a patient with initially diagnosed and treated GBM-PNET presenting as a PNET-only subdural recurrence. Special interest has been placed on utilizing DWI sequencing when suspicion for GBM-PNET occurrence is elevated as restricted diffusion in discrete regions can elucidate to PNET-like components.[1,2,10] Ali *et al*. studied the diffusion characteristics of GBM-PNET in 9 patients compared to 16 conventional GBM samples and concluded substantially reduced ADC values in GBM-PNETs (mean 581 × 10^{-6} mm^2/s, range 338–817) compared to conventional glioblastomas (1.030 × 10^{-6} mm^2/s).[1] Song *et al*. reviewed 10 patients with GBM-PNET and restriction diffusion was noted in 7 patients, which correlated with the presence of PNET-like components.[10] Hypercellular composition observed in PNETs is thought to cause restriction of water molecule movement (Brownian motion) resulting in suppressed ADC values. In our patient, the subdural collection illustrated high signal intensity on DWI and low signal intensity on ADC maps, suggestive of a subdural empyema. However, this presumed diagnosis was not evident on intraoperative inspection as gross tumor invading the subdural space was present.

CONCLUSION

The imaging characteristics of GBM-PNET are not well described and often propose a diagnostic dilemma. In the setting of glioblastoma neoplasms demonstrating restricted diffusion and lower ADC values compared to conventional glioblastoma, clinical suspicion for PNET-like components should remain elevated as areas of restriction may represent hypercellular neoplastic tissue. Moreover, DWI sequence utilization can assist in obtaining tissue for accurate histopathological diagnosis.

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Conflicts of interest
There are no conflicts of interest.

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