Case Report

rare tumors

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Polymorphous low-grade neuroepithelial tumor of the young: Rare tumor and review of the literature

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Abstract

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a recently described low-grade neuroepithelial tumor with an infiltrative growth pattern and oligodendrocyte-like cells that are CD34 immunopositive. Correlating histology and results from molecular testing is critical to correctly diagnosing PLNTY, as its histologic appearance is similar to oligodendrogliomas and shares genetic abnormalities common to other low-grade epilepsy associated tumors (LEATs). In this case report, we describe a 31-year-old female with intractable epilepsy found to have a temporal mass and diagnosed with PLNTY after histopathologic and molecular testing. We describe the radiographic, histologic, and genetic features in relation to the epileptic and oncologic outcomes for this patient. Then, we compare these features and outcomes to other cases of PLNTY described in the literature.

Keywords

Polymorphous low-grade neuroepithelial tumor of the young, low-grade epilepsy associated tumors, molecular analysis, BRAF, fibroblast growth receptor2, fibroblast growth receptor3

Introduction

There are a number of glial and glioneural tumors that commonly cause drug-resistant epilepsy in pediatric and young-adult populations. These tumors are part of a group known as low-grade epilepsy associated tumors (LEATs), an umbrella of developmental tumors with varying histologic appearances, associated with early-onset seizures. Glial tumors, such as pilocytic astrocytomas or pediatric oligodendrogliomas, usually have distinct diagnostic criterion that assist in further clinical management. However, glioneuronal tumors such as gangliogliomа (GG) and dysembryoplastic neuroepithelial tumors (DNET) have less distinct diagnostic criterion and therefore present a diagnostic challenge due to high intra-observer variability in pathologic diagnosis.[1] As these entities encompass a broad neuropathologic spectrum, predicting their clinical behavior can also be challenging.

The advent of molecular diagnostic testing has assisted in treating pediatric glioneuronal and glial tumors.[1] Molecular analysis has allowed tumors to be more accurately classified based on expression profiles and methylation patterns. Attempts to further characterize these epileptogenic neoplasms have led to discoveries of distinct entities. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) was first described in 2017.[2] It is notable for the presence of oligodendroglioma-like cellular components, CD34 immunopositivity, and an association with cortical

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dysplasia.[2] Molecular analysis has identified frequent genetic abnormalities involving the BRAF proto-oncogene or fibroblast growth receptor (FGFR), along with a distinct methylation pattern.[2] It lacks isocitrate dehydrogenase (IDH) mutations and 1p/19q codeletion.[2]

In our case report, we describe a 31-year-old female with intractable epilepsy found to have a temporal mass. We aim to describe our epileptic and oncologic outcomes, comparing it with other cases described in the literature.

Case report

Our patient was a 31-year-old right-handed female who had been experiencing intermittent seizures over the past two years. They were described as intermittent episodes of tongue tingling, decreased hearing, and inability to concentrate, occurring approximately once per week. The patient felt these episodes were triggered by stress. Her condition progressed until she experienced a generalized tonic-clonic seizure in October 2020. A CT brain without contrast demonstrated an intra-axial mass within the right temporal lobe (Figure 1(a)–(d)). The mass was cystic with hyperdensities thought to represent coarse calcifications in the periphery.

An MRI brain with and without contrast demonstrated a predominantly cystic, well-circumscribed, intra-axial lesion within the right temporal lobe measuring 1.8 × 2.2 × 1.8 cm. The mass did not enhance on post-contrast T1 weighted imaging (T1WI) and demonstrated hyperintensity on T2WI in the predominant cystic portion of the tumor. There was adjacent T2WI hyperintensity, which was felt to represent adjacent cerebral edema. Diffusion-tensor imaging demonstrated no involvement of major white matter tracts.

Following informed consent, the patient underwent a right temporal craniotomy for resection of the mass. Under the microscope, the dura was opened and a small corticectomy was performed. A small, fluid-filled mass with calcification and a thin tumor capsule was encountered and resected. No intraoperative complications were encountered and an MRI on postoperative day 1 demonstrated complete resection of the mixed solid and cystic lesion (Figure 1(e)).

Hematoxylin and eosin staining demonstrated a hypercellular lesion composed of small, monomorphic cells resembling oligodendrocytes and scattered micro-calcifications (Figure 2). The original panel of immunohistochemical staining performed at the time of diagnosis suggested the presence of an IDH mutation. Therefore, the diagnosis of oligodendroglioma was originally made. However, sequencing of the tumor demonstrated the wild-type IDH1 and IDH2 genes, indicating the IDH immunohistochemical staining was nonspecific (false positive). In addition, the 1p19q codeletion, the molecular signature of an oligodendroglioma, was not identified on chromosomal microarray. Instead, the tumor harbored a BRAF V600E mutation. Immunohistochemical staining with CD34 was diffusely positive, confirming a diagnosis of PLNTY.

The patient was readmitted two months later due to an episode of ringing in her ears and numbness of her tongue. An electroencephalogram demonstrated right temporal intermittent rhythmic delta activity, consistent with cortical irritability and the patient was diagnosed with a breakthrough seizure. After a dosage increase in her anti-epileptic regimen,

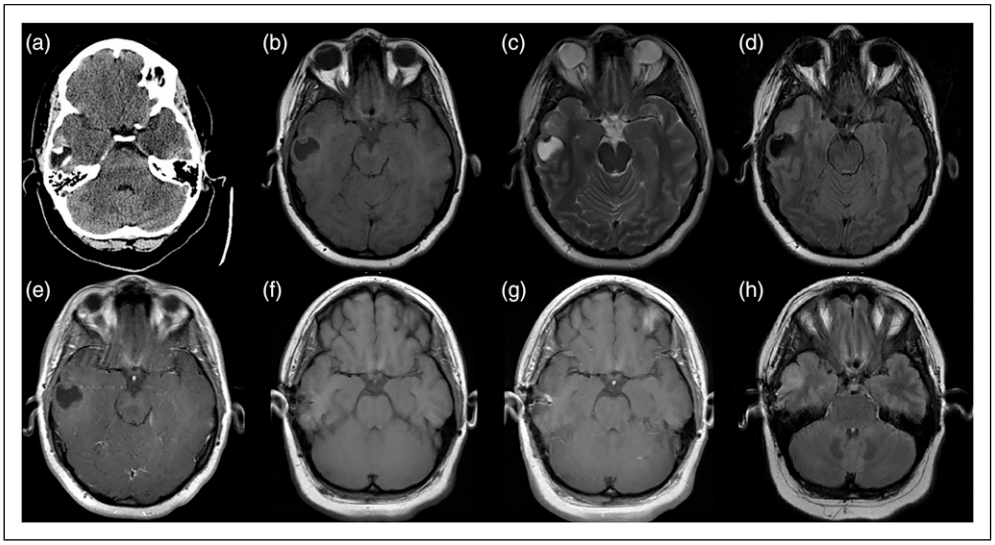

Figure 1. Preoperative axial brain CT (a), T1WI (b), and T2WI (c) without contrast demonstrate 1.8 × 2.2 × 1.8 cm cystic, calcified right temporal mass. Pre-operative T2 FLAIR demonstrates a FLAIR abnormality just anterior to the mass (d). Post-contrast T1 axial MRI was non-enhancing (e). Postoperative T1 FSE axial MRI pre-contrast (f) and post-contrast (g) have no findings suggestive of recurrence. Postoperative T2 FLAIR redemonstrates the FLAIR abnormality just anterior to the resection cavity (h).

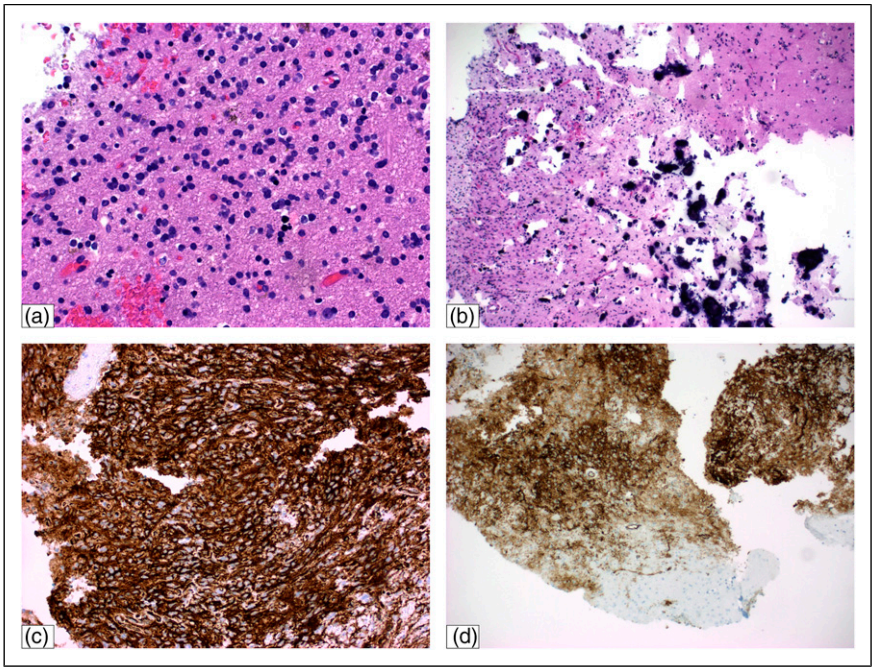

Figure 2. (a) Small, round oligodendroglioma-like cells with slight nuclear variability (hematoxylin and eosin [H&E] x40). (b) Dense calcifications seen with adjacent tumor and nontumor components (H&E x10). (c) CD34 immunohistochemical stain with intense reactivity in tumor (CD34 x20). (d) CD34 immunohistochemical stain demonstrating tumor with adjacent cortical tissue (CD34 x4).

the patient had no other seizures. An MRI brain with and without contrast at 3 months following surgery demonstrated no concern for recurrent disease (Figure 1(f)–(g)). However, there was evidence of prior blood products as suggested by a FLAIR abnormality anterior to the cavity, which was similar to the preoperative film (Figure 1(d) and (h)).

Discussion

PLNTY is a recently described low-grade neuroepithelial tumor which has an infiltrative growth pattern, oligodendrocyte-like cells that stain with CD34 immunopositivity, and either BRAF mutation or FGFR2/FGFR3 translocation.[2] We compare the imaging characteristics with oncologic and epileptogenic outcomes in other reported cases of PLNTY to further elucidate its morphology and behavior.

Concordance with histology

PLNTY is a low-grade tumor comprised of infiltrating "oligodendrocyte-like" cells with frequent calcifications. It is often associated with cortical dysplasia. The diagnostic challenge most often involves distinguishing this tumor from an oligodendroglioma, given the significant morphologic and clinical overlap. CD34 immunohistochemical staining can be helpful in making this distinction, with oligodendrogliomas staining negatively while PLNTY stain positively. Markers of glial differentiation, like GFAP and Olig2, may be positive in both. Importantly, PLNTY lacks neuronal differentiation and should not stain with neuronal markers such as NeuN. This helps to distinguish PLNTY from other tumors in the LEAT differential diagnosis. Often, the final diagnosis is made by interpreting the histology in light of the molecular profile. While oligodendrogliomas harbor IDH mutations and 1p/19q codeletions, PLNTY do not. Instead, they often demonstrate alterations in BRAF or FGFR2/FGFR3. Consistent with its low-grade classification, a Ki-67 labeling index will be low, typically less than 5%.

CD34 is a transmembrane phosphoglycoprotein that is found in progenitor cells and is expressed during early neurulation. It is not expressed in mature brain cells. Detecting the presence of CD34 is important, as CD34 positive lesions have been shown to be associated with a greater degree of drug-resistant epilepsy.[3,4]

BRAF V600E mutation

BRAF V600E is a missense mutation in which there is a replacement of valine with glutamic acid at codon 600. It is believed that this amino acid replacement at the N-terminal site creates a gain-of-function postulated to create a conformation that is similar to the phosphorylated state of the protein.[5] This allows it to activate the MAP kinase pathway in the absence of external signals. This mutation has different effects on cells. In cells that are destined for neuronal lineage, it has been shown to lead to increased neuron size

Table 1. Reported cases of PLNTY in the literature.

Study	Number of patients	Age and sex	Clinical presentation	Duration of symptoms	Location	Imaging characteristics	Treatment	Length of follow-up	Outcome	Reported mutation
Bale et al., 2021[8]	1	15 F	Seizure	NR	L Medial Temporal Lobe	Calcified, cystic, circumscribed, enhancing	GTR with recurrence 17 months post-resection, treated with NTR, focal proton radiotherapy, and TMZ	34 months	NR	FGFR3-TACC3 (original tumor and recurrence)
Bitar et al., 2018	1	31 M	Focal epilepsy refractory to partial temporal lobectomy	NR	R Posterior Temporal Lobe	NR	GTR without recurrence	12 months	Seizure Freedom	BRAF V600E
Chen et al., 2020[14]	3	14 F	Focal epilepsy	1 year	L Temporal Lobe	Calcified	GTR without recurrence	3 months	Seizure Freedom	FGFR3-TACC3
		15 M	Focal epilepsy	6 months	R Temporal Lobe	Calcified, circumscribed, enhancing	GTR without recurrence	3 months	Seizure Freedom	BRAF V600E
		16 M	Focal epilepsy	2 years	R Frontal Lobe	Calcified, cystic, enhancing	GTR without recurrence	36 months	Seizure Freedom	Not tested
Gupta et al., 2019[3]	1	30 M	Focal epilepsy	8 years	R Anterior Temporal Lobe	Circumscribed	GTR without recurrence	10 months	Seizure Freedom (episodic déjà vu without loss of awareness reported)	BRAF V600E
Huse et al., 2016	10	16 M	Epilepsy	More than 2 years	R Medial Temporal Lobe	NR	GTR without recurrence	53 months	Seizure Freedom	BRAF V600E
		18 F	Epilepsy	1 year	R Medial Temporal Lobe	Enhancing	STR with stable disease on imaging	18 months	Seizure Freedom	BRAF V600E
		23 F	Epilepsy	Unknown	R Temporal Lobe	NR	NR	NR	NR	BRAF V600E
		17 F	Epilepsy	Unknown	R Temporal Lobe	NR	GTR without recurrence	89 months	Seizure Freedom	FGFR3-TACC3
		4 M	Epilepsy	Unknown	L Temporal Lobe	NR	GTR without recurrence	86 months	Seizure Freedom	FGFR2-CTNNA3
		9 M	Epilepsy	6 years	R Frontal Lobe	Calcified, cystic, enhancing	GTR with new FLAIR signal abnormalities at 36 months post-resection	36 months	Seizure recurrence	FGFR2-KIAA1598
		10 M	Headaches and dizziness	6 days	R Occipital Lobe	NR	GTR without recurrence	62 months	N/A	FGFR2-KIAA1598
		23 F	Epilepsy	NR	R Medial Temporal Lobe	NR	GTR without recurrence	12 months	NR	No BRAF mutation, FGFR not tested
		32 F	Epilepsy	26 years	R Temporal Lobe	NR	GTR without recurrence	55 months	Seizure Freedom	Not tested
		24 F	Visual disturbances	2 years	R Occipital Lobe	NR	GTR without recurrence	12 months	N/A	Not tested

(continued)

Table 1. (continued)

Study	Number of patients	Age and sex	Clinical presentation	Duration of symptoms	Location	Imaging characteristics	Treatment	Length of follow-up	Outcome	Reported mutation
Johnson et al., 2019	9	12 F	NR	NR	L Temporal Lobe	Calcified, cystic, circumscribed	NR	NR	NR	FGFR2-KIAA1598
		12 F	NR	NR	L Parietal Lobe	Calcified, cystic, circumscribed	NR	NR	NR	FGFR2 rearrangement
		26 F	NR	NR	L Temporal Lobe	Calcified, cystic, circumscribed, enhancing	NR	NR	NR	BRAF V600E
		16 F	NR	NR	R Temporal Lobe	Calcified, circumscribed	NR	NR	NR	BRAF Fusion
		25 M	NR	NR	R Temporal Lobe	Cystic	NR	NR	NR	BRAF V600E
		15 F	NR	NR	L Temporal Lobe	Calcified, cystic, circumscribed	NR	NR	NR	None
		5 F	NR	NR	R Parietal Lobe	Calcified, cystic, circumscribed	NR	NR	NR	FGFR2-KIAA1598
		34 M	NR	NR	R Temporal Lobe	Calcified, cystic, circumscribed, enhancing	NR	NR	NR	BRAF V600E
		17 F	NR	NR	Third Ventricle	Calcified, cystic, circumscribed, enhancing	NR	NR	NR	BRAF V600E
Riva et al., 2018	1	57 M	Headache	Less than 1 month	R Frontal Lobe	Cystic	Unspecified resection without recurrence	12 months	N/A	FGFR3-TACC3
Sumdani et al., 2019	1	19 M	Epilepsy and headache	4 months	R Parietal Lobe	Calcified, circumscribed	Unspecified resection without recurrence	NR	Seizure recurrence	BRAF V600E
Surrey et al., 2019	6	7 M	Epilepsy	NR	Temporal Lobe	Cystic	GTR	8 months	NR (disease not progressive)	FGFR2-INA
		10 F	Epilepsy	NR	Parietal Lobe	-	GTR with recurrence 60 months post-resection	82 months	NR	FGFR2-INA
		14 M	Epilepsy	NR	Parietal and Temporal Lobes	Cystic	STR without recurrence	10 months	NR	FGFR2-CTNNA3
		16 M	Epilepsy	NR	Temporal Lobe	-	GTR without recurrence	10 months	NR	BRAF V600E
		8 M	Epilepsy	NR	Temporal Lobe	Cystic	GTR without recurrence	5 months	NR	BRAF V600E
		14 F	Epilepsy, vomiting	NR	Temporal and Occipital Lobes	Cystic	STR without recurrence	60 months	NR	BRAF V600E
Tateishi et al., 2020[15]	1	14 M	Epilepsy	1 year	L Temporal Lobe	Calcified, cystic, circumscribed	GTR without recurrence	16 months	Seizure Freedom	BRAF V600E

Abbreviations: F = Female; GTR = Gross Total Resection; L = Left; M = Male; N/A = Not applicable; NR= Not reported; NTR = Near Total Resection; PLNTY = Polymorphous Low-Grade Neuroepithelial Tumor of the Young; R = Right; STR = Sub-total Resection; TMZ = Temozolomide.

and epileptogenic potential. In cells of glial origin, it leads to proliferative capabilities.

BRAF V600E mutations are not only associated with PLNTY but are also common in gangliogliomas, another member of the LEAT family.[1] This mutation has also been described in other tumors of the central nervous system, including papillary craniopharyngioma and pleomorphic xanthoastrocytoma (PXA), and with much less frequency in pilocytic astrocytoma, anaplastic astrocytoma, epithelioid glioblastoma, gliosarcoma, rhabdoid meningioma, and atypical teratoid/rhabdoid tumor (AT/RT).[1]

FGFR alterations

The FGFR family is a group of transmembrane tyrosine kinase receptors (FGFR1-4) which homodimerize when ligand-bound and trigger downstream pathways including the MAPK and PI3K/Akt/mTor pathways.[6] Alterations in FGFR2 and FGFR3 have been described in PLNTY, with a number of different fusion partners. In a series by Surrey et al.,[7] fusions involving FGFR2 were identified, including a case with the rare FGFR2-CTNNA3 fusion. In the original description of PLNTY, Huse et al. identified multiple fusions involving FGFR2 and FGFR3, including FGFR3-TACC3, FGFR2-KIAA198, and FGFR2-CTNNA3.[2] These fusions were mutually exclusive with BRAF mutations. The result of these fusions is homodimerization and autophosphorylation of downstream effectors leading to enhanced activation of the MAP kinase pathway. FGFR3-TACC3 fusion has also been described in a subset of glioblastomas and other gliomas. This particular fusion product was present in the only documented case of PLNTY with malignant transformation.[8] The presence of FGFR alterations does not help to distinguish PLNTY from other tumors in the LEAT differential diagnosis, as they have also been reported in many of these tumors.

Of the 29 cases in the literature with documented molecular analysis, 16 harbored BRAF V600E mutations while 13 had FGFR fusion (Table 1). Upon reviewing these cases we identified in the literature, there were no overt differences in oncologic or epilepsy-associated outcomes based on molecular profiles. Further research is required to characterize the effect specific molecular profiles have on patient outcomes in PLNTY.

Imaging Concordance

The prototypical description of PLNTY is a well-circumscribed lesion with a calcified and cystic component.[9] These lesions have been reported to be primarily in the temporal lobe. In our review of the literature, we found that a majority of these tumors were located on the right side. As was seen in our case, PLNTY are primarily cystic with frequent calcification.

Association with Focal Cortical Dysplasia

The association with epilepsy has been linked to the expression of CD34 and BRAF V600E mutation.[3,4] These low-grade epilepsy associated tumors are associated with focal cortical dysplasia (FCD) and are classified as FCD type IIIb according to the ILAE classification system.[10] FCD in addition to other features of PLNTY may contribute to a prolonged disease course in these patients, as CD34 immunopositivity has been associated with chronic epilepsy.[3,4]

Prognosis and Clinical Course

Given the overlap between the clinical, radiologic, and histopathologic presentation of this tumors with others, specifically oligodendroglioma, the potential for misdiagnosis is significant.[2,3,11,12] PLNTY is associated with an indolent course and seizure control can typically be attained with gross-total resection. Oligodendroglioma is associated with a lower rate of epilepsy and a worse clinical prognosis.[3,13] Accurate diagnosis is critical in predicting clinical behavior and developing a treatment plan.

Conclusion

PLNTY is a low-grade epilepsy associated tumor associated with CD34 immunopositivity, cortical dysplasia, and either BRAF V600E mutation or FGFR2/FGFR3 fusions. As the histopathologic classification is challenging, molecular characterization can play a critical role in the diagnosis.

Contributorship

All authors made significant contributions and have approved the final manuscript.

Declaration of conflicting interests

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Ethical Approval

(Include full name of committee approving the research and if available mention reference number of that approval): This study was conducted in accordance with the Helsinki Declaration as revised in 2013. IRB approval was not required for the presentation of a single patient's case.

Informed Consent

Informed verbal consent was obtained from the patient reported in this manuscript.

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