Pearls & Oy-sters: Salt and Pepper Sign, PLNTY for Drug-Resistant Epilepsy

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Abstract

Drug-resistant epilepsy, defined as the failure of 2 or more antiseizure medications to achieve seizure freedom, is responsible for 2/3 of epilepsy cases. Tumors are responsible for up to 15% of all adult onset and up to 6% of childhood onset epilepsies. Among these tumors, commonly known subtypes DNET, ganglioglioma, and low-grade astrocytoma are often suspected. New advances in tumor classification have been made, with genetics playing a key role in tumor classification. Polymorphic low-grade neuroepithelial tumor of the young (PLNTY) is a highly epileptogenic subtype of tumors that may mimic low-grade gliomas but offer pathologic and genetic clues: oligodendroglioma-like cellular components and infiltration patterns and strong CD34-immunopositive stain. In addition, a key finding is radiologic: a unifocal abnormality best seen on MRI brain in FLAIR sequence as the "salt and pepper sign" and calcifications appreciated on CT head.

Pearls

- While mesial temporal sclerosis remains the most frequent pathologic finding in drug-resistant epilepsy, tumors are a frequent cause as well. The classical causes of tumor-related epilepsy have been attributed to long-term epilepsy-associated tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors.
- Polymorphic low-grade neuroepithelial tumor of the young (PLNTY) is a newly described, highly epileptogenic tumor, which can cause drug-resistant epilepsy.
- Imaging findings suggestive of PLNTY include unifocal abnormality best seen on MRI brain in FLAIR sequence as hyperintense cystic areas and areas of hypointensities within the lesion: the "salt and pepper sign," along with calcifications best appreciated on CT head.

Oy-sters

- PLNTY can be overlooked due to radiographic findings that are frequently mistaken for more well-known primary CNS tumors and not be considered due to its recent description of radiologic, genetic, and pathologic findings. This can be prevented by regular reviewing of previous and current imaging and pathology studies in patients who are nonresponsive to treatment.
- Correct identification of PLNTY tumors can potentially affect patient treatment and prognosis. When identifying the specific tumor type and molecular alterations associated with PLNTY, targeted surgery and medical treatment can be tailored specifically toward these molecular alterations.

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Drug-resistant epilepsy is defined as the failure of 2 or more antiseizure medications to achieve seizure freedom.[1] Drug-resistant epilepsy is seen in more than 2/3 of patients and is associated with early age at onset of epilepsy, abnormal EEG, febrile seizures, abnormal neurologic imaging (including tumors), among others.[2] When determined, the resection of the lesion that is involved in the seizure onset zone can potentially cure epilepsy.[3] Resection of "lesional" epilepsy onset zone is much more effective than "nonlesional" in achieving seizure freedom.[4]

Well-known tumors that cause epilepsy are DNET, gangliolglioma, and low-grade astrocytoma among others. There was a subtype of tumors that were described initially in 2016: pediatric type diffuse low-grade gliomas (PLNTY). It is largely heterogenous but offers pathologic and genetic clues: it is characterized by oligodendroglioma-like cellular components, infiltration patterns, and strong CD34-immunopositive stain. Radiologic findings highly suggest the diagnosis of PLNTY.

Case Report

A 20-year-old right-handed man with epilepsy had his first seizure at the age of 7 years. His seizures were characterized by staring, lip smacking, and accompanied by occasional left-hand automatisms. He was resistant to most antiseizure medications. General and neurologic examination was normal at age 8 years. MRI brain showed a low-grade tumor in the left anterior mesial temporal lobe measuring 1.7 cm in diameter without contrast enhancement (Figure 1A and B). CT head showed a parenchymal calcification within the lesion in the hippocampus (Figure 1C). Video electroencephalogram captured frequent left temporal interictal spikes (Figure 2D and E) and 6 clinical seizures over the left anterior temporal region (F7-T3-M1).

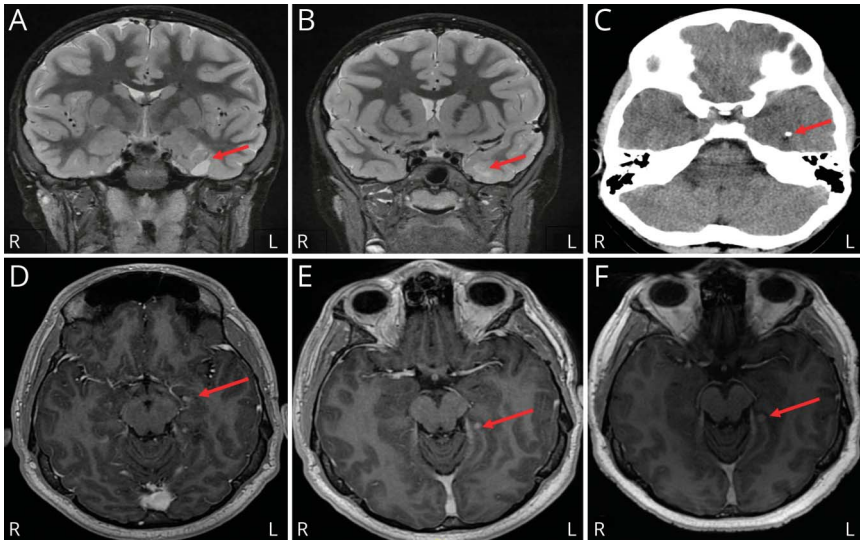
He underwent left anterior lobectomy at age 10 years. Histopathology revealed an infiltrative low-grade glioneural tumor characterized by morphologically normal neurons with uniform round nuclei, perinuclear halos, and delicate branching capillaries without necrosis, microvascular proliferation, or mitotic activity. The tumor cells displayed a variable expression of glial fibrillary acidic protein and patchy cytoplasmic expression of CD34. Only rare tumor cells and neurons were immunopositive for chromogranin A, and the neurofilament was immunonegative.

He experienced seizures with different semiology 6 months after the surgery. He initially had clusters of indescribable sensations followed by nausea and rising epigastric sensations intermittently over 30 minutes, lasting from 30 seconds to 45 minutes. He was readmitted for video EEG evaluation at age 20 years, but there were no EEG changes during his spells. Routine review with an experienced neuroradiologist of preoperative neuroimages revealed a cystic hyperintense lesion in T2-weighted brain MRI along with small hypointensities in the anterior temporal region (Figure 1A). Mixed granular signals were correlated with lesion-associated grit calcifications seen in the CT head (Figure 1C). Together, these findings are referred to as the "salt and pepper sign."

At age 20 years, brain MRI studies showed postoperative changes plus a small enhancing lesion measuring 3.2 mm in diameter in the left posterior parahippocampal gyrus (Figure 1D) that slightly augmented in diameter to 6 mm, then remained unchanged over the next year (Figure 1F). Given the deeper location of this very small lesion in the dominant temporal lobe, surgery was not considered.

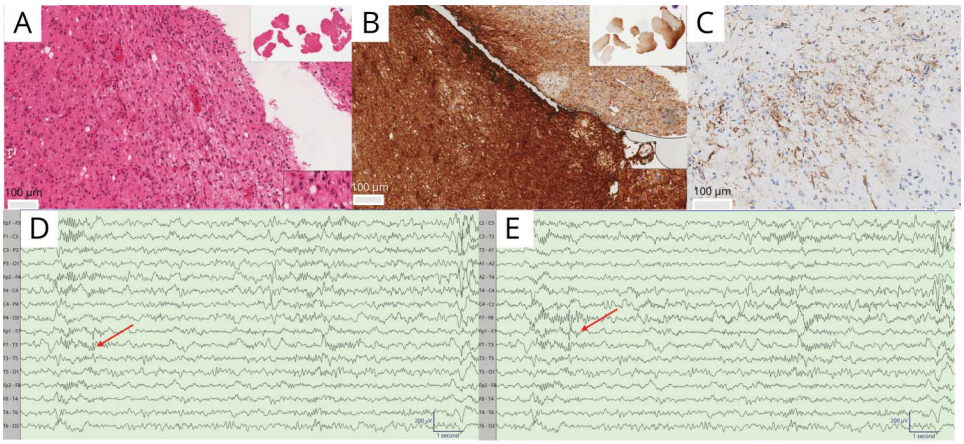
Reexamination of initial pathology tissue confirmed a low glioneuronal tumor (Figure 2, A–C) with no evidence of a deficiency in immunohistochemical staining of 4 DNA mismatch repair

Figure 1 MRI Brain Findings in PLNTY



(A) and (B) Coronal T2-weighted brain MRI shows hyperintense cystic lesion over the left mesial temporal region and small areas of hypointensities within the lesion: the "salt and pepper sign." (C) Axial CT brain shows punctate calcification over the left mesial temporal region. (D) Postoperative axial T1-postgadolinium contrast brain MRI shows enhancing 3.2 mm nodule in the left parahippocampal gyrus. (E) Postoperative, sequential axial T1-postgadolinium contrast brain MRI shows an increase in the size of the enhancing left para hippocampal gyrus nodule, that is, now measuring 6 mm. (F) Axial T1-postgadolinium contrast brain MRI shows stable enhancing left parahippocampal gyrus lesion measuring 6 mm 1 year later. PLNTY = polymorphic low-grade neuroepithelial tumor of the young.

Figure 2 Pathology and Electroencephalographic Findings



(A) Hematoxylin and eosin (H&E) stain shows tumors cells with round nuclei and clear cytoplasm. (B) Glial fibrillary acidic protein staining shows intense expression in tumor tissue. (C) CD34 staining shows cytoplasmic expression in the tumor cells. (D) and (E) Left anterior temporal interictal epileptiform discharges during sleep: bipolar anterior-posterior montage (D) and referential montage to contralateral ear (E) show spikes-and-slow waves with phase reversal indicating maximum electronegativity at F7-T3 electrodes. Sensitivity 10 µV/mm, filters 1–70 Hz.

proteins (MLH1, PSM2, MSH2, MSH6). The molecular testing confirmed BRAF (v-raf murine sarcoma viral oncogene homolog B1) V600E molecular alteration, consistent with PLNTY.

Based on these findings, medical management instead of stereoencephalography was pursued. If sequential MRI studies with gadolinium contrast show tumor progression, targeted therapy to the BRAF V600E variation with a BRAF inhibitor and mitogen-activated protein kinase (MEK) inhibitor would be considered, supported by the Roar trial.[5] Although these targeted therapies might be preferred over traditional chemotherapies, weekly vinblastine or carboplatin and vincristine could be considered.[6] Radiation is another treatment modality but is generally avoided in pediatric type low-grade gliomas due to risk of secondary transformation of the lesion to a higher-grade tumor (NCCN 2022: Version 1.2022, 06/02/22 © 2022 National Comprehensive Cancer Network). Based on the epilepsy burden and tumor growth, such patients could be treated with dabrafenib and tamatinib. Our patient will be followed with sequential MRI conservatively, and if there is clinical/radiologic progression, these treatments will be considered.

Discussion

Tumors are responsible for up to 15% of all adult onset and up to 6% of childhood onset epilepsies. Some characteristics determine whether tumors will be associated with epilepsy: tumor pathology (type, grade) and location. In general, lower grade tumors are more epileptogenic. Seizures are present in 40% of patients with meningiomas and 80% of patients with low-grade gliomas.[6] In a study of patients with oligodendrogliomas, 150 of 166 patients had epilepsy. Regarding tumor location and epilepsy, 56.3% of the cases are temporal, and 27% are extratemporal.[7–10]

In 2021, the WHO classification of CNS tumors was updated to include new subtypes of tumors because of advances in tumor genetics and classification.[9] PLNTY belongs to the category "gliomas, glioneuronal tumors, and neuronal tumors" and the subcategory "pediatric type diffuse low-grade gliomas" (PDLG).[10] It is a tumor that presents in childhood. It is distinct from more well-known proepileptogenic tumors in order of reported epileptogenicity: DNET, ganglioglioma, and low-grade astrocytoma (less frequently, meningioma, glioblastoma multiforme, and primary CNS lymphoma).[7] To date, only a few cases of PLNTY have been described.

PLNTY tumor differs from PDLG in its subcategories. While morphologically PLNTY shows variability, they are characterized by oligodendroglioma-like cellular components, infiltration patterns, and strong CD34 immunopositivity. This tumor type exhibits a distinct DNA methylation signature, very similar to the ganglioglioma, that is, the mitogen-activated protein kinase (MAPK), subject to tailored treatment. Although the exact tumor group/category has been debated among experts, the term "neuroepithelial" best describes its morphology.

The similarities between PLNTY and ganglioglioma are evident histologically as they relate to the MAPK pathway, but the expression of CD34 separates this subtype. These neoplasms represent a subset of tumors with a proposed term: "long-term epilepsy-associated tumors".[11] As this term suggests, these tumor types carry increased epileptogenic tendency.

PLNTY is frequently seen in temporal lobes in younger patients. It is often associated with chronic epilepsy with a benign course. Our patient had a tendency for breakthrough seizures. Owing to the histologic similarities, PLNTY and ganglioglioma cannot be discerned with pathology alone. Diagnostic features of PLNTY include focal drug-resistant epilepsy since childhood, lesion in the temporal lobe, and neuroimaging.[12] Neuroimaging findings include cystic lesions, calcifications on CT head, irregular

enhancement, solitary lesions, salt and pepper sign in T2WI, and slow growth rate. Two typical neuroimaging patterns highly suggest PLNTY: (1) poorly delineated cortical lesion with the salt and pepper sign in T2WI and (2) calcification on CT head imaging. [11] Differential diagnoses based on imaging include glioma, oligodendroglioma, DNET, and focal cortical dysplasia.

Histopathology provides clues to guide in diagnosis of PLNTY: oligodendroglioma-like cellular components with regional CD34 expression and genetic component of BRAFV600E molecular alteration either confirmed by immunohistochemistry or molecular testing. Genetic abnormalities include B-Raf proto-oncogene (BRAF) V600E and fibroblast growth factor receptors 2 and 3 (FGFR2, FGFR3). Gross total resection is the preferred first-line treatment, when possible. In the case of recurrence, post-gross total resection growth is typically gradual and addressed with a second surgery when amenable.[6]

Most pediatric-type diffuse low grade gliomas, including PLNTY, have MAPK pathway alterations. BRAF fusions such as KIAA 1549-BRAF fusion can be targeted by MEK inhibitors. BRAFV600 E molecular alteration can be targeted by BRAF inhibitors plus/minus MEK inhibitors, and FGFR3/FGFR2 alterations can be targeted by FGFR inhibitors or MEK inhibitors. Therefore, the molecular characterization of pediatric type gliomas may reveal a targetable MAPK pathway tumor driver that will change management.[13]

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Appendix *(continued)*

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