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

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PEARLS:

- While mesial temporal sclerosis remains the most frequent pathological 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 (LEATS) such as gangliogliomas and DNETs (dysembryoplastic neuroepithelial tumor).
- Polymorphic low-grade neuroepithelial tumor of the young (PLNTY) is a newly described, highly epileptogenic tumor, that 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 radiological, genetic, and pathological findings. This can be prevented by regular reviewing of previous and current imaging and pathology studies in subjects that are non-responsive to treatment.
- Correct identification of PLNTY tumors can potentially affect patient treatment and prognosis. When identifying the specific tumor type and genetic mutation associated with PLNTY, targeted surgery and medical treatment can be tailored specifically towards this mutation.

Key words: PLNTY; epilepsy; case report; CNS tumors; salt and pepper sign.

Abstract

Drug resistant epilepsy, defined as the failure of two 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. Amongst 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) are a highly epileptogenic subtype of tumors that may mimic low-grade gliomas but offer pathological and genetic clues: oligodendroglioma-like cellular components and infiltration patterns, and strong CD34immunopositive stain. In addition, a key finding is radiological: a unifocal abnormality best seen on MRI Brain in FLAIR sequence as the "Salt and pepper sign" as well as calcifications appreciated in Computed Tomography head.

Introduction

Drug resistant epilepsy is defined as the failure of two 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 electroencephalogram, febrile seizures, abnormal neurological 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 ¨non-lesional¨ in achieving seizure freedom.[4]

Well-known tumors that cause epilepsy are DNET, ganglioglioma, and low-grade astrocytoma among others. There was a subtype of tumors that were described initially in 2016: PLNTY. It is largely heterogenous but offers pathological and genetic clues: it is characterized by oligodendroglioma-like cellular components, infiltration patterns, and strong CD34 immunopositive stain. Radiological 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, accompanied by occasional left-hand automatisms. He was resistant to most anti-seizure medications. General and neurological examination was normal at age 8 years. MRI Brain showed a low-grade tumor in the left anterior mesial temporal lobe characterized by measuring 1.7centimeters in diameter without contrast enhancement. (Figure 1, A–B) CT Head showed a parenchymal calcification within the lesion in the hippocampus (Figure 1C). Video-electroencephalogram captured frequent left temporal interictal spikes (Figure 2, D–E) and 6 clinical seizures over the left anterior temporal region (F7-T3-M1).

He underwent left anterior lobectomy at age 10. 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 GFAP 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, but there were no EEG changes during his spells. Routine review with an experienced neuroradiologist of pre-operative 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 6mm, 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.

Re-examination of initial pathology tissue confirmed a low glioneuronal tumor (Figure 2, A–C) with no evidence of a deficiency in Immunohistochemical staining of four DNA mismatch repair proteins (MLH1, PSM2, MSH2, MSH6). The molecular testing confirmed BRAF V600E mutation, consistent with PLNTY.

Based on these findings, medical management instead of stereo- encephalography was pursued. If sequential MRI studies with gadolinium contrast show tumor progression, targeted therapy to the BRAF V600E mutation with a BRAF inhibitor and 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 do 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/radiological 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 if 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 out of 166 patients, had epilepsy. With regards to 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

due to 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 pro-epileptogenic tumors in order of reported epileptogenicity: DNET, ganglioglioma, and low-gradeastrocytoma (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, i.e. the mitogen-activated protein kinase (MAPK), subject to tailored treatment. Although the exact tumor group/category has been debated amongst 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" (LEATs).[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. Due to the histological 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 in 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 in 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 mutation 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 gliomas, including PLNTY, have MAP Kinase (MAPK) pathway alterations. BRAFV600 E mutation can be targeted by BRAF inhibitors plus/minus MEK
inhibitors and FGFR3/FGFR2 alterations can be targeted by FGFR inhibitors or MEK inhibitors.
FGFR inhibitors include Infagratinib and Erdagrafinib, with ongoing trials that support its effectiveness.[13] BRAF inhibitors include Dabrafenib and Vemurafinib. MEK inhibitors include trametinib and selumetinib.

Figure 1. MRI Brain Findings in PLNTY:

A,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. Post-operative axial T1-post-gadolinium contrast brain MRI shows enhancing 3.2 mm nodule in the left para-hippocampal gyrus.

E. Post-operative, sequential Axial T1-post-gadolinium contrast brain MRI shows an increase in the size of the enhancing left para hippocampal gyrus nodule, i.e. now measuring 6 mm.

F. Axial T1-post-gadolinium contrast brain MRI shows stable enhancing left parahippocampal gyrus lesion measuring 6 mm one year later.

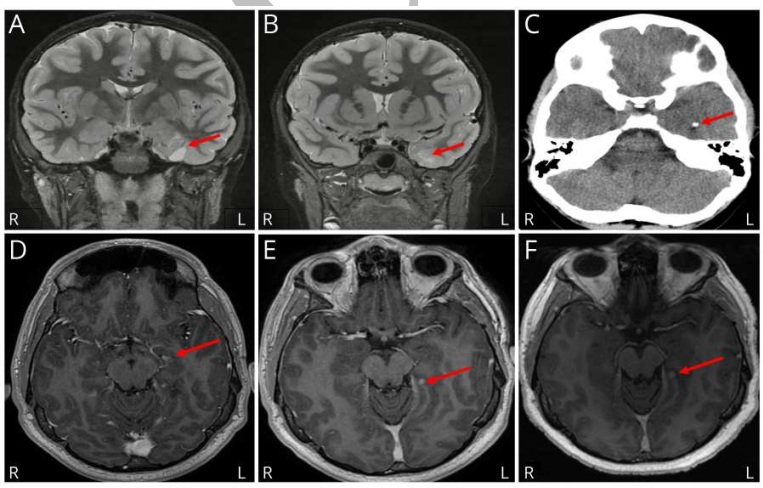
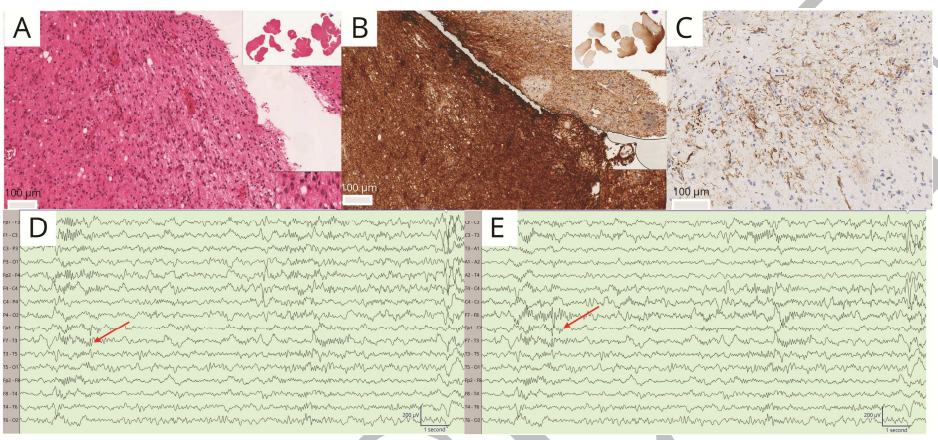


Figure 2. Pathology and Electroencephalographic Findings

A. Hematoxylin and eosin (H&E) stain shows tumors cells with round nuclei and clear cytoplasm.
B. GFAP staining shows intense expression in tumor tissue.

C. CD34 staining shows cytoplasmic expression in the tumor cells.

D-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 electro-negativity at F7-T3 electrodes. Sensitivity10 μV/mm, filters 1–70 Hz.



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