Stereo-electroencephalography evidence of an eccentrically located seizure-onset zone around a polymorphous low-grade neuroepithelial tumor of the young: illustrative case

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BACKGROUND Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a newly identified low-grade brain tumor with frequent epileptic presentation. Despite the facilitated use of invasive electroencephalography owing to the growing availability of stereo-electroencephalography (SEEG), intracranial features of tumor-related seizures are still scarcely described. This report provides the first description of SEEG-recorded seizures in PLNTY to provide an insight into its surgical strategy.

OBSERVATIONS Spontaneous clinical seizures were recorded with SEEG in a young adult patient with drug-resistant epilepsy associated with a PLNTY in the left lateral temporal cortex. The seizure onset was characterized by low-voltage fast activity (LVFA) and showed eccentric localization with respect to the tumor: LVFA was localized in the anterior portion of the tumor and spread toward the adjacent polar cortex. The language risks associated with the resection of the posterior temporal cortex could thus be minimized.

LESSONS PLNTY can show a focal and eccentric seizure-onset zone around the tumor. The present findings serve to improve the functional and seizure outcomes using the staged invasive approach in PLNTY.

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KEYWORDS epileptogenic zone; long-term epilepsy-associated brain tumor; low-voltage fast activity; polymorphous low-grade neuroepithelial tumor; resection; stereo-electroencephalography

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a recently identified rare entity of epilepsy-associated neuroepithelial tumor.1 PLNTY has distinctive histological and genetic features that consist of oligodendroglioma-like cellular infiltrates, components with variable morphological polymorphism, intense aberrant expression of CD34, and gene mutations involving the constituents of the mitogen-activated protein kinase pathway such as BRAF V600E or fibroblast growth factor receptors.1,2 As with other long-term epilepsy-associated brain tumors (LEATs),3 seizures are usually the first and the only symptom of patients with PLNTY and begin to occur during childhood or early adulthood. On imaging, PLNTY often shows cystic components or calcification,1,4 and the temporal lobe appears to be the most common location.1,4,5 PLNTY has recently been accepted into the 2021 World Health Organization classification of central nervous system tumors.6

While previous reports of PLNTY described the aforementioned clinical, imaging, and histopathological features,1,4,5 none has described intracranial EEG features. Here we report a case investigated with stereo-electroencephalography (SEEG) to help understand the relationship between the tumor and epileptogenic zone in this new entity of LEAT and thereby to provide an insight into its surgical strategy.

ABBREVIATIONS EEG = electroencephalography; LEAT = long-term epilepsy-associated brain tumor; LVFA = low-voltage fast activity; MRI = magnetic resonance imaging; PLNTY = polymorphous low-grade neuroepithelial tumor of the young; SEEG = stereo-electroencephalography.

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Illustrative Case

A 23-year-old right-handed woman had no prior medical conditions or family history of epilepsy other than her epilepsy. She initially presented with bilateral tonic-clonic seizures at the age of 18 years. They were suppressed after initiation of an antiseizure medication (lamotrigine) by a referral neurologist, but she continued to have aphasic seizures, which brought her to our epilepsy center. Scalp EEG showed focal interictal spikes in the left anterior temporal region with inversion of phase at F7 or T1. Her ictal symptoms were characterized by the lack of verbal comprehension, with or without being followed by impaired awareness and distal-dominant automatisms slightly preceding on the left. Postictal aphasia lasted several minutes. Ictal EEG showed a left temporal leading spike and then generalized background suppression with left temporal predominance for 5 to 6 seconds. This initial phase was followed by a low-amplitude alpha rhythm predominantly over the left temporal region, which then evolved into bihemispheric delta discharges. Her brain magnetic resonance imaging (MRI) revealed no structural or signal abnormalities in the hippocampi but a cystic cortical lesion that lay across the left superior and middle temporal gyri (Fig. 1A). There was neither calcification (Fig. 1B) nor contrast enhancement within or around the lesion (Fig. 1C and D). A [18F]-fluorodeoxyglucose positron emission tomography showed a focal left lateral temporal hypometabolism corresponding to the lesion (Fig. 1E). Her neuropsychological assessment showed preserved verbal as well as visual memory performance. LEAT was a possibility, but she pursued medical treatment until she continued to have seizures several times a month (up to six per month) despite trials of several antiseizure medications (lamotrigine 400 mg, levetiracetam 1,000 mg, and lacosamide 200 mg). Then she decided to receive an invasive EEG investigation. SEEG was performed to assess (1) whether the hippocampus is spared from ictal-onset discharges, (2) the extent of potentially MRI-negative epileptogenic zone/network, and (3) its relationship with the language area (see Fig. 2 for the SEEG implantation scheme). Interictal spikes were centered around the anterior portion of the cystic cortical lesion (Fig. 3A). Similarly, ictal low-voltage fast activity (LVFA) was localized anteriorly around the lesion and spread toward the polar region (Fig. 3B; see also Fig. 2 for the anatomo-electrical relationship). The posterior portion of the lesion as well as more posterior temporal cortex did not show LVFA but only brief fast activity without background suppression. The hippocampus was involved only in prolonged seizures (>15 seconds) with subsequent evolution into a focal-to-bilateral tonic-clonic seizure. Unlike focal cortical dysplasia, the lesion appeared to have a high epileptogenic threshold because electrical cortical stimulation (50 Hz, 1–5 mA) did not induce after-discharges or seizures.

The patient received extended resection that consisted of left anterolateral temporal corticectomy (complete resection of the lesion at the posterior limit) combined with polectomy. The histological examination showed...
sharply demarcated, infiltrative growth of oligodendrocyte-like tumor cells with intense CD34-immunopositivity in the cortex and subcortex (see Fig. 4 for the key histopathological findings). Tumor cells with pleomorphic, atypical nuclei were focally observed. They were also positive for the glial markers, including glial fibrillary acidic protein (GFAP) and oligodendrocyte transcription factor 2 (OLIG2), whereas no neuronal staining such as for synaptophysin, neuronal nuclear antigen (Neu-N), and neurofilament was observed. Nuclear expression of α-thalassemia mental retardation X-linked (ATRX) was retained, and only a few cells expressed p53 (<10%). The MIB-1/Ki-67 labeling index was very low (<1%), with virtually no mitosis, supporting the diagnosis of a low-grade tumor. Molecular analysis revealed a BRAF V600E mutation. Based on these morphological, immunohistochemical, and molecular features, a diagnosis of PLNTY was concluded. The depth electrodes were adjacent to but not within the core region with dense cellular infiltrates of the tumor, and histological differences among the electrode positions were not discernible. There was no associated cortical dysplasia, and complete resection of the tumor was confirmed both histologically and on postoperative MRI. At her last follow-up visit 1 year after the surgery, she remained free of seizures and showed no cognitive impairment.

Discussion

Observations

SEEG disclosed an eccentric seizure-onset zone relative to the tumoral lesion. LVFA representing the seizure-onset zone was limited to the anterior portion of the tumor and the adjacent polar region. By contrast, the posterior portion of the tumor as well as more posterior temporal cortex were spared from LVFA. Accordingly, complete tumor resection with extension to the pole was carried out without language complications and achieved complete seizure freedom. The histopathological examination confirmed the diagnosis of PLNTY, a new entity of LEAT whose anatomo-electrical relationships of seizures have yet to be reported.

Invasive EEG recordings of spontaneous clinical seizures are not frequently performed in tumor-related epilepsy: it has been estimated that only 10% of patients receiving resection for tumor-related epilepsy are monitored with chronic intracranial electrode implantation. However, this finding indicates the fact that >20% of cases continue to have seizures postoperatively, and therefore there is still room for improvement in the surgical strategy. Accurate delineation of the seizure-onset zone using invasive EEG monitoring has the potential to improve seizure outcomes in patients with tumor-related epilepsy.10 To date, however, only a single study has explicitly assessed the impact of the two-stage surgery approach with invasive EEG monitoring. Despite the limited variety of tumors in that study, it was suggested that excellent seizure outcomes can be achieved after complete resection of the seizure-onset zone, which can be widespread and eccentric to the tumoral lesion. To our knowledge, the current report is the first to demonstrate intracranially recorded seizures in PLNTY. Their onset was characterized by LVFA and showed eccentric localization with respect to the tumor. The latter finding is of particular importance when using SEEG as an invasive EEG tool in PLNTY because undersampling in the peritumoral region can result in failure to detect ictal-onset activity (LVFA) and thus an inability to delineate the seizure-onset zone to be resected. Indeed, the peritumoral spatial sampling in the present case allowed accurate definition of the seizure-onset zone, thereby maximizing the chance of seizure freedom. This also led to minimizing the language risk because the posterior temporal cortex was spared from LVFA. Considering the better patient
experience and lower procedural complication risks with SEEG than with subdural grids, there may be a greater opportunity to perform tailored resections using SEEG-recorded seizures in LEAT. Our findings would help refine the SEEG implantation scheme in future cases suspected of having PLNTY to better predict and optimize their surgical outcomes.

We were unable to find a specific correlation between the localization of seizure-onset and histopathological findings. This is a limitation that remains to be addressed in future studies.
using a large number of patients with sufficient peritumoral electrode coverage.

Lessons
PLNTY showed a focal seizure onset with LVFA that was eccentrically located around the tumor. When exploring it with SEEG, adequate spatial sampling in the peritumoral region is essential to successfully identify the seizure-onset zone and optimize the functional as well as seizure outcomes. The lessons learned from the present case will serve to improve the surgical strategy using the two-staged approach in PLNTY and potentially in other types of LEATs.

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Hagiwara, Kamada, Suzuki, Shigeto, Ohara, Akamatsu. Acquisition of data: Hagiwara, Kamada, Suzuki, Miyoshi, Tanaka, Shigeto, Ohara. Analysis and interpretation of data: Hagiwara, Suzuki, Tanaka, Shigeto, Ohara. Drafting the article: Hagiwara, Shigeto. Critically revising the article: Hagiwara, Suzuki, Ohara, Akamatsu. Reviewed submitted version of manuscript: Hagiwara, Suzuki, Miyoshi, Shigeto, Ohara, Akamatsu. Approved the final version of the manuscript on behalf of all authors: Hagiwara. Administrative/technical/material support: Hagiwara, Tanaka, Akamatsu. Study supervision: Hagiwara, Shigeto, Akamatsu.

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