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Rapid resolution of depression and epilepsy following resection of a septal region tumor: illustrative case

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BACKGROUND The authors present a case of a young patient who presented with depression symptoms and epilepsy. She was found to have a low-grade glioneuronal tumor located in the septal region, a critical limbic area involved in neuropsychiatric disorders. This region includes the ventral striatum, a key component of the brain's reward processing circuitry, which has been targeted in deep brain stimulation trials for treatment-resistant depression.

OBSERVATIONS Following resection of the septal region tumor, the patient experienced rapid remission of both her depression symptoms and epilepsy.

LESSONS This case illustrates the resolution of both seizures and mood disturbances following the removal of the septal region tumor and highlights the potential for lesions in key limbic structures to underlie both disruption of mood and epileptic activity.

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KEYWORDS depression; epilepsy; septal region; ventral striatum

Here, we describe the case of rapid remission of depression symptoms following resection of a low-grade glioneuronal tumor centered in the septal region. The septal region is a limbic area of outstanding interest given its role in the pathophysiology of neuropsychiatric conditions. Notably, it houses the ventral striatum, which is central to the brain's reward processing circuitry and has been targeted in deep brain stimulation trials for refractory depression.[1] Our case is an illustrative example of a focal lesion managed surgically with prompt resolution of both seizures and mood symptoms. It demonstrates that lesions located in key limbic areas can cause electrical signaling disruptions of neural circuits that underlie both mood disruptions and epileptic activity.

Illustrative Case

We present the case of an 18-year-old female who presented with seizures and depression and was found to have a grade 1 glioneuronal tumor centered in the left septal region. Following resection of the tumor, she experienced rapid, sustained relief of both her seizures and depression symptoms.

History of Present Illness

At the time of presentation in 2022, the patient was an 18-year-old female with a 7-year history of depression and a 5-year history of seizures. Regarding her depressive symptoms, she recalled feeling "deeply abnormal" beginning 7 years prior to presentation. She began to experience depressive episodes, characterized by sadness and isolation, lasting from a few days up to 2 weeks. During depressive episodes, it became more difficult for her to exercise, care for herself, and complete homework. Her appetite worsened, and she found it more difficult to socialize. She experienced hopelessness but denied suicidal ideation. She did not feel that she fully returned to normal between episodes. In 2022, her psychiatrist confirmed a *Diagnostic and Statistical Manual, Fifth Edition*, diagnosis of major depression. Her Patient Health Questionnaire-9 (PHQ-9) score was 7 during an

ABBREVIATIONS BNST = bed nucleus of the stria terminalis; EEG = electroencephalography; PHQ-9 = Patient Health Questionnaire-9; ROI = region of interest; SEEG = stereo-EEG.

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apparently low-symptom period, consistent with mild depressive symptoms. She experienced worsening of her mood symptoms during 2022, which prompted her psychiatrist to initiate venlafaxine in addition to continuing cognitive behavioral therapy.

Two years after the onset of depressive symptoms, the patient began having seizures. Her seizures were preceded by an aura of dread, doom, and severe dysphoric déjà vu, which are common in left temporal lobe semiology. Following the aura, she would experience an "epiphany," which would then progress to expressive aphasia, followed by postictal confusion for a few minutes. The patient did not note a temporal relationship between her depressive symptoms and her seizures. She described feeling "super down on most days," irrespective of recent seizure frequency. Despite therapeutic dosing of lamotrigine and lacosamide, her seizures occurred at least 2–3 times per week, and at worst 4–5 times per day. An escalation in seizure frequency in 2022 prompted the addition of clonazepam to her medication regimen, which decreased seizure frequency but resulted in drowsiness.

Scalp electroencephalography (EEG) revealed 2 seizures with ictal patterns localized over the left temporal lobe, congruent with her seizure semiology. However, her only radiographic finding on MRI was a nonenhancing, T2 hyperintense 1.3 × 1.7–cm lesion centered in her left septal region, most consistent with a low-grade glial or glioneuronal tumor (Fig. 1A and B). This lesion was discovered in July 2022 following her first MRI scan. The lesion remained stable in size throughout the following year as the patient underwent further workup and treatment planning.

The patient's case was discussed at our institution's multidisciplinary epilepsy conference. Multiple options for management were discussed, including intracranial stereo-EEG (SEEG) recordings to better characterize the relationship between the remote lesion location and

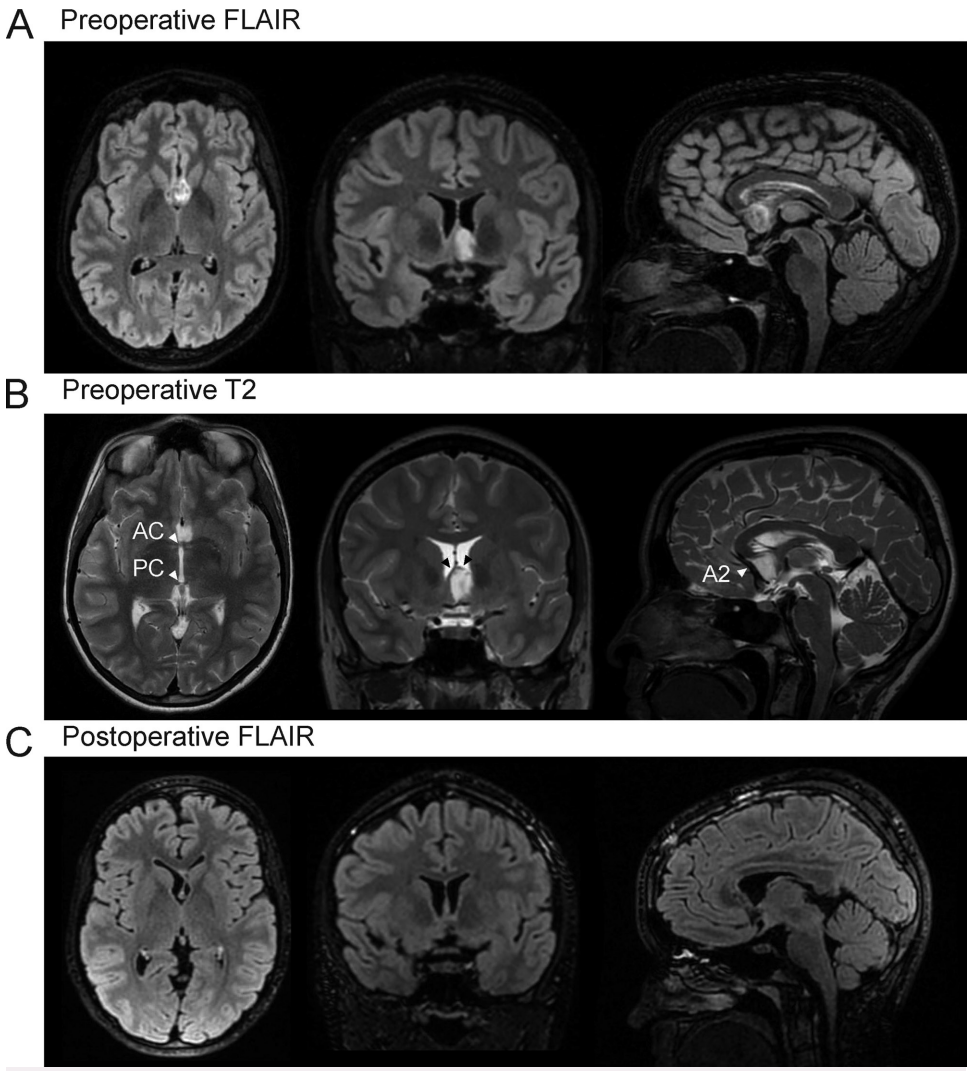

FIG. 1. A: Preoperative axial, coronal, and sagittal FLAIR MRI sequences demonstrating a 1.3 × 1.7–cm T2 hyperintense lesion centered in the left septal area. **B:** Preoperative axial, coronal, and sagittal T2-weighted MRI sequences again demonstrating the lesion, as well as anterior commissure (AC), posterior commissure (PC), fornices (*black arrowheads*), and A2 branch of the anterior cerebral artery (*white arrowheads*). **C:** Postoperative axial, coronal, and sagittal FLAIR MRI sequences demonstrating gross-total resection of the tumor.

the suspected temporal lobe seizure onset zone. However, given that the lesion would need to be removed regardless of seizure onset localization, lesionectomy was thought to be the most appropriate initial management step.

One ablative option was stereotactic laser interstitial ablation with lesion biopsy through the same stereotactic tract. If seizures persisted following this surgery, open surgical management could then be considered. Another option was an open interhemispheric approach to the lesion with gravity-assisted retraction. This option carried the advantage of definitive resection of the lesion as well as the opportunity to perform intraoperative electrocorticography to ensure the resolution of epileptiform activity. Following detailed risk-benefit conversations with the patient and her family, an open interhemispheric approach to the lesion with intraoperative electrocorticography was planned.

An ipsilateral interhemispheric transcallosal approach was planned to access the left-sided septal tumor. Our approach leveraged gravity retraction of the contralateral hemisphere and avoided resection of cortical tissue and associated risks such as postoperative seizures. One downside of our approach was the technical difficulty resulting from the long (nearly 8 cm) reach from the craniotomy to the lesion. An alternative approach would be an ipsilateral lateral transoperacular approach. However, this approach would necessitate cortical resection including the dominant lateral orbitofrontal cortex, which subserves important roles in decision-making and response selection.[2] Another alternative approach would be a subfrontal approach. This would necessitate removing the ipsilateral gyrus rectus. Furthermore, the A2 segment would be encountered prior to the tumor (Fig. 1B) and the superior extent of the tumor would be difficult to reach. We therefore opted for an interhemispheric approach.

Surgery and Outcome

We proceeded with a left interhemispheric, transcallosal approach craniotomy for resection of the septal lesion. The patient was in a semilateral position with her left side down to facilitate gravity retraction of the left hemisphere. Her head was secured in the Mayfield head holder, and neuronavigation was registered. Transcranial motor evoked potential neuromonitoring was used intermittently throughout surgery. Following the elevation of the craniotomy flap over the superior sagittal sinus, the dura was opened and reflected medially along the sinus. A stereotactic biopsy arm was used to guide the insertion of a 10-contact depth SEEG electrode (AdTech), with distal contacts terminating just at the lateral margin of the lesion. The deepest 3 contacts revealed intermittent abundant epileptiform activity (Fig. 2A). The SEEG lead was also used as an anatomical landmark to delineate the tumor boundary.

The intraoperative microscope was brought in to facilitate microdissection of the interhemispheric arachnoid plane. Bipolar electrocautery was used to create a 2-cm transection in the anterior corpus callosum. The septal vein, lateral caudate nucleus, and septum were visible within the left lateral ventricle, as well as the tumor, which was bulging superiorly into the ventricle. The tumor appeared gray and soft. The tumor was resected to its margins (anterior margin: A2 segment of the anterior cerebral artery; ventral margin: anterior communicating artery; lateral margin: depth electrode; posterior margin: anterior commissure). The epileptiform discharges initially observed on the depth electrode were abolished by the end of the operation (Fig. 2B).

The patient recovered well in the immediate postoperative period without complications. She was discharged to home safely with no rehabilitation needs on postoperative day 3. Postoperative MRI demonstrated gross-total resection (Fig. 1C), and interval 3-month and 1-year MR images (not shown) showed no evidence of residual or recurrent tumor. The lesion pathology revealed a low-grade glioneuronal neoplasm, most compatible with a myxoid glioneuronal tumor, WHO grade 1. Her tumor was found to have a solitary missense mutation at codon 385 in the platelet-derived growth factor receptor α (encoded by the *PDGFRA* gene), belonging to the rare and recently described entity, "Myxoid glioneuronal tumor, *PDGFRA* p.K385-mutant," which has a predilection for the septum pellucidum.[3,4] She has not experienced any seizures since surgery and has successfully tapered off levetiracetam. She is currently undergoing a gradual lamotrigine taper. She returned to college 6 months following surgery.

Remarkably, the patient experienced a rapid and sustained remission of her depression symptoms following surgery. She attributed her improvement in mood within 1 week following surgery to a newfound ability to regulate her emotions. She stated that, prior to surgery, "my mood felt volatile, uncontrollable, and super down most days," and "I felt completely shut down." Following surgery, she noted that "normal mood regulation techniques would work well," even while experiencing fluctuations in mood. She no longer takes antidepressant medications. She continues to find cognitive behavioral therapy helpful. Her most recent PHQ-9 score was 2 (normal).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

Here, we presented the case of a patient with both depression and epilepsy, both of which remitted following the resection of a septal lesion. Our case highlights the functional significance of the septal region in mood regulation through the resolution of depression symptoms following the removal of a focal tumor. The septal region has long been implicated in psychiatric disorders; self-stimulation of this area has been associated with pleasant and euphoric feelings,[5] and a recent personalized neurostimulation trial identified the nucleus accumbens, intimately associated with the septal region, as a highly effective stimulation site for treatment-resistant depression.[6] While no prior studies have directly linked the removal of a focal lesion in the septal region to rapid remission of depression, the well-established role of this region in mood-related circuitry suggests that our findings can be generalizable to other cases involving lesions in this critical limbic structure.

First, we will discuss the neuroanatomical basis of the patient's seizures. Her seizures were consistent with medial temporal lobe seizures, based on both semiology and electrographic characteristics observed on scalp EEG. Multiple white matter pathways link the septal region tumor to the mesial temporal lobe. Figure 3 shows the tracts seeded from a region of interest (ROI) placed at the lateral margin of the tumor (red) and a homologous ROI in the contralateral hemisphere (green). Diffusion tractography revealed that the lateral margin of the septal tumor connects to the amygdala via the ansa peduncularis[7] and to the amygdala and hippocampus via the fornix and stria terminalis. These robust white matter connections suggest that the mesial temporal lobe seizures in our case could have resulted from the spread of peritumoral epileptiform activity (as observed during intraoperative electrocorticography) along these pathways.

While not all patients with septal tumors present with both depression and epilepsy, our tractography analyses indicate that tumors in this region can contribute to both mood disturbances and mesial

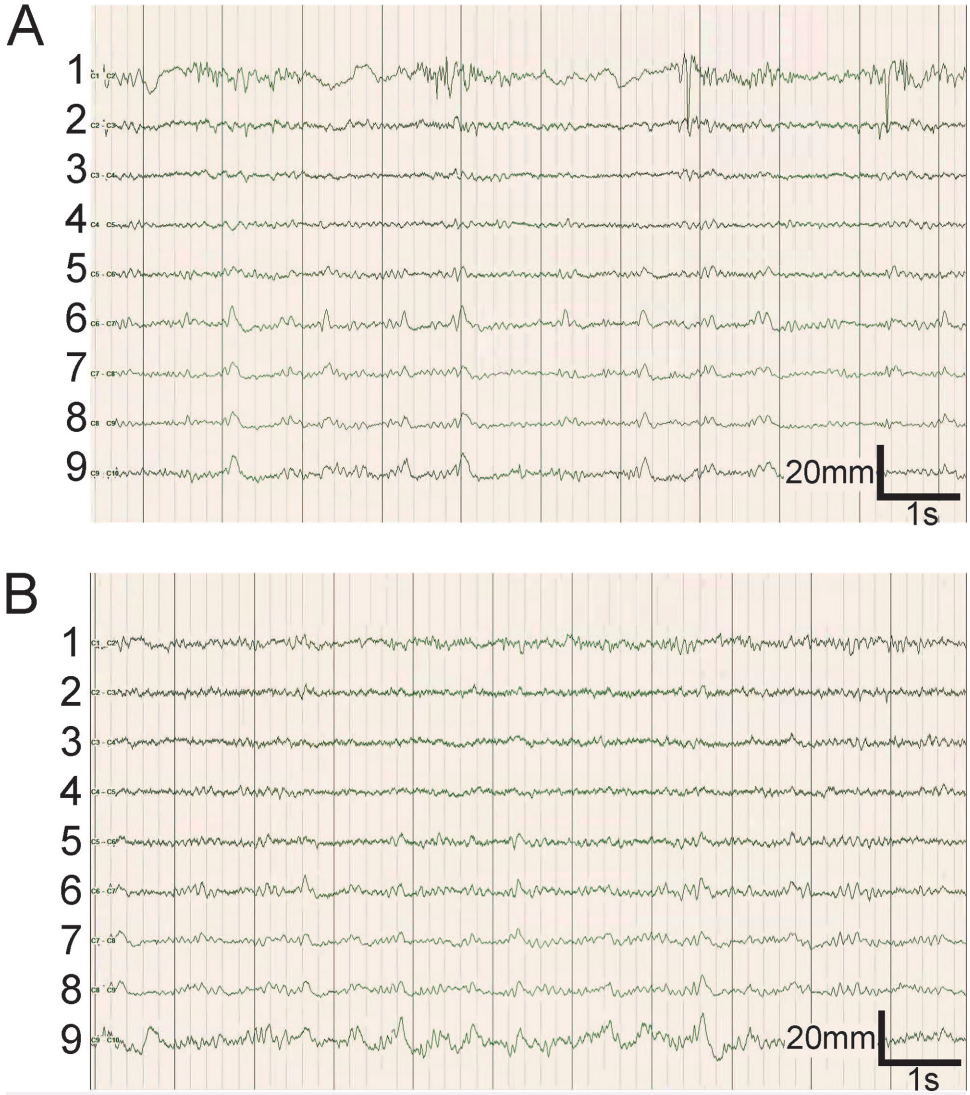

FIG. 2. A: Preresection intraoperative electrocorticography (ECoG) epoch reveals frequent focal interictal epileptiform disturbances of cerebral activity (spikes, polyspikes, and high-frequency oscillations) in the most distal contacts (mainly contact 1 with the field extending to contact 2, rarely to contact 3) of the depth electrode. These most distal contacts abut the lateral margin of the lesion. **B:** Postresection ECoG epoch recording from the same electrode (in the same location) following resection of the lesion. All epileptiform activity is abolished.

temporal lobe seizures. The close association of the tumor with fiber tracts such as the ansa peduncularis, fornix, and stria terminalis underscores the potential for a shared mechanism. In cases in which patients with septal tumors exhibit both depression and epilepsy, it is critical to consider the possibility that the lesion itself can underlie both conditions. This illustrative case also highlights the importance of integrating tractography findings into the clinical evaluation of patients with septal tumors to better understand and address the relationship between structural lesions and seizure localization.

We next consider the neural circuit basis of the patient's depression. We postulate that the patient's depressive symptoms were caused by abnormal interictal electrical activity in the septal region. The septal region is a complex gray matter structure containing multiple subnuclei located anterior to the anterior commissure and surrounded by a set of limbic structures that have each been implicated in the pathophysiology of depression and other psychiatric disorders. Specifically, the septal region is posterior to the subcallosal cingulate (area 25), anterior to the bed nucleus of the stria terminalis (BNST), and medial to the ventral striatum/nucleus accumbens. The ventral striatum, in particular, receives dopaminergic projections from the midbrain tegmentum and is important in reward-based learning,[8] and dysfunction in this region is implicated in deficits in reward processing and anhedonia in depression.[9] Meanwhile, the ventral striatum and subcallosal cingulate are the 2 most common targets for deep brain stimulation in severe refractory depression.[1,10] Finally, in our own results from a closed-loop stimulation trial for refractory depression,[6] the most effective stimulation site for mood amelioration was characterized by a pattern of connectivity between the BNST and amygdala through both

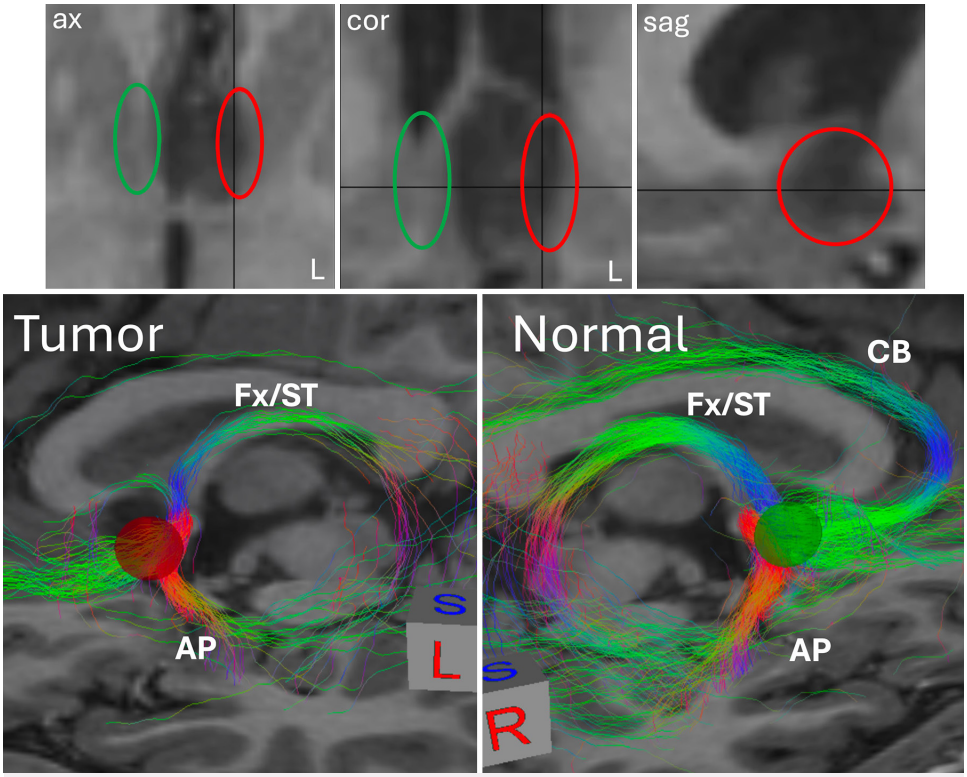

FIG. 3. Tractography seeded from the lateral margin of the tumor shows extensive connectivity to the medial temporal lobe. Diffusion imaging was used to visualize white matter tracts seeded from an ROI placed at the lateral margin of the tumor (*red*) and an ROI placed at the homologous location in the contralateral hemisphere (*green*), revealing connections between the tumor location and the amygdala via the ansa peduncularis (AP) and amygdala and hippocampus via the stria terminalis (ST) and fornix (Fx). Tractography was based on a preoperative 3T high angular resolution diffusion imaging (HARDI) sequence with 55 directions and a b-value of 2000. Preprocessing of diffusion data with QSIPrep[13] included denoising, motion and eddy current correction, and registration of the B0 image to a high-resolution (1 mm isotropic) T1 volumetric sequence. Tractography was performed with MRtrix[14] and included response function estimation, FOD estimation using constrained spherical deconvolution, and probabilistic whole brain tractography yielding 150K fibers. Definition of seed ROIs and visualization of recruited fibers were performed using MI-Brain.[15] ax = axial; CB = cingulum bundle; cor = coronal; sag = sagittal.

the stria terminalis and the ansa peduncularis—a connectivity pattern very similar to that recruited along the lateral margin of our patient's tumor (Fig. 3). Collectively, these data suggest that abnormal electrical activity in the septal region is anatomically poised to create mood disturbances through its impact on immediately adjacent structures and associated networks.

In the hypothetical scenario in which the patient presented solely with depression, without seizures, our options would be to either observe with serial imaging or surgically address the lesion, given its imaging characteristics consistent with a low-grade or glioneuronal tumor. The primary indication for surgery would be to achieve a definitive diagnosis and remove the neoplasm, rather than to directly treat the patient's depression. However, if depression relief following the removal of septal tumors can be consistently demonstrated in other cases, it could become a viable consideration when counseling patients about surgery. The primary options for surgical intervention would include 1) open resection, 2) stereotactic biopsy followed by open resection, or 3) stereotactic biopsy and stereotactic laser interstitial thermal ablation. In the absence of seizures, we would omit intraoperative electrocorticography from our approach, as it would not be necessary to map epileptiform activity to guide resection margins. If open surgery were chosen following a discussion with the patient and her family, we would have opted for the same interhemispheric surgical approach, as the focus would remain on the safe and effective removal of the tumor while minimizing disruption to adjacent neural structures.

Depression is among the most common psychiatric conditions that precede the diagnosis of a brain tumor.[11] The location of brain tumors associated with depression is not random, suggesting that disruption of key limbic networks can drive this association. One analysis demonstrated that tumors in areas functionally connected with the left striatum are more likely to cause depression, although none of the functionally connected tumors were actually located in the striatum.[12] To our knowledge, no prior reports have directly linked depressive symptoms to tumors in the septal region or adjacent ventral striatum. Our patient's tumor molecular profiling confirmed that it belongs to the rare, recently characterized entity known as myxoid glioneuronal tumors possessing a *PDGFRA* p.K385 mutation. These tumors have a predilection for the septum pellucidum and have since been characterized in a small number of patients.[3,4] Roughly half of patients

were asymptomatic at the time their tumor was discovered, and the most common presenting symptoms were headache and cognitive disturbances.[4] No seizures or depressive symptoms were reported. Therefore, our patient's case is an uncommon presentation of both seizures and depression in a rare histopathological entity.

Lessons

We believe that the patient's seizures and interictal depression can be linked to the tumor location in the septal region, via white matter spread to the mesial temporal structures and interictal discharges in a key limbic area, respectively. Our patient's case exemplifies the bidirectional hypothesis in a rare case that involves neural circuitry outside of the mesial temporal lobe: depression symptoms that predated seizure onset, lesion location in a well-known affective neuroanatomical hub, and swift resolution of depression symptoms following resection. In summary, focal neural circuit disruption can underlie both depressive and epileptic pathology.

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Author Contributions

Conception and design: Starkweather, Sugrue, Chang. Acquisition of data: Knowlton, Chang. Analysis and interpretation of data: Sugrue, Nedelec, Chang. Drafting the article: Starkweather, Sugrue, Nedelec. Critically revising the article: Sugrue, Krystal, Knowlton, Chang. Reviewed submitted version of manuscript: Starkweather, Sugrue, Nedelec, Krystal, Chang. Approved the final version of the manuscript on behalf of all authors: Starkweather. Statistical analysis: Sugrue. Administrative/technical/material support: Nedelec, Chang. Study supervision: Knowlton, Chang.

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