

## Exacerbation of Mania Secondary to Right Temporal Lobe Astrocytoma in a Bipolar Patient Previously Stabilized on Valproate

\*†Kenneth N. Sokolski, MD, and \*Thomas F. Denson, MA

### Abstract

#### Objectives:

To investigate breakthrough mania secondary to a right temporal lobe neoplasm in a bipolar patient previously stabilized on sodium divalproex.

#### Background:

Right hemispheric brain tumors involving the orbitofrontal or basotemporal cortex are a rare cause of secondary mania. In such cases, early neurologic signs may be difficult to distinguish from bipolar symptoms. Breakthrough mania secondary to brain neoplasm in a bipolar patient stabilized on medication is an extremely rare phenomena which has not been previously reported.

#### Method:

The clinical course of a bipolar subject stabilized on valproate who developed mania secondary to a right temporal lobe astrocytoma is described. Serial brain magnetic resonance imaging (MRI), baseline electroencephalogram (EEG), and neuropsychiatric evaluations were used to examine the relationship between the patient's brain mass and behavioral disturbances.

#### Results:

Symptoms were those that accompanied prior episodes of mania. In addition, signs of temporal lobe dysfunction were evident including periods of detachment, déjà vu experiences, and olfactory hallucinations. In the context of mania, depersonalization was initially attributed to bipolar symptoms. Only several months later, when olfactory hallucinations and alterations in consciousness became evident, was a temporal lobe lesion suspected. Neuropsychiatric abnormalities responded to a combination of surgical intervention, radiation therapy, and topiramate, however the tumor was advanced and invasive at diagnosis resulting in a poor prognosis.

#### Conclusions:

This case suggests that clinicians examining unexplained cases of breakthrough mania should be vigilant for early signs of temporal lobe dysfunction, which could aid in detecting treatable lesions.

**Key Words:** mania, astrocytoma, temporal lobe, seizures, Valproate, Topiramate

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Secondary mania is a rare complication of brain neoplasms originating in the right frontal and basotemporal cortex.<sup>1-3</sup> Few studies have documented the evolution of neuropsychiatric symptoms related to the expansion of brain masses.<sup>4</sup> Breakthrough mania associated with cerebral tumors in bipolar patients stabilized on medication has not been reported. The following case describes an exacerbation of mania associated with an invasive right temporal lobe grade IV astrocytoma in a patient with a primary diagnosis of bipolar I disorder whose condition had been previously well controlled on valproate. The emergence of early and late temporal lobe signs of increasing intensity and frequency is presented and contrasted with bipolar symptoms. The difficulty in detecting early signs of temporal lobe dysfunction in the context of mania is discussed.

### CASE REPORT

The patient, a 51-year-old Caucasian female, had experienced at least nine episodes of mania since age 21. Manic symptoms were severe enough to require hospitalization at ages 21, 33, 39, and 50. She was referred by her treating psychiatrist for a double-blind, placebo-controlled study of topiramate in bipolar disorder due to breakthrough mania following 8 months of euthymia on 1500 mg of valproate (serum levels = 90-110 µg/mL).

\*VA Long Beach Healthcare System, Mental Health Care Group, Long Beach, California; †University of California, Irvine, School of Medicine, Department of Psychiatry, Irvine, California, USA.

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Address correspondence and reprint requests to Dr. Kenneth N. Sokolski, VA Long Beach Healthcare System, 5901 East 7<sup>th</sup> Street (06/116a), Long Beach, CA 90822; E-mail: kenneth.sokolski@med.va.gov

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Just prior to referral, the patient had decreased her dosage of valproate to 1000 mg per day due to "side effects." Her symptoms included insomnia, hyperactivity, grandiosity, pressured speech, irritability, and hypersexuality. She also experienced episodes of detachment lasting several minutes and occurring once or twice a week in which she reported not being in touch with her emotions and feeling that "the world is an illusion" in which "everything is unreal." At all times during these episodes, she was reported to be awake, alert, and responsive.

Depersonalization episodes had begun about 2 months prior to study referral, concurrent with increasing symptoms of mania. Feelings of detachment, however, did not appear to be worsening in frequency or intensity. When measured against a background of disorganized thinking, pressured speech, and grandiose delusions, depersonalization was initially attributed to exacerbation of bipolar illness. This interpretation was consistent with reports that detached states may be associated with mood disorders in up to 20% of unselected patients, including conditions in the bipolar spectrum.<sup>5-7</sup>

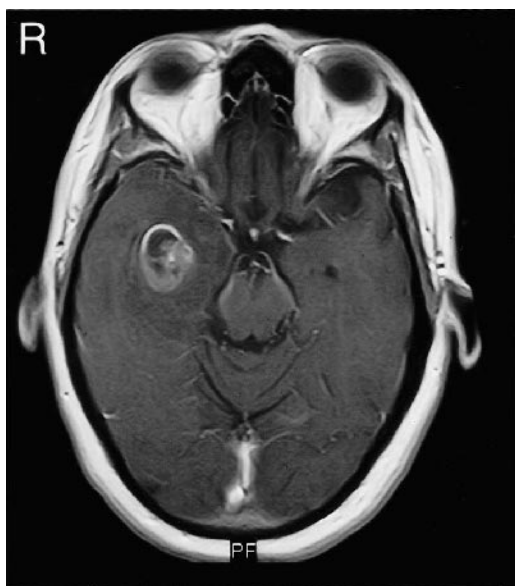
As part of the study protocol, the patient was hospitalized to washout divalproex and randomized to topiramate 400 mg, 600 mg, or placebo. During the third day of randomization, she experienced an episode of severe headache associated with vomiting and dizziness, which the patient and staff attributed to migraine. There were no other adverse events during the 2-week hospitalization, and she did not report any episodes of detachment during this period.

Initially, improvements were noted in sleep, mood, and agitation. On the second weekly outpatient visit, however, 2 months after her initial evaluation for the topiramate study and 4 months after first reporting depersonalization episodes, the patient's spouse noted a return of mild to moderate hyperactivity, talkativeness, and agitation. The patient was also complaining of mild nausea and unexplained episodes of dizziness. In addition, several previously unre-

ported symptoms were described including blackouts, meaningless verbalizations for which the patient had no memory, and déjà vu episodes. Periods of derealization were now occurring daily and preceded by a distinct "aura" in which she felt cold, had goosebumps on her skin, and experienced a burning acid smell lasting 2 to 3 minutes. They were also accompanied by staring spells and altered attention.

Due to these new symptoms, an electroencephalogram (EEG) was obtained that revealed marked right frontotemporal slowing. Sleep-deprived and 24-hour EEGs were also ordered to rule out epileptiform activity but were never performed. Computed tomography completed the following day confirmed a 2.5-cm round mass in the right medial temporal lobe. This was further characterized on magnetic resonance imaging (MRI) as a solitary lesion with an irregular border within the right medial temporal lobe displacing the right lateral ventricle, adjacent right temporal horn, and the right hippocampus superiorly and medially (Fig. 1). As a result of these findings, the patient was immediately taken off the research protocol and referred for neurosurgical consultation. At the patient's request, treatment with 100 mg topiramate twice per day was provided on an open-label basis resulting in increased mood stability. Due to the development of neurologic symptoms indicative of a temporal lobe lesion several months prior to topiramate exposure, there was no consideration of any association between topiramate and the development of the brain tumor.

An exhaustive search for a primary metastatic neoplasm was negative. The patient was transferred to another medical center where she underwent a craniotomy and resection, which removed over 90% of the brain mass. Pathology reported a grade IV invasive right temporal lobe astrocytoma portending a poor prognosis. Radiation therapy was initiated to improve quality of life. Unexpectedly, however, the combination of surgical resection and radiotherapy resulted in temporary remission of the tumor 7 months



**FIGURE 1.** Magnetic resonance image (*axial view*) revealing a 2.5-cm round grade IV astrocytoma of the right temporal lobe in a bipolar patient previously stabilized on valproate. The tumor was associated with reemergence of mania, accompanied by episodes of depersonalization, olfactory hallucinations, and déjà vu experiences.

after diagnosis. Regression of the tumor was associated with improvements in olfactory hallucinations, déjà vu experiences, depersonalization episodes, mood lability, pressured speech, and hyperactivity. The tumor remained in remission until 2 years after initial presentation when the neoplasm recurred with a rapidly deteriorating fatal course unresponsive to antineoplastics or to radiation therapy.

## DISCUSSION

Breakthrough mania has been reported in such diverse conditions as steroid exposure, amphetamine use, antineoplastic treatment, upper respiratory tract infections, hyperthyroidism, adrenal dysfunction, collagen vascular diseases, multiple sclerosis, epilepsy, and vitamin deficiencies.<sup>8</sup> While secondary mania has been described following left frontotemporal vascular events,<sup>9</sup> most cases have involved lesions of the right limbic orbitofrontal and basotemporal cortex as

well as right-sided deep gray structures including the head of the caudate and thalamus.<sup>10,11</sup> Mania associated with brain tumors is exceedingly rare with less than 20 cases documented in the literature.<sup>12,13</sup> The majority of tumor-related cases of secondary mania have been associated with right-sided gliomas, meningiomas, astrocytomas, or neuroomas as well as pituitary neoplasms and metastases.<sup>14-17</sup> When tumors have been treatable, resection along with anticonvulsants have improved behavioral symptoms.<sup>18</sup> While cortical lesions have resulted in unipolar mania, damage to subcortical structures has produced an alternating manic-depressive course.<sup>19</sup>

This is the first case to describe breakthrough mania secondary to a brain neoplasm in a bipolar patient previously stabilized on medication. While the breakthrough episode appeared typical of mania, it was accompanied by infrequent periods of depersonalization that were difficult to discern from psychiatric symptoms. Reports documenting depersonalization in patients with a variety of mood disturbances<sup>5-7</sup> further lowered suspicions that the patient's initial complaints were of neurologic origin. Only several months later, when her condition evolved into a more dramatic presentation, including frequent disturbing periods of depersonalization, déjà vu episodes, vivid olfactory hallucinations, and alterations in consciousness, was the diagnosis of temporal lobe pathology considered. The escalation of temporal lobe dysfunction following the withdrawal of valproate suggests that this medication may have limited initial symptoms by controlling seizure activity.

Although the patient had a 30-year history of bipolar I disorder, the breakthrough episode documented here involved a constellation of symptoms that were distinctly different from any she had experienced during prior episodes of mania. While bipolar pathology was present, she also exhibited symptoms indicative of temporal lobe compromise, including depersonalization, déjà vu experiences, and olfactory hallucina-

tions.<sup>20-25</sup> In addition, staring spells, dizziness, and vocalizations that are not specific to temporal lobe lesions, but may occur in association with partial complex seizures of the right temporal lobe, were also evident.<sup>26-28</sup> The occurrence of ictal verbalizations in this patient further suggests that seizure activity in the nondominant temporal lobe may have been involved in her clinical presentation.<sup>29,30</sup>

The mechanisms through which a right temporal lobe mass can produce secondary mania are unknown. Damage to right-sided frontotemporal limbic connections has been found in most cases of mania associated with cerebral lesions<sup>10</sup> and may represent a common pathway for the development of bipolar symptomatology. Alternatively, unilateral disruption of ascending biogenic amine pathways by frontotemporal brain masses may create hemispheric catecholaminergic imbalances thought to underlie mood disturbances.<sup>2</sup> The rarity of such lesions resulting in mania suggests that prior damage or atrophy of right limbic structures accompanied by a genetic predisposition may be a prerequisite for such an outcome.<sup>31</sup>

As already suggested, the potential involvement of seizure activity affecting temporo-limbic structures as a cause of both the neurologic and psychiatric symptoms of this patient must also be considered. This possibility is supported by the common association between invasive astrocytomas and epileptiform activity<sup>32</sup> as well as reports documenting the occurrence of mania in patients with seizure disorders.<sup>33-36</sup> Although epileptiform tracings were not noted in the EEG of this patient, such activity is often missed due to the brevity of studies or difficulty in analyzing foci not easily referenced by standard surface EEG leads. More revealing tests such as a sleep-deprived EEG and 24-hour monitoring, which might have uncovered ictal events, were not obtained.

This case illustrates the importance of recognizing early signs of temporal lobe dysfunction such as dissociative states that may indicate treatable lesions. Detection of cere-

bral pathology may be delayed in patients with mania due to the difficulty in distinguishing signs of early temporal lobe dysfunction from manic symptoms and due to the low index of suspicion related to the rarity of such events in clinical practice. In the present case, diagnosis of a right temporal lobe astrocytoma was made at a late, invasive stage only when symptoms of more advanced temporal lobe alterations were evident. Although the tumor was initially responsive to surgical resection, radiotherapy, and anticonvulsant treatment, prognosis was poor at diagnosis, and the neoplasm ultimately recurred. Increased vigilance to the presence of subtle temporal lobe signs in the context of breakthrough mania may allow for recognition of brain lesions at an earlier stage, improving the chances for more successful treatment.

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