Depression, or something else?

Elizabeth Guevara, MD, MSc, and Naalla Schreiber, MD, MS

Ms. A, age 60, presents with severe headaches and depression, including a suicide attempt. She's also been repeatedly sorting through her neighbors' trash. What's underlying her symptoms?

CASE Suicidal behavior, severe headaches

Ms. A, age 60, presents to the emergency department (ED) with depression, suicidal behavior, and 3 days of severe headaches. Neurology is consulted and an MRI is ordered, which shows a 3.0-cm mass lesion in the left temporal lobe with associated vasogenic edema that is suspicious for metastatic disease (***Figure, page 44***).

Ms. A is admitted to the hospital for further workup of her brain lesion. She is started on IV dexamethasone, 10 mg every 6 hours, a glucocorticosteroid, for brain edema, and levetiracetam, 500 mg twice a day, for seizure prophylaxis.

Upon admission, in addition to oncology and neurosurgery, psychiatry is also consulted to evaluate Ms. A for depression and suicidality.

EVALUATION Mood changes and poor judgment

Ms. A has a psychiatric history of depression and alcohol use disorder but says she has not consumed any alcohol in years. Her medical history includes hypertension, diabetes, and stage 4 non-small–cell lung cancer, for which she received surgery and adjuvant chemoradiotherapy 1 year ago.

On initial intake, Ms. A reports that in addition to the headaches, she has also been experiencing worsening depression and suicidal behavior. For the past 2 months, she has had a severely depressed mood, with notable anhedonia, poor appetite, insomnia, low energy, and decreased concentration. The changes in her mental health were triggered by her mother's death. Three days prior to admission, the patient planned to overdose on antihypertensive pills, but her suicide attempt was interrupted when her family called. She denies any current suicidal ideation, intent, or plan.

According to her family, Ms. A has been increasingly irritable and her personality has changed in the past month. She also has been repeatedly sorting through her neighbors' garbage.

Ms. A's current psychiatric medications are duloxetine, 30 mg/d; quetiapine, 50 mg every night at bedtime; and buspirone, 10 mg/d. However, it is unclear if she is consistently taking these medications.

On mental status examination, Ms. A is calm and she has no abnormal movements. She says she is depressed. Her affect is reactive and labile. She is alert and oriented to person,

Dr. Guevara is a PGY-1 Resident, Zucker Hillside Hospital, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, New York. Dr. Schreiber is Staff Psychiatrist, Barnabas Health Medical Group, Florham Park Behavioral Health, Florham Park, New Jersey.

Disclosures
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How would you handle this case?

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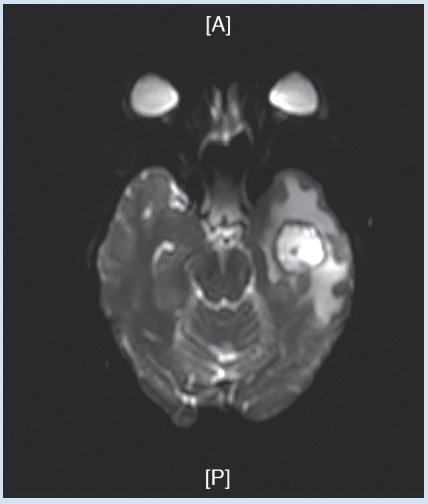
Fifty to 80% of patients with CNS tumors present with psychiatric symptoms

Figure

MRI of Ms. A's 3.0-cm metastatic brain tumor in the left temporal lobe with associated vasogenic edema



place, and time. Her attention, registration, and recall are intact. Her executive function is not tested. However, Ms. A's insight and judgment seem poor.

To address Ms. A's worsening depression, the psychiatry team increases her duloxetine from 30 to 60 mg/d, and she continues quetiapine, 50 mg every night at bedtime, for mood lability. Buspirone is not continued because she was not taking a therapeutic dosage in the community.

Within 4 days, Ms. A shows improvement in sleep, appetite, and mood. She has no further suicidal ideation.

What is your next step in Ms. A's treatment?

a) transfer her to inpatient psychiatry for treatment of depression
b) start lorazepam to treat alcohol withdrawal
c) ask the medical team to initiate a workup for limbic encephalitis
d) optimize duloxetine while the oncology team delineates a treatment plan

The authors' observations

Ms. A had a recurrence of what was presumed to be major depressive disorder (MDD) in the context of her mother's death. However, she also exhibited irritability, mood lability, and impulsivity, all of which could be part of her depression, or a separate problem related to her brain tumor. Because Ms. A had never displayed bizarre behavior before the past few weeks, it is likely that her CNS lesion was directly affecting her personality and possibly underlying her planned suicide attempt.

Fifty to 80% of patients with CNS tumors, either primary or metastatic, present with psychiatric symptoms.[1] ***Table 1***[1-3] (***page 45***) lists common psychiatric symptoms of brain tumors. Unfortunately, there is little reliable evidence that directly correlates tumor location with specific psychiatric symptoms. A 2010 meta-analysis found a statistically significant link between anorexia nervosa and hypothalamic tumors.[1] However, for other brain regions, there is only an increased likelihood that any given tumor location will produce psychiatric symptoms.[1,4] For instance, compared to patients with tumors in other locations, those with temporal lobe tumors are more likely to present with mood disorders, personality changes, and memory problems.[1] In contrast, patients with frontal lobe tumors have an increased likelihood of psychosis, mood disorders, and personality changes.[1] Patients with tumors in the pituitary region often present with anxiety.[1]

When considering treatment options for Ms. A, alcohol withdrawal was unlikely given the remote history of alcohol use, low alcohol blood level, and lack of evidence of unstable vital signs or tremor. Although she might have benefited from inpatient psychiatric treatment, this needed to wait until there was a definitive treatment plan for her brain tumor. Finally, although a paraneoplastic syndrome, such as limbic encephalitis, could be causing her psychiatric symptoms, this scenario is less likely with non-small–cell lung cancer.

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Although uncommon, CNS tumors can present with psychiatric symptoms as the only manifestation. This is more likely when a patient exhibits new-onset or atypical symptoms, or fails to respond to standard psychiatric treatment.[4] Case reports have described patients with brain tumors being misdiagnosed as having a primary psychiatric condition, which delays treatment of their CNS cancer.[2] Additionally, frontal and limbic tumors are more likely to present with psychiatric manifestations; up to 90% of patients exhibit altered mental status or personality changes, as did Ms. A.[1,4] Clearly, it is easier to identify patients with psychiatric symptoms resulting from a brain tumor when they also present with focal neurologic deficits or systemic symptoms, such as headache or nausea and vomiting. Ms. A presented with severe headaches, which is what led to her early imaging and prompt diagnosis.

Numerous proposed mechanisms might account for the psychiatric symptoms that occur during the course of a brain tumor, including direct injury to neuronal cells, secretion of hormones or other tumor-derived substances, and peri-ictal phenomena.[3]

Table 1

Psychiatric symptoms of brain tumors

Depression
Mania
Personality change
Irritability
Self-neglect
Apathy
Hallucinations
Amnesia
Disinhibition/impulsivity
Anorexia nervosa
Anxiety/panic attacks
Paranoia
Dementia
Delirium
Paraphilia

Source: References 1-3

TREATMENT Tumor is removed, but memory is impaired

Ms. A is scheduled for craniotomy and surgical resection of the frontal mass. Prior to surgery, Ms. A shows interest in improving her health, cooperates with staff, and seeks her daughter's input on treatment. One week after admission, Ms. A has her mass resected, which is confirmed on biopsy to be a lung metastasis. Post-surgery, Ms. A receives codeine, 30 mg every 6 hours as needed, for pain; she continues dexamethasone, 4 mg IV every 6 hours, for brain edema and levetiracetam, 500 mg twice a day, for seizure prophylaxis.

On Day 2 after surgery, Ms. A attempts to elope. When she is approached by a psychiatrist on the treatment team, she does not recognize him. Although her long-term memory seems intact, she is unable to remember the details of recent events, including her medical and surgical treatments.

What is the most likely cause of Ms. A's postoperative memory problems?

a) major neurocognitive disorder due to Alzheimer's disease
b) surgically acquired neurocognitive deficit
c) vascular dementia
d) late-life depression with associated cognitive dysfunction

The authors' observations

Ms. A's memory impairment may be secondary to a surgically acquired neurocognitive deficit. In the United States, brain metastases represent a significant public health issue, affecting >100,000 patients per year.[5] Metastatic lesions are the most common brain tumors. Lung cancer, breast cancer, and melanoma are the leading solid tumors to spread to the CNS.[5] In cases of

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Unlike depression in younger patients, late-life depression is more likely to be associated with cognitive impairment

Table 2

Management of cognitive deficits in a patient with a brain tumor

Cause of cognitive deficits	Treatment
Direct tumor invasion	Surgery
Brain edema	Steroids
Hydrocephalus due to tumor	Shunting
Mood disorder	Antidepressants
Seizures	Antiepileptics

Source: Reference 14

single brain metastasis, similar to Ms. A's solitary left temporal lobe lesion, surgical resection plays a critical role in treatment. It provides histological confirmation of metastatic disease and can relieve mass effect if present. Studies have shown that combined surgical resection with radiation improves survival relative to patients who undergo radiation therapy alone.[6,7]

However, the benefits of surgical resection need to be balanced with preservation of neurologic function. Emerging evidence suggests that a majority of patients have surgically-acquired cognitive deficits due to damage of normal surrounding tissues, and these deficits are associated with reduced quality of life.[8,9] Further, a study examining glioma surgical resections found that patients with left temporal lobe tumors exhibit more frequent and severe neurocognitive decline than patients with right temporal lobe tumors, especially in domains such as verbal memory.[8] Ms. A's memory impairment was persistent during her postoperative course, which suggests that it was not just an immediate post-surgical phenomenon, but a longer-lasting cognitive change directly related to the resection.

It is also possible that Ms. A had a prior neurocognitive disorder that manifested to a greater degree as a result of the CNS tumor. Ms. A might have had early-onset Alzheimer's disease, although her intact memory before surgery makes this less likely. Alternatively, she could have had vascular dementia, especially given her long-standing hypertension and diabetes. This might have been missed in the initial evaluation because executive function was not tested. However, the relatively abrupt onset of memory problems after surgery suggests that she had no underlying neurocognitive disorder.

Ms. A's presumed episode of MDD might also explain her memory changes. Major depressive disorder is increasingly common among geriatric patients, affecting approximately 5% of community-dwelling older adults.[10] Its incidence increases with medical comorbidities, as suggested by depression rates of 5% to 10% in the primary care setting vs 37% in patients after critical-care hospitalizations.[10] Late-life depression (LLD) occurs in adults age ≥60. Unlike depression in younger patients, LLD is more likely to be associated with cognitive impairment, specifically impairment of executive function and memory.[11] The incidence of cognitive impairment in LLD is higher in patients with a history of depression, such as Ms. A.[11,12] However, in general, patients who are depressed have memory complaints out of proportion to the clinical findings, and they show poor effort on cognitive testing. Ms. A exhibited neither of these, which makes it less likely that LLD was the exclusive cause of her memory loss.[13] ***Table 2***[14] outlines the management of cognitive deficits in a patient with a brain tumor.

EVALUATION Increasingly agitated and paranoid

After the tumor resection, Ms. A becomes increasingly irritable, uncooperative, and agitated. She repeatedly demands to be discharged. She insists she is fine and refuses medications and further laboratory workup. She becomes paranoid about the nursing staff and believes they are trying to kill her.

On psychiatric re-evaluation, Ms. A demonstrates pressured speech, perseveration

about going home, paranoid delusions, and anger at her family and physicians.

What should be considered in the differential diagnosis of Ms. A's agitation?

a) postoperative delirium
b) steroid-induced manic episode
c) neuropsychiatric adverse effect of levetiracetam
d) opioid intoxication
e) all of the above

The authors' observations

Ms. A's refusal of medications and agitation may be explained by postoperative delirium, a surgical complication that is increasingly common among geriatric patients and is associated with poor clinical outcomes. Delirium is characterized by an acute onset and fluctuating course of symptoms that include inattention, motoric hypo- or hyperactivity, inappropriate behavior, emotional lability, cognitive dysfunction, and psychotic symptoms.[15] Risk factors that contribute to postoperative delirium include older age, alcohol use, and poor baseline functional and cognitive status.[16] The pathophysiology of delirium is not fully understood, but accumulating evidence suggests that different sets of interacting biologic factors (ie, neurotransmitters and inflammation) contribute to a disruption of large-scale neuronal networks in the brain, resulting in cognitive dysfunction.[15] Patients who develop postoperative delirium are more likely to develop long-term cognitive dysfunction and have an increased risk of dementia.[16]

Another potential source of Ms. A's agitation is steroid use. Ms. A received IV dexamethasone, 8 to 16 mg/d, around the time of her surgery. Steroids are commonly used to treat brain tumors, particularly when there is vasogenic edema. Steroid psychosis is a term loosely used to describe a wide range of psychiatric symptoms induced by corticosteroids that includes, but is not limited to, depression, mania, psychosis, delirium, and cognitive impairment.[17] Steroid-induced psychiatric adverse effects occur in 5% to 18% of patients receiving corticosteroids and often happen early in treatment, although they can occur at any point.[18] Corticosteroids influence brain activity via glucocorticoid and mineralocorticoid receptors. These receptors are widely distributed throughout the brain and affect neurotransmitter systems, such as the serotonergic system, that are associated with changes in mood, behavior, and cognition.[17] While the adverse psychiatric manifestations of steroid use vary, higher dosages are associated with an increased risk of psychiatric complications; mania is more prevalent early in the course of treatment, and depression is more common with long-term use.[17,19] ***Table 3***[17,18] outlines the evidence-based treatment of corticosteroid-induced adverse psychiatric effects.

Although there are no clinical guidelines or FDA-approved medications for treating steroid-induced psychiatric adverse events, these are best managed by tapering and discontinuing steroids when possible and simultaneously using psychotropic medications to treat psychiatric symptoms. Case reports and limited evidence-based

Table 3

Pharmacotherapy for corticosteroid-induced adverse psychiatric effects

Treatment	Indication for use
Aripiprazole	Mania
Chlorpromazine	Mania
Haloperidol	Psychosis
Lithium	Mood changes
Olanzapine	Mood changes
Risperidone	Psychosis
Sertraline	Depression
Valproic acid	Mood changes

Source: References 17,18

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Psychiatric manifestations of steroid use include mania early in the course of treatment and depression with long-term use

Related Resource

- Madhusoodanan S, Ting MB, Farah T, et al. Psychiatric aspects of brain tumors: a review. World J Psychiatry. 2015;5(3):273-285.

Drug Brand Names

Aripiprazole • Abilify
Buspirone • Buspar
Chlorpromazine • Thorazine
Codeine • Codeine systemic
Dexamethasone • Decadron
Duloxetine • Cymbalta
Haloperidol • Haldol
Levetiracetam • Keppra
Lorazepam • Ativan
Lithium • Eskalith, Lithobid
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Valproic acid • Depakene

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Patients with CNS tumors are at risk for seizures and are often prescribed antiepileptics

literature have demonstrated that steroid-induced mania responds to mood stabilizers or antipsychotics, while depression can be managed with antidepressants or lithium.[17]

Additionally, patients with CNS tumors are at risk for seizures and often are prescribed antiepileptics. Because it is easy to administer and does not need to be titrated, levetiracetam is a commonly used agent. However, levetiracetam can cause psychiatric adverse effects, including behavior changes and frank psychosis.[20]

Finally, Ms. A's altered mental status could have been related to opioid intoxication. Opioids are used to manage post-surgical pain, and studies have shown these medications can be a precipitating factor for delirium in geriatric patients.[21]

TREATMENT Medication adjustments

At the request of the psychiatry team, levetiracetam is discontinued due to its potential for psychiatric adverse effects. The neurosurgery team replaces it with valproic acid, 500 mg every 12 hours. Ms. A is also tapered off steroids fairly rapidly because of the potential for steroid-induced psychiatric adverse effects. Her quetiapine is titrated from 50 to 150 mg every night at bedtime, and duloxetine is discontinued.

OUTCOME Agitation improves dramatically

Ms. A's new medication regimen dramatically improves her agitation, which allows Ms. A, her family, and the medical team to work together to establish treatment goals. Ms. A ultimately returns home with the assistance of her family. She continues to have memory issues, but with improved emotion regulation. Several months later, Ms. A is readmitted to the hospital because her cancer has progressed despite treatment.

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Bottom Line

Brain tumors may present with various psychiatric manifestations that can change during the course of the patient's treatment. A comprehensive psychiatric evaluation should parse out the interplay between direct effects of the tumor and any adverse effects that are the result of medical and/or surgical interventions to determine the cause of psychiatric symptoms and their appropriate management.

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