A Veteran Presenting With Altered Mental Status and Clonus

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Case Presentation: *A 69-year-old male veteran with a medical history of chronic obstructive pulmonary disease (COPD), coronary artery disease, heart failure with reduced ejection fraction, and significant tobacco use presented to the VA Boston Healthcare System (VABHS) emergency department with shortness of breath. Additional history included bipolar disorder, for which he took olanzapine and duloxetine, and a history of opioid use disorder, for which he took buprenorphine/naloxone. On initial evaluation, his blood pressure was 168/81 mm Hg with an oxygen saturation of 100% on 5 L of supplemental oxygen.*

A physical examination was notable for a confused gentleman in no acute distress. He had end-expiratory wheezing, and his skin was noted to be diaphoretic. He was found to have 3 beats of inducible clonus at his ankles bilaterally, and 3+ reflexes at his biceps and patellae bilaterally. Laboratory tests were notable for a leukocytosis to 12.5 K/uL and an elevated bicarbonate of 40 mEq/L (Table). A chest X-ray showed hyperinflated lungs without any masses, consolidation, or fluid. Shortly after arriving on the medicine floor, he became progressively more confused with visual hallucinations. Further history elicited from the patient's wife revealed that the patient had developed twitching of his extremities for several days prior to this admission, resulting in the patient spilling and dropping things.

➤ **Zachary Reese, MD, Chief Medical Resident, VABHS and Beth Israel Deaconess Medical Center (BIDMC):** Dr. Weller, the differential diagnosis for altered mental status is quite broad. How does the presence of clonus change or focus your approach to altered mental status?

➤ **Jason Weller, MD, Instructor of Neurology, Boston Medical Center (BMC) and VABHS:** The presence of clonus does not significantly narrow the differential. It does, however, suggest a central component to the patient's altered mental status. Specifically, it implies that the underlying process, whether systemic or neurologic, interferes with central nervous system (CNS) control of the neuromuscular system.[1] The differential is still quite broad and includes metabolic derangements (eg, uremia, electrolyte disturbances, hypercarbia, and thyroid dysfunction), medication toxicity from olanzapine or duloxetine, and vascular processes (eg, CNS vasculitis). Infectious etiologies, both within the CNS and systemically, can cause encephalopathy, as can autoimmune processes, such as immune-mediated encephalitis. Finally, primary neurologic conditions such as myoclonic epilepsy can be considered. Given the patient's medical history, serotonin syndrome must be considered.

➤ **Dr. Reese:** Given the concern for serotonin syndrome, the admitting medical team discontinued the patient's duloxetine. Dr. Weller, what is the pathophysiology of serotonin syndrome, and how is it diagnosed?

➤ **Dr. Weller:** Serotonin is ubiquitous throughout the body and brain. Serotonin syndrome is caused by excess endogenous or exogenous serotonin, and this is usually caused by a variety of medications. The symptoms range from tachycardia, agitation, and diaphoresis to sustained clonus, hyperthermia, and shock.[2,3] The extent of serotonin syndrome is typically thought to reflect the degree of serotonergic activity.[4]

Serotonin syndrome is a clinical diagnosis. While there are no tests that can confirm the diagnosis, the Hunter criteria can be used to assist with making the diagnosis.[5] Per the Hunter criteria, a patient can be diagnosed with serotonin syndrome if they have taken a serotonergic agent and have at least 1 of the following: spontaneous clonus, inducible

TABLE Patient Laboratory Results at Emergency Department Presentation

Tests	Results	Reference Range
White blood cells, K/uL	12.5	4.0-11.0
Hemoglobin, g/dL	10.0	14.0-18.0
Hematocrit, %	35.1	40-52
Platelets, K/uL	321	150-440
Mean corpuscular volume, fL	97	82-98
Sodium, mEq/L	137	135-145
Potassium, mEq/L	4.8	3.5-5.0
Chloride, mEq/L	91	100-110
Bicarbonate, mEq/L	40	20-30
Blood urea nitrogen, mg/dL	20	7-25
Creatinine, mg/dL	0.8	0.5-1.5
Glucose, mg/dL	106	70-105

or ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, or hypertonia with fever and clonus. This patient had taken duloxetine and had inducible clonus and diaphoresis, thus suggesting a diagnosis of serotonin syndrome.

➤ **Dr. Reese:** Aside from selective serotonin reuptake inhibitors (SSRIs), are there other medications that we typically prescribe that can cause serotonin syndrome?

➤ **Dr. Weller:** In addition to SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), other commonly prescribed medications that can cause serotonin syndrome are 5-HT3 antagonists (eg, ondansetron), 5-HT agonists (eg, triptans), and opioids (eg, fentanyl and tramadol). There are also case reports of atypical antipsychotics (eg, olanzapine) causing serotonin syndrome because of their antagonism of the 5-HT2 and 5-HT3 receptors.[2] Additionally, linezolid is commonly overlooked as a cause of serotonin syndrome given its action as a monoamine oxidase inhibitor.[4] In this patient, it would be prudent to discontinue olanzapine and duloxetine.

➤ **Dr. Reese:** Duloxetine, olanzapine, and buprenorphine/naloxone were discontinued given concern for serotonin syndrome. Although there are not strong data that buprenorphine/naloxone can cause serotonin syndrome, the team discontinued the medication in case it might be contributing to the patient's encephalopathy, while closely monitoring the patient for withdrawal. There was a rapid improvement in the patient's symptoms over the 24 hours after discontinuation of the 3 medications.

As part of the initial workup, the patient received a computed tomography (CT) scan of his chest to follow up pulmonary nodules identified 16 months prior. The CT scan showed interval growth of the pulmonary nodules in the right lower lobe to 2 cm with extension into the major fissure, which was concerning for malignancy. Plans were made for an outpatient positron emission tomography (PET) scan after hospital discharge.

Dr. Schlechter and Dr. Rangachari, what factors can help us determine whether or not further workup of a malignancy should occur before discharge or can be deferred to the outpatient setting?

➤ **Benjamin Schlechter, MD, Instructor in Medicine, BIDMC; and Deepa Rangachari, MD, Assistant Professor of Medicine, BIDMC:** Key considerations in this domain include rapidity of growth and any threat to critical end-organ function (ie, brain, heart, lungs, kidney, and liver). If the malignancy is bulky and/or rapidly progressing to the point that the patient has significant symptoms burden and/or end-organ dysfunction, then initiating the evaluation as an inpatient may be necessary. For suspected intrathoracic malignancies, considering whether this may be a high-grade process (ie, small cell lung cancer) is often a vital branch point. Key considerations in this regard are the following: Is it a bulky central tumor? Is there evidence of widespread metastatic disease, an obstructing mass, and/or tumor lysis? One final and critical aspect to consider is whether there are any patient-specific barriers to timely and reliable outpatient follow-up. If there is no evidence of rapid progression, bulky disease with threatened end-organ involvement, and/or issues with timely and reliable follow-up, then outpatient evaluation is often the best approach to ensure a comprehensive and well-coordinated effort on the patient's behalf.

➤ **Dr. Reese:** Buprenorphine/naloxone was restarted without return of the symptoms. The patient was discharged home with an outpatient PET scan scheduled the following week. Unfortunately, the patient was unable to keep this appointment. Three weeks after hospital discharge, the patient presented again to the emergency department with gradually worsening altered mental status, confusion, visual hallucinations, and myoclonic jerking of the arms and legs. Medication adherence was confirmed by the patient's wife, resulting in a low concern for serotonin syndrome. Physical examination revealed confusion, dysarthria, diffuse, arrhythmic, myoclonic jerking in all extremities, asterixis in the upper extremities, and hyperreflexia.

A CT scan of the brain did not reveal an intracranial process. A spot electroencephalograph (EEG) and magnetic resonance image (MRI) of the brain were obtained. Dr. Weller, what is the utility of spot EEG vs 24-hour EEG? When might we choose one over the other?

➤ **Dr. Weller:** If a patient is persistently altered, then a spot EEG would be sufficient to capture a seizure if that is what is causing the patient's altered mental status. However, if the patient's mental status is waxing and waning, then that may warrant a 24-hour EEG because the patient may need to be monitored for longer periods to capture an event that is causing intermittent alterations in mental status.[6] Additionally, patients who are acutely ill may require long-term monitoring for the purpose of treatment and outcome management.

➤ **Dr. Reese:** The spot EEG showed nearly continuous generalized slowing indicative of a diffuse encephalopathy. The MRI of the brain showed scattered, nonspecific periventricular T2 hyperintense foci, suggestive of advanced chronic microvascular ischemic changes.

A PET CT was obtained and revealed mildly fluorodeoxyglucose (FDG)-avid, enlarging nodules within the right lower lobe, which was suspicious for malignancy. There were no other areas of FDG avidity on the PET scan. Valproic acid was initiated for treatment of myoclonus with transition to clonazepam when no improvement was seen. After starting clonazepam, the patient's condition stabilized.

Dr. Weller, given the additional history, how has your differential diagnosis changed?

Clinical Takeaways

- Serotonin syndrome is a clinical diagnosis that should be considered in a patient who has recently taken a serotonergic medication and is presenting with clonus and diaphoresis.
- Continuous video electroencephalogram (EEG) is preferred over a spot EEG in a patient with waxing and waning mental status so as to increase the chance of capturing an event causing the altered mental status.
- A paraneoplastic syndrome occurs when an immunologic response to a malignancy erroneously targets self-antigens. It can precede a malignancy, and it can persist after a malignancy is treated. While there are serum antibody tests for paraneoplastic syndrome, a negative test does not rule out the diagnosis. If clinical suspicion is high enough, empiric treatment should be started.
- Lung cancers can be categorized as small cell and non-small cell. Small cell lung cancers typically evolve rapidly and are sensitive to chemotherapy, while non-small cell lung cancers typically progress more slowly and are less responsive to chemotherapy.
- There are many factors that contribute to the decision whether or not to proceed with surgical resection of non-small cell lung cancer, including pulmonary function tests, other comorbidities, anatomic location, and stage of disease. A multidisciplinary approach to treatment should be utilized in these cases.

➤ **Dr. Weller:** Given the patient's laboratory findings, we can be quite sure that there is not a contributing metabolic process. The findings suggestive of metastatic cancer, along with the profound neurologic changes, are most concerning for a paraneoplastic syndrome. I would suggest biopsy and consideration of a lumbar puncture. One can also send serum markers, including a paraneoplastic antibody panel.

➤ **Dr. Reese:** Biopsy of the mass in his right lower lobe revealed squamous cell lung cancer. Dr. Schlechter and Dr. Rangachari, do you have a framework for the different forms of lung cancer?

➤ **Dr. Schlechter/Dr. Rangachari:** The 2 broad categories of lung cancer are small cell and non-small cell (NSCLC). Small cell lung cancer has a tight association with tobacco exposure and is often clinically defined by rapid, bulky progression (ie, weeks to months).[7,8] NSCLCs are also commonly seen in those with tobacco exposure, though not always. The main subgroups in this category are adenocarcinoma and squamous cell carcinoma. These cancers often evolve at a slower pace (ie, months to years).[8] While small cell lung cancers are high-grade tumors and exquisitely sensitive to chemotherapy and radiation, NSCLCs tend to be less responsive to such therapies. The staging evaluation for either entity is the same and consists of defining localized vs metastatic disease.

➤ **Dr. Reese:** Because this patient had an MRI and PET scan that were both negative for metastatic disease, can we assume that this patient had stage I NSCLC?

➤ **Dr. Schlechter/Dr. Rangachari:** Not necessarily. While PET and MRI brain are exceptionally helpful in detecting distant metastases, they may over- or underestimate intrathoracic lymph node involvement by as much as 20%.[9] As such, dedicated lymph node staging—either via bronchoscopy (endobronchial ultrasound) or surgically (mediastinoscopy) is indicated as lymph node involvement can significantly alter the stage, prognosis, and optimal therapeutic approach.[10,11]

➤ **Dr. Reese:** After this diagnosis was made, the teams caring for this patient attributed his altered mental status to a paraneoplastic syndrome. What is a paraneoplastic syndrome, and how does a paraneoplastic syndrome from malignancy present? Does its presence worsen a patient's prognosis?

➤ **Dr. Schlechter/Dr. Rangachari:** A paraneoplastic syndrome is defined by an immunologic response to the cancer that ends up erroneously targeting self-antigens. Paraneoplastic syndromes are associated with a broad array of clinical findings—from endocrinopathy to encephalopathy—and certain neoplasms are more commonly associated with these syndromes than others (eg, small cell lung cancer and thymoma). Further, severity and onset of a paraneoplastic syndrome does not correlate with the burden of visible disease—and the syndrome may predate the cancer diagnosis by months to years.[11] While treatment of the cancer affords the best hope of resolving the paraneoplastic syndrome, the cancer and the paraneoplastic process may have a discordant trajectory, with the paraneoplastic syndrome persisting even after the cancer is maximally treated. Although one might assume that paraneoplastic syndromes portend worse outcomes, in some cases, a presentation with the paraneoplastic syndrome may afford sooner detection of an otherwise occult/asymptomatic malignancy.

➤ **Dr. Reese:** The following week, the serum paraneoplastic antibody panel that tested for anti-Yo antibody, anti-Ri antibody, and anti-Hu antibody came back negative. Dr. Weller, what does this mean? Since we have yet to obtain a lumbar puncture, might his symptoms still be caused by a paraneoplastic syndrome?

➤ **Dr. Weller:** The negative serum test just means that he does not have antibodies to those 3 antibodies. There are now over 30 different paraneoplastic antibodies that have been discovered, and there are always more that are being discovered. So this negative test result does not exclude a paraneoplastic syndrome in the appropriate clinical context.[12] Furthermore, the sensitivity and specificity for certain antibodies are different based upon source fluid, and cerebrospinal fluid testing would provide more diagnostic clarity. A negative test for paraneoplastic syndrome, by itself, would similarly not exclude a paraneoplastic syndrome. Often, empiric treatment is the best diagnostic option for paraneoplastic and autoimmune encephalopathies.

➤ **Dr. Reese:** The following week, the patient was discharged to rehabilitation with clonazepam for his symptoms and a scheduled follow-up. Given the patient's frailty and medical comorbidities, thoracic surgery recommended consultation with radiation oncology. Dr. Schlechter and Dr. Rangachari, when do we decide to use radiation vs chemotherapy for someone with lung cancer?

➤ **Dr. Schlechter/Dr. Rangachari:** Patients with early stage, nonmetastatic NSCLC may not always be candidates for surgical resection on the basis of pulmonary function, other medical comorbidities (as in this case), anatomic considerations, and/or patient preference. In these cases, if there is lung-limited disease without lymph node involvement (ie, stage I/II NSCLC) and the patient is not felt to be an operative candidate, then alternatives to surgery include either radiation or ablation.[13,14] As we care for an aging and comorbid population, evolving evidence suggests that well-selected patients with early stage disease undergoing these nonoperative approaches have roughly equivalent outcomes to those undergoing conventional surgical resection.[13] In such cases, multidisciplinary consultation with a team having dedicated expertise in these

various operative and nonoperative modalities is essential.

➤ **Dr. Reese:** The patient followed up with radiation oncology for consideration of radiation treatment, but his simulation CT scan showed some ground-glass opacity that were concerning for inflammation vs infection. The patient's case was discussed at the multidisciplinary tumor board, and it was determined to treat him with antibiotics for a possible pneumonia before proceeding with radiation therapy. After he completed antibiotic treatment, he underwent 10 fractions of radiation treatment, which he tolerated well.

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Disclaimer

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