The pharma-fever that almost got away

XIAO CHI ZHANG, MD, MS; MATTHEW SIKET, MD; WILLIAM BINDER, MD

From the Case Records of the Alpert Medical School of Brown University Residency in Emergency Medicine

DR. XIAO CHI ZHANG: A 68-year-old man was brought into the Emergency Department by his family with chills and altered mental status. Two days prior to his ED presentation, the patient had an episode in which he "spaced-out" and was unable to comprehend or acknowledge his wife. She reported that he did not have any signs of seizure activity and did not have any focal weakness. The episode lasted approximately 30 minutes and he returned to his baseline. Today he had another episode, but this time associated with chills and rigors. His past medical history was significant for chronic back pain due to bony metastasis from Stage IV non-small cell lung adenocarcinoma, requiring palliative gamma knife radiation, as well as a daily oral chemotherapy agent, erlotinib, an oral tyrosine kinase inhibitor. Additional medications included sertraline and methadone, which had recently been increased from 2.5 mg to 5 mg three times daily. Review of systems was negative for any recent travel, exposure to sick contacts, or pulmonary, abdominal and urinary complaints. Of note, the patient had developed a stable and unchanged truncal rash ever since he was started on erlotinib, 15 months prior to presentation.

On arrival to the ED, the patient's vital signs were 106.2 F (41.2 C), blood pressure 137/78 mm Hg, pulse rate of 109, respiratory rate of 20, with an oxygen saturation of 90% on room air. His physical exam was notable for normal reactive pupils without papilledema, a supple neck without meningismus, mild oral thrush, tachycardia with regular rhythm and a diffuse, blanchable, papular rash along the trunk and proximal extremities He was alert and oriented x4, fully conversant, with 3+ patellar reflexes bilaterally and mild clonus, but otherwise had a normal neurological and memory exam.

Initial laboratory studies including a complete blood count (CBC), a comprehensive metabolic panel (CMP), a lactic acid level, a urinalysis, and a point of care rapid strep and influenza were normal. A non-contrast CT of the brain was unremarkable, and a chest x-ray revealed an apical lung mass consistent with the patient's known lung cancer. An abdominal CT scan demonstrated an incidental pathologic acetabular fracture, but did not reveal any sources of infection.

DR. SARAH GAINES: A fever greater than 41.0°C is quite elevated and unusual. Is this dangerous? What was your differential?

DR. MATTHEW SIKET: Humans generally tolerate temperatures below 41° C (105.8° F). In contrast to hyperthermia, in which an imbalance between heat generation versus dissipation occurs without up-regulation of the hypothalamic set point, fever as a host defense against infection rarely reaches dangerous levels in neurologically competent individuals. Very high temperatures can be related to urosepsis, intraabdominal sepsis, C. difficile colitis, meningitis, and central venous catheter infections. Hyperpyrexia, defined as temperature > 41.5°C (106.7°F) is an uncommon result of infection and usually implies central fever, neurologic malignant syndrome, malignant hyperthermia, adrenal insufficiency, or a drug related cause.[1] Our patient was hyperpyrexic, suggesting either a limited spectrum of infectious diseases or a medication-related disorder.

DR. ELIZABETH GOLDBERG: What were your next steps in diagnosis and management of this patient?

DR. ZHANG: Our patient had a change in mental status as well as a remarkably elevated temperature. Our initial concern was for encephalitis or meningoencephalitis as delay in treatment can result in devastating morbidity and mortality. A lumbar puncture was performed with an opening pressure of 15cm H2O, 500+ RBCs in tube 4, 1 nucleated cell, 71% PMN, 17% lymphs, and normal glucose and protein. The patient was empirically treated for encephalitis of unclear etiology with IV cefepime, acyclovir, and vancomycin and was admitted to the floor for additional workup. Of note, his fever defervesced to 38.6 °C with 1g of IV acetaminophen.

DR. BRUCE BECKER: I have two questions. First, why did you obtain a CT of the brain prior to the lumbar puncture? Second, why was this patient treated with antiviral medication and antibiotics?

DR. ZHANG: While all patients with suspected encephalitis or meningitis should have a lumbar puncture for CSF evaluation, a computed tomography (CT) of the brain is not necessarily indicated as it can lead to a delay in appropriate treatment. A retrospective study in Sweden showed that

patients who underwent immediate LP without CT received antibiotics 1.6 hours earlier than those who had a CT. The treatment delay resulted in a relative increase in mortality of 13 percent per hour of delay.[2] If an LP is delayed or contraindicated (such as thrombocytopenia, history of epidural abscesses, or concern for herniation), the providers should obtain peripheral blood cultures and give empiric antibiotics.

The reasons for obtaining brain CTs prior to LPs are to assess for potential mass lesions or increased intracranial pressure, which may lead to a fatal cerebral herniation during removal of CSF. The indications for obtaining brain CTs include a history of immunocompromised states, malignancy, seizures, abnormal level of consciousness, focal neurologic deficit and papilledema.[3,4] Since our patient has a history of metastatic cancer with altered mental status, we felt that a CT prior to performing the LP was indicated.

HSV encephalitis is a fatal disease process if untreated, especially in patients presenting with diffuse cerebral edema or intractable seizures.[5] Prompt acyclovir therapy for HSV encephalitis can decrease one year mortality from 70% to approximately 14% although persistent neuropsychiatric and epileptic sequelae will persist in well over 20 percent of the surviving population.[6] Consequently, empiric IV acyclovir was initiated while awaiting confirmation from CSF studies, including CSF cultures, PCR, and viral serologies.

We administered empiric antibiotics prior to obtaining our CSF results because bacterial meningitis is a devastating disease with significant mortality despite appropriate and timely administration of antibiotics. The overall case fatality rate is 16.4%, with mortality increasing linearly with age, from 8.9% (age 18-34) to 22.7% (age 65+).[7] A delay in antimicrobial treatment for pneumococcal meningitis of more than 3 hours significantly increases mortality and results in greater neurologic deficits at discharge.[8]

DR. WILLIAM BINDER: Would empiric antibiotics have affected the gram stain and CSF cultures?

DR. ZHANG: Administration of antibiotics can reduce the yield of gram stain and cultures, but the pathogen can still be cultured from the CSF for several hours after antibiotics.[9] However, a special consideration should be made for patients with meningococcal meningitis, as one study demonstrated that three out of nine CSF cultures, obtained within one hour prior to LP, were negative.[10] This is in contrast to pneumococcal meningitis in which 4 to 10 hours were required before the CSF cultures were sterile after antibiotics.[11]

DR. ANDREW NATHANSON: It appears that you have covered the patient for infectious organisms. However, given the elevated temperature, was there further concern for a non-infectious cause of the hyperpyrexia?

DR. ZHANG: On admission, the patient was afebrile with unchanged repeated blood work. His blood, urine, and CSF (HSV, CMV) cultures and PCR were negative, his respiratory viral studies were normal, and consequently his antibiotics were discontinued. A careful review of the patient's medication revealed that his methadone dose was recently increased from 2.5mg TID to 5mg TID two weeks prior to hospital admission due to increased back pain. This coincided with the patient's initial febrile episode. In the setting of hyperpyrexia, hyperreflexia, and clonus, the patient was diagnosed with serotonin syndrome secondary to opiate dose increase. Sertraline was subsequently discontinued and he remained alert, oriented, and afebrile for the remainder of his hospital stay.

DR. JEFF FEDEN: How did methadone use lead to serotonin syndrome?

DR. ZHANG: Serotonin syndrome is a potentially dangerous condition associated with increased serotonergic activity in CNS, (i.e. autonomic hyperactivity, neuromuscular abnormalities, altered mental status) due to synergistic drug-drug interaction or intentional overdoses of serotonin reuptake inhibitors (SSRI or SNRI). It is usually more acute in onset (<12 hours) than neuroleptic malignant syndrome (NMS), which occurs over 1–3 days and is associated with akinesis and rigidity, decreased levels of consciousness, and mutism.[12] Additionally, the creatinine kinase (CK) level is usually markedly elevated (typically, greater than 1000 IU/L, and up to 100,000) in NMS. 13 Our patient's CK was 206 IU/L.

Serotonin syndrome is often associated with multiple medications which increase serotonin release. Co-intoxication with CNS stimulants (cocaine, amphetamine, MDMA) can also precipitate serotonin syndrome both increasing the release and impairing serotonin reuptake, while CNS depressants (opiates) can act as direct serotonin agonists. Approximately 8% of Caucasians are deficient in the cytochrome P450 2D6 enzyme and are more susceptible to serotonin toxicity if taking medications such as venlafaxine, paroxetine, tricyclics, dextromethorphan, and methadone.[14] There are no data to suggest that erlotinib is related to serotonin syndrome. However, erlotinib inhibits the cytochrome enzyme CYP3A4, which can result in the accumulation of serotonergic drugs such as methadone, and consequently may have contributed to this patient's syndrome.[15]

DR. ILSE JENOURI: Are there any specific diagnostic criteria for serotonin syndrome?

DR. ZHANG: Serotonin syndrome is diagnosed through clinical exam findings and detailed history consistent with worsening autonomic symptoms in the setting of known exposure to serotonergic substances. Common serotonin syndrome physical findings include agitation (or altered mental status), hyperthermia, hyper-reflexia, akathisia, tremors, diaphoresis, and muscle rigidity.[16] In the absence of additional medical co-ingestions, cerebral infections or mass effects, clinicians can use the Hunter Toxicity Criteria Decision Rules 17 to diagnose serotonin syndrome. The Hunter Criteria is 84% sensitive and 97% specific when compared with a diagnosis of serotonin syndrome made by a medical

toxicologist if a patient has taken a serotonergic agent and meets one of the following conditions:

- Spontaneous clonus
- Inducible clonus PLUS agitation or diaphoresis
- Ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus

There are no specific confirmatory laboratory tests to confirm serotonin syndrome; however, one may consider ordering CBC, CMP, CK, UA, drugs of abuse, coagulation studies, as well as radiographs, brain CT and/or lumbar punctures to narrow the differential diagnoses.

DR. EDWARD RUHLAND: What is the management of serotonin syndrome?

DR. ZHANG: The primary management of serotonin syndrome is discontinuation of the offending agent (i.e. serotonergic agents) and supportive care. Patients should be placed on placed on continuous cardiac monitoring, while receiving supplemental oxygen to maintain SpO2 > 94 percent and IV fluids for volume depletion. Benzodiazepines can be used to control agitation as well as elevated blood pressures and heart rates. While antipyretic agents, such as acetaminophen do not typically have a role in controlling for fever, as the increase in body temperature with serotonin syndrome is due to an increase in muscular activity as opposed to an alteration in the hypothalamic temperature set point, it is interesting to note that our patient defervesced after one dose of acetaminophen. Patients with persistent fever above 106F (41.1C) can be considered for sedation, paralysis and intubation. Cyproheptadine, a histamine receptor antagonist, may be considered if the patient continues to exhibit agitation and abnormal vital signs despite conservative supportive care and benzodiazepine.

DR. LAURA MCPEAKE: How did the patient fare after discharge?

DR. ZHANG: The patient returned to his psychiatrist two weeks after hospital discharge for additional therapeutic recommendations for treating his depression. After a long discussion, both physician and family agreed that prescribing additional antidepressants may result in recurrence of serotonin syndrome, especially in the setting of an expected increase in opiate prescription over time. Fortunately, the patient had great support from family and friends and demonstrated a realistic, yet positive view on his prognosis; he elected to seek alternative methods for managing his depression with palliative care and has not had any recurrent serotonin syndrome symptoms.

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Authors

Xiao Chi (Tony) Zhang, MD, MS, Emergency Medicine Resident, Alpert Medical School of Brown University.

Matthew Siket, MD, Assistant Professor of Emergency Medicine, Alpert Medical School of Brown University.

William Binder, MD, Associate Professor of Emergency Medicine; Alpert Medical School of Brown University.

Correspondence

William Binder, MD
Emergency Medicine Foundation
593 Eddy Street, Providence, RI 02903
401-444-5411
Fax 401-444-4307
William_Binder@brown.edu