August 2017 Critical Care Case of the Month

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History of Present Illness

The patient is a 26-year-old woman with who was admitted to the hospital for second cycle of chemotherapy for a large mediastinal synovial sarcoma diagnosed 2 months prior to admission. Symptoms started 6 months prior to presentation with cough. She related the cough to her cigarette smoking and quit. Upon persistence of symptoms, she was evaluated by her physician who ordered imaging. Work-up revealed a large 12 x 14cm synovial sarcoma with internal necrosis that encased the subclavian artery, and descending thoracic aorta, inseparable from pericardium and left atrium. It also encased the pulmonary veins, pulmonary arteries, and airways. Malignancy was complicated by extensive left upper extremity DVT for which she has been on anticoagulation since her last admission, SVC syndrome, and severe mucositis.

Past Medical History, Family History, and Social History

She has a past medical history significant for malignant melanoma surgically resected 7 years previously, as well as generalized an anxiety disorder. Her family history includes a maternal grandfather with esophageal cancer and maternal great-grandmother with pancreatic cancer. She is single and lives with her parents. She is a former 8 pack year smoker, and daily edible marijuana user. She worked as a hairdresser, but is now unable to work.

Current Medications:

- Escitalopram (Lexapro) 10mg PO daily
- Dalteparin
- Oxycontin 10mg PO BID + Oxycodone 5-10mg PO Q4H PRN pain
- Antiemetics: Compazine PRN, **Ondansetron** PRN, dexamethasone 4mg BID for 3 days following chemotherapy
- Lorazepam 1mg PO Q4H PRN anxiety
- Pegfilgastrim after chemotherapy
- Senna 3 tabs in AM, 2 tabs in PM

Hospital Course

After starting cycle #2 of chemotherapy (doxorubicin, ifosfamide, and mesna), she experienced significant nausea and anxiety and was prescribed scheduled ondansetron/dexamethasone, prochlorperazine, promethazine and lorazepam.

The night of hospital day #2, her providers noticed altered mental status and unusual behavior. They asked her draw a clock which is shown (Figure 1).

Figure 1. Clock drawn by patient.

What is on your **differential diagnosis** for this patient's altered mental status?

1. Delirium
2. Ifosfamide-induced encephalopathy
3. Toxic-metabolic encephalopathy secondary to the medications received
4. 1 and 3
5. All of the above

Correct!
5. All of the above

Ifosfamide is an alkylating agent used in the treatment of many solid tumors (1,2). One of the most serious side effects with its use is central nervous system (CNS) depression known as ifosfamide-induced encephalopathy (IIE). This is reported for as many as 10-30%, and even as high as 60% of patients receiving this chemotherapy. The clock drawn by the patient showing duplications (see double numbers above) and arrows pointing the wrong way suggested ifosfamide neurotoxicity.

The clinical picture of IIE can range from mild somnolence or agitation to confusion or hallucinations to deep coma. Low serum albumin, high serum creatinine, and presence of pelvic malignancy have been identified as factors that increase the risk of ifosfamide-induced encephalopathy. Symptoms begin hours or days after drug administration and usually resolve completely several days later. This encephalopathy is thought to result from accumulation of chloroacetaldehyde, one of the breakdown products of ifosfamide which is similar to the ethanol metabolite acetaldehyde, which exhibits an inhibitory effect on the CNS.

Other neurologic toxicities associated with ifosfamide are rare and include seizures, nonconvulsive (complex partial) status epilepticus, ataxia, weakness, cranial nerve dysfunction, neuropathies, or an extrapyramidal syndrome.

All of the patient's labs are checked and are unchanged from baseline. All vital signs are stable. She mental status continues to be altered with unusual behavior.

What should be **done next**?

1. Start patient on methylene blue
2. Hold further chemotherapy
3. Review medication list for potential contributors to her mental status
4. 1 and 2
5. All of the above

Correct!

5. All of the above

National Cancer Institute toxicity grading for encephalopathy spans Grade 1 (no encephalopathy symptoms), Grade 2: mild signs and symptoms, no interference with activities of daily living, Grade 3: signs or symptoms that interfere with activities of daily living, with hospitalization indicated, Grade 4: life-threatening and/or disabling signs and symptoms, Grade 5: death (3).

Most patients do not require specific treatment for IIE and the encephalopathy improves spontaneously. Although serious, long-term outcomes of encephalopathy are rare, they can include organic brain damage, coma, and death. Some reports suggest that methylene blue, dexmedetomidine, or thiamine may be useful for the treatment and/or prevention of IIE (4). The most benefit is seen in patients with Grade III or higher toxicity.

The patient's chemotherapy is held and she is started on methylene blue. A few hours later, she is found unresponsive in her room. She has marked tachypnea and increased work of breathing. She is newly tremulous and shaking diffusely, and is very restless. Labs again are unchanged. ABG reveals respiratory alkalosis. CXR is stable and CT head is without acute abnormality. On exam however, she is mildly febrile at 38°C, tachycardic to 164, tachypneic to 56, and appears ill. She has dilated pupils, and neurological exam reveals a Glasgow Coma Score of 5, and 3+ reflexes in biceps, brachioradialis, and patellar tendons bilaterally. She has sustained clonus at the ankles bilaterally.

What is the **most likely diagnosis** for her current presentation?

1. Neuroleptic malignant syndrome
2. Seizures
3. Sepsis
4. Serotonin syndrome
5. Superior vena cava syndrome

Correct!
4. Serotonin syndrome

Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (5). It is seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning. Many drugs can contribute to the onset of serotonin syndrome. SSRIs, MAO inhibitors, 5 HT agonists, and amphetamines all lead to increased serotonergic activity and, as in this case, act together to precipitate the syndrome.

The diagnosis of serotonin syndrome is made solely on clinical grounds. Therefore, a detailed history and thorough physical and neurologic examinations are essential. Serotonin syndrome is a clinical triad of mental-state changes, neuromuscular abnormalities, and autonomic hyperactivity caused by excessive serotonergic agonism in the central nervous system.

It encompasses a spectrum of disease where the intensity of clinical findings is thought to reflect the degree of serotonergic activity. Mental status changes can include anxiety, agitated delirium, restlessness, and disorientation. Patients may startle easily. Autonomic manifestations can include diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea. Neuromuscular hyperactivity can manifest as tremor, muscle rigidity, myoclonus, hyperreflexia, and bilateral Babinski sign. Hyperreflexia and clonus are particularly common; these findings, as well as rigidity, are more often pronounced in the lower extremities.

Upon review of the patient's medications, she was taking a selective serotonin uptake inhibitor (SSRI) escitalopram, as well as other agents that can increase serotonin including ondansetron and other anti-emetics. With the addition of methylene blue, which is a phenothiazine derivative and functions as an inhibitor of monoamine oxidase (MAO-I), she experienced the acute onset of serotonin syndrome (6,7).

What should be **done next** to treat this patient?

1. Stop all potentially serotonergic agents
2. Stop the methylene blue
3. Treat with cyproheptadine
4. 1 and 2
5. All of the above

Correct!
5. All of the above

Treatment for serotonin syndrome is largely supportive with removal of all serotonergic agents, sedation with benzodiazepines, and administration of serotonin antagonists (5). Cyproheptadine (Periactin) is most commonly used and is a histamine-1 receptor antagonist with non-specific 5-HT_{1A} and 5-HT_{2A} antagonistic properties. The patient should be carefully evaluated to assess the need to restart serotonergic agents upon resolution of symptoms. The patient's escitalopram, ondansetron, and methylene blue were stopped and she was treated with cyproheptadine and lorazepam. She returned back to her baseline mental status within 48 hours.

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