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Case of Serotonin Syndrome Initially Presenting as Diffuse Body Pain

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Data Collection B
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Data Interpretation D
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Patient: Female, 50
Final Diagnosis: Serotonin syndrome
Symptoms: Pain
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual clinical course

Background: Serotonin syndrome is a common yet potentially life-threatening condition caused by increased serotonergic activity, usually from serotonergic pharmaceutical agents. Primary features of serotonin syndrome include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. However, the presentation of serotonin syndrome is often quite variable, leading to its under-diagnosis.

Case Report: A 50-year-old female with chronic kidney disease on peritoneal dialysis presented to the Emergency Department with severe, diffuse body pain. Over the course of her hospital stay, she developed severe nausea, vomiting, and diarrhea followed by hyperreflexia and inducible clonus. Laboratory studies were remarkable for elevated liver transaminases. Review of her medications revealed several serotonergic agents, including duloxetine, tramadol, and ondansetron. Given her symptoms and the multiple serotonergic agents she was taking, she was diagnosed with serotonin syndrome. Discontinuation of the serotonergic agents led to resolution of her symptoms over the course of 4 days.

Conclusions: Our patient's initial presentation of diffuse body pain highlights the variable presentation of serotonin syndrome. Our case also demonstrates the importance of recognizing serotonin syndrome, as the supportive ondansetron we gave to alleviate her nausea and vomiting likely exacerbated her serotonin syndrome.

MeSH Keywords: Abnormalities, Drug-Induced • Antidepressive Agents • Serotonin Syndrome

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Background

Serotonin syndrome, or serotonin toxicity, is a constellation of symptoms that result from increased serotonergic activity. The syndrome is usually caused by increased serotonin levels as a result of medications that have serotonergic activity. Although serotonin syndrome is classically caused by selective serotonin reuptake inhibitors (SSRIs), other pharmaceutical agents have also been implicated. These including antipsychotics, narcotics, dietary supplements, anti-epileptics, and antibiotics, among many others [1]. The syndrome is quite common, although reliable estimates of its prevalence have been hampered by challenges with recognition of the syndrome owing to its variable presentation. However, a post-marketing surveillance study of the SSRI nefazodone identified an incidence of 0.4 cases per 1000 patient-months [2]. In addition, a study revealed that 14–16% of cases of overdose of SSRIs develop symptoms of serotonin syndrome [3].

Serotonin syndrome is the result of increased serotonin in the central nervous system (CNS) and peripheral nervous system [3]. It is believed that the serotonin receptor 5-HT_{2A} is primarily responsible for these effects, although other neurotransmitter receptors have also been implicated [4,5]. In the CNS, serotonin is normally produced from the median raphe nucleus and has a wide range of effects on behavior, mood appetite, autonomic function, thermoregulation, and nociception, amongst others. In the periphery, serotonin acts to modulate gastrointestinal motility and vascular tone. The clinical manifestations of serotonin syndrome are a reflection of the effects of excessive serotonin on these physiological systems.

The classic clinical triad of serotonin syndrome is comprised of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (Table 1). However, the clinical presentation of serotonin syndrome is quite variable and non-specific [6], often making the diagnosis quite challenging. Furthermore, no single laboratory test, including serum serotonin levels, can reliably confirm the diagnosis, and there are no pathognomonic clinical findings [7]. Currently, the Hunter Criteria is the best diagnostic criteria (Table 1), and has a reported sensitivity of 84% and specificity of 97% [7]. Timely diagnosis is imperative, as serotonin syndrome can be life-threatening given the autonomic instability. Life-threatening and related complications of the condition include severe hypertension and tachycardia that lead to shock, hyperthermia, rhabdomyolysis, renal failure, and disseminated intravascular coagulation, among others [1]. The cornerstone of treatment is discontinuation of all serotonergic agents and supportive measures [1], as well as possible administration of anti-serotonergic agents such as cyproheptadine in more severe cases [8].

Table 1. Symptoms associated with serotonin syndrome.

Hunter criteria symptoms of serotonin syndrome
• Clonus
– Spontaneous
– Inducible
– Ocular
• Tremor
• Hyperreflexia
• Hypertonia
• Hyperthermia
Other manifestations
• Altered mental status
• Autonomic instability
– Tachycardia
– Hyperthermia
– Hypertension
– Vomiting
• Diarrhea
• Mydriasis
• Diaphoresis
• Pain
• Flushing
• Trismus

Case Report

A 50-year-old female with medical history notable for stage 5 chronic kidney disease on nightly home peritoneal dialysis, type II diabetes mellitus, peripheral neuropathy, gastroesophageal reflux disease, hypertension, and unspecified chronic pain presented to the Emergency Department (ED) with a 1-day history of worsened nausea and severe diffuse body pain, most notably of her abdomen. Her pain began the evening prior to admission during a home peritoneal dialysis treatment, which she stopped promptly due to the development of her severe pain.

On review of her history, she had experienced similar symptoms approximately 1 month ago, also during a home peritoneal dialysis session. With the prior episode, the pain subsided when she stopped her dialysis session. It was later determined by her nephrologist that this pain was caused by gas introduced during dialysis.

On initial physical examination, she appeared anxious and acutely in distress from her pain. Vital signs revealed that she was afebrile and with blood pressure of 148/82 mmHg, heart rate of 109 beats per minute and respiratory rate of 18 breaths

Table 2. Selected laboratory measurements on admission.

Lab	Value	Reference range
White blood cell count	7.7	4.0–10.0 10 ³ /mL
Hemoglobin	9.8	12.0–16.0 g/dL
Hematocrit	29.7	35.9–45.0%
Mean corpuscular volume	94.2	78.0–100.0 fL
Platelet Count	230	150–400 10 ³ /mL
Aspartate aminotransferase (AST)	572	0–37 IU/L
Alanine aminotransferase (ALT)	391	0–41 IU/L
Direct Bilirubin	<0.2	0.0–0.2 mg/dL
Total Bilirubin	0.3	0.0–1.0 mg/dL
Alkaline phosphatase	433	35–129 IU/L
Blood urea nitrogen	75	6–20 mg/dL
Creatinine	10.42	0.40–0.9 mg/dL

Table 3. Peritoneal fluid analysis.

Lab	Value	Reference range
Appearance	Cloudy	NA
White blood cell count	1410	<5/mL
Eosinophil %	4	0–0%
Polymorphonuclear %	4	0–0%
Monocyte/macrocyte %	61	0–0%
Lymphocyte %	31	0–0%
Red blood cell count	570	0/mL

per minute. She complained of pain on light palpation to any portion of her body, including her entire abdomen. Her cardiac and pulmonary examinations were unremarkable. Her liver span and spleen size could not be determined as the patient was unable to tolerate examination. No ascites or edema was noted. She was able to move all extremities spontaneously, and no focal neurological deficits were observed. She did display bilateral asterixis. Her deep tendon reflexes were normal on initial exam, and her tone was judged to be normal.

In the ED, initial laboratory investigations revealed elevated blood urea nitrogen (BUN) and creatinine levels, consistent with her chronic kidney disease and not changed significantly from baseline (Table 2). She had a normocytic, normochromic anemia, which was unchanged from her baseline, but her white blood cell count and differential was within normal limits. Liver enzymes were notable for increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, but her bilirubin was within normal limits.

Hepatitis A, B, and C serologies were all negative. Serum lipase was not elevated. Peritoneal fluid analysis was also performed. Peritoneal fluid was cloudy and showed elevated white blood cells (WBCs) (4% neutrophils), but the gram stain of her peritoneal fluid did not show any organisms (Table 3).

Computed tomography with IV contrast of the abdomen was performed. It was remarkable for wedge-shaped areas of hypodensity in the spleen that were read as possibly representing infarction. A right upper quadrant ultrasound was unremarkable, with no abnormal findings in the liver, gallbladder, pancreas, or biliary tree.

She was admitted to the hospital with concern that her pain was again related to her peritoneal dialysis catheter or her dialysis treatment. Over the first 3 days of her hospitalization, her pain worsened. In addition, she developed worsening nausea, severe retching, non-bloody diarrhea, and recurrent non-bloody, non-bilious vomiting. She was given ondansetron

for symptomatic treatment of her nausea without relief. She was switched to promethazine, but her symptoms continued to worsen. She also had episodic hypertension, with systolic blood pressure as high as 234 mmHg. She continued to display asterixis, and on day 3 of hospitalization, she was found to have inducible clonus and new patellar hyperreflexia bilaterally.

Given the negative workup, her medication history was reviewed carefully in search for an underlying cause for her symptoms. On further review, it was noted that she had been taking multiple pharmaceutical agents with serotonergic properties. She was prescribed duloxetine (30 mg oral twice a day) for her peripheral neuropathy and had been using tramadol (50 mg oral) on an as needed basis for pain as well. She also was taking promethazine (12.5–25 mg oral) at home as needed for mild nausea. During her hospital stay, she was given a total of 16 mg in doses of 4 mg of ondansetron for symptomatic treatment of her nausea and vomiting, which was switched to promethazine when ondansetron was ineffective and received one 25 mg dose of intravenous promethazine. Duloxetine, tramadol, and ondansetron all have serotonergic properties and have been known to cause or contribute to serotonin syndrome [1]. Given her overall presentation and when considering her medication use, she was diagnosed with serotonin syndrome.

Following our diagnosis of serotonin syndrome, we discontinued all of her serotonergic medications, including duloxetine, tramadol, and ondansetron. We also discontinued her promethazine, as promethazine is associated with neuroleptic malignant syndrome, an important differential diagnosis whose features can mimic serotonin syndrome (see Discussion). As she did not exhibit life-threatening autonomic instability, more aggressive measures such as cyproheptadine were not warranted in her case. She was closely observed, with daily laboratory investigations and close tracking of her vital signs. She started to improve symptomatically within 1 day of discontinuation of her serotonergic agents. By day 3 (hospital day 6) following discontinuation of her serotonergic agents, her diffuse pain, clonus, and tremor had resolved. Her liver enzymes also trended down and were nearly completely normalized by day 6 of hospitalization.

With resolution of her symptoms, she was discharged after discontinuation of her serotonergic agents. She was instructed to follow up with her primary care provider to consider restarting her duloxetine for her underlying chronic pain under close monitoring.

Discussion

This patient initially presented with a variety of symptoms that did not fit a single unifying diagnosis. Her initial

presenting symptoms of severe, diffuse, non-anatomical pain that was seemingly temporally related to her peritoneal dialysis caused us to consider primarily gastrointestinal and somatoform etiologies. However, when she developed clonus and hyperreflexia as well as numerous autonomic symptoms (nausea, vomiting, diarrhea, and episodic hypertension) during her hospital stay, we were able to recognize her constellation of symptoms as serotonin syndrome.

Careful medication review did reveal several serotonergic agents the patient was taking prior to admission – duloxetine and tramadol. Furthermore, as her symptoms progressed and worsened during her stay, she was given ondansetron and promethazine at increasing dosages for symptomatic relief. Ondansetron inhibits the serotonin receptor 5-HT₃, and for unclear reasons, has been associated with serotonin syndrome [9,10]. The combination of these medications allowed more classic symptoms and exam findings of serotonin syndrome (e.g., clonus and hyperreflexia) to manifest and allowed us to make the diagnosis. Our diagnosis was corroborated by the rapid resolution of symptoms following discontinuation of the serotonergic agents over the course of 4 days.

A confounding aspect of this case is the temporal relationship of her symptoms to her peritoneal dialysis. In the present incident, as well as in the incident 1 month prior, she experienced severe diffuse pain following peritoneal dialysis. In the incident 1 month prior, her nephrologist had determined that gas had entered the peritoneum to trigger the pain episode. However, during this episode, no malfunction of the peritoneal dialysis catheter or the dialysis process itself could be identified. We believe that in both episodes, a possible malfunction related to her peritoneal dialysis occurred, but at this point, we do not believe that the peritoneal dialysis itself was the direct instigator of her serotonin syndrome.

A diagnostic consideration in this case was neuroleptic malignant syndrome (NMS). NMS is associated with use of antipsychotics, including promethazine, which the patient was taking prior to admission and which was additionally given to her for nausea while in the hospital [11]. NMS is classically associated with fever, muscular rigidity, and autonomic dysfunction, thus sharing many features with serotonin syndrome. However, there were several reasons why we favored serotonin syndrome over NMS. First, the patient was afebrile on admission. Second, the patient did not display frank muscle rigidity that is classic for NMS. Lastly, NMS is usually associated with abrupt escalations in the causal agent, and there was no indication that this was the case prior to her admission. Nonetheless, NMS is an important differential diagnosis in cases of serotonin syndrome. Another diagnostic consideration in this case was malignant hyperthermia, which is characterized by fever, muscular rigidity, and tachycardia [12].

However, malignant hyperthermia is usually associated with use of depolarizing anesthetic agents (which the patient was not taking), and the patient was afebrile.

In addition, the patient had moderately elevated liver transaminases on admission (Table 2). They were noted to be down trending on follow-up labs on hospital day 2 and continued to downtrend to near normal levels after we discontinued her serotonergic agents. Prior reports have also indicated that increased liver transaminases can be seen in serotonin syndrome [1,13]. Our report provides additional evidence of elevated liver transaminases as a possible feature of serotonin syndrome.

The patient's presenting symptom of diffuse pain is not typically associated with serotonin syndrome. However, a recent 12 patient case series identified generalized pain in 4 patients (33%) with serotonin syndrome [14]. Moreover, clonus, which is often considered as a cardinal symptom of serotonin syndrome, was only seen in 5 of the 12 patients in that study (42%). These results highlight the significant variability of

serotonin syndrome and the importance for clinicians to be vigilant for this diagnosis.

An important point in this case is our initial use of ondansetron – a drug with serotonin-modifying properties – for symptomatic treatment of the patient's nausea. Our liberal use of these medications very likely exacerbated her serotonin syndrome, worsening her nausea, vomiting, and diarrhea and allowing the clonus and hyperreflexia to manifest. Thus, it is important to recognize serotonin syndrome early, as symptomatic treatment of its symptoms may involve use of medications that will greatly worsen the condition.

Conclusions

Diffuse body pain may be an initial presentation of serotonin syndrome. Medications such as ondansetron used to symptomatically treat the nausea and vomiting that may accompany serotonin syndrome can actually exacerbate the condition.

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