Dilated Cardiomyopathy after an Episode of Serotonin Syndrome

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Introduction
Serotonin syndrome is an increasingly common clinical diagnosis due to increased utilization of SSRI’s, SNRI’s and other antidepressants. Despite its increasing incidence, the disease is often missed by clinicians, given the disease’s varied and diverse clinical presentations. Serotonin syndrome has a set of diagnostic criteria known as the Hunter Criteria to establish a diagnosis. The Hunter Criteria include exposure to a serotonogenic agent in the last 5 weeks and either spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, or hypertonia, temperature greater than 38 C and ocular or inducible clonus.

Background
It appears there may be an association between serotonin syndrome and Takotsubo cardiomyopathy, or apical ballooning of the left ventricle following a stressful event with normal coronary arteries, evidenced by multiple case reports. One such case was a woman who was being treated with isocarboxazid and lithium and subsequently developed serotonin syndrome after taking phenethylamine. Another study demonstrated elevated levels of serotonin in patients with Takotsubo cardiomyopathy, similar to the levels seen in STEMI’s. The authors hypothesized that elevated levels of serotonin could participate in the pathology of Takotsubo Cardiomyopathy. A case in Japan demonstrated a patient who developed Takotsubo Cardiomyopathy after the treatment with maprotiline (a TCA) and dextromethorphan. The patient developed cardiogenic shock and even required IABP to maintain blood pressure; only on the next hospital day did the patient begin to show the symptoms of serotonin syndrome. In addition, there also seems to be an association with SNRI’s and reversible cardiomyopathy. A group of Australian researches performed a prospective study examining 110 patients with Takotsubo Cardiomyopathy and found that 6 were receiving SNRI therapy on presentation, with a majority having having elevated normetanephrine and BNP levels. Another patient who overdosed on 300 mg of Venlafaxine subsequently developed chest pain, T wave inversions on ECG, apical and midventricular akinesis and EF of 25% on ECHO was diagnosed with Takotsubo cardiomyopathy after cardiac catherterization excluded coronary disease. There are two reported cases in which a patient was taking milnacipran and developed a cardiomyopathy syndrome. The first case, the patient intentionally ingested 3000 mg of the drug in a suicide attempt and developed transient acute cardiac dysfunction with an EF of 30% and global hypokinesis. The second occurred while the patient was taking the drug for fibromyalgia, and developed a syndrome of hypertension, tachycardia, and cardiomyopathy with severe diastolic dysfunction and a EF of 30%. However, to our knowledge, an association of serotonin syndrome with other forms of cardiomyopathy have not been published in the literature. (See Table 1).

Case Presentation
A 66-year-old female with past medical history of bipolar disorder treated with lithium, difficult to manage depression treated with Fluoxetine and Bupropion, and history of breast cancer presented to our facility as a transfer from an outside hospital for suspected serotonin syndrome. The patient was admitted there for Lithium toxicity which resolved with hydration and withholding of lithium. She became increasingly lethargic, rigid, unable to speak, and her eyes and mouth were clenched shut. Upon arrival to our institution, the patient was unresponsive, with eyes and mouth clenched closed. Her extremities were held in a flexed position and she exhibited diffuse hyperreflexia and bilateral ankle clonus on examination. She exhibited mild hypertension in the 140s systolic and a temperature of 37.9C. Transfer records indicated that she was being treated with Prozac, Wellbutrin, and Zofran among other medications at the other facility with the last doses of Prozac being on day of admission to our facility. The patient exhibited the classical symptoms of inducible clonus, hyperreflexia, hypertonia based on the Hunter Criteria was diagnosed with serotonin syndrome.
The patient was started on IV Lorazepam and NG tube was placed to administer cyproheptadine and patient was unable to take PO. All of her psychiatric medications were withheld. Over the next several days, the patient slowly improved and began speaking in short sentences and becoming less rigid. On hospital day 5, the patient had multiple episodes of asymptomatic supraventricular tachycardia (SVT). For this reason, we obtained an TTE. This demonstrated an ejection fraction of 25-35% with moderate to severe diffuse hypokinesis with regional variations and mild grade 1 diastolic dysfunction. Upon talking with the patient and her family, she has had episodes of SVT for 40 years but declined further intervention at that time. In addition, the patient had been getting regular TTE due to her history of breast cancer and chemotherapy treatment. Her most previous one was 2 months prior to this admission which demonstrated a normal EF and no wall motion abnormalities. The patient was started on metoprolol. The patient slowly improved and was eventually started on lamictal for mood stabilization and discharged to a skilled nursing facility for further rehab. Approximately 6 weeks after her original TTE, a follow up TTE was obtained which showed an improvement in her EF to 45-50% with diffuse hypokinesis still present but no evidence of regional wall motion abnormalities. The patient was discharged from rehabilitation facility after a short stay and has been doing well. No further follow up TTE’s are available within our EMR as the patient does not follow within our health system.

Discussion

There are numerous causes of dilated cardiomyopathy, especially in a patient who is elderly. Some of these causes include infectious or viral myocarditis, chemotherapy or radiation, drugs and alcohol, nutritional deficiencies, disorders of inflammation and autoimmune diseases, endocrine disorders and tachycardia induced to name a few. Our patient had several of these underlying conditions, however we do not believe that these contributed to her new onset cardiomyopathy.

The patient had a remote history of breast cancer treated with lumpectomy and adjuvant chemotherapy. It is well known that anthracycline based chemotherapy can lead to cardiac toxicity at any time after treatment but chronic doxorubicin cardiotoxicity has an incidence of only 1.7% and it is usually evident within 30 days of the last administered dose but can be up to 10 years after its administration.8 For this reason, her PCP was getting regular surveillance TTE’s, which never showed any cardiomyopathy. In fact, she had gotten one several months before the admission which showed a normal EF of 60%. We feel it would be very unlikely that a sequelae of the chemotherapy would suddenly occur during this acute illness given the large amount of normal TTE she had completed previously. Another plausible explanation for her cardiomyopathy is related to her SVT episode. After discussion with the patient’s husband, we discovered she had episodes of SVT for approximately 40 years. The patient had never been treated for these in the past and had declined any workup. While it is certainly possible that the SVT episode while in the hospital could have contributed to the cardiomyopathy, her prolonged history of SVT episodes and no previous evidence of cardiomyopathy makes this less likely. Her inpatient TTE was completed when she was reverted back to sinus rhythm and normal rate. Lastly she had hypothyroidism but her TSH was within the normal range upon admission. She had no history of excessive alcohol use, illicit drug use, known coronary artery disease, autoimmune diseases, or nutritional deficiencies to contribute to her cardiomyopathy.

We believe serotonin syndrome was the most likely cause of the cardiomyopathy in this patient. Mechanisms which this could happen are not well understood and or documented in the literature. Potential causes would be catecholamine release or activation of serotonin receptors in the myocardium. Previous studies have suggested that there could be multiple mechanisms which serotonin syndrome could...
induce cardiomyopathy including catecholamine mediated multi-vessel epicardial spasm, microvascular coronary spasm, or direct catecholamine mediated myocyte injury. Interestingly enough, a previous study demonstrated that noepinephrine resulted in a concentration based reduction in cardiac contractility. Excessive androgenic stimulation leads to an cyclic-AMP overload of the myocyte resulting in decreased activity and or viability. Thus, in serotonin syndrome, the high levels of circulating androgens could overload the myocytes reducing their function and leading to a cardiomyopathy, possibly explaining this clinical entity.

**Conclusion**

Serotonin syndrome is a condition clinicians should be aware of, as many cases are mild in nature and occur rapidly upon initiation of the medication or an overdose. A careful review of the medication list is mandatory, as failure to withdraw the agent or use additional agents which can cause the syndrome can have severe consequences including death. Fortunately, early recognition usually leads to favorable outcomes.

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**References**