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CLINICAL VIGNETTE

Orthostatic Hypotension in a Patient with Oropharyngeal Cancer

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Case Report

A 67-year-old African-American man with a previous history of alcohol abuse, HTN, and BPH presented to the hospital with profound fatigue, lightheadedness, and dyspnea on exertion, which had been progressively worsening over the past month. The patient could only walk for 5 minutes before needing to stop and sit down. Otherwise, he became syncopal. The patient had presented to the hospital 7 months prior with similar symptoms, which resolved with IV fluids. On review of systems, the patient reported an unintended weight loss of 7 kg in the past 6 months and oropharyngeal pain with swallowing.

His medications included lisinopril, metoprolol, and tamsulosin. He lived with his wife and was independent with his activities of daily living. He was a former smoker with a 30 pack-year history and drank heavily until a month prior to admission. His family history was significant for a prior stroke in his father and type 2 diabetes mellitus in his mother and siblings.

Initial examination showed a temperature of 98.2°F, heart rate of 82, blood pressure of 138/68 mmHg, respiratory rate of 18, and oxygen saturation of 100% on room air. Orthostatic vital signs were notable for blood pressures of 120/63 (lying), 92/56 (sitting), and 72/39 (standing) with an increase in heart rate from 66 to 105 upon lying to standing.

The patient was pleasant, conversant, and oriented. Head and neck exam was notable for tender anterior bilateral cervical lymphadenopathy with tonsillar erythema and moist mucus membranes. Cardiac exam was normal with no carotid bruits. Neurologic exam showed normal cranial nerves II-XII and normal motor exam. Sensory exam was normal to light touch and pinprick, but revealed decreased vibratory sensation in the bilateral lower extremities. Deep tendon reflexes were absent at the ankles. Babinski, cerebellar maneuvers, and Romberg exam were negative. Gait could not be assessed due to the patient's extreme lightheadedness with standing.

Initial laboratory evaluation was notable for anemia of chronic disease with a hemoglobin of 9.6 g/dL, acute kidney injury with creatinine of 1.59 mg/dL, and hypoalbuminemia of 2.6 g/dL. Given concern for orthostatic hypotension secondary to hypovolemia and poly-pharmacy, he was aggressively hydrated and his anti-hypertensive medications, including tamsulosin, were held. Evaluation for heart failure, occult bleeding, and vitamin deficiencies were negative. The remainder of his work-up, which included brain MRI (with T1, T2, and FLAIR sequences), TTE, carotid doppler ultrasound, routine

chest X-ray, and EKG, was unremarkable. No events on telemetry were observed.

Despite adequate rehydration with improvement in renal function, his symptoms continued. At this time, neurology was consulted for workup of potential causes of autonomic dysfunction. The following additional analyses of serum and urine were normal: HIV, RPR, RF, ANA, UPEP/SPEP, cortisol, TSH, B12, folate, thiamine, A1C, and cryoglobulins with the paraneoplastic panel (Anti-Hu, Anti-Yo, Anti-Ri) pending at that time. ESR was elevated to 130. EMG/NCS was notable for mild sensorimotor length-dependent polyneuropathy. The patient was started on midodrine with minimal improvement of his symptoms. A trial of fludrocortisone was discontinued after the patient developed supine hypertension. After some improvement in his ability to do his ADLs, the patient was discharged with follow-up appointments with his PMD and the neuromuscular clinic. Shortly after, his paraneoplastic panel results returned with Anti-Yo, Anti-Hu, and Anti-Ri nuclear fluorescence antibody positivity. Western blot subsequently returned negative. The patient received an outpatient PET-CT scan, which showed an irregular, 5 cm hypermetabolic mass at the right base of the tongue, with several intensely hypermetabolic level I and II cervical lymph nodes. The patient later underwent biopsy of the mass showing squamous cell carcinoma of the base of the tongue.

Discussion

The normal physiologic response to standing involves blood pooling in the lower extremities, resulting in decreased venous return to the heart, a reduction in ventricular filling leading to lower cardiac output, which lowers blood pressure, and a compensatory reflex triggered by baroreceptors in the aortic arch and carotid bodies to increase sympathetic tone, which increases peripheral vascular resistance.^{1,2} This limits the fall in blood pressure after standing. The delayed response of the renin-angiotensin-aldosterone system and ADH secretion in response to prolonged standing then increases circulating blood volume secondary to water retention. Orthostatic hypotension is defined as ≥ 20 mmHg fall in systolic pressure and/or ≥ 10 mmHg fall in diastolic pressure after three minutes of quiet standing. Symptoms associated with this decrease in blood pressure include dizziness, light-headedness, confusion, blurred vision, or syncope. In rare cases, generalized seizures can result.^{1,4} Our patient met the criteria for symptomatic orthostatic hypotension.

One method of classifying the categories of orthostatic hypotension is into neurologic (central, spinal cord, or peripheral), drug, or cardiovascular causes. Cardiovascular causes can then be further divided into hypovolemia, impaired vasomotor tone, or impaired cardiac output. The most common causes of orthostatic hypotension are volume depletion (often GI loss or skin loss) and medications.¹ Studies have shown that the elderly (≥ 65 years old) are at particular risk for orthostatic hypotension due to age-related decreases in baroreceptor sensitivity, especially with concomitant use of antihypertensive medications, opiates, tricyclic or phenothiazine antidepressants, and alcohol.^{1,2} Arnold et al³ estimates the prevalence of orthostatic hypotension at 16.2% for community dwellers 65 years old and older, 54% in elderly nursing home residents, and 68% for patients in geriatric wards. Orthostatic hypotension in the elderly is a risk factor for falls, cardiovascular events, and all-cause mortality even in asymptomatic patients. Therefore, it is important to identify and treat.³

Treatment of orthostatic hypotension varies depending upon its etiology but often involves discontinuing medications that predispose the patient to orthostatic hypotension and performing simple maneuvers to decrease risk of blood pooling in the lower extremities, such as gradual movement from sitting to standing, use of compression stockings, maintaining adequate hydration, and ingestion of salt tablets.^{3,4} For more severe cases of orthostatic hypotension, pharmacologic intervention is often indicated and may include fludrocortisone for renal sodium reabsorption and midodrine for short-acting vasoconstriction.^{3,4} Additionally, pyridostigmine can be used for primary autonomic failure, and octreotide has shown efficacy in preventing venous pooling by constricting splanchnic circulation.³ Our patient was treated with midodrine and fludrocortisone, but symptoms persisted despite this pharmacologic intervention.

Our patient is an interesting presentation of orthostatic hypotension caused by autonomic neuropathy with a previously undiagnosed malignancy, although it remains unclear if this represents a true paraneoplastic syndrome or a neurological syndrome that merely coincides with malignancy. True autonomic paraneoplastic neuropathies are most commonly associated with anti-Hu, anti-CV2/CRMP-5, and anti-AchR antibodies. Autonomic neuropathies are seen in 30%, 31%, and 21% of patients seropositive for anti-Hu, anti-CV2/CRMP-5, and anti-AchR, respectively.⁵ This is consistent with our patient's presentation of autonomic neuropathy in the setting of initially positive anti-Hu nuclear fluorescence antibody. Our patient's clinical picture was confused by a subsequent negative Western blot for anti-Hu suggesting either a false negative or an unrecognized antibody similar to anti-Hu. A negative western blot in presence of positive fluorescence antibodies should be interpreted in the context of clinical findings and history. It does not exclude the possibility of malignancy or a paraneoplastic neurological syndrome.

Anti-Hu antibody was the first recognized auto-antibody marker of small cell cancer and much of the literature describes anti-Hu antibody in relation to this type of cancer. In one study, malignancy was present in 88% of patients who had anti-Hu antibodies, with 93% of those cancers being secondary to small cell lung cancer, with the remainder of the cancers being

prostate cancer, breast cancer, melanoma, lymphoma, or squamous-cell lung carcinoma. Thirty percent of the patients in this study had features of autonomic PNS dysfunction, including orthostatic hypotension, hypothermia, hypoventilation, gastroparesis, intestinal pseudo-obstruction, and cardiac arrhythmias.^{5,6} Although our patient was later found to be anti-Hu and anti-Purkinji Western blot negative, the presentation of autonomic peripheral neuropathy in the presence of an underlying cancer makes paraneoplastic syndrome likely. The neuromuscular specialists who evaluated our patient diagnosed his autonomic neuropathy as being autoimmune or inflammatory in nature. His symptoms are likely related to his malignancy, but our current standard paraneoplastic panels may have not identified the involved antineuronal antibody. Both neurology and oncology expected improvement in his symptoms with treatment of his malignancy. The presentation of orthostatic hypotension in our patient is unusual in that most cases of autonomic neuropathies associated with underlying malignancy are seen in lung cancers and are less likely to be found in oropharyngeal cancers.⁵⁻⁸

Major risk factors for SCC of the oropharynx include HPV (seen in 73% of base of tongue SCC), tobacco use, and alcohol with minor risk factors being low socioeconomic status, family history, EBV infection, and HIV-positive status.⁹ Our patient was at risk due to his remote smoking history and his history of alcohol abuse.

Treatment of possible paraneoplastic autonomic neuropathy in a patient with base of tongue cancer involves treatment of the underlying malignancy, including surgery, radiation, systemic chemotherapy, and/or targeted therapy.⁹

Conclusion

Orthostatic hypotension is prevalent in a large percentage of elderly patients and is important to identify as it is an independent risk factor of cardiovascular events, falls, and all-cause mortality. The possible etiologies of orthostatic hypotension are numerous, although most cases in the elderly are due to medications and/or volume depletion. The patient described in this case report represents a unique presentation of orthostatic hypotension leading to the diagnosis of a base of tongue cancer. Although it is unclear whether this represents a true paraneoplastic neurologic syndrome or orthostatic hypotension with concomitant malignancy, the patient did improve with treatment.

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