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Diagnostic Treatment Dilemma: Baroreflex Failure or Autoimmune Autonomic Ganglionopathy?

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Dear Editors,

A 77-year-old male with a history of squamous cell carcinoma (SCC) of the nasopharynx was treated with chemotherapy and extensive neck radiotherapy. After treatment, he developed severe hypertension (systolic blood pressure (SBP) >200 mmHg) with alternating episodes of orthostatic hypotension (OH) (upright SBP 50 mmHg). His hypertensive episodes occurred four times weekly and resolved spontaneously with rest. He was diagnosed with baroreflex failure. Over the years, his episodes of hypertension improved while his OH worsened in frequency and severity. Six months prior to admission, he developed presyncopal symptoms while seated, and daily syncopal events particularly in the mornings. His OH therapy escalated to the use of midodrine 10 mg TID, 100 mg of droxidopa TID, and enalapril 10 mg daily, which he rarely used.

Evaluation

Orthostatic vital signs were blood pressure (BP) 104/66 mmHg supine, falling to 65/46 mmHg on standing without compensatory tachycardia (HR supine 65 and standing 70 bpm). Physical examination revealed low body mass index of 21 and skin atrophy in the neck region. He had a percutaneous endoscopic gastrostomy (PEG) tube for nutritional delivery.

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Conflict of interest

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Ethical standards

This work was approved by the Institutional Review Board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

His neurological exam was within normal limits. Ancillary tests including complete blood count, basic metabolic panel, cortisol stimulation test, SPEP, and UPEP were normal. Plasma metanephrine levels were <0.10 nmol/L (reference value <0.49), and normetanephrine levels were 0.51 nmol/L (reference value <0.89). Laboratory work up for AChRgn (ganglionic acetylcholine receptor) antibody revealed an elevated titer of 0.24 nmol/L (reference value <0.02).

Autonomic function testing to assess sympathetic vasoconstriction function and cardiovagal function consisted of a short (10 minute) tilt table test, Valsalva maneuver (VM), and controlled breathing. The figure shows the HR, continuous BP and breathing tracings during these stimuli (Fig. 1). Our case is depicted in the right column, and we included normal (left) and baroreflex failure (middle) tracings for comparison. During head up tilt, there was a significant decrease in BP without compensatory tachycardia in the baroreflex patient (middle) and in our case (right). It is noteworthy that in baroreflex failure, BP varies significantly, even more so than in the normal control. This is a gross estimation of sympathetic vasoconstrictor activity and suggests increased activity. In our case, however, BP variability is low, consistent with autonomic failure. During VM, we also observed significant differences in all three tracings. Sympathetic vasoconstriction activity is usually assessed by an increase in BP during phase II late and an overshoot in BP in phase IV (normal, left) as reported previously. Normally, in response to changes in BP, HR responds in an opposite direction as a compensatory mechanism; this reflex arch is modulated by a functioning baroreflex. In our case, there is no BP increase in phase II late or phase IV, and there are no compensatory changes in HR. In baroreflex failure, however, phase II late is present, and there is a BP overshoot in phase IV suggesting increased sympathetic vasoconstriction activity. Of note, in early phase II (Ile), characterized by a decrease in BP related to reduced cardiac pre-load, the HR also decreases indicating impaired baroreflex buffering. The sinus arrhythmia was impaired in both the case and baroreflex failure versus normal control. The final diagnosis was autonomic failure, neurogenic orthostatic hypotension (nOH) secondary to autoimmune autonomic ganglionopathy (AAG).

Discussion

This case presents a diagnostic dilemma wherein a patient with a prior diagnosis of baroreflex failure developed worsening OH. Cases of chronic baroreflex failure have been reported as late sequelae of neck irradiation manifesting as labile hypertension and orthostatic intolerance [1].

Interestingly, our patient's history revealed a pattern of alternating hypertensive and hypotensive episodes that transitioned exclusively to severe episodes of OH. While OH is a common feature of autonomic failure, it is not a primary clinical feature of baroreflex failure [2]. The severity of OH in this patient suggested a different etiology, which prompted autonomic function testing. Results were typical for autonomic failure with impaired sympathetic vasoconstriction. Review of his records raised suspicion for a secondary cause of autonomic failure; he had a clinically insignificant seropositivity for anti-AChRgn antibodies (0.09 nmol/L) that increased over the next 5 years to 0.24 nmol/L and correlated with his worsening OH. Therefore, we concluded that this patient with baseline baroreflex

failure due to neck radiation later developed AAG. The non-cardiovascular symptoms of AAG include severe OH, sudomotor abnormalities, tonic pupils, dry eyes and mouth, bladder dysfunction, gastroparesis, and impotence [3].

This case also represents a treatment dilemma as the recommended treatment for AAG is immunotherapy by intravenous immunoglobulin (IVIG) or plasmapheresis with subsequent immunosuppression [3]. AAG likely masked baroreflex failure by decreasing his sympathetic vasoconstrictor activity. Of note, the treatment of baroreflex failure consists of central sympatholytic agents such as clonidine and methyldopa, which primarily target the unmodulated sympathetic vasoconstrictor activation. [2]

Considering that the patient's major concern was disabling nOH and syncope, the treatment was focused on improving pre-syncope symptoms rather than treating the underlying AAG. The patient, however, was referred to local oncologist for follow-up and evaluation of possible recurrence. The patient failed non-pharmacological measures and midodrine monotherapy[4]. He was receiving low doses of droxidopa, which is usually contraindicated in baroreflex failure as it could cause severe hypertension crisis. Considering that the final diagnosis in this case was AAG that masked baroreflex failure, we decided to increase the doses of droxidopa to therapeutic levels [5]. The patient started treatment with 500 mg droxidopa BID and 5 mg midodrine in the morning as needed. Enalapril was stopped. A 5–10° elevation was recommended while sleeping, and BP was closely monitored for hypertension. After improvement, he was discharged. One-week follow-up revealed no syncope with improved symptoms. Droxidopa was increased to 600 mg TID, midodrine was increased to 5 mg TID, and an abdominal binder was used for symptomatic relief. He refused immunotherapy including IVIG, plasmapheresis, and immunosuppression for AAG to prevent exacerbation of autonomic failure. We determined this regimen to be successful and appropriate management for this patient. This combination of medical, mechanical and lifestyle therapies is warranted in cases of superimposed baroreflex failure/autonomic failure and AAG nOH.

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Fig. 1. Results of autonomic evaluation for a healthy subject (left), a typical baroreflex failure subject (middle), and the case (right). Evaluation included tilt table testing, Valsalva maneuver, and deep breathing sinus arrhythmia testing