JACC: CASE REPORTS VOL. 4, NO. 13, 2022

CASE REPORT

ADVANCED

CLINICAL CASE: IMAGING AND GENERAL CARDIOLOGY

MEN2B Masquerading as Postural Orthostatic Tachycardia Syndrome

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ABSTRACT

Multiple endocrine neoplasia type 2B is a genetic disorder characterized by pheochromocytoma, medullary thyroid carcinoma, and marfanoid features. Although hypertension and stress cardiomyopathy are known cardiovascular complications of pheochromocytoma, clinical presentation maybe subtle. Elevation in heart rate and lightheadedness induced by catecholamine excess may mimic clinical features of postural orthostatic tachycardia syndrome, as shown in our case report. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:814–818) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 29-year-old woman with a presumed history of postural orthostatic tachycardia syndrome (POTS) was seen at our Hypertension Clinic at the University of Texas Southwestern Medical Center in Dallas, Texas for evaluation of unexplained hypertensive episodes. She was not taking any antihypertensive agents at the time of evaluation. Nine years before her visit, she began experiencing intermittent nausea, diaphoresis, and lightheadedness, triggered by standing up or bending forward. Episodes occurred every few months and resolved with sleep. She sought evaluation when these episodes began occurring 1 to 2 times weekly. She was referred to a dysautonomia center and underwent tilt-table testing. She was informed that she had POTS with an elevated plasma norepinephrine level. Findings on echocardiography were normal.

Following relocation to Dallas, she noticed elevated home blood pressure (BP) readings associated with diaphoresis and pallor (Table 1). She was seen by an autonomic neurologist and underwent repeated tilt-table testing (Table 2), which showed evidence of tachycardia with a heart rate increased by 37 beats/min after 3 minutes of head-up tilt at 70°. However, she was also noted to have orthostatic hypotension (Table 2). Because orthostatic hypotension and episodic hypertension are unusual manifestations of POTS, 24-hour urinary metanephrine and catecholamine levels were obtained. Physical examination revealed the following: normal seated BP of

LEARNING OBJECTIVES

- To recognize the range of clinical signs and symptoms associated with pheochromocytoma vs POTS.
- To understand cardiovascular complications associated with MEN2B.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 14, 2022; revised manuscript received April 5, 2022, accepted April 13, 2022.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.04.009

TABLE 1 Home Blood Pressure Report Transmitted by Electronic Health Records, Uploaded by the Patient as Single Measurement Readings

Heart Rate, beats/min	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg
73	130	83
73	126	82
42	185	112
42	163	104
45	206	115
44	201	123
58	116	75
57	117	79
47	179	116
49	228	138
46	255	155

109/76 mm Hg, heart rate of 119 beats/min, weight of 71 kg, height of 177 cm; and normal body mass index of 22.7 kg/m^2. She was noted to have mucosal wall neuromas (Figure 1) and palpable thyroid nodules bilaterally. Cardiovascular and abdominal examinations were unremarkable. Extremities were notable for long, slender fingers and toes. Hypermobility of her fingers was noted (total Beighton Score: 6/9).

PAST MEDICAL HISTORY

The patient had no significant past medical history other than impaired fasting plasma glucose in the prediabetes range.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included POTS, vasovagal syncope, and orthostatic hypotension. Patients with carcinoid syndrome and systemic mastocytosis may present with intermittent episodes of flushing and hypotension, and thus these conditions should also be considered. POTS is defined as the presence of chronic orthostatic intolerance (at least 6 months) that is accompanied by an excessive rise in heart rate ≥30 beats/min within 10 minutes of assuming an upright posture and in the absence of orthostatic hypotension (a decrease in BP >20/10 mm Hg).[1] Hypermobility of joints may be a feature of Ehlers-Danlos syndrome, which is often is associated with POTS.[2] However, elevation of epinephrine and norepinephrine is atypical of POTS, as is the presence of orthostatic hypotension, which excludes the diagnosis of POTS. In addition, paroxysmal hypertension is not a feature of POTS, and it raises the suspicion of pheochromocytoma or paraganglioma. Furthermore, the clinical pictures of bilateral thyroid masses and marfanoid features are consistent with the hereditary form of pheochromocytoma and MEN2B. Arrhythmias such as supraventricular tachycardia should also be given consideration in a young patient experiencing episodic tachycardia associated with nausea. Although the patient never truly experienced syncope, vasovagal syncope was considered given the patient's positional lightheadedness and fluctuations in BP.

TABLE 2 Changes in Heart Rate and Blood Pressure During Head-up Tilt at 70° Angle

	Blood Pressure, mm Hg	Heart Rate, beats/min	Symptoms
Supine	134/88	80	–
1 min (70°)	128/77	100	Lightheaded, warm
3 min (70 °)	114/75	117	Tired
5 min (70°)	111/71	126	No symptoms
7 min (70°)	114/79	131	Weak
10 min (70°)	109/79	137	Tired
Return to supine	133/76	72	–

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CT = computed tomography

MEN2B = Multiple endocrine neoplasia type 2-B

MTC = medullary thyroid carcinoma

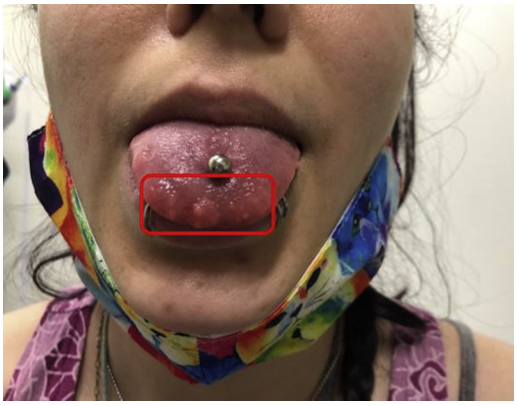
POTS = postural orthostatic tachycardia syndrome

INVESTIGATIONS

Hormonal evaluation showed an elevated 24-hour urinary normetanephrine level of 5,680 μg/day (normal, 103-390 μg/day), a metanephrine level of 14,580 μg/day (normal, 30-180 μg/day), and total metanephrines of 20,260 μg/day (normal, <1,300 μg/day). The patient's 24-hour urine 5-hydroxyindoleacetic acid was minimally elevated at 7 mg/24 hours (normal, <6.5 mg/day). Serum calcitonin was elevated at 10,089 pg/mL (normal, <7.6 pg/mL). Computed tomography (CT) of the abdomen revealed bilateral, adrenal masses (4.4 cm on right, 3.4 cm on left), concerning for bilateral pheochromocytomas (Figure 2). Subsequently, gallium-68 dotatate positron emission tomography combined with CT showed intense uptake of the contrast agent in both adrenal glands consistent with bilateral pheochromocytomas (Figures 3A and 3B). Additionally, bilateral calcified thyroid nodules with variably elevated dotatate avidity were found, consistent with medullary thyroid carcinoma (MTC). Thyroid ultrasound examination confirmed the presence of

JACC: CASE REPORTS, VOL. 4, NO. 13, 2022
JULY 6, 2022:814–818

FIGURE 1 Mucosal Neuromas on the Patient's Tongue



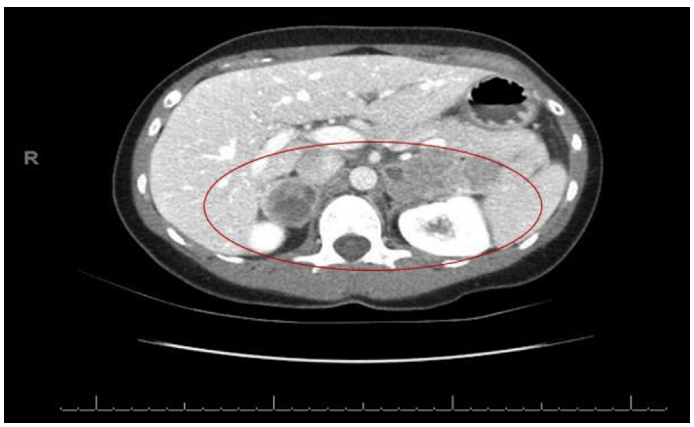
The neuromas are outlined in **red**.

bilateral thyroid nodules, with calcified level 2 to 6 cervical lymph nodes bilaterally. Finally, genetic testing confirmed a *RET* codon 918 mutation consistent with a diagnosis of MEN2B.

MANAGEMENT

Following confirmation of MEN2B, the first priority was to address the patient's bilateral pheochromocytomas. The patient was started on α-adrenergic receptor blockade with doxazosin, which was uptitrated to a maximal-tolerated dose of 4 mg twice daily. After 2 weeks of α-blockade, metoprolol (25 mg twice daily) was added to maintain the patient's seated heart rate <70 beats/min. She subsequently underwent successful bilateral laparoscopic adrenalectomy, with surgical histopathologic examination confirming bilateral pheochromocytomas. Metoprolol and doxazosin were discontinued following surgery because the patient remained normotensive postoperatively. The patient was started on glucocorticoid and mineralocorticoid replacement. It was planned that following her adrenalectomy, she would need total thyroidectomy for MTC.

FIGURE 2 Computed Tomography of the Abdomen with Intravenous Contrast Showing Large, Bilateral Adrenal Masses



The area of the masses is circled in **red**. R = right.

DISCUSSION

MEN2B is an autosomal dominant genetic disorder stemming from mutations in the *RET* proto-oncogene residing on chromosome 10. This disorder is extremely rare, such that the exact incidence is unknown, but it is estimated at 4 per 100 million per year.[3] MEN2B should be suspected in young patients (<35 years of age) with classic features defined by signs and symptoms of pheochromocytoma, marfanoid body habitus, mucosal neuromas in the oral cavity, or intestinal ganglioneuromas. The diagnosis of MEN2B is based on these distinctive findings and the *RET* mutation or autosomal dominant familial inheritance of MEN2B.[4]

MEN2B results in MTC in nearly all patients, with thyroidectomy performed in affected individuals after pheochromocytoma is addressed. Prognosis of MTC relies heavily on the age of the patient and the stage of the disease at diagnosis, with younger patients and individuals with lower-stage disease having a significantly better prognosis.[5] Pheochromocytoma manifests in nearly 50% of patients with MEN2B and commonly appears with the "classic triad" of paroxysmal hypertension, headaches, and diaphoresis. Less common cardiac complications that can arise from pheochromocytomas include orthostatic hypotension from low intravascular volume and cardiomyopathy from catecholamine excess.[6,7]

All patients with MEN2B should undergo screening for pheochromocytoma and MTC. Initial screening includes plasma and/or 24-hour urinary metanephrines as for pheochromocytoma and serum calcitonin and thyroid ultrasound examination for

the presence of MTC. MEN2B gene carriers should undergo prophylactic thyroidectomy.

The clinical presentation of pheochromocytoma may often be confused with POTS because of the paroxysms of hyperadrenergic symptoms.[1] Because patients with POTS are commonly referred to cardiovascular specialists for management of tachycardia and fluctuations in BP, clinicians should suspect the possibility of pheochromocytoma.

FOLLOW-UP

The patient described significant improvement in her symptoms following bilateral adrenalectomy. She is currently receiving glucocorticoid and mineralocorticoid replacement therapy and has not experienced recurrent episodes of hypertension or lightheadedness. She is awaiting total thyroidectomy. Her parents underwent genetic screening and tested negative for the *RET* mutation, thus suggesting a de novo mutation in the index case.

CONCLUSIONS

MEN2B is a rare and challenging disorder with a constellation of symptoms affecting multiple organ systems. Patients can experience a complex clinical course resulting from difficulty in controlling BP and heart rate. It is crucial to recognize that the cardiovascular system is commonly affected, given that more than 50% of these patients have associated pheochromocytoma.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Institutes of Health grant T32DK007257. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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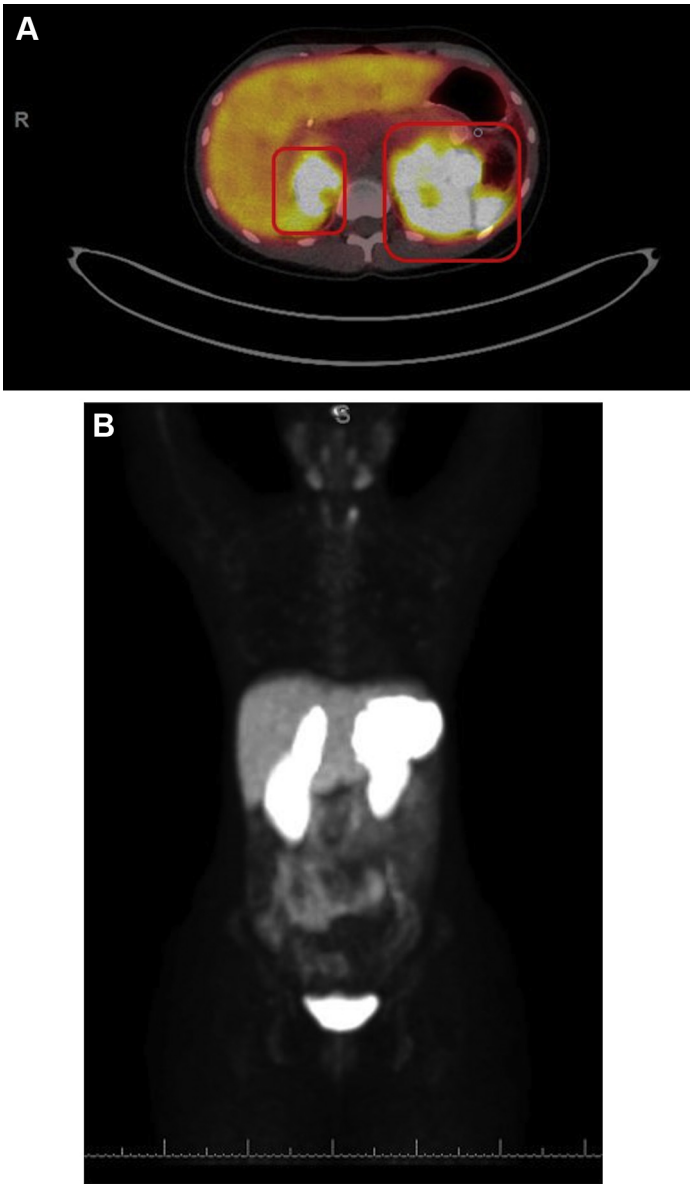
FIGURE 3 Gallium-68 Dotatate Positron Emission Tomography With Computed Tomography



(A) Cross-sectional image at the level of the adrenal glands. **(B)** Coronal section from the base of the skull to the mid-thigh. The masses are outlined in **red**.

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JULY 6, 2022:814–818

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KEY WORDS **awareness, cancer, cardiomyopathy, genetic disorders, hypertension, tachycardia**