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Case Report

Diaphoresis as the Prominent Manifestation of Pheochromocytoma

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ABSTRACT

Objective: Pheochromocytoma is a rare neuroendocrine tumor, affecting 0.6 to 0.8 of 100,000 people per year. The "classic triad" of headache, diaphoresis, and tachycardia is well documented in the literature, although its clinical utility has come into question. Diaphoresis is part of the "classic triad" and occurs in <50% of patients with pheochromocytoma. There are few reports of diaphoresis as the sole symptom of pheochromocytoma. Our objective is to report a patient with diaphoresis as the only prominent manifestation of pheochromocytoma.

Case Description: A 20-year-old man presented with 5 years of worsening diaphoresis; diffuse, but predominantly in the upper half of his body. No other symptoms were present. His blood pressure was 138/82 mm Hg and had a heart rate of 60 bpm. The physical examination was unremarkable. Thyrotoxicosis, infection (including tuberculosis), and lymphoma/leukemia were ruled out. The 24-hour urine norepinephrine level was 1002 ug/24hours (0-135 ug/24 hours), plasma normetanephrine was 2873 pg/mL (0-145 pg/mL), and plasma norepinephrine was 2869 pg/mL (0-874 pg/mL). Computed tomography of the abdomen revealed a 4.0 × 3.1 × 4.3 cm left adrenal mass. After pre-operative preparation with doxazosin, the patient underwent laparoscopic left adrenalectomy. The diaphoresis resolved. Pathology confirmed a completely resected pheochromocytoma. Genetic testing for germline mutations was negative.

Discussion: This patient was a young adult and did not exhibit features of pheochromocytoma common to the pediatric/adolescent or adult populations. Monosymptomatic presentations are sparse in the literature.

Conclusion: This case reflects an atypical presentation of pheochromocytoma, a disease with high cardiovascular morbidity and mortality, and helps to establish the need to better quantify individual symptoms of patients to better understand the entire spectrum of this disease.

Introduction

Pheochromocytoma is a rare catecholamine-secreting neuroendocrine tumor of the chromaffin cells, with an incidence of 0.6 to 0.8 per 100 000 people per year.[1,2] In addition, the incidence may be increasing secondary to incidental findings with the rise in diagnostic imaging.[3] The disease is characteristically defined by the "classic triad" of symptoms: headache, diaphoresis, and tachycardia. However, the "classic triad" has recently been demonstrated to occur in only around 25% of all pheochromocytoma cases,[4] thus emphasizing the need to look at individual symptoms and clinical scenarios. Hypertension can be useful and is reportedly present in around 85% of all pheochromocytoma cases.[4] Conversely, symptoms like diaphoresis only occur in <50% of patients with pheochromocytoma.[4] Major studies fail to address when individual symptoms occur alone or in a constellation of symptoms. This case reflects an atypical presentation of pheochromocytoma in an otherwise healthy young man, in which the patient's only symptom was diaphoresis.

Case Report

A 20-year-old man with no significant past medical history presented with a complaint of generalized sweating that had progressively worsened over 5 years. At the time, a thorough review of systems did not unveil any other symptoms, specifically, no fevers, tremors, flushing, palpitations, headache, diarrhea, chest or abdominal pain. The patient's body mass index (BMI) was 28.86 kg/m^2.

Abbreviation: BMI, body mass index.

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Presenting vitals included a blood pressure of 138/82 mm Hg and a heart rate of 60 bpm. Significant findings on routine laboratory testing showed a mild-elevation of white blood cell count of 11 000 cells/mL, with a normal differential without shift, and elevated fasting glucose of 111 mg/dL. Upon further questioning, the patient reported that his sweating was generally worse in the summer months and when he was more active. The patient noted the pattern of distribution of the sweating to be generalized, but mostly affecting the upper half of his body. Further workup included normal thyroid studies (free thyroxine, 1 ng/dL [0.78-1.33 ng/dL]) and a negative purified protein derivative skin test for tuberculosis. The 24-hour urine collection for norepinephrine was 1002 ug/24 hours (0-135 ug/24 hours), 24-hour urine epinephrine was 10 ug/24 hours (0-20 ug/24 hours) and the 24-hour urine dopamine level was 301 ug/24 hours (0-510 ug/24 hours). The plasma normetanephrine level was 2873 pg/mL (0-145 pg/mL) and the norepinephrine level was 2869 pg/mL (0-874 pg/mL). Other catecholamine levels and their degradation products were within normal limits as follows: plasma metanephrine value of 53 pg/mL (0-62 pg/mL), plasma epinephrine <15 pg/mL (0-62 pg/mL), and plasma dopamine level of <30 pg/mL (0-48 pg/mL) (Table). The plasma metanephrines, 24-hour urine metanephrines, and urine catecholamines were assayed with liquid chromatography and tandem mass spectrometry. The plasma catecholamines were assayed by high-pressure liquid chromatography with electrochemical detection of the frozen plasma specimen. A computed tomography scan with enhanced Hounsfield units of 129 demonstrated a 4.0 × 3.1 × 4.3 cm left adrenal mass. Despite normotensive blood pressures of close to 120/80 mm Hg on previous office visits, the patient was noted to have a blood pressure reading of 150/80 mm Hg in an office visit before surgery after the diagnosis had been established, potentially indicating paroxysmal hypertension that had not been unmasked on prior visits. He underwent surgical resection of the pheochromocytoma after pre-operative treatment with 1-mg doxazosin for alpha-adrenergic blockade for the resolution of hypertension and 12.5-mg metoprolol peri-operatively. Pathology confirmed a completely excised pheochromocytoma. The diaphoresis resolved within 4 weeks after resection of the pheochromocytoma. The patient underwent genetic testing for hereditary cancer syndromes and tested negative for 14 possible gene mutations, including *MEN1, NF1, RET, SDHx,* and *VHL.*

Discussion

Herein, we present a 20-year-old man with a norepinephrine–secreting pheochromocytoma who presented with diaphoresis as the major symptom, but lacked overt hypertension, headache, flushing, tachycardia, or other features of pheochromocytoma. Unlike 40% to 45% of patients between the ages 11 and 20,[5] this patient did not appear to have an underlying genetic predisposition. The differential diagnosis for this patient with generalized sweating included lymphoma, adrenal insufficiency, tuberculosis, thyrotoxicosis, and pheochromocytoma. Lymphoma was less likely due to his normal white blood cell differential. The lack of fatigue, nausea, weight loss, or evidence of orthostatic hypotension put adrenal insufficiency lower on the differential. Tuberculin skin test was negative, ruling out tuberculosis. Thyroid studies were normal, eliminating hyperthyroidism. A pheochromocytoma became the most likely diagnosis, despite no other signs and symptoms of catecholamine excess, and was confirmed with the laboratory data, computed tomography scan, and pathology.

Table
Pertinent Laboratory Results Where Elevations in All Norepinephrine and Norepinephrine–Derivatives Can Be Seen

Laboratory test	Patient value	Reference range
24-hour urine norepinephrine	1002 ug/24 hours	0-135 ug/24 hours
Plasma normetanephrine	2873 pg/mL	0-145 pg/mL
Plasma norepinephrine	2869 pg/mL	0-874 pg/mL

Pheochromocytomas are primarily tumors of the medulla of the adrenal gland and secrete catecholamines (norepinephrine and epinephrine). They are associated with significant cardiovascular morbidity and mortality, in up to 20% of those afflicted.[6,7] The signs and symptoms noted above (hypertension, headache, flushing, tachycardia, etc) have been attributed to the direct effects of catecholamines systemically, including their effects on vascular smooth muscle and the central nervous system. For example, norepinephrine has a high affinity for alpha-1 receptors, which are primarily responsible for vasoconstriction, and thus, hypertension is a common finding in pheochromocytoma. Epinephrine traditionally has a stronger affinity for beta receptors, particularly beta-2 receptors, at lower physiologic levels, but will also bind to alpha receptors at higher concentrations. Both norepinephrine and epinephrine have some affinity for beta-1 receptors, which can induce tachycardia. Excess catecholamines are the primary cause of the cardiovascular morbidity and mortality associated with pheochromocytoma. Cardiovascular sequelae include arrhythmias, myocardial infarction, cardiomyopathy, stroke, and peripheral vascular disease.[6] Appropriate and prompt management of pheochromocytoma is necessary to prevent these effects.

Diaphoresis was the predominant symptom of pheochromocytoma in this case. Sweat glands, particularly apocrine glands, are primarily controlled by alpha-1 sympathetic signaling. Eccrine sweat glands are also controlled by sympathetic activity but are driven by acetylcholine, rather than catecholamines, as the neurotransmitter in contact with muscarinic receptors (Fig.).[8] Additionally, alpha-1 receptors are responsible for peripheral vasoconstriction, which may cause heat dysregulation and lead to neurohormonal activation of eccrine sweat glands. In pheochromocytoma, it has been proposed that catecholamines can increase cellular thermogenesis, leading to increased cellular heat production, which when combined with vasoconstriction, could lead to heat sensitivity and excessive sweating.[9] Central effects on the hypothalamus by catecholamines alter thermoregulation and can induce sweating.[9] One hypothesis in primary or essential hyperhidrosis is that there is an overstimulation of sympathetic fibers passing through the upper dorsal sympathetic ganglia, most of which are noradrenergic neurons.[10] In primary hyperhidrosis, catecholamine levels are usually normal, which contrasts to our patient who showed elevations in norepinephrine. These same circuits also tend to supply the heart and lungs with autonomic input, which when stimulated, should cause tachycardia. With norepinephrine–secreting tumors, the stimulation of the alpha-1 receptors can cause diaphoresis; however, it is unclear why this patient had diaphoresis as a monosymptomatic presentation.

In the pediatric populations, the prevalence of diaphoresis in pheochromocytoma ranges from 17% to 50%.[11,12] However, there is very little evidence of sweating as the only presenting symptom in pediatric or adolescent populations. Studies on symptoms of pheochromocytoma for adults also fail to distinguish which symptoms occur alone or in tandem with other symptoms, creating a lack of evidence for monosymptomatic presentations. Therefore, although this patient is a young adult, he had an abnormal, monosymptomatic presentation for both adults and pediatrics.

This patient presented with diaphoresis and did not seem to have true hypertension on initial presentation—a very common sign of pheochromocytoma.[4] It is important to note that paroxysmal hypertension was not adequately ruled out, as the patient did not undergo ambulatory blood pressure monitoring and did have

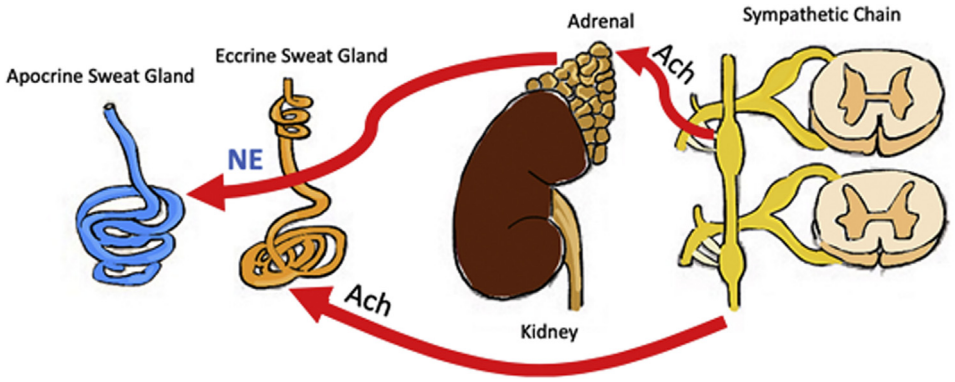

Fig. Sympathetic control of sweat glands. From the sympathetic chain, acetylcholine is released to signal the adrenal glands to release catecholamines, or directly stimulates eccrine sweat glands. The catecholamines released from the adrenal glands (predominantly norepinephrine) then stimulate apocrine sweat glands. Figure transformed from Reference 8.

an isolated blood pressure of 150/80 mm Hg after the already highly suspected diagnosis of pheochromocytoma. However, hypertension is a highly common presenting feature of pheochromocytoma in the pediatric and adolescent populations, with sustained hypertension occurring in up to 90% of cases.[11] The single detection of elevated blood pressure in this patient was clearly not sustained as it commonly is in younger patient cohorts, and it was not documented until after the diagnostic workup had already revealed high catecholamine levels and the diagnosis was essentially established.

This case is unique in terms of the elevations of norepinephrine with few signs and symptoms. Studies in adults have shown that patients with hypertension and pheochromocytoma had urine norepinephrine elevations >750 ug/24 hours, whereas normotensive patients with pheochromocytoma had smaller elevations closer to 250 ug/24 hours.[13] With urine norepinephrine values >1000 ug/24 hours, this patient is more closely aligned with the hypertension and pheochromocytoma group, despite his normotensive presentation. Additionally, scoring systems for pheochromocytoma diagnosis and correlation to catecholamine production incorporate symptoms, BMI (lower BMI equates to a higher score), and heart rate. With only a single symptom (BMI >25 and normal heart rate), this patient was less likely to have had significant elevations in catecholamine levels,[4] however, laboratory tests showed significant elevations.

Conclusion

Here, we report a patient with an unusual presentation of pheochromocytoma, a disease with cardiovascular morbidity and mortality.[6,7] This case report suggests that there is little known about monosymptomatic presentations of pheochromocytoma. Future studies, including, large prospective studies, are required to substantiate the spectrum of individual symptoms. Since pheochromocytoma can be potentially fatal and can have significant cardiovascular impacts if not managed properly, any suspicion should be followed with prompt clinical evaluation. Despite the fact that over 200 years have passed since the first description of pheochromocytoma,[2] there is still much to learn about this disease.

Disclosure

The authors have no multiplicity of interest to disclose.

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