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The importance of pheochromocytoma case detection in patients with neurofibromatosis type 1: A case report and review of literature

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Abstract

Neurofibromatosis type 1 is a complex, multi-system genetic disorder that is associated with an increased prevalence of pheochromocytoma and paraganglioma compared to the general population, 1.0%–5.7% versus 0.2%–0.6%, respectively. A delay in pheochromocytoma and paraganglioma diagnosis or undiagnosed pheochromocytoma and paraganglioma, as seen in normotensive and asymptomatic patients, may portend a significant morbidity and mortality risk due to excess catecholamine secretion. Currently, there are no generally accepted guidelines of screening for pheochromocytoma and paragangliomas in asymptomatic individuals of this population with approaches and practices varying considerably between physicians. Emerging data suggest benefit in routine pheochromocytoma and paraganglioma screening of all individuals with neurofibromatosis type 1. Herein, we present a case to highlight how routine case detection screening would have identified pheochromocytoma earlier in an active duty military member.

Keywords

Pheochromocytoma, neurofibromatosis type 1, screening, metanephrine, catecholamine

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder which carries an increased risk for pheochromocytoma and paraganglioma (PPGL). PPGLs are neuroendocrine tumors arising from adrenal medullary cells and extra-adrenal chromaffin cells, respectively, which commonly hypersecrete one or more catecholamine: epinephrine, norepinephrine, and/or dopamine.[1] In the general outpatient clinic setting, the prevalence of PPGLs in patients with hypertension is 0.2%–0.6%, but in those with NF1, the prevalence is increased at 1.0%–5.7% with even higher rates in those with NF1 and hypertension at 20%–50%.[2–4] Detrimental effects of catecholamine excess and higher PPGL malignancy rates associated with NF1 contributes to significant morbidity and mortality when unrecognized or diagnosis is delayed.[1] Literature suggests that a significant portion of NF1 patients with PPGLs may go undetected due to lack of catecholamine-associated symptoms and/or hypertension. Currently, there is no general consensus for the screening and detection of PPGLs in asymptomatic individuals with NF1. Recent literature suggests a benefit in routine screening for PPGLs in all patients with NF1.[1,3] We explore a case in which routine screening would have identified pheochromocytoma earlier in an active duty military member.

Case presentation

A 24-year-old Hispanic male presented to the emergency department (ED) for a 7-day history of left-sided abdominal pain without any other pertinent positive review of systems. Past medical and surgical history was unremarkable, other than a 7-month history of genetically proven NF1. He denied

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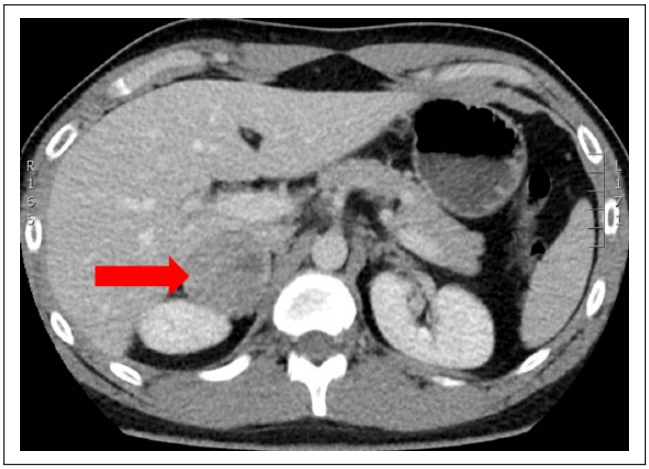

Figure 1. CT abdomen with contrast—heterogeneous, 6.4 cm × 4.9 cm × 4.8 cm right adrenal mass (red arrow).

any current medication, tobacco, alcohol, or illicit drug use. Family history was pertinent for NF1 in his mother, but otherwise non-contributory. Vital signs were normal, and the only pertinent positive physical exam finding was left upper quadrant abdominal tenderness. Laboratory evaluation was unremarkable in the ED, including complete blood count, complete metabolic panel, urinalysis, urine culture, and lipase. A computed tomography scan of the abdomen and pelvis with contrast (Figure 1) revealed a heterogeneous 6.4 cm × 4.9 cm × 4.8 cm right adrenal mass, but without definitive etiology of his left-sided abdominal pain.

Endocrinology initiated a biochemical work up of his adrenal incidentaloma, which included the following elevated 24-h urine labs: dopamine of 1257 mcg/24 h (0–150), epinephrine of 390 mcg/24 h (0–20), metanephrine of 12,087 mcg/24 h (45–290), normetanephrine of 4332 mcg/24 h (82–500), and vanillymandelate of 22.5 mg/24 h (0–7.5). During his endocrinology evaluation, he admitted to the recent onset of intermittent symptoms, at that point in evaluation (>1 month post-ED evaluation), which included headache, palpitations, and tremors. Physical exam was pertinent for café au lait macules scattered on the arms, face, and trunk (Figure 2(a)) in addition to small neurofibromas on his abdomen, arms, and back which have been present since childhood. Eye exam displayed Lisch nodules (Figure 2(b)). Labs, imaging, and history were consistent with pheochromocytoma. To prevent perioperative cardiovascular complications, target blood pressure (<130/80 mmHg) and heart rate (60–70 beats per minute) were obtained via alpha-adrenergic blockade (phenoxybenzamine) with addition of beta-adrenergic blockade (propranolol) prior to surgical intervention. The patient underwent an uncomplicated robotic-assisted right adrenalectomy with surgical specimen shown (Figure 2(c)) and pathology confirming encapsulated pheochromocytoma. He experienced resolution of his symptoms and normalization of biochemical assessment following resection.

Discussion

NF1 is an autosomal dominant disorder caused by a mutation in the NF1 tumor suppressor gene. Clinical diagnosis is based on two or more of the following National Institute of Health diagnostic criteria: café au lait macules, axillary/inguinal freckling, neurofibromas, Lisch nodules, distinctive osseous lesions, optic pathway glioma, and/or first degree relative with NF1.[1] Annual screening for optic pathway gliomas and cognitive deficits, especially in childhood, is recommended due to the increased frequency and potential complications of the conditions. Alternatively, regular asymptomatic case detection investigations for PPGL, malignant peripheral nerve sheath tumors, and cerebral tumors are not currently routinely recommended, and practices vary considerably between providers.[5] Specifically concerning PPGLs, the prevalence in all patients with NF1 is higher than the general population, up to 5.7%.[4] Zinnamosca et al.[6] suggest that this is likely even higher, up to 14%, due to the lack of general consensus on PPGL case detection in the asymptomatic and normotensive NF1 population. PPGLs have the potential for excess catecholamine secretion, which can lead to elevated cardiovascular morbidity and mortality if undiagnosed or there is a delay in treatment. In spite of elevated catecholamine production, 24% of NF1 patients with PPGLs will remain without catecholamine-associated symptoms and 61%–80% will not have hypertension, despite having similarly elevated plasma and urine metanephrine concentrations compared to symptomatic patients.[1]

Nearly one-third of patients with PPGLs have a disease-causing germline mutation, with common genetic syndrome associations to include: NF1, von Hippel-Lindau (VHL), and multiple endocrine neoplasia (MEN) type 2A and type 2B.[2,7] VHL and MEN syndromes also have higher PPGL prevalence compared to the general population, 31%–63%, with recommendations for routine yearly biochemical screening for PPGLs in all individuals.[1] Although NF1 patients have a lower PPGL prevalence compared to those with VHL and MEN syndromes, it remains much higher than the general population, but the only current recommendations include screening in those with catecholamine-associated symptoms and/or hypertension.[3] There are currently no generally accepted clinical practice guidelines for screening asymptomatic patients with NF1, as seen in the other PPGL-associated genetic syndromes. Recent literature has suggested routine screening for PPGL of all individuals with NF1. Kepenekian et al.[8] identified an underestimation of PPGL prevalence with the use of current strategies which only explore symptomatic patients with NF1.[1] Gruber et al. also found similar evidence to support an underestimation of prevalence of pheochromocytomas in patients with NF1. Both Kepenekian and Gruber suggest biochemical screening in asymptomatic individuals with NF1, with Gruber et al. suggesting screening as routinely as every 3 years starting at age 10–14 years. Every 3-year screening was determined to be sufficient in this population, compared to yearly in VHL and MEN syndromes, as the prevalence is somewhat lower in NF1 individuals.[1]

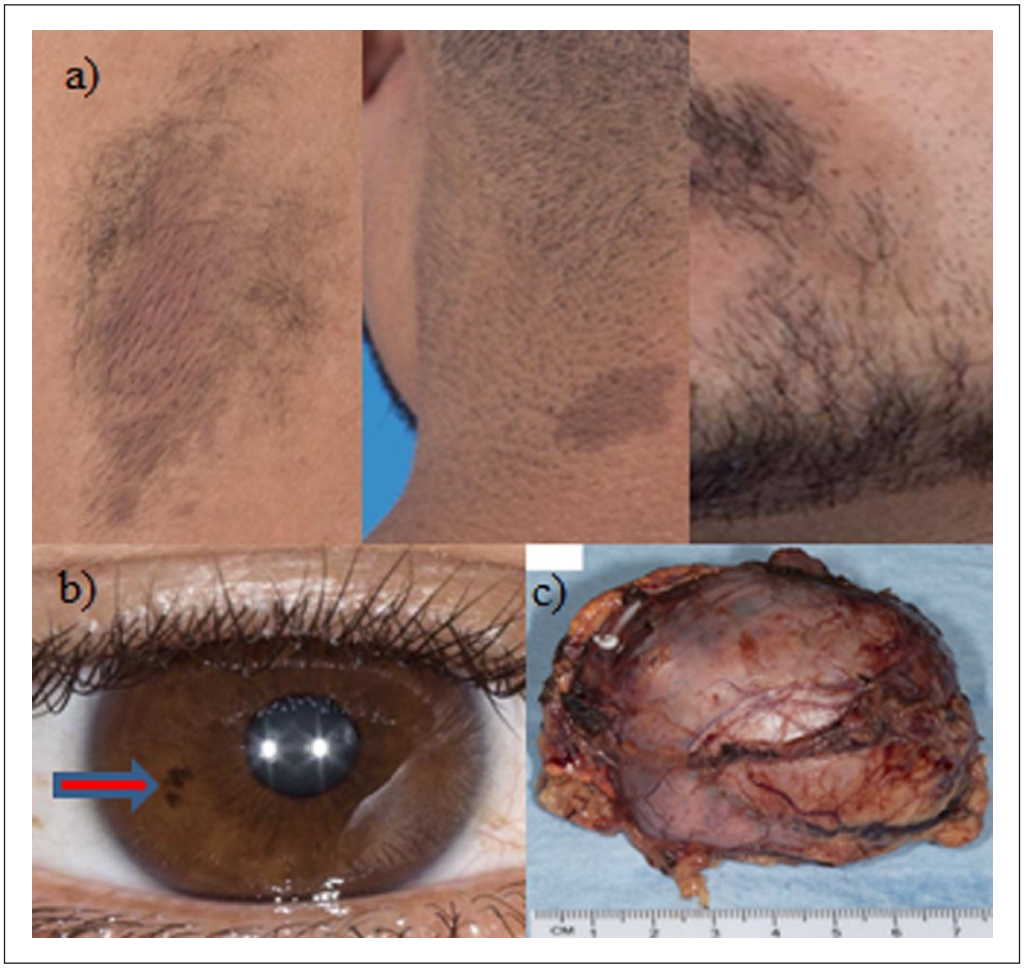

Figure 2. (a) Café au lait macules on trunk, neck, and face; (b) Lisch nodule within the iris (red arrow); and (c) gross surgical specimen—right adrenal pheochromocytoma.

The patient above benefited from incidental notation of his pheochromocytoma, but without the incidentaloma work up above, he may have had a significant delay in diagnosis, as he remained asymptomatic and normotensive for a prolonged period of time, potentially resulting in worsened morbidity and potential growth in tumor size. Routine PPGL screening may have benefited him by providing an earlier diagnosis, avoidance of catecholamine-associated symptoms, and potential for discovery of tumor at a smaller size.

Conclusion

Despite higher prevalence of PPGLs in patients with NF1 compared to the general population, many remain asymptomatic and a majority remain normotensive. Therefore, prevalence is likely higher than previously estimated as this population remains undiagnosed or with a delayed diagnosis. We highlight the importance of routine PPGL screening of all NF1 patients to prevent worsening morbidity and mortality risks associated with undiagnosed catecholamine excess.

Authors' note

The views expressed herein are those of the author(s) and do not reflect the official policy of the United States Air Force, Department of Defense, or the US Government.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

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