CLINICAL VIGNETTE

Panic Attacks in Patient with Neurofibromatosis Type 1

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Case

A 65-year-old female with recurrent major depression, hypertension, neurofibromatosis type 1 (NF1) established primary care with a geriatrician after becoming eligible for Medicare. She previously did not have health insurance and was seen at a community free clinic. She reported depression for most of her life complicated by panic attacks. Mood symptoms were often exacerbated by social stressors and she drank a bottle of wine each night to cope. Evaluation also revealed osteoporosis, diabetes and hyperlipidemia. Over the next four years, she experienced exacerbations in mood, fatigue, weakness, nausea, GERD and hypertension. Exacerbations in her mood disorder and fatigue improved with decrease in alcohol intake and increase in regular physical activity and regular fluid hydration. Psychiatry adjusted her psychotropics to duloxetine and methylphenidate and, as needed, busipirone. Gastrointestinal symptoms improved with lowering metformin dose to 500mg daily, increasing fluid hydration, and treating constipation.

At the age of 69, she restarted having "bad anxiety attacks out of the blue." These episodes persisted for the next 5 months. Panic attacks manifested with feeling really shaky and dizzy, accompanied by palpitations. Extra buspirone doses helped her symptoms. She was also noted to have labile blood pressures during this time. These panic attacks persisted despite stopping alcohol.

During this time, she also developed acute kidney injury (AKI) with creatinine 1.42 mg/dL (up from baseline of creatinine 0.7 to 0.9 mg/dL). Renal function eventually improved with increase in hydration and discontinuation of ibuprofen that she took for knee pain.

Evaluation for the AKI included a renal ultrasound which showed "3.5 cm mass superior to right kidney. Ddx favors an adrenal etiology." Subsequent magnetic resonance imaging (MRI) of the abdomen showed a T2 hyperintense right adrenal mass suspicious for primary adrenal neoplasm and cluster of mesenteric masses concerning for metastatic disease in the left upper quadrant. PET CT scan showed "intense NETSPOT uptake associated with the newly diagnosed right adrenal mass most consistent with a neuroendocrine tumor, possibly pheochromocytoma." 24-hour urine collection showed urine metanephrine 976 ug/d (36-229 ug/d), urine metanepherine-to-CRT ratio 1389 (0-300 ug/g CRT), and urine normetanepherine-to-CRT-ratio703 (0-400 ug/g CRT).

Patient underwent resection of the pheochromocytoma with complete resolution of her panic attacks and improvement of her labile blood pressures and hot flashes. However, she continued to have a poor appetite and constipation. Further endocrine testing post-operatively did not show adrenal insufficiency but did show persistently elevated normetanepherine levels. The left upper quadrant mesenteric masses were resected and pathology revealed them to be gastrointestinal stromal tumors (GISTs) in the small bowel, which are also seen in NF1.

Two years later, she continues to have non-specific gastrointestinal symptoms but has not had recurrent panic attacks or palpitations. PET CT imaging has been negative for recurrence of her pheochromocytoma or GISTs. Normetanepherine levels remain mildly elevated.

Discussion

Neurofibromatosis is an autosomal dominant disease that was first described by Von Recklinghausen in 1849. It affects approximately 1:3000 people worldwide. It presents with multiple soft tissue neurofibromas, café-au-lait macules, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central nervous system gliomas, peripheral nerve sheath tumor, macrocephaly and cognitive deficits.[1,2] Neurofibromatosis Type 1 (NF1) results from mutation of the NF1 gene, a tumor suppressor found on chromosome 17q11.2 that leads to its inactivation.[3] This gene mutation predisposes those who have it to neoplasms that affect the tissues of the eye, skin and nervous system. Rarely, it predisposes to less common tumors of neuroectodermal or mesenchymal origin, including pheochromocytoma.[4]

Pheochromocytoma is a neuroendocrine tumor of the adrenal medulla or the extra-adrenal chromaffin tissue that failed to involute after birth. The tumor produces excessive amounts of catecholamines resulting in tachycardia and hypertension.[5] The gene responsible for the association between NF1 and pheochromocytoma is still unknown.

In the general population, the incidence of pheochromocytomas is 1 per 100,000 persons per year or less, but occurs in 0.1-5.7% of patients with NF1 and 20-50% in NF1 patients with hypertension, compared to 0.1% of all patients with hypertension.[6] A rare case of NF1 presenting with a pheochromocytoma was reported by Zafar et al in 2015.[7] This patient presented with

nausea, vomiting and weight loss but did not have the typical symptoms one would expect from catecholamine excess, such as headache, diaphoresis, tremors, pallor, shortness of breath and panic attack symptoms. He had sinus tachycardia and blood pressure readings ranging from 140/75 to 225/110. Given his history of NF1, further evaluation with abdominal imaging and biochemical testing was done to look for a pheochromocytoma, which was found. Data from observational studies suggest that all patients with NF1 and hypertension should undergo biochemical testing for pheochromocytoma, which includes serum and urine catecholamines, metanephrines and vanillylmandelic acid.[8]

Both this case and the case report from Zafar et al illustrate a key learning point that patients who have both NF1 and hypertension should be screened for pheochromocytomas regardless of clinical presentation. While our patient had long-standing depression with somatic symptoms that confounded her presentation of pheochromocytoma, resection of the pheochromocytoma significantly improved her quality of life. She no longer experiences episodes that she described as panic attacks. While her normetanepherine levels remain mildly elevated post-resection of the pheochromocytomas, the mild elevations may be related to the duloxetine and methylphenidate that she continues for her mood disorder and does not necessarily indicate a recurrence.[9,10] She will continue routine surveillance to monitor for recurrence with biochemical testing and imaging.

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