Neurofibromatosis Syndrome with Pheochromocytoma

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ABSTRACT
Generalized neurofibromatosis (von Recklinghausen’s disease) is one of the commonest form of neurocristopathies. It is characterized by multiple cutaneous neurofibromas, neurologic and skeletal abnormalities and inherited in an autosomal dominant pattern. Pheochromocytoma occurs in less than 1% of neurofibromatosis syndromes. Clinicians have to consider it in the differential diagnosis of a familial pheochromocytoma.

Keywords: Neurofibromatosis, Pheochromocytoma, Café-au-lait spots, Iris hamartoma.

INTRODUCTION
Pheochromocytoma is a tumor arising from the adrenal medulla. Pheochromocytomas can be familial and syndromic in up to 25% of cases.1 Neurofibromatosis (NF), otherwise known as von Recklinghausen’s disease, is a common neuroectodermal syndrome occurring with a frequency of 1 in 3,500 new births.2 Though, NF associated pheochromocytomas are rare, it is one of the common causes of familial pheochromocytomas due to higher community incidence of NF. In this article, we describe a prototype case of NF associated pheochromocytomas with a brief review of literature to highlight its clinical features and facts.

CASE DETAILS
A 30-year-old man presented to a general surgeon with sudden onset of severe abdominal pain, palpitations and dehydration. His measured blood pressure (BP) was 220/130 mm Hg. Ultrasound revealed a right adrenal mass and he was referred to our department with a suspicion of pheochromocytoma for further management. Detailed clinical evaluation revealed history of repeated paroxysmal attacks of drenching sweats, palpitations and bursting headache with blurring of vision lasting for 10 to 15 minutes at an approximate frequency of once in a fortnight since 1 year. History of loss of appetite and weight were present. There was no history suggestive of renal dysfunction, drug abuse or neurologic disease. On examination, there were multiple cutaneous and mucosal swellings throughout his body suggestive of generalized neurofibromatosis. Multiple light to dark brown macules throughout body, suggestive of café-au-lait spots and axillary freckling were present (Fig. 1). Eye examination revealed bilateral exophthalmos and iris patches, the latter was diagnosed to be iris hamartomas (Lisch nodules) on slit lamp test (Fig. 2). Biopsy of a cutaneous nodule was confirmatory of neurofibroma. His family pedigree chart is depicted in Figure 3. In all seven of his evaluable 1st and 2nd degree relatives were afflicted with generalized neurofibromatosis (grand father, mother, sister, three maternal aunts and daughter). Thyroid function test revealed euthyroid status ruling out Graves’ disease. 24-hour urinary vanillyl mandelic acid (VMA) was 28 mg (6-8) and total metanephrine level was 3.5 mg (0.4-0.9), which were diagnostic of hypercatecholamine.
Contrast enhanced computerized tomogram (CECT) revealed a heterogeneously enhancing mass lesion of right adrenal and normal left adrenal gland. According to our departmental protocol, preoperative preparation was done by graduated anti-hypertensive medications with Prazosin 10 mg/day (final dose), Nifedipine 20 mg/day, high salt and fluid intake. On 12th day after starting alpha blockade, we performed right laparoscopic adrenalectomy. There was no evidence of invasive tumor, retroperitoneal lymphadenopathy or extra-adrenal tumors with normal renal vasculature and opposite adrenal gland. Intraoperative BP fluctuations were present as expected, but no major hemodynamic events occurred perioperatively. Size of the tumor was 7.5 × 6 × 4.2 cm and weighing 185, ex vivo. Histopathology was confirmatory of a benign pheochromocytoma with two mitotic figures/10 high power field, no atypical mitoses and PASS score of 3. There was evidence of adrenal medullary hyperplasia with corticomedullary ratio of 2.5:1 at the thickest portion of gland. At 4 months follow-up, he was asymptomatic with BP of 130/80 mm Hg on Nifedipine 10 mg/day. Two of his first degree relatives were evaluated with biochemical evaluation for hypercatecholinism but revealed no evidence of pheochromocytoma in them.

DISCUSSION

Pheochromocytomas are tumors arising from adrenal medulla and extra-adrenal chromaffin tissue that hypersecrete catecholamines, resulting in severe hypertensive and metabolic related clinical features and complications. They are predominantly sporadic, but incidence of familial forms is on the raise due to discovery of associated syndromes and better screening of the family members. Various familial syndromes associated with pheochromocytoma are multiple endocrine neoplasia (type 1 and 2), von Hippel-Lindau disease, neurofibromatosis 1, paraganglioma syndromes, and the list is ever expanding. Incidence of familial pheochromocytoma varies from 10 to 84 % depending on the age group, multifocality and presence of extra-adrenal tumors. 1, 4

NF was first described by Smith in 1849. Fredrick von Recklinghausen coined the name of the disorder in 1882. 5 It is characterized by neoplastic and non-neoplastic disorders involving tissues of neuroectodermal and mesenchymal origin. The neurofibromatosis has two clinical variants: NF1 and NF2. The most common type is NF1 and less commonly as NF2. It is a common autosomal dominant neurocutaneous disorder associated with mutations of NF1 gene. NF1 gene is a tumor supressor gene mapping to chromosome 17q 11.2.7 The phenotype is characteristic with striking clinical signs. Clinical features are caused by disorderly growth of melanocytes and glocytes and characterized by cutaneous and mucosal neuromas, café-au-lait spots and many pleiotropic manifestations.8 People with NF1 are at increased risk for malignant conditions, especially malignant peripheral nerve sheath tumor (MPNST), leukemia and rhabdomyosarcoma. The diagnosis for NF1 was established by the NIH Consensus Development Conference. 9 NF1 is diagnosed if two or more of the following are present:

1. Six or more café-au-lait macules (brown spots) are present > 1.5 cm after puberty and 0.5 cm in prepubertal individuals.
2. Two or more neurofibromas (tumors).
3. Freckling in the axillary or inguinal regions (Crowe’s sign).
5. Two or more Lisch nodules.
6. A distinctive, osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of the long bones.
7. A first-degree relative (parent, sibling or offspring) with NF1 by the above criteria.

Our case had 5/7 requisite criteria, i.e. about 25 café-au-lait spots (of variable sizes, the largest one being 5 cm), numerous neurofibromas, axillary freckling, multiple Lisch nodules and two involved first-degree relatives, leading to an obvious diagnosis of NF1.

Pheochromocytoma occurs in 0.1 to 5.7% of patients with von Recklinghausen’s disease. 2 While the incidence of pheochromocytoma is 1 in 100,000 general population. 10 The coexistence of pheochromocytoma and NF were first reported by Suzuki. 11 Mean age of diagnosis of pheochromocytoma in NF is about 42 years. 2 Hypertension in NF may be caused by associated vascular anomalies like renal artery stenosis, aneurysms or coarctation of aorta, the most common renal artery stenosis due to arterial wall neurofibromas. 12 One needs to be cautious in establishing the exact cause of hypertension.
At imaging and surgery, clinicians need to look for abnormalities in both the adrenals, retroperitoneum, renal vasculature and other possible paragangliomas. Inspite of low expressivity of pheochromocytoma in NF, the condition of NF associated pheochromocytoma is very common due to high prevalence of NF in the community. The genetic diagnosis of NF is not easy, as routine genetic analysis is cumbersome due to large gene (240 kilo base pairs) and high rate of new spontaneous mutations.

CONCLUSION

Incidence of pheochromocytoma in NF is low, but high prevalence of NF should prompt the clinicians to look for its stigmata routinely even in an apparent case of sporadic pheochromocytoma. They need to be aware of all the clinical findings of NF for appropriate family counseling and surveillance.

REFERENCES