



Metastatic Pheochromocytoma Diagnosed with ^{131}I -MIBG SPECT/CT Imaging in a Patient with Pathogenic VHL Mutation

Kousik Vankadari¹ Raman Boddula² Aditya Gajanan Hegde² Chimutai Chinte²

¹Department of Nuclear Medicine, Yashoda Hospital, Secunderabad, Telangana, India

²Department of Endocrinology, Yashoda Hospital, Secunderabad, Telangana, India

Address for correspondence Kousik Vankadari, DNB, Department of Nuclear Medicine and PET/CT, Yashoda Super Speciality Hospital, Alexander Road, Kummari Guda, Shivaji Nagar, Secunderabad-500003, Telangana, India (e-mail: kousik43@gmail.com).

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Abstract

Keywords

- ▶ metastatic pheochromocytoma
- ▶ missense VHL mutation
- ▶ MIBG
- ▶ Arg167Gln

Pheochromocytoma is a rare catecholamine secreting neuroendocrine tumor arising from chromaffin cells of adrenal medulla with approximate prevalence of 0.1 to 0.6% in patients suffering from hypertension. Hypertensive control followed by surgical resection remains the primary treatment of choice. Although it is considered a slow growing benign tumor, it rarely leads to recurrence of tumor in the lymph nodes, liver, and lungs. Association of benign pheochromocytoma with familial or de novo Von Hippel-Lindau (VHL) mutations is well reported in literature. Here, we report a case of metastatic pheochromocytoma arising from commonly seen benign VHL mutation.

Introduction

Von Hippel-Lindau (VHL) disease is a monogenic autosomal dominant inherited disorder characterized by benign and malignant tumors involving blood-rich organs of body such as central nervous system (cerebellar, spinal, and retinal hemangioblastoma), kidney (clear cell carcinoma), adrenal glands (pheochromocytoma), pancreas (neuroendocrine tumors, cystadenoma) as well as endolymphatic sac tumors, paragangliomas, and visceral cysts.^{1,2} Diagnosis of this disease is based on family history of VHL-related tumors associated with pathogenic VHL mutation on exon 1–3 of short arm of chromosome 3.³

Case Report

A 45-year-old male patient came to our department with recent onset occasional episodes of headache and palpita-

tions associated with vague abdominal pain. His past history was suggestive of operated right adrenal pheochromocytoma 4 years back with pathogenic VHL mutation. ^{131}I -metaiodobenzylguanidine (^{131}I -MIBG) imaging was done for further evaluation. Planar anterior and posterior whole-body images (▶**Fig. 1A,B**) show multiple foci of increased tracer uptake in the abdomen and pelvis along with faint tracer uptake in the left lower neck. Axial computed tomography and fused single-photon emission computed tomography/computed tomography images localize the increased uptake to tracer avid lesion in right adrenal fossa postoperative bed adjacent to surgical sutures (▶**Fig. 1C,D**, solid arrow) along with multiple tracer avid retroperitoneal abdominopelvic (▶**Fig. 1E,F**, dotted arrow) lymph nodes and faintly tracer avid left supraclavicular lymph node (▶**Fig. 1G, H**, dashed arrow). His plasma free normetanephrines were elevated (656 pg/mL; normal value < 196). Based on aggressive ^{131}I -MIBG imaging features of tumor recurrence in the

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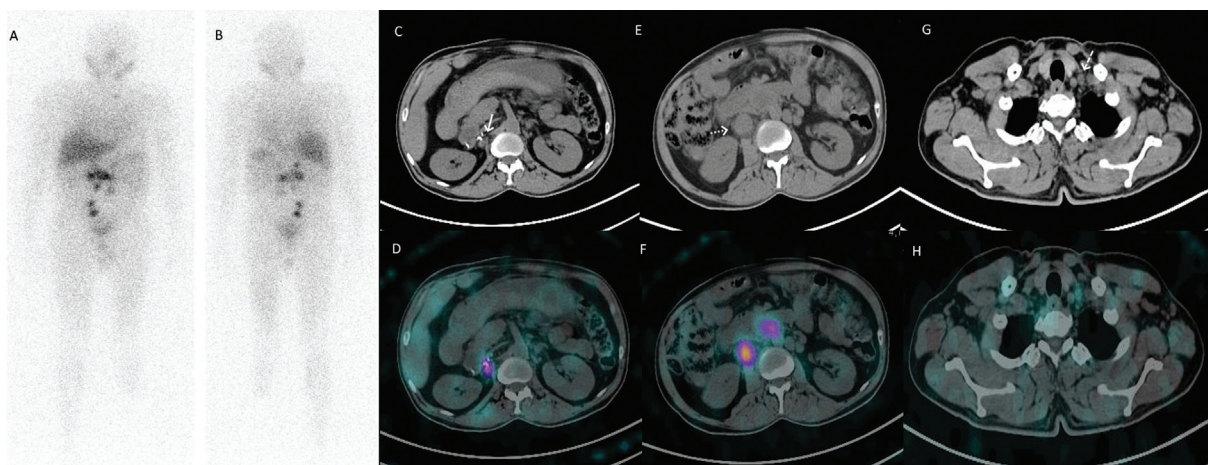


Fig. 1 Whole body anterior (A) and posterior view (B) I-131 MIBG images showing tracer avid foci in the abdominopelvic region and left lower neck. Hybrid single-photon emission computed tomography/computed tomography images localize the increased tracer uptake to soft tissue lesion in the right adrenal postoperative bed (C,D) along with tracer avid retroperitoneal (E,F) and left supraclavicular lymph nodes (G,H).

right adrenal fossa with multiple tracer avid lymph node metastases and elevated plasma free normetanephrines, a diagnosis of metastatic pheochromocytoma was considered and patient was planned for ¹³¹I-MIBG therapy. Family

pedigree assessment of the proband (→**Fig. 2, solid arrow**) done for genetic counselling shows pathogenic VHL mutation in one of his children, suggesting autosomal dominant inheritance of the disease. However, both of his parents

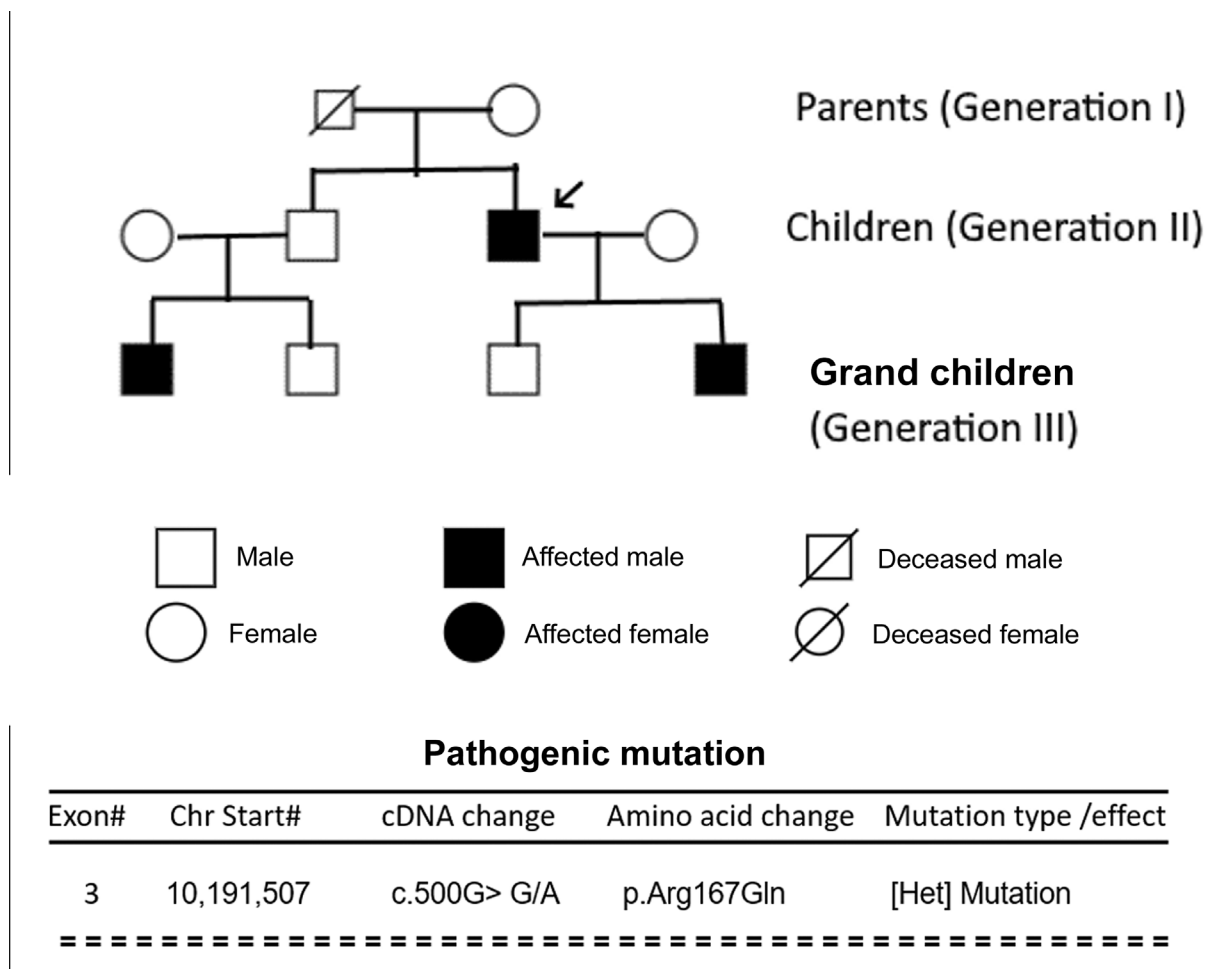


Fig. 2 Family pedigree chart of the index case.

were unaffected by the disease signifying de novo appearance of mutation in the index case. DNA sequencing done in our patient and his children was suggestive of heterozygous missense mutation (c.500G > G/A) involving codon 167 of exon 3 in VHL gene replacing arginine with glutamine amino acid (p. Arg167Gln).

Discussion

VHL disease was seen to be associated with more than 500 VHL mutations till date with most of them (80%) inherited from affected parents and approximately 20% of them arising de novo as seen in our case.^{4,5} Based on type of mutation, VHL disease is broadly classified into two types with truncating, large deletion mutations associated with type 1 disease and missense mutations seen in type 2 disease. Missense mutation involving codon 167 of exon 3 is seen to be strongly associated with pheochromocytoma followed by lower risk for pancreatic neuroendocrine tumor and clear cell renal cell carcinoma.^{6,7} Lower penetrance for renal cell carcinoma in case of VHL missense pathogenic variants is possibly due to the partial retention of function of VHL protein preserving inhibition of hypoxia inducible factor-1.⁵ Around 10 to 20% of pheochromocytoma are familial in origin and are associated with common genetic syndromes such as multiple endocrine neoplasia type 2, VHL, neurofibromatosis, familial pheochromocytoma syndrome as well as recently identified causative genes like succinate dehydrogenase B (SDH-B), transmembrane protein 127, and MYC associated X (MAX).⁸ Among these germ line mutations, malignant pheochromocytoma was mostly reported from SDH-B and MAX genes.⁹ Although Arg167Gln missense VHL mutation is commonly reported with benign familial pheochromocytoma, this index case shows the image findings of seldom reported locoregional recurrence of malignant pheochromocytoma and lymph node metastasis associated with this mutation.

Consent

Appropriate patient consent is obtained for publishing the images and clinical information regarding the patient without revealing patient identity.

Funding

None.

Conflict of Interest

None declared.

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