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RESEARCH ARTICLE

Insights into Bilateral Pheochromocytoma- A Clinical Case Series from South India

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Abstract

Bilateral Pheochromocytoma (PCC) is a rare condition characterized by the presence of catecholamine-secreting tumours in both adrenal glands. Hereditary Pheochromocytomas occur at a younger age and tend to be multifocal and/or bilateral at presentation. This case series presents three patients diagnosed with bilateral Pheochromocytoma, highlighting their clinical presentation, diagnostic approach, surgical management, and outcomes. All patients had sustained severe hypertension associated with the classic symptoms of Pheochromocytoma. Two patients had synchronous tumours whereas one patient had a metachronous presentation. Imaging studies including CECT abdomen and Ga-68 DOTANOC PET/CT showed bilateral adrenal lesions in all cases along with renal hilar paraganglioma in one case. Biochemical phenotype of the tumours was predominantly normetanephrine secreting type. Genetic testing done in two patients showed missense mutation (p.Arg167Gln in exon 3 and Gly93Ser in exon 1) of VHL tumour suppressor gene. All three patients underwent open bilateral adrenalectomy with resolution of symptoms and normalization of catecholamine levels. Pathology confirmed the diagnosis of Pheochromocytoma in both adrenal glands. None of them developed symptoms of adrenal insufficiency during the follow-up period. Two patients became normotensive after surgery, while one patient continues to have persistent hypertension, although with a reduced need for antihypertensive medications compared to the preoperative period. Remarkable remission of diabetes mellitus was noticed in two patients after tumour removal. This case series highlights the importance of recognizing bilateral Pheochromocytoma, the role of genetic evaluation, and the necessity for life-long follow up to optimize outcomes.

Keywords: Adrenalectomy, Bilateral Pheochromocytoma, Hereditary Pheochromocytoma, VHL Syndrome

1. Introduction

Pheochromocytomas and Paragangliomas (PPGL) are rare neuroendocrine tumours with an annual incidence of 2 to 8 cases per 1 million people[1]. These tumours occurs most commonly in the fifth to sixth decades of life with an equal gender predilection. It is often referred as the 'great mimic' because the presenting symptoms are similar to more than 30 medical disorders. A subtle terminology change is seen in the 2022 World Health Organisation (WHO) classification of Paragangliomas and Pheochromocytomas (PCC) where they defined Pheochromocytoma as "a neuroendocrine neoplasm that originated from chromaffin cells of adrenal medulla and is an intra-adrenal paraganglioma"[2]. 85% of cases arise from adrenal medullary chromaffin tissue and about 15% of cases arise from extra-adrenal chromaffin tissue. Although the majority of PPGL are benign, approximately 10% of Pheochromocytomas and around 15–35 % of extra-adrenal abdominal paragangliomas are malignant[3]. Although most of these tumours arise sporadically, a germline mutation in a known susceptibility gene can be found in approximately 30–35 % of PPGLs[4]. Bilateral Pheochromocytomas (PCC) are very rare (7–10 %) and between 60% and 90% of these patients harbours a germline mutation[5]. Classic

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hallmarks of hereditary PPGLs include a positive family history, an early age at onset, bilateral, multiple primary tumours and metastatic tumours, extra adrenal disease. In this series we report three cases of bilateral Pheochromocytoma and their management.

2. Aim and Objectives

To review familial disease and the frequency of bilateral Pheochromocytoma in the different syndromes with assessment of Indian data compared to international data.

3. Review of literature

Bilateral Pheochromocytoma has been the focus of several key case reports and series, each contributing to our understanding of its clinical presentation, diagnosis, management, and genetic underpinnings.

In a study by R. Pai *et al.,* investigating mutations in 50 cases of Pheochromocytoma and Paraganglioma (PPGL) from South India, 32% (16/50) of the patients were found to carry genetic mutations including mutations for VHL (37.5%), RET (25%), SDHB (18.7%), and SDHD (18.7%)[6] Among the cohort, 14% (7/50) of patients presented with bilateral Pheochromocytomas. Of these, 5 patients had mutations in the VHL gene, while 2 patients carried RET gene mutations.

In a study by Gaurav Agarwal *et al.*, examining the genetic profile of Pheochromocytoma and Paraganglioma (PPGL) patients from North India, genetic mutations were identified in 20% of the study population (n=50)[7]. Among those with positive genetic tests, 60% had RET mutations, while VHL and SDHB mutations were each found in 20% of patients. Bilateral Pheochromocytomas were observed in 12% (6/50) of the patients, with 3 cases linked to RET mutations and 2 cases associated with VHL mutations.

Reshma Pandit *et al.* reported on germline mutations and genotype–phenotype correlations in Asian Indian patients with Pheochromocytoma and Paraganglioma (PPGL)[8]. Among the study population (n=150), 49 patients (32.7%) were found to have germline mutations, distributed as follows: VHL: 23 (15.3%), RET: 13 (8.7%), SDHB: 9 (6%), SDHD: 2 (1.3%), and NF1: 2 (1.3%). Bilateral Pheochromocytomas were identified in 15.5% (16/150) of the patients. Of these, 6 cases had VHL mutations, 7 had RET mutations, and no mutations were detected in the remaining 3 patients.

One of the landmark reports by Neumann *et al.*,[5] provided comprehensive insights into the genetic basis of Pheochromocytomas, establishing the prevalence of bilateral tumors in patients with von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), and SDH mutations. This study highlighted the importance of genetic screening in patients presenting with bilateral adrenal masses.

Buffet *et al.* conducted a comprehensive study spanning a decade (2001–2010) to evaluate the genetic testing landscape for PPGL[9]. The study analyzed a large cohort of patients to identify the prevalence of germline mutations and assess genotype–phenotype correlations. Germline mutations were found in a significant proportion of cases (n=363), 269 in SDHx genes, 64 in VHL, 23 in RET, and 7 in TMEM127. This decade-long analysis underscored the evolving role of genetic screening in identifying hereditary syndromes, guiding personalized management, and enabling family risk assessment in patients with PPGL.

Recent advancements in surgical management were highlighted in a study by Walz *et al.*,[10] which explored the outcomes of laparoscopic adrenal-sparing surgery in bilateral Pheochromocytomas. The authors reported reduced dependency on lifelong steroid replacement while maintaining excellent tumor control in carefully selected patients. This approach has been echoed in subsequent series advocating for adrenal-sparing surgery, especially in patients with hereditary conditions.

These major reports and series collectively highlight the critical role of genetic evaluation, multidisciplinary management, and advances in surgical techniques in improving outcomes for patients with bilateral Pheochromocytoma. Asian Indians with PPGL differ from Western cohorts in having preponderance of VHL mutations in multifocal tumours and apparently sporadic unilateral PCC.

4. Materials and Methods

This case series describes three patients diagnosed with bilateral Pheochromocytoma, managed at a tertiary care centre in south India between June 2022 and August 2024. A total of 15 Pheochromocytoma

cases were operated during this period. Patients with confirmed bilateral Pheochromocytoma based on biochemical, radiological, and pathological findings were included in the study. All cases were managed by a team of Endocrine surgeons. Clinical data including detailed patient history, presenting symptoms, and family history of endocrine disorders, data on biochemical analysis, imaging studies and genetic testing were retrieved from the records. Surgical records were evaluated for the description of operative approaches and histopathological data was collected. A comparison of clinical presentations, diagnostic findings, genetic profiles, surgical approaches, and postoperative outcomes across the three cases was performed, along with a comparative analysis with the existing literature.

5. Results

5.1 Presentation of Cases

Case 1

A 33-year-old male presented with chief complaints of episodic palpitation, sweating, headache and abdominal pain for the past six months. He is a known case of recurrent Pheochromocytoma with a history of open right adrenalectomy ten years ago. He was asymptomatic for the next one year and then developed symptoms of headache and palpitation. On evaluation he was found to have a left adrenal Pheochromocytoma and he underwent an open left adrenalectomy elsewhere. He was symptom free for the next two years when he started having symptoms of episodic palpitation, headache and sweating again. He tolerated the symptoms and attributed it to the steroid tablets which he was taking. He presented to us with persistent symptoms. There was no history of proximal myopathy, bony pain, renal stones, multiple fractures, cerebrovascular accident or cardiovascular events. There was no family history of hypertension, thyroid malignancy or renal stone disease.

On general physical examination, he had a pulse rate of 120/min and a blood pressure of 220/110 mm of Hg in supine position with a postural drop to 80/60 mm of Hg. Abdominal examination showed scars of previous surgery and was negative for any abdominal mass. Laboratory testing revealed an elevated 24 hour urine total metanephrine level of 2.2mg/24hrs (NR ≤1mg/24hrs). CT (Computed Tomography) abdomen showed a thickened left adrenal gland with a 1.8 x 1.3 cm nodule arising from the medial limb of left adrenal gland. Another heterogeneously enhancing lesion measuring 2.3 x 4 x 3.2 cm was seen in the left para aortic region at the level of left renal hilum which was avid in the Ga-68 DOTANOC PET/CT scan (Figure 1(A)). ECG and ECHO were normal. After adequate alpha blockade he underwent exploratory laparotomy. Intraoperatively there was a 5x4x4 cm firm mass in the left renal hilar region adherent to renal vein and a 1.5x1.3x1 cm lesion arising from the residual left adrenal gland. Open left adrenalectomy and excision of the renal hilar mass was done. Highest intra-op BP recorded was 240/120 mm of Hg during tumour manipulation and the lowest recorded BP post excision of the lesions was 90/60 mm of Hg when he was started on ionotropic supports. Histopathological examination confirmed the diagnosis of left adrenal Pheochromocytoma and paraganglioma in the renal hilar region with a GAPP score of 2 and 4 respectively (Figure 1(B)). He got completely relieved of his symptoms and became normotensive after the surgery. Patient was discharged on post operative day 10. 24 hr urine metanephrine and nor-metanephrine done after two weeks showed normal values. On six months follow up he is asymptomatic and is on replacement dose of steroids.

Case 2

A 51-year-old male a known diabetic, came with complaints of abdominal pain, vomiting and

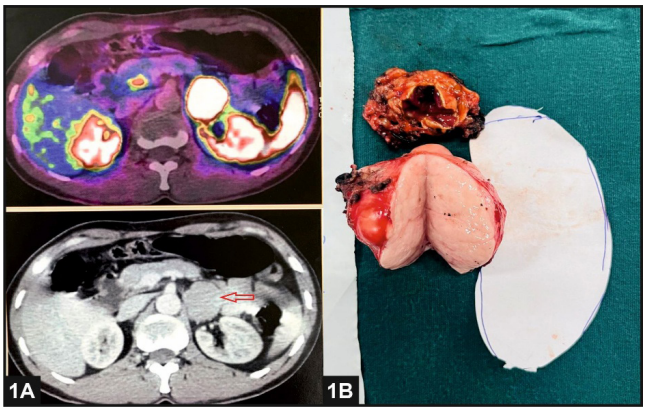

Figure 1 **(A).** Ga-68 DOTANOC PET/CT image showing left renal hilar mass. **(B)** Specimen picture showing left renal hilar mass and left adrenal mass.

palpitation with associated sweating of two weeks duration. On clinical evaluation, blood pressure was 180/100 mmHg, pulse rate was 127 beats/min, heart sounds were normal and the chest was clear. There is no thyroid enlargement, hypercortisolism features or any features of syndromic association. Abdominal examination was unremarkable and there were no palpable masses. On evaluation thyroid function was normal, renal function tests showed an elevated serum urea and creatinine (Urea 58, Creatinine 3.9). 24-hr Urine Metanephrine and Normetanephrine values were 79.8µg/24 hr (NR<400 µg/24 hr) and 373.45 µg/24 hr (NR 128-484 µg/24 hr) respectively. There was no elevation of plasma aldosterone, renin and cortisol levels. The abdominal CT showed bilateral adrenal lesions measuring 4.7 x 4.2 x 5.7 cm with foci of calcification on right side and 2.9 x 2.4 x 3.2 cm on left side. Ga68 DOTANOC scan showed avid soft tissue lesions involving bilateral adrenal glands. Treatment was initiated with alpha adrenergic blocker prazosin and calcium channel blocker Amlodipine. Later beta blockers were added. He underwent open bilateral adrenalectomy (anterior transabdominal approach). Intraoperatively right adrenal lesion measured 6 x 5 x 4cm and left adrenal lesion measured 3.5 x 3 x 2.5 cm (Figure 2(A)). Histopathological examination confirmed bilateral Pheochromocytoma with no capsular invasion or extension into the peri-adrenal adipose tissue (Figure 2(B)). The PASS score was 1 with Ki 67 <2%, which was indicative of a benign course. He was counselled for genetic testing but he was not willing for the same. The patient recovered very well from the operation and is still under our care for follow-up. 24 hour urine Metanephrines repeated after 2 weeks showed values within normal range. On follow up his blood pressure is controlled with single antihypertensive drug and he is euglycemic without any oral antihyperglycemic agents.

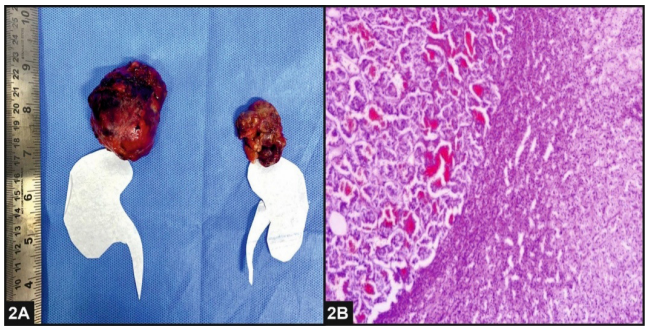

Figure 2 **(A).** Specimen picture showing bilateral adrenal pheochromocytoma(right>left). **(B)** Histo-pathology showing adrenal medulla with neoplasm consisting of tumour cells arranged in Zellballen pattern-Pheochromocytoma.

Case 3

A 42 year-old male presented with a history of abdominal pain and multiple episodes of vomiting for past one month associated with weight loss of 5 kgs over the past six months. He gives a history of left vagal paraganglioma excision six years back. He is a known case of type 2 diabetes mellitus on medication for past six years. There was no history of hypertension, any headache, sensory or motor deficits, ataxia, visual field defects or hearing loss. He gives a history of brain tumour in his father at the age of 60 years and also mentioned that his uncle was blind since childhood. On physical examination, Body Mass Index (BMI) was 16.4kg/m^2, blood pressure was 150/92 mmHg and pulse rate was 80 beats/min. Abdominal examination revealed a palpable intra abdominal mass in the left hypochondrium which was firm and non tender. Systemic examination was unremarkable. Basic blood investigations were normal except for low haemoglobin (8.3g/dl). Plasma nor metanephrine was raised 1002 pg/ml (NR<216), plasma metanephrine levels were normal (22 pg/ml, NR<100). Serum cortisol, plasma aldosterone and DHEA levels were normal. Serum gastrin levels were 203 pg/ml(<180pg/ml). ^{68}Ga DOTANOC whole body PET CT showed a heterogeneously enhancing retroperitoneal soft tissue mass with central necrosis of size 9.3 x 8.5 x 9.4 cm (SUV max=4.5) in the left adrenal region and a similar enhancing lesion of size 3.2 x 2.3 cm (SUV max =4.1) involving right adrenal gland (Figure 3(A)). Few tiny enhancing foci (9x7mm) were noted in the posteromedial aspect of head and uncinate process of pancreas with no uptake. ECHO showed mild concentric left ventricular hypertrophy. Treatment was initiated with alpha adrenergic blocker prazosin and beta blockers were added four days before surgery. Open bilateral adrenalectomy was done. Tumour on the left side measured 9.5 x 9 x 5cm and right side measured 4 x 3.5 x 3cm in size (Figure 3(B)). Histopathology suggested bilateral adrenal Pheochromocytoma with no capsular or vascular invasion or extension into

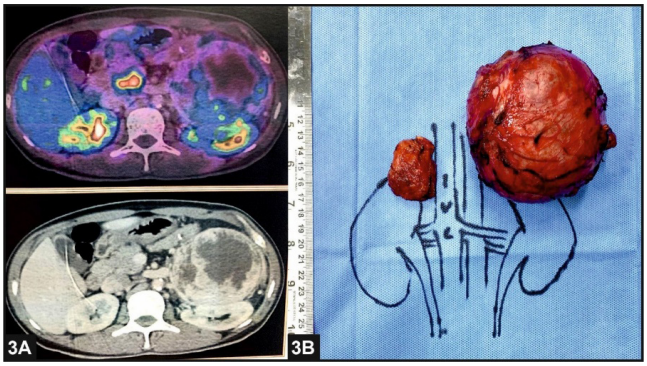

Figure 3 **(A).** 68Ga DOTANOC PET CT showing bilateral adrenal lesions. **(B)** Specimen picture showing bilateral pheochromocytoma (Left>right).

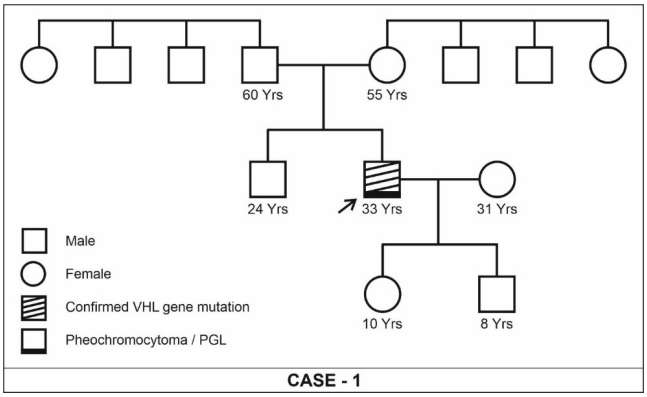

Figure 4. Pedigree chart, Case 1.

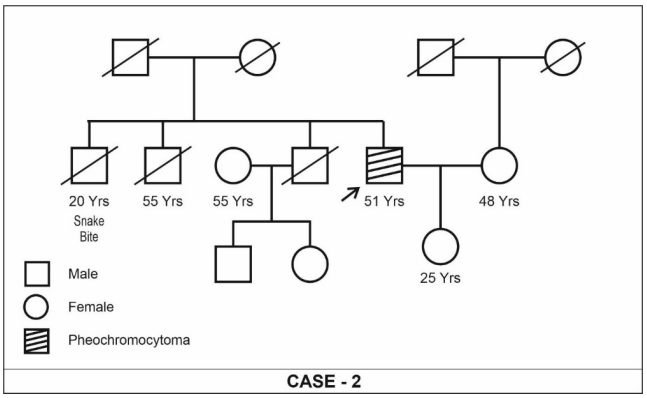

Figure 5. Pedigree chart, Case 2.

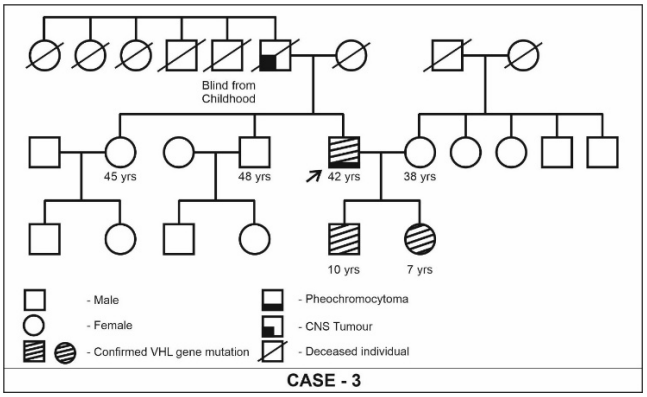

Figure 6. Pedigree chart, Case 3.

the peri-adrenal adipose tissue with a PASS score of 2/20.Genetic testing showed missense mutation (p.Arg167Gln in exon 3) of VHL tumour suppressor gene which classifies him under type 2 VHL disease. He doesn't have any other associated features of the syndrome at present. On genetic screening of the family, his son and daughter was found to have VHL gene mutation and they have been advised screening for the same. He became normotensive and achieved euglycemic status after surgery and was started on replacement dose of steroids and he is doing well on 7 months follow up.

Pedigree charts (Figures 4, 5, 6) shows the family tree of each case with affected family members.

6. Discussion

Bilateral Pheochromocytomas are more frequently associated with syndromes like Multiple Endocrine Neoplasia (MEN) type 2A and type 2B, von Hippel– Lindau disease (VHL), the paragangliomas syndromes types 1 and 4 caused by mutations in the Succinate Dehydrogenase Subunit D (SDHD) and B (SDHB) genes, respectively and less commonly with neurofibromatosis type 1 (NF1), SDHA, SDHC, SDHAF2), transmembrane protein 127 (TMEM127), MYC-associated factor X(*MAX*)[5]. A minority of bilateral tumors appear in sporadic cases as well. Paragangliomas can arise from both the sympathetic and parasympathetic nervous systems. 80-90 % of parasympathetic paragangliomas are non- functional and are located in the skull base, neck and upper mediastinum. Around 75% of functioning sympathetic paragangliomas arise in the abdomen, most frequently at the junction of the vena cava and left renal vein or at the organ of Zuckerkandl[11]. Identifying the rare patient with PPGL is a diagnostic challenge to the physicians as they present with symptoms mimicking other medical disorders.

The median age at diagnosis of bilateral tumours is 30 years (IQR 22-41) which is lower than the unilateral

tumours[5]. Two patients in our series were more than 40 years at the time of diagnosis. Two patients had synchronous tumours whereas one patient had a metachronous presentation. Genetic testing done in two of our patients showed missense mutation (p.Arg167Gln in exon 3 and Gly93Ser in exon 1) of VHL tumour suppressor gene located on chromosome 3p25-26. Based on the genotype phenotype correlation VHL patients are divided into two types. Type 1 includes the full phenotype of CNS hemangioblastomas (cerebellum, spinal cord, brainstem), retinal angioma, cysts or solid tumors in the brain, spinal cord, pancreas, kidney, spleen, Renal Cell Carcinoma (RCC), pancreatic neuroendocrine tumours, endolymphatic sac tumours, papillary cystadenomas of epididymis, broad ligament but no Pheochromocytoma. Type 2 is divided into type 2A, B and C based on the risk of development of Pheochromocytoma. Patients with type 2A have a low risk of RCC while type 2B patients have a high risk of RCC. VHL type 2C confers an increased risk of Pheochromocytomas without other manifestations of the disease[12]. Average age of detection of PCC in VHL disease is 20-29 years[13]. In VHL 10-25% of patients develop Pheochromocytoma. The incidence of VHL is approximately one in 36,000 and the lifetime penetrance approaches 100% by age 75[14]. Our patients didn't have any other phenotype expression of VHL at the time of presentation.

In a report of the National Institute of Health about 64 patients with VHL disease and Pheochromocytomas, a total of 106 tumours were identified. Of these, 12% originated outside the adrenal gland, and 35% of the patients were asymptomatic, without hypertension or evidence of increased catecholamines production[15]. Our patients had sustained severe hypertension associated with the classic symptoms of Pheochromocytoma and one patient had a paraganglioma along with PCC. Pheochromocytomas associated with VHL has an exclusively noradrenergic phenotype with predominant production of norepinephrine. Our cases were predominantly normetanephrine secreting type. Remarkable remission of diabetes mellitus was noticed in two of our patient after tumour removal. Catecholamine excess affects insulin secretion, causes increased insulin resistance and decreased glucose uptake in the peripheral tissues leading to overt diabetes mellitus[16]. Prior studies have shown that the incidence of long-term persistent hypertension following PPGL surgery ranges from 10% to 43.8%[17]. Two patients in our series became normotensive after surgery, while one patient continues to have persistent hypertension, although with a reduced need for antihypertensive medications compared to the preoperative period.

In bilateral Pheochromocytomas, total adrenalectomy vs cortical sparing adrenalectomy remains an open question. The 2014 Endocrine Society management guidelines recommend cortical-sparing adrenalectomy for bilateral and hereditary Pheochromocytoma based on low grade of evidence[18]. Although favourable short-term outcomes are reported from few specialised centres uncertainty remains because of the risk of metastatic Pheochromocytomas (>10%) and the potential of developing new ipsilateral Pheochromocytomas[19]. In the multicenter consortium-based registry of 625 patients treated for bilateral Pheochromocytomas, 39.6% patients underwent cortical sparing adrenalectomy and found that 23% of patients developed adrenal insufficiency, requiring lifelong steroid replacement. All patients undergoing bilateral total adrenalectomy became steroid dependent[5]. All three patients in our series underwent total adrenalectomy and are currently on replacement steroids (Prednisolone 5mg and Fludrocortisone 0.1mg). None of them developed symptoms of adrenal insufficiency during the follow-up period.

On screening the family members of our patients, none of them were found to be hypertensive but VHL gene mutation was found in the first-degree relatives of patient#3. Due to the risk of recurrence and metastatic disease, post-surgical surveillance is mandatory for all PPGL patients. A personalised syndrome-based approach is required for the same. Post surgical follow up of PPGL associated with VHL disease includes an annual measurement of plasma free metanephrine and normetanephrine. Annual MRI of abdomen and optic fundus examination, CNS MRI every 2-3 years is also recommended[20,21].

Patient #3 in our series had a past history of Vagal paraganglioma. Most patients with Head and Neck Paragangliomas (HNPs) caused by germline mutations have alterations in one of the following genes: SDHB, SDHC, or SDHD. The occurrence of HNPs in non-SDHx paraganglioma syndromes, such as VHL and MEN2, has been reported only anecdotally[22]. Hence

this is a rare case of synchronous bilateral PCC with a history of HNP in VHL mutation.

The frequency of bilateral Pheochromocytoma varies across populations and syndromes, reflecting genetic and environmental differences. According to the data from European-American-Asian-Bilateral-Pheochromocytoma-Registry which included 625 patients with bilateral disease, 64% patients had synchronous disease and 36% patients had metachronous disease[5]. MEN 2 was the most frequent genetic mutation found (53.6%) followed by VHL (35%) and NF1 (3.2%). In a study by Sofia Maria *et al.,* involving 14 patients with bilateral Pheochromocytomas, 64.2% presented with synchronous bilateral tumors, while 35.7% had contralateral metachronous tumors[23]. Among these patients, 78.5% were found to have a germline mutation, including eight with RET mutations linked to MEN2A syndrome, three with VHL syndrome, and three who were not tested.

International data indicates a predominance of RET-associated bilateral PCC, whereas VHL syndrome is reported as the most common cause of bilateral Pheochromocytoma in the Indian patients. Studies by R. Pai *et al.,* and Reshma Pandit *et al.,*[6,8] report bilateral Pheochromocytomas in 14% and 15.5% of their cohorts, respectively, with the majority linked to VHL mutations. Among bilateral cases, VHL mutations account for approximately 37-40 %, reflecting a strong genotype-phenotype correlation.

7. Conclusion

Our series adds to the genetic mutation data for the Indian PPGL patients which can aid in understanding their profile, clinical presentation and emphasising need for genetic testing. Our findings align with other Indian studies, highlighting that Indian patients with PPGL differ from Western cohorts by exhibiting a higher prevalence of VHL mutations in multifocal tumors and apparently sporadic unilateral PCC. Hereditary PPGLs are characterised by a unique molecular-clinical-biochemical-imaging phenotype and a personalised approach to patient management is required. A close follow-up of these cases with VHL mutations will help in the early detection of other tumors thereby reducing morbidity and mortality and will profoundly alter the management of these patients.

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