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Pathology

Adrenal and Extra Adrenal Paragangliomas: A Clinico Pathologic Analysis

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Abstract **Original Research Article**

Introduction: Catecholamine producing tumours are termed as "pheochromocytomas" in the adrenal medulla and "paragangliomas" in an extra-adrenal location. Presenting features are mostly explained by catecholamine production. The diagnosis is based on detection of mass lesion coupled with biochemical and radiological correlation. ***Materials & Methods:*** The present study is a retrospective and prospective study done for a period of seven years. All the detailed clinical history and all relevant investigations were noted. Along with clinical details, radiological and histopthological findings were also considered. ***Results:*** A total of 70 cases (34-adrenal and 36 extra-adrenal) were included in the study. In 34 pheochromocytomas, the age range was 8-60 years with 16cases (45.45 %) of males and 18 females (54.54 %). Familial association was seen in 2(6.06%) cases- one each of MEN I and IIB; Rest all were sporadic (93.94%). The most common presenting feature was headache which was seen in 30/33(90%) cases, followed by hypertension in 28/33(85%) cases. Other symptoms seen were palpitations, anxiety and diaphoresis. And asymptomatic in 2 cases (6.06%). ***Conclusion:*** Adrenal pheochromocytomas and extra adrenal paragangliomas are rare tumours originating from neural crest cells. Adrenal pheochromocytomas are most common in the age group of 20–30 years (3^{rd}-4^{th} decade). Hence, in Indian population pheochromocytomas occur in earlier age group compared to Western population. There is equal gender distribution of adrenal pheochromocytomas in Western studies, while the present series shows female predominance. Most common clinical triad of presentation was headache, hypertension and palpitations. Around 90% of patients have these symptoms. Anxiety and mass per abdomen were other clinical presentations. Adrenal pheochromocytomas are functionally active in 75% cases, with elevated levels of VMA and catecholamine levels. Most of the adrenal masses were distributed in right side compared to left side. Two cases were bilateral in distribution.

Keywords: Paraganglioma, adrenal, extra adrenal, pheochromocytoma.

INTRODUCTION

Pheochromocytomas are relatively uncommon tumours with a prevalence of 0.3% to 0.95% in autopsy series. Patients with pheochromocytomas have a potentially curable cause of hypertension and if undetected pheochromocytomas present a high risk of morbidity and mortality especially during surgical procedures and pregnancy. Tragically as many as 50% of the pheochromocytomas are discovered at autopsy, mainly because the diagnosis of this neuroendocrine tumour is not considered. Missing the diagnosis almost invariably results in devastating cardiovascular complications or death.

Clinicians must always think of pheochromocytoma whenever evaluating a patient with sustained or paroxysmal hypertension or any manifestations suggesting hypercatecholaminemia. Very rarely, familial pheochromocytomas may cause any hypertension symptoms or signs. But biochemical testing can always establish the presence or absence of a pheochromocytoma, and localization with magnetic resonance imaging, computed tomography, or ^{131}I or ^{123}I-MIBG is almost always possible.

Catecholamine secretion in pheochromocytomas is not regulated in the same manner as in healthy adrenal tissue. Unlike the healthy adrenal medulla, pheochromocytomas are not innervated, and catecholamine release is not precipitated by neural stimulation. The trigger for catecholamine release is unclear, but multiple mechanisms have been postulated, including direct pressure, medications, and changes in tumour blood flow.

Relative catecholamine levels also differ in pheochromocytomas. Most pheochromocytomas secrete norepinephrine predominantly, whereas secretions from the normal adrenal medulla are composed of roughly 85% epinephrine. Familial pheochromocytomas are an exception because they secrete large amounts of epinephrine. Thus, the clinical manifestations of a familial pheochromocytoma differ from those of a sporadic pheochromocytoma.

MATERIALS & METHODS

This study is both prospective and retrospective in nature. All the cases of adrenal and extra adrenal paragangliomas presented to the Department of pathology, have been included in this study, which was approved by the Institutional Ethics Committee.

For retrospective cases clinical history was collected from the institute's Medical Record Department and concerned department registers. For prospective study all surgical specimens sent to the Department of Pathology for histopathological examination in 10% formalin were included. Few cases from other institutions submitted for opinion were also included in this study.

The demographic data, clinical presentation, imageological data (wherever available) and pathologic details were recorded for each case (proforma enclosed).

RESULTS

All surgical specimens diagnosed as adrenal pheochromocytoma and paraganglioma were analysed. A total of 70 cases formed the study material, which included 34 cases of adrenal pheochromocytomas and 36 cases of extra adrenal paragangliomas in various locations.

In 34 cases of pheochromocytoma, 33 cases (96.9%) were sporadic in onset; one case (3.1%) was familial with MEN 2B association.

Among 33 cases of sporadic pheochromocytomas, 31 (93.9%) cases were benign pheochromocytomas, one case was composite pheochromocytoma with pheochromocytoma and ganglioneuroma juxtaposed side by side of benign nature and one case was malignant pheochromocytoma with supra clavicular lymph node metastasis. One case was an autopsy finding.

Most common presenting symptoms were hypertension, headache, anxiety, diaphoresis and mass per abdomen. Thirty patients presented with headache and 28 patients reported with hypertension. Only two patients were asymptomatic who were diagnosed during routine health checkups as mass per abdomen (incidentalomas). Clinical presentation was not available in one patient (Table-1).

Table-1: Clinical presentation in adrenal pheochromocytomas

Clinical Presentations	Number Of Patients	Percentage (%)
Headache	28	93.3
Hypertension	27	90.0
Palpitations	25	83.39
Anxiety / perspiration	27	90.0
Abdominal mass (Ultra sonography)	26	86.6
Asymptomatic	2	6.6
No history available	1	3.03

Among 30 patients of pheochromocytomas, biochemical evaluation of vanillyl mandelic acid level (VMA) was available in 22. VMA levels were elevated in 17 (74.6%) patients and were within normal range in 5 (22.7%) cases.

Pre-operative blood pressure fluctuation and post-operative hypertension were present in 4 /30 (13.39%) patients.

Out of 30 cases, surgical specimens were submitted in 29 cases (adrenalectomy specimens) to department of pathology and in one case, only slides were available.

21/30 (70.6%) adrenal pheochromocytoma was located on right side and 8 (26.6%) on left side and one tumour was bilateral (3.33%). Out of 30 cases, gross specimens were mainly single lesions in 28 (93%) cases and 2 (6%) were multicentric in location.

All surgically resected specimens sent for histopathological examinations were enlarged in size with alteration in shape. Size varied from 3.5 cms to 14 cms (normal weight of adrenal 5-6 gms). The weight of the tumour ranged from 20-650 gms (mean 82 gms).

Most of the specimens were well encapsulated externally. Cut section of specimens showed homogeneous grey white appearance in 8 cases (26.6%) and remaining 21 (76.64%) cases showed grey white areas with focal haemorrhagic areas and calcification. All the specimens turned tan to brown colour on immersion in 10% formalin solution.

Microscopically all adrenal pheochromocytomas showed "Zellballen" pattern. Cells were arranged in nests, trabeculae separated by vascular channels and fibrous septae (Figure-1). Most of them had similar morphology with bland looking benign cells but, pleomorphism was seen in 11 (36.6%) cases, foci of necrosis in 5/30 (16.6%) cases. Mitoses were sparsely present in many cases but 3 (10%) cases showed frequent mitosis >3/10 high power field. Foci of necrosis was seen in 4/30 (13.3%) cases. Focal hyalinisation was seen in 20 cases (66.6%) while 2 (6%) cases had extensive hyalinisation. 30/30 of sporadic cases showed no evidence of any tumour emboli or vascular emboli. Native adrenal tissue was present in 27 cases (90%).

In the present study, 36 cases of extra adrenal paragangliomas were included, with the most common location being head and neck region. Carotid body (17/36) followed by spinal (extra dural) paraganglioma (5/36) and glomus jugulare (3/36) were most common locations observed in the head neck region. Other sites were external ear, nose, central nervous system (falx cerebri), tympano mastoid and parapharyngeal space.

Fig-1: Gross appearance of pheochromocytoma Adrenal

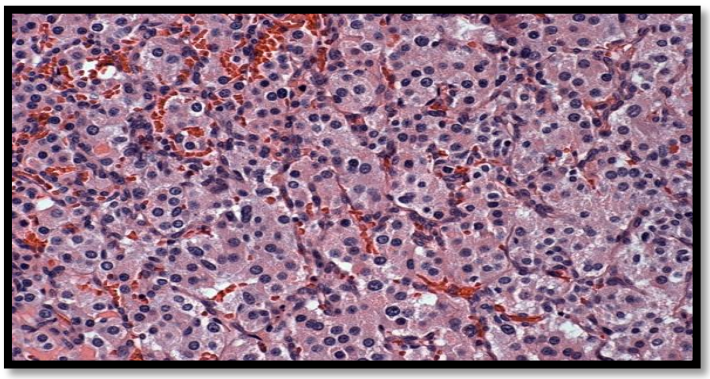

Fig-2: Section showing Pheochromocytoma showing nests of cells arranged in Zell ballen pattern [H&E,x40]

DISCUSSION

The World Health Organization reserves the term pheochromocytoma for tumours arising from chromaffin cells in the adrenal medulla. Closely related tumours in extra-adrenal sympathetic and parasympathetic ganglia are classified as extra-adrenal paragangliomas. A pheochromocytoma is an intra-adrenal sympathetic paraganglioma [1].

Pheochromocytomas are estimated to occur in 0.05-0.3% of hypertensive patients [2]. The chromaffin cells of adrenal medulla originate from the neuroectoderm. Sympathetic neurons are formed from the same precursors, which migrate to their destinations adjacent to the arterial vessels and cranial nerves of the head and neck, and sympathetic plexus and chains in the neck, thorax, abdomen and pelvis [3]. Ten to twenty per cent of pheochromocytomas develop in these ectopic sites [4] the organs of Zuckerkandl being one of the most frequent sites.

Pheochromocytoma is the "tumour of tens:" 10% are extra-adrenal, 10% are bilateral, 10% are malignant, 10% are found in asymptomatic patients, and 10% are hereditary [5]. The incidence of pheochromocytoma is <0.5% in patients with hypertensive symptoms[6] and can be as high as 4% in patients with adrenal incidentalomas [7].

Classic triad of pheochromocytoma presentation is episodic headache, sweating, and palpitations [8, 9].

The presenting symptoms are manifestations of catecholamine excess, and include hypertension (56 to 90%), headache (49 to 56%), sweating (44 to 47%), palpitations (34 to 37%), dizziness (15%), anxiety

(15%), and hypertension during anaesthesia (7%). In the present study, headache (90%) was the most common presentation followed by hypertension. (84%) Other features were less common.

Biochemical testing for possible pheochromocytoma is usually done with 24-hour urine collection for metanephrines and vanillyl mandelic acid (VMA), with a false negative rate of only 2%. In the present study, VMA level was raised in 17/33(54.8%) cases which is less when compared to that reported in literature.

The morphology of classic pheochromocytomas and paragangliomas at other sites has been well described. A fraction of these cases may occur in combination with ganglioneuroma. One of our cases was a composite pheochromocytoma belonging to this category- a finding that has only occasionally been reported in literature [10, 11].

Although most pheochromocytomas are typically well-encapsulated, localized benign growths, approx. 5–10% are malignant, which is more common among extra-adrenal tumours. Because histopathology is not reliable, malignancy is diagnosed by distant metastatic spread of the tumour, commonly to the bone, lung, lymph nodes or liver. Currently, only the presence of *SDHB* gene mutation suggests a high probability of malignant disease, up to 35%. One patient in our study had malignant pheochromocytoma.

Prior to 2000, it was generally accepted that 10% of pheochromocytomas were associated with familial syndromes; however, it is now recognized that the frequency of germ line mutations in apparently sporadic presentations is as high as 15%–24% [12, 13].

Amongst extra-adrenal pheochromocytomas, carotid paragangliomas are the most common paraganglioma of the head and neck comprising approximately 60% of the total. Spinal (vertebra), glomus jugulare, retroperitoneal location

CONCLUSION

Correlating the histomorphology and immunohistochemistry with clinical, radiological, biochemical, and surgical findings, it may be concluded that adrenal pheochromocytomas and extra adrenal paragangliomas are treatable, but produce devastating complications when under-diagnosed. Hence, high degree of clinical suspicion of paraganglioma is needed in young patients who clinically present with high blood pressure and headache.

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