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Pheochromocytoma - Histopathological and Clinical Update

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Abstract: ***Background: The pheochromocytoma or paraganglioma PPGL is a metabolically active tumor originating from the chromaffin cells of adrenal medulla (pheochromocytomas) or from sympathetic or parasympathetic autonomic ganglia (paragangliomas).The exact incidence of pheochromocytoma is unknown, but it is estimated to occur in 2–8 cases per million people per year. It has been termed the great masquerader since clinical characteristics may mimic large variety of disease & result in erroneous diagnosis The estimated prevalence of pheochromocytoma in hypertensive adults is thought to range from 0.1 to 0.6%.The foremost investigation in cases where pheochromocytoma is suspected is usually increased urinary and plasma levels of catecholamines and their metabolites (metanephrines, normetanephrines & VMA). Radiological investigations are performed to localize the tumor in cases where blood works confirm the presence of this tumor. Histopathological and immunohistochemical features are accustomed to authenticate the diagnosis. Aim: In this study, the most frequently diagnosed tumor of adrenal gland-Pheochromocytoma along with their detailed histopathological, biochemical and clinical characteristics were studied in detail. Material and Method: A retrospective 5 year study was carried out from 2015 to 2019 of pheochromocytomas. Brief clinical history was taken along with other relevant biochemical investigations, hormonal assays and radiological findings. Histopathological data was collected and relevant details were noted from the records maintained in the department of pathology at SKIMS Srinagar. Routine Hematoxylin and Eosin stain andchromaffin reactions were employed. Immunohistochemistry was done wherever required. The clinical and findings of H&E sections, special stains and immunohistochemistry were compiled to arrive at a final diagnosis. The results of the study were compared with the literature. Results: Out of 70 cases of adrenal masses, pheochromocytoma (31 cases) was the most common tumor observed. The most common symptom was hypertension, followed by sweating attacks along with palpitations.CT scan done on 28 cases revealed heterogenous mass which showed greater enhancement on contrast phase.The 24-hr urinary levels of VMA was elevated in 16 (51.6%) cases of pheochromocytoma and the values were ranging in between 44.5mg-76mg/24h.Grossly, cut-section was dark brown due to chromaffin reaction.7 cases were showing cystic degeneration and confluent necrosis was present in 14 cases and 3 cases showed vascular invasion histologically. Pass score was ≥4 in 9cases and <4 in remaining 22 cases. Immunohistochemistry panel used included chromogranin, synaptophysin, S- 100, Melan-A, Inhibin, PanCK (AE1, AE30) out of which positivity for Chromogranin, S-100, synaptophysin was noted. Conclusion: We conclude that the following clinicopathological parameters should be taken into account for proper diagnosis and risk assessment of malignant behavior of pheochromocytoma.- proper clinical evaluation biochemical markers, location, size, PASS score, Immunohistochemical markers. Application of these criteria to a large cohort of cases will help in clinical practice.***

Keywords: Pheochromocytoma, hypertension, VMA, PASS score, IHC markers

1. Introduction

The World Health Organization (WHO) reserves the term *pheochromocytoma* for adrenal medullary paraganglioma. Closely related tumors in extra-adrenal sympathetic and para- sympathetic paraganglia are classified as extra-adrenal paragangliomas (EAPs).The exact incidence of pheochromocytoma is unknown, but it is estimated to occur in 2–8 cases per 1 million people per year. [1]

2. Clinical Presentation

Pheochromocytoma present with wide morphological spectrum and clinical manifestation, which can give rise to diagnostic confusion. [2]

The rare but classical cause of uncontrolled secondary hypertension with minority showing superimposed paroxysmal hypertensive crises. patient may present with cardiac and neurological events. [3] Pheochromocytoma are characterized by variable hormonal activity, depending upon their size.Small tumors are usually more active secreting large amount of catecholamines into the bloodstream. [4]. In pheochromocytoma patients, increased 24 hour urinary excreation of VMA was more frequent than in patients of other adrenal tumors. Patients with malignant pheochromocytoma found to have increased dopa levels and therefore it is the hypotensive effect of dopa that is regarded as the possible explanation of normal blood pressure in subset of patients. [5]

Radiological Presentation

The first and foremost investigation in suspected cases of pheochromocytoma is catecholamines and its metabolites levels followed by imaging to localize the tumor. CT is the first imaging modality to be used as 98% of tumors located in abdomen of which 90% are in adrenal gland. Pheochromocytomas are large, heterogenous masses with areas of necrosis and cystic change and tend to have greater enhancement on contrast phase. [6] Sometimes these lesions are clinically suspected, but more often they are incidentalomas (i.e., adrenal masses discovered during diagnostic testing for another condition), which represent tumors or tumor-like conditions that a radiologist will initially assess, categorize, and potentially diagnose, thus influencing the trajectory of clinical management (7). In

our study we are discussing about the most common tumor of adrenal gland, the pheochromocytoma having 31 cases out of 70 cases, with clinicopathologic findings.

Histopatholgy

Symptoms are often due to adrenergic excess, and the diagnosis is supported by elevated levels of circulating or excreted metanephrines and normetanephrines and VMA end products of catecholamines metabolism. [8] The adrenal masses encountered in clinical practice are functioning/non-functioning and also most of the masses are nonpalpable. Even if they are palpable, there size and extent of lesion is not possible. With the advent of imaging modalities like CT, MRI & I-131 MIBG scintigraphy majority of the masses can be easily detected in patients and the diagnosis is confirmed on histopathology. [7]

In the adult, the adrenal medulla occupies 8 to 10 % of gland volume and has an average weight of 0.44gms [9]. The major portion of medulla lies within head of the gland and tail does not normally contain medullary tissue. Medulla is composed of chromaffin cells that are arranged in nests or sheets and produce catecholamines, both epinephrine and norepinephrine with epinephrine predominating. Chromaffin cells are typically concentrated in the head (inferomedial) and body (central) of the gland [7]. At gross examination, the tumors are usually well-circumscribed masses ranging in size from 3–5 cm [8].

One of the most utilized score of Pass are most useful because of their reliance on histologic features. These include large nest or diffuse growth (more than 10% of volume), confluent necrosis, high cellularity, cellular monotony, tumor cell spindling, mitotic figures >3/10 HPF, atypical mitotic figures, extension into adipose tissue; each of them given a score of 2. Vascular invasion, capsular invasion, nuclear pleomorphism and nuclear hyperchromasia; each of them is given score 1 and the total score is 20. A PASS score <4 or ≥4 and usually suggest benign vs malignant lesion respectively [10].Pheochromocytoma are usually negative for cytokeratins. They exhibit positivity for chromogranin, synaptophysin and S-100.

3. Aims and Objective

The goal was to study the most frequently diagnosed adrenal neoplasm by taken into account both histopathological and clinical parameters.

4. Materials and Methods

A five year study was conducted and included all the adrenal specimens as well as biopsies received in the Department of pathology at Sher-i - Kashmir Institute of Medical sciences (SKIMS) Srinagar, Kashmir.

The retrospective study was carried out from 1st Jan 2015 to 31st Dec. 2019 comprised of adrenal masses. In each case brief clinical history was taken along with other relevant biochemical investigations, hormonal assays and radiological findings were recorded. Histopathological data was collected and relevant details were noted from the records maintained in the department of pathology at SKIMS.

Samples were collected in 10% formalin for routine histopathological examination. After overnight fixation each specimen were grossed thoroughly. Representative bits were taken, subjected to routine processing, embedded in paraffin, stained with routine Hematoxylin and Eosin. Immunohistochemistry was done wherever required. The findings of H and E sections, special stains and Immunohistochemistry were compiled to arrive at a final diagnosis. The results of the study were compared with the literature.

Statistical Methods

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA).

5. Results and Observations

The study was conducted on a total of 70 cases of adrenal gland out of which pheochromocytoma (31 cases) was the most common tumor observed as shown in [table-1].Age ranged from 24 to 70 years and was predominantly seen in females. [table- 2]. More common on right side and mean weight of the lesion was 82.5gms. [table-3]. The most common symptom was hypertension, 6 cases were showing sweating attacks along with palpitations and rests of the patients were asymptomatic. [table-4]. CT scan was done on 28 cases revealed heterogenous mass which showed greater enhancement on contrast phase. [table-5]. VMA was the most common biochemical test done. The 24-hr urinary level of VMA was elevated in 16 (51.6%) cases of pheochromocytoma and the values were ranging in between 44.5mg- 76mg/24h. [table-6]. Grossly out of 31 cases of pheochromoctoma 26 cases were well-encpsulated. cut-section was dark brown due to chromaffin reaction.7 cases were showing cystic degeneration and necrosis was present in 11 cases. [table-7]. The microscopic findings showed cellular monotony in 9 cases. None of case revealed tumor cell spindling. Zellbalen was the most common pattern followed by solid and one case showed alveolar pattern. Confluent necrosis was present in 14 cases and 3 cases showed vascular invasion [table-8]. PASS scoring was done to demonstrate benign vs malignant behavior of the tumor histopathologically. Pass score was ≥4 in 9 cases and <4 in remaining 22 cases. Out of 9 cases in which Pass was ≥4, three cases were clinically malignant and 2 cases were clinically benign. All the cases in which Pass was <4 were clinically benign.4 cases in which pass was 6 had benign behavior, thus pass score between 4 and 6 need long term follow up. [table-9]. Immunohistochemistry panel used included Melan-A, Inhibin, PanCK(AE1, AE30), synaptophsin, chromogranin, S-100 as shown in table-10

Table 1

Mass	Frequency	Percentage
Total cases	70	100
Pheochromocytoma	31	44.3

Mean Age of Pheochromocytom

Table 2: Showing mean age of various masses

Mass	Mean	SD	Min	Max
Pheochromocytoma	39.7	14.25	24	70

Table 3: Mean Weight in GMS of Pheochromocytoma.

Mass	Mean	SD	Min	Max
Pheochromocytoma	82.5	203.94	2	900

Table 4: Showing clinical symptoms of pheochromocytoma

Mass	Sweating attacks HT & palpitatinon	Virilization	Muscle weakness	Abdomin al mass (palpable)	HTN
Pheochromocytoma	6	0	2	15	18

Table 5: Radiological findings on CT

Mass	CT Done	CT Not Done
Pheochromocytoma	28	3

Table 6: Biochemical tests and hormonal assays

Biochemical levels	Increased	Decreased	Normal	Not Done
VMA	16	0	4	11
ACTH	-	-	-	-
Aldosterone	2		8	21
Cortisol			11	20
DHEAS			5	25

Table 7: Gross findings (Pheochromocytoma)

	Gross Findings	Frequency
Capsule	Well Encapsulated	26
	Partially Encapsulated	4
	Not Encapsulated	1
Color	Grey Yellow	12
	Grey Brown	9
	Cystic grey yellow	4
	Cystic grey brown	3
	Nodular grey yellow	2
	Nodular grey brown	1

Necrosis Present 11
Absent 20

Table 8: Microscopic findings (Pheochromocytoma)

	Microscopic Findings	Frequency
Cellular Monotony	Present	9
	Absent	22
Tumor Cell Spindling	Present	0
	Absent	31
Pleomorphism	Present	21
	Absent	10
Cellular pattern	Alveolar pattern	1
	Zellbalen Pattern	23
	Solid	7
Chromatin	Salt &pepper	19
	Non Specific	12
>3 Mitosis per10 HP	Present	13
	Absent	18
Hemorrhage	Present	18
	Absent	13
Confluent Necrosis	Present	14
	Absent	17
Vascular Invasion	Present	3
	Absent	28
Capsular Invasion	Present	2
	Absent	29

Table 9: PASS Scoring system

Scoring System	Frequency
< 4	22
≥ 4	9
Total	31

Table 10: Immunohistochemistry in various adrenal neoplasms

Tumor type	Markers done (frequency)	Inhibin	Melan-A	Synaptophysin	Chromogranin	S-100
Pheochromocytoma	21	-	-	+	+	+
				17/21	19/21	16/21

6. Discussion

Distribution:

Pheochromoctoma has been called 10% tumor. However the current literature depicts that >30% cases are associated with familial syndromes such as Men type-II, VHL, Neurofibromatosis type -1 with involvement of RET, VHL, NF1 gene respectivel. Other genes involved are SDHC &SDHB out of which SDHB gene is associated with metastatic malignant tumors. The newer genes are identified are SDHA, SDHAF2, & TMEM127. [11] In our study, out of 70 cases, pheochromocytoma was the most common tumor which is comparable to a study conducted by Patel RD et al, 2012 [12] in which pheochromocytoma was the commonest adrenal tumor noted in 68.9% (n = 20). Similarly in a study conducted by kumari NS et al 2016 [13] pheochromocytoma was the most common tumor found in 50% of cases

Age

The age group in our study was ranging between 2 to 70 years. They can occur at any age. We found the mean age was 39.7 years for pheochromocytoma. Which was comparable to study conducted by Patel RD et al, 2012 [12]. Billimoria KY et al, 2008 [14] comparable to our study.

Gender

In our study, pheochromocytoma were seen more in females compared to males.which was consistent in a study conducted by Gao et al [15] 2007, and Audenet et al., 2013 [16] found incidence of Pheochromocytoma more in females which is in line with our study.

Weight

Mean weight of pheochromocytoma was 82.5±203.94 (range 2-900 grams). Study conducted by **Lester D.R Thompson [**10] mean weight of pheochromocytoma was 222 grams.

Laterality:
In our study, Pheochromocytoma was more common on right side which is consistent with our study conducted by **Fitzgerald et al., 2006 [17]**.

Symptoms
In our study most common presenting clinical features was hypertension in pheochromocytoma, Similar results were observed in a studies conducted by **Gavin Low and Kamal Sahi [18]; Mehdiabadi et al., 2013 [19]**.

Biochemical marker
In a study conducted by **Maniraman D et al 2016 [20]** and **Patel R.D** et al, [12] and VMA levels were elevated in 55% of cases of pheochromocytoma which is comparable to our study.

Gross findings
In our study most cases of pheochromocytoma were well-encapsulated. 12 cases were grey-yellow, 9 were grey brown, 7 were cystic and 3 were nodular. Necrosis was present in 11 cases. In a study conducted by **Patel R.D et al, [12]** pheochromocytoma tumors were soft to firm in consistency, well circumscribed with variegated appearance, yellow brown in color and showing rare areas of hemorrhage and necrosis and surrounded by thick fibrous capsule in all cases.

Histopathological findings of pheochromocytoma
In our study out of 31 cases, Zellbalen pattern was seen in 23 cases, solid pattern in 7 cases and 1 case had alveolar pattern. Capsular invasion was seen in 2 cases and vascular invasion was seen in 3 cases. Confluent necrosis was seen in 14 cases and haemorrhage was present in 18 cases. Mitosis was present in 13 cases.

Similarly in a study conducted by **Patel R.D et al, [12]** Histopathological features were comparable with our research, However none showed features of malignancy in the form of capsular invasion or distant metastasis. In our study most cases of pheochromocytoma were well-encapsulated. 12 cases were grey-yellow, 9 were grey brown, 7 were cystic and 3 were nodular. Necrosis was present in 11 cases. pheochromocytoma tumors were soft to firm in consistency, well circumscribed with variegated appearance, yellow brown in color and showing rare areas of hemorrhage and necrosis and surrounded by thick fibrous capsule in all cases.

Pass scoring system {pheochromocytoma of adrenal gland scaled score}:
In a study done on 11 patients done by **Milka M et al 2013, [21]**it was found that PASS score ≥ 4identifies malignant pheo with a a sensitivity 50%& specificity45%.the authors suggested that PASS helps to reserve the more aggressive treatment & narrow the follow

up for malignant tumors. In our study, Pass score was >4 in 9 cases and <4 in remaining 22 cases. Out of 9 cases in which Pass was >4, three cases were clinically malignant and 2 cases were clinically benign. All the cases in which Pass was <4 were clinically benign.4 cases in which pass was 6 had benign behavior, thus pass score between 4 and 6 need long term follow up.

7. Conclusion

To conclude, we encountered 70 cases of adrenal masses. The most commonly diagnosed tumor was pheochromocytoma by taking into consideration the above mentioned clinicopathologic parameters. The pathologic features that are incorporated correctly identified tumors with more aggressive behavior. Pheochromocytoma although not so common, they are encountered in routine practice, proper clinical evaluation and early surgical modalities can cure the lesion.

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Figure 1a: Cut section of pheochromocytoma was grey-white with extensive areas of necrosis along with few areas of hemorrhage

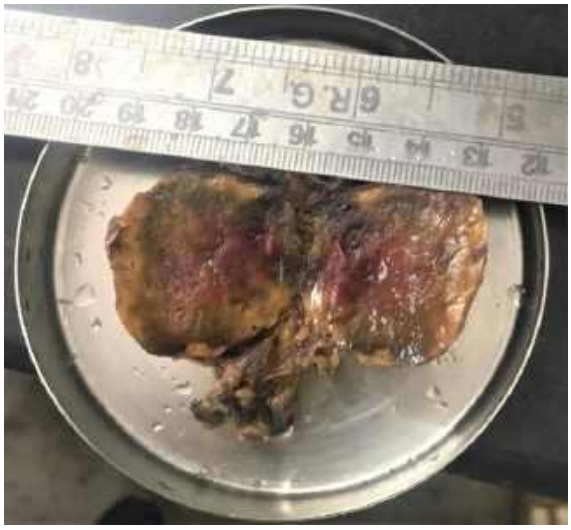

Figure 1 b: Cut section shows well encapsulated mass with chromafin reaction positive.

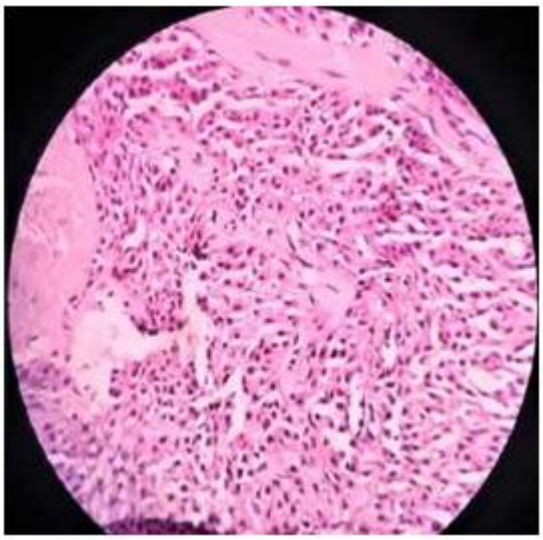

Figure 2b: low power image show solid pattern with areas of hyalinization

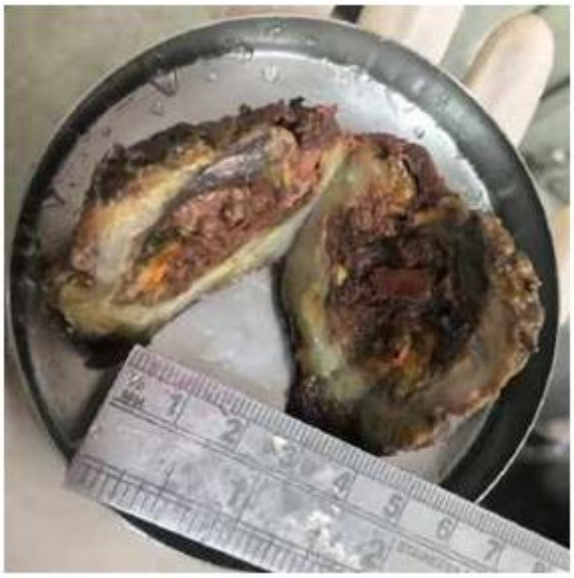

Figure 1c: Cut section shows grey-white mass of pheochromocytoma with central area of necrosis.

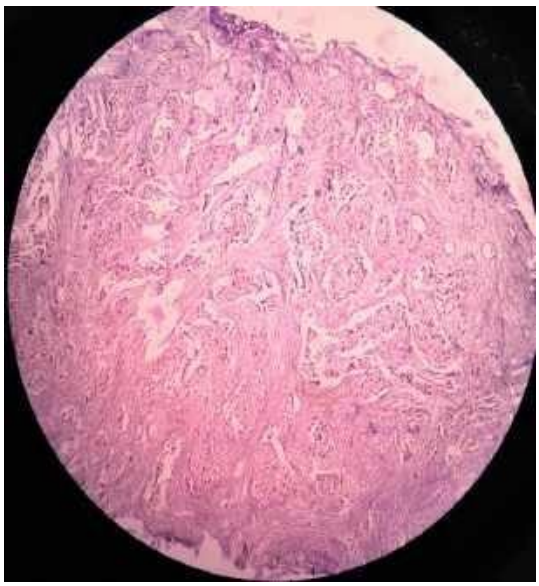

Figure 2c: rare alveolar pattern of pheochromocytoma 10x view.

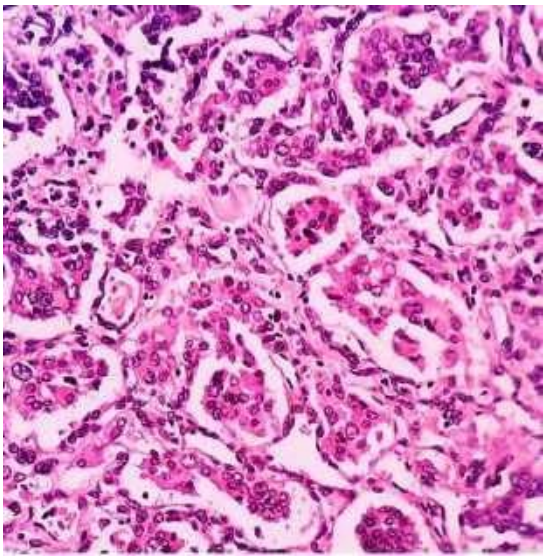

Figure 2a: 40x view of pheochromocytoma shoe zellballen pattern

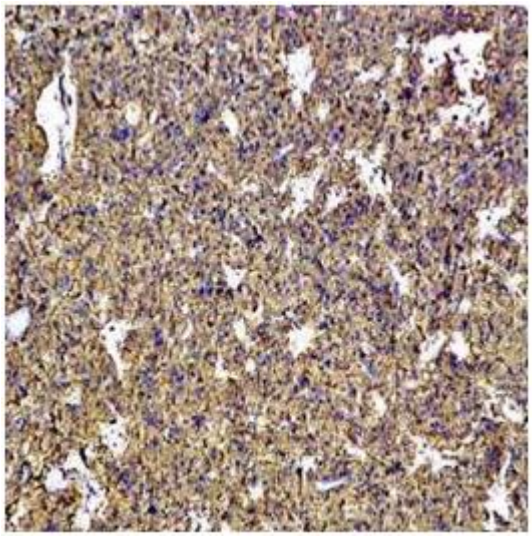

Figure 3a: 10x view show chromogranin cytoplamic positivity in tumor cells

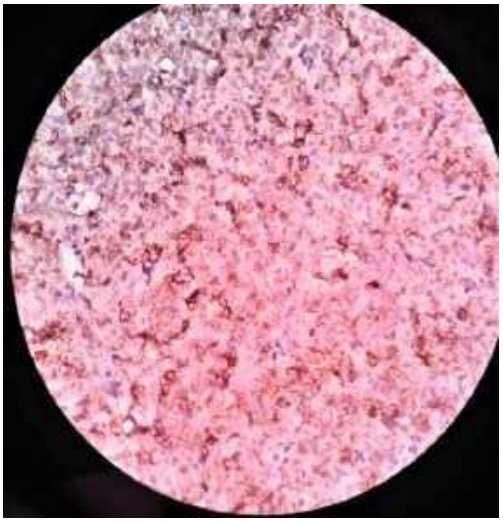

Figure 3b: weak synaptophysin cytoplamic positivity in tumor cells