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Commentary

Ooze and Seep-Pheochromocytoma

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Pheochromocytoma is denominated as a paraganglioma arising from adrenal medulla and configures around ~7% of primary adrenal neoplasms. Tumefaction is composed of chromaffin cells which secrete catecholamine. Additionally designated as adrenal paraganglioma, pheochromocytoma is distinct from paraganglioma or extra-adrenal pheochromocytoma which emerges from chromaffin cells constituting sympathetic ganglia.

Frequently, pheochromocytoma emerges as a sporadic lesion with malignant metamorphosis occurring within 10% tumours. An estimated 40% neoplasms are accompanied by genetic syndromes wherein pathogenic mutations are discernible within 20% tumours. Thus, cogent genetic evaluation is comprehensively warranted.

The predominantly sporadic pheochromocytoma commonly represents within fourth decade or fifth decade. Neoplasms associated with hereditary syndromes may manifest within second decade to third decade and are commonly bilateral.

Preponderantly, pheochromocytoma emerges from medulla of adrenal gland [1,2].

Germline mutations engendered within pheochromocytoma are associated with:

- Von Hippel-Lindau syndrome which is an autosomal dominant condition with deletion or missense mutation of VHL tumour suppressor gene situated upon chromosome 3p25-26, pheochromocytoma (~20%) along with hemangioblastoma of central nervous system, renal cysts, clear cell renal cell carcinoma, pancreatic cyst, pancreatic neuroendocrine tumour, endolymphatic sac tumour or epididymal cystadenoma.
- Multiple endocrine neoplasia type 2 (MEN 2) which emerges as an autosomal dominant condition with activating mutations within RET proto-oncogene confined to chromosome 10q11.2 along with pheochromocytoma (50%) and medullary thyroid carcinoma. MEN 2A may represent with hyperparathyroidism. MEN 2B may represent with Marfanoid habitus and multiple mucosal ganglioneuromas.
- Neurofibromatosis type 1 (NF1) is an autosomal dominant condition demonstrating inactivating mutations within NF1 tumour suppressor gene located upon chromosome 17q11.2, pheochromocytoma (7%), café au lait spots, iris hamartoma, axillary or inguinal freckling, osseous dysplasia and optic pathway glioma.
- Familial paraganglioma is accompanied by inactivating mutations within succinate dehydrogenase tumour suppressor gene, pheochromocytoma (5%), paraganglioma, gastrointestinal stromal tumour, carcinoma breast and papillary thyroid carcinoma. Pheochromocytoma is associated with genomic mutations within SDHB and SDHD genes wherein SDHB mutation enhances possible malignant metamorphosis. Aforesaid mutations may be identified with cogent immunohistochemistry. Additionally, mutations within TMEM127 and MYC associated factor X (MAX) gene are encountered within familial instances whereas HRAS mutation may ensue within somatic lesions [1,2].

Altered components of normal catecholamine biosynthesis may engender proliferation of chromaffin cells, excessive secretion of catecholamine and dysregulation of chromaffin cellular division. Chromaffin cells composing pheochromocytoma release catecholamine in the absence of sympathetic innervation or neuronal stimulation. Besides, certain regulatory molecules or enzymes confined to neoplastic adrenal medulla may be altered [1,2].

Approximately 30% pheochromocytoma appear as hereditary neoplasms concurrent with autosomal dominant disorders as:

- Von Hippel-Lindau syndrome
- Multiple endocrine neoplasia type 2 (MEN2)
- Neurofibromatosis type 1 (NF1)
- Familial paraganglioma [2,3].

Specific clusters of mutations induce pathological and physiological modifications within pheochromocytoma which are denominated as:

- Cluster 1 induces a hypoxic cellular reaction in the absence of true hypoxia with consequent excessive methylation of phenylethanolamine N methyltransferase. Pre-eminently a germline mutation, neoplasms may be intra-adrenal or extra-adrenal and predominantly secrete norepinephrine with minimal epinephrine. Aforesaid mutations are associated with dysregulation of tricarboxylic acid (TCA) cycle with appearance of SDH mutations or may be concurrent with Von Hippel-Lindau (VHL) syndrome related tumours.
- Cluster 2 exhibits elevated mitogen activated protein (MAP) kinase and activity of P13K/AKT pathway which enhances cellular proliferation and catecholamine synthesis. Nearly 20% germline mutations are encountered whereas somatic mutations are predominant. Typically, intra-adrenal tumours secrete epinephrine. Tumours are associated with RET, NF1, TMEM-127, MAX or HRAS genes [2,3].
- Cluster 3 exemplifies altered signalling of Wnt pathway along with attenuated phenylethanolamine N methyltransferase expression. Associated mutations are somatic. The intra-adrenal neoplasm secretes epinephrine intermediate to cluster 1 and cluster 2 tumours. Genetic mutations within CSDE1or MAML3 may ensue.

Hereditary aetiology of pheochromocytoma is indicated with:

- Family history or occurrence of a symptomatic syndrome
- Bilateral neoplasms
- Tumour occurrence < 45 years
- Emergence of paraganglioma concurrent with pheochromocytoma [2,3].

Clinically, a classic triad of episodic headaches, sweating and tachycardia is encountered in ~ 30% subjects. Alternatively, palpitations, anxiety, postural hypotension and paroxysmal hypertension may ensue. Up to 30% subjects represent with adrenal incidentaloma and an absence of clinical symptoms, as exemplified with subclinical pheochromocytoma.

Additional features or clinical symptoms may appear within hereditary syndromes associated with pheochromocytoma [2,3].

Grossly, a well circumscribed, un-encapsulated neoplasm is encountered. Cut surface is solid, white to reddish/brown and haemorrhagic. Benign lesions demonstrate a mean tumour diameter of 4 centimetres to 6.5 centimetres. Few neoplasms appear < 1 centimetre. Malignant or metastatic tumours are enlarged and demonstrate a mean diameter of 7centimetres to 9 centimetres.

Benign neoplasms exhibit a mean weight of ~150 grams whereas malignant neoplasms delineate a mean weight of ~280 grams.

Upon frozen section, tumour architecture emerges as vaguely nested with cellular crowding and vesicular, overlapping nuclei [2,3].

Upon microscopic examination, tumour cells demonstrate a trabecular, solid or nested configuration with articulation of a 'zellballen'. Tumour cell nests are circumscribed by sustentacular cells which appear immune reactive to S100 protein. Tumour cells are enlarged, polygonal, uniform and significantly vacuolated. Cells appear imbued with abundant fine, granular, reddish purple cytoplasm with pigmented granules constituted of hemosiderin, melanin, neuro-melanin or lipofuscin. Tumour cell nuclei are uniform, spherical to elliptical or exhibit significant anisonucleosis and prominent nucleoli [2,3].

Composite pheochromocytoma is a pheochromocytoma occurring in with concurrence with ganglioneuroma, ganglioneuroblastoma, neuroblastoma or peripheral nerve sheath tumour [2,3].

Upon ultrastructural examination, numerous intracytoplasmic dense secretory granules of 200 nanometres to 300 nanometres appear permeated with catecholamine. Majority of granules are composed of norepinephrine. Epinephrine granules appear as centric dense core granules devoid of a halo. Norepinephrine granules configure eccentric dense core circumscribed by a vacant halo [2,3].

Clinical features	Young age, norepinephrine secretion
Gross features	Tumour magnitude and weight
Histological features	Increased cellularity, mitotic rate, atypical mitosis, necrosis, cellular spindling and monotony, nuclear pleomorphism, large nests, diffuse growth, capsular and vascular invasion with invasion of peri-adrenal fat, hyperchromasia
Ancillary studies	↑Ki67, SDHB, VHL, RET mutation

Table 1: *Clinical and histological features of malignant pheochromocytoma [3,4].*

Histologic feature	Score
Periadrenal adipose tissue invasion	+2
> 3 mitosis/10 high power fields	+2
Atypical mitosis	+2
Necrosis	+2
Cellular spindling	+2
Marked nuclear pleomorphism	+1
Cellular monotony	+2
Large nests or diffuse growth	+2
High cellularity	+2
Capsular invasion	+1
Vascular invasion	+1
Hyperchromasia	+1

Table 2: *Adrenal gland pheochromocytoma scaled score [3,4].*
Score ≥ 4 is indicative of malignant metamorphosis.

Grading of adrenal pheochromocytoma and paraganglioma (GAPP) [3,4]:

- Histological pattern:
  - Zellballen: 0
  - Large and irregular cell nests: +1
  - Pseudo-rosette: +1
- Cellularity (number of cells in 10 mm^2 at high power magnification):
  - Low cellularity with 150 cells: 0
  - Moderate between 150 to 250 cells: +1
  - High cellularity with > 250 cells: +2
- Comedonecrosis: +2
- Capsular or vascular invasions: +1
- Ki67 labelling index:
  - < 1%: 0
  - 1% to 3%: +1
  - > 3%: +2
- Catecholamine subtype:
  - Non functional: 0
  - Epinephrine or epinephrine and norepinephrine: 0
  - Norepinephrine or norepinephrine and dopamine: +1.

Scoring on aforementioned features is denominated as:

- Well differentiated tumour: score 0 to 2
- Moderately differentiated tumour: score 3 to 6
- Poorly differentiated tumour: score 7 to 10.

TNM staging of pheochromocytoma [3,4]:

- Primary tumour:
  - TX: Primary tumour cannot be assessed
  - T1: Tumour is < 5 centimetre magnitude and confined to adrenal gland
  - T2: Tumour is ≥ 5 centimetre magnitude and confined to adrenal gland OR a symptomatic paraganglioma T3: Tumour of variable magnitude which invades adjacent anatomical structures as hepatic parenchyma, pancreas, spleen or renal parenchyma.
- Regional lymph nodes:
  - NX: Regional lymph nodes cannot be assessed
  - N0: Regional lymph node metastasis absent
  - N1: Regional lymph node metastasis present
- Distant metastasis:
  - M0: Distant metastasis absent
  - M1a: Distant metastasis confined to the bone

- M1b: Distant metastasis confined to distant lymph nodes and hepatic or pulmonary parenchyma
- M1c: Distant metastasis confined to bone and diverse sites.

Staging of pheochromocytoma or paraganglioma is designated as:

- Stage I: Tumour is < 5 centimetre diameter and confined to adrenal gland (T1, N0, M0)
- Stage II: Tumour is ≥ 5 centimetre magnitude and confined to adrenal gland OR a symptomatic paraganglioma (T2, N0, M0)
- Stage III: Tumour is < 5 centimetre magnitude and confined to adrenal gland with regional lymph node metastasis (T1, N1, M0) OR tumour is ≥ 5 centimetre magnitude and confined to adrenal gland OR a symptomatic paraganglioma with regional lymph node metastasis (T2, N1, M0) OR tumour of variable magnitude which invades abutting tissues as hepatic or renal parenchyma, pancreas or spleen (T3, any N, M0)
- Stage IV: Tumour of variable magnitude along with or devoid of regional lymph node metastasis and with distant metastasis (Any T, any N, M1) [3,4].

Recurrent pheochromocytoma or paraganglioma is a neoplasm which reappears following therapy and requires cogent evaluation in order to assess extent of tumour reoccurrence.

Pheochromocytoma or paraganglioma can be generally categorized as:

- Localized pheochromocytoma wherein preliminary detection of tumour confined to medulla of unilateral or bilateral adrenal gland ensues.
- Localized paraganglioma wherein preliminary tumour detection is associated with tumour confined to singular site.
- Regional pheochromocytoma or paraganglioma wherein tumour invasion occurs within adjacent anatomical structures and/or regional lymph nodes.
- Metastatic pheochromocytoma or paraganglioma wherein distant tumour metastasis ensues [3,4].

Pheochromocytoma is immune reactive to chromogranin A, synaptophysin, S100 protein, GATA3, CD10, vimentin, MAP2 or SDHB. Pheochromocytoma is immune non reactive to calretinin, MelanA, HMB45, inhibin A, cytokeratin AE1/AE3, CK7, CK20, PAX8, SF1 or CAIX [4,5].

Pheochromocytoma requires segregation from neoplasms such as adrenocortical carcinoma, adrenal medullary hyperplasia or adrenal medulla, adrenocortical adenoma or composite pheochromocytoma and metastatic neoplasms as renal cell carcinoma, malignant melanoma or primaries from lung, colon or breast.

Besides, conditions such as hyperthyroidism, carcinoid tumour, hypoglycaemia, medullary thyroid carcinoma, mastocytosis, menopausal syndrome, heart failure, arrhythmias, ischemic heart disease, migraine, stroke, epilepsy, meningioma, postural orthostatic tachycardia syndrome (POTS), porphyria, panic disorder or anxiety, factitious disorders due to sympathomimetic drugs as ephedrine, drug therapy with monoamine oxidase inhibitors, sympathomimetic drugs, withdrawal of clonidine or consumption of cocaine require distinction [4,5].

Pheochromocytoma is appropriately ascertained with clinical or biochemical evaluation and confirmation with diverse imaging techniques. Exceptionally, a core needle tissue sample demonstrates morphological appearance simulating normal adrenal medulla. Appropriate disease discernment is necessitated in order to circumvent severe surgical complications associated with intervention of an obscure pheochromocytoma devoid of cogent adrenergic blockade.

Pheochromocytoma may secrete norepinephrine, epinephrine or dopamine. Catecholamine or associated metabolites may be appropriately detected within serum or urine through high performance liquid chromatography or tandem mass spectroscopy [4,5].

Plasma and urine free metanephrines are an optimal and recommended diagnostic modality for discerning the tumefaction. Borderline elevation of aforesaid parameters requires follow up with clonidine suppression test and assessment of plasma normetanephrine.

Chromogranin A is secreted by chromaffin cells and can be detected within serum in a majority (~90%) of instances.

Exceptionally, adrenal lesions may manifest pheochromocytoma-like symptoms along with borderline or elevated metanephrines, denominated as pseudo-pheochromocytoma. Diverse catecholamine producing lesions confined to adrenal gland may emerge as adenoma, hydatid cyst, oncocytoma, endothelial cyst or malignant melanoma [4,5].

Computerized tomography (CT) is an optimal and recommended imaging modality for visualizing lesions ≥ 0.5 centimetre magnitude. Upon computerized tomography (CT) malignant neoplasms exhibit unenhanced attenuation of ≤ 10 Hounsfield unit. Besides, spherical contour, enhancement of neoplastic perimeter and sharply defined, necrotic margin is commonly discerned in pheochromocytoma.

Magnetic resonance imaging (MRI) is adopted for assessing tumefaction with distant metastasis or upon contraindication to radiation exposure. Tumours undetectable by computerized tomography (CT) with suggestive clinical and biochemical features may be subjected to manoeuvers such as ^{123}I metaiodobenzylguanidine (MIBG) uptake scintigraphy which is sensitive and specific for detecting sporadic pheochromocytoma ≥ 1 centimetre diameter.

Positron emission tomography with 18F fluorodeoxyglucose (^{18}F-FDG), ^{18}F fluoro l dihydroxyphenylalanine (^{18}F-DOPA) or ^{68}Ga labelled somatostatin receptor analogues may be optimally adopted to evaluate the neoplasm [4,5].

Surgical extermination of tumefaction through total adrenalectomy is an optimal strategy for treating pheochromocytoma, except in bilateral tumours. Bilateral neoplasms can be subjected to cortical sparing adrenalectomy, a strategy adopted to decimate complications concurrent to lifelong replacement of glucocorticoids.

Preoperative administration of alpha adrenergic blockers is recommended in order to circumvent intraoperative hypertensive crisis. Also, volume expansion is necessitated in order to counterbalance catecholamine mediated volume contraction.

Metastatic tumours may be amenable to surgical eradication. Although insufficiently curative, surgical excision may ameliorate disease associated survival [4,5].

Chemotherapy with cyclophosphamide, vincristine and dacarbazine may be employed to treat neoplasms unamenable to surgical resection.

Pertinent histologic or molecular biomarkers differentiating benign from malignant neoplasms are absent.

Inferior prognostic outcomes are associated with:

- Ethnic hispanic groups
- Enlarged or metastatic neoplasms with mean tumour diameter
- 7 centimetres to 9 centimetres
- Neoplasms with mean weight
- 280 grams or metastatic tumours with enhanced tumour weight.

Superior prognostic outcomes are encountered with:

- Family history of disease occurrence
- Young incriminated subjects
- Absence of cogent clinical symptoms or incidental features
- Bilateral neoplasms [4,5].

Occurrence of metastases is indicative of malignant neoplasms wherein metastasis commonly ensues into regional lymph nodes, bone and hepatic or pulmonary parenchyma. Distant metastasis is encountered in ~10% of pheochromocytomas whereas ~9% of resected tumours exhibit localized reoccurrence. A 5 year survival of ~65% and 10 year survival of ~35% is encountered. Median duration of tumour reoccurrence is ~35 months.

An estimated 25% of tumour reoccurrences appear devoid of metanephrine elevation. Thus, cogent monitoring necessitates annual imaging with computerized tomography (CT) [4,5].

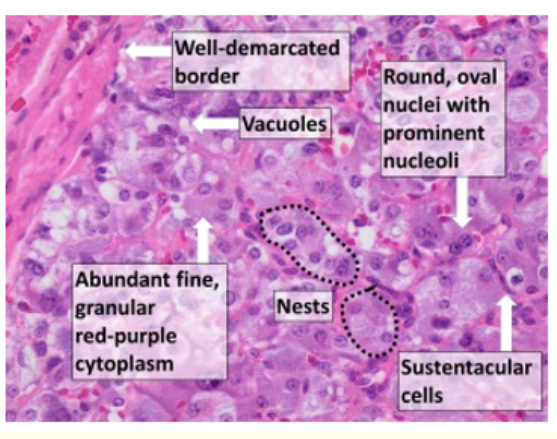

Figure 1: *Pheochromocytoma demonstrating nests of enlarged cells with abundant, granular eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli surrounded by sustentacular cells and dividing fibrous tissue septa [6].*

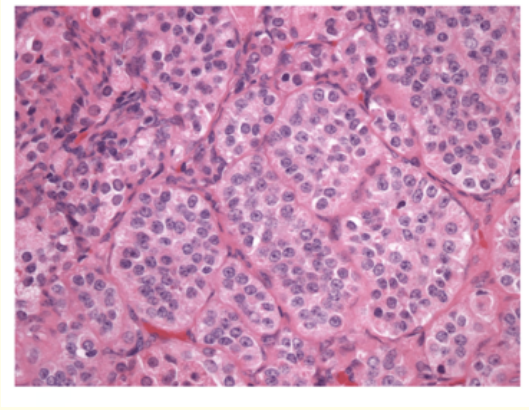

Figure 2: *Pheochromocytoma delineating nests of enlarged cells with abundant, granular, eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli with circumscribing sustentacular cells and traversing fibrous tissue septa [7].*

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6. Image 1 Courtesy: Wikipedia.
7. Image 2 Courtesy: Research gate.

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