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Phaeochromocytoma with Histopathologic Aspects

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1. Introduction

Phaeochromocytoma is a term used for catecholamine secreting tumors that arise from chromaffin cells of sympathetic paraganglia. The new World Health Organisation (WHO) classification of endocrine tumors has recommended to reserve the term phaeochromocytoma for intraadrenal tumors only and the others are defined as sympathetic or parasympathetic paragangliomas, further categorised by site. Although it was the first adrenal tumor to be recognised, the term phaeochromocytoma was introduced many years later by Pick in 1912. The name is based on the fact that the tumors get dark brown after exposure to potassium dichromate because of chromaffin reaction.

2. The usual adrenal medulla

2.1 Anatomy

The human adrenal glands are located in retroperitoneum superomedial to kidneys. They are composite endocrine organs made up of cortex and medulla which have different embryonic origin, function and histology. On fresh or formalin fixated cut surface the two portions, a relatively thick outer yellow cortex and inner, pearly gray medulla, is readily visible. The medulla is mainly situated in head and partly body of the organ. It may variably extend to tail and focally to alae. It's weight comprises about 8%-10% of the total. Medulla is of neuroectodermal origin and secretes and stores catecholamines, especially epinephrine.

2.2 Histology

On histological examination the cortex-medulla junction is sharp with no intervening connective tissue but the border is irregular. The medulla is mainly composed of chromaffin cells (phaeochromocytes, medullary cells) that are arranged in tight clusters and trabeculae separated by a reticular fiber network. Embryologically, they are modified sympathetic postganglionic neurons which have lost their axons. They are all innervated by cholinergic endings of preganglionic sympathetic neurons. There are sustentacular cells at the periphery of clusters which can only be demonstrated by immunostaining for S-100 protein. The chromaffin cells are polygonal to columnar and larger than cortical cells. They have basophilic cytoplasm which have fine secretory granules and/or vacuoles. These granules contain catecholamines and derivatives of tyrosine which transform to colored polymers by

oxidizing agents such as potassium dichromate and ferric chloride. This staining is called chromaffin reaction which is replaced by formaldehyde methods for detection of catecholamins because of its relatively low sensitivity.

Among chromaffin cells are randomly scattered individual or group of parasympathetic ganglion cells that are often associated with a nerve. Small clusters of cortical cells are also a usual component of the medulla. Small groups of lymphocytes and plasma cells may be seen within the medulla but their significance is unknown.

2.3 Ultrastructure

Ultrastructural examinations have shown that epinephrine and norepinephrine are secreted by two different types of cells. Epinephrine secreting cells have smaller, moderately electron-dense granules that are closely applied to their limiting membranes. Norepinephrine secreting cells' granules are larger, more electron-dense and have an electron-lucent layer beneath the surrounding membrane forming a halo. The nuclei are usually larger than cortical cells and have finely or coarsely clumped chromatin. Most nuclei are spheroidal and show slight pleomorphism.

3. The paraganglia

Sympathetic paraganglia (SP) are distributed along paraaxial regions of the trunk along the prevertebral and paravertebral sympathetic chains and in connective tissue in the walls of pelvic organs. However parasympathetic paraganglia (PSP) are found along cranial and thoracic branches of the glossopharyngeal and vagus nerves. Among SP the organ of Zuckerkandl is characteristic, located at the origin of the inferior mesenteric artery, because of being the only macroscopic extraadrenal paraganglia. Similarly PSP are highly variable in number and location and don't have specific names except from carotid bodies which are located between the carotid arteries just above the carotid bifurcation. Apart from different clinical standpoint SP and PSP are similar at cellular level.

4. Histopathology of phaeochromocytoma

Sporadic phaeochromocytomas make up of about 50% of all phaeochromocytomas and are usually unilateral and unicentric while more than 50% of familial forms are bilateral and coexist with extraadrenal sympathetic and parasympathetic paragangliomas. Patients with MEN type 2, VHL or NF type 1 are known to have an increased risk for pheochromocytoma.

4.1 Macroscopic examination

Gross examination highlights a tumor 3-5 cm in diameter which can be more than 10 cm. Tumor weight may range from a few grams to over 3500g, with an average of 100 g in hypertension patients. The cut surface is solid, gray-white, light tan or dusky red and darkens on exposure to air (Figure 1). Hemorrhage, central degeneration, necrosis, cytic change and calcification is not uncommon. The adrenal gland can usually be seen compressed or incorporated within the tumor. An adrenal gland containing phaeochromocytoma should be carefully dissected since diffuse and nodular hyperplasia can be found suggestive of a familial form.

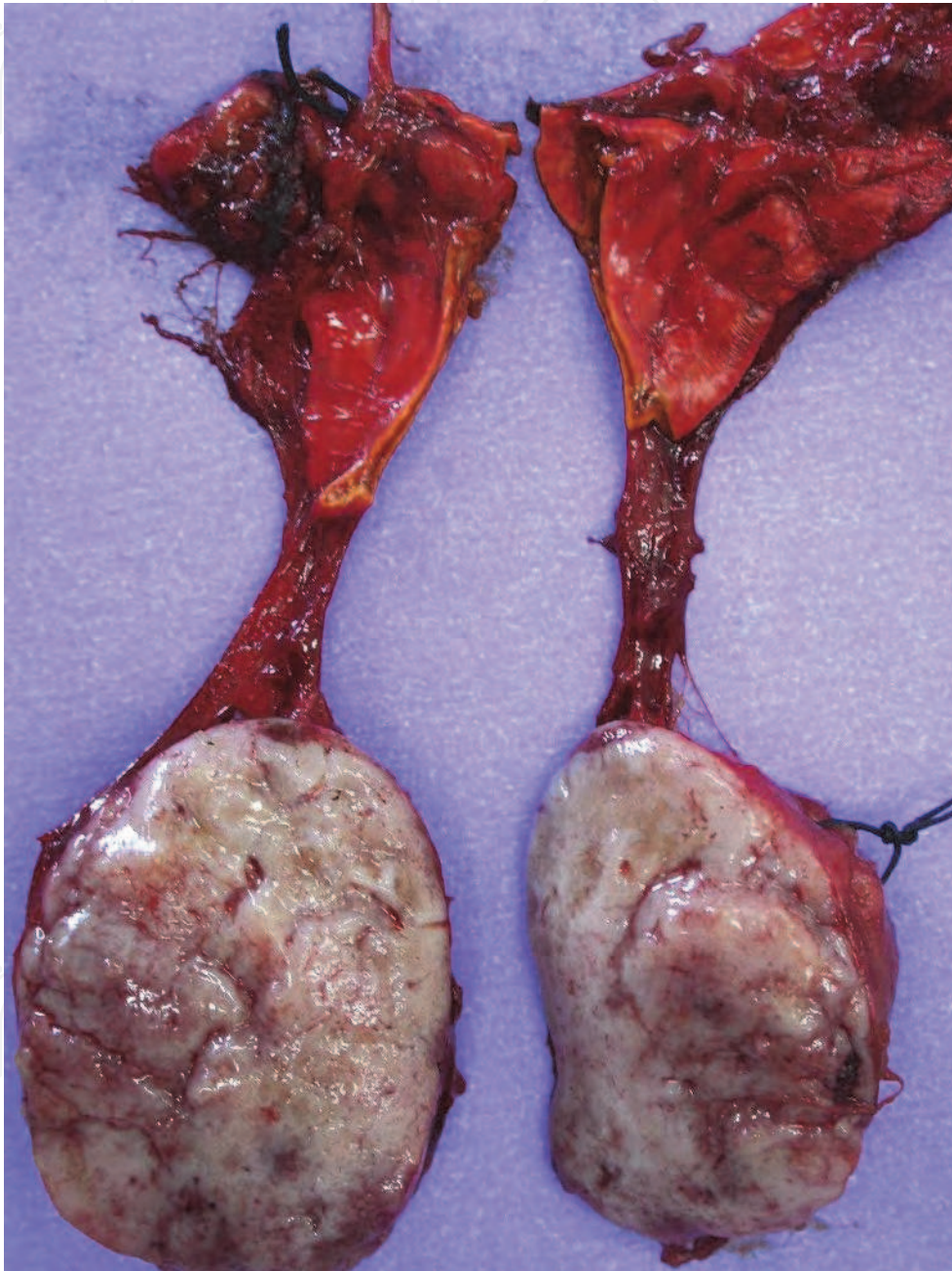


Fig. 1. Extra-adrenal paraganglioma with a nodular, tan cut surface. Adrenal gland can be encountered in orange above the tumor (by courtesy of Prof. Dr. Filiz Ozyilmaz).

4.2 Microscopic examination

Microscopically, similar to usual corticomedullary border, cortex-tumor border is irregular and there's a pseudocapsule rather than a true capsule. The most common histologic pattern is alveolar (Zellballen) and trabecular or a mixture of the two, bound by a delicate fibrovascular stroma (Figure 2). Diffuse or solid pattern can also be encountered. Tumor cells resemble usual chromaffin cells but are slightly larger. Sometimes nuclear and cellular pleomorphism is pronounced. Nuclear pseudo-inclusions can be seen resulting from deep cytoplasmic invaginations. Occasional mitotic figures are present but they don't exceed 1/30 hpf. Intracytoplasmic hyaline globules are common. Their presence may aid to differentiate pheochromocytoma from adrenal cortical neoplasms. Interstitial amyloid deposition and small amounts of melanin pigment representing neuromelanin may be present. Hemorrhage and hemosiderin deposits are common and scattered ganglion cells can be encountered. Sometimes tumor cells may undergo lipid degeneration and this may lead to confusion with cortical tumors. Exceptionally, the cells of pheochromocytoma may contain a large number of mitochondria which give the cells oncocytic appearance. Spindle shaped sustentacular cells form a second cell component of pheochromocytoma forming a peripheral rim around Zellballen, similar to usual adrenal medulla. These cells have been encountered more frequently in pheochromocytomas associated with MEN and benign forms.

Histopathologic diagnosis of pheochromocytoma is based on morphology but immunohistochemical techniques are usually used to confirm the diagnosis. Immunopositivity for neuron specific enolase, chromogranin-A and synaptophysin is characteristic.

Extra-adrenal SP are mostly solitary in adults and histologically resemble adrenal counterpart. Dispersed along the paravertebral sympathetic chain, they are most common in the superior (45%) followed by inferior (30%) paraaortic region. Urinary bladder, intrathoracic and cervical paragangliomas can occasionally be seen. More than 25% of these tumors are functional and usually secrete norepinephrine. Approximately 50% of extraadrenal tumors are malignant giving rise to metastases.

PSP seldomly produce catecholamine excess. Carotid body and jugulotympanic tumors are more common than aortic and vagal lesions. Carotid body tumors are more commonly bilateral in familial cases. Also people living at high altitude is ten times at a higher risk for paraganglioma because of hyperplastic response to hypoxic stimulus.

4.2.1 Malignant pheochromocytoma

Malignant pheochromocytomas comprise up to 10% of all pheochromocytomas. WHO 2004 classification of endocrine tumors defines malignant pheochromocytoma only when there is metastasis to sites where paraganglial tissue is not otherwise found. As a matter of fact there's no reliable histological criteria for classifying pheochromocytoma as malignant at present, therefore no lesion can be definitely predicted as benign. There are new approaches to find significant histologic criteria for defining pheochromocytoma malignant. Large nests of tumor cells, necrosis, high cellularity, cellular monotony, nuclear hyperchromasia, macronucleoli, vascular or capsular invasion, increased mitotic figures and high Ki-67 proliferation index, extension of tumor into adjacent fat, catecholamine phenotype and absence of hyaline globules are all shown to be correlated with malignant behaviour in scoring studies in both pheochromocytomas and extraadrenal sympathetic

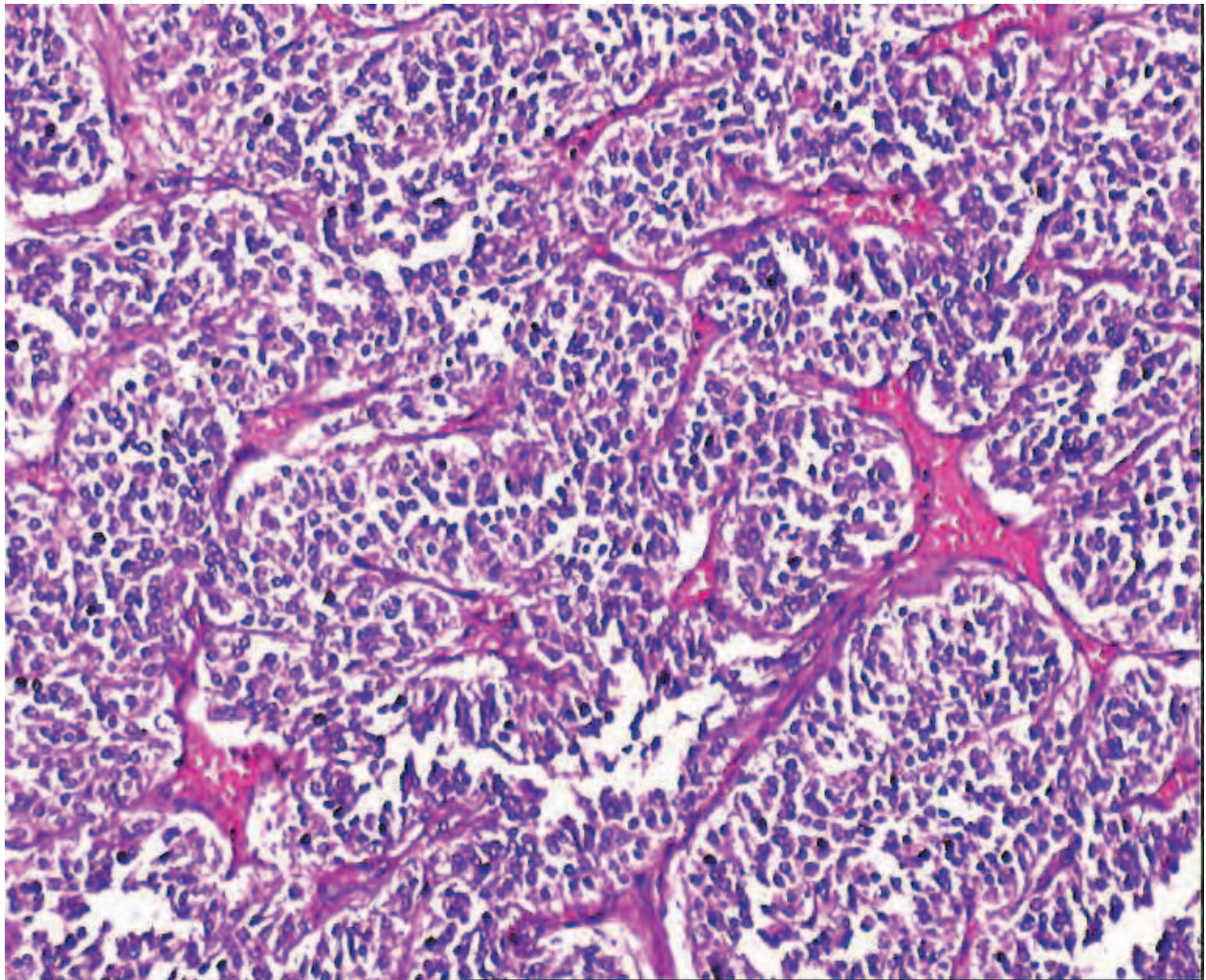


Fig. 2. Typical Zellballen pattern of phaeochromocytoma (HEx200) (by courtesy of Prof. Dr. Filiz Ozyilmaz).

paragangliomas. Unfortunately none of these criteria give exact discrimination thus histological gold standard is still not possessed.

4.2.2 Composite pheochromocytoma

Composite pheochromocytoma or paraganglioma refers to histological combination of pheochromocytoma and paraganglioma with features of ganglioneuroma, ganglioneuroblastoma, neuroblastoma or peripheral nerve sheath tumour. There are fewer than 40 cases in the literature. The tumour was combined with ganglioneuroma in 80%, and with paraganglioma in 20% of all reported cases. They are usually seen in adults and symptoms are similar to typical pheochromocytoma as with genetic abnormalities. About 90% occur in adrenal gland and the remainder in the urinary bladder. Although ordinary pheochromocytomas can contain scattered neuron-like or ganglion cells the histopathological diagnosis of composite tumour requires both different architecture and cell population. Present evidences show that the origin of neurons in these tumours is preexisting chromaffin or paraganglioma cells. Cell culture studies favor that both normal and neoplastic human pheochromocytoma cells can undergo neuronal differentiation.

4.2.3 Adrenal medullary hyperplasia

Lastly, diffuse or nodular adrenal medullary hyperplasia may cause excess amount of catecholamine secretion and may lead to clinical pheochromocytoma.

5. Conclusion

It is easy to define usual pheochromocytoma histopathologically but diagnosing malignant forms is problematic. Many studies should be done and molecular techniques should be designed to overcome this dilemma.

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The book is divided into six sections. The first three sections focus on the pathophysiology of the disease, showing anatomo- and histopathological aspects, experimental models and signaling pathways and programmed cell death related to pheochromocytoma. The fourth discusses some specific aspects of clinical presentation, with emphasis on clinical manifestations of headache and heart. The fifth section focuses on clinical diagnosis, laboratory and imaging, including differential diagnosis. Finally, the last section discusses the treatment of pheochromocytoma showing clinical cases, a case about undiagnosed pheochromocytoma complicated with multiple organ failure and other cases about catecholamine-secreting hereditary tumors. Thus, this book shows the disease "pheochromocytoma" in a different perspective from the traditional approach. Enjoy your reading.

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