Composite Pheochromocytoma: A Rare Form of Tumor

Abstract

The pheochromocytomas are one of the rare and curable causes of secondary hypertension arising from adrenal medulla, commonly presenting with hypertension; either paroxysmal or persistent. Very rarely they may show cells belonging to more than one line of differentiation and are called as mixed or composite pheochromocytoma.

Keywords: *Composite pheochromocytoma, lactic acidosis, secondary hypertension*

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Introduction

Pheochromocytomas are catecholamine -secreting tumors that arise from chromaffin cells of the adrenal medulla or sympathetic ganglia, are rare neoplasms, probably occurring in less than 0.2% of patients with hypertension and most common in the fourth to fifth decade, and are equally common in men and women.[1,2] Composite tumors of the adrenal medulla consisting of pheochromocytoma and nonpheochromocytoma components are rare tumors, accounting for less than 3% of all sympathoadrenal tumors.[3,4] These tumors display more than one line of differentiation, in which pheochromocytoma cells may be mixed with neuroblastoma, ganglioneuroma, ganglioneuroblastoma, neuroblastomas, schwannoma, or spindle-cell carcinoma, and recently metastatic squamous cell carcinoma. Although pheochromocytoma is a tumor that originates from the adrenal medullary chromaffin cells, other component, like ganglioneuroma, represents a tumor from autonomic ganglion cells or their precursors. Embryologically, both pheochromocytoma and nonpheochromocytoma components have common origin from cells of neural crest cells.[3,4] In this issue of the *Indian Journal of Nephrology* (IJN), Mathi Manoj Kumar *et al*. have reported an interesting case report of composite pheochromocytoma (CP) presenting as severe lactic acidosis and back pain to emergency department of their institute.

Symptoms

The pheochromocytoma is usually suspected by either the history in a symptomatic patient, or discovery of an incidental adrenal mass, or the family history in a patient with familial disease. In 1 report of 107 patients, the average age at diagnosis was 47 years, and the average tumor size was 4.9 cm.[2] Commonly, pheochromocytomas present with sustained or paroxysmal hypertension, headache, and generalized sweating, and only minority of patients present with classical triad of episodic headache, sweating, and tachycardia.[1,2]

The composite tumors may vary in their presentation and symptoms are usually due to hormonal hypersecretion by either component of the tumor. The clinicopathological diagnosis of CP is, at times, a clinical dilemma because it is not known whether the nonpheochromocytoma component has any therapeutic and/or prognostic implications as compared to the standard pheochromocytoma.[3,4] Less common presentations of pheochromocytomas may include reversible changes in carbohydrate metabolism and lactic acidosis; both were among the initial symptoms in the presented case of this issue of IJN, which is rare.[5,6]

Histopathology

Most pheochromocytomas measure 3–5 cm in diameter, with a wide range from 1 to more than 10 cm. In cross-section, the tumor is gray-white to tan, firm, usually sharply circumscribed, and may appear encapsulated. Microscopicaly

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pheochromocytomas usually have a trabecular or alveolar pattern with distinct nests of cells ("Zellballen"), or a mixture of both. The cytoplasm of the pheochromocytoma cells is often lightly basophilic and finely granular.[3,4] Intermixed with this tumor, sheets of mature ganglion cells, Schwann cells, and Schwann-like cells may be found in representing composite nature of tumor. Rarely, they may be intermixed with ganglioneuroblastoma, neuroblastomatosis-1, and more rarely schwannoma.[3,4] The reported case had features of phaeochromocytoma and ganglioneuroma, thereby suggesting the diagnosis CP.

Immunohistochemical Diagnosis

Adrenal medullary and extraadrenal paraganglionic cells and their tumors typically exhibit positivity for a variety of neuroendocrine markers, such as chromogranin A, synaptophysin, and neuron-specific enolase (NSE). Chromogranins are major proteins in the neurosecretory granules of neuroendocrine cells and sympathetic nerves and are expressed in more than 95% of pheochromocytomas. The immunoreactivity of normal cells is generally more intense than that of neoplastic cells. Synaptophysin is a membrane glycoprotein of presynaptic vesicles. Antibody to synaptophysin, stains specifically the neuronal, adrenal, and neuroepithelial components of tumors. NSE is a glycolytic isoenzyme specifically detected in neurons and neuroendocrine cells, and their corresponding neoplasms. The pheochromocytoma component may be weakly positive for NSE. The gangliocytes will show strong positivity for NSE and S-100, an additional marker for Schwann cells and sustentacular cells. It may be difficult to differentiate a pheochromocytoma from an adrenocortical carcinoma, or from a metastatic carcinoma, such as renal cell carcinoma, hepatocellular carcinoma, or metastatic adenocarcinoma. This distinction can be facilitated by using certain immunohistochemical staining (cytokeratin, human melanoma black [HMB45] epithelial membrane antigen, carcinoembryonic antigen), which is typically negative in pheochromocytoma.[3,4] The presented case was confirmed by immunohistochemistry, showing positivity for chromogranin, synaptophysin, and S-100 stains and negativity for calretinin in phaeochromocytoma cells. Calretinin, chromogranin, synaptophysin, and S-100 stains were positive in the ganglioneuromatous component.

Treatment

Primary surgical resection is the treatment of choice if the disease is limited at the time of diagnosis. The most important initial aspect in the preoperative management is control of blood pressure. Nonselective alpha (α) and beta (β) blockade with phenoxybenzamine and propranolol were used previously for control of hypertension and tachycardia.[1,2] Phenoxybenzamine is a nonselective alpha blocker with longer action; so, chances of postoperative hypotension are increased. Hence, more selective and short-acting drugs are preferable. Nowadays, preoperative control of blood pressure is being done with selective α- and β-blockers like prazosin and metoprolol.[7] The presented case was successfully treated by laparoscopic removal of the tumor after preoperative stabilization with phenoxybenzamine and β-blocker. The hyperglycemia, lactic acidosis, and hypertension subsided after the surgery in the reported case, confirming their etiology as pheochromocytoma.

The advances in minimally invasive techniques have made; laparoscopic adrenalectomy an option in comparison to open surgery for majority of patients with solitary intra-adrenal pheochromocytomas that have no malignant radiologic features.[1,2] Both the laparoscopic transabdominal and retroperitoneal approaches have been used successfully, although there are some evidence that the retroperitoneal approach is preferable.[1,2]

In conclusion, CPs are rare, can have variable presentation, and can be diagnosed only by microscopy with battery of immunohistochemical markers; and the overall impact of nonpheochromocytoma component on treatment and prognosis needs further studies.

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Conflicts of interest

There are no conflicts of interest.

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