

Composite pheochromocytoma-ganglioneuroma of the adrenal gland: A case report with immunohistochemical study

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Abstract

Composite tumors of the adrenal medulla consisting of pheochromocytoma and ganglioneuroma are rare tumors accounting for less than 3% of all sympathoadrenal tumors. These tumors display more than one line of differentiation in which normal and neoplastic chromaffin cells are capable of differentiating into ganglion cells under the influence of nerve growth factors. To the best of our knowledge, we report the second case with a composite tumor of the adrenal medulla in a normotensive patient from India.

Key Words: Composite adrenal medullary tumor, ganglioneuroma, immunohistochemistry, pheochromocytoma

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INTRODUCTION

Composite pheochromocytoma (CP) and ganglioneuroma of the adrenal medulla are rare tumors that make up less than 3% of sympathoadrenal pheochromocytoma. It is apparent that composite tumors may display symptoms referable 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. We recently diagnosed a case of composite adrenal medullary tumor with elements of both pheochromocytoma and ganglioneuroma in a normotensive patient.

CASE REPORT

A 37-year-old lady presented with complaints of palpitation, headache and dyspnea for 5 months along with pain in the abdomen and off and on fever for 6 months to the Endocrine Surgery Department at Sanjay Gandhi Postgraduate Institute of Medical Science, Lucknow. She had a past history of one episode of encephalopathy as well as a hysterectomy under spinal block. There was no history of hypertensive episodes or endocrine problems in the family. USG and CT scan showed a well-defined heterogeneous left adrenal mass with solid and cystic components. MIBG Scan revealed a left adrenal mass. S. Cortisol level was 0.65 ml micro gm/dl after overnight dexamethasone suppression test (ONDST) showed normal suppression [Figure I] urinary metanephrine was elevated i.e., 2.56/24 hrs (normal <1). Rest of the general parameters were within normal limits. Left adrenalectomy was done through transperitoneal anterior abdominal approach. The operative findings showed a highly vascular nodular tumor arising from the left adrenal, lying superomedial to the left kidney. Intact capsule with dense adhesions to the retroperitoneal and left crus of the diaphragm was seen.

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Pathological findings

Gross feature

Left adrenalectomy specimen measuring $6.5 \times 5.5 \times 3$ cm and weighing 113 g. Cut surface showed two cystic lesions each measuring 3×1.5 and 2×2 cm filled with grey brown material and rest of the surface was yellowish [Figure 2]. Capsule was intact.

Histopathological examination

Sections from left adrenal mass showed a tumor composed of polygonal cells arranged in well-defined nests surrounded by a delicate fibrovascular stroma (Zellballen pattern) [Figure 3]. These tumor cells had moderate to abundant amount of granular eosinophilic to amphophilic cytoplasm, round to oval nuclei and single prominent nucleoli. Intermixed with this tumor, are areas showing sheets of mature ganglion cells surrounded by fascicles of Schwann-like cells [Figures 4 and 5]. Areas of hemorrhage, necrosis, dense fibrocollagenous tissue and mixed inflammatory cell infiltrate were also seen within the tumor. At places, these cells showed multinucleation, intranuclear inclusions and hyaline globules which were positive for periodic acid Schiff stain (PAS). Normal adrenal gland was also seen at the periphery of the tumor. Primitive neuroblastic

cells were not observed. The final histopathological diagnosis of CP-ganglioneuroma was made.

Immunohistochemical study

On immunohistochemical staining, pheochromocytes which contained neurosecretory granules were relatively strongly positive for Chromogranin A [Figure 6] and Synaptophysin and were weakly positive for neuron-specific enolase (NSE) [Figure 7]. In gangliocytes, the NSE was strongly positive. S-100 protein in the ganglioneuroma component was positive while HMB45 and CK in the pheochromocytoma component were negative.

DISCUSSION

The term composite tumor is used when an additional component of nonpheochromocytoma is present, theoretically arising from a common embryonic progenitor i.e., neural crest. Nonpheochromocytoma elements can be ganglioneuroma, ganglioneuroblastoma, neuroblastomatosis-I and more rarely

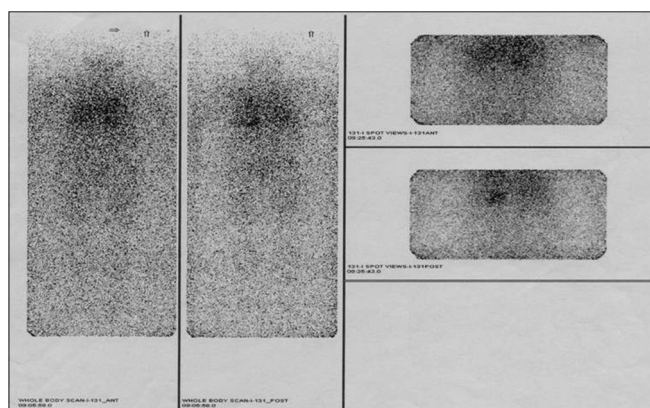


Figure 1: MIBG scan showed left adrenal mass



Figure 2: Left adrenalectomy specimen measuring $6.5 \times 5.5 \times 3$ cm and weighing 113 g. Cut surface showed two cystic lesions each measuring 3×1.5 and 2×2 cm filled with yellowish brown material

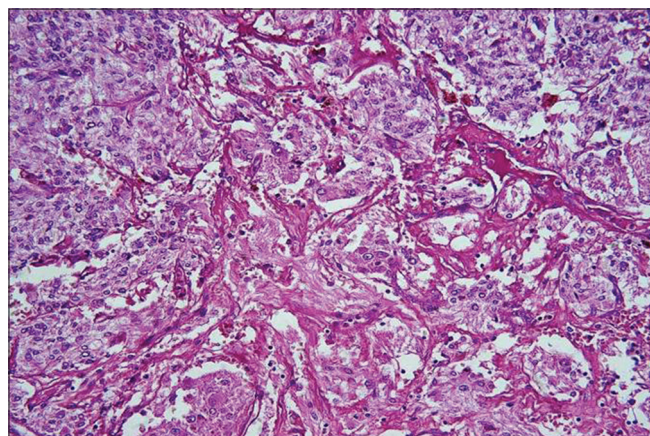


Figure 3: Section showed polygonal tumor cells arranged in well-defined nests surrounded by a delicate fibrovascular stroma (Zellballen pattern)

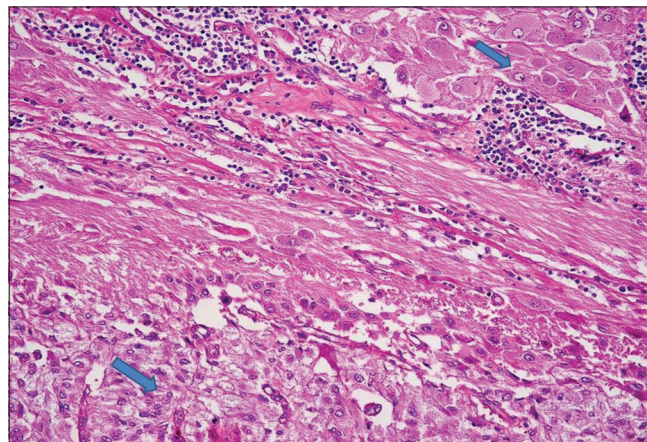


Figure 4: Section showed intermixed with atypical polygonal chromaffin cells (down arrow) with sheets of mature ganglion cells surrounded by fascicles of Schwann-like cells (up arrow) and inflammatory cells

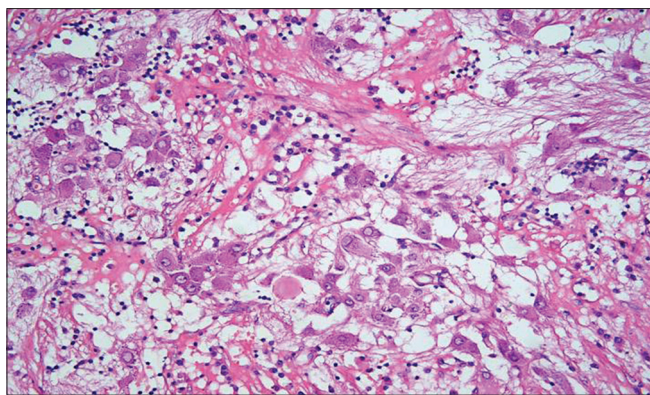


Figure 5: Section showed predominantly sheets of ganglion cells and schwann cells

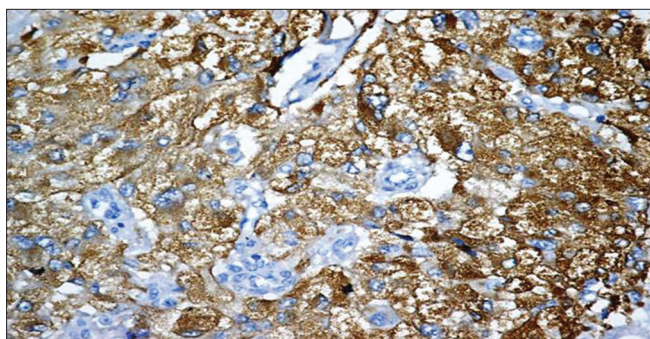


Figure 6: Tumor cells are strongly positive for chromogranin immunostaining

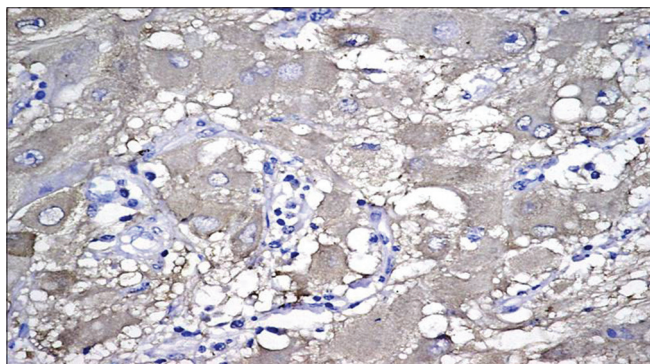


Figure 7: Neurone-specific enolase immunostaining is positive in ganglion cells and schwann cells

schwannoma. Less than 50 cases of CP have been described in the medical literature. In our case the nonpheochromocytoma component was ganglioneuroma. Although pheochromocytoma may occur at multiple sites and in association with a number of other tumors, the presence of both pheochromocytoma and ganglioneuroma within a single tumor is extremely rare. Only a few cases have been described previously.^[1,2] While pheochromocytoma is a tumor that originates from the adrenal medullary chromaffin cells, ganglioneuroma represents a tumor from autonomic ganglion cells or their precursors. Embryologically, both chromaffin and ganglion cells are derived from neural crest cells and migrate to somatic areas.^[3] Any

disturbance in migration or maldevelopment of the neural crest might result in the development of composite tumors. Because these cell populations have similar derivation, one might expect these tumors to be more common than what is apparent from the literature, and this finding may represent under-reporting or under recognition of this condition.^[4] It is apparent that a composite tumor of pheochromocytoma and ganglioneuroma may display symptoms referable to hormonal hypersecretion by either component of the tumor^[1] and other described hormonal hypersecretion in approximately three-fourths of the reported cases.^[5] Immunohistochemically, the individual components of these tumors are, for the most part, the same as they would be in a normal adrenal gland and in pure tumors of the same type. A useful battery of functional markers consists of chromogranin A, synaptophysin and catecholamine biosynthetic enzymes.^[6] Although these markers are expressed by chromaffin cells and neurons, subtle differences in their expression may yield important information about their cellular maturation and lineage. An additional marker is S-100 protein, which will identify Schwann cells and sustentacular cells. Clinically active pheochromocytoma may produce the classic symptoms of headache, palpitation and excessive perspiration in 50% of the cases. In addition, hypertension, either sustained or paroxysmal, is the cardinal feature of pheochromocytoma.^[7] In our case, while the 24-hr urinary metanephrine level was elevated to 2.56/24 hrs (normal < 1), no definite manifestations referable to catecholamine hypersecretion were identified prior to diagnosis. In other words, the patient had no any classic symptoms of pheochromocytoma. She had only complained of palpitation, headache and dyspnea. Various authors have placed frequency of hypertension at 72.4%, with that of sustained hypertension at only 47.9% in pheochromocytomas^[8] and a study noted that only four of the 13 patients had associated hypertension in composite adrenal medullary tumors^[5] The reason for a lack of endocrine abnormalities and symptoms of pheochromocytoma component in some composite adrenal tumors has not been worked up conclusively.

Recently a case of composite tumors of the adrenal medulla, containing pheochromocytoma and ganglioneuroma is a rare cause of hypertension reported in a 27 year-old-male with dyspnea from India.^[9]

Pheochromocytomas commonly do not behave in the classic manner, which may render prompt recognition elusive. The signs and symptoms are often absent and can be unusually presented as catecholamine-induced cardiomyopathy^[10] or hyperamylasemia.^[11] The malignant potential of the pheochromocytoma component is extremely rare in these composite tumors. Most adrenal pheochromocytomas are “pure”-composed of only chromaffin cells-whereas, in rare cases (3%), pheochromocytomas are associated with

other tumors.^[12] If the latter show the same embryological origin as pheochromocytoma (the neural crest), the term “composite pheochromocytoma”^[13] is used, and the tumors usually involved are ganglioneuromas, malignant schwannoma, neuroendocrine carcinomas,^[14] and recently, metastatic squamous cell carcinoma.^[15] Metastatic lesions from these tumors are almost always derived from the neural component; however, their presence does not necessarily imply a poor prognosis. A study demonstrated that neither CP nor classic pheochromocytoma harbour N-myc amplification. The neuroblastic elements in CP recapitulate favorable histological neuroblastoma in their pathological features, low mitotic-karyorrhectic index, absence of N-myc amplification and favorable outcome. These results suggest that CP does not have adverse prognostic significance conferred by the neuroblastic elements.^[16] A recent review described the characteristics and behavior of all reported cases of CPs with an emphasis on those with ganglioneuromas in the English-language literature for the past 70 years.^[17]

In conclusion, a composite tumor of adrenal medulla can present in a variety ways without hypertension and classic symptoms. Therefore, it is vital to identify the rare presentations of CP to avoid an unsuspected lethal course. We present a case with incidentally discovered a composite adrenal medullary tumor of pheochromocytoma and ganglioneuroma without hypertension.

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