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Composite Pheochromocytoma or Paraganglioma of Adrenal Gland: A Case Report with Immunohistochemical Studies and Electron Microscopic Examination

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Composite pheochromocytoma or paraganglioma of the adrenal gland is a well-recognized, yet extremely rare tumor with only one case reported in Korea. We report a case of incidentally found composite pheochromocytoma and ganglioneuroma of the adrenal gland in a 44-year-old female composed of intermingled components of pheochromocytom, ganglioneuroma, and cells with intermediate features. On immunohistochemical staining, the pheochromocytoma component was positive for synaptophysin and chromogranin, but negative for S-100 protein. Staining for the S-100 protein revealed sustentacular cells which formed a peripheral coat around the "Zellballen" and Schwann cells. The Fontana-Masson stain defined neuromelanin granules of ganglion cells and the ganglion cells expressed neural markers such as neurofilament proteins. Ultrastructural findings revealed pheochromocytes with a round or ovoid nucleus and occasionally prominent nucleolus containing numerous adrenaline and noradrenaline granules.

Key Words: Composite pheochromocytoma and ganglioneuroma, Pheochromocytoma; Paraganglioma; Adrenal glands

Composite pheochromocytoma or paraganglioma is an extremely rare, but well-recognized group of adrenal tumors that arise from neural crest derived cells[1-4] and coexist with pheochromocytoma and non-pheochromocytoma components. The reported non-pheochromocytoma components of the tumor include ganglioneuroma,[1,2,5-10] ganglioneuroblastoma,[4] neuroblastoma,[11] and more rarely, neuroendocrine carcinoma.[12] Most cases of composite adrenal medullary tumors have been reported in the adrenal gland. However, extra-adrenal composite adrenal medullary tumors have also been reported.[7] Few reports exist on the prognosis of these tumors, including malignancy. To our knowledge, only one case of composite pheochromocytoma and ganglioneuroma of adrenal gland has been reported in Korea.[13] We report on a case of composite pheochromocytoma consisting of pheochromocytoma and ganglioneuroma with immunohistochemical studies and an electron microscopic examination.

CASE REPORT

A 44-year-old woman was referred to our hospital for evaluation of an incidentally found right adrenal tumor. Abdominal computed tomography displayed a 10 cm, well-capsulated, round and cystic mass on the right suprarenal region, deviating from the right kidney inferiorly and compressing the right lobe of the liver (Fig. 1A). There was no evidence of systemic involvement, except for a small amount of left-sided pleural effusion on chest radiograph.

Her past medical history was significant for hypercholesterolemia. Upon admission, she showed no evidence of hypertension and her heart rate was 100 beats/min. Laboratory data of 24-hour urine collections showed an elevated metanephrine level (3.553 mg/day; normal range, 0.0 to 1.3 mg/day) and vanillylmandelic acid of 25.01 mg/day (normal level < 8 mg/day). The levels of epinephrine and norepinephrine were within normal range (range, 8.6 to 60.5 μg/day).

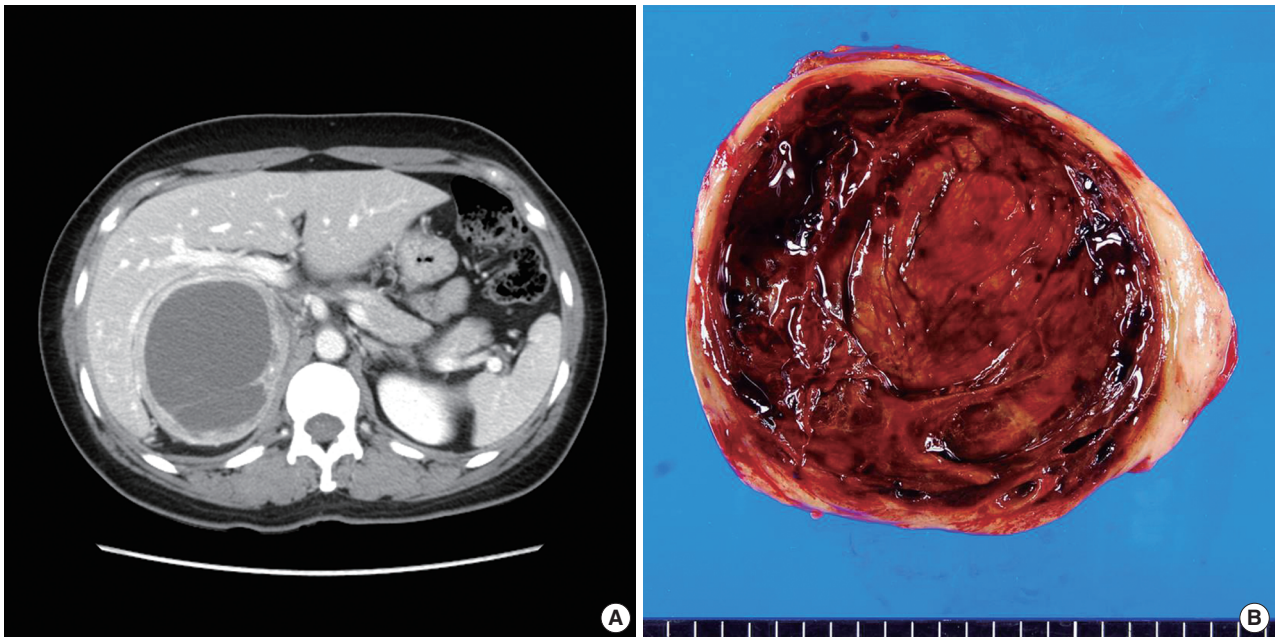

Fig. 1. (A) Abdominal computed tomography. A well capsulated, round, cystic tumor, 10cm in diameter on right suprarenal region is noted. (B) Gross photography. The cut surface was dark brown and had cystic degeneration with fresh blood and blood clots.

The mass was surgically removed without any intraoperative complications, and the postoperative course was uneventful. The left adrenal gland was grossly normal at surgery and was preserved. Post operative analysis showed normal levels of urinary catecholamines and metabolites. Ultrasonography-guided pleural fluid aspiration was done to evaluate left pleural effusion. Laboratory analysis revealed non-infectious transudate. The tumor was a well encapsulated round mass, measuring 11.5×10.5×10.1 cm and weighing 440 g. A fragment of remaining normal adrenal gland was attached, measuring 4.1×1.2×0.5 cm. The cut surface was dark brown and showed cystic degeneration with fresh blood and blood clots (Fig. 1B). The cortex was not distinct. The solid portion was mainly dark grayish with a relatively centrally located yellowish area. Microscopic examination demonstrated that the solid component of the tumor was composed of intermingled components of pheochromocytoma, ganglioneuroma, and cells with intermediate features. The grossly yellowish portion was mainly composed of solid sheets or clusters of chromaffin cells while the relatively dark grayish looking peripheral portion was loose fibrillar matrix of the ganglioneuroma component. Necrosis was not noted and the hemorrhage was diffusely dispersed in two components of the tumor. The pheochromocytoma component was occupying about 60% of the tumor area. The sheets of the tumor cells were polygonal with sharply defined cell borders, and amphophilic with a finely granular cytoplasm. They were arranged in predominantly alveolar ("zellballen") or trabecular patterns and supported by a delicate fibrovascular stroma (Fig. 2A). The ganglioneuroma component displayed fully differentiated ganglion cells which showed compact eosinophilic cytoplasm occasionally containing neuromelanin granules with distinct cell borders and a single eccentric nucleus with a prominent nucleolus in the fibrillary background. The Fontana-Masson stain defined neuromelanin granules of ganglion cells and the ganglion cells expressed as neural markers such as neurofilament proteins (Fig. 2B). No neuroblastomatous element or malignant pheochromocytoma was found. But some of the tumor cells showed intermediate features between neurons and chromaffin cells and defining their origin was impossible (Fig. 2C). Even the cells showing pheochromocytoma-like arrangement showed neuronal or ganglionic features.

On immunohistochemical staining, most of the pheochromocytoma component was positive for synaptophysin and chromogranin, but negative for S-100 protein. However, staining for the S-100 protein revealed sustentacular cells that form a peripheral coat around the "zellballen" and Schwann cells (Fig. 3). Special stains for Fontana-Masson and Grimelius were helpful for further defining of the origin of tumor cells with intermediate features, but were not completely defined. The pheochromocytes were positive for Grimelius stain.

Ultrastructural findings showed that pheochromocytes were compactly organized, sometimes with numerous cell processes

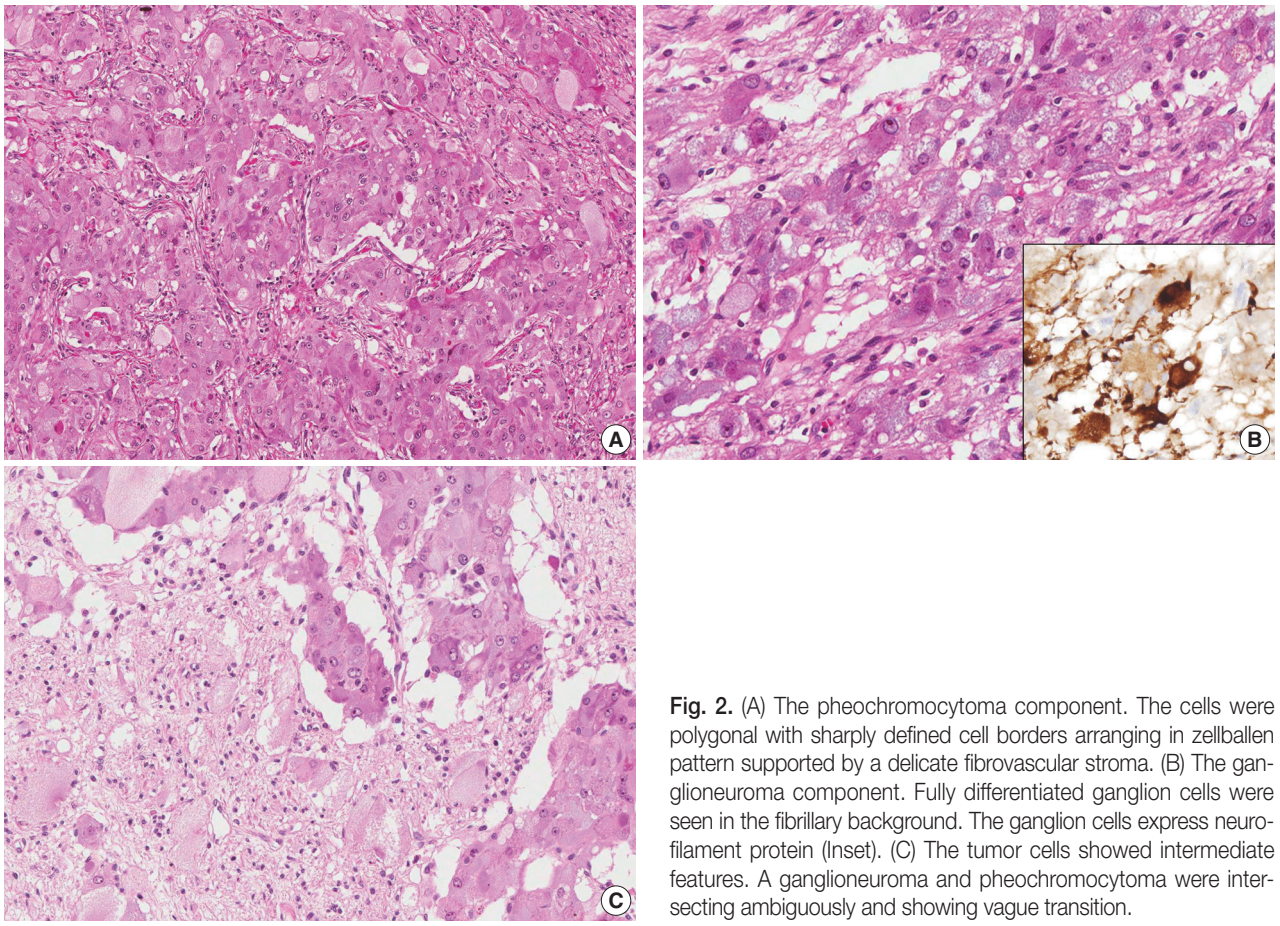

Fig. 2. (A) The pheochromocytoma component. The cells were polygonal with sharply defined cell borders arranging in zellballen pattern supported by a delicate fibrovascular stroma. (B) The ganglioneuroma component. Fully differentiated ganglion cells were seen in the fibrillary background. The ganglion cells express neurofilament protein (Inset). (C) The tumor cells showed intermediate features. A ganglioneuroma and pheochromocytoma were intersecting ambiguously and showing vague transition.

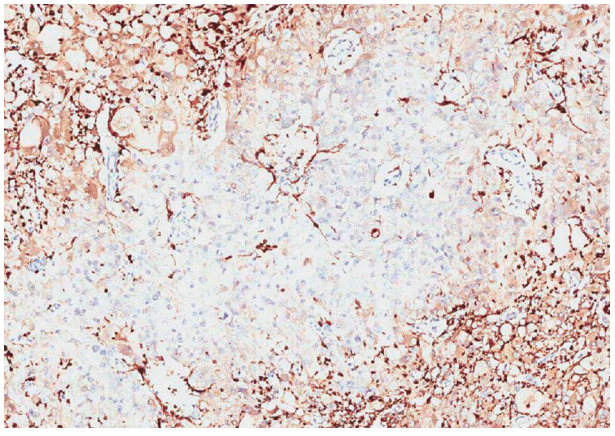

Fig. 3. Immunohistochemical stain. S-100 protein revealed sustentacular cells which form a peripheral coat around the "Zellballen" and Schwann cells.

that were frequently interdigitated. The nucleus was round or ovoid, and occasionally showed prominent nucleolus. The cells containing adrenaline granules showed quite large, round or elongated medium-density granules with a particulate substructure (Fig. 4A). On the other hand, cells containing noradrenaline granules showed small electron-dense granules lying in a large lucent vacuole. Their measurements varied from 100 nm to 400 nm (Fig. 4B). Upon electron microscopic examination, the non-pheochromocytoma component was not identified.

DISCUSSION

Composite pheochromocytoma and ganglioneuroma of adrenal gland is an extremely rare tumor of adrenal gland with only one report to date in Korea.[13] Choi *et al.*[13] reported a case of a composite adrenal medullary tumor of pheochromocytoma and ganglioneuroma masquerading as acute pancreatitis. The tumor was a well defined solid mass measuring 3 cm. On microscopic examination, the tumor showed an abrupt transition of two components. According to Khan *et al.*,[10] in the past 70 years, 45 cases of composite pheochromocytoma were reported, and 75% of them had coexisting ganglioneuroma. Major symptoms of previously reported composite pheochromocytoma and ganglioneuroma of adrenal gland were hypertension, watery diar-

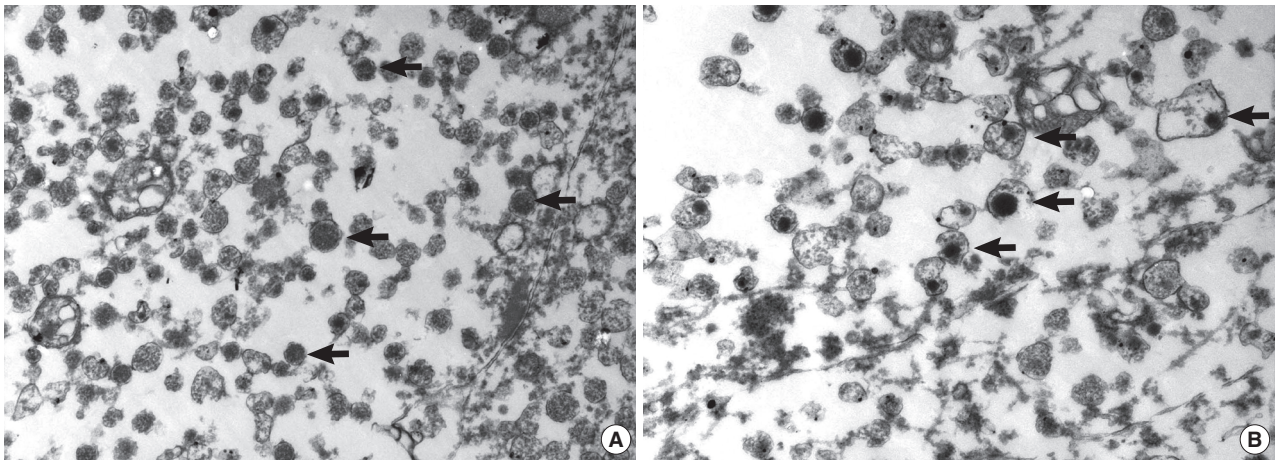

Fig. 4. Ultrastructural finding. The cells containing adrenaline granules showed quite large round or elongated medium-density granules with a particulate substructure (×17,000) (A). Cells containing noradrenaline granules showed small electron-dense granules lying in a large lucent vacuole (×20,000) (B).

rhea, and palpitations, which disappeared after tumor removal.[5,12,14] However, our case consisted of an incidentally found mass and the patient was free of symptoms. The previously reported composite tumors of adrenal glands were densely packed solid masses without cystic degeneration. According to the series by Linnoila *et al.*,[15] which reviewed 120 sympathoadrenal paragnaliomas, 4 cases were reclassified to composite pheochromocytoma presenting as a single solid adrenal mass. Khan *et al.*[10] also mentioned that these tumors usually resemble typical pheochromocytoma with a firm mass in the ganlioneuroma region. Even though previously reported cases manifested as solid masses, our case showed extensive cystic change. Many authors reported an abrupt transition between the two components. However, our case demonstrated a considerable area of intermediate cells. This intermediate feature was also mentioned many times in the previous reports.

Embryologically, both the chromaffin cells of the pheochromocytoma portion and the ganglion cells of the ganglioneuroma are derived from neural crest cells.[2] Previous reports indicated that a neoplastic transformation occurred at the level of sympathogonia, which was followed by a bidirectional maturation process.[2,8] Cells in composite tumors with intermediate features between ganglion cell and chromaffin cells might therefore represent transitional phenotypes. Mendelsohn and Maksem[16] suggested that transition of chromaffin cells to neuron-like phenotypes might be accompanied with an increased production of vasoactive intestinal peptide. Tischler *et al.*[17,18] also reported an experimental report about chromaffin cells from human pheochromocytomas, and argued that they can exhibit extensive spontaneous and nerve growth factor-induced outgrowth of neurite-like processes *in vitro*. For these reasons, the transition between the different components may be gradual or abrupt.

In this case, the adrenal tumor was composed of intermingled components of pheochromocytoma, ganglioneuroma and cells with intermediate features between them. Therefore in some areas, the morphologic distinction of the two components was impossible or indistinct on routine hematoxylin and eosin staining. However, the immunohistochemical and special studies enabled differentiation of chromaffin cells from ganglion cells to some degree. The immunohistochemical stains for S-100 protein, synaptophysin, and chromogranin, and the special stain for Fontana-Masson and Grimelius were helpful in correctly identifying adrenal tumors. Immunoreacivity for chromogranin was found mainly in chromaffin cells and neuronal processes and was weak in ganglionic cells; however, the reaction was too variable to clearly define the separation between the two components. An electron microscopic examination revealed that many of these cells with intermediated features were pheochromocytes that were closely packed with round or ovoid nucleus. The cytoplasm contained neurosecretory granules and we made an effort to find ganglionic type cells having a large nucleus with a prominent nucleolus and abundant cytoplasm in electron microscopic examination, but they were not observed in the sampled areas. This might be due to the fact that there was a relatively small amount of scattered ganglion cells in fibrillar stroma.

In summary, we report a case of composite pheochromocytoma and ganglioneuroma of the adrenal gland, showing extensive cystic change, considerable areas of intermediate cells with immunohistochemical studies and electron microscopic examination.

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