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Morphological Characteristics of Composite Pheochromocytoma with Ganglioneuroma

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ABSTRACT

This report highlights the pathological features of composite pheochromocytoma. A 70 year old man was diagnosed with pheochromocytoma. His tumor was found to be composite pheochromocytoma with ganglioneuroma. Microscopic examination revealed an intricate mix of pheochromocytoma and ganglioneuroma. The two components were blended continuously. We believe that they are derived from common stem cells. Past literature concerning composite pheochromocytoma confirmed our hypothesis. The morphological features of composite pheochromocytoma indicate its tumorigenesis.

Keywords: Adrenal gland, Pheochromocytoma, Ganglioneuroma, Composite pheochromocytom

CASE PRESENTATION

A 70 year old man was referred to our hospital for examination of a left adrenal tumor. He had a history of hypertension and diabetes. Enhanced abdominal computed tomography was performed **(Figure 1A)**. Urine examination showed a catecholamine level of 193.9 µg/day (normal range: 3-15 µg/day) and a metanephrine level of 6890 µg/day (normal range: 40-180 µg/day). 131I-metaiodobenzylguanidine (MIBG) scintigraphy imaging showed significant incorporation into the left adrenal tumor **(Figure 1B)**. Laparoscopic left adrenalectomy was performed and complete resection of the tumor was done. After the surgery, urine catecholamine and metanephrine levels normalized.

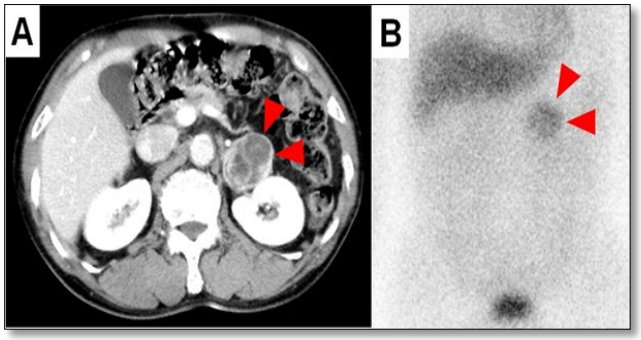

Figure 1. (A) Enhanced abdominal computed tomography revealed a left adrenal tumor (arrow heads). (B) 131I-MIBG scintigraphy showed marked uptake to the tumor (arrow head).

Macroscopy revealed a well-defined tumor coated with a fibrous capsule. The cut surface was yellowish brown. There were cystic degenerations and hemorrhage in the tissue cross-section. The tumor thrusted pre-existing normal adrenal tissue to the verge **(Figure 2)**.

Microscopy revealed that the tumor comprised two histological types. The first component was pheochromocytoma and the second was ganglioneuroma. The two components were blended continuously and merged intricately each other **(Figure 3)**. In the pheochromocytoma-predominant component, the tumor cells proliferated with an alveolar pattern, much like normal chromaffin cells of the adrenal medulla. Reticular fibers with abundant capillary vessels surrounded tumor nests. Tumor cells had numerous basophilic granules, which were strongly positive for chromogranin A **(Figure 4)**. In the ganglioneuroma-predominant component, mature ganglion cells, which have large and acidophilic cytoplasm, were scattered in abundant

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nerve fibers. The nerve fibers were Schwann-like cells and were positive for S-100 protein **(Figure 4)**. The Ki-67 labeling index was less than 1% for both pheochromocytoma and ganglioneuroma. The two components were quite complex and mixed in a macular pattern **(Figure 4)**.

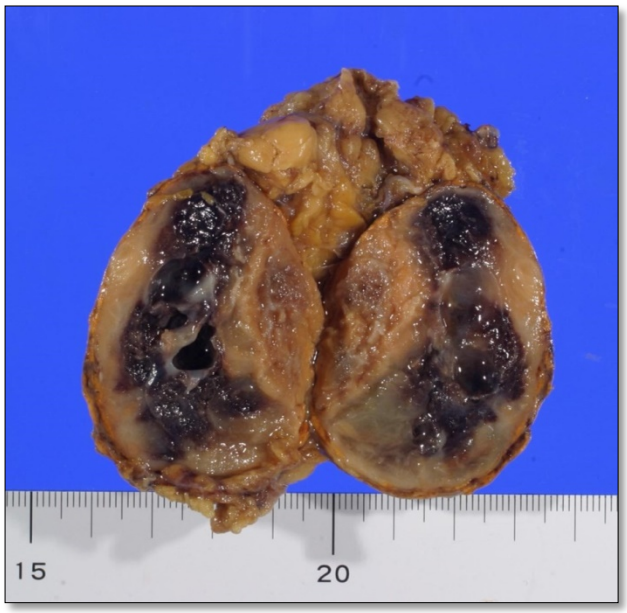

Figure 2. Cut section of left adrenal tumor. The tumor was coated with a fibrous capsule and involved cystic degeneration and hemorrhage. Non-tumoral adrenal tissue became thin due to the tumor.

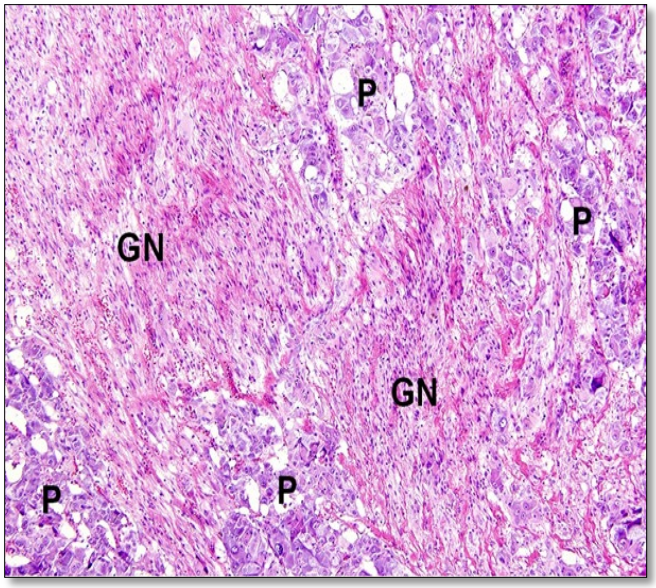

Figure 3. Pheochromocytoma (P) and ganglioneuroma (GN) components were blended continuously and merged intricately each other.

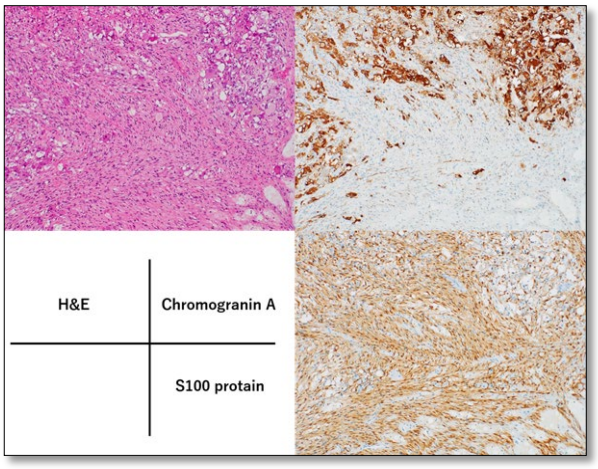

Figure 4. Granules of pheochromocytoma cells were strongly positive for chromogranin A. Nerve fibers of ganglioneuroma were positive for S-100 protein. The two components were quite complex and mixed in a macular pattern.

DISCUSSION

Composite pheochromocytoma is a rare adrenal tumor, accounting for 3% of all adrenal tumors, with less than 70 cases reported to date. It is described as pheochromocytoma with pheochromocytoma and non-pheochromocytoma components [1]. Ganglioneuroma, ganglioneuroblastoma, neuroblastoma, malignant peripheral nerve sheath tumor and neuroendocrine carcinoma are reported as histological types of non-pheochromocytoma [2-13]. In addition to the small number of cases, there are very few studies describing the pathological features of composite pheochromocytoma. Past literature has described only the histological features of composite pheochromocytoma. The relationship between pheochromocytoma and non-pheochromocytoma has not been investigated in detail and the nature of composite pheochromocytoma is largely unknown. Here we investigate the morphological features of composite pheochromocytoma in this case and discuss those mentioned in past literature.

First, we demonstrated the remarkable affinity between pheochromocytoma and ganglioneuroma. We tried to map pheochromocytoma and ganglioneuroma; however, they mixed so intricately that we could not detect their localization in detail. We also evaluated past literature on composite pheochromocytoma, particularly the studies concerning its pathological features [2-13]. We focused on the histology of the non-pheochromocytoma component, localization of pheochromocytoma and non-pheochromocytoma, state of boundaries, and presence of partition **(Table 1)**. As a result, 5 of 13 cases showed mixed localization. Some studies did not investigate localization. From a total of 14 cases, 10 showed a blended boundary, and all cases showed no partition. Interestingly, Brady et al. [2] reported intermediate cells with characteristics of both pheochromocytoma and ganglioneuroma cells.

Table 1. Pathological features of composite pheochromocytoma in recent case reports.

Authors	Age/Sex	Side	Non-P component	P/non-P localization*	P/non-P boundary**	Partition
Brady et al. [2]	34/M	L	GN	-	Blended	-
Matias-Guiu and Garrastazu [3]	49/M	L	GB	Separated	Clear	-
Juarez et al. [4]	69/F	R	NEC	Separated	Clear	-
Onozawa et al. [5]	47/F	L	GN	Separated	Blended	-
Choi et al. [6]	48/M	L	GN	Separated	Clear	-
Lisewski et al. [7]	82/F	L	GN	Separated	Blended	-
Ch'ng et al. [8]	37/F	L	MPNST	Mixed	Blended	-
Thiel et al. [9]	9/F	R	GB	Mixed	Blended	-
Lau et al. [10]	64/F	R	GN	Mixed	Blended	-
Menon et al. [11]	27/M	L	GN	Mixed	Blended	-
Wilsher [12]	52/F	L	GN	-	Blended	-
Zhang et al. [13]	70/M	R	GN	Separate or Mixed	Blended	-
Present case	70/M	L	GN	Mixed	Blended	-

P: Pheochromocytoma; non-P: non-Pheochromocytoma Component; GB: Ganglioneuroma; GN: Ganglioneuroma; MPNST: Malignant Peripheral Nerve Sheath Tumor; NEC: Neuro Endocrine Carcinoma
**P/non-P localization was divided into two pattern "separated" and "mixed" according to the figures in the references*
***P/non-P boundary was divided into two patterns "clear" and "blended" according to the figures in the references*

We hypothesized that the two components of composite pheochromocytoma arise from common stem cells. The adrenal medulla is embryologically derived from neural crest stem cells. Stem cells of the neural crest migrate into the adrenal glands and divide into two lines of differentiation. The endocrine system produces chromaffin cells and the neural system produces sympathetic ganglion cells. The adrenal medulla comprises these systems. American Forces Institute of Pathology (AFIP) describes that pheochromocytoma arising from chromaffin cells collide with ganglioneuroma arising from sympathetic ganglion cells [14]. According to this theory, the tumor should show clearly divided compartments. However, in many cases, pheochromocytoma and ganglioneuroma showed high

affinity. In our opinion, they may have arisen from common stem cells before functional differentiation. Recently, a molecular pathological mechanism has been found. Kimura et al. [15] reported the loss of neurofibromin-NF1 gene product associated with the tumorigenesis of composite pheochromocytoma. According to this hypothesis, a decrease in neurofibromin induces proliferation of Schwann cells and increases in neurotrophin. Neurotrophin causes simultaneous proliferation of ganglion cells and pheochromocytes. We believe this hypothesis suggests that pheochromocytes and sympathetic ganglion cells are closely related to each other because they have a common origin **(Figure 5)**.

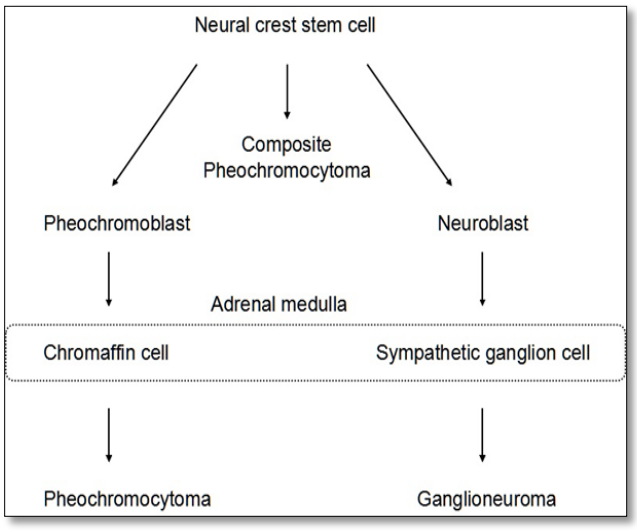

Figure 5. Composite pheochromocytoma derives directly from neural crest stem cells or sympathogonia.

We believe this hypothesis suggests that pheochromocytoma and sympathetic ganglion cells are closely related to each other because they have a common origin and composite pheochromocytoma manifests in various combinations, such as pheochromocytoma with ganglioneuroma, ganglioneuroblastoma, neuroblastoma, malignant peripheral nerve sheath tumor and neuroendocrine carcinoma, as previously reported [2-14]. Although there are also reports that nerve growth factor (NGF) affects chromaffin cells to differentiate into neural cells [16,17]. Ch'ng et al. [8] reported a case followed up for 28 years in which pheochromocytoma transformed into a malignant peripheral nerve sheath tumor. It is also possible that pheochromocytoma transforms secondarily into non-pheochromocytoma components. However, it is likely that composite pheochromocytoma arises from common stem cells because of the remarkable affinity between pheochromocytoma and ganglioneuroma in this case.

CONCLUSION

In summary, this study revealed the morphological features of composite pheochromocytoma, which were missing from many past studies. Our findings suggest that composite pheochromocytoma is derived from common stem cells. Morphology is suggestive of tumorigenesis. Nevertheless, there are few cases and pathological descriptions. Further studies should be undertaken to further reveal the nature of composite pheochromocytoma.

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