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Case Report

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A composite tumor in the adrenal gland: Pheochromocytoma and ganglioneuroma

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ABSTRACT

Composite tumor in the adrenal medulla is a rare tumor containing endocrine and neural components. Pheochromocytoma together with ganglioneuroma combination is the most common compound tumor in the adrenal medulla. Pheochromocytoma originates from the chromaffin cells in adrenal medulla and the ganglioneuroma originates from autonomic ganglion cells. A 49-years-old male patient refers to hospital with the complaint of abdominal pain which had started 1month ago. A mass was detected in his right adrenal gland, and he underwent right adrenalectomy. Macroscopic study of the adrenalectomy material section revealed a 7 x 5 x 4.5 cm dark brown-yellow mass. Histopathological studies revealed that the tumor was consisted of two components 1) areas compatible with pheochromocytoma characterized by islands of polygonal cells with eosinophilic cytoplasm, round-oval nucleus and a prominent nucleolus, and forming small nodules with well-defined margins in a fibrovascular stroma and 2) mature ganglion cells scattered in a stroma with Schwann-like cells. In immunohistochemical study, pheochromocytoma foci were stained positive for chromogranin, synaptophysin and tyrosine hydroxylase. Schwann and ganglion cells were stained positive with S100. On the basis of histomorphological and immunohistochemical findings, the patient diagnosed with compound tumor of pheochromocytoma and ganglioneuroma. Although ganglioneuroma is encountered as a rare tumor, it should be kept in mind in the differential diagnosis of the adrenal masses.

1. Introduction

Composite tumor is a rare tumor which occurs most frequently in the adrenal medulla and is consisted of endocrine and neural components (Rai et al., 2012). The dominant component in this tumor is pheochromocytoma, and the second component is ganglioneuroma in 60-80% of the cases. Rare secondary components are the ganglioneuroblastoma and the neuroblastoma and more rarely the malignant peripheral nerve sheath tumor (Comstock et al., 2009; Menon et al., 2011; Gorgel et al., 2014). Little is known about its biological potential and molecular genetic profile (Comstock et al., 2009). Since these tumors are rarely seen, we would like to present our case of composite tumor of pheochromocytoma-ganglioneuroma together with the data in the literature.

2. Case

The patient was a 49-years-old male. He referred to our hospital with the complaint of abdominal pain which had started 1 month ago. A mass was detected in the right adrenal gland of the patient who had a hypertension history, and he underwent right adrenalectomy.

The macroscopic study of the 10 x7x4.5 cm adrenalectomy material section revealed a 7 x 5 x 4.5 cm tumor. Tumor's margins were well-defined, and it

was covered with a dark brown-yellow fibrous capsule. In histopathological examination, tumor was observed with relatively well-defined margins that had normal adrenal gland tissue around itself. Tumor was also included foci of necrosis and hemorrhage. There were 2 main components in the tumor. Areas compatible with pheochromocytoma were characterized by islands of polygonal cells with eosinophilic cytoplasm, round-oval nucleus and a prominent nucleolus, and forming small nodules with well-defined margins in a fibrovascular stroma (Figs. 1, 2). Second component was consisted of mature ganglion cells scattered in a stroma with Schwann-like cells (Fig. 3). Neuroblastoma-like immature small cell components were not observed. Mitosis was rare in both components. There were large areas of necrosis in the tumor, but no lymphovascular invasion was seen. The tumor showed limited extensions into the neighboring fat tissue.

In the immunohistochemical study, pheochromocytoma foci showed positive staining with chromogranin (monoclonal antibodies, SP12, 1:200, Thermo Scientific, Fremont, USA), synaptophysin (monoclonal antibodies, Clone EP158, 1:200, BioSB, Santa Barbara, USA) and tyrosine hydroxylase (Clone 1B5, 1:40, Novocastra, USA) (Fig. 4). Sustentacular cells showed positive stainingwith S100, and Ki-67 index was lower than 1% (polyclonal Antibodies, Genemed, San Francisco, USA). Typical zellballen islets were observed with the help of silver (Fig. 5). As for ganglioneuroma component, it showed focal positive staining with chromogranin, positive with synaptophysin and tyrosine hydroxylase and diffuse-strongly positive for s100 (Fig. 6). Ki-67 index was lower than 1%. On the basis of the histomorphological and immunohistochemical findings, the patient was diagnosed with compound tumor of pheochromocytoma-ganglioneuroma.

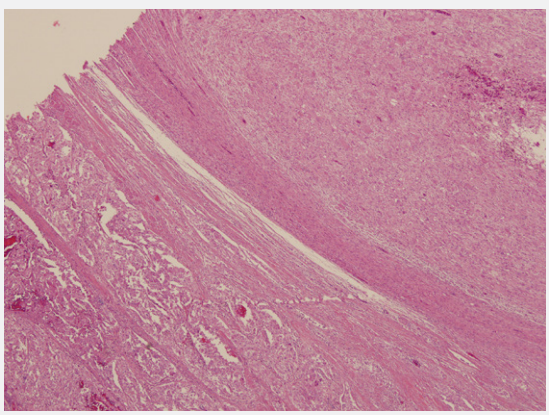

Fig. 1. Two distinct component of tumour (HE X 40).

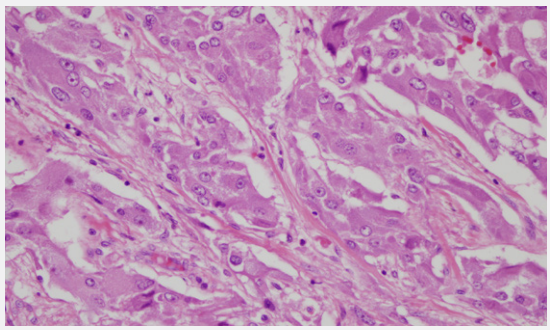

Fig. 2. Pheochromocytoma component (HE X400).

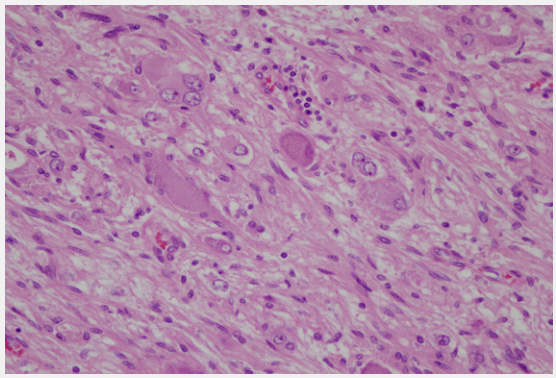

Fig. 3. Ganglioneuroma component (HE X 400).

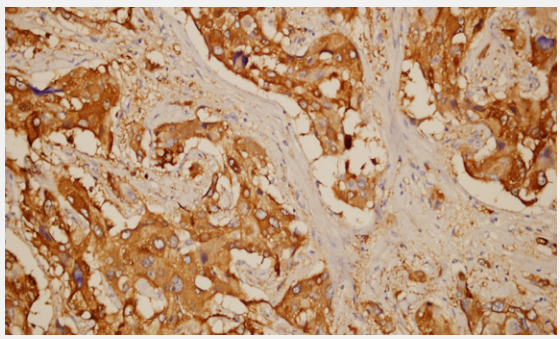

Fig. 4. The chromaffin cells were strongly positive of Tyrosine Hydroxylase (DAB X 200).

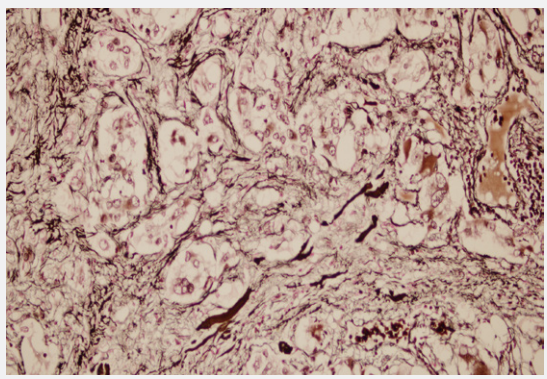

Fig. 5. Zellballen islets (Silver X 200).

Fig. 6. Ganglioneuroma component showed diffuse-strongly positive for S100 (DAB X 400).

3. Discussion

Composite tumors of the adrenal medulla are rare tumors, and they account for less than 3% of the sympatho adrenergic pheochromocytomas (Choi et al., 2006; Rao et al., 2014). While pheochromocytoma originates from adrenal medulla chromaffin cells, ganglioneuroma develops from autonomic ganglion cells. Embryologically, chromaffin and ganglion cells arise from neural crest cells and from the migration into somatic field. Compound tumor can occur due to faulty migration into the somatic area or due to disrupted development of neural crest cells (Choi et al., 2006; Rao et al., 2014). Both components of the compound tumor can cause hormonal hypersecretion, and symptoms related to hypersecretion can occur. Clinically headache, tachycardia, excessive sweating can be observed in 50% of the patients with active pheochromocytoma. A continuous or paroxysmal hypertension is the basic symptom of pheochromocytoma (Choi et al., 2006; Rai et al., 2012; Rao et al., 2014). Moore et al. reported hypertension only in 4 patients out of 13 patients with composite tumor (Choi et al., 2006). Our patient also had a hypertension history. Aqueous diarrhea due to increased vasoactive intestinal peptide (VIP) has been reported in some patients. Both components of the composite tumor can secrete VIP (Mahajan et al., 2010; Hu et al., 2013).

The patients reported in the literature are usually over 30 years old, most of them are in the fifth decade. Similar to the patients in the literature, our patient was 49 years old. Tumor is equal in males and females. Significant numbers of the patients are sporadic. But it can rarely be comorbid with the syndromes of hereditary pheochromocytoma/paraganglioma outside the adrenal gland, syndromes of familial tumor such as neurofibromatosis type 1 (NF), multiple endocrine tumor (MEN) syndromes or adrenocortical tumors (Lam and Lo 1999; Gücin et al., 2003; Comstock et al., 2009; Hu et al., 2013; Shida et al., 2013). In our patient, MEN, NF or adrenocortical tumor were not observed.

The differential diagnosis includes adrenocortical adenoma or hyperplasia and other adrenal tumors such as of adrenocortical carcinoma and pheochromocytoma. Pathological study is essential in determining the components of compound tumor. Microscopic study should be performed carefully in large areas. In a study including 46 patients, compound tumor with ganglioneuromatous component was detected in 4 patients. The cases displayed heterogeneous radiological, macroscopic and microscopic features (Menon et al., 2011). Compound tumors in the bladder, retroperitoneum and caudaequina have also been reported (Hu et al., 2013). It is difficult to estimate the biological behavior of the compound tumor. Prognosis of these tumors varies. Metastatic lesions of compound tumor almost always develop from the neural component. Accordingly, in microscopic evaluation, immature neuroblastic component should be studied carefully for the metastatic potential. Autopsies revealed liver metastasis only in one of the patients with pheochromocytoma ganglioneuroma (Comstock et al., 2009; Rao et al., 2014). In one study, N-myc amplification was studied both in the compound tumor and pheochromocytoma. It was found out that neuroblastic elements in the compound tumor had low mitotic- karyorrhectic index and positive histological features, but no N-myc amplification was detected. These results indicate that neuroblastic elements have no prognostic importance in composite tumors (Comstock et al., 2009; Rao et al., 2014). In our study, neuroblastoma-like immature small cell components were not observed. The main treatment of compound tumor is surgical resection. Clinical follow-up is recommended for the malignancy potential (Hu et al., 2013).

In conclusion, composite tumor of pheochromocytoma-ganglioneuroma is a rare tumor. Components of tumors can be identified in the adrenal tumor resection specimens with careful macroscopic, microscopic and immunohistochemical study. Metastasis is rare. It is mostly observed together with ganglioneuroblastoma, so microscopic examination should be performed carefully in large areas. Neuroblastoma-like foci elimination is important for the recurrence and follow-up of metastasis.

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