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Case Report

Diverse proportion in composite pheochromocytoma-ganglioneuroma may induce varied clinical symptom: comparison of two cases

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Abstract: Composite pheochromocytoma-ganglioneuroma is extremely rare. We described two cases of composite pheochromocytomas in the adrenal medullar. Case 1 was a 70-year-old male presenting with lower abdominal pain and normal blood electrolytes. Case 2 was a 48-year-old female with palpitation and back tenderness. Biochemical investigations showed hypocalcium, hypokalemia and high level of vma. The histological images and the immunohistochemical staining demonstrated the two cases composed of pheochromocytoma and ganglioneuromoma components. Ganglioneuroma component in case 2 accounted for more proportion than that in case 1. We speculated that the varied clinical symptoms were related with the diverse proportions in composite pheochromocytome-ganglioneuroma.

Keywords: Composite pheochromocytoma, pheochromocytoma, ganglioneuroma, clinical symptom

Introduction

Composite pheochromoytoma (CP) is a rare tumor which composed of pheochromocytoma or paraganlioma with non-pheochromocytoma components, and make up less than 3% of pheochromocytoma in adrenal medulla [1]. Up to 2014, less than 70 cases of CP have been reported. Clinical manifestation presented diversity, which was related with age, gender of the patients, tumor size, and admixed component of the tumor. Here we report 2 cases of CP in adrenal medullary with pheochromocytoma and ganglioneuroma component in period of 2000-2014. The 2 cases showed different clinical manifestation, the reason of which may be diverse proportion of the admixed component.

Case report

Case 1. A 70-year-old male presented with a week history of lower abdominal pain, and came to the second affiliated hospital of Zhejiang university on 23rd Sep, 2009. General physical examination was unremarkable. Routine blood test and biochemical parameters were within normal reference. CT scan revealed a mass measured 8×6×4 cm in size above the right kidney (**Figure 1A**, **1B**). The urinary vanilmandelic acid (vma) level was not detected. During the laparotomy, a mass in right adrenal was found with no obvious capsular, adhered with the tissue surrounding. A right adrenalectomy was performed and the surgical specimen submitted to the pathology department. Grossly, it was found a nodular mass measured 9×7×3 cm in size, with clear boundary and tan-pink to dark red cutting surface. Microscopic sections showed the tumor wrapped by incomplete fibrous capsule, and with little adrenal cortex surrounding. The tumor cells were composed of two types morphology. The primary morphology was consisted of basophilic cell nests in patchy or “zellballen-like” pattern. The basophilic cell component area contained rich blood sinus, and consisted of medium-sized cells. These cells had abundant cytoplasm and round vesicular nucleus, with mild nuclear edge accumulation and indistinct

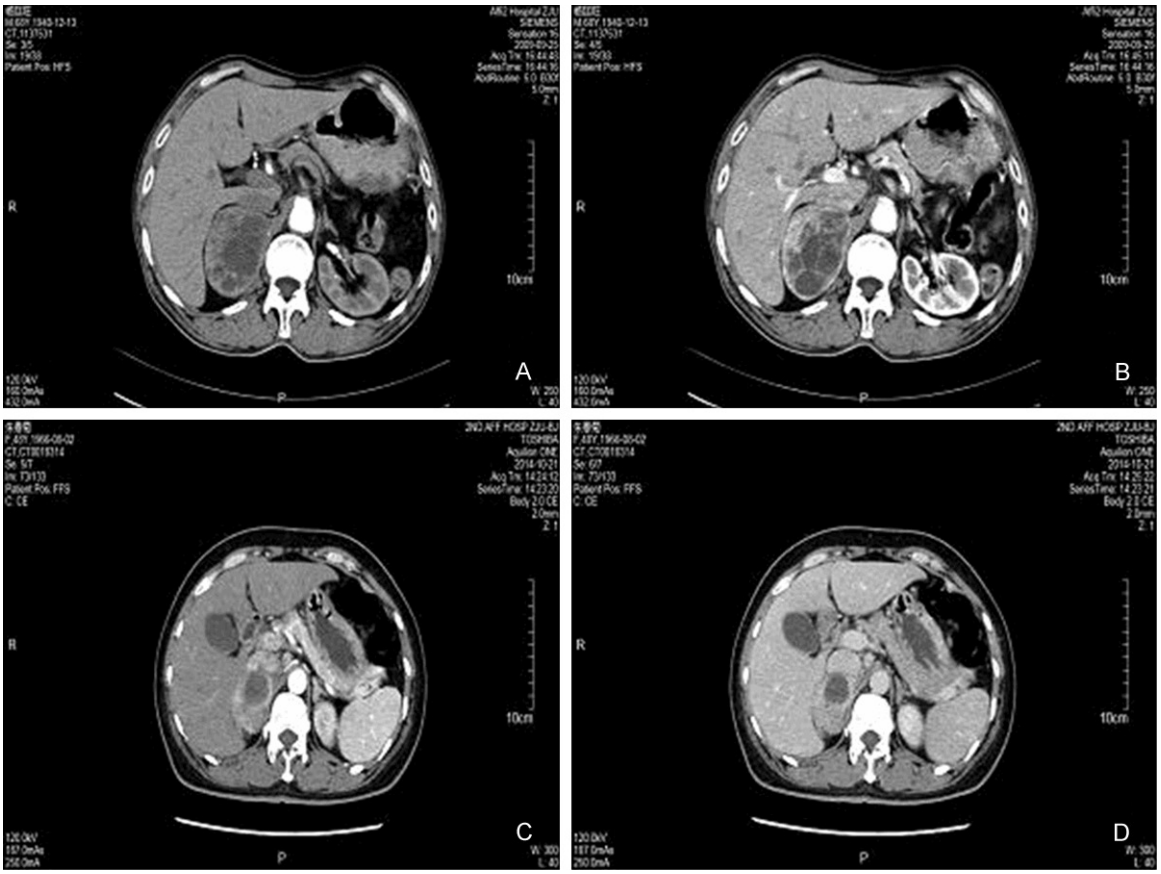

Figure 1. Radiologic images A+B of case 1, the enhancement CT scanning showed a mass measured 8×6×4 cm in size inter hepatonephric (A. Arterial phase; B. Potal vein phase). Images C+D of case 2, the enhancement of CT scanning showed a mass measured 6×6×4 cm in the right adrenal (C. Arterial phase; D. Potal Vein phase).

nucleoli. The minor morphology was composed of scattered large cells with ill-defined cell borders and abundant amphophilic cytoplasm. The amphophilic cells presented with large nuclei, fine chromatin and infrequent nucleoli. The two components demonstrated separate or mixed distribution with each other in the same section (**Figure 2A**, **2B**).

Case 2. A 48-year-old female was admitted to our hospital on 17th Oct, 2014 for palpitation and back tenderness for one day. She had no history of hypertension, headache or diarrhea. Blood electrolytes analysis found the level of kalium 3.0 mmol/L (normal 3.50-5.50), calcium 1.98 mmol/L (normal 2.20-2.65), vma 111.40 μmol/24 hours (normal 0.1-68.6). CT enhanced scan showed a mass measured 6×6×4 cm in the right adrenal (**Figure 1C**, **1D**). A right open adrenalectomy was performed and a mass was found in the right adrenal. The mass located behind the vena cava, and adhered with right liver. The specimen received was a nodule measured 7.5×5.5×5 cm in size without capsular. The cut surface of the solid tumor was tan-pink to yellowish with focal dark red color. Multiple sections from the representative areas of the specimen revealed polymorphic tumor cells distributed irregularly with focal lymphocyte infiltration, fresh or stale hemorrhage and little adrenal cortex. Similar to the case 1, the tumor of case 2 was composed of the prominent “zellballen-like” basophilic cell nests and the minor scattered large amphophilic cells. Different from the case 1, there were more amphophilic large cells, partly extensive coagulation necrosis and bundles of spindle cells gathered in case 2. The spindle cells presented with abundant cytoplasm and mild nuclei. No mitosis was identified in total sections. Scattered amphophilic large cells were embedded in the spindle cells background (**Figure 3A**, **3B**). The tumor capsuled by hyperplastic fibrous tissue was adhered to the right

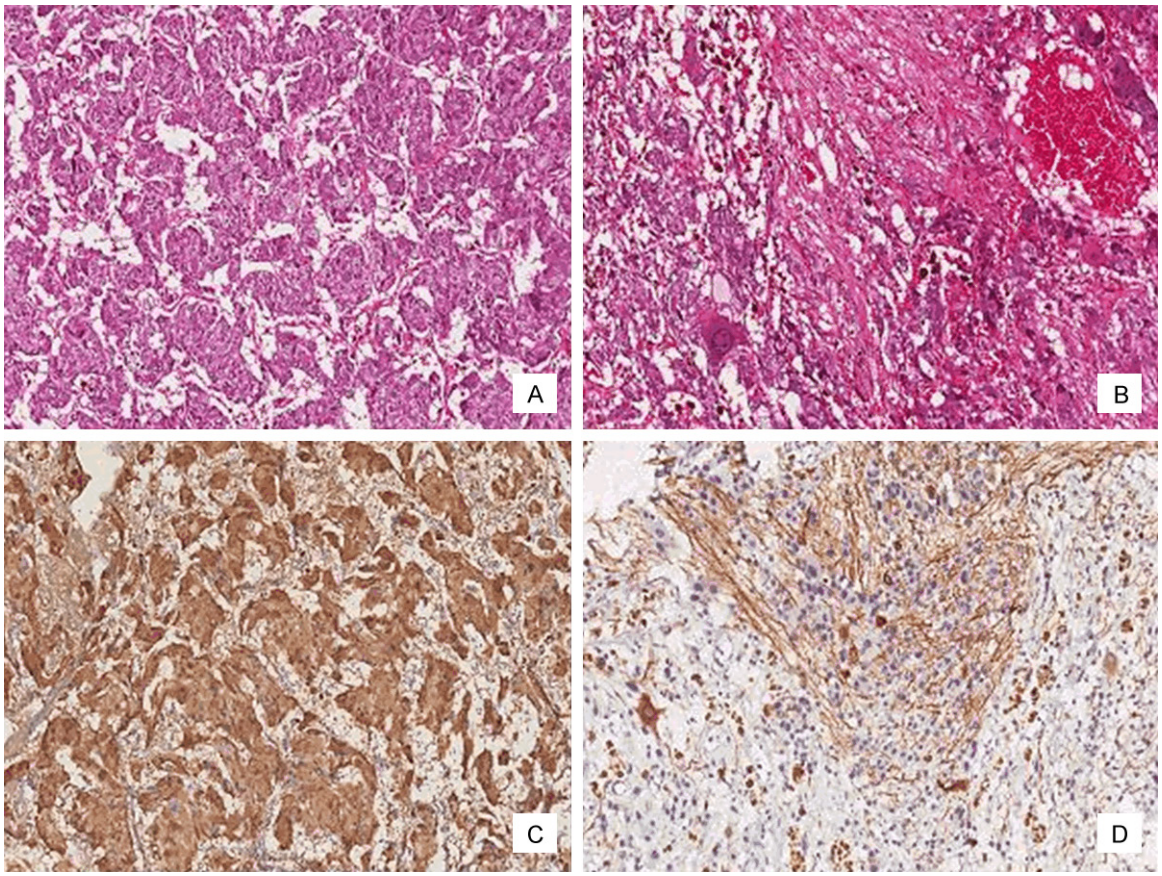

Figure 2. Histologic and immunohistochemical features of case 1. The tumor was composed of predominant pheochromocytoma component (A. H&E, ×100) and scattered ganglion cells (B. H&E, ×100). Pheochromocytoma component was diffused positive for CgA (C. ×100). NF staining highlighted the scattered ganglion cells and unremarkable shwann cells of ganglioneuroma component (D. ×100).

liver, however, no tumor cells invaded into the liver.

Immunohistochemical staining (**Figures 2C**, **2D**, **3C**, **3D**) showed the basophilic cells in both cases strongly positive for chromogranin A (CgA) and synaptophysin (Syn), but negative for neurofilament (NF), of which composed the peochromocytoma component. The staining signal of CgA was located in the cytoplasm of the pheochromocytoma cells in case 1, while partially diffused positive in cytoplasm and partially dotted positive beside the nucleus in case 2. In contrast, the scattered amphophilic large cells were stained weakly for CgA and Syn in cytoplasm, while strong positive for NF and S100. It prompted that these amphophilic large cells were ganglion cells existed. The positive staining for S100 in the sustentacular cells outlined the chromaffin cell nests. NF and S100 staining highlighted the spindle cells (schwann cell), even in case 1 where no remarkable spindle cell was observed in routine H&E staining slides.

Combined the morphologic and immunohistochemical features, both cases herein were diagnosed as CP with component of ganglioneuroma. As the minor component, ganglioneuroma in case 2 accounted for more proportion than that in case 1.

Discussion

The types of pheochromocytoma, according to different histological elements having common embryologic ancestry, are assigned as “composite” and “mixed” pheochromocytoma. The non-pheochromocytoma components reported in the “composite” pheochromocytoma theoretically are of the same embryonic origin with pheochromocytoma, including ganglioneuroma [2], ganglioneuroblastoma [3], neuroblastoma,

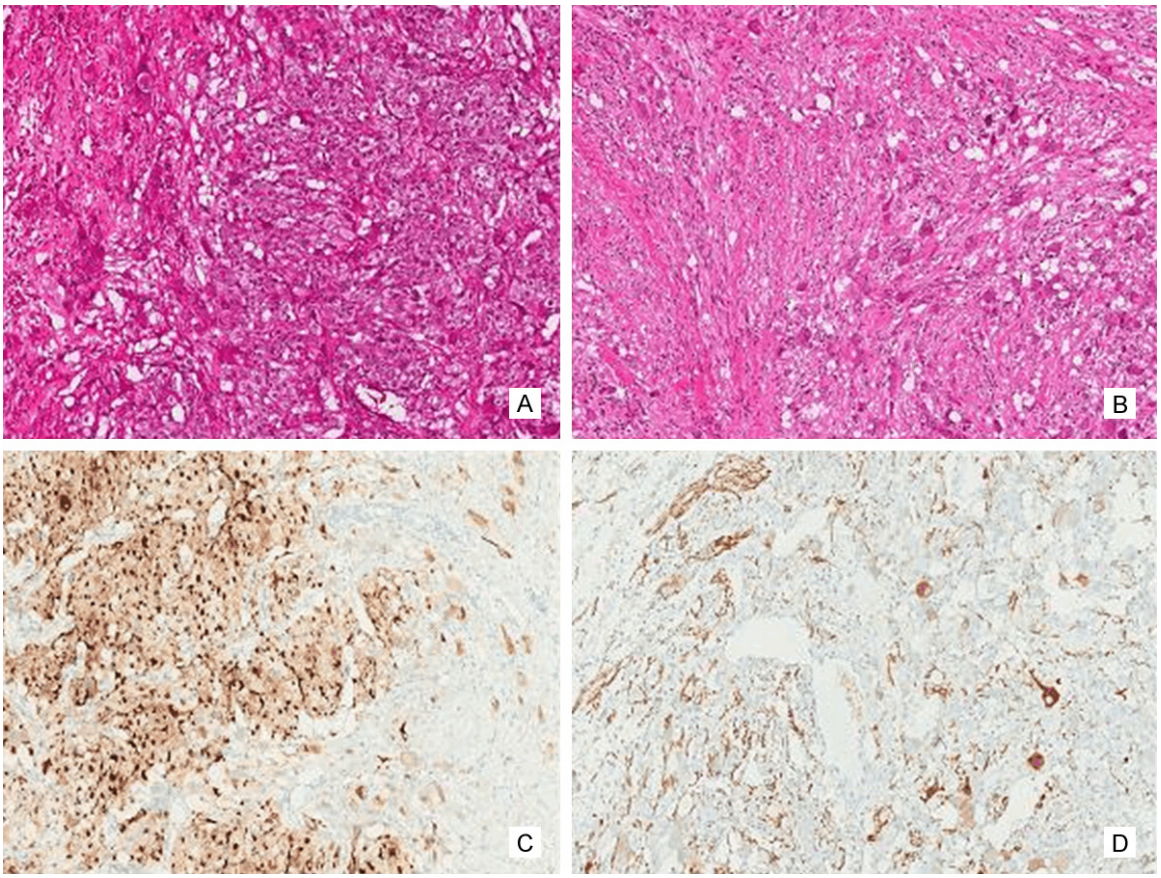

Figure 3. Histologic and immunohistochemical features of case 2. The patchy pheochromocytoma component (A. H&E, ×100) and the ganglioneuroma component (B. H&E, ×100) admixed. Partial pheochromocytoma cells were dotted positive beside the neucleus for CgA (C. ×100). NF staining highlighted the ganglioneuroma component (D. ×100).

malignant schwannoma and neuroendocrine carcinoma [4]. Ganglioneuroma is the most common accompanying second tumor component in CP and reaching up to 70% in total. Pure pheochromocytoma represents a tumor from the adrenal medullary chromaffin cells, however, ganglioneuroma originated from autonomic ganglion cells or their precursor. Embryologically, both chromaffin and ganglion cells are derived from neural crest cells and migrates to somatic areas [5].

Most (>92%) CPs were located in the adrenal gland with a slight right adrenal preponderance. Males and females had approximately equal risk involving the tumor [6]. The patient age ranged from 5 to 82 years old, with media age 51.5 years old [7]. The surgical specimens of CP appeared as solid nodule with or without capsule, usually attached with some gold-yellow adrenal gland. The tumor size ranged from 1.8 to 35.0 cm in diameter, with the average being 4 to 6 cm [7]. Grossly, CP presented as similar to pure pheochromocytoma. The cut surface of tumors showed yellowish and tan-pink areas, with focal hemorrhage and congestion. Microscopic sections revealed the tumor composed of typical pheochromocytoma admixed separately or closely with ganglioneuroma component. These characters were in accordance with ours. The proportion of ganglioneuroma in different individuals varied apparently, ranged from very prominent ganglioneuroma component to very sporadic ganglion cells observed. Carefully examination of the resected specimens, adequate sampling and carefully microscopic observation were necessary. Immunohistochemical staining was usually used to identify the histomorphological diversity of a composite tumor. CgA and Syn stained strong positive in chromaffin cells, however, weakly or focally positive in mature gan-

glion cells. Except the expression intensity, the expression site of CgA varied in case 2, which was dotted positive beside the nucleus in partial pheochromocytoma cells. The meaning of the special expression pattern was not clear. However, this difference was helpful to differentiate the diverse components. S100 protein was stained in the schwann cells of ganglioneuroma component and sustentacular cells at the periphery of chromaffin cells nest.

Clinically, most cases of CP were functional, completely non-functional cases were very rare. The classic symptoms of CP presented with headache, palpitations, and excessive perspiration. However, hypertension, either sustained or paroxysmal, was the cardinal feature of the tumor [8], reaching over 62% of the patients [9]. The symptoms displayed were correlated with the increased level and the corresponding metabolites of VIP and catecholamine [10, 11]. Clinical manifestations of watery diarrhea, hypokalemia and achlorhydria syndrome (WDHA) associated with secretion of VIP. Both pheochromocytoma and non-pheochromocytoma components could release VIP, which further supported its homology [12, 13]. Catecholamine mainly secreted by pheochromocytome component, could result in the symptoms of hypertension, headache, palpitation and excessive perspiration [8]. Some patients with composite tumor presented with normotensive or hypotensive. Related possible hypothesis is ganglioneuroma component may autonomic modify the hormone section symptoms of pheochromocytoma component by metabolizing the catecholamine [2]. The patient of case 1 came to our hospital with abdominal pain. Biochemical investigations showed normal blood electrolytes. Vma level had not been detected. Another patient of case 2 complained of palpation and back tenderness with hypocalcium, hypokalemia and high level of vma. The comparison of vma could not be actualized due to lack of data in case 1. Both cases presented with normal blood pressure, which manifested the autonomic regulation of the ganglioneuroma component. Except regulating the hypertension, the ganglioneuroma component caused hypocalcium and hypokalemia in case 2 mainly by secreting VIP, while no any abnormity of blood electrolyte in case 1. The histologic observation and immunohistochemical analysis found obviously more ganglioneuroma component in case 2 than that in case 1. It was speculated that the more proportion of ganglioneuroma component produced the greater regulation effect. That is, diverse proportions in composite pheochromocytoma-ganglioneuroma may induce varied clinical symptoms.

Moreover, the symptoms of some CP cases were altered during a prolonged follow up, which suggested histologic transformation and expansion of hormone-producing cells during the development of composite tumor [12]. The mechanism of the transformation has not been illustrated with detail. Tischler AS et al. [14] described the neuro-like cells presented in cases of pheochromocytoma. Chromaffin cells substantiated in vitro may differentiate to neuronal cells with neuritis [15]. This histologic transformation resulted in additional hormones production and modification of the clinical symptoms. E S Ch'ng et al. [16] reported a 9-year-old girl with pheochromocytoma had a malignant transformation to CP with MPNST over a time span of 24 years, and 4 years later the patient died of MPNST. Therefore, long-term follow up about the endocrine symptoms and peptide hormone level was necessary to the CP. In case with no metastasis, completely surgical resection was sufficient. Some patients received chemotherapy but had no effect on survival [17]. However, this type sample size was too small to be statistical significance. The patients of our cases just accepted complete tumor resection. The main complaint disappeared after the surgery. Closely followed up for 69 months and 8 months, no recurrence or metastasis was found in both patients.

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Disclosure of conflict of interest

None.

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