

Original Article

Composite pheochromocytoma/ganglioneuroblastoma of the adrenal gland: a case report and review of literature

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Abstract: A 41-year-old female presented with left retroperitoneal mass. The mass arose from the left adrenal gland, and the left adrenalectomy was performed. Pathological diagnosis was composite pheochromocytoma (CP)/ganglioneuroblastoma. The patient recurred 28 months later. After palliative excision, the diagnosis of left adrenal Neuroblastoma (differentiated type) was made. The second recur occurred 19 months later at subdural space of 3-5 cervical spine. Laminectomy and laminoplasty was manipulated. The pathological diagnosis was spinal canal neuroblastoma (poor-differentiated type). Here, we presented a case of composite adrenal gland tumor with compounds of both pheochromocytoma and ganglioneuroblastoma. From the complete follow-up investigation of this patient and reviewing the past literatures, we noticed that more careful monitoring should be paid by pathologists and clinicians when the patients are diagnosed as CP.

Keywords: Composite pheochromocytoma, adrenal gland, neuroblastoma, prognosis

Introduction

Composite tumors consisting of pheochromocytoma and ganglioneuroblastoma of adrenal gland are rarely seen less than 0.9% of all symthoadrenal tumors [1]. Composite pheochromocytoma (CP) always combines such as ganglioneuroma, ganglioneuroblastoma, neuroblastoma, peripheral nerve sheath tumor or neuroendocrine carcinoma [2]. Among cases reported by literatures, CP compositing with ganglioneuroma accounts 81% [3], compositing with ganglioneuroblastoma accounts 10% [4]. Because CP/ganglioneuroblastoma is very rare, the recognition to clinical manifestation, diagnosis and prognosis of this disease needs to be improved.

Case presentation

A 41-year-old female presented to the 1st affiliated hospital of Dalian Medical University in May 2009, with 5-month history of upper abdominal and backache. The patient had a past

history of duodenal bulb ulcer 3 years prior, but did not reveal a history of hypertension or endocrine disease herself or in her family. Additionally, she was not a consumer of alcohol or tobacco.

The patient had a pulse of 78/min and a blood pressure (BP) of 118/82 mmHg. Physical examination revealed a soft abdomen, no tenderness, no organomegaly, no ascites and no palpable masses. Ultrasonography (USG) of the abdomen showed a left adrenal mass. Magnetic resonance imaging (MRI) examination confirmed a well-circumscribed heterogeneous mass measuring 5.4×4.0×4.0 cm, which located in the left retroperitoneal area (**Figure 1A**). It presented T1w hypo-intensity and T2w hyper-intensity. Pancreas was pushed forward, and the left kidney was pushed backward. The left adrenal gland was not apparent. Other laboratory results were within the reference ranges except urine vanillylmandelic acid (VMA) (27.34 mg/24 hr) (reference range: 1.9~13.6 mg/24 hr). The patient underwent left adrenal-

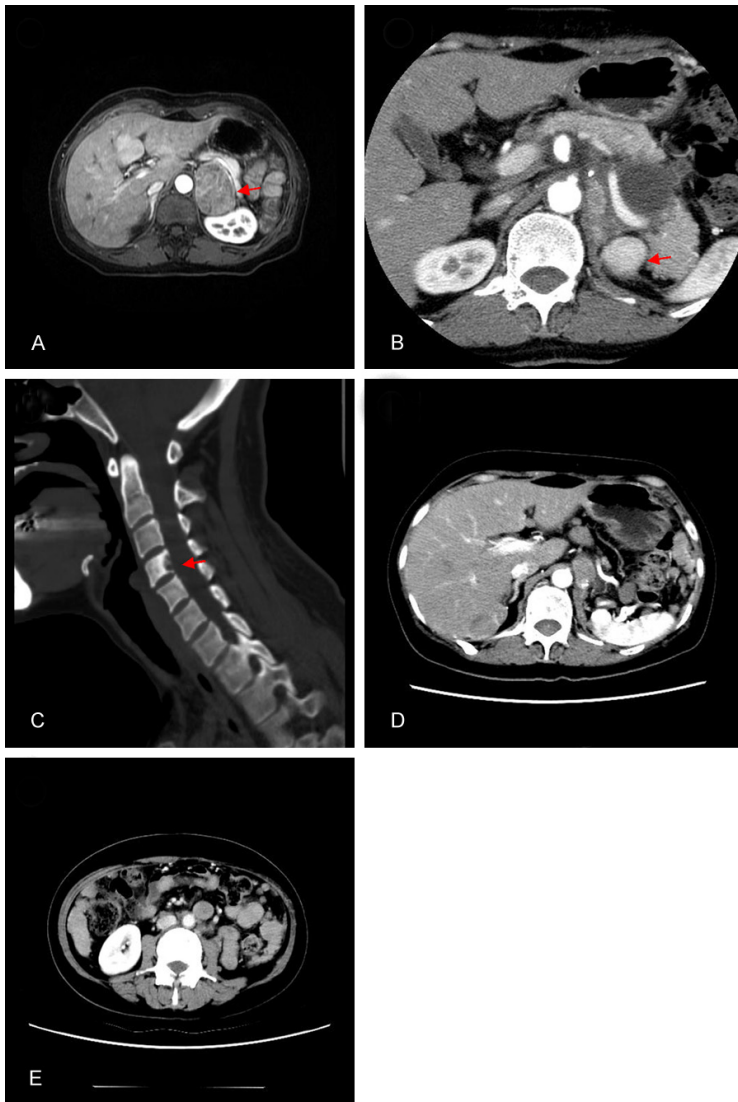


Figure 1. A. Magnetic resonance imaging (MRI) confirming a left retroperitoneal mass (Red arrow) (2009.05). B. Computed tomography (CT) examination of 9 months after first operation, the left adrenal gland zone was clear and no recurrent tumor was observed. C. CT examination confirming a signal-enhancing mass (7.2×6.6 cm) (Red arrow) with heterogenous density and clear border in the left adrenal gland area (2011.11). D. Cervical CT presented a spindle heterogenous mass at subdural space from superior of 3rd cervical spine to inferior of 5th cervical spine (2013.05). D and E. The recurred tumor (2014.03 and 2014.07) located in left adrenal gland area. Systematic metastasis including several lymph nodes and peritoneum was confirmed by MRI.

ectomy. During the operation, the mass (d=5 cm) was noted to locate in the left adrenal gland with a complete capsule. It showed gray-yellow and soft tan appearance surrounded with few fat tissue. The cut surface of mass was yellow-white at periphery but dark brown at center with local cystic change (**Figure 2**). Dissecting near the main tumor made the

patient's BP rise up to 180/120 mmHg, while, made BP go down to 120/70 mmHg as the complete resection was done. The patient remained normotensive in the postoperative period. Her postoperative urine VMA fell to 13.62 mg/24 hr. Subsequent pathological examinations of the surgical specimen showed left adrenal gland composite pheochromocytoma including some ganglioneuroblastoma compounds. The patient recovered well after first resection without postoperative adjuvant chemotherapy or radiotherapy. Long-term follow-up was suggested. Computed tomography (CT) examination of 9 months after first operation, the left adrenal gland zone was clear and no recurrent tumor was observed (**Figure 1B**).

After 28 months, in October 2011, the patient presented to our hospital again with complaint of dull backache. CT examination showed a signal-enhancing mass (7.2×6.6 cm) with heterogenous density and clear border in the left adrenal gland area (**Figure 1C**). Pancreas and Spleen artery and vein were move forward. Pancreatic tail, left spleen and left kidney were invaded. No enhanced lymph-node was observed. No distant metastasis of lung or liver was found by USG and X-ray. Urine VMA was 63.75 mg/24 hr before operation. Other laboratory results were within the reference ranges. During the operation, vascular tortuosity was

observed on the tumor surface. Spleen and vessel was moved upward. Resection of tumor was done. Postoperative urine VMA was 19.92 mg/24 hr. The tumor presents lobulated pattern and reddish black section. Subsequent pathological examinations of the surgical specimen showed left adrenal Neuroblastoma (differentiated type).

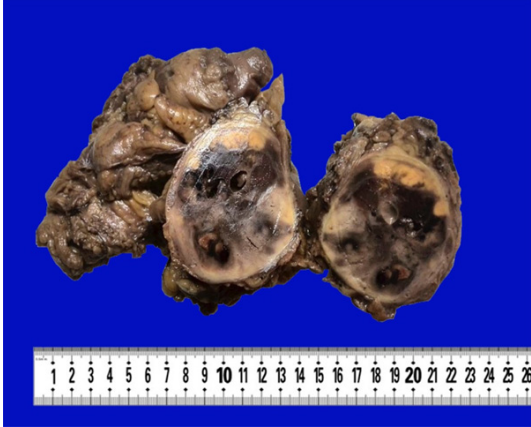


Figure 2. Macroscopic appearance of the original tumor in left adrenal gland.

In May 2013, 19 months after the second operation, this patient was hospitalized in the third time complaining of 12-month history of left neck and shoulder pain with no acroanesthesia and no incontinence. Cervical CT presented a spindle heterogenous mass at subdural space from superior of 3rd cervical spine to inferior of 5th cervical spine. The mass measured 4.3×1.0 cm, and had a clear border. There was bone destruction in 4th cervical spine. Cervical CT presented that the mass (3×0.6 cm) revealed T1w1 and T2w1 iso-intensity or slight hyper-intensity and homogeneous enhancement (**Figure 1D**). Emission Computed Tomography (ECT) examination revealed bone and joint of whole body are almost normal except heterogeneous enhancing radionuclide distribution in the cervical spine symmetrically. Abdomen CT showed 42HU mass in left adrenal gland zone. No obvious changes were observed comparing with March 2013. Average urine VMA was 18.32 mg/24 hr. Laminectomy and laminoplasty were performed. Postoperative urine VMA was 9.82 mg/24 hr. Pathology report showed spinal canal neuroblastoma (poor-differentiated type).

Pathology finding

First pathology finding: Sections from left adrenal mass showed a tumor composing with 40% elements of polygonal cells arranged in well-defined nests-structure. Delicate fibrovascular stroma (so-called Zellballen pattern) surrounded these nests. These polygonal tumor cells showed abundant amount of granular eosinophilic or amphophilic cytoplasm, oval nuclei

with single prominent nucleoli (**Figure 3A**). The residual composed of 60% elements include 20% ganglioneuroma elements (**Figure 3D**) and 40% ganglioneuroblastoma elements (nodular type) (**Figure 3G, 3H**) which surrounded by fascicles of Schwann-like cells. Areas of hemorrhage, necrosis, dense fibrocollagenous tissue and mixed inflammatory cell infiltration within the tumor were also seen within the tumor. There were normal adrenal glands at the periphery of the tumor. However, the primitive neuroblastic cells were not observed. Immunohistochemistry study showed pheochromocytoma components: synaptophysin (+), chromogranin (+), glial fibrillary acidic protein (+), neurofilament (-), Vimentin (-), S-100 (+) for supporting cells (**Figure 3B, 3C**); ganglioneuroma components: synaptophysin (+), S-100 (+) for Schwann cells (**Figure 3E, 3F**); ganglioneuroblastoma components: synaptophysin (+), chromogranin(+), fibrillary acidic protein (-), neurofilament (-), Vimentin (-), Ki67 (+5%) (**Figure 3G-I**). The final diagnosis of CP/ganglioneuroblastoma was made.

Second pathology finding: In the background of abundant neuropil, neuroblastoma cells of different differentiated degree were observed. Major of them presented few cytoplasm, oval or spindle shape and round or oval nuclei with little prominent nucleoli. Some of them had large nuclei, bubble chromatin, single prominent nucleoli, abundant cytoplasm and amphophilic. Diameter of cytoplasm was bigger than two-fold of nuclei's. These suggested that those cells (>5%) came to differentiate to ganglion cells (**Figure 4A**). Amount of hemorrhage in tumor tissue were observed. Nuclear division were >10 cells/10 high magnifications. Immunohistochemistry study showed synaptophysin (+), NSE (+), Ki67 (10% +), chromogranin (-), glial fibrillary acidic protein (-), S-100 (-), neurofilament (-) (**Figure 4B-D**). The final diagnosis was neuroblastoma (Differentiated type).

Third pathology finding: In the background of abundant neuropil, amount of distributed small cells were observed. Major of these cells showed few cytoplasm, round shape, hyperchromatic nuclei and no nucleoli. Less than 5% of these cells presented slightly bigger nuclei, bubble chromatin, single and prominent nuclei, abundant cytoplasm and double tropism. Immunohistochemistry study showed synaptophysin (+), chromogranin (+), S-100 (-), neurofil-

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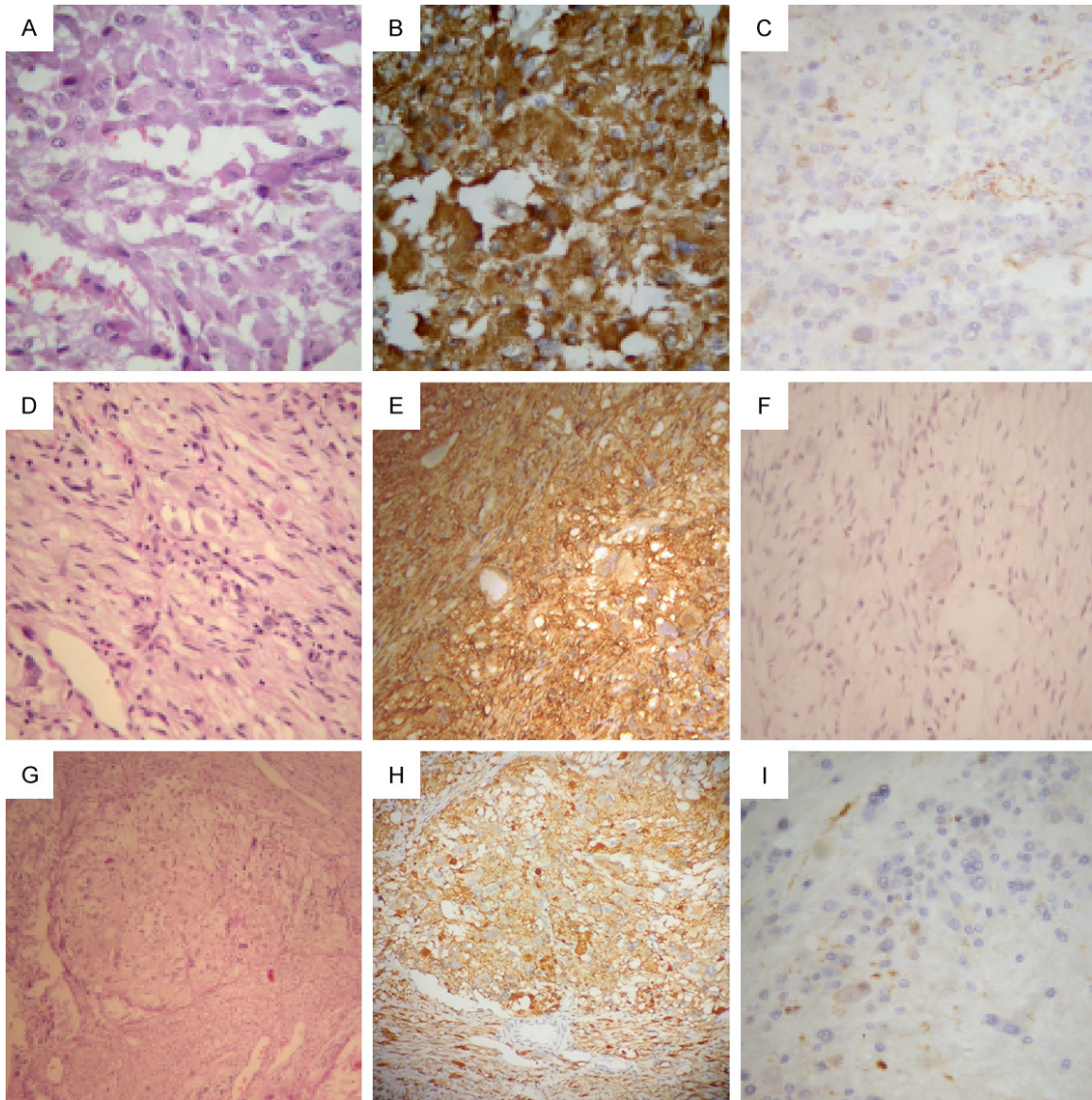


Figure 3. Histopathology of the resected adrenal gland (including the tumor) of the first operation. A. Pheochromocytoma cells, magnification $\times 400$. B. Chromogranin positivity in pheochromocytoma cells, magnification $400\times$. C. S-100 positivity in supporting cells, magnification $\times 400$. D. Ganglioneuroma cells magnification $\times 400$. E. S-100 positivity in ganglioneuroma cells and Schwann cells, magnification $\times 400$. F. Synaptophysin positivity in ganglioneuroma cells, magnification $\times 400$. G. Ganglioneuroblastoma cells, magnification $\times 100$. H. Chromogranin positivity in ganglioneuroblastoma cells, magnification $\times 400$. I. Ki67 5% positivity in ganglioneuroblastoma cells, magnification $\times 400$.

ament (-), ki67 (5% +) (**Figure 5B-D**). The final diagnosis of neuroblastoma (Poor-differentiated type) was made (**Figure 5A**).

Discussion

CP is exceedingly rare, accounting for 50 cases that have been reported previously. CP combines features of pheochromocytoma or paraganglioma with different proportion of gan-

glioneuroma, ganglioneuroblastoma, neuroblastoma, peripheral nerve sheath tumor or neuroendocrine carcinoma [2]. The histogenesis of composite tumors has been attributed to the common embryologic origin from the neural crest. In another words, when aberrant differentiation occurred in the period of differentiating-regulation and migration, the neural crest differentiated into non-chromaffin cells: ganglioneuroma, ganglioneuroblastoma, neu-

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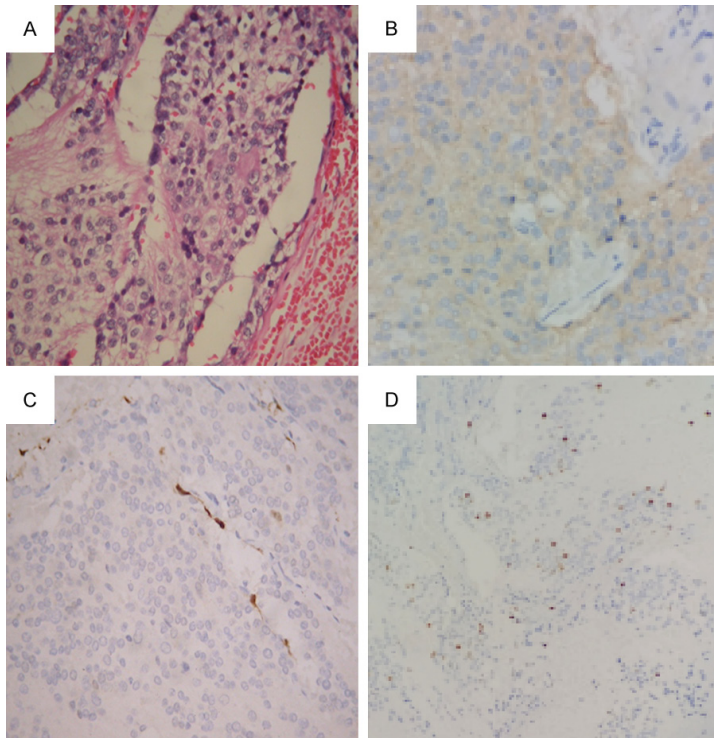


Figure 4. Histopathology of the recurrent tumor (2011.10). A. Neuroblastoma cells (differentiated type), more than 5% of tumor cells were differentiating to ganglion cells. magnification $\times 400$. B. Synaptophysin positivity in neuroblastoma cells (differentiated type), magnification $\times 400$. C. S-100 negativity in neuroblastoma cells (differentiated type), magnification $\times 400$. D. Ki67 10% positivity in neuroblastoma cells (differentiated type), magnification $\times 100$.

roblastoma, peripheral nerve sheath tumor or neuroendocrine carcinoma [5].

In our case, the nonpheochromocytoma component of original tumor was ganglioneuroma and ganglioneuroblastoma. We reviewed 30 cases CP published previously. Of the 30 cases, 25 cases were diagnosed as CP-ganglioneuroma including 2 cases combined with I-Neurofibromatosis [6, 7], Of the other 5 cases, 1 case combined with cortical adenoma-pheochromocytoma-ganglioneuroma [8]. 2 cases combined with ganglioneuroblastoma [9, 10], 1 case combined with ganglioneuroblastoma-parathyroidoma [11], 1 case combined with neuroblastoma [12]. Most of the CP arise from adrenal medulla, retroperitoneal space [2, 13, 14] or the sites where sympathetic chain located. Few cases in adult arise from bladder [15] or cauda equine [16]. The age of onset of 3 cases CP/ganglioneuroblastoma is 53, 9 or 55. The age of onset of 1 case composite pheochromocytoma/neuroblastoma is 61. 30 cases occurred

in male 12 and female 18, with M-F ratio of 1:1.5, most were female. Clinical signs and symptoms of CP are similar with general pheochromocytoma. Catecholamine and its metabolites levels in plasma or urine always increase, patients constantly have paroxysmal or continuous hypertension. Catecholamine induces the changes of hormones like insulin, glucagon, TSH, calcitonin (CT), somatostatin (GHRH), 5-HT, prolactin and so on. Sometimes changes of these hormones do not correspond with clinical features [17]. Vasoactive intestinal peptide (VIP) from tumors could cause watery diarrhea hypokalemia achlorhydria syndrome. CP onsets occult, and is difficult to detect early. Among 30 cases of CP, 8 cases had history of hypertension, partial patients had clinical features like palpitation, headache, diarrhea or pectoralgia. 12 cases had increase of catecholamine and metabolites of catecholamine, 5 cases had increase of VIP, 2 cases had increase of parathormone and calcitonin, 1 case had accom-

panied symptoms like immunologic thrombocytopenic purpura, 1 case accompanied with gastrointestinal stromal tumor, 1 case had catecholamine-induced cardiomyopathy [18] and/or hyperamylasemia [19]. 1 case had increase of somatostatin, insulin and prolactin [20]. In our case, the BP was normal before the operation. However, when the mass was touched, the BP was up to 180/130 mmHg, then went back to general level after resection. When recurrence or metastasis occurred, the BP was still normal. The urine VMA before the first operation was up to 27.34 mg/24 hr, and down to 13.62 mg/24 hr after operation. However, urine VMA was up to 63.75 mg/24 hr as the first recurrence, was down to 19.92 mg/24 hr after the second operation (still over the reference level). It was up to 18.32 mg/24 hr as the second recurrence and down to 9.82 mg/24 hr after the third operation. Unfortunately, after half year the patient's urine VMA was up to 25.48, 88.71, 180.32 mg/24 hr gradually. VMA is the metabolite of catecholamine. Our data

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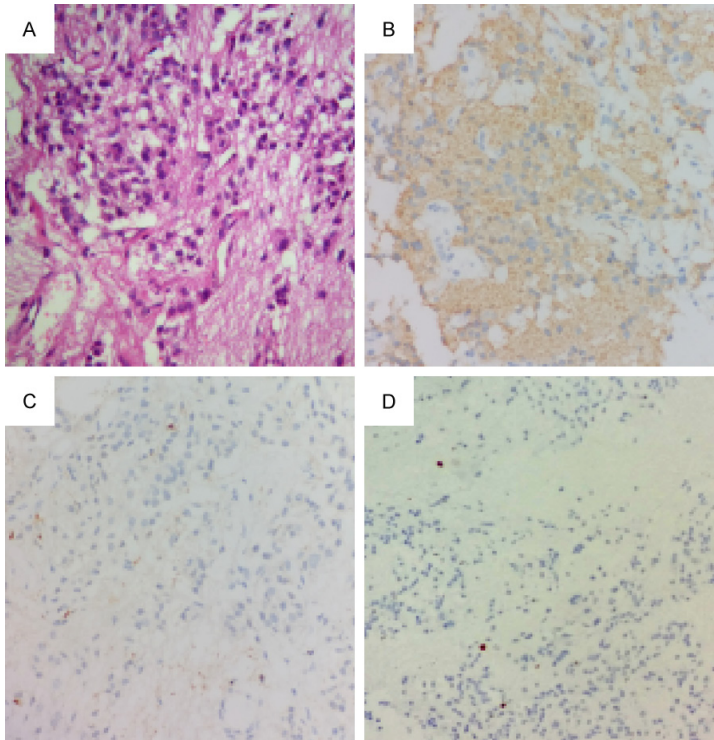


Figure 5. Histopathology of the second recurrent tumor (2013.05). A. Neuroblastoma cells (differentiated type), more than 5% of tumor cells were differentiating to ganglion cells, magnification $\times 400$. B. Synaptophysin positivity in neuroblastoma cells (Poor-differentiated type), magnification $\times 400$. C. S-100 negativity in neuroblastoma cells (Poor-differentiated type), magnification $\times 400$. D. Ki67 5% positivity in neuroblastoma cells (Poor-differentiated type), magnification $\times 1$.

suggested that urine VMA arises up when pheochromocytoma composites with ganglioneuroblastoma or neuroblastoma. Additionally, VMA reduced when the tumor was resected. This suggested that we could predict recurrence or metastasis of composite pheochromocytoma by detecting urine VMA. Yuki K. reported a 12-year-old girl diagnosed as primary pheochromocytoma with increase of adrenarine and noradrenarine, but went down to normal level after resection [21]. Liver and lung metastasis were detected at 15-year-old. Finally, she died as widespread brain metastasis at 26-year-old with the increase of adrenarine, noradrenarine and dopamine. Both this case and our case suggest the increase of catecholamine and it's metabolites associate with recurrence and metastasis of tumor. Thus, recurrence and metastasis of these kinds of tumors could be predicted by quantifying urine VMA level. Additionally, Joshi VV have reported that patients with $NSE > 100$ ng/ml had poor outcome [22]. This report just corresponds with our case which showed the high NSE and CA125 level.

CP-ganglioneuroblastoma always show diffused positivity of Chromogranin A and Synaptophysin for components of pheochromocytoma cells, positivity of S-100 for supporting cells (Schwann cells), slightly or focal positivity of Chromogranin A and Synaptophysin for ganglion cells and neuroblastoma cells. While staining for neurofilament proteins could aid in identification of axon-like processes. Additionally, catecholamine-synthesizing enzymes such as tyrosine hydroxylase (TH) and phenylethanolamine N-methyltransferase (PNMT) are used for identifying catecholamine-producing cells and exceeding the specific of the tumor cells to produce catecholamines [23]. Immunoreactive VIP was found predominantly in neuronal components of the CP with watery diarrhea-hypokalemia-achlorhydria syndrome. However, VIP was still found positive for components of phaeochromocytoma cells rarely [6, 24].

A large fraction of CP has well outcomes after surgical resection [15, 23]. Among 30 cases of CP, only one 12-year-old woman with CP-ganglioneuroblastoma recurred three years later, metastasized systemically, then dead at 26-year-old. One 61-year-old man with mass at retroperitoneum had subsequent pathological examinations of the surgical specimen revealing CP-neuroblastoma with multiple metastases of bone and liver, and dead as metastasized systemically 10-month later. From these cases, it seems that CP-ganglioneuromas have good outcome, survival ratio is 96% (24/25). However, the outcome of CP-ganglioneuroblastomas are very poor, mortality ratio is 100% (1/1). Ganglioneuroblastomas are intermediate stage of neurogenic tumors, and are often seen in infant age and are exceedingly rare after the age of 10 [26]. 3-year-overall survival of 95% was achieved in patients with clinical stage I and II. Fujiwara reviewed seven cases of children with compound tumor of pheochromocytoma and ganglioneuroblastoma, 2 cases dead because of metastasis of pheochromocytoma, 5 cases are still alive after chemotherapy

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and radiotherapy [27]. Actually, CP-ganglioneuroblastomas are extremely rare in adult patients. Our patient (41-year-old) with primary adrenal CP-ganglioneuroblastoma, recurred at retroperitoneal space 28 months after surgical resection. The recurrent tumor was diagnosed as neuroblastoma (high-differentiated type). 19 months later, the metastasis of 3-5 cervical spine was detected. The pathological diagnosis of partial tumor was neuroblastoma (Poor-differentiated type).

In our case, we observed that: 1. CP mixed with ganglioneuroblastomas is easy to recur; 2. When the ganglioneuroblastoma component appears, the biological behavior of tumor becomes worse; 3. Relapse and metastasis always occur in neuroblastoma cells with worse biological behavior in CP-neuroblastomas. With the relapse and metastasis, degree of cell differentiation becomes worse, furthermore transfer from differentiated type to poor differentiated type of neuroblastoma; 4. CP usually metastasizes by logical lymph route, and metastasizes to bone or liver; 5. This kind of tumor seems not to be sensitive to chemotherapy; 6. CP-ganglioneuroblastomas always have a poor outcome.

In summary, it is very difficult to predict biological behavior of CP. If these biological characters like: 1. Compounding histological types including ganglioneuroblastoma, neuroblastoma, malignant neurinoma or malignant neuroendocrine tumor, 2. Nuclear division >10 cells/10 high magnificant, 3. Necrosis, 4. Ki67>5%, 5. MYCN gene amplification, 6. Expression of TrkA or CD44 were observed, it usually means tumor cells have more aggressive biological behavior and more invasive ability. Consequently, it is necessary to assess the risk of tumor after surgical resection. Surgeon should perform extensive resection and when the diagnosis of CP is made. Also comprehensive management including chemotherapy and radiotherapy and more careful follow-up care should be provided for the postoperative patients like monitoring the change of urine VAM, examination of MRI to estimate the recurrence and metastasis of tumor timely. Without doubt, pathologists should process CP tissues broadly to find the elements like neuroblastoma or ganglioneuroblastoma.

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Disclosure of conflict of interest

None.

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