Extra-adrenal composite pheochromocytoma-ganglioneuroma

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ABSTRACT

Composite tumors containing pheochromocytoma and ganglioneuroma are rare tumors typically arising in the adrenal glands. Very few were reported outside of the adrenals. We present the case of a middle-aged woman with a retroperitoneal mass that was discovered when she complained of local signs of compression and systemic signs of catecholamine hypersecretion. On pathology the mass was composed of large polygonal and pleomorphic cells arranged in nests characteristic of pheochromocytoma that were mixed with clusters of mature ganglion cells and bundles of spindle cells characteristic of ganglioneuroma. The histological features were benign, but due to its invasion of the inferior vena cava and of the right renal artery, we had concerns about the malignant potential of the pheochromocytoma component, which is extremely rare in these composite tumors.

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The composite tumors formed by pheochromocytoma and well-differentiated ganglioneuroma belong to a rare but well-recognized group of adrenal tumors that arise from the neural crest derived cells.[1] Their neoplastic behavior and secretion patterns are random, and cover a wide spectrum of clinical manifestations and outcomes. A few have been described in patients with personal or familial genetic defects such as the neuro-ectodermal phakomatoses and the multiple endocrine neoplasia type II syndrome.[2,3] Most reported compound tumors were benign and originated from the adrenal glands; some were seen in the bladder, and cauda equina.[4,5] To our knowledge we are reporting the second patient with a retroperitoneal extra-adrenal composite pheochromocytoma-ganglioneuroma (ECPG).[6]

Case Report. A 41-year-old Caucasian woman without any significant previous medical history was referred to the Department of Surgery at Hotel-Dieu de France Hospital, Beirut, Lebanon, for the treatment of a retroperitoneal mass. She had been complaining for a year of a dull right flank pain with nausea and vomiting. Three months prior to her admission, her condition worsened with new-onset palpitations, headaches, disturbed bowel movements, anorexia, fatigue, 3 kg weight loss, hypertension, and orthostatic hypotension. On physical examination, her blood pressure was 152/65 mm Hg and her heart rate was 93 beats/min. She had right flank tenderness. The abdominal ultrasound and CT showed a 4 cm retrocaval mass at the level of the pancreatic head, just above the right renal artery and inferior to the intrahepatic portion of the inferior vena cava (IVC).

Figure 1 - Abdominal ultrasound that shows the well-defined, hypoechoic mass (arrow heads) posterior to the inferior vena cava (arrow), which is smoothly compressed.

Figure 3 - Macroscopic specimen resected from the retroperitoneum. The composite tumor (black arrow) is covered by an elliptical portion of the inferior vena cava (arrow heads). An invasive nodule (white arrow) protrudes though the lumen of the vein.
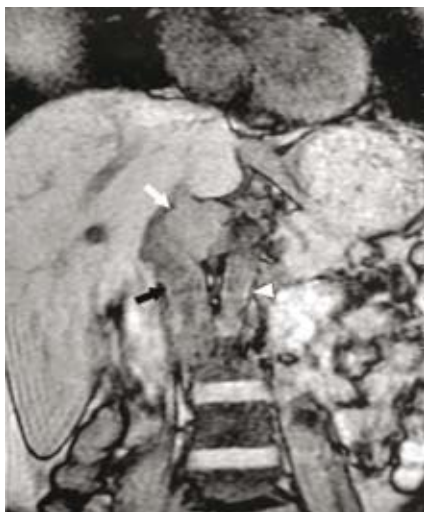

Figure 2 - Magnetic resonance imaging of the retroperitoneum after intravenous injection of gadolinium. The retrocaval mass (white arrow) is enhanced. It constricts and diverts the inferior vena cava (black arrow) without a cleavage plane evident between the 2 structures. Aorta (arrow head).
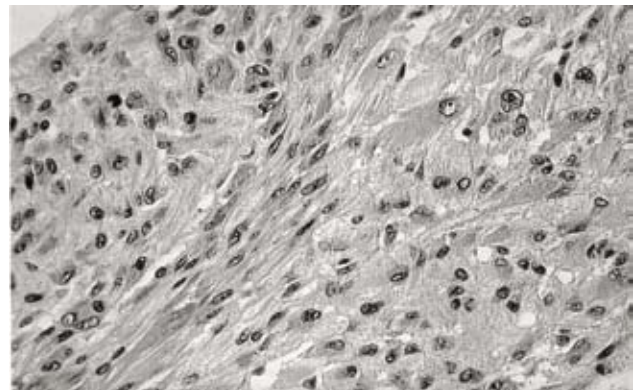

Figure 4 - Microscopic image (x200) stained by hematoxylin-eosin. We can recognize the admixture of the 2 components; the pheochromocytoma that is formed by the large polygonal chief cells (peripheral areas) surrounds a central area of proliferating Schwann cell.

It compressed and laminated the IVC without any cleavage plane noticeable between the tumor and the vessel wall (**Figure 1**). On MRI, the mass appeared with a bright signal on T2-weighted images and was independent of the adrenal gland. The IVC was partially compressed but patent without dilatation distal to the obstruction. No retroperitoneal lymphadenopathies were detected (**Figure 2**). The Doppler ultrasound showed a mild stenosis of the IVC with a flux speed of 1.2 m/s. A 24 hour urinary total catecholamines and vanillylmandelic acid were within the normal range, but based on the clinical presentation, we suspected a functional paraganglioma that we decided to resect surgically. The patient was medicated for 6 days preoperatively by phenoxybenzamine that was started at 20 mg per day and increased to 50 mg per day prior to the surgery.

An experienced general surgeon and a vascular surgeon specialized in peripheral vascular and aortic diseases were primarily involved in this case. We carried out a right subcostal incision. At the retroperitoneal dissection, we isolated a 4 cm nodule compressing the IVC. The tumor was unrelated to the adrenal glands, and it infiltrated the IVC and the right renal artery. We resected the tumor en bloc with parts of the adherent vessels, and replaced the IVC by Hemashield® prosthesis (Meadox Medicals, Oakland, NJ), and the right renal artery by a right aorta-renal

bypass using an expanded polytetrafluoroethylene graft. A retroperitoneal hematoma complicated the immediate postoperative course. It was evacuated surgically. Thereafter, the patient recovered uneventfully. After one year of follow up, she was asymptomatic and no recurrent disease was detected on the abdominal CT. On pathology, the gross examination of the specimen showed a 4x2x4.4 cm tumor without encapsulation and firm in consistency that was covered by an elliptical IVC wall portion (**Figure 3**). On cut section, the tumor was grayish tan with a roughly whorled pattern. The specimen was fixed in a 10% buffered formalin solution. On light microscopy, the hematoxylin-eosin stained sections showed the admixture of 2 distinct components.

The pheochromocytoma part was composed of large, polygonal and pleomorphic cells arranged in nests with some focal areas of atypia, and the ganglioneuroma part was formed by clusters of mature ganglion cells associated with bundles of wavy spindle cells (Schwann cells) (**Figure 4**). The tumor dissected through the wall layers of the IVC, and a nodule extended under the endothelial lining. The surgical margins were free from tumor cells. On immunohistochemistry, the pheochromocytoma component stained positively for PS100, chromogranin A and synaptophysin. In some parts, the proliferative index went up to 5%. The ganglion and spindle cells stained positively for neurofilament. The diagnosis of a composite tumor containing both pheochromocytoma and ganglioneuroma was proposed.

Discussion. This is a case of ECPG in a patient without familial or personal history of genetic syndromes. The patient presented with local signs of compression and systemic symptoms that suggested catecholamine hypersecretion. Moore and Biggs[1] reported that three quarters of these tumors show hormonal hypersecretion. Other reports described neural crest derived cell tumors that secreted products of the amine and precursor uptake and decarboxylation system like vasoactive intestinal peptide, gastrin, and others.[7] Thus, the clinical manifestations of neurogenic composite tumors encompass a spectrum from the locally compressive effects to the lethal complications of amine release.

An ECPG is difficult to diagnose. Although in one report, the diagnosis was made by fine needle aspiration before surgery.[8] Most of the compound tumors were diagnosed postoperatively on pathology. In the literature, we did not find specific imaging signs for ECPG. To narrow our differential diagnosis we relied on some established radiological features: Ganglioneuromas are characterized by being well circumscribed, surround a major vessel with little or no narrowing effect, have a homogeneous attenuation less than that of muscle on non-contrasted CT, and have a heterogeneous high-intensity signal on T2-weighted images on MRI;[9] Paragangliomas typically present as a para-aortic tumor associated with the clinical findings of catecholamines hypersecretion,[10] and have a high signal intensity on MRI T2-weighted images.[11]

A few cases of adrenal composite tumors were reported to contain malignant ganglio/neuro blastic tissue.[12] In our patient, the histological pattern of the ganglion and spindle cells confirmed the benign nature of that component. No neuroblastic or immature elements were detected. The malignant potential of a paraganglioma is dependent solely on the presence of metastasis or on the aggressive local behavior.[10,13] Pathological characteristics such as the size, the presence of necrosis, the polylobular aspect, a proliferative index above 5%, the lack of PS100 or of chromogranin A, are only tentative.[10,12,14] These features are important to consider for the follow up plan.[10] Due to the risk of malignancy harbored by extra-adrenal paragangliomas (more than 30%), and because of the aggressive invasion of the IVC wall, we were concerned about its malignant potential. Therefore, we preferred to perform a laparotomy to a laparoscopic approach. Surgical resection is the best treatment to prolong survival for retroperitoneal paragangliomas, and ultimately obtaining clear margins during the surgical resection is the best approach for minimizing the risk of local recurrences. Adjuvant therapies could have a role in increasing the rate of resection of locally invasive and unresectable paragangliomas.[13,15]

The effect of the proportion of each component in ECPG on prognosis is still unknown, but from the conclusions of studies on paragangliomas, we considered that postoperative surveillance is of utmost importance. Krygger-Baggessen et al[15] suggested that the follow up based on imaging studies, such as ultrasound, CT and eventually MIBG, must be carried out at a regular interval of 3 to 6 months, and must be extended for years. The chance to treat radically a recurrent retroperitoneal paraganglioma is much higher with early detection.[15] It is not known how long the surveillance should be extended, but many authors admit that for familial and extra-adrenal pheochromocytomas, it should be indefinite.

The management of this case of retroperitoneal ECPG was inspired from reports about paragangliomas. Many questions remain unanswered: What is the most specific diagnostic test for ECPG? Should we treat and follow up on ECPG differently

than for paragangliomas? What is the role of genetic screening in sporadic tumors? As more cases of composite tumors are being reported, larger series may be studied to define better their natural history and subsequent management.

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