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Case study

Synchronous adrenocortical neoplasms, paragangliomas, and pheochromocytomas: syndromic considerations regarding an unusual constellation of endocrine tumors☆

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Summary The most common clinical syndromes presenting with paragangliomas and/or pheochromocytomas as their endocrine components are multiple endocrine neoplasia type 2, neurofibromatosis, Von Hippel–Lindau syndrome, Carney-Stratakis syndrome, Carney triad, and the recently described hereditary paraganglioma syndrome. Only Carney triad is known to also present with adrenocortical adenomas, currently representing the only described syndrome in which all 3 of the aforementioned tumors are found together. In most cases, prototypical lesions of the triad such as gastrointestinal stromal tumor and pulmonary chondromas are also seen. We present a case of a young woman with synchronous paragangliomas, adrenal/extra-adrenal cortical neoplasms, and pheochromocytoma without genetic mutations for multiple endocrine neoplasia 2, Von Hippel–Lindau syndrome, neurofibromatosis, and succinate dehydrogenase. We speculate that this represents a previously undescribed presentation of Carney triad and, at the very least, indicates the need for monitoring for the development of other tumors of the triad.

1. Introduction

The most common clinical syndromes presenting with multiple endocrine tumors which include paragangliomas and/or pheochromocytomas are multiple endocrine neoplasia (MEN) type 2, neurofibromatosis, Von Hippel–Lindau (VHL) syndrome, Carney-Stratakis syndrome, Carney triad, and the recently described hereditary paraganglioma syndrome. Up to 25% of paragangliomas/pheochromocytomas occur in the setting of a hereditary syndrome, and it has been proposed that all patients diagnosed with these tumors should consider genetic testing [1,2]. Unfortunately, only one of the aforementioned syndromes, Carney triad, lacks a specific germline alteration that can be used to confirm the diagnosis [3].

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Carney triad was originally described in 1977 and is *classically* composed of gastrointestinal stromal tumors (GISTs), extra-adrenal paragangliomas, and pulmonary chondromas [4]. Definitive diagnosis is made by the presence of all 3 tumors, and a presumptive diagnosis can be made when at least 2 of the classic tumors are present [5]. In most cases, patients manifest only 2 of the 3 tumors and GISTs are the most common presenting lesion [6], whereas paragangliomas are the least frequent classic component [7]. Carney [6,7], however, has recently described 2 additional tumors of the triad: the adrenocortical adenoma and the esophageal leiomyoma, the latter of which is now considered the least frequent. Thus, according to a 2009 report by Carney [6], "…the condition initially reported as a triad of tumors is at least a pentad. The presence of any two of the five tumors multifocally in a young patient warrants a presumptive diagnosis of incomplete expression of the triad." As such, Carney triad more accurately represents a pentad (referred to from here on as *Carney pentad*) and is the only described syndrome that includes the co-occurrence of adrenocortical tumors and paragangliomas/pheochromocytomas. In patients who manifest adrenocortical adenomas, these are generally the last component of the syndrome to be detected [7].

The current case describes a young woman who presented with a combination of intra-adrenal and extra-adrenal cortical tumors, multiple abdominal paragangliomas, and a pheochromocytoma. She did not manifest any of the other described tumors of Carney pentad and, thus, to the authors' knowledge, represents the first reported case of this co-occurring constellation of tumors without other findings of the pentad. In addition, her adrenocortical tumors were of the oncocytic type as opposed to the more characteristic clear cell/vacuolated or mixed type recently described by Carney et al [7]. We postulate that this may represent a case of Carney pentad with delayed presentation of the other tumors versus an unusual form of incomplete expression of the pentad; although without a specific genetic test, we acquiesce that nonsyndromic MEN remains a possibility.

2. Case report

2.1. Clinical presentation

A previously healthy 19-year-old woman presented to the University of New Mexico Hospital with reported intermittent episodes of headache, blurry vision, palpitations, diaphoresis, and abdominal pain. Upon examination, she was found to be hypertensive with a systolic blood pressure greater than 180 mm Hg in addition to exhibiting tachycardia of 140 beats/min. Her physical examination was otherwise unremarkable, and her family history was noncontributory (no history of endocrine tumors or other neoplasms). Laboratory investigation revealed elevated serum normetanephrine (11.9 nmol/L; reference range, 0.00-0.89 nmol/L), normal serum metanephrine (0.3 nmol/L; range, 0.00-0.49 nmol/L), and elevated 24-hour urine norepinephrine (1528 μg/g; reference range, 0-18 μg/g) and normetanephrine (5227 μg/g; reference range, 82-500 μg/g). Results from electrolyte studies were normal, as were all thyroid function tests and parathyroid hormone levels.

2.2. Radiologic findings and surgical intervention

A contrast computed tomographic scan demonstrated multiple lesions described as follows: there was a left adrenal nodule, a mass near the inferior vena cava, and 2 bilateral periaortic nodules with calcifications. A positron-emission tomogrophic scan demonstrated fludeoxyglucose uptake in the left adrenal nodule, the mass near the inferior vena cava, and the left periaortic nodule. In combination with the clinical and laboratory data, these findings were concerning for metastatic pheochromocytoma. No other lesions were seen in the lungs or gastrointestinal tract.

The patient was subsequently taken to surgery for a left adrenalectomy and metastatectomy of the visualized lesions. All described lesions were removed in addition to a posterior caval mass identified behind the right kidney that was not seen on the imaging studies (5 total lesions removed).

2.3. Pathologic examination

The left adrenal gland harbored a cortical nodule measuring 2.0 cm (Fig. 1A). The 4 extra-adrenal masses ranged in size from 2.7 to 5.5 cm. All lesions were similar in gross appearance. They were well circumscribed and had a purple to red cut surface without necrosis. An adrenal medullary lesion was not seen grossly.

On microscopic examination, the adrenal cortical nodule was composed exclusively of oncocytes demonstrating abundant eosinophilic, granular cytoplasm with nuclei harboring occasional prominent nucleoli (Fig. 1B). There was notable scattered bizarre nuclear atypia (Fig. 1C) in addition to degenerative foci of hyalinization, calcification, and ossification. There was no necrosis or mitotic activity. Immunohistochemical stains were diffusely positive for inhibin, calretinin, and melan-A, whereas stains for pancytokeratin and synaptophysin were only focally positive. Negative stains included S-100, chromogranin, and cytokeratin AE1/AE3. The immunomorphologic features were diagnostic of an oncocytic adrenocortical neoplasm. Scattered areas of invasion into extra-adrenal fat indicated that this was not a typical benign oncocytic adrenocortical adenoma but met histologic criteria for an oncocytic adrenocortical neoplasm of uncertain malignant potential (OANUMP) [8].

The posterior caval mass not seen on the prior imaging studies had the same immunomorphologic features as the adrenal cortical nodule and was thus also diagnosed as an extra-adrenal OAUMP. Finally, a third incidental microscopic