Pheochromocytoma, papillary thyroid carcinoma

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ABSTRACT

وصف حالة مريض يبلغ من العمر 53 عام ويعاني من ارتفاع شديد وغير مستقر في ضغط الدم بالرغم من علاجه بثلاثة أنواع من الأدوية الخافضة لضغط الدم. بينت الأشعة الصوتية والأشعة الطبقية وجود عقدة في الغدة الدرقية بحجم 1.8 سم، أثبتت نتيجة الخزعة من العقدة وجود سرطان الغدة الدرقية الحلمي. كانت النتائج المخبرية من وظائف الغدة الدرقية، كالستونين، الكالسيوم، هرمون الغدة الجار درقية في المستوى الطبيعي. في حين كان معدل الميتانفرين في البول المجمع لمدة 24 ساعة ثلاثة مرات أعلى من المعدل الطبيعي. وجد ورم الغدد الصم العصبي من الغدة الكظرية عند عمل أشعة (131I–MIBG). استؤصلت الغدة الكظرية والغدة الدرقية جراحيا. كانت النتيجة النهائية لتحليل أنسجة باثولوجيا ورم الغدد الصم العصبية من الغدة الكظرية وسرطان الغدة الدرقية الحليمي. كان التحليل المخبري للطفرة الجينية (c-ret proto–oncogene) سلبي. تمثل هذه حالة نادرة لورمين بمريض واحد.

A 53-year-old woman presented with labile and difficult to control hypertension on 3 different anti-hypertensive medications. Abdominal computed tomography and ultrasonography of the thyroid gland showed a 1.8 cm thyroid nodule. Fine needle aspiration biopsy of the thyroid nodule revealed papillary thyroid carcinoma. Serum thyroid stimulating hormone and free thyroxine, calcitonin, carcinoembryonic antigen, intact parathyroid hormone, and calcium levels were within normal limits. A 24-hour urine metanephrine showed significant elevation in urine metanephrine of approximately 3 times the upper limit of normal, and the result of 131I-metaiodobenzyleguanjdjne (131I-MIBG) scintography confirmed that the adrenal mass was pheochromocytoma. Right adrenalectomy and total thyroidectomy were performed. The final pathology was pheochromocytoma and papillary thyroid carcinoma. An analysis of c-ret porto-oncogene mutation yielded a negative result. This unusual association of 2 tumors represents a new entity.

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Pheochromocytoma is a rare, catecholamine-secreting tumor arising from chromaffin cells of the adrenal medulla that represents a potentially curable form of endocrine hypertension. The estimated incidence ranges from 0.005-0.1% of the general population, and from 0.1-0.2% of the adult hypertensive population.[1] While pheochromocytomas, occur most commonly as sporadic tumors, approximately 17-25% of pheochromocytomas occur through autosomal dominant inheritance either independent or as part of a familial syndrome. There are 8 defined genetic syndromes for hereditary pheochromocytomas and paragangliomas. Four of these, neurofibromatosis type I (NF1), von HippeI-Lindau (VHL), multiple endocrine neoplasia type 1 (MEN1), and MEN2, are disorders composed of multiple tumor types; the other 4, parasympathetic paragangliomas (PGLs) have parasympathetic paragangliomas, and/or pheochromocytomas, or sympathetic paragangliomas as their only type of tumor manifestation.[2] Association of medullary thyroid carcinoma with pheochromocytoma is well known in MEN type 2A (MEN 2A, Sipple's syndrome).[3] The syndrome is caused by germline mutations of the c-ret proto-oncogene, which are mostly (80-96%) found in RET exons 10, 11, and 16.[4] However, the association between papillary thyroid carcinoma (PTC) and pheochromocytoma is rare. To date, fewer than 11 cases of pheochromocytoma associated with PTC have been reported, and the relationship between these 2 tumors remains unclear.[5,6] We present a case of a

woman who developed a pheochromocytoma and PTC, and discuss the possible existence of a new entity.

Case Report. A 53-year-old woman presented with intermittent palpitation, facial flushing, and feeling unwell for the last 9 months prior to presentation. She was diagnosed with hypertension one year earlier. Her blood pressure had been labile and difficult to control on 3 anti-hypertensive medications including losartan 100 mg, indapamide 1.5 mg, and atenolol 100 mg daily. Her family history was unremarkable. Physical examination on admission showed a healthy-appearing female. Her blood pressure recumbent was 180/95 mm Hg with heart rate of 106 beats per minute, and there was no significant postural drop. On palpation of the thyroid, a 1.5 cm mass in the right thyroid lobe was found, with no cervical adenopathy. From a 24-hour urine sample, urinary metanephrine was 5.8 µmol/d (0.2-1.8), normetanephrine was 4.9 µmol/d (0.4-4.0), and 3-methoxytyramine levels was 2.4 µmol/d (0.2-2.5). Interestingly, her urine epinephrine was actually undetectable. Her thyroid stimulating hormone (TSH) and free thyroxine (FT4) were normal. Serum calcitonin and carcinoembryonic antigen (CEA) were within normal limits, serum intact PTH and calcium levels were also within normal limits (**Table 1**). An abdominal MRI and CT scan of the abdomen showed a 2.5 cm left adrenal mass (**Figure 1a**). The 13I-metaiodobenzyleguanjdjne (131-MIBG) scintography confirmed that the adrenal mass was pheochromocytoma (**Figure 1b**). Ultrasonography of the thyroid gland showed a 1.8 cm thyroid nodule, and subsequently this was biopsied by fine needle aspiration and diagnosed as a PTC. She underwent adrenalectomy and total thyroidectomy. The final pathological diagnosis was adrenal pheochromocytoma (**Figure 2a**) and PTC (**Figure 2b**). The hypertension and related symptoms were resolved after the left adrenalectomy, and the level

Table 1 - Pre- and post- operative laboratory data on 24-hours urine catecholamine.

Laboratory data	Preoperative values µmol/d	Postoperative values µmol/d	Normal range
Metanephrine	5.8	0.2	0.2-1.8
Normetanephrine	4.9	1.2	0.4-4.0
3-methoxytyramine	2.4	1.4	0.2-2.5
Epinephrine	<25	-	0-100
Norepinephrine	218	-	0-470
Dopamine	1038	-	0-2500

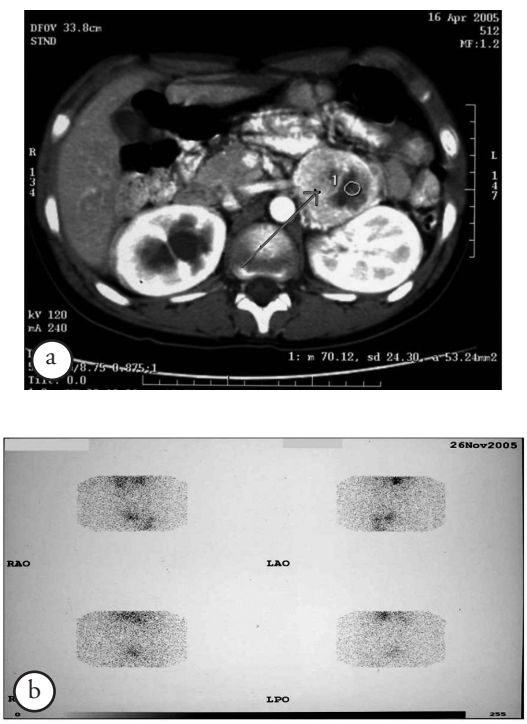

Figure 1 - a) Magnetic resonance imaging post contrast showed left adrenal mass. b) Metaiodobenzylguanidine (131l-MIBG) scintigraphy showed increase uptake at adrenal mass indicated pheochromocytoma.

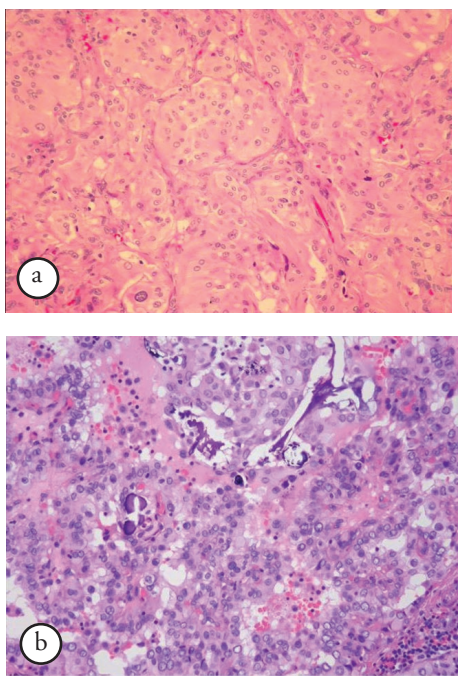

Figure 2 - Microscopic picture of a) pheochromocytoma after adrenalectomy (hematoxylin and eosin x20) showing nests of monotonous cells around central nuclei and abundant granular cytoplasm. b) Papillary carcinoma thyroid (hematoxylin and eosin x20). Papillary fronds lined by cells showing nuclear enlargement, intranuclear cytoplasmic inclusion (Psammoma bodies).

of urinary catecholamine metabolites recovered to their normal values (**Table 1**).

Mutation detection. A 5 mL sample of blood was used for genomic DNA extraction and sent to Mayo Medical Laboratories, Minnesota, USA, to analyze the specimen for a detectable mutation in the c-ret porto-oncogene. The coding exons and their flanking introns of the RET (exons 10, 11, 13, 14, and 16 of the c-ret proto-oncogene (codons 609, 611, 618, 620, 634, 768, 804, and 918) were amplified. Analysis of the c-ret proto-oncogene yielded no mutation. Should this unusual aggregation of tumors represent a new entity, a number of genetic alterations have now been excluded?

Discussion. The incidence of thyroid carcinoma in patients with pheochromocytoma is 14 times greater than in the general population, which might be due to the fluctuating thyrotropin secretion caused by circulating catecholamines.[2] The significance of this association is heightened by the finding that in MEN2A (Sipple's syndrome) the thyroid cancer is of the medullary type.[3] We have described a rare case of pheochromocytoma associated with PTC. The association of PTC with pheochromocytoma is quite rare, and the relationship between the 2 is still unclear.[7] Possible explanations for the increased incidence of PTC in patients with pheochromocytoma include statistical coincidence or a new "MEN" syndrome. Three well-recognized multiple endocrine neoplasia (MEN) syndromes are autosomal dominant traits and all have been tentatively mapped to specific chromosomes,[5] other forms of endocrine tumor syndromes have been suggested either as new entities or as subtypes of the existing MEN syndromes. The PTC is an infrequent observation in MEN2A patients and its occurrence is unrelated to the presence of pheochromocytoma.[8] Oishi et al[5] reported a case of MEN 2A with PTC and a recurrent pheochromocytoma in a surgically operated residual adrenal gland.[5] Rossi et al[7] reported 2 cases with familial MTC associated with distinct foci of PTC. Genetic factors might play an important part in the association of the 2 tumors. Supporting a genetic cause, are reports of MEN 2 patients with PTC.[7] The ret proto-oncogene locus, shown to be structurally rearranged in human papillary thyroid cancers, has tight linkage to the MEN 2A locus.8 Decker6 concluded that the expression of PTC in MEN 2A may be due to the presence of a structural alteration affecting several contiguous genes spanning the putative MEN 2 region.[6] There have been no definite opinions about this association, but PTC was once thought to be one of the features of MEN. In our case, analysis of the RET porto-oncogene for possible mutation in exons 10, 11, 13, 14, and 16, which is the most common known mutation in MEN-2A cases have been excluded. There are a few MEN2 families in which RET mutations have not so far been identified. A systematic family history failed to reveal features suggestive of MEN2 in first and second-degree relatives, with attention to thyroid, adrenal, and parathyroid disease. Lack of family history does not exclude heritable disease. The disease may not be apparent in relatives because of 'skipped' generations; or an isolated case may be the start of a new family. Should this unusual aggregation of tumors represent a new sub type of MEN syndrome? Whenever 2 or more uncommon neoplasms are detected synchronously or metachronously in a given individual, the suspect of a novel entity arises. Steiner et al[9] suggested that association of parathyroid tumors and PTC might occur as MEN 3.9 The coexistence of PTC and pheochromocytoma has been reported in the literature in 15 cases, 11 of them were observed in Japan. These 15 cases of pheochromocytoma were mostly single (12 patients) and located in the adrenals (9 patients). Metastatic spreading was recorded in only one. Two patients had coexisting MEN 2A and PTC. One patient had adrenal and extra adrenal pheochromocytoma.[10]

In conclusion, we report a case of PTC and a pheochromocytoma. We suggest that the association with pheochromocytoma and PTC might occur as MEN syndrome type 4. In any case, our patient suggests the possibility that it is a new type of familial disease causing 2 diseases by a genetic abnormality that is not characterized yet. Although the occurrence of multiple tumors in the same individual suggests a genetic etiology, we were unable to identify the underlying genetic mutations possibly associated with the observed tumors. Clinical data of patients suffering from pheochromocytoma and PTC should be collected by an international registry, and a joint effort should be undertaken to define possible underlying mutated genes in those patients.

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