CASE REPORT

Multiple endocrine neoplasia type 2A/localized cutaneous lichen amyloidosis associated with malignant pheochromocytoma and ganglioneuroma

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ABSTRACT. We hereby present a rare variant of multiple endocrine neoplasia type 2A (MEN2A) associated with a rare skin disease primary cutaneous lichen amyloidosis and discrete malignant pheochromocytoma in both adrenal glands and pancreatic tail, and interestingly accompanied ganglioneuroma located in retroperitoneum in a 34-yr-old female. The presence of composite tumor of pheochromocytoma and ganglioneuroma arising in the adrenal glands has been described previously in MEN2A and in sporadic cases. The patient displayed classical signs and symptoms of catecholamine excess. Biochemical screening proved pheochromocytoma. Computed tomography revealed multiple mass lesions in both adrenal glands. It also showed a large heterogeneous mass that clearly discriminated from right adrenal gland in retroperitoneal location. After surgical exploration, both adrenal glands and the suspicious mass in pancreatic tail were removed successfully together with subtotal resection of the retroperitoneal tumor. Histopathologic examinations confirmed the presence of pheochromocytoma in both adrenal glands as well as pancreatic lesion. A retroperitoneal ganglioneuroma was also present. Symptomatic and biochemical evidence of pheochromocytoma subsided after the operation. Further evaluation for medullary thyroid carcinoma and primary hyperparathyroidism confirmed MEN2A. Mutation analysis of the ret proto-oncogene revealed a missense point mutation at position 634 in exon 11, which gives rise to the substitution of a cysteine codon with a tyrosine residue.

INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant inherited cancer syndrome that affects tissues derived from neural crest cells (1). Three hereditary variants of MEN2 are known: MEN2A is characterized by a medullary thyroid carcinoma (MTC) in almost 100% of patients, pheochromocytoma in about 50% of patients, and/or primary hyperparathyroidism in about 20% of patients. The MEN2B syndrome consists of MTC, pheochromocytoma, mucosal neuromas, ganglioneuromatosis of the gut and marfanoid habitus. Familial MTC is the only MTC syndrome that is not associated with other endocrinopathies, and inherited predisposition to MTC is the only disease feature (2). Cutaneous lichen amyloidosis (CLA) is a rarely seen dermatological disorder characterized by skin deposits of amyloid and pruritis in the interscapular region (3). MEN2A associated with hereditary primary CLA has been defined in a small number of families. Mutations in codon 634 have been found in all families (3-14). Germline mutations of ret proto-oncogene responsible for MEN2 syndromes were identified in 1993 (15, 16). Ret is a member of receptor tyrosine kinase family comprising 21 exons. The receptor has a cysteine-rich extracellular receptor domain. Mutations responsible for MEN2A are distributed mainly in exons 10 and 11. We hereby describe a patient...
with MEN2A associated with CLA. Further interesting disease features were metastatic pheochromocytoma and retroperitoneal ganglioneuroma.

**CASE REPORT**

A 34-yr-old female patient was admitted to our hospital with chief complaints of severe paroxysmal attacks of hypertension, palpitation, headache and excessive sweating. After clinical evaluation of the patient revealing classical symptoms of catecholamine excess, the measurement of 24 h urinary vanillylmandelic acid and metanephrine was found to be elevated. Screening for pheochromocytoma by computed tomography imaging detected multiple mass lesions in both adrenal glands. Also, a large heterogeneous mass that was clearly discriminated from the right adrenal gland, partially surrounding porta hepatitis and displacing the inferior vena cava anteriorly, was shown in retroperitoneal location above the right kidney. Bilateral subcostal incision was performed under the suspicion of a functioning adrenal tumor extending to adjacent tissues. Upon surgical exploration, the tumor in the left adrenal gland was removed successfully together with a 2x1 cm suspicious mass lesion in pancreatic tail. On the right, a para-adrenal 15x12 cm diameter mass that could be clearly discriminated from adrenal tumor was found in the retroperitoneal space. Subtotal resection of the tumor was performed together with right adrenalectomy. Histopathologic examination of both adrenals and pancreatic lesion confirmed the presence of pheochromocytoma (Fig. 1). Histological examination of the other mass on the right showed that the lesion was an extraadrenal retroperitoneal ganglioneuroma composed of mature ganglion cells and a spindle cell schwannian matrix (Fig. 2). Symptoms and signs of excess catecholamine subsided. The measurement of 24-h urinary vanillylmandelic acid and metanephrine levels was also within the normal ranges shortly after surgery.

Further evaluation for MTC revealed elevated calcitonin level and a scintigraphic cold nodule located in right thyroid lobe. Fine needle aspiration biopsy proved MTC. Biochemical evidence of primary hyperparathyroidism was also present. Total thyroidectomy with right central lymph node dissection and subtotal parathyroidectomy was performed. The thyroid specimen showed multifocal MTC in both thyroid lobes and bilateral C-cell hyperplasia with metastatic lymph nodes. Parathyroid histology was normal. These findings confirmed MEN2A syndrome.

Six months after surgery, pentagastrin stimulated calcitonin levels remained abnormal and biochemical evidence of primary hyperparathyroidism was still present. Localization studies with Doppler ultrasonography and technetium 99m sestamibi pointed out a parathyroid adenoma on the left side. The patient underwent bilateral modified radical neck dissection with negative tumor histology and parathyroid adenoma excision.

The mutational analysis of the family started with the sequencing of the index patient. After genomic DNA extraction and polymerase chain reaction (PCR) under defined conditions, PCR-amplified DNA was sequenced. A missense point mutation at position 634 in exon 11, which gives rise to the substitution of a cysteine codon with a tyrosine residue was de-

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**Fig. 1** - Pheochromocytoma: nests of polygonal cells and residual adrenal tissue, HE×200.

**Fig. 2** - Schwann cells and a few ganglion cells in ganglioneuroma, HE×200.