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A strange combination

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Workshop: Miscellaneous endocrine disorders and oncology

A 35 year old woman had been known to our outpatient department since 1996, with a diagnosis of acromegaly. At the time, the pituitary macroadenoma was already inoperable and she was treated with radiotherapy, octreotide, quinagolide and from 1997-2000 with pegvisomant. Since then she had panhypopituitarism, for which she received medication. Over the years she developed hypertension and diabetes mellitus. Otherwise she was doing very well and had a fulltime job.

In February 2007 she was admitted to our ward because of worsening edema of the upper and lower extremities, shortness of breath, perspiration and flushing. On physical examination she was hypertensive, and besides the edema, had a reddish-purple, reticular pattern of the skin on her legs. Because of her symptoms we were considering a cardiac problem, auto-immune disease or a malignancy.

Initial blood tests showed a normal complete blood count, a raised ESR and slight cholestatic liver function test. The pituitary functions were adequately supplied and there were no signs of auto-immune diseases.

A chest x-ray showed no redistribution or cardiomegaly, the electrocardiogram showed left ventricular hypertrophy, and an echocardiogram revealed a good left ventricular function, no valvular dysfunction and left ventricular hypertrophy. Because no explanation for her symptoms had been found, a CT of the abdomen was performed and showed a tumorous mass at both the adrenal glands. Plasma metanephrines and 24-urinary catecholamines were raised and an 111-In-pentetreotide scintigraphy (Octreoscan) showed positivity at both glands. This made the diagnosis of bilateral pheochromocytoma apparent. She was pretreated with combined alpha- and beta-adrenergic blockade and a bilateral adrenalectomy was performed.

The combination of a pituitary adenoma and a pheochromocytoma has only been described in 25 case reports. In most of these cases the adenoma was producing growth hormone, but prolactinomas, ACTH-producing tumors or non functional adenomas have also been described. The combination of tumors can not be attributed to the MEN 1 (parathyroid, pituitary, enteropancreatic tumor) or MEN 2 (medullary thyroid cancer, pheochromocytoma with/without parathyroid hyperplasia) syndrome.

Recently a new syndrome, the MEN X syndrome was described, in which the combination of pituitary adenoma and pheochromocytoma does occur. This syndrome is inherited in a recessive manner and is caused by a mutation in the CDKN1B gene whose protein product is cyclin-dependent kinase inhibitor p27kip1. When a mutation in this gene occurs less p27kip1 is produced, indicating that this must be a tumor suppressor protein. An article by Pellegata et al (2006) described rats with the CDKN1B-mutation. Rats that were killed after 2 months showed hyperplasia of the adrenal glands, after 4 months pituitary hyperplasia was seen and after 6 months the rats had pheochromocytoma, pituitary adenomas and hyperplasia of the medullary thyroid cells. Because of the involvement of the thyroid in this study we decided to perform an ultrasound of the thyroid, which showed a suspicious node in the right lobe of the thyroid with microcalcifications. Furthermore calcitonine and CEA were raised. After the patient had recovered from the first surgery, a hemithyroidectomy was performed. The pathology report, however, did not show a medullary carcinoma, but a papillary carcinoma.

The question is, does this patient have several primary tumors pure by coincidence, or is there a genetic cause for this rare combination of tumors. Genetic analysis for MEN1, RET, VHL, SDH and the CDKN1B-gene are being performed and may give us some answers.

