Features of Malignancy in a Benign Pheochromocytoma

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Pheochromocytomas are rare conditions with a prevalence of 1-2/100,000 in the general population and 1/1,000 hypertensive subjects [1]. 10% of pheochromocytomas are malignant and various attempts have been made to find useful prognostic indicators of malignancy. In general, increased plasma or urine dopamine concentrations or increased homovanillic acid excretion and lack of 131-methyl-iodo-benzylguanidine uptake have been associated with malignancy [2]. However, to date no specific metabolic, radio-logic or histopathologic features of either benign or malignant pheochromocytomas allowing the safe diagnosis of one or the other have been identified. The diagnosis of malignant pheochromocytoma can be made only in the presence of local tissue invasion or distant metastases. We present a benign pheochromocytoma exhibiting several features suggestive of malignant disease.

A 20-year-old patient was referred to hospital with a 2-year history of paroxysmal palpitations most recently accompanied by severe headache and flushing. Latest blood pressure readings were persistently above 200 mm Hg systolic and 120 mm Hg diastolic. In addition, an increased dislike of sweets together with exaggerated salt-hunger was reported. Except for hypertension the physical examination was unrevealing. Abdominal ultrasound showed a left adrenal mass which was confirmed by CT scan but undetectable by methyl-iodo-benzylguanidine scanning.

Laboratory investigations performed in the appropriate manner revealed 10-fold elevated plasma and urinary norepinephrine concentrations and 3- to 4-fold elevated plasma and urine dopamine levels as shown in table 1. Neuron-specific enolase was at the upper limit of normal (12.9 µg/l). Resting serum aldosterone of 459 pg/ml (normal range < 160) and plasma renin activity of 7.98 ng/ml/h (normal range < 1.6) were increased, while prolactin, growth hormone, thyroid function tests, calcitonin, adrenocorticotropin and cortisol were all normal. The patient underwent left adrenalectomy and thorough abdominal exploration. With the adrenal capsule intact no signs of local tissue invasion by the tumor were detected.

Microscopy confirmed the diagnosis of pheochromocytoma but showed neither angioinvasive nor capsule penetration. Post-operatively, blood pressure and catecholamine levels returned to normal. During the follow-up period of 55 months, the patient has led a normal life without clinical symptoms of pheochromocytoma or elevated urine or plasma catecholamines (table 1).

The intraoperative findings and the histology report in conjunction with a 5-year follow-up without recurrence of symptoms or abnormal catecholamines allowed us to establish the diagnosis of a benign pheochromocytoma in this patient. Preoperatively, however, several findings were indicative of malignant pheochromocytoma.

Young age at presentation has generally been associated with an increased likelihood of malignancy [3]. Furthermore, although norepinephrine was the predominantly ele-

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Table 1. Concentrations of plasma and urine catecholamines before and after surgery

Free plasma dopamine, ng/dl (1-15) Free plasma norepinephrine, ng/dl (10-60) Free plasma epinephrine, ng/dl (1-8) Urine dopamine, µg/24 h (190-440) Urine norepinephrine, µg/24 h (23-105) Urine epinephrine, µg/24 h (4-20) Urine 3-methoxytyramine, µg/24 h (< 60) Urine normetanephrine, µg/24 h (105-354) Urine metanephrine, µg/24 h (74-298) Urine homovanillic acid, µg/24 h (1.5-16.7) Urine vanillinmandelic acid, µg/24 h (0.9-10.8)

The normal ranges are given in parentheses.

Increased catecholamine, increased dopamine secretion has been found in two thirds of malignant versus less than 10% of benign pheochromocytomas [4]. The markedly elevated urine 3-methoxytyramine concentrations, an exclusive metabolite of dopamine, further substantiated the excessive dopamine production in our patient. In addition, the normal epinephrine concentrations, despite excessive norepinephrine levels as a result of the tumor's inability to N-methylate, reflect tissue immaturity [5]. Finally, failure to take up 131-methyl-iodobenzyl-guanidine occurs in only 10% of benign versus 60% of malignant pheochromocytomas of the adrenal [6].

Although exhibiting the four characteristics that are frequently found in malignant pheochromocytoma and have been tried as prognostic indicators, our patient had a benign tumor. We thus conclude that the currently discussed markers, either singly or in combination, are of limited clinical use in predicting the malignant status of a pheochromocytoma in an individual patient. Therefore novel predictors of malignancy are needed.

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