Case report

Extra-adrenal functional paraganglioma (phaeochromocytoma) associated with renal-artery stenosis in a pregnant woman

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Introduction

Paraganglioma represents the nosological term for tumours arising from both chromaffin cells (pheochromocytes) of the adrenal medulla and chromaffin cells of the paraganglion sympathetic system. Paraganglioma of the adrenal medullary gland is more commonly referred to as pheochromocytoma, a term which is currently used for tumours of the sympathetic paraganglia as well [1]. Functional pheochromocytoma, a catecholamine-secreting tumour, is a rare cause of arterial hypertension, which is often diagnosed only at autopsy. In a few cases it has been reported in association with renal-artery stenosis [2–4]. Pheochromocytoma in pregnancy is associated with a high morbidity and mortality for both mother and foetus [5–7]. However, the diagnosis may be overlooked because of its rarity and because the clinical symptoms often mimic those of pre-eclampsia [6]. The diagnosis of an extra-adrenal paraganglioma (pheochromocytoma) associated with renal-artery stenosis was made in a hypertensive pregnant woman.

Case

A 25-year-old, secundigravid, non-parous woman was referred for evaluation of resistant hypertension. She had complained of recurrent headaches for 3–4 years. Two years previously her first pregnancy had resulted in a spontaneous abortion. Six months before the admission, a Doppler ultrasound scan aroused suspicion of stenosis of the left renal artery and the urinary vanillylmandelic acid was slightly elevated (9.5 mg/24 h; normal values (n.v.) 2.00–7.00 mg/24 h).

On admission the patient was in the seventh week of her second pregnancy and her blood pressure was 150/100 mmHg. Peripheral plasma renin activity (PRA) and aldosterone levels were elevated, in both supine and upright position (PRA 3.9 ng/ml/h and 17 ng/ml/h respectively; n.v. 0.2–2.8 ng/ml/h and 15.5–5.7 ng/ml/h, respectively; aldosterone 200 pg/ml and 600 pg/ml respectively; n.v. 10–150 pg/ml and 35–300 pg/ml respectively). Urinary excretion of dopamine and noradrenaline was elevated (1177.6 mg/24 h and 606.7 mg/24 h respectively; n.v. 0–400 mg/24 h and 0–87 mg/24 h respectively), while adrenaline was normal (9.3 mg/24 h; n.v. 0–23 mg/24 h). The kidneys and adrenal glands appeared normal on ultrasound scan, while the eye fundoscopic examination showed a grade II retinopathy and an echocardiogram revealed a mitral valve prolapse. Treatment with atenolol and nifedipine was started.

At 20 weeks, the blood pressure was satisfactorily controlled, the foetal growth was regular, urinary adrenaline was normal (16.7 µg/24 h), while both dopamine and noradrenaline were elevated (1353.5 µg/24 h and 599.8 µg/24 h respectively). A clonidine suppression test was then performed, but its result was inconclusive in that 3 h after oral administration of 0.3 mg of clonidine, plasma adrenaline decreased from 18.8 pg/ml to 10.1 pg/ml, and noradrenaline decreased to 857.5 pg/ml, a value not below the level of 500 pg/ml which could have ruled out a pheochromocytoma [8].

At 26 weeks of gestation, with the foetus still growing regularly, the test was repeated after discontinuation of atenolol. The plasma catecholamines were unaltered; after clonidine, adrenaline, decreased from 18.8 pg/ml to 10.1 pg/ml, and noradrenaline from 1336.6 pg/ml to 1298.9 pg/ml. The patient refused to undergo magnetic
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resonance imaging (MRI) because of her claustrophobia and because blood pressure was adequately controlled by medical treatment (methyldopa instead of atenolol). We agreed to delay further diagnostic tests until after the delivery.

At 33 weeks, however, intrauterine foetal death occurred, and a caesarean section was performed.

Diagnostic evaluation was completed by performing imaging scans. $^{131}$I-meta-iodobenzylguanidine (MIBG) scintigraphy showed only weak activity in the area of the adrenal glands 72 h after radioisotope injection. An abdominal CT scan revealed a solid tumour mass of about 5.0 cm in diameter on the left side of the aorta, at the level of the upper half of the kidney, and a right 5-cm ovarian cyst in the pelvic cavity. The kidneys were normal, as were the liver, the spleen, and the pancreas. Thoracic and cranial CT scans were also normal. A percutaneous transfemoral aortogram showed a bilateral duplex renal artery, confirming the intra-abdominal expansive lesion, whose intense and inhomogeneous vascularization came from the left adrenal artery and from the left lower duplex renal artery. The tumour encased both the ipsilateral renal arteries, which appeared narrowed and infiltrated (Figure 1). The tumour was surgically removed along with a total left nephrectomy and ipsilateral adrenalectomy. The tumour appeared grossly encapsulated on its external surface and brownish in colour on the cut surface. Light microscopy revealed classical morphological features suggesting a diagnosis of paraganglioma (Figure 2), including some areas of striking pleomorphism (Figure 3). The diagnosis was firmly established from a positive argyrophilic reaction (Grimelius stain) and positive

![Image](image1)

**Fig. 1.** The aortogram shows an expansive lesion on the left side of the aorta, narrowing and infiltrating both the left renal arteries.

![Image](image2)

**Fig. 2.** Cellular morphology and architecture of the neoplasm. In this field, tumour cells, mainly of light or vacuolated type, are arranged in a mixed alveolar/trabecular pattern and intermingled with thin fibrovascular septa. A cytoplasmic intranuclear pseudoinclusion (arrowhead), commonly seen in neuroendocrine tumours, and a mitotic figure (arrow) are also visible. (HE × 250).

**Inset:** positive intracytoplasmic immunohistochemical detection of chromogranin A revealed with diaminobenzidine, using a streptavidin–biotin peroxidase conjugated system. (Nuclear counterstain with haematoxylin, × 250).

![Image](image3)

**Fig. 3.** In this field a striking pleomorphism of tumour cells, mainly of the eosinophilic type, is pictured with marked nuclear enlargement and hyperchromasia. This finding is said not to have prognostic implication in neuroendocrine tumours in general, and specifically in paragangliomas. (HE × 450).

![Image](image4)

**Fig. 4.** The external boundary of the neoplasm is shown. The encapsulated tumour (triangle) is visible toward the bottom, while a seeding neoplastic nodule (curved arrow) has penetrated beyond the capsule (double-headed arrow) into the neighbouring fibrous fatty tissue. This feature has an important clinical prognostic impact. (HE × 110).
immunostaining for chromogranin A (Figure 2, inset). Some findings pointing to local aggressive behaviour were also observed, such as capsular invasion and tumorous nodules protruding beyond the capsule itself (Figure 4). Mitoses were only occasionally seen (less than one per 50 high power field) and necrosis was not observed. Kidney and adrenal gland were histologically unremarkable.

Post-operative laboratory investigations revealed normal serum calcium and basal serum calcitonin (0.85 pg/ml; n.v. 0–25 pg/ml), whilst serum parathyroid hormone (PTH) was elevated (106 pg/ml; n.v. 11–54 pg/ml); ultrasound scan of the parathyroid glands appeared normal. The patient was discharged on the 12th day after surgery with a good blood pressure without any medication.

Urinary assays of catecholamines, performed at 1 and 4 weeks, were within normal limits.

Discussion

Phaeochromocytoma is a rare catecholamine-secreting tumour whose incidence ranges from 0.3 to 0.95 per 100 000 person-years [9]. The secretion of catecholamines typically results in arterial hypertension associated with headaches, diaphoresis and palpitations. The tumour accounts for 0.05–0.1% of causes of hypertension, but it is estimated that only 50% of patients with phaeochromocytoma have persistent hypertension, while 45% are normotensive between paroxysms of hypertension, and 5% remain normotensive [10].

Most tumours of this type arise from the adrenal medulla (phaeochromocytomas or adrenal gland paragangliomas), while others arise from the extra-adrenal paraganglion system (extra-adrenal paragangliomas or extra-adrenal phaeochromocytomas), mainly intra-abdominal at a para-aortic site and near the renal hilum. In the approximately 40 reported cases of renal-artery stenosis with phaeochromocytoma, the former was due to compression by the tumour or to structural changes (i.e. fibrosis) of the renal-artery wall caused by a chronic catecholamine-induced spasm [2,4]. A case of fibromuscular dysplasia of renal artery has been recorded in association with phaeochromocytoma [11]. In this case, we strongly suspect that the stenosis of both the ipsilateral renal arteries was due to neoplastic infiltration. In fact, intra-abdominal, extra-adrenal phaeochromocytomas are thought to be more aggressive than orthotopic adrenal ones [1] and the histological finding of tumour capsular invasion suggests that the artery walls could well be involved in such a process. However, the direct neoplastic infiltration of renal-artery wall was not demonstrated because the tumour was extricated from the arteries which were then resected downward from the implantation site.

Phaeochromocytoma is rare in pregnancy; a few hundred cases have been reported, with an incidence of 18.5 per million live births [6,7]. To the best of our knowledge, this is the first report of adenocortical and extra-adrenal phaeochromocytoma with renal-artery stenosis in pregnancy. Fatal hypertensive crises can be precipitated by vaginal delivery, uterine contractions, and anaesthesia. The maternal mortality rate, which was 48% before 1969, has subsequently fallen to 11%. When the diagnosis is made antepartum, the mortality rate is zero [5–7]. In addition, early diagnosis and improved control of maternal hypertension has reduced the overall foetal loss from 67% before 1969 to 15% when the diagnosis is made antenatally [5,6].

Our patient suffered from persistent systolic and diastolic hypertension, probably related to the exclusive release of noradrenaline, as it usually occurs with extra-adrenal phaeochromocytomas. Furthermore she secreted a large amount of dopamine, a precursor of noradrenaline, for which a vasoconstriction-preventing action was suggested [12] and which could account for the paucity of symptoms in patients with this secretion pattern.

This patient did not complain of any other important symptom but recurrent headache. In this case, activation of the renin–angiotensin system could have played a contributory role. Stimulation of renal beta-adrenergic receptors by catecholamines can increase renin secretion and subsequently that of angiotensin II, which in turn enhances the release of noradrenaline at presynaptic sites [10,13]. Although activation of the renin–angiotensin system in pregnancy is well known, we may have misinterpreted the finding of an elevated PRA.

The equivocal results of the clonidine suppression test performed at 20 weeks and the weak activity in the area of the adrenal glands on MIBG scintigraphy performed post-partum, that could have led us to rule out a phaeochromocytoma, could be explained on the basis of a probable drug interference, as both the tests were performed when the patient was undergoing therapy (with atenolol and nifedipine respectively).

Prolapse of the mitral valve was demonstrated, which should be included in the list of cardiac changes, such as catecholamine-induced cardiomyopathy [1] and focal myocarditis [14], observed in association with this tumour.

Phaeochromocytoma is a feature of two disorders with an autosomal dominant pattern of inheritance, multiple endocrine neoplasia type 2 (MEN-2) and von Hippel–Lindau (vHL) disease, both associated with high morbidity and mortality [15]. In our patient the clinical, laboratory, and radiographic findings allowed us to firmly rule out the vHL disease, but not MEN-2, a syndrome characterized by phaeochromocytoma (of the adrenal gland), medullary carcinoma or C-cell hyperplasia of the thyroid, and parathyroid chief-cell hyperplasia. In our case, the elevated serum PTH in the absence of enlargement of parathyroid glands as determined by ultrasound scan can be explained on the basis of microscopic foci of parathyroid chief-cell hyperplasia. Thus, the association of phaeochromocytoma with a (hypothetical) parathyroid chief-cell hyperplasia could even suggest a fruste form of MEN-2 syndrome. However, this possibility remains speculative; to date, MEN-2 phaeochromocytomas have been
located in the adrenal gland and a C-cell disorder of
the thyroid has always been a constant feature.

Finally, this patient did not have stigma of von
Recklinghausen neurofibromatosis, an autosomal
dominant disease sometimes found in patients with
phaeochromocytoma and renal-artery stenosis [4,16].
Unfortunately, the pregnancy resulted in foetal death,
an unexpected event since the foetal growth had been
regular and the maternal blood pressure was satisfact-
orily controlled. The foetal outcome might have been
better if an earlier diagnosis had been made. MRI is
emerging as the procedure of choice in localizing
tumours because of its good sensitivity (95–100%) and
because it does not require administration of contrast
medium and does not expose the patient (either mother
or foetus) to ionizing radiation [17].

Our patient is now closely followed, because her
tumour might display aggressive behaviour, a point of
concern because capsular invasion had been observed
on histology.

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