Recurrent pulmonary oedema and severe hypertension after renal transplantation: other reasons than renal artery stenosis

Nada Kanaan¹, Alexandre Persu¹,², Gregory Van Ingelgem¹, Jacques Malaise³ and Eric Goffin¹

¹Department of Nephrology, ²Department of Cardiology and ³Department of Transplant Surgery, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

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Case

In November 2004, a 65-year-old man presented to the emergency room for severe interscapular pain associated with shortness of breath. Two months earlier, he had undergone renal transplantation after four years on haemodialysis. End-stage renal failure had been ascribed to nephrosclerosis because of a 14-year history of hypertension, absence of haematuria, mild proteinuria, and absence of morphological renal abnormalities. On admission, he was afebrile, tachycardic, and blood pressure was measured at 230/80 mm Hg (usual blood pressure around 140/90 mm Hg). Pulmonary crackles were noted upon auscultation. Laboratory measurements revealed a rise in the creatinine value to 3.2 mg/dl (versus 1.8 mg/dl routinely) and a glycaemia at 407 mg/dl (versus normal values at last visits). CPK (creatine phosphokinase) and troponin serum concentrations were normal. LDH (lactate dehydrogenase) was slightly elevated at 198 UI/l (normal values: 98–192). Platelet level was normal. Electrocardiogram was unchanged. Thoracic CT scan confirmed the subacute pulmonary oedema and excluded an aortic dissection. A dilated left auricle was noted on cardiac echography but left ventricular function was normal. Ultrasound examination ruled out graft and homolateral iliac arterial stenosis, and pulmonary embolism was excluded by scintigraphy. Renal biopsy showed no sign of rejection or malignant hypertension. One week after admission, the patient experienced the same crisis with very intense interscapular pain along with dyspnoea, sweating and tremor. Blood pressure was measured at 202/94 mm Hg and pulse rate was 113/min. Hyperglycaemia and a rise in creatinine value to 3.4 mg/dl were noted in the laboratory tests. Chest X-ray showed interstitial overload compatible with subacute oedema.

Questions

What is your diagnosis?
What laboratory test could have oriented your diagnosis?
What paraclinical investigation would you recommend?

Answers

Our patient had a pheochromocytoma.

The more plausible diagnosis in the present case, a pulmonary oedema secondary to an arterial stenosis on the iliac or renal graft arteries [1,2] was rapidly ruled out by the ultrasound imaging. Malignant hypertension was also excluded, because although LDH were slightly increased, platelet level was normal and renal biopsy did not show any histological changes compatible with malignant hypertension. The unusually elevated serum glucose concentration, in the context of paroxysmal hypertension and pulmonary oedema associated with sweating and tachycardia, is a diagnostic clue reflecting an overproduction of catecholamines with subsequent carbohydrate metabolism dysregulation. The diagnosis of pheochromocytoma was made after a 24-h urine catecholamines, and metanephrines determination displayed an increase in metadrenaline to 1.7 mg/24 h (normal: 0.02–0.25 mg/24 h), in normetadrenaline to 0.75 mg/24 h (normal: 0.1–0.6 mg/24 h) and in vanillylmandelic acid to 8.8 mg/24 h (normal: 1–6.5 mg/24 h). Urinary adrenaline and noradrenaline were normal. Dopamine level was decreased to 36 µg/24 h. MRI of the abdomen was then performed and detected a right adrenal mass measuring 32 × 27 mm, with high signal intensity on T2-weighted images and progressive enhancement after gadolinium injection, compatible with a pheochromocytoma (Figure 1). Laparoscopic resection of the right adrenal gland was performed 15 days later. A histological analysis of the tumour confirmed the diagnosis of pheochromocytoma with tumour cells positive for IGF2 and tyrosine.
hydroxylase. Proliferation index estimated with Ki67 was less than 5%. Genetic testing for mutations in the RET (ret proto-oncogene), VHL (von Hippel-Lindau), NF1 (neurofibromatosis type 1), SDHB (succinate dehydrogenase-B) and SDHD (succinate dehydrogenase-D) genes was negative. Following surgery, serum creatinine returned to its baseline level, glycaemia normalized and blood pressure stabilized. Currently, the patient is doing well and the urinary level of metanephrines remains normal.

Comment

Pheochromocytomas are rare catecholamine-secreting tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. If unrecognized, they can cause life-threatening complications [3]. Because symptoms are non-specific, a delay of 3 years is not unusual between initial clinical presentation and the final diagnosis [4]. However, typical attacks characterized by headache, palpitations, and sweating with hypertension must evoke the diagnosis [5]. In half of the patients, hypertension is paroxysmal, while in most others, it is permanent [5,6]. Hyperglycaemia, as noted in our patient, reflects abnormalities in carbohydrate metabolism related to endogenous catecholamine excess that resolve with tumour removal [7]. Our patient also experienced a reversible increase in serum creatinine level likely to be explained by haemodynamic effects. Indeed, catecholamines are potent vasoconstrictors increasing vascular resistance in glomerular arterioles, with a subsequent decrease in renal blood flow [8]. Retrospective anamnesis of our patient disclosed a satisfactory blood pressure control while on dialysis, with the occurrence of four episodes of paroxysmal hypertension during haemodialysis sessions in the last 2 years, associated with chest pain and headache. Therefore, we assume that the tumour was present for at least 2 years before transplantation and that the pheochromocytoma was missed while on dialysis, where diagnosis can be even more difficult as hypertension is a common finding [9,10]. In addition, our patient had long-lasting hypertension, which had eventually led him to an end-stage renal disease. Clinical suspicion of pheochromocytoma requires biochemical confirmation. Measurement of plasma-free metanephrines was recently described as the most sensitive test. However, because of its restricted availability, measurement of urinary-fractionated metanephrines remains the diagnostic test of choice [5,11]. In our patient, the restoration of renal function and urinary output by successful transplantation has allowed the urine dosage of catecholamines and metanephrines leading to the diagnosis of pheochromocytoma. While on dialysis, urine determination of catecholamines is impossible because patients are anuric, and diagnosis has to rely on plasma measurements. Because concentrations of catecholamines are commonly increased in patients on haemodialysis, a diagnosis of pheochromocytoma is suspected when concentrations are beyond a three-fold elevation [12].

Prognosis is excellent after removal of sporadic solitary pheochromocytoma [3]. Although rare, tumour recurrence is possible, occurring more often in patients with extra-adrenal disease and in those with familial pheochromocytomas [4]. Therefore a yearly follow-up is recommended for at least 10 years after surgery and should be lifelong in patients with familial, large, extra-adrenal or bilateral tumours [3,13]. Genetic testing should be considered in all patients with pheochromocytomas, especially in case of young age at onset, bilateral, extra-adrenal, multiple or malignant tumours. Indeed, accumulating evidence suggests that up to 25% of patients with pheochromocytomas harbour a mutation in one of the known susceptibility genes (VHL, RET, NF1, SDHB, SDHD) [14]. In the presence of such a mutation, familial screening should be proposed [15].

This case illustrates the fact that pulmonary oedema and hypertension occurring shortly after renal transplantation are not always related to renal artery graft stenosis. Secondary causes of hypertension must therefore be sought in renal patients in the presence of uncontrolled hypertension.

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