Nephrol Dial Transplant (1997) 12: 2740–2743

Nephrology
Dialysis
Transplantation

Case Report

Pulmonary lymphangioleiomyomatosis and renal papillary cancer: incomplete expression of tuberous sclerosis?

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Key words: papillary renal cell carcinoma; pulmonary lymphangioleiomyomatosis; tuberous sclerosis

Introduction

Idiopathic pulmonary lymphangioleiomyomatosis (LAM) is a rare disorder that affects only women of child-bearing age. The typical presenting manifestations of LAM are recurrent spontaneous pneumothorax, haemoptysis and chylothorax [1]. Histologically, LAM is characterized by abnormal smooth muscle proliferation around the airways, blood vessels and lymphatic vessels. There may also be retroperitoneal lymph node involvement and renal hamartomas which are usually asymptomatic [2].

LAM can be easily diagnosed from radiological findings, especially by high resolution-CT that shows diffuse thin-walled pulmonary cysts with normal or increased lung volume [3].

The usual outcome of LAM is respiratory failure within 10 years after diagnosis, a favourable effect of progesterone and oophorectomy has recently been advocated but not yet proven. Lung transplantation can be a valuable therapy for patients with end-stage LAM [1,4].

We describe a patient in whom the presenting manifestation was gross haematuria due to a renal papillary carcinoma, without any respiratory symptom in spite of the presence of pulmonary LAM. We then discuss the relationship between LAM and tuberous sclerosis.

Case report

A 40-year-old woman was admitted to hospital because of a three-month history of flank pain and gross haematuria. There was a history of splenectomy after splenic trauma at the age of 18, and of left oophorectomy for cysts at the age of 23. Three months before admission she had gross haematuria and right flank pain for the first time; thereafter the patient experienced a few episodes of haematuria. Five days before entry, an ultrasound scan of the abdomen showed a tumour lesion, more than 10 cm in diameter, with non-uniform echogenicity at the lower pole of the right kidney.

The patient worked as a hawker; she had normal menses; two sisters and one brother were well; her father died of coronary heart disease; her mother was alive but with hypertension and non-insulin-dependent diabetes mellitus; her husband and one child were well; there was no family history of renal or other hereditary or systemic disease. She had smoked 5–10 cigarettes day for many years and consumed little alcohol.

Her temperature was 36.6°C, her pulse was 80, respirations were 14 and her blood pressure was 135/80. Physical examination was negative but the abdomen presented a palpable mass occupying the right flank. There were no skin or ungueal lesions. A funduscopic examination was not performed. There were several red blood cells in the urinary sediment; three cytological examinations of urine were inconclusive but one was suspect for neoplastic cells. All the routine haematological and biochemical tests were normal.

Chest X-rays showed a fine interstitial pattern. A high resolution CT scan of the thorax (Fig. 1) revealed multiple thin-walled cysts, up to 15–20 mm, uniformly distributed in both lungs. No pulmonary nodules, lymphoadenopathy or pleural abnormalities were observed. These radiological findings were considered diagnostic of LAM of the lung.

Arterial blood gas analysis was normal. The results of pulmonary-function tests showed normal lung volumes with initial obstructive syndrome, not responsive to beta-adrenergic agonists, and marked alteration in alveolar-capillary CO transfer (DLCO: 6.97 ml/min/mmHg—28% of predicted; Krogh index: 1.71 l/min/mmHg—28% of predicted).

A CT scan of the abdomen and pelvis showed a mass of 13 cm in the right kidney containing microcal-

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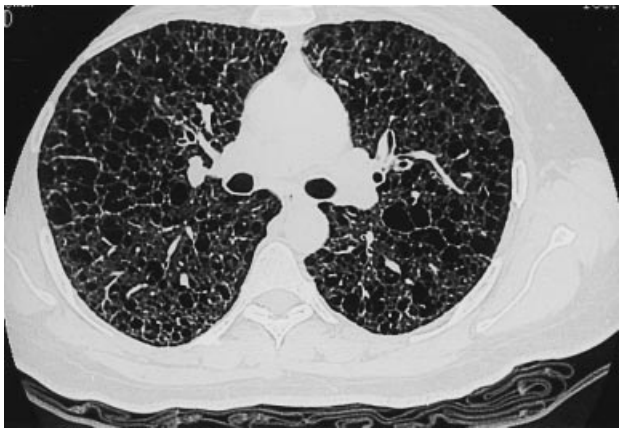

Fig. 1. High resolution CT scan of the thorax showing multiple thin-walled cysts.

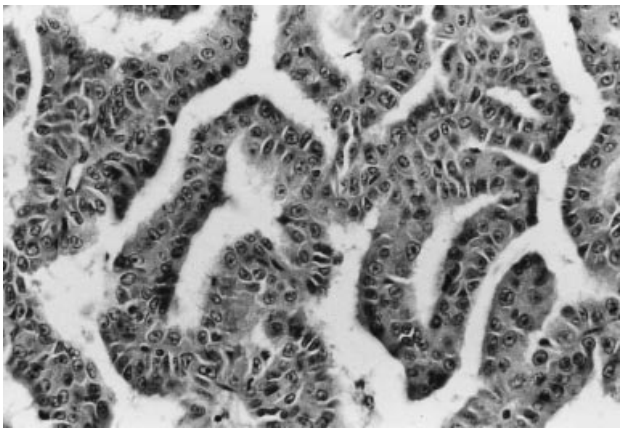

Fig. 3. Typical features of renal-cell carcinoma of the papillary type. ×400, EE staining.

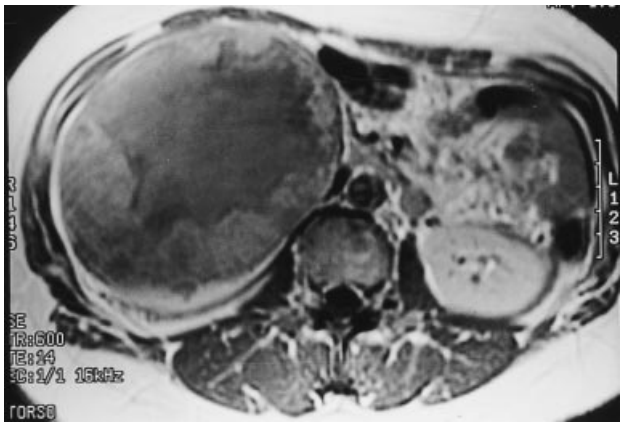

Fig. 2. MR scan of the abdomen showing central stellate scar of the right kidney tumour.

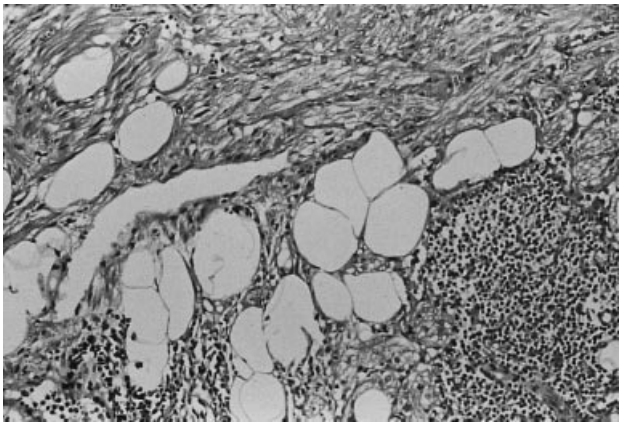

Fig. 4. Regional node of the right kidney showing characteristic angiolipomyomatosis. ×400, EE staining.

cifications and peripheral enhancement; there were no other pathological findings. An MR scan (Fig. 2) of the abdomen revealed a 13 cm well-circumscribed lesion in the right kidney with some slightly hyperintense areas in T1-weighted scan, compatible either with fat or high protein fluid and a hyperintense stellate core in T2-weighted scan. The gadolinium-enhanced scan did not show any hypervascular area. The central stellate scar suggested the presence of an oncocytoma, even if this radiological pattern is not specific and cannot exclude the possibility of other lesions [5].

A cranial CT scan was negative and did not exhibit either tuberous features or periventricular calcifications. A whole body bone-scan was also negative.

The patient underwent right nephrectomy with lymphadenectomy. On microscopical examination right kidney findings were consistent with a high grade renal-cell carcinoma of the papillary type (Fig. 3). There was a necrotic component; the surgical margins and the renal vein were disease-free; some of the regional nodes were involved by angiolipomyomatosis (Fig. 4); immunohistochemical methods were used to study the node-involvement: HMB45, vimentin, smooth muscle actin and desmin were strongly expressed; estrogen receptor was weakly expressed and progesterone receptor was very weakly expressed; vessels were strongly positive for CD34 and factor VIII. We were not able to perform any genetic investigations for technical reasons. The patient was urged to stop smoking and was advised to begin hormonal therapy.

Discussion

The patient came to our attention because of the classical triad of a renal tumour—flank pain, gross haematuria and palpable mass [6]—eventually shown to be a papillary renal-cell carcinoma limited to the right kidney, treated by surgical resection.

We also found pulmonary LAM with retroperitoneal node involvement. The pulmonary disease, although still asymptomatic, is already severe as shown by the reduced diffusing capacity of carbon monoxide, and will probably be the survival-limiting disease.

We think that all the clinical manifestations of the patient, renal papillary carcinoma and pulmonary LAM with node-involvement, could be related to a single disease.

Tuberous Sclerosis Complex (TSC) is an autosomal dominant hereditary disorder with high variability in clinical expression and high percentage of new mutations [7] (80%).

The classical triad of Bourneville's phacomatosis—epilepsy, mental retardation and adenoma sebaceum—is not found in all patients and, moreover, the disease has been characterized by systemic involvement of different organs besides the neurological and cutaneous disorders. Multiple retinal astrocytomas and other retinal hamartoma, cardiac rhabdomyoma, bone cysts, gingival fibromas and enamel pittings, and multiple ungueal fibromas have all been reported in association with TSC. The kidney is the most involved organ and the second cause of death in TSC after neurological disorder [8].

The renal involvement in TSC consists of angiomyolipomas, which are usually multiple and bilateral, and, although less frequently, cysts that can mimic polycystic kidney disease. Renal-cell carcinoma has been described in association with TSC as well. The renal involvement can lead to end-stage renal disease, and renal failure can be the presenting manifestation of TSC [9].

Only a small proportion (0.1–1%) of patients with TSC have pulmonary involvement with histopathologic findings of the lung that are identical to those seen in LAM. This close relation between TSC and LAM is intriguing and has led some authors to consider idiopathic LAM an incomplete expression of TSC even though there are some striking differences in the clinical features. LAM occurs almost exclusively in women of child-bearing age, does not have any familial inheritance and does not seem to be associated with neurological and cutaneous involvement.

The patient presented here re-emphasizes the close relationship between LAM and TSC. According to the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association [10], the patient should be classified as 'suspected TSC' from the histologic confirmation of node hamartoma, a tertiary feature, and the radiographic evidence of pulmonary LAM, another tertiary feature. Histologic confirmation of pulmonary LAM, a secondary feature, would satisfy the criteria for 'probable TSC'. The classification does not consider as renal involvement (another secondary feature, resulting in the classification of 'definite TSC') the presence of renal-cell carcinoma which is a known manifestation of TSC but, to our knowledge, it has never been described in association with pulmonary LAM.

Two genes involved in Bourneville's phacomatosis have been detected—TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13.3 [11]. Recently a conserved linkage group on Eker rat chromosome 10q and human chromosome 16p13.3 has been identified. Eker rat is an excellent example of hereditary predisposition to specific cancer. In fact, virtually all heterozygotes develop renal cell carcinoma by the age of 1 year through multiple steps, from early preneoplastic lesions to adenomas. The Eker rat mutation on chromosome 10q is tightly linked to the TSC2 gene. Loss of heterozygosity (LOH) on chromosome 10q is found in renal carcinomas developed in rats carrying the Eker mutation, indicating that in heterozygotes at least two events (one inherited and one somatic) are necessary to produce the disease. The gene on rat chromosome 10q works as a tumour suppressor gene. In humans, hamartomas developing in TSC patients have LOH at the TSC2 locus, supporting a similar tumour-suppressor nature. Tumour suppressor genes are recessive in oncogenesis but render a heterozygous carrier highly susceptible to a disease that appears in pedigrees as a dominantly inherited disorder, such as TSC [12].

A similar role for the TSC1 gene in renal cell carcinogenesis has been reported in a family with hereditary multifocal papillary renal cell carcinoma [13].

While mutations on the short arm of chromosome 3 are tightly linked to development of renal cell carcinoma of clear cell type [6], the renal cell carcinoma in TSC are histologically of the oncocytic or papillary type but not of clear cell type [13].

In conclusion, it is interesting to note the abdominal nodes' positivity for HMB45; this monoclonal antibody reacts with a sialated glycoconjugate present in cells with active melanogenesis, but is not restricted to melanoma cells. In fact it has also been found in renal and hepatic angiomyolipoma and in pulmonary LAM, all lesions related to TSC [14,15].

In the future, a diagnostic genetic approach will be widely available and we hope to very soon be able to ascertain if the same genes are involved in LAM. The intriguing relation between TSC and LAM will, eventually, become clear!

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Received for publication: 21.2.97
Accepted in revised form: 11.6.97