An exceptional minute tumour incidentally found in a renal biopsy

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Abstract
Pathological analysis of renal biopsies performed to investigate a nephrological disease may exceptionally reveal incidental tumours, in addition to expected glomerular, tubulointerstitial or vascular pathology. We present the first case to date of a minute angiomyolipoma (AML), found incidentally in a renal biopsy specimen, performed in the assessment of proteinuria. AML is an uncommon kidney tumour, composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells. Immunohistochemistry is mandatory for a definitive diagnosis, showing a specific perivascular epithelioid differentiation. The diagnosis of renal AML justifies the search for tuberous sclerosis-associated tumours.

Keywords: angiomyolipoma; incidental tumour; tuberous sclerosis

Background
Pathological analysis of renal biopsies performed to investigate a nephrological disease may exceptionally reveal incidental tumours, in addition to expected glomerular, tubulointerstitial or vascular pathology. We present one case of an incidental rare renal neoplasm, not reported to date in renal biopsy specimens.

Case report
A 47-year-old woman originating from Sub-Saharan Africa had been previously diagnosed as having mixed connective tissue disease with joint manifestations, puffy fingers, myositis and interstitial pneumonitis. Anti-RNP, anti-nuclear and anti-DNA antibodies were specifically present at time of diagnosis. The patient had been treated for 5 years with steroids and methotrexate, with clinical efficiency. Nephrotic-range proteinuria was noticed during follow-up and a renal biopsy was performed.

There were 10 glomeruli present in the renal tissue core submitted for light microscopy, 7 of which were globally sclerosed. There was diffuse widening of the glomerular basement membranes with slight segmental vacuolization of glomerular basement membranes after Jones methenamine silver stain, suggestive of membranous nephropathy. Immunofluorescence confirmed the presence of diffuse membranous deposits mainly composed of IgG.

Moreover, a micro-tumour ∼0.5 mm in diameter was present in the subcapsular area (Figure 1A). This lesion was composed of eosinophilic spindle cells, associated with few adipocytes (Figure 1B). Immunohistochemistry showed a diffuse immunostaining with anti-smooth muscular actin antibody (Figure 1C), while few cells were stained with melan-A and HMB-45 antibodies (Figure 1D). Thus, histological and immunohistochemical data were consistent with an incidental minute angiomyolipoma (AML) of the kidney.

Thereafter, histological findings, in association with bioclinical data, prompted a diagnosis of lupus-related glomerulonephritis (Class V according to the ISN/RPS 2003 classification). Subsequently, therapeutic intensification with rituximab infusions was decided, leading to the remission of the renal and extrarenal manifestations 10 months after treatment initiation.

Otherwise, thorough clinical examination did not reveal any evidence of tuberous sclerosis (TS) and there was no family history of phakomatosis.

Discussion
The interest of this case lies in the incidental finding of a minute AML on a renal biopsy carried out in the investigation of a nephrological disorder. To our knowledge, this is the first reported case of microscopic AML on a kidney biopsy not performed to investigate a renal mass.
Incidental tumours are exceptionally described in renal biopsies. There is indeed only one published series focusing on incidental neoplasms in renal biopsies, with an incidence of 0.2% [1]. In this series of 25 patients, reported neoplasms were papillary lesions (22 patients), renal cell carcinoma (2 patients) and in situ carcinoma in a collecting duct (1 patient). These data illustrate that papillary lesions may be not infrequently found in renal biopsies. This is not surprising as both papillary adenomas and carcinomas preferentially develop when chronic damage of renal parenchyma exists, which is frequent in the context of kidney diseases. On the other hand, the series of Pankhurst et al. [1] demonstrates that non-papillary lesions are exceedingly rare in the context of nephrological (rather than urological) renal biopsies. Besides, the incidental diagnosis of a renomedullary interstitial cell tumour in a kidney biopsy performed for haematuria has to be mentioned [2].

AML is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, with abnormal thick-walled blood vessels. AML is an uncommon kidney tumour that accounts for ~1 percent of surgically removed renal tumours. It occurs in two forms: sporadic or as part of a TS complex, sporadic forms being four times more frequent than TS-associated cases. AML belongs to PEComas, a term including a family of lesions such as lymphangioleiomyomatosis, clear cell ‘sugar’ tumour of the lung and immunophenotypically similar lesions arising at a variety of visceral and soft tissue sites [3]. PEComas are characterized by proliferation of perivascular epithelioid cells, which are supposed to originate from the walls of blood vessels. Immunohistochemistry is useful to demonstrate the perivascular epithelioid differentiation of PEComas, showing expression of smooth muscle actin in conjunction with melanocytic markers, i.e. melanosome-associated protein HMB-45 and Melan-A (MART-1). The immunohistochemical profile of AML is thus specific and helps to differentiate this neoplasm from other spindle cell tumours of the kidney such as renomedullary interstitial cell tumour, leiomyoma or sarcomatoid renal cell carcinoma. At the ultrastructural level, the presence of premelanosomes might be demonstrated in tumour cells [3].

 Although not reported to date on ‘nephrological’ renal biopsies, microscopic nodules of AML similar to the present cases are relatively well known. Such lesions have indeed been reported in studies focusing on peritumoural areas of nephrectomy specimens removed for large AMLs. These small nodules are considered as precursor lesions of macroscopic AML [4,5]. As in our case, they are predominantly composed of spindle and epithelioid cells, the proportion of adipocytes increasing as the lesions become larger [4,5]. Intraglomerular microlesions consisting of few adipocytes or smooth muscle cells within the glomerular capillary tuft have been described as well [5,6]. These small AMLs are relatively frequent in elderly individuals, allowing Chowdhury et al. [4] to hypothesize that small nodules of AML in non-TS patients do not increase in size or that their growth rate is very slow.

In addition to genetic data, which represent the gold standard, clinical data are useful to distinguish between renal AML linked with TS from sporadic cases. First, AML associated with TS develop in younger patients than in cases without TS (mean age at diagnosis between 25 and 35, and between 45 and 55, respectively). Secondly, TS patients usually have symptomatic lesions of the central nervous system, distinctive skin lesions, cardiac rhabdomyomas and lymphangioleiomyomatosis [5]. Furthermore, renal AML in TS is often multiple and bilateral. In our case, the age of the patient, the absence of medical history of tumour and the absence of TS-related lesion after clinical and radiological examination (in particular, no other renal tumours) are all features that do not support TS-associated AML.

Obviously, the clinical management of incidental AML is not defined. However, it should be stressed that activation of the mammalian target of rapamycin (mTOR) pathway has been shown to be common in sporadic AMLs [7]. Thus, the use of mTOR inhibitors such as rapamycin has been proposed for this type of neoplasm [7], particularly for tumours not accessible by surgery. In our case, the minute tumour has probably been totally removed by needle biopsy and no specific treatment is indicated.

Conflict of interest statement. None declared.

References
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Fig. 1. (A) Subcapsular tumour composed of eosinophilic spindle cells (hematoxylin–eosin–safron; original magnification × 100). (B) The tumour is composed of bland smooth muscle-type cells (hematoxylin–eosin–safron; original magnification × 200). (C) Diffuse expression of smooth muscle actin by tumour cells (immunoperoxidase; original magnification × 100). (D) Few tumour cells were immunostained with melan-A antibody (immunoperoxidase; original magnification × 400).
Aggregated serum free light chains may prevent adequate removal by high cut-off haemodialysis

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Abstract
Free light chain (FLC) removal by high cut-off haemodialysis has been described as an adjuvant therapy for the management of patients with severe renal failure complicating multiple myeloma. The two cases reported here are the first patients in whom this treatment did not remove FLCs. In both patient’s sera, size-exclusion chromatography identified large FLC aggregates, with molecular weights above the cut-off of the dialyser. It is important for clinicians to be aware of FLC aggregates as a reason for failure to remove FLCs by this new modality.

Keywords: cast nephropathy; high cut-off haemodialysis; serum-free light chain

Background
Removal of immunoglobulin free light chains (FLCs) by high cut-off haemodialysis (HCO-HD) has recently been described as a new treatment option for patients with biopsy-proven cast nephropathy, secondary to multiple myeloma [1]. In an uncontrolled pilot study, 14 of 19 patients with myeloma kidney and dialysis-dependent renal failure subsequently became independent of dialysis following treatment with HCO-HD and chemotherapy [2]. Two randomized controlled trials [EuLITE [3] and MYRE (NCT01208818)] are further evaluating this new treatment to determine if FLC removal by HCO-HD increases the rate of renal recovery. In parallel with these studies, the treatment continues to be used and evaluated by clinicians internationally. The purpose of the case reports presented here is to discuss why HCO-HD could not effectively remove FLCs in two patients.

Case reports

Case 1
A 63-year-old man presented with dysuria and rapidly progressive renal failure. On admission, his serum creatinine level was 150 μmol/L (1.69 mg/dL), haemoglobin 8 g/L, calcium 2.5 mmol/L and serum total protein 70 g/L. By Day 3, the serum creatinine had risen to 636 μmol/L (7.2 mg/dL). Serum protein electrophoresis (SPE) and subsequent immunofixation detected an IgA lambda monoclonal gammopathy [9.68 g/L by SPE densitometry (SPED)] with lambda FLC (not quantifiable by SPED) and associated hypogammaglobulinaemia. Serum-free lambda light chain concentration was 7510 mg/L (Freelite; The Binding Site, Birmingham, UK). Bone marrow examination showed a clonal proliferation of plasma cells (10%) and a renal biopsy demonstrated cast nephropathy and 25% interstitial fibrosis.

A chemotherapy regime consisting of bortezomib and dexamethasone was commenced. Initially, standard haemodialysis was used to support the patient's renal failure and when myeloma kidney was diagnosed, protein permeable dialysis was initiated. Five single-dialyser 5-h sessions with