The importance of a histology-based diagnosis of interstitial nephropathy in two patients with renal insufficiency

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Case 1

A 68-year-old Belgian woman was referred in November 1997 for evaluation of renal failure (serum creatinine 2.8 mg/dl). Her past medical history included hypothyroidism treated by L-thyroxin since 1992, resection of an endometrial polyp in 1996 and chronic constipation for many years. Her current treatment included various laxatives (lactulose, bisacodyl) and anxiolytics (flupentixol). She acknowledged the previous intake of phenacetin and dexfenfluramine, but denied that of Chinese herbs or any other herbal phytotherapy.

On admission, the patient was thin: body weight 49 kg, height 1.59 m; her blood pressure was 200/90 mmHg. Biochemical tests disclosed advanced renal failure (creatinine clearance 20 ml/min) and severe anaemia (haemoglobin 8.9 g/dl); her 24-h proteinuria was 390 mg. Urinalysis and urine cytology were normal. Both kidneys were small at ultrasonography. Chronic interstitial nephropathy (IN), possibly secondary to phenacetin and laxative abuse, was diagnosed. Further deterioration in renal function necessitated peritoneal dialysis in February 1999. Two consecutive episodes of peritonitis secondary to Alcaligenes xylosoxidans required the switch to haemodialysis (HD) in November 1999. A left-sided cadaveric renal transplantation was performed in January 2000. Pathological examination of the controlateral kidney and ureter disclosed a similar histological picture. Repeated cystoscopies were normal. Currently, serum creatinine is stable (1.05 mg/dl); urine cytology is normal as well as cystoscopy (repeated periodically).

Case 2

A 53-year-old woman was referred in April 1996 for severe renal failure (serum creatinine 7.35 mg/dl). Her past medical history included cervical osteoarthritis (treated by non-steroidal anti-inflammatory drugs), recurrent headaches for the last 12 months (treated with over-the-counter medications containing salicylates and caffeine) and hypertension, first detected in December 1995 (treated with isradipine). Serum creatinine was 1.7 mg/dl in May 1994 and 2.7 mg/dl in December 1995.

The patient complained of muscle cramps, nausea and itching. On admission her body weight was 59.1 kg and height 1.59 m; her blood pressure was...
220/120 mmHg. Other findings included a marked pallor, an aortic systolic murmur 2/6 and no oedema. Biochemical tests disclosed severe renal failure (serum creatinine 13.3 mg/dl) and anaemia (haemoglobin 8.2 g/dl). Proteinuria was 900 mg/24 h. Urinalysis was normal without glycosuria. Fundoscopy showed stage III retinopathy. Both kidneys were small on ultrasonography with no signs of renal artery stenosis. The patient acknowledged attendance of the X clinic in 1988–1989, thus before the addition of Chinese herbs to the slimming regimen incriminated in AAN [1]. A diagnosis of IN of unknown aetiology, probably drug induced, was made. HD was started.

In September 1997, recurrence of severe hypertension (blood pressure 290/110 mmHg) despite increased ultrafiltration and treatment with prazosine, captopril and labetolol led to an arteriography of the renal arteries and the discovery of a severe ostial stenosis of the right renal artery (treated by percutaneous angioplasty and stenting), and a stenosis of a segmental artery of the left lower pole (treated by percutaneous transluminal angioplasty). As blood pressure remained poorly controlled, a bilateral nephrectomy was performed.

Pathological examination of the kidneys showed typical lesions of AAN: an extensive hypocellular interstitial fibrosis of the medullae as well as of the cortex with tubular atrophy and global sclerosis of glomeruli with a decreasing cortico-medullary gradient. Moderate amounts of interstitial lymphocytes were visible mainly in the medullary rays and at cortico-medullary junctions. Interlobular arteries showed intimal fibrous thickening. Arcuate, interlobar and segmental arteries displayed intimal mucoid fibroblastic hyperplasia. Atypia in the epithelial lining were absent in the collecting ducts and focal in the pyelo-calyceal urothelium [1–7]. AA-DNA adducts were detected in the right kidney (patient 8, table I, in [9]) [8,9].

A right-sided cadaveric transplantation was performed in November 1999 together with the resection of remnant ureters. Pathological examination showed urothelial atypia in the mid-ureter and extensive high-grade flat transitional cell carcinoma (TCC) in situ in the upper ureter. Endoscopic resection of a bladder tumour performed 4 months later revealed a low-grade (I) non-invasive papillary TCC (Figure 2), treated by intravesical mitomycin instillations. Currently serum creatinine is 1.8 mg/dl; urinary cytology and cystoscopies (repeated periodically) are normal.

Discussion

Our two patients denied the intake of suspicious herbal regimens on interrogation and were diagnosed as IN either secondary to the abuse of phenacetin or of unknown origin, respectively [10]. Still, pathological examination of native kidneys, removed during renal transplantation in the first case and for severe intractable hypertension during HD in the second case, disclosed typical features of AAN: extensive hypocellular interstitial fibrosis associated with tubular atrophy and global sclerosis of the glomeruli starting in the peripheral cortex and progressing towards the deep cortex [4,5], as well as atypia in the epithelium of collecting ducts (case 1) and in the pyelo-calyceal urothelium (both cases) [6]. The presence in both cases of a focal moderate interstitial lymphocytic infiltration and a marked fibrosis in the medullae suggest a possible contribution of analgesics [10]. Noteworthy, some cases of AAN have been associated with a moderate interstitial lymphocytic infiltration and evoking the possibility of a superimposed pathology (our unpublished data).

AAN is associated with the development of urothelial carcinomas in 40–46% of the patients: its diagnosis is thus not purely of academic interest [6,7]. In all tested species (rat, mouse, rabbit and human), AA has proven to be a potent carcinogenic compound [11] with the formation of AA-DNA adducts [8].
AA-DNA adducts in the kidney tissue, assessed in the second patient were associated with urothelial malignancy in the upper ureter and bladder. Our two patients are now subject to regular assessment of urinary cytology and cystoscopies. Prophylactic removal of both native kidneys and ureters, followed by a close monitoring of the remaining bladder is recommended in such cases.

Teaching points

(i) When AAN is suspected, biopsy (at early stages) or per transplantation nephrectomy should be seriously considered: the histological picture is highly suggestive and the detection of AA-DNA adducts is confirmatory.

(ii) The diagnosis of AAN is crucial as it is associated with a high risk of urinary tract carcinoma. Bilateral nephro-ureterectomy should be performed systematically at the time of transplantation, with subsequent follow-up of urine cytology and periodic cystoscopy.

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References