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Teaching Point
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Furosemide, orlistat and non-steroidal anti-inflammatory agents—too much for the kidneys to handle!

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Introduction

Drug-induced acute kidney injury (AKI) is commonplace. The drugs involved are numerous, and their nephrotoxicities can take on various histopathological patterns that include acute tubular necrosis, renal vasculitis, glomerular disease and acute/chronic tubulo-interstitial disease. Renal prognosis may be improved by the discontinuation of the offending agent, but this is not always the case.

This presented patient is unique for two reasons. First, the renal toxicities of chronic furosemide abuse and orlistat use have received only scant attention in the adult nephrology literature [1–4]. Secondly, this patient, once again, demonstrates that the renal dangers of prolonged nonsteroidal anti-inflammatory drug (NSAID) therapy should never be diminished in importance, especially in the setting of chronic kidney disease (CKD).

Case report

In August 2008, a 60-year-old woman presented with rapidly progressive renal failure (serum creatinine ∼6 mg/dl). In April 2008, the patient's serum creatinine was 0.9 mg/dl (Cockcroft–Gault creatinine clearance ∼60 cc/min).

Relevant past history included an obsessive attitude to weight. At age 18 the patient weighed 120 kg; 4 years later she weighed 80 kg and at presentation the patient weighed 52 kg. Repeated history taking led to a reluctant revelation from the patient that furosemide had been used since age 18, first at low daily doses (40–60 mg), but over the preceding 5 years furosemide dosage had increased to ∼1000 mg/day. Orlistat (120–240 mg/day) had also been used continuously over the previous 3 years. Intermittent attacks of acute ankle monoarthritis were self-treated by NSAID. In the month prior to presentation, ankle pain had been sufficiently severe to prevent normal walking and the patient had taken etoricoxib (90 mg/day) for an entire month.

On examination, the patient was normotensive and without orthostatism. Tophi were not detected, and the patient was not edematous. Investigations revealed sterile leucocyturia, microhaematuria (without RBC casts) and proteinuria ∼0.7 g/day. The serum eosinophil count was normal. Serum potassium: 5.0–5.5 mEq/l, bicarbonate: ∼20 mEq/l, calcium and magnesium: within normal levels. All serological parameters were normal. Repeated urinary calcium levels, performed during hospitalization, were ∼20 mgEq/l. Urinary oxalate levels were not taken. Renal calcifications were not seen on plain abdominal XR. Renal sonography showed normal kidney size bilaterally, without any evidence of calcifications, cortical scars or hydronephrosis. A dietary consultation revealed that the patient's daily intake was ∼500 kcal and 30 g of protein.

A closed renal biopsy was performed and showed (a) moderate-to-severe chronic interstitial fibrosis and tubular atrophy with a secondary global glomerulosclerosis in 5/15 glomeruli, (b) acute tubular necrosis, (c) patchy areas of lymphocytic and eosinophilic infiltration of the interstitium (Figure 1) and (d) extensive intratubular calcifications. Some calcifications stained positive with the Von Kossa stain (Figure 2), while the other calcifications were strongly birefringent with polarized light (Figure 3). These calcifications were therefore designated as consisting of both calcium phosphate (nephrocalcinosis) and calcium oxalate (oxalate nephropathy). Immunofluorescence was negative, and electron microscopy showed partial effacement of some foot processes.

Oral prednisone (40 mg/day) was given for 3 weeks, but without any improvement in renal function. The patient is now on a chronic haemodialysis programme, and undergoing psychiatric evaluation before being deemed an appropriate candidate for renal transplantation.

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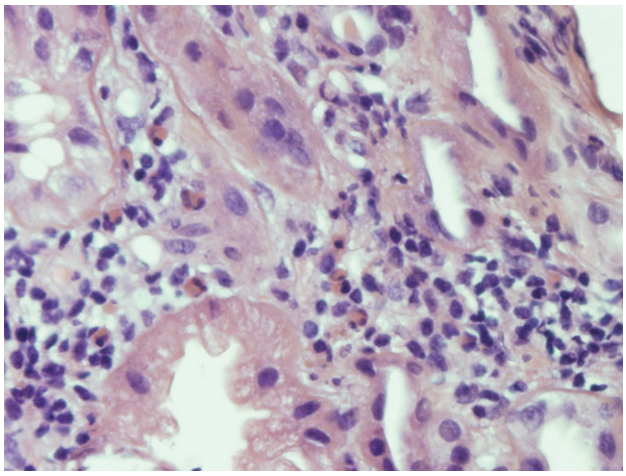

Fig. 1. Interstitial inflammation composed of lymphocytes and eosinophils (H&E stain; 400×).

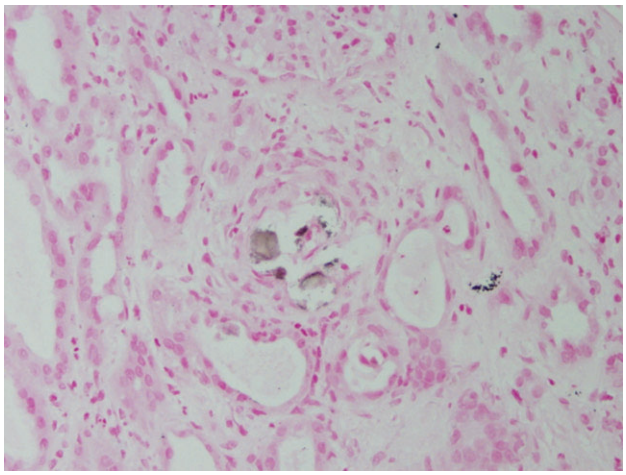

Fig. 2. Positive Von Kossa stain of intratubular calcification (100×).

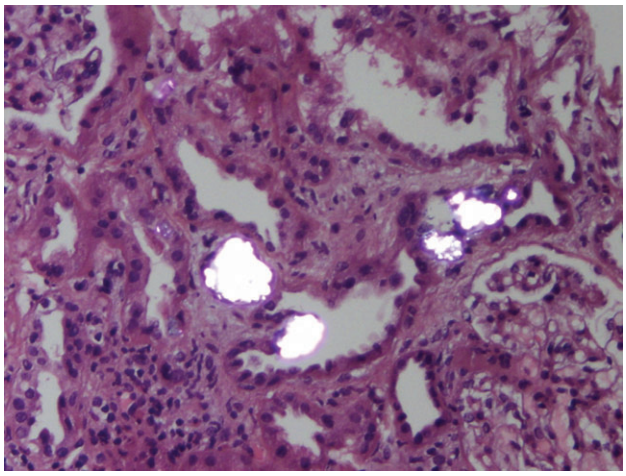

Fig. 3. Birefringent intratubular calcifications, indicating calcium oxalate crystals (H&E stain; 100×).

Discussion

Clinically, this patient presented with CKD and a superimposed acute and irreversible deterioration of renal function. Renal biopsy findings showed that the CKD was attributable to nephrocalcinosis/oxalate nephropathy, resulting in a chronic tubulo-interstitial nephropathy, while acute tubular necrosis, probably as a result of NSAID, explained the AKI. But, interestingly, many nephrological questions remained unanswered. What were the underlying causes of the nephrocalcinosis and the oxalate nephropathy–two separate renal calcium deposition diseases [5]? And could the patchy cellular tubulo-interstitial nephritis also be NSAID induced, and, therefore responsive, not only to cessation of NSAID, but also to corticosteroid therapy?

Nephrocalcinosis results from the intra-tubular deposition of calcium phosphate. Most commonly, it is associated with hypercalciuric states, involves all tubular segments and presents as CKD with little proteinuria [5]. Over the last few years, nephrocalcinosis has gained recognition as a possible complication of high phosphate-containing bowel cleansers [5,6]. In 1984, Hufnagle *et al.* were the first to implicate furosemide therapy as a possible cause of renal calcifications and nephrocalcinosis [7]. The authors described 10 preterm infants with respiratory and cardiac disease who required furosemide in large doses (≥2 mg/kg/day). Since then, numerous studies have substantiated the possibility of furosemide-associated nephrocalcinosis, both in preterm and fullterm infants [8,9]. Furthermore, even after cessation of furosemide, renal function may remain impaired and calcium content in renal tissue high. This was elegantly shown in an animal study conducted by Alon *et al.* [10]. Pathogenetically, furosemide may be responsible for nephrocalcinosis via its hypercalciuric effect although other mechanisms may also play a role [11].

To the best of our knowledge, only one article describes adult-onset nephrocalcinosis in the setting of chronic furosemide abuse [1]. In 2001, Kim *et al.* described 18 adult patients, of which 17 were women. All had an 'intense concern about their appearance and weight'. Fifteen patients were diagnosed as having nephrocalcinosis, either via radiological studies or renal biopsy. In these affected patients, the duration of furosemide abuse ranged from 3 to 25 years, while the furosemide dose was high (538 ± 174 mg/day). After stopping furosemide, the mean plasma renin activity and aldosterone levels remained high, and creatinine clearance remained depressed at 70 cc/min [1].

Oxalate nephropathy occurs primarily in the setting of hyperoxaluric states. This may be difficult to distinguish from nephrocalcinosis, without proper preparation of the studied renal tissue. Both nephropathies appear as intratubular calcifications, but only calcium phosphate stains positive with either the Von Kossa or Alizarin red stains [10], while calcium oxalate deposits are brightly birefringent with the use of polarized light. Although oxalate deposits may be seen in acute tubular necrosis [3], this was not the case in this patient. Additionally, no other possible cause for hyperoxaluria seemed apparent.

Enteric hyperoxaluria is the end result of a number of disease states, or operations, which lead to fat/bile salt malabsorption [12]. These fats then bind to intraluminal calcium within the small bowel, leaving free oxalate to enter the large bowel, to be absorbed into the circulation and eventually excreted, in pathological amounts, into the urine [12,13]. Orlistat (Xenical® Roche, Israel) is a non-systemically acting drug that binds to gastric and pancreatic lipases in the proximal small intestine. In this way it causes an iatrogenic fat malabsorption of ∼30% and weight loss. For this very reason, orlistat has FDA approval for use as a weight-reducing drug. But, could the drug be capable of producing an enteric hyperoxaluric state?

In 2004, Ferraz *et al*. studied the short-term renal effects of orlistat on adult rats [13]. They showed that the drug was capable of increasing urinary oxalate levels many-fold, especially in rats fed high fat or oxalate-enriched diet. A rise in the ion-activity product of calcium oxalate was also demonstrated. Interestingly, no renal depositions of oxalate were seen on examination of renal tissue after termination of the study, a fact probably explained by the relatively short period of time (4 weeks only) that the animals were treated with orlistat [13]. Three short clinical publications further add weight to the possibility of an orlistat-induced oxalate nephropathy [2–4]. In 2007, Singh *et al*. described a diabetic woman with acute-on-chronic kidney injury, 2 months after starting orlistat. A renal biopsy revealed oxalate nephropathy, superimposed on nephrosclerosis. After stopping the drug, the patient's renal function returned to her baseline levels, and on repeat renal biopsy, the intratubular oxalate deposits were no longer seen [2]! Also in 2007, Courtney *et al*. described a woman with CKD, who developed irreversible, dialysis-dependent renal failure 5 months after starting orlistat. On renal biopsy, extensive intratubular oxalate deposits were seen [3]. Finally, in 2008, Karamadoukis *et al*., retrospectively examined more than 800 renal biopsies, looking specifically for the combined presence of acute tubular necrosis and crystal deposition. Eleven such biopsies were found. Two of these 11 patients had calcium oxalate crystal deposits. Both patients had been treated with orlistat [4]!

NSAID are nephrotoxic and their prolonged use, in predisposed populations, can lead to acute tubular necrosis. But they are also capable of producing an acute tubulo-interstitial nephritis (ATIN), which, most commonly, occurs after weeks to months of therapy. Most commonly, heavy proteinuria accompanies a significant deterioration in renal function. Renal tissue examination reveals ATIN and minimal change disease with effacement of foot processes. In 1990, Porile *et al*. analysed 43 patients with NSAID-associated ATIN [14]. Two important points emerged from this retrospective study. First, in 9/43 patients, ATIN occurred without an accompanying glomerulopathy. Secondly, after stopping the offending NSAID, the addition of steroid therapy made no difference to the extent of, or time to, renal function recovery [14]. However, a recent study in *Kidney International* placed emphasis on the potential beneficial role of early steroid therapy in drug-induced ATIN [15]. This study included a separate analysis in 20 patients with ATIN secondary to NSAID. Results in this subgroup of patients also showed that early steroid therapy improved renal function [15].

Our patient received steroid therapy, but without any improvement in renal function. Two possibilities behind the failure of this therapy are that (a) the acute tubular necrosis was the main causative problem underlying this patient's irreversible renal failure and (b) the patches of cellular tubulo-interstitial infiltrate may not be part of a suspected ATIN, rather part of a mild inflammatory response, which at times, can accompany chronic tubulo-interstitial diseases [12].

Teaching points

1. Patients with anorexia nervosa will not reveal drug use readily. Slow and repeated history taking is necessary if the true extent of drug abuse is to be acquired.
2. High-dose furosemide is capable of causing nephrocalcinosis and a chronic tubulo-interstitial disease in adults.
3. Orlistat is a potential nephrotoxin, capable of causing oxalate nephropathy and, in some patients, an irreversible and severe CKD.
4. NSAID have become over-the-counter drugs for all age groups. Surely, the nephrology community must aim to keep the use of these drugs to a minimum, and if indicated then their use should be restricted for short periods of time.

Conflict of interest statement. None declared.

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