CASE REPORT

Chronic tubulointerstitial nephritis induced by 5-aminosalicylate in an ulcerative colitis patient: a rare but serious adverse event

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SUMMARY

The 5-aminosalicylate is widely prescribed in inflammatory bowel disease patients. Its potential for renal damage has been seldom described. We report a case of a 23-year-old man who started 5-aminosalicylate after being diagnosed with ulcerative colitis. One year after, a significant decline on his creatinine clearance was noted, however, at that time, he was on an acute flare of his bowel disease and the 5-aminosalicylate dose was increased. Six months later, his renal function kept worsening and, on drug-induced toxicity suspicion, 5-aminosalicylate was halted and a kidney biopsy demonstrated a chronic tubulointerstitial nephritis. Steroids and azathioprine were started leading to partial recovery and stabilisation of his renal function. Physicians who prescribe 5-aminosalicylate to patients with inflammatory bowel disease should be aware of this adverse event.

BACKGROUND

Patients with mild-to-moderately active inflammatory bowel disease (IBD), mainly ulcerative colitis (UC), benefit from the use of 5-aminosalicylate (5-ASA), thus prescribing this drug to patients with IBD is common.¹ Although rarely reported, an increasing number of case reports of nephrotoxicity due to 5-ASA have been published.^{2–10} So far, 46 cases have been described and the reported incidence is 0.26% *per* patient-year.¹¹ It is apparent that an idiosyncratic mechanism is more likely than a dose-related effect.^{12–16} When renal impairment due to 5-ASA is suspected, the drug should be withdrawn immediately. If serum creatinine (sCr) does not start to decrease, a renal biopsy may be considered.² For those patients in whom renal function does not respond to drug withdrawal alone, steroids and azathioprine have been prescribed, however, data on their benefit are scarce and reports are anecdotal.¹⁷ A recovery of renal function is seen in most patients (40%–85%) after 5-ASA withdrawal, with better changes after early discontinuation (within the first 10 months).^{2, 18} However, it has been estimated that up to 10% of patients will develop end-stage renal disease.¹⁹

CASE PRESENTATION

We report a case of an obese 23-year-old man, an active smoker, without a known history of personal or familial kidney or urological diseases. In January 2010, he was diagnosed with UC during a moderate flare and was prescribed 5-ASA, 3000 mg/day; he rapidly achieved disease remission. After

symptomatic remission, the 5-ASA dose was reduced to 1500 mg/day. On a scheduled consultation, 10 months later, he had another mild-to-moderate flare of his bowel disease, leading to an increase in 5-ASA dosage (4500 mg/day). At this time, besides mild anaemia (haemoglobin=10 g/dL), blood chemistries demonstrated a twofold increase in sCr (2 mg/dL) and serum urea. This was interpreted as a consequence of diarrhoea, dehydration and IBD activity. Two weeks later, the disease quickly achieved clinical remission and the previous 5-ASA dose was resumed. Seven months later, with his IBD in complete clinical remission, a fourfold increase in sCr (4 mg/dL) was noted. He was asymptomatic and referred a normal urinary output. Brief hospitalisation was decided on.

INVESTIGATIONS

At admission, the patient was normotensive, normocardic and afebrile, his physical examination was unremarkable and no peripheral oedema was noted. Laboratory tests showed mild anaemia (haemoglobin=11.3 g/dL), slightly elevated erythrocyte sedimentation rate (31 mm/h), hyperparathyroidism (serum parathyroid hormone 3×ULN), fourfold increase in sCr (4 mg/dL) and an increased serum urea (83 mg/dL). His creatinine clearance (CrCl; Cockcroft-Gault) was 19 mL/min. Urinalysis and cultures demonstrated a sterile pyuria and a non-nephrotic proteinuria. Further analyses ruled out infectious diseases (HIV, hepatitis B virus, hepatitis C virus and syphilis) and an autoimmune process (no autoantibodies, normal serum complement). An abdomino-reno-vesical ultrasound demonstrated no changes in kidney dimensions, parenchymal thickness or parenchymo-sinusal differentiation, and no obstruction was seen. A kidney biopsy was performed (figure 1A–E), demonstrating a lymphocytic infiltrate with some eosinophilic component in the cortical interstitium. Other findings were: mild interstitial oedema, tubulitis, cellular debris inside the tubular lumen, moderate tubular atrophy and mild interstitial fibrosis. No pathological findings were seen in the glomeruli. The vascular vessels were intact and staining for amyloid and immunofluorescence was negative. Based on these findings, a diagnosis of active chronic tubulointerstitial nephritis was assumed.

DIFFERENTIAL DIAGNOSIS

The three most important aetiologies to exclude were: IgA glomerulonephritis (Berger disease), secondary amyloidosis and 5-ASA nephrotoxicity.

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Figure 1 Histological aspects of tubulointerstitial nephritis caused by 5-aminosalicylate (5-ASA). No glomerular changes are noted. Interstitial oedema and a marked interstitial infiltrate consisting primarily of lymphocytes and monocytes ((A) H&E; original magnification $\times 200$). Eosinophils were also present ((B) hollow arrows; H&E; magnification $\times 400$). Tubulitis lesion ((C) H&E; magnification $\times 400$): many of the inflammatory cells are actively invading the tubules leading to disruption of the tubular basement membranes. Two white cell casts are present in the tubules. Tubules are separated by inflammation and oedema, and the interstitium is expanded by fibrosis, with distortion of tubules and periglomerular fibrosis. ((D and E); Periodic Acid-Schiff and Masson's trichrome; magnification $\times 400$).

Figure 2 Renal function evolution since 5-ASA initiation, withdrawal and subsequent therapeutic management. 5-ASA, 5-aminosalicylate; EPO, erythropoietin; ACEi, ACE inhibitor.

TREATMENT

5-ASA was stopped, and steroids (60 mg/day) and azathioprine (150 mg/day) were promptly initiated. A slow recovery of the patient's renal function was initially documented (figure 2). Currently (24 months later), he is medicated with prednisolone (5 mg/day), azathioprine (100 mg/day), ACE inhibitor and β -erythropoietin (bi-weekly), and his CrCl remains stable at 52.26 mL/min.

OUTCOME AND FOLLOW-UP

The patient is currently asymptomatic and his urinary output is normal. His CrCl remains stable at 52.26 mL/min.

DISCUSSION

Nephrotoxicity has been described in some patients with IBD treated with 5-ASA. However, despite the reported cases and the theoretics behind the condition, a clear cause-effect mechanism is yet to be proven. Recommendations are that 5-ASA oral formulations should be avoided in patients with known chronic renal disease or in those with baseline risk factors for nephrotoxicity.¹ During the first year after 5-ASA initiation, more frequent sCr measurements are recommended.¹ However, the best monitoring schedule remains to be established.

Learning points

- Nephrotoxicity is a rare but serious complication of 5-aminosalicylate (5-ASA) therapy.
- Regular monitoring of renal function during treatment may allow an earlier and effective intervention, especially during the first year of treatment.
- Physicians who prescribe 5-ASA to patients with inflammatory bowel disease should recognise the potential nephrotoxic effect of this drug.

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