We describe the case of a 36-year-old woman with renal function decline due to acute interstitial nephritis, confirmed by biopsy, after the use of mesalazine to treat Crohn’s disease. Improvement of renal function occurred after discontinuation of mesalazine and administration of corticoids. There was neither clinical nor histopathological evidence of vasculitis in the present case study. Nephrotoxicity has been associated with the use of 5-aminosalicylates in inflammatory bowel diseases; however, the exact pathogenic mechanisms of this rarely described condition remain unknown. The Naranjo scale score revealed a probable drug-adverse effect of mesalazine. Case reports may contribute to increase the knowledge about possibly unreported clinical entities.

Key words. Aminosalicylic acid; Crohn’s disease; inflammatory bowel disease; interstitial nephritis; mesalazine.

RESUMO

Nefrite intersticial em mulher com 36 anos etários com uso de mesalazina para doença de Crohn


Palavras-chave. Ácido aminosalicílico; doença de Crohn; doença inflamatória intestinal; nefrite intersticial; mesalazina.
**INTRODUCTION**

Sulfasalazine is metabolized to sulfapyridine and mesalazine or 5-aminosalicylic acid (5-ASA) and is a first-choice drug to treat inflammatory bowel disease (IBD); however, it can be associated with nephrotoxicity.\(^1\)\(^-\)\(^8\) Although relatively scarce, cases of interstitial nephritis and of nephrotic syndrome have been described in patients with Crohn’s disease and ulcerative colitis treated with this class of drugs.\(^1\)\(^-\)\(^8\) Clinical features, laboratory and histopathological findings are nonspecific, including granulomatous tubulointerstitial nephritis and effacement of podocyte foot processes on ultrastructural studies.\(^1\)\(^-\)\(^8\)

We report the case study of interstitial nephritis occurring in a 36-year-old woman. She was undergoing treatment with isolated mesalazine to control a flare-up of Crohn’s disease. High suspicion indexes can contribute to prevention or early detection of the adverse effects of this drug, and case studies might increase awareness about conditions that are probably underdiagnosed.

**CASE REPORT**

A 36-year-old woman diagnosed with ulcerative colitis in 2009 was admitted to the emergency division because of an acute, severe watery diarrhea, without blood or pus in the stools. She also had fever and colic pain in the lumbar region and was taking mesalazine 800 mg four times daily. Except for signs of mild dehydration, her physical examination was unremarkable. Routine tests showed anemia and renal dysfunction (table 1), with eGFR under 60 mL/min using the Cockcroft-Gault formula; HBsAg: negative, anti-HBs: positive, IgM and IgG anti-HBc: negative, anti-HCV: negative; tests for HIV-1 and HIV-2: negative; CMV IgG and IgM antibodies: negative; C3: 118 mg/dL and C4: 28 mg/dL. Urinalysis was unremarkable, and a pre-renal mechanism was the strongest hypothesis.

She underwent adequate volemic repositioning and, without the use of mesalazine, her clinical evolution was uneventful. Because of the changes observed in urea and creatinine levels, she was referred to the nephrology outpatient service. The ambulatory evaluation showed that urea and creatinine serum levels were within normal ranges. Three weeks after hospital discharge, she resumed the mesalazine regimen and control exams of renal function revealed abnormalities. The Naranjo Adverse Drug Reaction Probability scale score showed a probable drug-adverse effect.\(^9\) Mesalazine was discontinued and a renal biopsy was performed to further elucidate the diagnosis. Histopathology showed glomeruli with focal tubular atrophy and discrete interstitial fibrosis, and small arterioles appeared normal (figure 1). Renal specimens were also incubated with fluorescein-conjugated human anti-globulins (A, G and M); C1q and C3c fractions of the complement; fibrinogen; and kappa and lambda light chains; all these exams were negative. Laboratory tests of control specimens have shown moderate increases of urea and creatinine blood levels. Therefore, 5-ASA and similar products have been considered contraindicated to treat this patient. She is currently asymptomatic and has been under nephrology surveillance at the outpatient service.

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**Figure 1.** A: photomicrography of renal sample, showing discrete parenchymal changes (PAS 4X); B: area of interstitial enlargement, and signs (arrow) of tubular atrophy (PAS 100X); C: details of interstitial fibrosis are highlighted in blue (arrow) at the same site (trichrome of Masson 100X).
DISCUSSION

This 36-year-old woman presented renal dysfunction following the isolated use of mesalazine to treat Crohn’s disease. Her renal condition improved shortly after the drug was discontinued. Histopathology showed focal tubular atrophy, discrete interstitial fibrosis, and deposits of immunoglobulins; fractions of complement or fibrinogen were not found by immunohistochemistry.

Adverse effects of 5-ASA include headache, dyspepsia, nausea, pancreatitis, and skin disorders. Recurrent events of mesalazine-induced myocarditis have been reported in patients with IBD. The putative mechanism of recurrence was attributed to a hypersensitivity reaction, as it occurred right after mesalazine remedication and disappeared soon after withdrawal of the drug. Several reports have confirmed the nephrotoxicity caused by 5-ASA.

Naranjo Adverse Drug Reaction Probability scale scores have shown probable adverse reactions. Velciov et al. studied patients with IBD and found asymptomatic hematuria and or proteinuria in 20% of them, related to glomerulonephritis and nephrotic and nephritic syndromes. IBD usually leads to dehydration and a status of malnutrition due to reduced ingestion of food and gastrointestinal losses of body water, which are predisposing factors for renal function impairment. Moreover, relapsing interstitial nephritis has been reported in people with IBD without use of 5-ASA. Nevertheless, Riley et al. studied the renal function of patients who had been using mesalazine from six months to over six years and concluded that the nephrotoxic effects of this drug are of allergic nature, without a dose-response relationship, and may occur with all derivatives of salicylic acid.

Mesalazine toxicity involves organic anion-transporting polypeptides (OATPs), which play a role in drug tolerability, and there is a negative correlation between blood levels of the drug and intensity of intestinal inflammation. Mesalazine is metabolized to inactive N-acetyl-mesalazine in the intestinal epithelium and hepatocytes, and up-regulation of OATPs occurs in inflamed tissues. Interestingly, drug effects can be significantly modified by the concomitant use of other drugs that interact with OATPs, as is the case of clarithromycin, cyclosporine, pravastatin, and rifampin; and this phenomenon may be related to individual differences in plasma concentrations of mesalazine. Nevertheless, most mesalazine-induced nephrotoxicity is not dose-related, but idiosyncratic. Conclusive evidence that 5-ASA nephrotoxicity causes chronic nephropathy is currently lacking. These disturbances are rare (0.26% per patient-year) and reversible after drug withdrawal; however, corticosteroids may be necessary for recovery of renal function in some cases.

As observed in the present case study, images of renal ultrasonography are usually normal, and biopsy shows mild interstitial lymphocytic infiltrate, eosinophils, edema, and tubular changes. Moreover, effacement of podocyte foot processes has been disclosed by electron microscopy. Considering that diverse salicylic acid derivatives have been widely employed to treat IBD, routine evaluation of renal function should be done before and during the administration of these drugs. Case studies about drug adverse effects may increase the suspicion index and contribute to clarify whether the disturbance is an extra-intestinal manifestation of IBD or mesalazine-induced hypersensitivity.

REFERENCES


