

## Mesalazine induced tubulointerstitial nephritis

### Nefrite tubulointersticial associada à mesalazina

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#### ■ ABSTRACT

Inflammatory bowel disease and its various treatments may affect the kidney in several ways. Tubulointerstitial nephritis is a rare but serious complication of longer-term mesalazine use. There are few cases reported in the literature. We report the first two cases of mesalazine-induced tubulointerstitial nephritis, recently diagnosed in our department. The first one refers to a patient with ulcerous colitis and the second one to a patient with Crohn's disease. Then the authors present a review of literature about the renal involvement in the inflammatory bowel disease. New cases of mesalazine nephrotoxicity should be reported to allow more accurate incidence estimation of this serious adverse effect. Routine monitoring of renal function is simple, inexpensive and allows an early diagnosis of this complication.

**Key-Words:** Inflammatory bowel disease; kidney disease; mesalazine; tubulointerstitial nephritis.

#### ■ RESUMO

A doença inflamatória intestinal e as terapêuticas que lhe estão associadas podem afetar o rim de várias formas. A nefrite tubulointersticial é uma complicação rara, mas potencialmente grave inerente à terapêutica com mesalazina. Há alguns casos descritos na literatura. Os autores descrevem os dois primeiros casos de nefrite tubulointersticial associados ao uso de mesalazina, recentemente diagnosticados no nosso Serviço; um deles num doente com colite ulcerosa, outro num doente com doença de Crohn. Apresentam uma revisão da literatura sobre o atingimento renal na doença inflamatória intestinal. Os casos de nefrotoxicidade associada à mesalazina devem continuar a ser descritos para permitir estabelecer uma incidência mais precisa desde efeito adverso. A monitorização da função renal durante o tratamento é simples, barata e pode ajudar a diagnosticar precocemente esta complicação.

**Palavras-Chave:** Doença inflamatória intestinal; doença renal; mesalazina; nefrite tubulointersticial.

## INTRODUCTION

Inflammatory bowel disease (IBD) is associated with a large spectrum of kidney disease. The kidney may be an extra-intestinal target of IBD. It could be affected by the secondary complications of bowel inflammation, such as stones and amyloidosis; there are some reported associations of glomerular disease<sup>1</sup>. On the other hand, some drugs used in its treatment, including mesalazine, may be associated with tubulointerstitial renal disease<sup>1-3</sup>. Acute and chronic interstitial nephritis are rare but serious complications of longer-term mesalazine use<sup>4</sup>. There are some reports in the literature<sup>1,5-7</sup>. This adverse drug reaction is likely idiosyncratic. The clinical presentation is usually non-specific and more frequent in men than in women<sup>8,9</sup>.

We report two cases of tubulointerstitial nephritis (TIN) associated with mesalazine treatment, recently diagnosed in our department. The first refers to a patient with ulcerous colitis (UC) and the second one to a patient with Crohn's disease (CD). Then the authors present a literature review about renal involvement in IBD.

## CASE REPORTS

### Case 1

A man with a past history of controlled hypertension and healed prostatic neoplasm had a diagnosis of UC at 59 years old (in 2011). At this time, he had 1.05 mg/dl serum creatinine and no urinalysis abnormalities, namely proteinuria, leukocyturia or erythrocyturia. Due to disease activity, he began treatment with oral mesalazine (1600 mg/day) and prednisolone. One year later, he had a 1.9 mg/dl serum creatinine. At that moment, the UC was in activity and mesalazine dose was increased (1.6 to 3.6 g/day). Three months later, the serum analysis showed an increase in creatinine (2.1 mg/dl) and urinalysis showed proteinuria (100 mg/dl), leukocyturia (25-50 WBC/field) and erythrocyturia (25-50 RBC/field). At Nephrology evaluation, IBD was in clinical remission. The patient had no symptoms and no abnormalities on physical examination. Initial laboratory results were: normal haemoglobin, normal leucocyte, eosinophils and platelets count; blood urea nitrogen 80 mg/dl, serum

creatinine 2.1mg/dl; normal serum sodium, potassium, calcium and phosphorus. Urinalysis revealed: an albumin/creatinine ratio 1420 mg/g, a protein-creatinine ratio 1.5g/g, erythrocyturia and leukocyturia. The urine culture was negative. Serology revealed normal C<sub>3</sub>, C<sub>4</sub>, IgG, IgM, IgG; negative anti-nuclear antibody (ANA); positive anti-saccharomyces cerevisiae (ASCA) test. Renal ultrasound did not reveal any hydronephrosis, nephrolithiasis or cortical atrophy; both kidneys were of normal size. Kidney biopsy showed an acute interstitial nephritis with lymphomononuclear cells and a granulomatous reaction without central necrosis (Figs. 1 and 2). The vessels were normal; there was 40% fibrosis and 20% tubular atrophy. Immunofluorescence with auto-antibodies to albumin, C<sub>3</sub>, C<sub>4</sub>, C<sub>1q</sub>, IgA, IgM and IgG was positive to mesangial and peripheral deposits for C<sub>3</sub> and linear IgA(+).

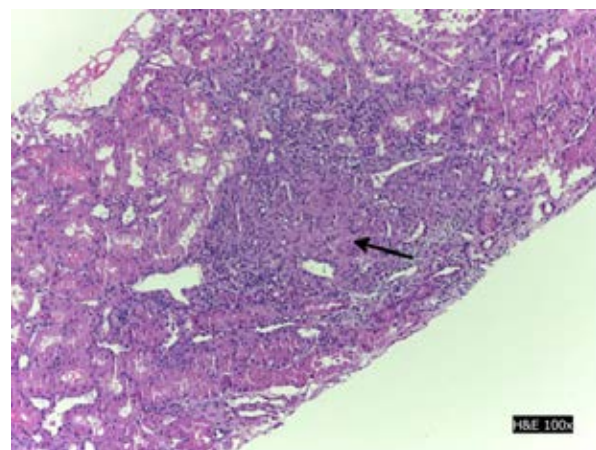
Mesalazine was discontinued and azathioprine was introduced (2 mg/Kg) in combination with prednisolone (5mg/day). Two months later, serum creatinine decreased to 1.5 mg/dl and urinalysis revealed no white blood cells/field and 2-5 red blood cells/field; proteinuria/creatinine ratio decreased to 0.3 g/g.

### Case 2

A man with Crohn's disease and no other relevant medical history was sent to Nephrology consultation

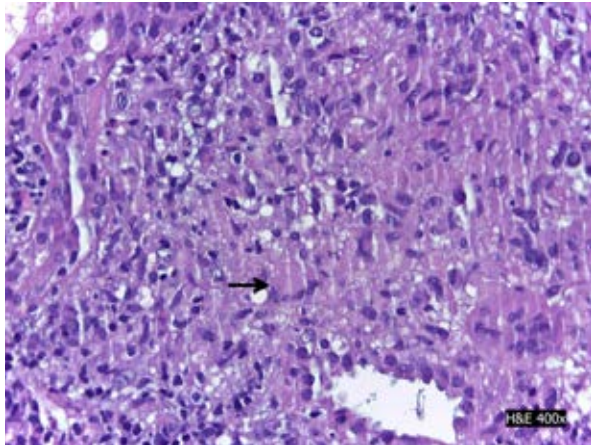
**Figure 1**

Acute interstitial nephritis. The granulomata (black arrow) involving and destroying the tubules. Necrotizing features were not identified (H&E x100).



**Figure 2**

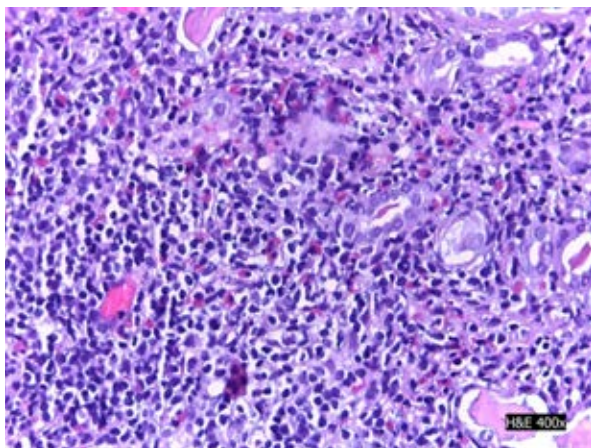
The granulomata with multinucleated giant cell (black arrow) (H&E x400).



for chronic kidney disease. Inflammatory bowel disease had been diagnosed when he was 35 years old (in 2009). At that moment, he had a serum creatinine of 0.8mg/dl, with no abnormalities in urinalysis. He started oral mesalazine (4g/day) and prednisolone (60 mg/day) with a gradual decrease of doses and clinical remission. One year later he had 1.48 mg/dl serum creatinine. After two years, he had 1.80 mg/dl serum creatinine and leukocyturia (25-50 WBC/field) in urinalysis. Mesalazine was discontinued and he started azathioprine (AZA) (1mg – 2mg/kg/day)

**Figure 3**

Marked interstitial inflammatory infiltrate with numerous eosinophil and mononuclear cells, most of them lymphocytes (H&E x400).

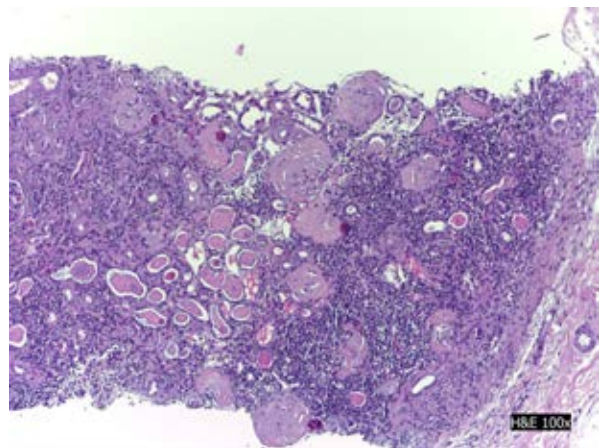


with poor control of IBD activity and need to increase the corticosteroids (CT) dose (1mg/kg/day) with a gradual decrease and clinical remission. At Nephrology evaluation, the patient had only gastro-intestinal symptoms (abdominal discomfort and diarrhoea). Abdomen examination revealed increased bowel sounds and diffuse tenderness to palpation with no other abnormalities. Initial laboratory results were: haemoglobin 13g/dl; normal leucocyte, eosinophils and platelets count; blood urea nitrogen 120, serum creatinine 2,6mg/dl and a normal serum sodium, potassium, calcium and phosphorus. Urinalysis revealed: albumin, red blood cells (10 RBC/field) and white blood cells (25-50 WBC/field). The urine culture was negative. Serology revealed normal C3, C4, IgG, IgM, IgG; negative anti-nuclear antibody (ANA); positive ASCA test. Renal ultrasound was normal. Kidney biopsy showed glomerulosclerosis (30%) and a marked interstitial inflammatory infiltrate with eosinophils in 30% of cortex extension and mononuclear cells (Fig. 3). Vessels were normal. There was 50% cortical atrophy (Fig. 4). Immunofluorescence with auto-antibodies to albumin, C3, C4, C1q, IgA, IgM and IgG was negative.

Three months after stopping mesalazine, serum creatinine decreased to 1.5 mg/dl and urinalysis revealed no white or red blood cells. Six months after treatment with AZA and lower doses of prednisolone (5 mg/day), the IBD became active. AZA was increased to 2 mg/kg/day and CT to 1 mg/kg/

**Figure 4**

Mixed inflammatory cells infiltrating the renal cortex. Glomerulosclerosis can be observed. Tubular atrophy is remarkable (H&E x100).





day with clinical remission. AZA was stopped two months later due to pancytopenia. The patient was proposed for further treatment with anti-TNF due to refractory IBD.

## DISCUSSION

Aminosalicylates compounds are widely used in acute phase and remission maintenance therapy of IBD<sup>10</sup>. Mesalazine also known as 5-aminosalicylic acid (5-ASA), is a derivative of salicylic acid and it is the active moiety of sulfasalazine (without the adverse effects attributed to the latter one). A number of reports have linked oral mesalazine therapy to tubulointerstitial nephritis. Although this association is currently well established there are no guidelines for monitoring renal function in patients who are receiving this treatment<sup>11</sup>.

The first reports were published in 1989, and in 1990 the Committee on Safety of Medicines (CSM) issued a warning of nephrotoxic reactions to mesalazine. From 1985 to 1997, the CSM had received 35 reports implicating the drug in interstitial nephritis. In recent editions of nephrology textbooks, mesalazine is one of the drugs that could be associated with acute and chronic interstitial nephritis<sup>9,12,13</sup>. The true incidence of this problem is not really known. Primas *et al.* showed that renal impairment, defined as any increase in serum creatinine, may occur in up to one in 100 patients treated with this drug<sup>14</sup>. The incidence of clinically significant interstitial nephritis was estimated to be less than one in every 500 patients treated, when serum creatinine is monitored regularly. In a larger study of 223 outpatients with IBD, Schreiber *et al.* found an increased prevalence of tubular proteinuria in patients who were receiving high dosages of 5-ASA<sup>11</sup>. All reports of interstitial nephritis in IBD patients are associated with drugs used in its treatment<sup>9</sup>.

The nephrotoxicity associated with mesalazine takes the form of an acute or an indolent chronic and progressive interstitial nephritis. It can be severe and lead to chronic kidney disease<sup>14,15</sup>. The development of tubulointerstitial nephritis is independent of treatment duration. Fifty per cent of patients present within the first 12 months of starting therapy but some are diagnosed within 5 years after beginning

treatment<sup>1</sup>. It has been suggested that undercurrent steroid therapy used in the IBD treatment may delay presentation.

Signs and symptoms are scanty and non-specific. Patients may be asymptomatic, such as those who presented. A minority of patients have systemic symptoms like fever, myalgia, anorexia and weight loss<sup>16</sup>. An increase in serum creatinine is a late event but may be the first evidence of nephrotoxicity. Reagent strip urinalysis can be normal, or positive to blood and protein. Proteinuria can be mild to heavy and can be influenced by IBD activity. Sterile pyuria may be present. Eosinophilia has been recorded but it is not a specific finding<sup>16-18</sup>.

The pathogenic basis of mesalazine associated interstitial nephritis is not completely known. In the acute stage of the disease, there is a mixed inflammatory cell infiltrate composed of B and T lymphocytes and macrophages, with interstitial oedema, which is comparable to that seen in renal allograft acute cellular rejection. It has been suggested that this represents a delayed cell-mediated hypersensitivity response<sup>16-20</sup>. Only a minority of patients manifest a systemic type-I hypersensitivity reaction with fever and eosinophilia<sup>8</sup>.

In the chronic stage, the cellular infiltrate is accompanied by interstitial fibrosis and tubular atrophy, as it happened in our second case. The extent of these hallmarks means an irreversible renal impairment and is predictive of progression to chronic renal failure<sup>21</sup>.

Mesalazine is structurally related to salicylic acid; salicylates inhibit the synthesis of intra-renal prostaglandins, which are vasoactive mediators of intra-renal blood flow, uncouple oxidative phosphorylation in mitochondria and inhibit the pentose phosphate shunt rendering the kidney susceptible to oxidative damage<sup>22-25</sup>. All of these effects cause a disturbance in intra-renal blood flow and promote local tissue hypoxia. Direct tubular toxicity in addition to tissue hypoxia is also suggested<sup>20,21</sup>. After reperfusion injury, there is an inflammatory response that may contribute to chronic inflammation and interstitial fibrosis<sup>23-26</sup>.

Due to the small number of cases described and the inability to determine the degree of systemic absorption, is impossible to say if nephrotoxicity is

dose-related. Tubulointerstitial nephritis has been reported in patients taking doses of mesalazine as low as 400 mg/day. The systemic bioavailability is determined by the route of administration and by the location and extent of the IBD. Systemic absorption of rectal mesalazine is approximately 50% of oral mesalazine; there is no report of significant nephrotoxicity in patients using only rectal formulation; the nephrotoxicity could be an idiosyncratic effect<sup>20,24</sup>.

In the Dutch Pentasa Study, over 150 subjects were screened prospectively for renal toxicity. They were randomized to receive two dosages of oral slow-release mesalazine (1.5 vs. 3.0 g per day), and followed-up for 12 months. There were no differences in toxicity or compliance rate between the high and low dose groups. Two patients (1.3%) developed modest, reversible renal impairment, but only one of them had biopsy proven interstitial nephritis<sup>21</sup>.

Mesalazine should be withdrawn when the renal impairment is not explained by other factors. A renal biopsy provides diagnostic and prognostic information. It is indicated in subjects with impaired renal function that is not explained by other factors, in which renal function does not recover to baseline following withdrawal of the drug, or in those who present with atypical features such as nephrotic range proteinuria, which may suggest an alternative diagnosis. The response to drug withdrawal is variable. It leads to recovery of renal function in 85% of cases where the diagnosis is made within 10 months of starting treatment. When the diagnosis is delayed beyond 18 months from the start of treatment only one-third of cases show some recovery of renal function and this is usually only partial<sup>20-23</sup>. Active chronic tubulointerstitial nephritis was described in biopsies from patients in whom mesalazine has been withdrawn several months prior to biopsy<sup>19,22,26</sup>.

Steroids and azathioprine have been used for IBD treatment with a good response, but this depends of level on the established chronicity lesions in renal biopsy. Nevertheless, a trial of high dose steroid (1 mg/day/kg, maximum 60 mg/day for up to 3 months) is recommended in patients whose renal function does not respond to drug withdrawal alone. This may be preceded by pulsed intravenous methylprednisolone in severe cases (0.5 to 1 g on three successive days).

Both our patients had improvement in renal function after discontinuation of the drug and none of them made an intensive course of corticosteroid therapy. In both cases, the low-dose of corticosteroids may have contributed to the improvement of the renal function.

#### ■ Other manifestations of renal disease in patients with inflammatory bowel disease (IBD)

Extraintestinal manifestations (EIM) of IBD are common. These manifestations can involve nearly any organ system – including the renal but also the musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, and pulmonary systems<sup>9</sup>. Symptoms of renal impairment are not always specific and since the underlying bowel disease is preponderant, renal function deterioration may be underestimated<sup>10</sup>.

Renal or urinary complications can occur in 4%-23% of patients; the most common manifestations are kidney stones, enterovesical fistulas and ureteral obstruction. Patients with IBD have a 10 to 100 time higher risk of nephrolithiasis compared with the general population. The risk is higher in adults than in children and in patients with CD. Kidney stones in IBD are composed primarily of calcium oxalate or uric acid<sup>26</sup>.

Fistulas between the gastrointestinal tract and the urinary system are uncommon, occurring in 1%-8%; they are more common in patients with ileal or ileocecal disease than in patients with colonic disease<sup>27</sup>.

Morphological changes in the glomeruli – podocyte effacement, mesangial deposition of immunoglobulin and complement have been well described. There are also reported associations with membranous glomerulonephritis, rapidly progressive glomerulonephritis, mesangiocapillary glomerulonephritis, IgA nephropathy (as in our first case), and thin basement membrane disease<sup>1,9,26-31</sup>. Glomerulonephritis presenting as nephrotic syndrome in patients with IBD is rare<sup>16</sup>. Tubular damage was seen in 31% of CD and in 23% of UC patients who were not on ASA therapy. Granulomatous interstitial nephritis, interstitial nephritis with hyperoxaluria and renal tubular acidosis have also been reported<sup>32-35</sup>.

Secondary amyloidosis (AA amyloidosis) is a rare but serious complication that may occur in chronic

inflammation diseases, including IBD, mainly long-standing Crohn's disease. The reported prevalence of secondary amyloidosis in IBD patients varies from 0.5 to 29% in CD and from 0 to 0.4% in UC with a higher prevalence at autopsy<sup>16,29</sup>.

The majority of patients have renal involvement with asymptomatic proteinuria or manifestations of nephrotic syndrome. Differential diagnosis of primary systemic amyloidosis presenting as regional enteritis should always be considered. The response of IBD-related secondary amyloidosis to treatment is variable. It is reported that medical or surgical treatment has stabilized or improved renal disease but there exist reports suggesting no benefit with them<sup>30</sup>.

There is only a retrospective review study to date that examined the histopathology of 83 renal biopsies performed in IBD patients. The authors present 45 and 38 cases CD and UC, respectively. IgA nephropathy was the most common finding (24%), followed by interstitial nephritis (19%), arterionephrosclerosis (12%), acute tubular injury (8%), proliferative GN (7%), and minimal-change disease (5%). Of the 16 cases of interstitial nephritis, nine (56%) had current or recent past exposure to aminosaliclates, including all cases of granulomatous interstitial nephritis<sup>17</sup>.

There are no specific guidelines for surveillance of renal function. Frandsen *et al.* recommend measurement of serum creatinine prior to the start of mesalazine treatment and every 6 months thereafter<sup>4</sup>.

## CONCLUSIONS

These are the first two cases of TIN associated with mesalazine identified by renal biopsy in our Hospital.

Management of mesalazine-induced interstitial nephritis includes discontinuation of drug and sometimes a trial of corticosteroid therapy. In both cases, the history of inflammatory bowel disease, mesalazine use and the histopathology, support the diagnosis of a drug-associated renal injury.

It is very important to recognize renal impairment early, to prevent the progression to an end-stage

renal disease. We suggest regular monitoring of renal function (serum creatinine and urinalysis) in patients treated with mesalazine; it is simple, inexpensive and it is the only way to diagnose new cases early. Further epidemiological data are needed to clarify the causal mechanisms of nephrotoxicity. Similar data should be reported to estimate the true incidence of this serious adverse effect. These cases show us the need to create some protocols for routine renal function surveillance in IBD patients.

**Conflicts of Interest:** None declared.

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