Mesalazine induced tubulointersticial nephritis

Nefrite tubulointersticial associada à mesalazina

Andreia Campos¹, Sofia Santos¹, Josefina Santos¹, Jorge Malheiro¹,², Anabela Rodrigues¹,², Luísa Lobato¹,², J. Ramón Viscaíno³, António Cabrita¹

¹ Department of Nephrology, Centro Hospitalar do Porto – Hospital de Santo António. Porto, Portugal.
² Multidisciplinary Unit for Biomedical Research UMIB, Instituto de Ciências Biomédicas Abel Salazar, University of Porto. Porto, Portugal.
³ Department of Pathology, Centro Hospitalar do Porto – Hospital de Santo António. Porto, Portugal.

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. On the other hand, some drugs used in its treatment, including mesalazine, may be associated with tubulointerstitial renal disease. Acute and chronic interstitial nephritis are rare but serious complications of longer-term mesalazine use. There are some reports in the literature about renal involvement in IBD.

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 2.1 mg/dl; normal serum sodium, potassium, calcium and phosphorus. Urinalysis revealed: an albumin/creatinine ratio 1420 mg/g, a protein-creatinine ratio 1.5 g/g, erythrocyturia and leukocyturia. The urine culture was negative. Serology revealed normal C3, C4, 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 lymphoplasmacellular 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, C3, C4, C1q, IgA, IgM and IgG was positive to mesangial and peripheral deposits for C3 and linear IgA(+).

Mesalazine was discontinued and azathioprine was introduced (2 mg/Kg) in combination with prednisolone (5 mg/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).
Inflammatory bowel disease (IBD) had been diagnosed when he was 35 years old (in 2009). At that moment, he had a serum creatinine of 0.8 mg/dl, with no abnormalities in urinalysis. He started oral mesalazine (4 g/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) (1 mg–2 mg/kg/day) with poor control of IBD activity and need to increase the corticosteroids (CT) dose (1 mg/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 13 g/dl; normal leucocyte, eosinophils and platelets count; blood urea nitrogen 120, serum creatinine 2.6 mg/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/
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\(^\text{10}\). 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\(^\text{11}\).

The first reports were published in 1989, and in
1990 the Committee on Safety of Medicines (CSM)
issued a warning of nephrotoxic reactions to mesala-
zine. From 1985 to 1997, the CSM had received 35
reports implicating the drug in interstitial nephritis.
In recent editions of nephrology textbooks, mesala-
zine is one of the drugs that could be associated
with acute and chronic interstitial nephritis\(^\text{9,12,13}\).
The true incidence of this problem is not really
known. Primas \textit{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\(^\text{14}\). The incidence of clinically significant inter-
stitial 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 out-
patients with IBD, Schreiber \textit{et al.} found an increased
prevalence of tubular proteinuria in patients who
were receiving high dosages of 5-ASA\(^\text{11}\). All reports
of interstitial nephritis in IBD patients are associated
with drugs used in its treatment\(^\text{9}\).

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\(^\text{16,15}\). The develop-
ment of tubulointerstitial nephritis is independent
of treatment duration. Fifty per cent of patients pres-
ent within the first 12 months of starting therapy but
some are diagnosed within 5 years after beginning
treatment\(^\text{1}\). 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\(^\text{16}\). 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 record-
ed but it is not a specific finding\(^\text{16-18}\).

The pathogenic basis of mesalazine associated
interstitial nephritis is not completely known. In the
acute stage of the disease, there is a mixed inflam-
matory cell infiltrate composed of B and T lympho-
cytes 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 hypersensi-
tivity response\(^\text{16-20}\). Only a minority of patients mani-
fest a systemic type-I hypersensitivity reaction with
fever and eosinophilia\(^\text{8}\).

In the chronic stage, the cellular infiltrate is accom-
panied by interstitial fibrosis and tubular atrophy,
as it happened in our second case. The extent of
these hallmarks means an irreversible renal impair-
ment and is predictive of progression to chronic
renal failure\(^\text{21}\).

Mesalazine is structurally related to salicylic acid;
salicylates inhibit the synthesis of intra-renal prosta-
glandins, 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 dam-
age\(^\text{22-25}\). All of these effects cause a disturbance in
intra-renal blood flow and promote local tissue hypox-
ia. Direct tubular toxicity in addition to tissue hypoxia
is also suggested\(^\text{20,21}\). After reperfusion injury, there
is an inflammatory response that may contribute to
chronic inflammation and interstitial fibrosis\(^\text{23-26}\).

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.

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.

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.

Active chronic tubulointerstitial nephritis was described in biopsies from patients in whom mesalazine has been withdrawn several months prior to biopsy.

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. Symptoms of renal impairment are not always specific and since the underlying bowel disease is preponderant, renal function deterioration may be underestimated.

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 times 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.

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.

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, mesangiopapillary glomerulonephritis, IgA nephropathy (as in our first case), and thin basement membrane disease. Glomerulonephritis presenting as nephrotic syndrome in patients with IBD is rare. 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 hyperoxalouria and renal tubular acidosis have also been reported.

Secondary amyloidosis (AA amyloidosis) is a rare but serious complication that may occur in chronic
inflammation diseases, including IBD, mainly longstanding 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 autopsy16,29.

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 them30.

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 surgery, mesalazine treatment and every 6 months thereafter4.

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 thereafter4.

**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.

**References**


Correspondence to:
Drª Andreia Campos
Department of Nephrology, Centro Hospitalar do Porto – Hospital Geral de Santo António
Largo Prof. Abel Salazar 4099-001 PORTO – Portugal
E-mail: andcriscampos@hotmail.com