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Minimal change disease associated with balsalazide therapy for ulcerative colitis

Ahmad M. Al-Tae^{1*}, Sami A. Almaskeen^{2,3}, Farrukh M. Koraishy^{1,4}

¹Department of Internal Medicine, Saint Louis University, School of Medicine, 3635 Vista Ave, FDT 9th Floor, St Louis, MO, USA

²Gastroenterology Section, John Cochran VA Medical Center, 915 North Grand, 6th Floor, St. Louis, MO, USA

³Renal Section, John Cochran VA Medical Center, 111B-JC, 915 North Grand, St. Louis, MO, USA

⁴Division of Gastroenterology, Washington University in St. Louis, 660 S. Euclid Ave, St. Louis, MO, USA

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ABSTRACT

Introduction: 5-aminosalicylic acid (5-ASA) compounds have been used in the management of ulcerative colitis for decades. Nephrotoxicity has been previously described in patients treated with 5-ASA compounds and usually manifests as interstitial nephritis, however a few cases of nephrotic syndrome have been reported. Balsalazide is a pro-drug composed of 5-ASA linked to an inert carrier.

Case Presentation: Here we report the case of a 74-year-old man with a history of ulcerative proctosigmoiditis treated with balsalazide who presented to our clinic with bilateral lower extremity edema three months after initiation of balsalazide. Laboratory workup showed nephrotic range proteinuria without an apparent secondary etiology. Given worsening proteinuria and renal function despite cessation of balsalazide, the patient underwent renal biopsy that revealed minimal change disease. High dose steroids were started and complete remission of proteinuria was achieved one month into therapy which was slowly tapered over the next five months. Eventual resolution of edema and return of creatinine back to patient's baseline level was achieved.

Conclusion: To our knowledge, this is the first report of nephrotic syndrome manifesting soon after initiation of balsalazide therapy. Our work highlights the importance of maintaining a high clinical suspicion for nephrotoxicity when using balsalazide.

Implication for health policy/practice/research/medical education:

Clinicians need to be familiar with nephrotic syndrome as a potential complication of balsalazide therapy.

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Introduction

Minimal change disease (MCD) accounts for most cases of nephrotic syndrome in children ($\approx 90\%$) but a minority ($\approx 10\text{--}15\%$) of adult cases (1). Secondary MCD has been associated with a number of medications (2). Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase (COX)-2 inhibitors are the most common cause of secondary MCD. Other commonly associated drugs include; antimicrobials (e.g. penicillin, rifampicin and cephalosporins), lithium, D-penicillamine, bisphosphonates, trimethadione and gamma interferon. The mechanisms behind drug-induced MCD has been postulated to be either direct toxic injury to the glomerulus and/or immune-mediated injury from

drug-induced autoimmunity (3).

5-aminosalicylic acid (5-ASA) compounds have been used in the management of ulcerative colitis for decades. Nephrotoxicity has been previously described in patients treated with 5-ASA compounds and usually manifests as interstitial nephritis (4) although MCD has been reported (5). Balsalazide is a pro-drug composed of 5-ASA linked to an inert carrier. It has been approved for the management of mild to moderate active ulcerative colitis.

Case Report

A 73-year-old white male presented as a new consult to the renal clinic for bilateral lower extremity edema, weight gain and frothy urine for one month. He was following

*Corresponding author: Ahmad Al-Tae, Email; ahmad.altaee@health.slu.edu

regularly in the gastroenterology clinic for his ulcerative proctosigmoiditis. His disease was previously controlled with mesalamine enemas which patient discontinued due to muscle cramps. He was switched to balsalazide 750 mg capsules three times daily for the past three months with significant improvement in diarrhea without blood or fecal urgency. Past-medical history was also notable for atrophic left kidney (renal artery stenosis) but normal serum creatinine, well controlled type 2 diabetes mellitus, gastroesophageal reflux disease, hypertension and well controlled post-traumatic stress disorder. Outpatient medications included balsalazide 750 mg three times daily, aspirin 81 mg once daily, hydrochlorothiazide 25 mg once daily and omeprazole 20 mg once daily. He reported no tobacco, alcohol, or illicit drug use. He denied any family history of inflammatory bowel disease or renal disease.

Vital signs were within normal limits. Laboratory testing showed a normal complete blood count, serum creatinine (sCr) 1.2 mg/dL (reference range: 0.7-1.3 mg/dL), blood urea nitrogen 9 mg/dL (reference range 9-25 mg/dL), estimated glomerular filtration rate (eGFR) of 58.2 ml/min (reference range > 90 mL/min), serum albumin (sAlb) 1.9 g/dL (reference range 3.4-5 g/dL) and an elevated serum glucose of 151 mg/dL (reference range 72-99 mg/dL) with a hemoglobin A1c of 7 (reference range 4-6). Baseline sCr was 1.1-1.2 mg/dL and sAlb was 4.5 g/dL. Lipid profile showed significantly elevated total cholesterol (409 mg/dL, reference range <200 mg/dL) and LDL-C (296 mg/dL, reference range <130 mg/dL), while triglycerides and HDL-C were at baseline. A urinalysis was obtained and showed an elevated urine protein > 500 mg/dL (reference range trace-29.9 mg/dL) but no microscopic hematuria was otherwise unremarkable. No casts or dysmorphic RBCs were noted on urine sediment exam. Urine protein to creatinine ratio was 12 g/g. A 24-hour urine protein was 14.9 g. There was no proteinuria at baseline. Further laboratory testing including anti-nuclear antibody, complement C3, C4, C-reactive protein, serum and urine protein electrophoresis, HIV assay, hepatitis B and C serologies, and rapid plasma reagin were all unremarkable. Renal ultrasound with dopplers showed an atrophic left kidney with left renal artery stenosis but normal right kidney without right renal artery stenosis.

Balsalazide was discontinued and patient was started on furosemide 40 mg twice daily and lisinopril 10 mg once daily. However, patient's edema, proteinuria, and sCr worsened over the next 3 weeks. Therefore, a biopsy of the right kidney was performed. Light microscopy showed acute tubular injury with tubular epithelial attenuation and interstitial expansion due to edema (Figure 1) but normal glomeruli (Figure 2). Severe fibrointimal arterial thickening was also noted (Figure 1). Immunofluorescence staining showed no immune

deposits. Electron microscopy revealed diffuse effacement of the podocyte foot processes (Figure 3). There was no evidence of diabetic glomerulopathy. Congo red stain, immunofluorescence assay, and phospholipase A2 receptor antibodies were negative. Hence the diagnosis was minimal change disease with acute tubular injury in a background of chronic vascular disease.

The patient was started on prednisone 80 mg once daily and complete remission of proteinuria was achieved 1 month into therapy. Prednisone was slowly tapered over the next five months to complete a 6-month course. This resulted in complete resolution of edema and return of sCr back to baseline. Patient was also given prophylaxis with calcium/vitamin D, trimethoprim-sulfamethoxazole and ranitidine when the steroid dose remained over 20mg per day. The only side effect noted was mood swings that resolved after the steroid taper. On follow-up 6 months later (over a year since initial remission), our patient continues to do well with no evidence of edema, proteinuria, or change in renal function. His ulcerative proctosigmoiditis remains stable despite being off balsalazide over 1.5 years.

Discussion

Sulfasalazine has been used in the management of mild

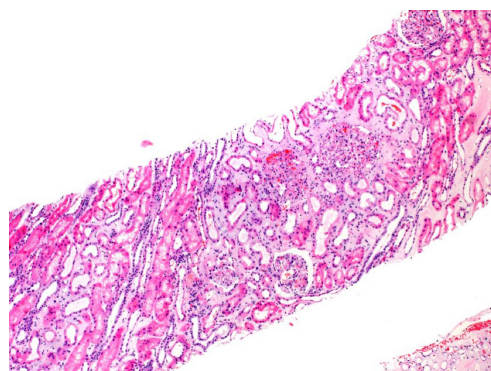


Figure 1. Light microscopy showing acute tubular injury with tubular epithelial attenuation, interstitial expansion due to edema and fibrointimal arterial thickening.

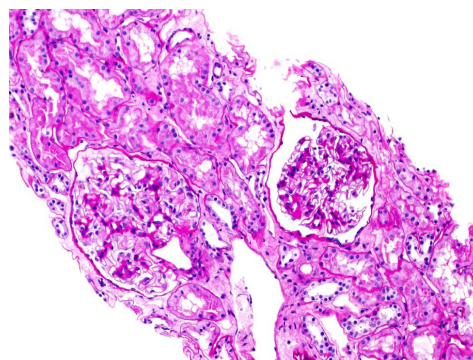


Figure 2. Light microscopy showing normal glomeruli.

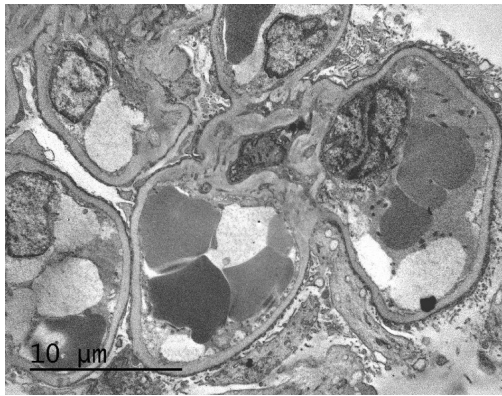


Figure 3. Electron microscopy shows diffuse foot process effacement.

to moderate ulcerative colitis (UC) since the 1970s (6). 5-ASA (also called mesalamine) is the therapeutically active component of sulfasalazine (7). Compared with sulfasalazine, 5-ASA compounds have the advantage of a more favorable safety profile and have become the standard of care in the management of ulcerative colitis for decades.

Nephrotoxicity has been described in inflammatory bowel disease (IBD) patients treated with 5-ASA therapy. This adverse event is reported to affect less than 0.5% of patients using 5-ASA therapy (8). It is an idiosyncratic reaction that can present any time after initiation of therapy, but usually manifests within the first 12 months of therapy. Interstitial nephritis has been reported in the vast majority of cases. To our knowledge, only a few cases of MCD secondary to 5-ASA use have been described in the literature (9,10). Fornaciari et al reported, MCD in a 44-year-old patient with UC controlled with oral mesalamine. This responded to cessation of mesalamine and course of steroids (methylprednisolone 1 g IV for three days followed by prednisone 0.6 mg/kg/d for 2 weeks and prednisone taper to complete a total course of two months) (10). Course was also complicated by a newly diagnosed colorectal cancer. Therefore, the authors attributed MCD to either mesalamine use or colorectal carcinoma. Novis et al reported MCD in a 61-year old male with history of ulcerative colitis controlled with oral mesalamine that responded to cessation of mesalamine and steroids (prednisone 1 mg/kg/d for 6 weeks which was tapered over 4 months) (9). In another case report, Firwana et al described a case of MCD secondary to mesalamine that responded to discontinuation of the drug and use of losartan without the need for steroids (5).

Discontinuation of the offending medication is the cornerstone of management of drug-induced MCD, however, some patients may require treatment with corticosteroids or immunosuppressive medications. With timely recognition and early discontinuation of the

offending agent, renal recovery is expected in the majority of cases. In our case, we initially followed the conservative approach of balsalazide discontinuation and use of renin-angiotensin blocker. However, this did not lead to resolution of nephrotic syndrome until high steroid were started. This was followed by a slow prolonged taper as reported in the two cases above (9, 10). The mechanism of glomerular injury associated with balsalazide similar to other 5-ASA related agents is not clear, but direct podocyte toxicity or an immune mediated injury are both possible. The improvement in our patients with steroids suggests the latter to a dominant mechanism.

Balsalazide has been first reported in 1983 as an alternative to sulfasalazine therapy with a more favorable side effect profile (11). It is a pro-drug composed of 5-ASA (the active compound) linked to 4-aminobenzoyl-beta-alanine (an inert carrier) by an azo bond (12). This bond is cleaved by bacterial azo-reductases in the colon resulting in release of the active compound. It has been shown in randomized trials to be more effective than mesalamine in the induction of remission in patients with UC (13,14). The Food and Drug Administration has approved Balsalazide for the management of mild to moderate ulcerative colitis in 2000. The recommended maximum daily dose was 6.75 g which provides an equivalent of 2.4 mg of 5-ASA in the colon. Balsalazide is generally well tolerated. Common side effects are similar to mesalamine and include headache, gastrointestinal side effects, and arthralgias (15). Despite the favorable side effect profile, rare cases of hypersensitivity reaction (16), myocarditis (17), eosinophilic pneumonia (18), and granulomatosis with polyangiitis (19) secondary to balsalazide use have been reported. Nephrotic syndrome secondary to Balsalazide use has been reported in one case before (20). Gera et al described a 56-year-old man with a 10-year history of UC controlled with Balsalazide for five years who presented with clinical and laboratory features of nephrotic syndrome. Renal biopsy was consistent with minimal change disease which responded to cessation of balsalazide and a 3-week course of steroids.

Conclusion

To our knowledge, this is the first report of nephrotic syndrome due to MCD manifesting soon after initiation of balsalazide therapy. Our work highlights the importance of maintaining a high clinical suspicion for nephrotoxicity when using balsalazide. We recommend monitoring of serum creatinine, proteinuria and clinical signs and symptoms of nephrotic syndrome in IBD patients treated with balsalazide. Timely recognition and early discontinuation of the offending agent are crucial. Besides discontinuation of Balsalazide, steroid therapy might be required to achieve remission.

Authors' contribution

AMA have drafted the initial manuscript which was further modified by SAA and FMK. FMK provided the light and electron microscopy figures. All authors have reviewed and agreed on the final version of this manuscript prior to submission.

Conflict of interest

There is no conflict of interest in this case report.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patient has provided informed consent to publish as a case report.

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