

# Focal Segmental Glomerulosclerosis Secondary to Mesalamine Use in a Patient with Ulcerative Colitis

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## Abstract

**Background:** The association between Ulcerative Colitis (UC) and Focal Segmental Glomerulosclerosis (FSGS) is an unexpected condition. Herein we reported a case of FSGS secondary to mesalamine use in a Kuwaiti patient with UC.

**Case presentation:** A 32 years-old man, with a 6-month's history of UC, was admitted with proteinuria and elevated serum creatinine after the use of mesalamine. On March, 2016, there was repeated vomiting, fresh bleeding per rectum for which sigmoidoscopy and rectal biopsy done on April, 2016 and revealed UC and mesalamine was started. On October, 2016, the patient started to complain from puffiness of eyelids, LL oedema and headache. There was a positive family history of renal failure. Physical examination, there was hypertension, bilateral mild pitting lower limb oedema. Laboratory investigations demonstrated serum creatinine 143 umol/L and proteinuria 1.9 g/24 h. The old values showed serum creatinine level of 76 umol/L and 24h urine protein level of 140mg/day before starting mesalamine. All immunology and virology tests were negative. Kidney ultrasound was normal, so kidney biopsy was performed and revealed FSGS. The patient treated with prednisolone 30 mg/day, valsartan 160 mg/day with discontinuation of mesalamine. Blood pressure was controlled and kidney function tests and proteinuria improved.

**Conclusion:** Mesalamine use in patients with UC can be associated with FSGS, warranting, the necessary of following the kidney function and proteins in urine while the patients with UC on mesalamine treatment.

## Introduction

Focal Segmental Glomerulosclerosis (FSGS), is currently recognized as one of the most common causes of primary glomerular diseases in adults, and the incidence of FSGS has been increasing in recent years [1,2]. FSGS causes asymptomatic proteinuria or Nephrotic Syndrome (NS) with or without renal insufficiency.

Although clinical features are suggestive, a diagnosis of FSGS is confirmed only by histopathology findings [3]. The disease represents several patterns of glomerular injury, and biopsy findings provide no insights into the pathogenesis. FSGS arises through idiopathic (primary) or secondary causes. Ulcerative Colitis (UC) is one of the 2 major types of Inflammatory Bowel Disease (IBD), along with Crohn's disease. Unlike Crohn's disease, which can affect any part of the gastrointestinal tract, UC characteristically involves the large bowel.

The exact etiology of UC is unknown, but certain factors have been found to be associated with the disease, and some hypotheses have been presented as genetic factors, immune system reactions, environmental factors, Nonsteroidal Anti-Inflammatory Drug (NSAID) use, low levels of antioxidants, psychological stress factors, a smoking history, and consumption of milk products [4].

The treatment of UC relies on initial medical management with corticosteroids and anti-inflammatory agents, such as sulfasalazine, in conjunction with symptomatic treatment with antidiarrheal agents and rehydration. Surgery is contemplated when medical treatment fails or when a surgical emergency (eg: perforation of the colon) occurs [5-7].

The coexistence of UC and FSGS is an unexpected condition. Lately, case reports have been published documenting the development of nephropathy after treatment of UC with mesalamine or sulfasalazine. In cases in the literature, this coexistence has been identified as associated with 5-Aminosalicylic Acid (5-ASA) therapy. In our case, we report a case of FSGS secondary to the use of mesalamine in a Kuwaiti patient with UC.

## Case presentation

A 32 years-old Kuwaiti man, with a 6-month's history of UC, was admitted with rising serum

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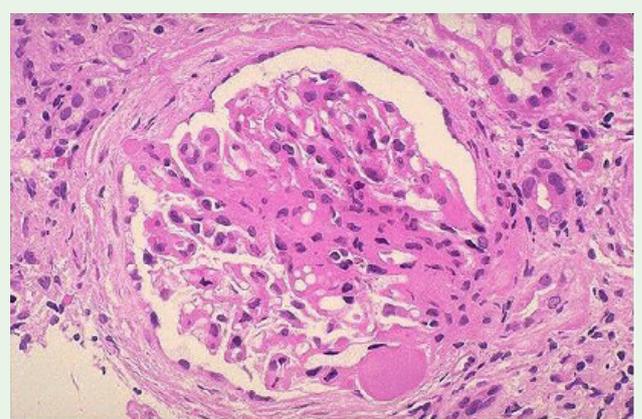
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**Table 1:** Time course of laboratory parameters, mesalamine treatment and kidney biopsy of the reported patient.

Variables	March 2016	October 2016	November 2016	December 2016
Serum creatinine	76 umol/L	143 umol/L	108 umol/L	96 umol/L
Blood urea	8 mmol/L	12.3 mmol/L	6 mmol/L	7 mmol/L
24 h urinary ptn	140 mg/day	1900 mg/day	620 mg/day	340 mg/L
ANA		-ve		
C3(0.83-1.77 g/L)		1.52		
C4(0.15-0.45 g/L)		0.34		
P-ANCA		-ve		
C-ANCA		-ve		
HbsAg		-ve		
HCVab		-ve		
Mesalamine	800 mg TDS	Discontinued	Discontinued	Discontinued
Kidney biopsy		FSGS		

ANA, Antinuclear Antibodies; ANCA, Anti-Neutrophil Cytoplasmic Antibodies; HBsAg, Hepatitis B surface Antigen; HCV ab, Hepatitis C Antibodies; FSGS, Focal Segmental Glomerulo Sclerosis

creatinine and proteinuria following the use of mesalamine for treatment of UC. There was no fever, nausea, vomiting or infection. On August, 2015, the patient started to complain from loss of appetite and generalized fatigue (No specific treatment at that time). On March, 2016, there was repeated vomiting, fresh bleeding per rectum for which sigmoidoscopy and rectal biopsy done on April, 2016 and revealed UC. Mesalamine was started (800 mg tds) plus rectal supp then gradually decreasing dose to 400 mg BD only. On October 2016, the patient started to complain from puffiness of eyelids, LL oedema and headache. There was a positive family history of renal failure, his father has renal failure on dialysis (hypertensive nephrosclerosis), and kidney transplantation was done for his brother due to renal failure of unknown cause (mostly cortical necrosis) post septicemia and prolonged intensive care unit admission. Positive family history of renal stones (his brothers). Physical and clinical examination, there was hypertension 170/100 mmHg, HR 82/min, temperature 37.3, bilateral mild pitting lower limb oedema. Chemistry values showed serum creatinine 143 mmol/L, blood urea nitrogen 12.3 mmol/L, serum potassium 4.8 mmol/L, serum sodium 134 mmol/L and albumin 31 g/L. Total Ca 2.23 mmol/L, phosphorous 1.26 mmol/L. White blood count was  $5.76 \times 10^7$  /L, hemoglobin 114.00 mmol/L, hematocrit 0.36 L/L, platelet  $322.00 \times 10^7$  /L. Erythrocyte sedimentation rate was 58 mm/h. Total cholesterol 5.4 mmol/L, high density lipoprotein-cholesterol 2.13 mmol/L and triglycerides 2.24 mmol/L. Liver enzymes were normal. The urine sediment contained 10-20 red blood cells and 2-3 white blood cell/hpf and 24 urinary proteins was 1900 mg/day. All immunology and virology tests were negative (Table 1). Abdominal ultrasound revealed normal both kidneys in position, size and echotecture with normal corticomedullary differentiation. Chest X-ray, electrocardiography and echocardiography were normal. The old values showed serum creatinine level of 76 umol/L, blood urea nitrogen level of 8mmol/L and 24-h urine protein level of 140mg/day before starting mesalamine [Table 1]. The professional differential diagnosis was kidney injury as an extraintestinal manifestation of UC as Glomerulonephritis (GN) from minimal change nephropathy to



**Figure 1:** Focal Segmental Glomerulosclerosis (FSGS). An area of collagenous sclerosis runs across the middle of this glomerulus. As the name implies, only some (focal) glomeruli are affected and just part of the affected glomerulus is involved (segmental) with the sclerosis.

rapidly progressive crescentic GN, tubulointerstitial abnormalities (interstitial nephritis, granulomatous interstitial nephritis, nephrocalcinosis and renal tubular acidosis), drug-induced (5-ASA) related disease (GN, Interstitial nephritis) or familial disease due to positive family history of renal disease. Kidney biopsy was performed in order to establish the diagnosis.

### Kidney Biopsy

With light microscopy, there were 46 glomeruli of which 2 were globally sclerosed. Two of the viable glomeruli showed segmental sclerosis and the rest showed mild mesangial matrix prominence. Negative for any significant proliferative activity. Interstitium had no inflammation. Tubulo-interstitium showed no tubular atrophy and fibrosis (5-10%). Blood vessels had mild arteriosclerosis. Immunoperoxidase was negative for IgG, IgA, IGM, C3C, C1q. Conclusion was FSGS [Figure 1].

Our diagnosis was secondary FSGS as an extraintestinal manifestation of UC mostly drug-induced (mesalamine). So the treatment of our patient was discontinuation of mesalamine, valsartan 160 mg/day, prednisolone 30 mg/day (for 2 months and then tapered to 20 mg daily), Omega 3 plus twice a day and atorvastatin 20 mg daily with proper following up of his blood pressure, renal function tests and 24 hours urine protein in nephrology OPD. With follow-up, the proteinuria decreased from 1900 mg/day to 340 mg/day and serum creatinine decreased from 143mmol/L to 96 mmol/l and still on close follow-up.

### Discussion

Extra-intestinal manifestations of IBD are common, occurring in about 40% of patients [8], many of which are postulated to be associated with autoimmune pathogenesis [9]. Renal involvement in IBD, however, has rarely been reported. Sulfasalazine used for IBD, either as initial therapy or to maintain remission. Sulfasalazine reaches the colon intact, where it is metabolized to 5-Aminosalicylic Acid (5-ASA, mesalazine, mesalamine) and a sulfapyridine moiety. Adverse effects are mainly caused by the sulfapyridine moiety and include headache, vomiting, and abdominal pain. A reduction in dose is usually beneficial. Newer 5-ASA preparations lack the sulfa

moiety of sulfasalazine and are associated with fewer side effects. Mesalamines are slow-release formulae of 5-ASA and are effective as a primary tool for initial and maintenance therapy of IBD. Rare hypersensitivity reactions occur and include pneumonitis, pancreatitis, and hepatitis. Because of adverse effects of these agents, differentiation of renal involvement associated with these drugs use from the true extraintestinal manifestations of IBD were difficult [10,11].

Glomerular diseases are described in patients with active UC. Likely drug-induced interstitial nephritis, and NS due to minimal change disease, have been reported in a few patients with UC on treatment with mesalazine and sulfasalazine (5-ASA) [10,11,12]. We report a 32 years-old male Kuwaiti patient with 6-months history of well controlled UC who recently developed rising of serum creatinine and non nephritic-range proteinuria after the use of mesalamine and kidney biopsy revealed FSGS with improvement of kidney function and proteinuria after discontinuation of mesalamine.

Fofi et al., describe a 33 years-old patient with a 5-years history of UC who recently developed NS associated with microscopic haematuria. Blood pressure and renal function were normal. The patient was on Azathioprine (AZA), mesalazine and sulfasalazine during the last year for his colitis, with good control of bowel disease. Renal biopsy revealed FSGS associated with mesangial IgA deposits; no signs of interstitial nephritis were found. 5-ASA was discontinued, AZA was reduced and a rapid remission of the NS was observed after 6 weeks of steroid therapy (1 mg/kg/day) associated with ramipril 5 mg/day, with a follow-up of 9 months and concluded that, the occurrence of NS during UC is suggestive of an association between UC and FSGS, but a possible role of mesalazine and /or sulfasalazine in its pathogenesis cannot be excluded. Mesangial IgA deposits could be an "occasional" further occurrence, considering the chronic inflammation of colonic mucosa and the altered immune response of patients with UC [12].

Also Chirumamilla et al., describe a 15 years-old African American girl with well controlled UC presented to the Johns Hopkins Hospital with a four-day history of high fever, malaise, generalized body aches, and productive non-bloody cough. Over the next three days, she developed acute renal failure with fluid retention, and elevated serum creatinine and blood urea nitrogen. A kidney biopsy showed drug-induced acute interstitial nephritis and FSGS with viral inclusion bodies likely secondary to cytomegalovirus concluded that when treating UC patients with a history of underlying renal disease, it is advised to carefully monitor renal function while on mesalamine therapy [13].

Sulfasalazine, mesalazine, mesalamine or 5- ASA should be withdrawn when renal impairment occurs in a patient with IBD in whom no other cause can be readily identified. If withdrawal of 5- ASA treatment does not result in a decrease in serum creatinine, then the patient should be considered for kidney biopsy to diagnose whether interstitial nephritis or GN associated with IBD is the cause of the persistent impaired kidney function.

UC is typically associated with Antineutrophil Cytoplasmic Antibodies of Perinuclear Type (pANCA). These antibodies are not usually considered to carry potential for the development of systemic vasculitis as they lack specificity for Proteinase 3 (PR3) or

Myeloperoxidase (MPO). ANCA-positive patients with UC were followed for a year during which no evidence of GN was found [14].

IgA nephropathy reported to be associated with UC and can be primary in most cases or secondary but is rarely associated with UC [15,16,17].

There was a report of patient with UC who has developed acute interstitial nephritis and the subsequent renal failure following a long pause of the treatment with mesalazine [18]. In this case, there was progressive decline in renal function in a patient with UC. Although the patient exhibited stable levels of serum creatinine during the 3 years period after the treatment with mesalazine and sulfapyridine was discontinued, he developed severe interstitial nephritis associated with moderately active UC. His renal biopsy samples showed evidence of severe active tubulointerstitial nephritis along with intense renal interstitial infiltration of CD3-positive T cells. Colonic fiberoptic examination also revealed moderate UC activity and the mucosal infiltration of CD3-positive cells, thus suggesting the common immune mechanism possibly mediated by T-cell dysregulation. Since the patient had not used any nephrotoxic agent for at least three years, it was reasonable to conclude that the main precipitating cause of the progression of renal injury during the medication free period is attributable to the disease activity of UC per se, rather than the flare-up of the reminiscence of mesalazine effect.

Drug-induced nephropathy constitutes a critical problem that prevents the continued use of the agent. Indeed, several types of kidney disease have been documented, including GN, membranous nephropathy and NS as rare extraintestinal manifestations of IBD [19,20]. Furthermore, a strong correlation between disease activity and tubular proteinuria has been reported in IBD [21].

The kidney constitutes a target organ involved in the UC-induced systemic disorders. Furthermore, many drugs and their metabolites are condensed in situ and excreted in the urine, so the kidney is susceptible to the nephrotoxicity of these drugs. Of more clinical importance, our case sheds light on the kidney as an organ affected in IBD albeit low incidence reported so far. Our observation would emphasize the need for increasing awareness of the kidney function and the presence of protein in urine during the management of IBD with mesalamine, sulfasalazine, mesalazine or 5-ASA.

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