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Nephritis Associated with Ulcerative Colitis

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1. Introduction

Ulcerative colitis (UC) is an idiopathic chronic inflammatory disease of the colon and rectum, characterized by mucosal inflammation and typically presenting with bloody diarrhea. Crohn's disease is characterized by transmural inflammation of the gut wall and can affect any part of the tubular gastrointestinal tract. Although the underlying etiology and exact pathogenesis remain fully unclarified, current hypothesis favors dysregulation of gastrointestinal immune system in genetically predisposed individuals [1]. Extra-intestinal manifestations of inflammatory bowel disease (IBD) are common, ensuing in approximately 40% of patients [2], many of which are postulated to be associated with autoimmune mechanisms [3]. Renal manifestations associated with IBD, however, have rarely been reported. Sulfasalazine reaches the colon intact, where it is metabolized to 5-aminosalicylic acid (5-ASA, mesalazine, mesalamine) and a sulfapyridine moiety. It is therefore used for colonic disease, either as initial therapy or to maintain remission. 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 hypertensitivity reactions occur and include pneumonitis, pancreatitis, and hepatitis. Recently, several case reports have been published suggesting an association between the use of 5-ASA and the development of chronic tubulointerstitial nephritis in patients with IBD [4, 5]. Because of adverse effects of these agents, differentiation of renal complications subtending these therapies from the true extraintestinal manifestations of IBD involves much difficulty.
In this review, we note the drugs including 5-ASA associated nephrotoxicity and also show case reports of UC related nephritis.

2. Drugs of the treatment for IBD associated nephrotoxicity

2.1 Epidemiology of nephrotoxicity in IBD

Sulfasalazine has been used in the treatment of IBD, both for UC and for Crohn's disease. 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. Azad Khan et al. studied the therapeutic activity of the component parts of sulfasalazine and found that 5-ASA was the

therapeutically active component of the drug [6]. In moderate active UC, both sulfasalazine and 5-ASA have proven to be effective in inducing and maintaining clinical remission. However, a number of cases have shown the 5-ASA related toxicity [7, 8]. In particular, nephrotoxicity has been described in some patients with IBD treated with 5-ASA [7, 8]. In this respect, both acetylsalicylic acid and phenacetin, which have been implicated in the occurrence of nonsteroidal antiinflammatory drug-induced nephropathy, share structural similarities with 5-ASA [9, 10]. Furthermore, previous studies reported that 5-ASA may cause injuries to tubular epithelial cells in animals when fed in high doses [9, 10]. The actual incidence of nephrotoxicity in IBD patients with 5-ASA therapy has not been determined, but it has been suggested that renal impairment may occur in up to 1% of patients treated with 5-ASA. A recent prospective study revealed that renal impairment was observed in 2-3% of IBD patients with and without concomitant 5-ASA treatment [11]. More recently, a case-control analysis found that IBD patients treated with 5-ASA had an increased risk of renal disease [12]. However, after adjustment for several factors and variables, the risk of 5-ASA users was comparable to controls. This study found that IBD patients without 5-ASA also had increased risk of renal disease. Taken together, although users of 5-ASA may have an increased risk of renal disease, it may be partly attributable to the underlying disease [12].

2.2 Monitoring markers in IBD

Microalbuminuria has been demonstrated to be present in the majority of IBD patients, and it seems to be related to disease activity. However, other studies have shown that microalbuminuria is not present in patients with IBD [13]. Some authors have concluded that an increased prevalence of tubular proteinuria may be attributed to high doses of 5-ASA [14]. Nevertheless, differences among these studies may be related to differences in disease activity of IBD. Taken together, it is important to conduct a systematic evaluation of the effect of 5-ASA treatment on renal function in patients with IBD.

5-ASA treatment-related nephrotoxicity is reported most often within the first 12 months, but also delayed presentation after several years has been observed. Thus, regular monitoring of renal function should be performed during the therapy.

Several attempts have been made to measure early signs of renal impairment in patients with IBD treated with 5-ASA using sensitive markers of glomerular and tubular dysfunction. Riley et al. found that the incidence of elevated urinary markers such as N-acetyl-D-glucosamidase is low in patients with quiescent UC, which is independent of the dose and duration of 5-ASA treatment [15]. When renal damage occurs, its presence is unlikely to be detected by urinalysis in its early remediable stages. Although tubular enzymuria may be a more sensitive and specific marker of renal damage, it is not yet available as a screening method and the correlation between the several urinary markers of renal damage and 5-ASA treatment remains unproven. These limitations emphasize the importance of monitoring serum creatinine in patients with IBD treated with 5-ASA.

2.3 The incidence of renal disease in IBD

It has been suggested that mesalazine may induce renal impairment more frequently than sulfasalazine [16]. In an analysis of spontaneous reports of adverse events in the UK, 5-ASA-related nephrotoxicity seemed more frequent in mesalazine-treated patients compared with

sulfasalazine-treated patients [17]. Recently, data from the UK General Practice Research Database were used to estimate the incidence of renal disease in adult patients with IBD, and mesalazine and sulfasalazine users had comparable risks of nephrotoxicity (0.17 versus 0.29 cases per 100 person-years, respectively) [12]. It can be conluded that the nephrotoxicity potential of mesalazine and sulfasalazine seems to be similar, and,even if differences exist, they are probably small. Mesalazine should be withdrawn when renal impairment manifests 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 fall in serum creatinine, then the patient should be referred for consideration of renal biopsy to make sure whether interstitial nephritis or glomerulonephritis associated with IBD is the cause of the persistent impaired renal function.

2.4 Treatment for renal impairment in IBD

Steroids and azathioprine have been used in patients with renal impairment due to mesalazine-associated interstitial nephritis, but the evidence for beneficial roles is anecdotal and uncontrolled. Partial improvement or even complete recovery of renal function after steroid therapy has been reported by several authors. However, other studies have been unable to demonstrate a beneficial effect of these immunosuppressive drugs. Nevertheless, it has been suggested that a trial of high-dose steroid (60 mg/day or 1 mg day/kg for up to 3 months) may be recommended in patients whose renal function does not respond to drug withdrawal alone [7]. Although most case reports indicate reversibility after cessation of the drug, in some cases permanent clinical kidney dysfunction has been observed. Thus, it has been calculated that 10% of the patients with 5-ASA nephrotoxicity will develop end-stage renal disease [5].

3. Case reports of UC related nephritis

3.1 ANCA related nephritis

UC is typically associated with antineutrophil cytoplasmic antibodies of perinuclear type (p-ANCA). 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 can be detected in sera from patients with a wide variety of inflammatory diseases including UC. In one study of 50 patients with UC, 54% were shown to be either p-ANCA or c-ANCA positive but none of these antibodies reacted with PR3 or MPO [18]. In another study, ANCA-positive patients with UC were followed for a year during which no evidence of glomerulonephritis was found [19].

3.2 IgA nephropathy

UC may be associated with a number of extraintestinal complications, involving almost any organ system. The organs most commonly involved include the skin, joints, biliary tract and eyes [3, 20]. However, renal and genitourinary tract manifestations are quite rare, particularly glomerulonephritis. They reported that a patient of IgA nephropathy with UC and chronic intermittent episodes of indolent macrohematuria [21]. IgA nephropathy can be primary in most cases or secondary but is rarely associated with UC [22, 23]. Altered T-helper cells' function might be the initial common derangement of both UC and IgA nephropathy [24, 25]. In IgA nephropathy such alteration in CD4-positive T

cells causes a nonspecific stimulus on plasma cells in the bone marrow to secrete polymeric IgA1 into the circulation [26, 27] and of IgG1 and IgG3 in UC [28, 29] culminating in both cases with a common state of local cytokine secretion and tissue inflammation.

3.3 UC related interstitial nephritis

Lately, we reported a patient with UC who has developed acute interstitial nephritis and the subsequent renal failure following a long pause of the treatment with mesalazine [30]. In this case, we observed progressive decline in renal function in a patient with UC. Although the patient exhibited stable levels of serum Cr during the 3 year period after the treatment with mesalazine and sulfapyridine was discontinued, he developed severe interstitial nephritis associated with moderately active UC (Figure 1). His renal biopsy samples showed evidence of severe active tubulointerstitial nephritis along with intense renal interstitial infiltration of CD3-positive T cells (Figure 2). Colonic fiberscopic 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

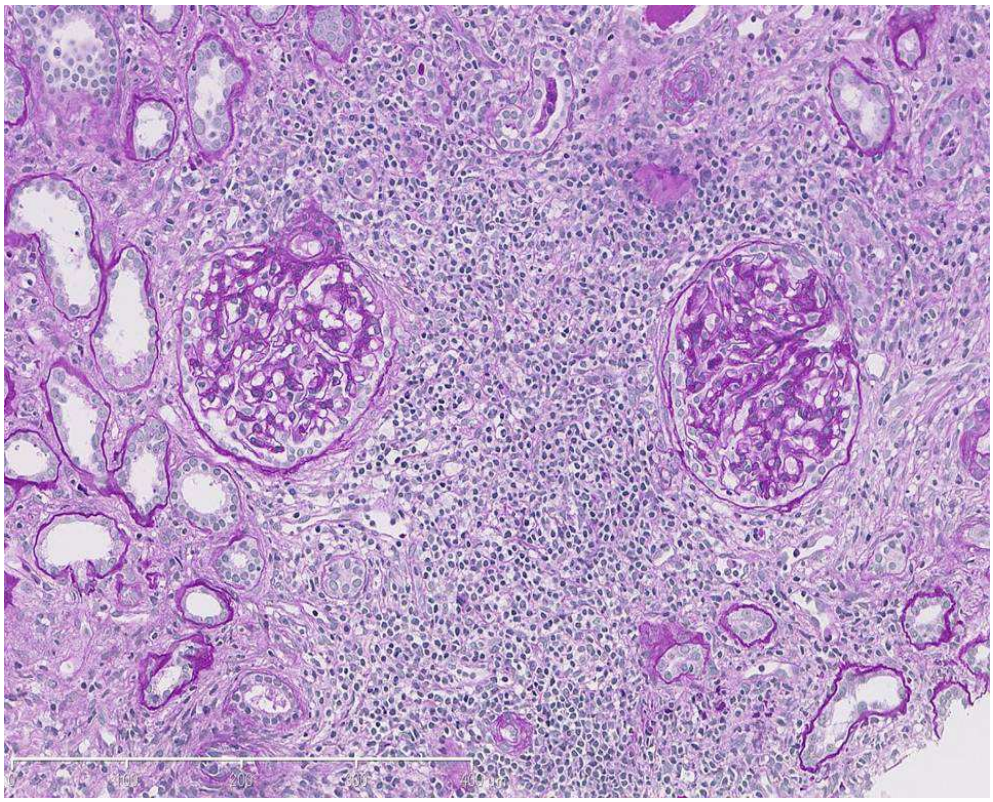

Fig. 1. UC related interstitial nephritis (PAS staining)

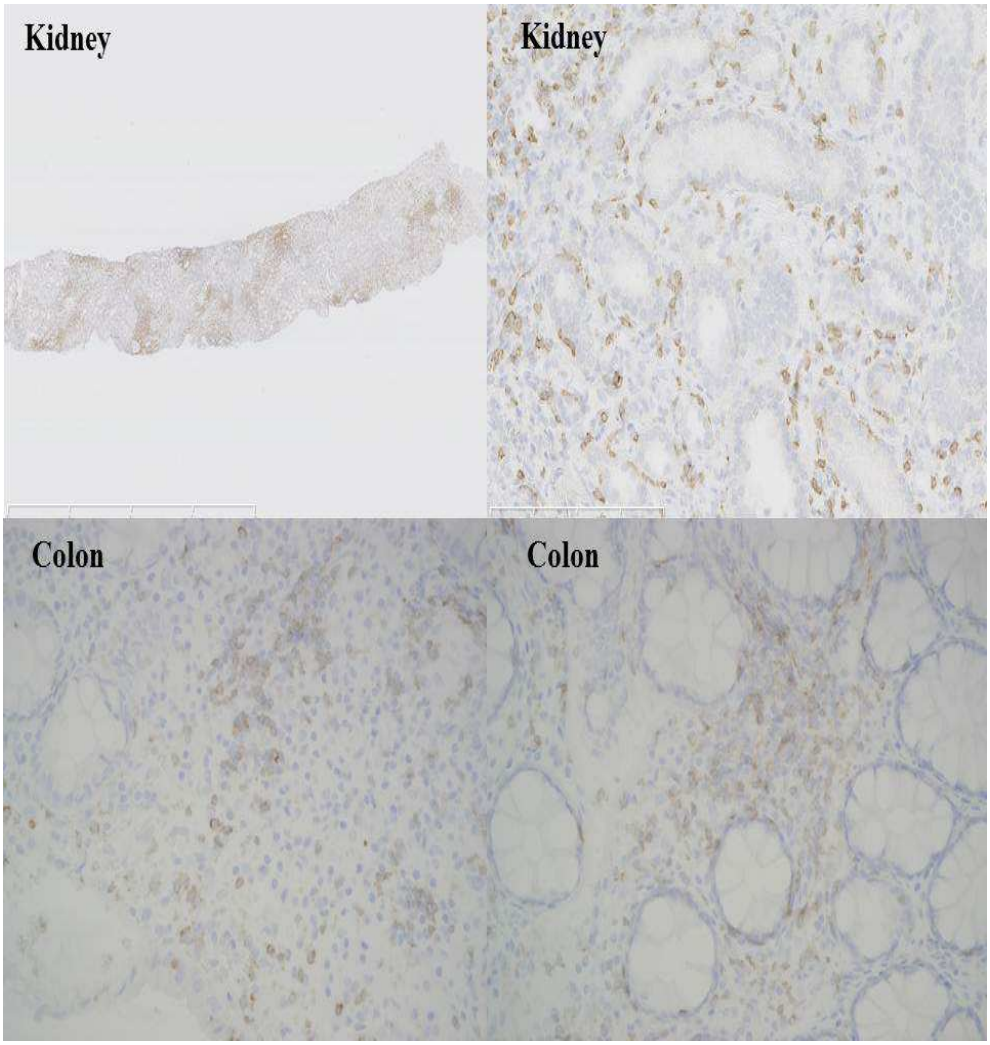

Fig. 2. Intense interstitial infiltration of CD3-positive T cells was detected in the kidney (Upper). The infiltration of CD3-positive cells into the intestinal mucosa was also observed (Lower)

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 precludes the continued use of the agent. Nephrotoxicity has been described in patients with IBD treated with 5-ASA [4, 5]. In the literature survey, 5-ASA-associated nephrotoxicity is reported most often within the first 12 months from the initiation of the drug [31], but delayed presentation has also been shown rarely, with the onset of the renal manifestation after several years of the

treatment [32, 33]. In most of their reports, however, 5-ASA was given continuously during the latent period. In our case, by contrast, nephrotoxic agents, including mesalazine or sulfapyridine, were discontinued for at least three years, during which renal function remained relatively stable. Collectively, it appears unlikely that the aggravating process after the cessation of the drugs is associated with the direct nephrotoxic effect of these agents.

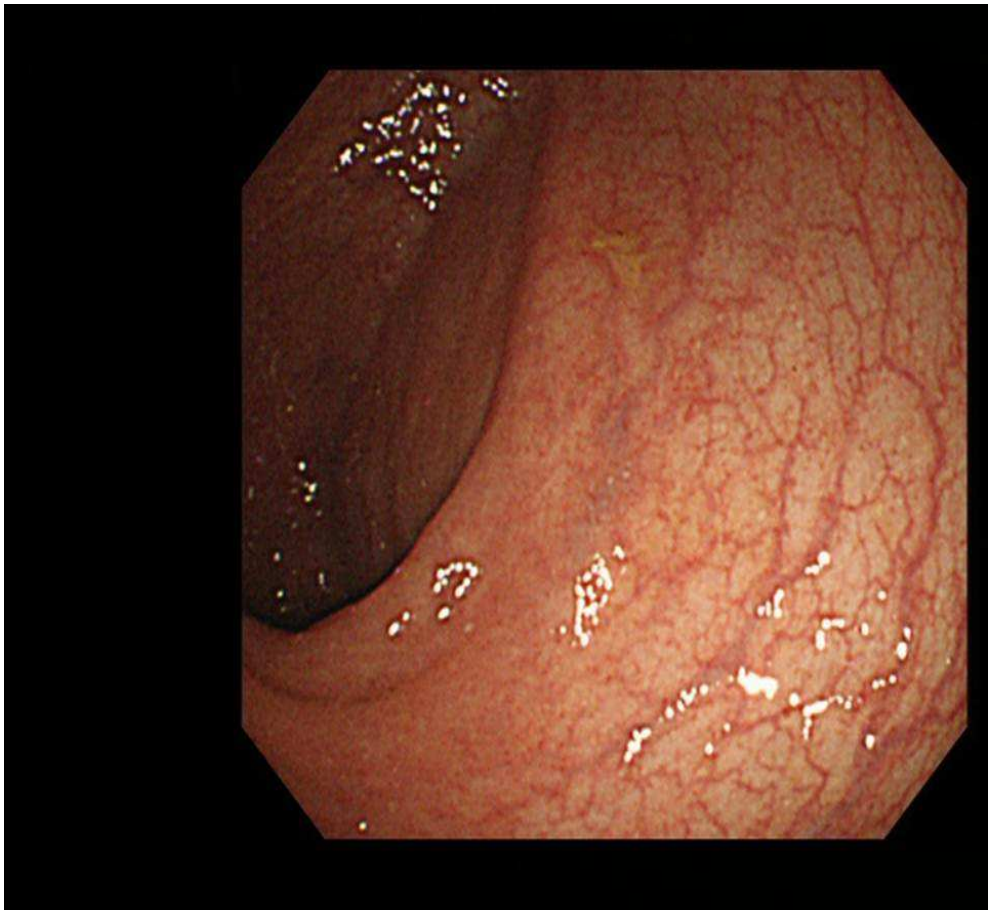

Fig. 3. Colonic fiberscopic findings unveiled moderate UC activity

Since IBD is acknowledged as autoimmune disease affecting multiple extraintestinal organs, it is possible that the kidney is a target organ for the UC-associated systemic injury. Indeed, several types of kidney disease have been documented, including glomerulonephritis, membranous nephropathy and nephrotic syndrome as rare extra-intestinal manifestations of IBD [34-35]. In contrast to glomerular disease, tubulointerstitial nephritis unrelated to nephrotoxic agents has rarely been reported hitherto [36]. Of note, it has been shown that a substantial number of patients manifest

pathological enzymuria [37]. Furthermore, a strong correlation between disease activity and tubular proteinuria has been reported in IBD [38]. In our recent case report, the patient shows moderate UC activity (Figure 3) and progressive course of interstitial nephritis with no nephrotoxic agent given during the antecedent 3-year period. Although there reported one case showing that the renal injury does not parallel the activity of IBD [33], the absence of other aggravating factors rather favors the recognition of the UC activity as a precipitating mechanism in this case.

Link between IBD and kidney disease merits comment. As shown in the present case, the kidney constitutes a target organ involved in the UC-induced systemic disorders. Furthermore, the kidney, where various drugs and their metabolites are condensed *in situ* and excreted in the urine, is susceptible to the nephrotoxicity of these agents. Of more clinical importance, the present case sheds light on the kidney as an organ affected in IBD albeit low incidence reported so far. To the extent that the kidney disease contributes substantially to the development of cardiovascular events, our observation would emphasize the need for increasing awareness of the kidney in the management of IBD.

4. Conclusion

A large number of biological agents as well as many biochemical substances and molecules specifically for the medical treatment of patients with IBD, have been developed. Sulfasalazine has been used in the treatment of IBD, both for UC and for Crohn's disease. Mesalamines are slow-release formulae of 5-ASA and are effective as a primary tool for initial and maintenance therapy of IBD. Recently, several case reports have been published suggesting an association between the use of 5-ASA and the development of chronic tubulointerstitial nephritis in patients with IBD. Because of adverse effects of these agents, differentiation of renal complications subtending these therapies from the true extraintestinal manifestations of IBD involves much difficulty. Since IBD is acknowledged as autoimmune disease affecting multiple extraintestinal organs, it is possible that the kidney is a target organ for the UC-associated systemic injury. Indeed, several types of kidney disease have been documented, including glomerulonephritis, membranous nephropathy and nephrotic syndrome as rare extra-intestinal manifestations of IBD. We also reported the case of acute interstitial nephritis associated with UC. As noted in our case report, we assume that the renal manifestation is attributed to intrinsic disease process of the UC-mediated immune dysregulation, and emphasize the need for the pathophysiological evaluation of the intestine and other organs in clinical situations.

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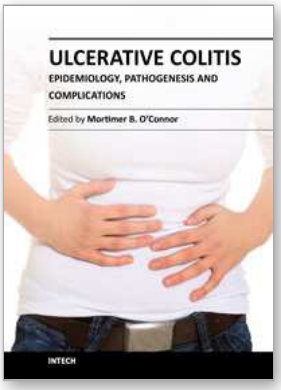

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