Case Report

5-AMINOSALICYLIC ACID ASSOCIATED CHRONIC TUBULOINTERSTITIAL NEPHRITIS IN A PATIENT WITH CROHN'S DISEASE

Mehmet Koç, M.D.* / İshak Çetin Özener, M.D.* / Azra Bihorac , M.D.*
Işın Kılıçaslan, M.D. / Emel Akoğlu, M.D.***

* *Sub-department of Nephrology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey.*

** *Department of Pathology, School of Medicine, Istanbul University, Istanbul, Turkey.*

ABSTRACT

5-Aminosalicylic acid (5-ASA) is the most commonly used drug for the treatment of inflammatory bowel disease (IBD). 5-aminosalicylic acid induced nephrotoxicity has recently been reported. We report a case of female with Crohn's disease treated with mesalazine for 60 months and sulphasalazine for additional 12 months. The patient presented with loin pain, sterile pyuria and raised serum creatinine. Percutaneous renal biopsy revealed chronic interstitial nephritis and yellow-brown pigment deposition in proximal tubular cells. Steroid treatment was commenced for 4 months and there has been no improvement in renal function. Due to widespread use of mesalazine, and its insidious onset of nephrotoxicity, renal function screening and urinalysis should be routinely performed to detect the toxicity of mesalazine and related drugs.

Key Words: Chronic interstitial nephritis, 5-ASA, Sulphasalizine, mesalazine.

INTRODUCTION

5-Aminosalicylic acid (5-ASA) is the most commonly used drug for the treatment of inflammatory bowel disease (IBD). In order to avoid the toxic effects of sulphasalazine, the actual tendency is to use formulations of olsalazine or 5-ASA. Although 5-ASA is considered relatively safe and effective drug, a number of renal side effects of 5-ASA have been reported. These side effects include interstitial nephritis, chronic tubulointerstitial nephritis, minimal change disease, renal tubular disease, and diabetes insipidus (1-5). Chronic interstitial nephritis associated with 5-ASA use is very rare (5). We describe a patient with Chron's disease receiving 5-ASA and sulphasalazine who developed asymptomatic chronic interstitial nephritis potentially caused by 5-ASA treatment.

CASE REPORT

A 40 -year old previously healthy woman presented to a gastroenterologist in 1992, because of 4 months duration of bloody diarrhea. Clinical examination, blood counts, urine analysis, urea and electrolytes were normal at presentation. Flexible colonoscopy showed inflammation, aphtoid ulceration and fissures of the mucosa of colon and terminal ileum. Biopsy of colonic mucosa revealed linear mucosal ulceration, cryptic atrophy, and loss of goblet cells, mononuclear cell infiltrate and fibrosis in

(Accepted 16 June, 2000)

Marmara Medical Journal 2000;13(4):226-229

the lamina propria. These findings supported the diagnosis of Crohn's disease. The serum creatinine value was 0.8 mg/dl at that time and treatment with mesalazine (Salofalk®) was started at a dose of 3x1000 mg/day. The patient remained in remission under 5-ASA treatment. However, the patient developed monoarthritis of left knee joint in October 1997, and sulphasalazine was added to mesalazine at a dose of 3000 mg/day. The patient was admitted to hospital in November 1998, because of loin pain, sterile pyuria and an increased serum creatinine level. Physical examination was unremarkable. Serum creatinine level was 1.4 mg/dl and creatinine clearance was 44-ml/min. Twenty-four hour protein excretion was 0.2 g/day. Urinary sediment examination revealed 15-20 leukocytes per high power field. Urine cultures, direct examination for acid-fast bacilli and culture for mycobacterium tuberculosis were all negative. Biochemical tests, hepatic viral markers, ANA, rheumatoid factor and complements were either normal or negative. Mantoux test was also negative. On ultrasonographic imaging, both kidneys were normal in size and shape. Percutaneous biopsy of kidney revealed thickening of basement membrane, tubular atrophy and dilatation, interstitial fibrosis, interstitial infiltrates comprised of few eosinophils and focal intense mononuclear cell infiltrate (fig. 1). Yellow-brown granular pigment deposition was also detected in tubular epithelial cells (fig. 2). Masson-Fontana and Prussian blue stains were performed to explain the nature of pigment deposition but they were all negative. Direct immunofluorescence for IgG, IgA, IgM, and C3 were all negative.

Mesalazine and sulphasalazine stopped. Treatment with prednisone (1 mg/kg/day) was started for both interstitial nephritis and Crohn's disease. Steroid dose was tapered to 10 mg/day over a period of 4 months. After 6 months of steroid treatment, serum creatinine and creatinine clearance remained at 1.4 mg/dl and 40 ml/min respectively. At the end of 1 year of follow up, serum creatinine levels were 1.3 mg/dl and the patient remained asymptomatic for both her Crohn's disease and interstitial nephritis.

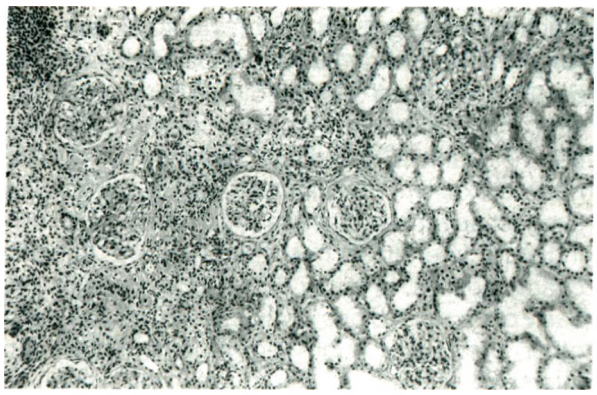

Fig. 1: Light microscopy. HE. Periglomerular and interstitial fibrosis with interstitial mononuclear cell infiltration and tubular atrophy. X 200.

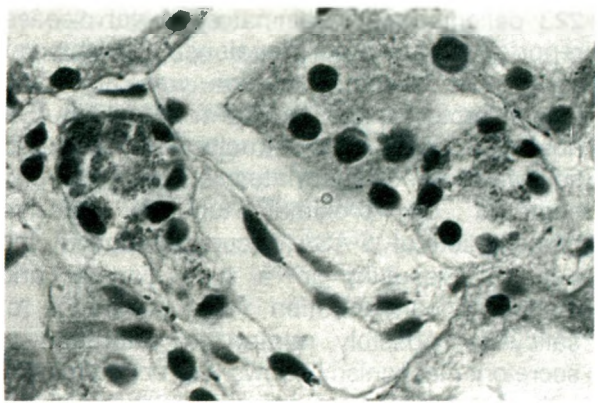

Fig. 2: Light microscopy. HE. Yellow-brown granular pigment deposition in tubular epithelial cells. X 200.

DISCUSSION

Acute and chronic tubulointerstitial nephritis is caused by a variety of agents. The chronic tubulointerstitial nephritis in our patient was probably caused by 5-ASA (mesalazine) as the patient did not use any known etiological factors and had normal renal functions before the treatment.

The incidence of 5-ASA induced nephrotoxicity has not been determined. However, it has been suggested that minimal increment in creatinine concentration after 4 months of mesalazine treatment may occur in up to 1 in 100 patients, whereas, clinically important interstitial nephritis occurs in only 1 in 500 patients (6).

Interstitial nephritis appears after several months of treatment and clinical features of allergic

reaction are scant although symptoms such as fever rash, arthralgia and eosinophilia have occasionally been described (6). Microhematuria, sterile pyuria and low specific urine gravity may be the earliest pathologic findings of 5-ASA nephrotoxicity. Proteinuria and hypertension suggest advanced disease (7). Therefore, 5-ASA induced interstitial nephritis has no specific characteristics. In many cases, it is necessary to carry out a renal biopsy which, as in our case and other previously published reports, shows an interstitial nephritis without any distinguishing specific features of 5-ASA nephrotoxicity (6).

In experimental and clinical models, 5-ASA was shown to be nephrotoxic (8,9). Schreiber et al in 223 patients with inflammatory bowel disease reported that the prevalence of tubular membrane protein excretion was high and tubular protein excretion was related to 5-ASA dose (9). 5-ASA is structurally similar to salicylates and salicylates are filtered and secreted by proximal tubules. Passive reabsorption of 5-ASA occurs throughout the nephron, resulting in a high cortical and medullary concentration (10). Clearance of salicylate, possibly related to saturation of secretory mechanism, shows a direct correlation with urine flow and a negative correlation with the plasma concentration. The reason of renal damage caused by 5-ASA may be similar to that of salicylates, probably causing hypoxia of renal tissues either by uncoupling oxidative phosphorylation in renal mitochondria or by inhibiting the synthesis of renal prostaglandins.

In our case, the patient also used sulphasalazine for 12 months. The nephrotoxic role of sulphapyridine moiety of sulphasalazine remains unclear. However, direct tubular toxicity of sulphonamides is well known (11). In a biopsy of a patient with oliguric acute renal failure who was taking sulfadiazine, interstitial nephritis with focal tubular necrosis was documented. Biopsy taken months later, after clinical recovery, showed interstitial fibrosis and tubular atrophy (12). Renal toxicity has also been reported with sulphasalazine use and the etiologic agent accused was 5-ASA in these cases (13-15).

The aetiology of deposited yellow-brown granular pigment in our case is difficult to explain. Despite theoretical risk of microcrystallization of sulphapyridine moiety of sulphasalazine, even early biopsy specimens carefully prepared under oil to prevent crystal dissolution have failed to support crystal deposition in several cases (16). However, additional tubular toxicity of sulphapyridine in IBD patients should be further determined.

The long-term prognosis of patients with 5-ASA nephrotoxicity remains unclear. Restoration of renal function may be seen on withdrawal of medication. World et al reported that 6 of 7 cases, who received 5-ASA containing drugs up to 10 months, recovered after withdrawal of the drug. However, 5 of 6 patients who received 5-ASA containing drugs more than 18 months showed no improvement after withdrawal of the drugs even though two patients in this group further took azathioprine and steroids. Furthermore, partial remission of renal function obtained in only one third of cases who received 5-ASA compounds more than 18 months (6). It is suggested that serum creatinine should be monitored every 4 weeks during the first three months of therapy to identify patients who may be at risk of developing progressive renal damage. Monitoring frequency can then be reduced to 3-monthly and at the end of first year to annually.

In conclusion, we described a case of chronic interstitial nephritis in relation to 5-ASA. Sulphapyridine moiety of sulphasalazine might have also contributed to nephrotoxicity. Due to widespread use of mesalazine or sulphasalazine in patients with inflammatory bowel disease, renal function screening and urinalysis should be routinely monitored to detect the toxicity of mesalazine and related drugs.

REFERENCES

1. *Witte T, Olbricht CJ, Koch KM. Interstitial nephritis associated with 5-aminosalicylic acid. Nephron 1994;67:481-482.*
2. *De Broe ME- Stolear JC, Nouwen EJ, et al. 5-aminosolicylic acid (5-ASA) and chronic tubulointerstitial nephritis in patients with chronic inflammatory bowel disease; is there a link? Nephrol Dial Transplant 1997;12:1839-1841.*
3. *Hamling J, Raedler A, Helmhen U, et al. 5-aminosalicylic acid - associated renal tubular acidosis with decreased renal function in chron's disease. Digestion 1997;58:304-307.*

4. Korzets Z, Bernheim J. Minimal-change nephropathy induced by 5-aminosalicylic acid. Nephrol Dial Transplant 1996;11:1817-1818.
5. Rhodes JM, Masson EA. Mesalazine associated nephrogenic diabetes insipidus presenting as weight loss. Gut 1992;33:563-564.
6. World MJ, Stevens PE, Ashton MA, et al. Mesalazine associated interstitial nephritis. Nephrol Dial Transplant 1996;11:614-621.
7. Riley SA, Lloyd DR, Mani V. Test of renal function in patients with quiescent colitis. Gut 1992;33:1348-1352.
8. Casadevall G, Moreno JJ, Franch MA, et al. N-acetyl-D glucosaminidase (NAG) and alanine aminopeptidase (AAP) excretion after acute administration of acetaminophen, salsalate and aspirin in rats. Res Commun Chem Pathol Pharmacol 1983;81:77-89.
9. Schreiber S, Hamling J, Zehnter F, et al. Renal tubular dysfunction in patients with inflammatory bowel disease treated with aminosalicylate. Gut 1997;40:761-766.
10. Duggin GG. Mechanisms in the development of analgesic nephropathy. Kidney Int 1980;18:553-561.
11. Nadasdy T, Racusen LC. Renal injury caused by therapeutic and diagnostic agents and abuse of analgesics and narcotics. Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Heptinstall's Pathology of the Kidney, 5th ed. Philadelphia: Lippincott-Raven Publishers, 1998;811,861.
12. Robson M, Levi J, Dolberg L, Rosental JB. Acute interstitial nephritis following sulfadiazine therapy. Isr J Med Sci 1970;6:561-566.
13. Chester AC, Diamond LH, Schreiner GE. Hypersensitivity to salicylazopyridine. Renal and hepatic toxic reactions. Arch Intern Med 1978;138:1138-1139.
14. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. BMJ 1990;301:818.
15. Dwarakanath AD, Michael J, Allan RN. Sulphasalazine induced renal failure. Gut 1992;33:1006-1007.
16. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (third of three parts). No Engl J Med 1977;296:784-787.