Methyldopa-Induced Colitis in a Patient with Membranoproliferative Glomerulonephritis

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A 76-year-old man with membranoproliferative glomerulonephritis complicated by methyldopa-induced colitis is reported. Eight months after administration of methyldopa, mucous bloody stool was noted. A barium enema examination showed disappearance of haustra and a spastic rectosigmoid with pseudo-polyposis. Biopsy specimens obtained from the sigmoid mucosa revealed interstitial edema and small inflammatory cells. After cessation of methyldopa treatment, the sigmoid findings, blood pressure, and proteinuria were improved, suggesting that methyldopa not only induced the acute colitis but also worsened the nephrotic syndrome in this patient.

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Introduction

The most widely known side effect of methyldopa, a drug commonly used in the treatment of hypertension, is the development of a positive direct Coombs' test that may lead to hemolytic anemia and hepatitis. The authors here report an infrequently noted but serious complication of methyldopa, manifesting as acute colitis in a patient with membranoproliferative glomerulonephritis.

Case Report

A 76-year-old man was admitted to our hospital on February 2, 1989 because of pretibial edema. He had had mild hypertension since 1980, for which no treatment had been given. Since 1985 he had been receiving an antihypertensive drug (thiazide) at another clinic. On admission a urinary examination revealed proteinuria of 6 to 9 g daily, with hyaline and granular casts, and glycosuria. GTT (75 g) revealed a diabetic pattern. Serum creatinine level was 1.8 mg/dl, creatinine clearance was 24 ml/min. Examination of the fundus oculi revealed simple retinopathy. His blood pressure and proteinuria were controlled by the administration of antihypertensive drugs including nifedipine, captopril, prazosin, guanabenz, furosemide and methyldopa. Blood sugar levels were fairly well controlled by dietary restriction alone. On September 14, 1989, he was readmitted to the hospital because of dyspnea, anorexia, lower abdominal pain and diarrhea (Fig. 1). There was prominent peripheral edema with a 13 kg increment of body weight within the preceding two months. The blood pressure was 200–104 mmHg. His physical examination showed wheezing in the chest and massive ascites and tenderness in the lower abdomen.

A urinary examination revealed proteinuria of 1.5 g daily. On peripheral blood examination, anemia was found with a red blood count of 196 x 10⁴/mm³, hemoglobin of 6.4 g/dl and hematocrit of 20.2%. White blood cell count was 3,800/mm³ with 68% neutrophils, 28% lymphocytes, 4% monocytes, 0% eosinophils and 0% basophils. Blood chemistry examination revealed total serum protein of 4.3 g/dl and albumin, 2.6 g/dl. Blood urea nitrogen was 46 mg/dl, creatinine was 1.9 mg/dl and uric acid was 8.6 mg/dl. Sodium was 142 mEq, potassium 6.9 mEq and chloride 101 mEq/l. Liver function studies were normal. Antinuclear antibody, Coombs' test and LE test were negative. C3 was 38 mg/dl (normal: 50–127). CH₅₀ was 26 U/ml (normal: 30–40). Two weeks after admission, mucous bloody stool was found. Microscopic examination of freshly passed stool specimens showed no ova or parasites, but numerous erythrocytes were seen. A stool specimen culture yielded only normal flora. His blood pressure was 240–120 mmHg...
and proteinuria was 6g daily. A barium enema examination on October 2 revealed disappearance of haustra and a spastic rectosigmoid with pseudo-polypsis (Fig. 2-a). On October 5, a sigmoidoscopic examination showed a hyperemic, friable mucosa, many small petechiae, and a thin layer of blood coating the mucosa in some areas. Biopsy specimens obtained from the sigmoid mucosa revealed interstitial edema and small inflammatory cells.
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Fig. 3. a. A biopsy specimen obtained from sigmoid mucosa, revealing interstitial edema and small inflammatory cells (HE stain, ×200). b. The second sigmoid biopsy findings, showing reversion to normal (HE stain, ×200).

(Fig. 3-a). On October 24, administration of methyldopa was stopped, and after 3 days mucous bloody stool was no longer found. The second barium enema examination on October 28 showed an improvement in the recto-sigmoid spasticity and appearance of haustra (Fig. 2-b). Blood pressure was 160−100 mmHg, proteinuria was 2 g daily, and peripheral edema was decreased. Results of sigmoid mucosal biopsy on November 18 were normal (Fig. 3-b). Three months after the initiation of prednisolone, the level of proteinuria decreased to less than 1 g daily. A renal biopsy specimen obtained on February 1, 1990 contained 43 glomeruli. In sections stained with periodic acid Schiff (PAS), mesangial lobulation and double capillary outlines were observed (Fig. 4-a). In one third of glomeruli, fibro-cellular crescent formation was found. These findings were compatible with membranoproliferative glomerulonephritis. The percentage of glomerular sclerosis was 23%, with fibrin cap

Fig. 4. a. A renal biopsy specimen showing mesangial lobulation and double outlines of capillary which were compatible to membranoproliferative glomerulonephritis (PAS stain, ×200). b. A renal biopsy specimen, showing edema with inflammatory cell infiltration and fibrotic changes in the interstitium (HE stain, ×100).
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lesions found in severely sclerotic glomeruli. The interstitium was edematous with inflammatory cell infiltration and fibrotic changes (Fig. 4-b), and atrophy of the tubulus was prominent. Fibrotic thickening of the intrarenal arterioles and hyaline changes of the intima were also observed. Immunofluorescent studies revealed deposition of IgG and IgM in the mesangium and capsula present as +1. Less intense deposition of C3 and C1q was also observed in some parts of the mesangial areas. Electron microscopic examination was not performed.

Discussion

A 76-year-old man with membranoproliferative glomerulonephritis (MPGN) complicated by acute colitis is reported. At the time of initial methyldopa administration, it is thought that MPGN already existed in the patient. After 8 months of treatment with methyldopa, the colitis appeared, while upon cessation of the drug, the colitis, hypertension and nephrotic syndrome were improved without steroid therapy.

The primary site of action of methyldopa is within the central nervous system. Reducing the sympathetic outflow from the central nervous system, the fall in blood pressure mainly results from a decrease in peripheral resistance with little effect on cardiac output (1). As renal blood flow is well maintained, methyldopa has been widely used in hypertensive patients with impaired renal function. The side effects due to the decrease sympathetic outflow include sedation, dry mouth, orthostatic hypotension, and galactorrhea (1). However, the most widely known side effect of methyldopa is the development of a positive direct Coombs’ test that may lead to hemolytic anemia and hepatitis (2, 3). However, although much less frequently, it has also been reported that methyldopa induces colitis (4-6). The mechanisms involved in methyldopa-induced colitis are unknown, although allergic reaction of the drug was proposed in a reported patient because rechallenge precipitated a return of symptoms within 14 hours (6). It is difficult to estimate the frequency of methyldopa-induced colitis because of its rarity. It is also difficult to speculate on differences in mechanisms between hypertensive patients with and without nephrotic syndrome. In our case, MPGN and diabetes mellitus were underlying diseases. Although methyldopa-induced colitis has not previously been described as a complication of either disease. The renal biopsy findings in the patient were not suggestive of diabetic nephropathy. Although the duration of diabetes were unknown, it was not longer than the duration of hypertension. The development of ordinary diabetic nephropathy, in general, requires more than ten years (7). The fibrin cap lesions were thought to be due to arteriosclerosis.

On the second admission, several factors might have worsened the patient’s nephrotic syndrome. His blood pressure was not controlled at that time, and protein loss into the intestinal tract due to the acute colitis might have induced hypoproteinemia. On the other hand, based on the renal biopsy findings, interstitial edema and inflammatory cell infiltration were found after steroid therapy. As methyldopa can cause acute interstitial nephritis (8), acute interstitial nephritis might have played a role in the worsening nephrotic syndrome. We cannot, however, exclude the possibility that methyldopa directly worsened the glomerulonephritis.

It is interesting that pseudo-polyposis was found on barium enema examination. To our knowledge, pseudo-polyposis in patients with methyldopa-induced colitis has never been reported. Two case of ulcerative colitis associated with nephrotic syndrome have been reported, in both of which humoral immune mechanisms were thought to be pathogenetically important (9). However, ulcerative colitis was excluded in the present patient because of the absence of rectal lesions, the clinical course and the colon biopsy findings. Methyldopa-induced colitis should be considered in the differential diagnosis of pseudo-polyposis.

Severe anemia was also found in the patient. Neither hemolysis nor bleeding in the upper gastrointestinal tract was found. The erythropoietin level was not low. The bone marrow picture indicated erythroid hyperplasia. The causes of anemia in the patient were thought to include chronic lower tract bleeding and malnutrition resulting from the nephrotic syndrome.

In summary, methyldopa-induced acute colitis is a very rare but serious complication of methyldopa therapy. After cessation of methyldopa treatment, the sigmoid findings, blood pressure, and proteinuria were improved, suggesting that methyldopa not only induced the acute colitis but also worsened the nephrotic syndrome in this patient. It is recommended that physicians withdraw the methyldopa when lower abdominal symptoms including mucous bloody stool are noted in patients treated with this agent.

References

