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CASE REPORT

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Cimetidine-induced tubulointerstitial nephritis with both MPO-ANCA and PR3-ANCA

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Abstract
We describe a 75-year-old man with tubulointerstitial nephritis (TIN) with myeloperoxidase (MPO)-antineutrophil antibody (ANCA) and proteinase-3 (PR3)-ANCA. He had a slight fever and eruption with itching after taking cimetidine (prescribed after gastrectomy for gastric cancer) and he was admitted to a nearby hospital. There, he showed proteinuria, serum creatinine (sCr) of 2.9 mg/dl, and creatinine clearance (Ccr) of 44 ml/min per 1.73 m^2. His MPO-ANCA titer was 267 EU, and PR3-ANCA titer was 112 EU. Abnormal concentrations in bilateral kidneys were found by gallium scintigraphy. For these reasons, he was transferred to our hospital. Percutaneous renal biopsy was performed after admission. Severe tubular atrophy, mild interstitial fibrosis, and severe mononuclear cell infiltration of the interstitium were noted. Drug-induced renal impairment was suspected, and cimetidine administration was withdrawn. Lymphocyte stimulation tests (DLSTs) were performed. The cimetidine titer was positive, at 2,537 cpm. After the withdrawal of cimetidine, the PR3-ANCA titer was reduced gradually, and, next, the MPO-ANCA titer was also reduced. The sCr level was reduced to 1.2 mg/dl. In summary, we report herein the first case of cimetidine-induced TIN associated with both MPO-ANCA and PR3-ANCA.

Key words MPO-ANCA · PR3-ANCA · Cimetidine · Tubulointerstitial nephritis

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Introduction

A growing number of drugs cause drug-induced tubulointerstitial nephritis (TIN). There are some reports of drug-induced TIN associated with myeloperoxidase (MPO)-antineutrophil antibody (ANCA) or with proteinase-3 (PR3)-ANCA,[1–9] but these reports of drug-induced TIN associated with MPO-ANCA and PR3-ANCA are few.[9] We experienced a case of cimetidine-induced TIN associated with MPO-ANCA and PR3-ANCA. Little is known about the pathological mechanism of drug-induced TIN associated with ANCA. Here, we have reported the first case of cimetidine-induced TIN associated with MPO-ANCA and PR3-ANCA.

Case report

A 75-year-old man was admitted to a nearby hospital in November 2000. There, he received endoscopic mucosal gastrectomy for early-stage gastric cancer. After that, he was medicated with 800 mg/day of cimetidine. From September 2001, he had a slight fever and eruption with itching, and he was admitted to that hospital. His blood pressure (BP) was high, at 152/70 mmHg, and renal dysfunction, with a serum creatinine (sCr) concentration of 2.9 mg/dl, was revealed. His myeloperoxidase (MPO)-antineutrophil antibody (ANCA) titer was 267 EU, and proteinase-3 (PR3)-ANCA titer was 112 EU. Abnormal concentrations in bilateral kidneys were found by gallium scintigraphy. For these reasons, he was transferred, in November 2001, to the Department of Nephrology, Osaka City University Hospital, for examination of renal failure. On admission, his BP was elevated, at 160/60 mmHg. Body temperature was 36.2°C.

Laboratory findings of the patient were as follows. Urinalysis showed no hematuria and no proteinuria. Creatinine clearance (Ccr) was 44 ml/min per 1.73 m^2. Hemoglobin was 12.4 g/dl, leukocyte count, 4300/μl; and platelets, 11.0 ×

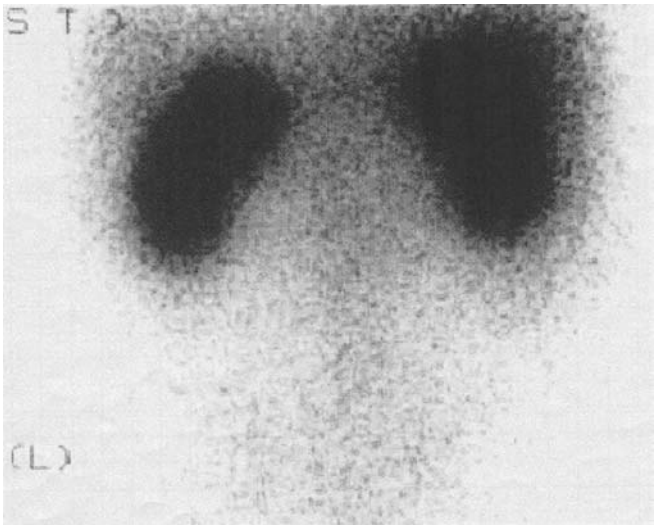

Fig. 1. Gallium scintigraphy, showing slightly abnormal concentric scintigraphy of the bilateral kidneys

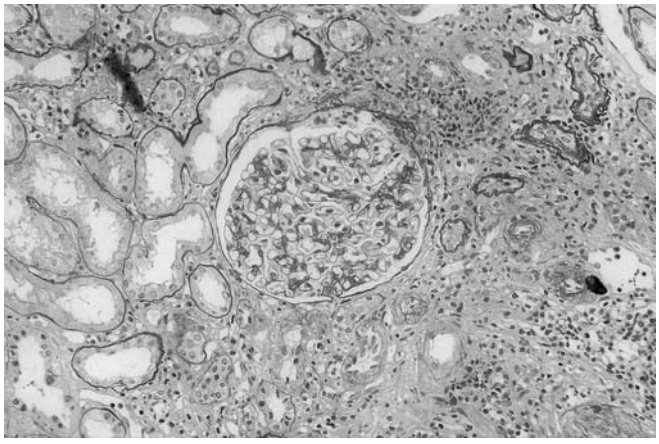

Fig. 2. Light microscopy, showing severe tubular atrophy, mild interstitial fibrosis, and severe mononuclear cell infiltration of the interstitium. No infiltration to the vessels was noted. The glomerulus was intact. Periodic acid schiff (PAS), ×100

10^4/μl. Blood chemistry showed serum creatinine, 2.1 mg/dl; total protein, 8.2 g/dl; albumin, 3.2 g/dl; total cholesterol, 179 mg/dl; aspartate-aminotransaminase (AST), 37 IU/l; alanine-aminotransaminase (ALT), 32 IU/l; and alkaline phosphatase (ALP), 744 IU/l. The anti-streptolysin O (ASO) titer was 208 IU/ml; anti-streptokinase (ASK), 640 IU/ml; C3, 117 mg/dl; C4, 28 mg/dl; CH50, 40 U/ml; immunoglobulin (Ig) G, 3110 mg/dl; IgA, 289 mg/dl; IgM, 105 mg/dl; and IgE, 1160 U. Anti-hepatitis B virus surface antigen, anti-hepatitis C virus antibody, and antinuclear antibody were negative. The MPO-ANCA titer was 318 EU, and the PR3-ANCA titer was 246 EU. Anti-glomerular basement membrane antibody was negative. Rheumatoid factor (RF) titer was negative. Bacterial cultures from the pharynx were negative.

Renal ultrasonoechography findings showed normal size and normal echography findings. Gallium scintigraphy of the total body showed only slightly abnormal scintillation of the kidneys (Fig. 1).

Percutaneous renal biopsy was performed 6 days after admission. Light microscopic examination of specimens stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and periodic acid methenamine-silver (PAM) showed 16 glomeruli in the biopsy material; all glomeruli were intact. But severe tubular atrophy, mild interstitial fibrosis, and severe mononuclear cell infiltration of the interstitium, with no infiltration to the vessels, were noted (Fig. 2). Immunofluorescence microscopy showed no fluorescent deposition in the mesangial area or capillary loop. Electron microscopic examination revealed no abnormal findings of the glomeruli. Drug-induced renal impairment was suspected, and on December 13, cimetidine administration was withdrawn. Lymphocyte stimulation tests were performed. The cimetidine titer was positive, at 2537 cpm, but the titers of other drugs which he had received, i.e., loxoprofen sodium, rabeprazole sodium, famotidine, and acetaminophen were negative. From the time of cimetidine withdrawal, the PR3-ANCA titer was reduced gradually,

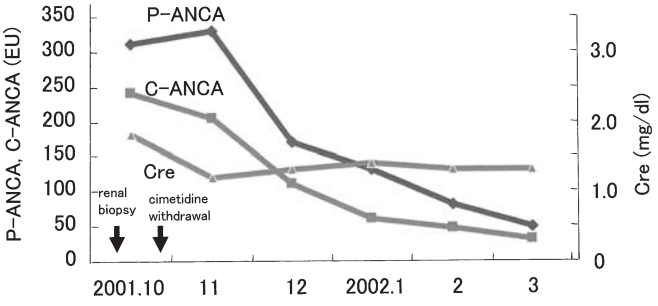

Fig. 3. Clinical course of the patient. Both myeloperoxidase-antineutrophil antibody (MPO-ANCA) levels and proteinase-3 (PR3)-ANCA levels decreased after cimetidine medication was stopped. *Cre*, serum creatinine; *P-ANCA*, MPO-ANCA; *C-ANCA*, PR3-ANCA

and, next, the MPO-ANCA titer was also reduced (Fig. 3). sCr was reduced to 1.2 mg/dl. On January 10, 2002, he was discharged from our hospital.

Discussion

We have reported a case of cimetidine-induced tubulointerstitial nephritis (TIN) associated with MPO-ANCA and PR3-ANCA. Drug-induced interstitial nephritis has been reported with antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDS), diuretics, phenytoin, allopurinol, cimetidine, and other agents.[10,11] From our literature review, we note that drug-induced interstitial nephritis associated with MPO-ANCA has been reported with cephotazime,[1] indomethacin,[2] omeprazole,[3] hydralazine,[4] ciprofloxacin,[5] phenytoin,[6] propylthiouracil,[7] and cimetindine[8] (Table 1). In addition, Kitahara et al.[8] reported a patient with cimetidine-induced interstitial nephritis with three kinds of ANCA (anti-MPO, anti-elastase, and anti-lactoferin). Dolman et al.[9] reported two patients with propylthiouracil-induced interstitial nephritis with MPO-

Table 1. Reports of drug-induced ANCA-related glomerulonephritis and tubulo interstitial nephritis

No.	Year	Authors	Age (years)	Sex	Drug	c-ANCA	p-ANCA	Renal function
1	1992	Vogt et al.	8	M	PTU	Negative	Positive	Declined
2	1993	Vogt et al.	15	F	PTU	ND	Positive	Improved
3	1993	Dolman et al.[9]	32	F	PTU	Positive	Positive	Improved
4	1993	Dolman et al.[9]	45	F	PTU	Negative	Positive	Improved
5	1993	Dolman et al.[9]	37	F	PTU	Positive	Positive	Improved
6	1994	Ito et al.	82	F	PTU	Negative	Positive	Improved
7	1995	Tanemoto et al.	22	M	PTU	ND	Positive	Improved
8	1995	Tanemoto et al.	60	F	PTU	ND	Positive	Improved
9	1995	Tanemoto et al.	82	F	PTU	ND	Positive	Improved
10	1995	Tanemoto et al.	82	F	PTU	ND	Positive	Improved
11	1995	Kudo et al.	52	F	PTU	Positive	Positive	Declined
12	1995	Toda et al.	54	F	PTU	Positive	Positive	Improved
13	1995	Hirano et al.	48	F	PTU	ND	Positive	Improved
14	1995	Aoki et al.	22	F	PTU	ND	Positive	Improved
15	1995	D'cruz et al.	62	M	PTU	ND	Positive	Improved
16	1997	Kitahara et al.[7]	39	F	PTU	Postive	Positive	Improved
17	1995	Shih et al.[5]	81	M	Ciprofloxacin	ND	Positive	ND
18	1999	Sakai et al.[2]	83	M	Indomethacin	ND	Positive	Death
19	2000	Feriozzi et al.[1]	65	M	Cephotaxime	Negative	Positive	Improved
20	1996	Parry et al.[6]	59	M	Phenytoin	Positive	Negative	Improved
21	2000	Kitahara et al.[8]	63	M	Cimetidine	Negative	Positive	Improved
22	1992	Almroth et al.[4]	ND	ND	Hydralazine	ND	Positive	ND

PTU, propylthiouracil; ND, not described

ANCA and PR3-ANCA. However, cases of cimetidine-induced interstitial nephritis associated with MPO-ANCA and PR3-ANCA have not been reported previously.

The pathological mechanisms of drug-induced interstitial nephritis were suggested to be: (1) induction of enzymes that cross-react with other enzymes, (2) changes of enzyme construction brought about by neutrophils connecting with them, and (3) activation of polyclonal B cells, as occurs in drug-induced lupus.[7–9] These mechanisms were not certain. In addition, our patient showed prominent invasion mononuclear cells with little invasion of plasma cells, and in our patient, the titers of both IgE and IgG were high. There may be a possibility of the involvement of immunomodulatory actions in TIN with MPO-ANCA, and there may be heterogeneity among MPO (p)- and PR3 (c)-ANCA systems. Of note, our patient had gastric cancer. It is often reported that cancer is associated with nephritis.[12,13] Carcinogenic substances may affect ANCA-related nephritis. Further studies are needed to elucidate the mechanisms of such nephritides.

In summary, we have described the first case of cimetidine-induced TIN associated with MPO-ANCA and PR3-ANCA. It may thus be necessary to add cimetidine to the list of drugs that can induce TIN associated with MPO-ANCA and PR3-ANCA.

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