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CASE REPORT

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Rheumatoid arthritis complicated with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis: a case report

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Abstract This article describes a patient with rheumatoid arthritis (RA) with crescentic glomerulonephritis (CrGN) associated with myeloperoxidase–antineutrophil cytoplasmic antibodies (MPO-ANCA), who responded well to methotrexate (MTX). A 48-year-old woman with a 4-year history of RA was admitted with fever and elevated C-reactive protein. On laboratory evaluation, her level of MPO-ANCA was 422 EU, and urinalysis revealed proteinuria and hematuria. Because she was also suffering from episcleritis, vasculitis was considered. A renal biopsy was performed, which revealed necrotizing CrGN. We diagnosed RA complicated with MPO-ANCA-associated vasculitis. We considered treatment with high-dose oral prednisolone for vasculitis, but the patient refused this treatment. We started MTX at a dose of 8 mg/week for RA from the time of admission, and the patient responded immediately. Biochemical parameters, including C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and MPO-ANCA, improved. Seven months later, MPO-ANCA had decreased to 46 EU. In clinical studies, few patients have been reported with RA complicated with ANCA-associated CrGN. This case differs from previous cases in the treatment given. No high-dose steroid with intensive immunosuppression or plasma exchange was required.

Key words Crescentic glomerulonephritis (CrGN) · Methotrexate (MTX) · Myeloperoxidase–antineutrophil cytoplasmic antibody (MPO-ANCA) · Rheumatoid arthritis (RA)

Introduction

Myeloperoxidase–antineutrophil cytoplasmic antibodies (MPO-ANCA) are found in patients with crescentic glomerulonephritis (CrGN), Churg and Strauss syndrome, microscopic polyarteritis, and polyangiitis overlap syndrome.[1] Few patients have been reported with rheumatoid arthritis (RA) complicated with MPO-ANCA-associated CrGN. Most of these have been refractory to high-dose prednisolone or immunosuppressive therapy. We encountered a patient with RA and CrGN associated with MPO-ANCA, who responded well to low doses of methotrexate (MTX).

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Case report

A 48-year-old woman was brought to our hospital in December 2001 with fever, hoarseness, and polyarthritis, which progressed rapidly. She had a 4-year history of RA. The patient had been treated with disease-modifying antirheumatic drugs (DMARDs: bucillamine for several years at first, changed to MTX for a year, then finally changed to auranofin 6 months previously) and oral prednisolone (7.5 mg/day) from the time of diagnosis at another clinic. The DMARDs had been discontinued by her doctor since October 2001 for reasons unknown to us. The patient was diagnosed with acute laryngitis and treated with antibiotics in the Department of Otolaryngology. Although her laryngitis improved, she still suffered from fever. Laboratory findings revealed elevated C-reactive protein (CRP). She was admitted to our ward for treatment for active RA.

On admission, the patient's physical condition was not severe except for episcleritis. A finger-joint X-ray revealed mild erosive changes equivalent to stage II on Steinbrocker grading (Fig. 1). No nodule was demonstrated.

Laboratory evaluations were as follows: leukocytes 4000/l (segmented neutrophils 58%, lymphocytes 34%, monocytes 5%, basophils 1%, eosinophils 2%), erythrocytes 409×10^4/l, hemoglobin 9.4 g/dl, hematocrit 28.6%, platelets 38.0×10^4/l, CRP 5.69 mg/dl, erythrocyte sedimentation rate (ESR) 60 mm/h, IgG 1608 mg/dl, IgA 279 mg/dl, IgM 208 mg/dl, CH_{50} 38.7 U/ml, MPO-ANCA 422 EU (normal $<$ 10 EU), rheumatoid factor 38 IU/ml (normal $<$ 25 IU/ml), antinuclear antibody 1:640 (homogeneous and

nucleolar pattern), serum protein 7.0 g/dl, albumin 2.9 g/dl, zinc turbidity test 15 K-U, lactate dehydrogenase 496 IU/l, blood urea nitrogen 9 mg/dl, creatinine 0.4 mg/dl, and uric acid 4.2 mg/dl. Other blood chemistry was normal. Urinalysis was weakly positive for protein, strongly positive for hematuria, and negative for oliguria and cast. Urine protein was 0.52 g/day. Creatinine clearance was 143.75 ml/min. Chest X-ray was normal.

Because the patient was also suffering from episcleritis, we considered vasculitis. A renal biopsy was performed (Fig. 2). The kidney biopsy specimen contained 19 glomeruli. One showed segmental necrosis, three exhibited segmental necrotic lesions and cellular crescent formation, and one showed fibrotic crescent formation, indicating necrotizing CrGN. Other glomeruli and blood vessels were normal. Under immunofluorescence, IgM linear deposits of weak intensity were detected along the mesangium. No other segmental granular deposits of immune complexes were observed.

We diagnosed the patient as having RA complicated with MPO-ANCA-associated vasculitis. Although we had already started MTX treatment (8 mg/week) for RA from the time of admission, we considered administering high-dose oral prednisolone for her vasculitis. However, the patient refused this therapy because of familial problems. She responded immediately to MTX. Laboratory data, including CRP, ESR, rheumatoid factor, and MPO-ANCA, unexpectedly improved (Table 1). Seven months later, MPO-ANCA had decreased to 46 EU.

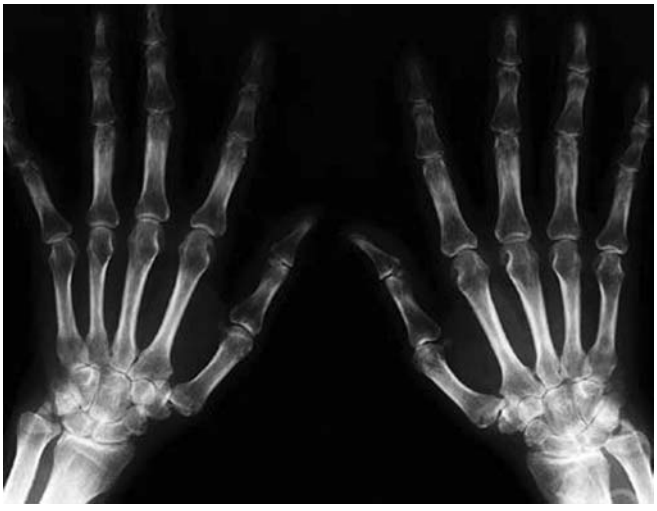

Fig. 1. X-ray of the patient's finger joint revealed mild erosive changes equivalent to stage II on Steinbrocker grading

Discussion

Antineutrophil cytoplasmic antibodies have been described as sensitive and specific markers for systemic vasculitis and CrGN.[2] These can be distinguished as proteinase-3 (PR3)-ANCA, MPO-ANCA, and atypical ANCA by enzyme-linked immunosorbent assay (ELISA).

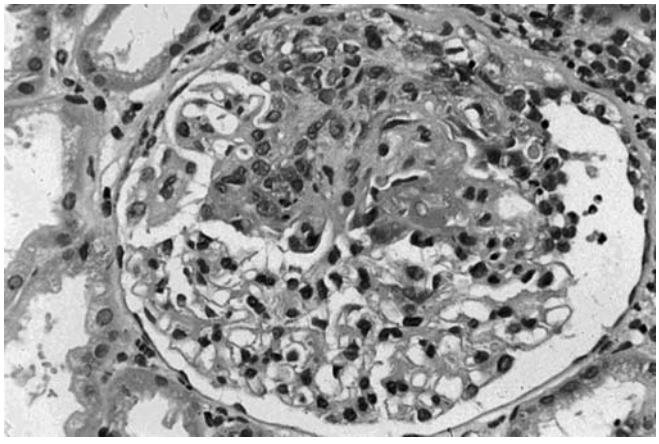

Fig. 2. Renal biopsy. The kidney biopsy specimen contained 19 glomeruli. One showed segmental necrosis, three exhibited segmental necrotic lesions and cellular crescent formation (shown here), and one showed fibrotic crescent formation, indicating necrotizing crescentic glomerulonephritis. Other glomeruli and blood vessels were normal. Under immunofluorescence, IgM linear deposits of weak intensity were detected along the mesangium. No other segmental granular deposits of immune complexes were observed

Table 1. Clinical course

	Date							
	2001.12.20	2002.1.24	2002.2.12	2002.3.26	2002.5.7	2002.6.4	2002.7.30	2002.10.8
PSL (mg/day)	7.5	→	→	→	→	→	→	→
MTX (mg/week)	0	8	→	→	→	→	→	→
MPO-ANCA (EU)	422	431	327	187	69	46	33	21
ESR (mm/h)	60	19	30	22	13	66	23	28
CRP (mg/dl)	5.69	0.77	1.24	1.22	0.63	2.6	0.26	1.26
Cr (mg/dl)	0.4	0.5	0.5	0.6	0.6		0.5	0.6
Urinary protein	+		3+	3+	2+		2+	2+
Urinary occult blood	3+		3+	3+	2+		2+	+
Urinary RBC	16–20/F				7–10/F			4–6/F
Urinary cast	−				−			−

Cr, creatinine; PSL, prednisolone; MTX, methotrexate; MPO-ANCA, myeloperoxidase–antineutrophil cytoplasmic antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RBC, red blood cells

Table 2. Rheumatoid arthritis complicated with ANCA-associated crescentic glomerulonephritis

First author[Ref.]	Age (years) /sex	Duration of RA (years)	Treatment prior to diagnosis	Associated vasculitis	Cr (mg/dl)	Immunology	ANCA	Renal biopsy findings	Treatment	Outcome
Yoshihara[17]	44/F	24	Steroid	(−)	2.7	RF 457 IU/ml ANA 3+	MPO-ANCA 293 EU	CrGN	CY 50 mg/day PSL 40 mg/day	RPGN HD
Harper[18]	69/F	16	DMARDs (Ch, S)	Scleritis PH	11.2	RF	p-ANCA Strong	FSNGN	PSL, CY, PX	Died at 18/12
	64/M	22	NSAIDs	(−)	9.6	RF 1:256 ANA 1:40	Weak	FSNGN	PSL, CY, PX	Improved
	57/M	15	Steroid DMARDs (G, S)		1.2	RF 1:256 ANA 1:40	Weak	FSNGN	PSL	NC
	44/M	13	NSAIDs	Purpuric rash	2.6	RF	p-ANCA 1:400	FSNGN	PSL, CY	Died at 18/12
Messiaen[19]	73/M	9	Steroid	(−)	2.2	ANA 1:200	MPO-ANCA > 30 U	CrGN	IV CY	Improved
			DMARD (G)						PSL 1 mg/kg	
	74/F	40	Steroid	Cerebral	6.1	(−)	MPO-ANCA > 100 U	CrGN	PSL 1 mg/kg	Improved
			DMARD (G)						SP	
Amano[20]	50/F	1	Steroid	Peripheral nervous	0.6	RF 172 IU/ml	MPO-ANCA	CrGN	PSL 60 mg	Improved
			DMARD (G)			ANA 1:320	712 EU			
Qarni[21]	62/M	30	MTX	(−)	3.1	RF	p-ANCA 1:256	CrGN	SP, CY	Improved
	53/F	3	MTX	PH	6.7	RF 159 IU/ml ANA 1:640	p-ANCA 1:256	CrGN	SP, CY	HD
Present case	48/F	4	Steroid (PSL 7.5 mg) DMARDs (S, G, B)	Episcleritis	0.4	RF 38 IU/ml ANA 1:640	MPO-ANCA 422 EU	CrGN	MTX 8 mg	Improved

RA, rheumatoid arthritis; y, year; Cr, creatinine; PSL, prednisolone; DMARDs, disease-modifying antirheumatic drugs; Ch, chloroquine; S, salazosulfapyridine; G, gold; B, bucillamine; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PH, pulmonary hemorrhage; PX, plasma exchange; CY, cyclophosphamide; IV CY, intravenous administration of pulses of cyclophosphamide; RF, rheumatoid factor; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase–ANCA; p-ANCA, perinuclear ANCA; RPGN, rapidly progressing glomerulonephritis; CrGN, crescentic glomerulonephritis; FSNGN, focal segmental necrotizing glomerulonephritis; SP, steroid pulse therapy; HD, hemodialysis; NC, no change; 18/12, one and a half years after the treatment

Myeloperoxidase–ANCA, in particular, have been shown to stimulate neutrophils, resulting in damage to endothelial cells,[3] which suggests a relationship with CrGN.

Antineutrophil cytoplasmic antibodies have been found in 12%–36% of patients with RA.[4–8] They usually exhibit a perinuclear pattern, and lactoferrin and MPO are commonly antigens.[7,8] Although other antigens (such as PR3, MPO, elastase, lactoferrin, and cathepsin G) have been detected in sera from patients with RA, antibody levels were usually low, and more than one specificity was often found in the same serum by ELISA and Western blotting.[9] Myeloperoxidase–ANCA could be induced by some drugs such as propylthiouracil and D-penicillamine. However, these drug-induced MPO-ANCA are usually considered to be low titer and not to relate with clinical symptoms.[10] Also, our patient had not been treated with such drugs and showed a high titer of MPO-ANCA related with CrGN.

The incidence of MPO-ANCA-positive patients with RA is reported to range from 7% to 38%.[4,6,11] Although some of these might suffer vasculitis, few patients have been described with RA complicated with ANCA-associated CrGN (Table 2). About 25% of patients with rheumatoid vasculitis (so-called malignant RA in Japan) exhibit renal dysfunction,[12] but there are few reports of vasculitis defined from renal biopsies of these patients.[13–16]

Yoshihara et al. reported three patients with RA complicated with MPO-ANCA, which rapidly progressed to renal dysfunction. One patient had CrGN, whereas another patient had end-stage hyalinization of the renal tissue, which is not classified as CrGN. The third patient could not undergo renal biopsy because of progressed atrophic kidney. These patients all had high titers of MPO-ANCA (293, 147, and 652 EU, respectively). When they were admitted with renal dysfunction, serum creatinine levels were elevated to 2.7, 3.8, and 4.7 mg/dl, respectively. Renal function did not improve despite high doses of steroids, immunosuppressive therapy, and plasma exchange.[17]

Harper et al. described ten patients with RA who developed focal segmental necrotizing glomerulonephritis, four of whom were ANCA-positive. They were treated with prednisolone, immunosuppressive therapy, and plasma exchange. It was suggested that ANCA titers and extrarenal vasculitis might correlate with prognosis.[18]

Messiaen et al. reported two patients with RA who developed necrotizing CrGN associated with MPO-ANCA. These patients responded to prednisolone, cyclophosphamide, and pulse therapy.[19] Amano et al. reported a patient hospitalized with fever, weight loss, mononeuritis multiplex, and microscopic hematuria. Although the titer of MPO-ANCA was high, serum creatinine was normal, and the patient responded well to prednisolone.[20] Qarni et al. reported two cases of p-ANCA-positive pauci-immune necrotizing CrGN associated with RA.[21] Both patients were treated with MTX. While one lacked other symptoms of vasculitis and responded well to the treatment of steroid pulse and oral cyclophosphamide, the other had pulmonary hemorrhage and failed to respond to the same treatment because of delay of the therapy.

All of these clinical studies suggested that intensive therapies, such as high doses of steroids, were required to reduce the activity of the vasculitis. In our patient, although the MPO-ANCA titer was high and urinalysis revealed hematuria and proteinuria, renal function was still normal. The patient was treated with low-dose MTX only because of the familial problem, and she unexpectedly responded well. However, as Qarni et al. reported that the RA patients treated with MTX could develop CrGN, careful evaluations are needed for each patient. Although previous reports have described high doses of prednisolone and immunosuppressive therapy with cyclophosphamide as a treatment option for ANCA-associated vasculitis, this case suggests that MTX can also be effective.

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