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CASE REPORT

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Crescentic glomerulonephritis with antimyeloperoxidase antibodies developing during the course of IgA nephropathy in a patient with rheumatoid arthritis

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Abstract Glomerulonephritis, such as membranous nephropathy, IgA nephropathy, and p-antineutrophil cytoplasmic autoantibody (ANCA)-related crescentic glomerulonephritis, has been shown to occur in rheumatoid arthritis (RA). However, the occurrence of two types of glomerulonephritis in a patient with RA is rarely observed. Here, we describe a patient with RA who developed crescentic glomerulonephritis with antimyeloperoxidase (MPO) antibodies during the course of IgA nephropathy. This case indicates that crescentic glomerulonephritis and IgA nephropathy may occur together in association with p-ANCA in RA.

Key words Antimyeloperoxidase (MPO) antibodies · Crescentic glomerulonephritis · IgA nephropathy · Rheumatoid arthritis

Introduction

Renal dysfunction is frequently observed in rheumatoid arthritis (RA). It is usually related to drug toxicity or secondary amyloidosis, and rarely to rheumatoid vasculitis.[1] Glomerulonephritis, such as membranous nephropathy, mesangial glomerulonephritis, and IgA nephropathy, has also been demonstrated in RA.[2,3] Recently, the close relationship between antineutrophil cytoplasmic antibodies (ANCA) and systemic vasculitis or rapidly progressive glomerulonephritis (RPGN) with crescent formation has been well established.[4] ANCA are detected in some RA patients, but pauciimmune crescentic RPGN is rarely observed.[5] Here we report on a patient with RA who showed crescentic glomerulonephritis and IgA nephropathy in the presence of increased serum levels of IgG antimyeloperoxidase (MPO) antibodies.

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Case report

A 48-year-old woman was referred to hospital in July 1995 because of persistent low-grade fever. A chest film showed infiltration of both lungs and a small pleural effusion on the right. The patient was admitted to our hospital in October 1995. Laboratory tests revealed a normal urinalysis, with a WBC count of 7000/μl, serum creatinine of 0.7 mg/dl, rheumatoid arthritis passive agglutination (RAPA) of 1:160, and C-reactive protein of 1.3 mg/dl. Bronchoscopy and bronchoalveolar lavage showed nonspecific inflammation with mild lymphocyte infiltration, and no infectious agent was detected. A diagnosis of her pulmonary disease could not be made at this time. The patient was treated with prednisolone (20 mg/day) from January 1996. Although her pleural effusion resolved with this treatment, the pulmonary infiltrates did not improve. Following a gradual decrease in prednisolone, she developed arthritis of the hands and knees in January 1999. Laboratory test results were as follows: urinalysis was normal, erythrocyte sedimentation rate was 48 mm per h, C-reactive protein was 2.0 mg/dl, RAPA was 1:2560, IgG was 2200, IgA was 892, IgM was 405 mg/dl, and antinuclear antibodies (ANA) were negative. The patient subsequently developed severe arthralgia with swelling and erythema of the inflamed joints. She was admitted again in October 1999 because of severe joint pain and leg edema lasting for 3 weeks (Fig. 1).

At this time, the patient had arthritis with joint swelling of bilateral interphalangeal joints, metacarpophalangeal (MCP) joints, wrist joints, metatarsophalangeal (MTP) joints, and knee joints, rheumatoid nodules, and pitting edema of her legs. Examination of skin, eyes, and peripheral nervous system indicated no signs of systemic vasculitis. Blood pressure was 150/80 mmHg. Radiographs of the

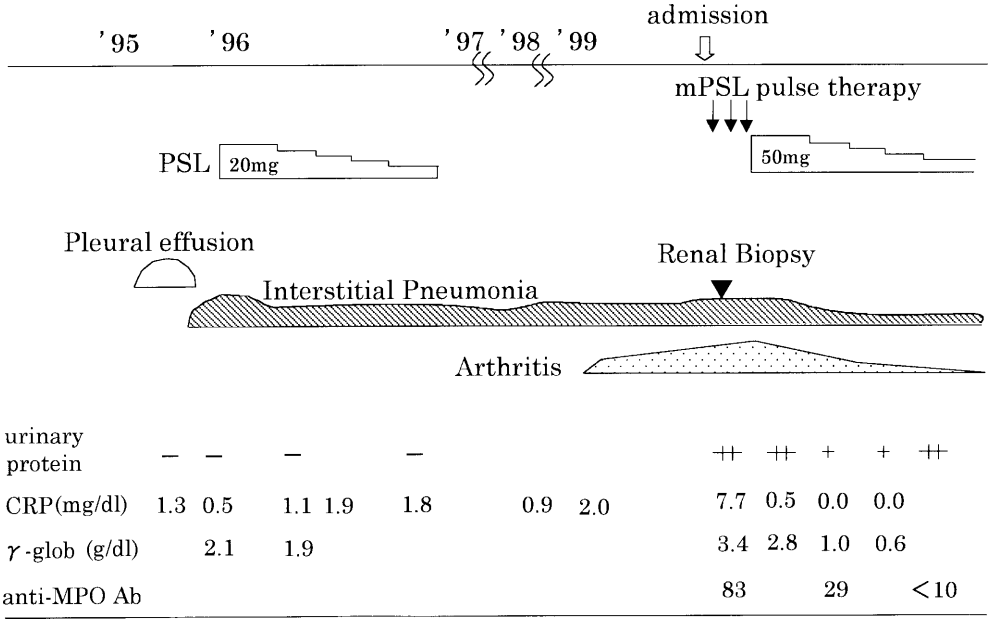

Fig. 1. Clinical course of the present patient. *PSL*, prednisolone; *CRP*, c-reactive protein; *MPO*, myeloperoxidase

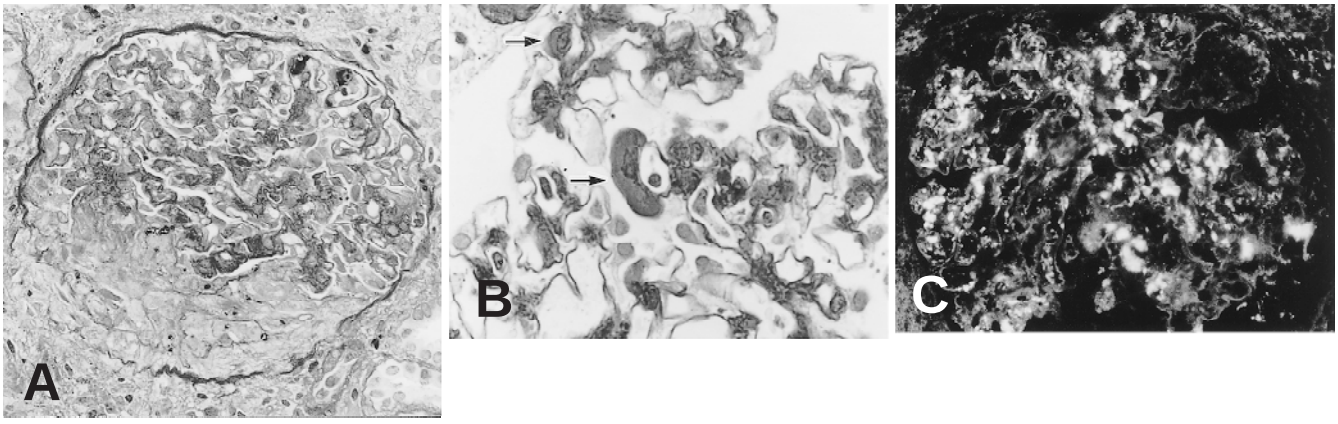

Fig. 2. A Glomerulus showing cellular crescent formation (H&E) ×320. **B** Part of a glomerulus showing hemispherical deposits (*arrow*) (PAS) ×330. **C** Immunofluorescent micrograph of a glomerulus demonstrating IgA deposits in the mesangial area and in part along capillary walls. ×230

joints showed decreased joint space and marginal erosions, findings which were consistent with a diagnosis of RA. A chest film showed interstitial infiltration of both lungs, and computed tomography of the chest indicated interstitial pneumonia. Schirmer's test and rose bengal staining indicated keratoconjunctivitis sicca. Technetium radioisotope scanning showed decreased salivary gland function. Urinalysis revealed proteinuria, hematuria, and nephritic sediment. C-reactive protein was 7.7 mg/dl, serum creatinine was 1.8 mg/dl, RAPA was 1:5120, IgG was 3900, IgA was 780, IgM was 330 mg/dl, and circulating immune complex was 3.4 μg/ml. ANA, anti-DNA antibodies, anti-SS-A antibodies, anti-SS-B antibodies, and cryoglobulin were all negative. Serum complement levels were normal. No antibodies against hepatitis B, hepatitis C, or HIV were found. p-ANCA were detected by indirect immunofluo-rescence. Examination of the immunoglobulin isotype of the patient's p-ANCA by indirect immunofluorescence assay using isotype-specific antibodies indicated IgG, but not IgA. Serum levels of IgG anti-MPO antibodies were 83 (normal value <10), but anti-PR-3 antibodies were negative. The phenotype of the HLA-DR locus was DR2 and 10.

Renal biopsy revealed diffuse crescentic glomerulonephritis with moderate tubulointerstitial nephritis (Fig. 2A). Cellular and fibrocellular crescents were found in 8 out of 16 glomeruli. Another three glomeruli showed global sclerosis. The remaining glomeruli had mild to moderate mesangial proliferation and an increase of the matrix. Typical hemispherical deposits in the mesangial area were clearly observed in some glomeruli (Fig. 2B). Tubular atrophy, interstitial cell infiltration, and fibrosis were seen focally. There was no evidence of angiitis. Immunofluorescence revealed an apparent deposition of IgA, IgM, and C3 in a mesangial pattern (Fig. 2C). Electron microscopy

showed small deposits in the mesangium, and the infiltration of leukocytes and monocytes in the capillary lumens.

The patient was treated with methylprednisolone pulse therapy (1000 mg/day for 3 days) followed by oral prednisolone (50 mg/day). After treatment for 6 weeks, her proteinuria disappeared and her serum creatinine level was 1.0 mg/dl. Anti-MPO antibodies became undetectable after 10 weeks of treatment.

Discussion

ANCA have been demonstrated in various rheumatic diseases, although the clinical significance of these antibodies has not been established. In patients with RA, p-ANCA are detected in about 40% of cases.[6] The presence of p-ANCA in RA is generally associated with longstanding and severe disease, an increased inflammatory response, and nephropathy, but a relationship between p-ANCA and vasculitis has not been identified in RA.[7] Recently, p-ANCA-positive crescentic glomerulonephritis has been documented sporadically in RA patients.[8,9]

IgA nephropathy is the most common form of glomerulonephritis in the world,[10] and the occurrence of IgA nephropathy has been demonstrated in some patients with RA.[3] However, in such cases, it is difficult to be sure whether primary IgA nephropathy occurs during the course of RA, or secondary IgA nephropathy occurs as a form of RA nephropathy. IgA nephropathy is generally an insidious disease and often has a slowly progressive course.[11] However, some studies have documented the rapid decline of renal function in a small group of patients with IgA nephropathy.[12] Furthermore, a crescentic form of glomerulonephritis with p-ANCA has been observed in some of these patients.[13,14]

The present patient had crescentic glomerulonephritis with mesangial IgA deposits and increased serum levels of anti-MPO antibodies. She had severe erosive arthritis, but did not show any evidence of systemic vasculitis. Furthermore, she had not been treated with antirheumatic drugs. These findings indicate two possibilities regarding the occurrence of her renal disease. One is the coincidental association of two independent renal diseases, p-ANCA-related crescentic glomerulonephritis and IgA nephropathy, and the other is a crescentic form of IgA nephropathy associated with serum p-ANCA. It is very hard to distinguish between these possibilities because of the absence of direct evidence. In the renal biopsy specimen, typical hemispherical deposits were detected in the mesangial areas. These deposits generally indicate long-standing IgA nephropathy, apart from the presence or absence of urinary abnormalities.[15] Therefore, it is possible to speculate that IgA nephropathy existed in a latent form for a long period in this patient before the onset of crescentic glomerulonephritis. Allmaras et al.[16] have recently reported three patients with rapidly progressive IgA nephropathy and high titers of anti-MPO antibodies, and they concluded that these cases were a novel subset of crescentic IgA glomerulonephritis associated with anti-MPO antibodies, constituting an overlap syndrome between microscopic polyangiitis and IgA nephropathy. The clinical course and pathological findings of these patients were very similar to those of our case. Although the relationship between crescentic glomerulonephritis and IgA nephropathy is still obscure, the present case suggests that these two types of glomerulonephritis may occur together in association with anti-MPO antibodies.

Our patient also showed arthritis and interstitial pneumonia during her disease course. The diagnosis of RA was made based on the findings of severe symmetrical polyarthritis with marginal erosions. Pulmonary involvement has been shown in patients with microscopic polyangiitis.[17] We failed to determined serum levels of p-ANCA at her first admission of 1995. Therefore, it is not known whether the interstitial pneumonia in this patient occurred as a pulmonary involvement of RA or microscopic polyangiitis.

In conclusion, we presented a patient with RA who showed crescentic glomerulonephritis and IgA nephropathy in the presence of increased serum levels of anti-MPO antibodies. This is a rare case, and may be the first documented association with RA.

References

1. Boers M. Renal disorders in rheumatoid arthritis. Semin Arthritis Rheum 1990;20:57–68.
2. Helin HJ, Korpela MM, Mustonen JT, Pasternack AI. Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis Rheum 1995;38:242–7.
3. Nakano M, Ueno M, Nishi S, Shimada H, Hasegawa H, Watanabe T, et al. Analysis of renal pathology and drug history in 158 Japanese patients with rheumatoid arthritis. Clin Nephrol 1998;50:154–60.
4. Jennette JC, Charles LA, Falk RJ. Anti-neutrophil cytoplasmic antibodies: disease associations, molecular biology and pathophysiology. Int Rev Exp Pathol 1991;32:193–221.
5. Braun MG, Csernok E, Schmitt WH, Gross WL. Incidence, target antigens, and clinical implications of antineutrophil cytoplasmic antibodies in rheumatoid arthritis. J Rheumatol 1996;23:826–30.
6. Mulder AHL, Horst G, van Leeuwen MA, Limburg PC, Kallenberg CGM. Antineutrophil cytoplasmic antibodies in rheumatoid arthritis. Arthritis Rheum 1993;36:1054–60.
7. Mustila A, Korpela M, Mustonen J, Helin H, Huhtala H, Soppi E, et al. Perinuclear antineutrophil cytoplasmic antibody in rheumatoid arthritis: a marker of severe disease with associated nephropathy. Arthritis Rheum 1997;40:710–7.
8. Yorioka N, Taniguchi Y, Amimoto D, Miyata H, Yamakido M, Taguchi T. Chronic rheumatoid arthritis complicated by myeloperoxidase antineutrophil cytoplasmic antibody-associated nephritis. Am J Nephrol 1999;19:527–9.
9. Hiroshige K, Soejima M, Yuu K, Muta T, Takasugi M, Kuroiwa A. Report of a patient with rheumatoid arthritis developing rapidly progressive glomerulonephritis associated with anti-glomerular basement membrane antibody and antineutrophil cytoplasmic antibody. Clin Exp Nephrol 1997;1:62–6.
10. D'amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med 1987;64:709–27.
11. Galla JH. IgA nephropathy. Kidney Int 1995;47:377–87.
12. Abuelo JG, Esparza AR, Matarese RA, Endreny RG, Carvalho JS, Allegra SR. Crescentic IgA nephropathy. Medicine 1984;63:396–406.
13. Roccatello D, Ferro M, Coppo R, Giraudo G, Quattrocchio G, Piccoli G. Report on intensive treatment of extracapillary glom-

erulonephritis with focus on crescentic IgA nephropathy. Nephrol Dial Transplant 1995;10:2054–9.
14. Ramirez SB, Rosen S, Niles J, Somers MJG. IgG antineutrophil cytoplasmic antibodies in IgA nephropathy: a clinical variant? Am J Kidney Dis 1998;31:341–4.
15. Shigematsu H, Kobayashi Y, Tateno S, Hiki Y, Kuwano S. Ultrastructural glomerular loop abnormalities in IgA nephritis. Nephron 1982;30:1–7.
16. Allmaras E, Nowack R, Andrassy K, Waldherr R, Van Der Woude F, Ritz E. Rapidly progressive IgA nephropathy with antimyeloperoxidase antibodies benefits from immunosuppression. Clin Nephrol 1997;48:269–73.
17. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis. Clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999;42:421–30.