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CASE REPORT

Myeloperoxidase-antineutrophil cytoplasmic antibody-related crescentic glomerulonephritis after treatment for clinically amyopathic dermatomyositis: a coincidental combination or not?

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Abstract A 60-year-old Japanese man exhibited rapidly progressive glomerulonephritis 10 years after receiving prednisolone therapy for clinically amyopathic dermatomyositis (CADM). Upon admission, there were no signs of dermatomyositis. Laboratory analyses revealed the presence of myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) at 1,280 EU in the absence of anti-glomerular basement membrane antibody and anti-melanoma differentiation-associated gene 5 antibodies, which are typically expressed in CADM. A renal biopsy demonstrated that 14 of 29 glomeruli showed global sclerosis, and the remaining 15 glomeruli exhibited fibrotic and fibrocellular crescent formation without immunoglobulin and complement. Following treatment with 500 mg/day methylprednisolone pulse therapy for 3 days, the patient was started on 30 mg/day of prednisolone orally. On the third day of hospitalization, we began hemodialysis for uremia and anuria with three treatments of plasma exchange starting on the tenth hospital day. Unfortunately, the patient's renal function did not recover, despite decreases in CRP and MPO-ANCA levels to the normal range. This case is the first English language report of MPO-ANCA-related crescentic glomerulonephritis in a patient who had recovered from CADM.

Keywords Crescentic glomerulonephritis · Clinically amyopathic dermatomyositis (CADM) · Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)

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Introduction

The incidence of crescentic glomerulonephritis in Japan is between 1,300 and 1,600 patients per a year [1]. Almost 40% of crescentic glomerulonephritis is pauci-immune type; myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) are seen in 80% of cases of pauci-immune type crescentic glomerulonephritis. Although MPO-ANCA can also be positive in a subset of patients with collagen diseases such as microscopic polyangiitis, systemic lupus erythematosus, and progressive systemic sclerosis, no patients with polymyositis/dermatomyositis (PM/DM) have been reported to express MPO-ANCA [2, 3]. Renal involvement in PM/DM is typically the result of acute tubular injury due to myoglobinuria from muscle destruction; glomerulonephritis is not commonly found in PM/DM [4].

This is the first English language case report demonstrating that MPO-ANCA-related crescentic glomerulonephritis occurred 10 years after treating clinically amyopathic dermatomyositis (CADM), a PM/DM subtype. Although this combination of conditions may be coincidental, we discuss the relationship between MPO-ANCA-related crescentic glomerulonephritis and CADM through a review of the literature.

Case report

A 60-year-old Japanese man was admitted to Aichi Medical University Hospital because of acute renal failure. Ten years prior to admission, he had been admitted to the Department of Dermatology for a heliotrope rash and positive Gottron's sign. He was diagnosed with amyopathic dermatomyositis based on no elevation in creatine phosphokinase, slightly elevated lactose dehydrogenase and

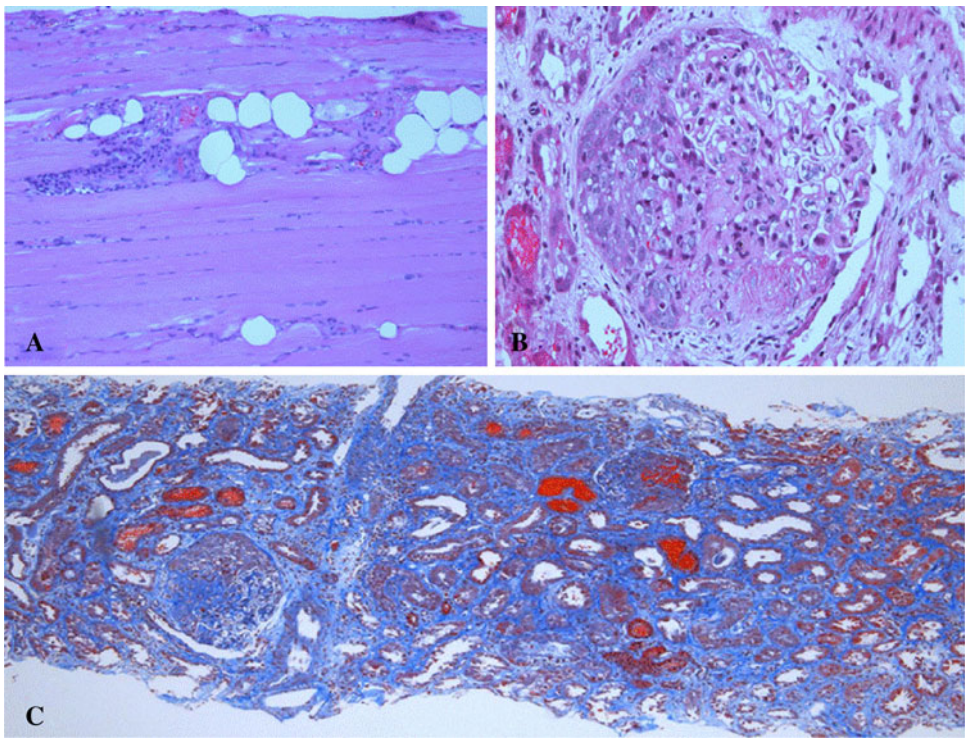

Fig. 1 **a** Light microscopic examination of a muscle biopsy specimen. No cellular infiltration into muscle fibers was observed, but there was a slightly increased number of cells surrounding the muscle cells (H&E, ×100). **b** Light microscopic examination of a kidney biopsy specimen. A fibrocellular crescent and segmental necrosis were observed in glomeruli (H&E, ×400). **c** Light microscopic examination of a kidney biopsy specimen. Fibrous crescent formation and severe interstitial fibrosis were observed (Masson trichrome, ×100)

aldolase, the absence of anti-Jo-1 antibodies, a muscle biopsy demonstrating no cellular infiltration into the muscle fibers, and a slightly increased number of cells surrounding the muscle cells (Fig. 1a); all are signs consistent with CADM. He was then treated with 40 mg/day of prednisolone. Chest and abdominal computed tomography (CT) scans and endoscopic examination of the upper and lower alimentary tracts did not reveal any malignancies. A urinalysis revealed no abnormalities. Although the prednisolone dose was tapered to 20 mg/day during his hospital stay, he decided to stop taking prednisolone after he was discharged. Two months prior to admission to our hospital, he visited a local physician because of fever, cough, diarrhea, and vomiting. At that visit, the patient was determined to have impaired kidney function. Two weeks before admission, he developed lower extremity edema. Upon admission, there were no signs of CADM and the patient had a normal mental status, height of 170 cm, and weight of 55 kg. His body temperature was 36.4°C, pulse was 60 beats/min and regular, respiratory rate was 15 breaths/min, and blood pressure was 162/84 mmHg. A physical examination revealed lower extremity edema. Chest and abdominal CT scans revealed no findings of interstitial pneumonia and indicated that both kidneys were swollen (Fig. 2). Laboratory studies indicated 3+ proteinuria, 3+ urine occult blood reaction with a white blood cell count (WBC) of 6,200/μL, red blood cell count (RBC) of 333×10^6/μL, 100 RBC/high-power field (HPF) and 3–4 WBC/HPF, hemoglobin of 10.0 g/dL, hematocrit of 28.7%, platelet count of 25.1×10^4/μL, albumin of 3.1 g/dL, blood urea nitrogen of 87.3 mg/dL, serum creatinine of 11.7 mg/dL, and total cholesterol of 131 mg/dL. His sodium was 137 mEq/L, potassium was 5.4 mEql/L, chloride was 104 mEq/L, aspartate aminotransferase was 5 U/L, and alanine aminotransferase was 9 U/L. His lactate dehydrogenase was 342 IU/L, creatine kinase was 144 IU/L, and C-reactive protein (CRP) was 1.7 mg/dL. MPO-ANCA were detected at 1,280 EU, and antinuclear antibody levels were 80-fold higher than normal (homogenous and speckled). Upon admission, his sera was negative for anti-glomerular basement membrane (GBM) antibodies, proteinase (PR3)-ANCA, hepatitis B antigen, hepatitis C virus antibodies, and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies. C3 and C4 levels were 76 mg/dL (normal range 65–135) and 32.2 mg/dL (normal range 13.0–35.0), respectively.

A renal biopsy demonstrated that 14 of 29 glomeruli had global sclerosis, and the remaining 15 glomeruli exhibited fibrotic and fibrocellular crescentic formation with segmental necrosis (Fig. 1b). Within the glomeruli, there was no increase in the number of mesangial cells. Furthermore, there were no findings of vasculitis. The observation of several shrinking glomeruli with irregular GBMs and moderate-to-severe patchy atrophy of interstitial areas with mononuclear cell infiltration and fibrotic changes suggested chronic ischemic changes (Fig. 1c). Immunofluorescence microscopy did not reveal any staining for immunoglobulin (Ig) G, IgM, IgA, C1q, C3, fibrinogen, κ, or λ.

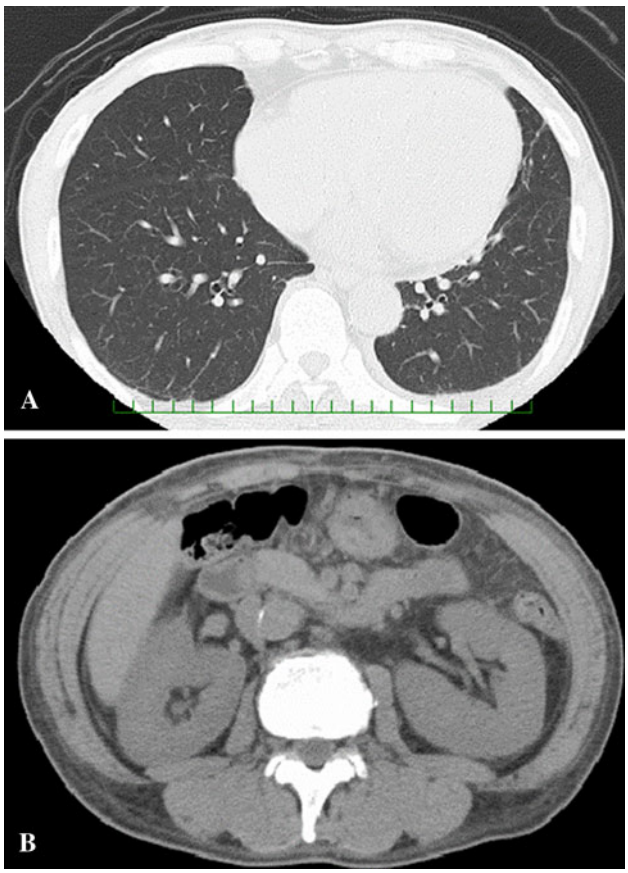

Fig. 2 **a** Chest CT scan. No findings of interstitial pneumonia were found. **b** Abdominal CT scan. Both kidneys were swollen but no signs of hydronephrosis were observed

Clinical course

We started the patient on 500 mg/day of intravenous methylprednisolone for 3 days because we suspected the patient had pauci-immune type crescentic glomerulonephritis based on the rapidly progressive glomerulonephritis. Following methylprednisolone pulse therapy, we administered 30 mg/day oral prednisolone. On the third day of hospitalization, we began hemodialysis for uremia and anuria and performed three treatments of plasma exchange beginning on the tenth hospital day. Unfortunately, the patient's renal function did not recover, despite decreases in CRP and MPO-ANCA levels into the normal range.

Discussion

PM and DM are idiopathic inflammatory myopathies that are relatively rare collagen diseases. In 1991, only 3,000 cases of each of these diseases had been reported in Japan; the number of patients per 0.1 million people is estimated at approximately six [5]. Recently, PM/DM was divided into four clinical subtypes; [1] polymyositis showing predominant muscle destruction without skin lesions, [2] typical dermatomyositis with skin and muscle damage, [3] hypomyopathic dermatomyositis, which is predominantly associated with skin lesions like the heliotrope rash on the eyelids and Gottron's sign on the joint surfaces, and displays only minimal destruction of muscles, and [4] amyopathic dermatomyositis, exhibiting skin lesions, but no muscle damage. The third and fourth subtypes are called CADM, because of the difficulty distinguishing between hypomyopathic and amyopathic dermatomyositis [6, 7].

An extensive review of the literature discovered two previous Japanese case reports (abstracts only) describing the combination of MPO-ANCA-related crescentic glomerulonephritis and CADM [8, 9] (Table 1). The first case was a 54-year-old woman who complained of multiple joint pain, muscle weakness, and periorbital heliotrope and Gottron's sign. She was diagnosed with dermatomyositis without anti-Jo-1 antibodies 3 years prior to admission. Oral prednisolone improved the clinical signs. She was admitted to hospital because of proteinuria, hematuria, and impaired kidney function. Upon admission, she did not show clinical signs of dermatomyositis. A laboratory test revealed a high MPO-ANCA titer at 420 EU, and a kidney biopsy demonstrated that half of the remaining glomeruli had crescent formation. Methylprednisolone pulse therapy ameliorated the proteinuria and hematuria, but unfortunately her kidney function did not recover [8]. The second case was a 39-year-old woman who received oral prednisolone based on a diagnosis of dermatomyositis 10 years before admission. Two years and 5 months prior to admission, she complained of arthralgia. One year and 8 months before admission, a urinary abnormality was detected, and she was treated with 10 mg/day of prednisolone based on the fact that she had an MPO-ANCA level of 149 EU at 18 months before admission. One month prior to admission, her kidney function rapidly declined, as evidenced by serum creatinine levels of 2.2 mg/dL. A kidney biopsy revealed pauci-immune-type crescentic glomerulonephritis, even though her MPO-ANCA titer was within the normal range. Methylprednisolone pulse therapy, plasma exchange, and hemodialysis did not improve her kidney function [9]. A comparison of our case with those two cases indicated those patients also developed MPO-ANCA-positive crescentic glomerulonephritis several years after diagnosis and treatment for dermatomyositis; both also exhibited poor prognosis for the recovery of kidney function as seen for our patient. Our patient, however, differed from the previous patients by being of male gender and having CADM without muscle damage. Further accumulation of similar cases will help reveal the

Table 1 Case reports describing the combination of MPO-ANCA-related crescentic glomerulonephritis and dermatomyositis

References	Age/sex	The onset of DM before RPGN (years)	Therapy for DM	Signs of RPGN	Titers of MPO-ANCA	Outcome
Kushihata et al. [8][a]	54/F	3	Oral PSL	Proteinuria, hematuria, impaired kidney function	420 EU	Chronic renal failure
Iwabuchi et al. [9][a]	39/F	10	Oral PSL	Arthralgia, Proteinuria, hematuria, impaired kidney function	149 EU	Hemodialysis
Present case	60/M	10	Oral PSL	Fever, cough, proteinuria, hematuria, impaired kidney function	1,280 EU	Hemodialysis

DM dermatomyositis, *PSL* prednisolone, *RPGN* rapidly progressive glomerulonephritis

[a] Japanese abstract

relationship between MPO-ANCA-related crescentic glomerulonephritis and CADM.

CADM, a subtype of PD/DM, was reported by Sato et al. [10] to be associated with a specific autoantibody against a 140-kDa protein, namely anti-CADM-140 antibody. Thirty percent of ani-CADM-140 antibody-positive patients also exhibit progressive interstitial pneumonia. This autoantibody reacts with an RNA helicase encoded by MDA5 [11, 12]. Our patient, however, did not express an anti-MDA5 antibody.

Gunawardena et al. [13] later demonstrated that an autoantibody to a 140-kDa protein (p140) seen in juvenile dermatomyositis is associated with calcinosis. This antibody is identical to anti-NXP-2 antibody, previously named anti-MJ antibody. Patients with anti-NXP-2 antibodies typically exhibit juvenile onset of DM, are more likely to live in the United States of America or Argentina, have chronic and relapsing type disease, and sometimes show an associated vasculitis [14, 15]. There is no detailed information, however, concerning the incidence of vasculitis and other autoantibodies, such as ANCA. In this case report, we could not analyze serum levels of anti-p140 or NXP-2 antibodies. It remains unclear if additional autoantibodies are present in CADM and in this patient in particular.

This is the first English language case report demonstrating the development of MPO-ANCA-related crescentic glomerulonephritis several years after the patient recovered from CADM. Although a coincidental combination cannot be ruled out, an accumulation of similar case reports will support a related pathogenesis.

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Conflict of interest None declared.

References

1. Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol. 2009;13:633–50.
2. Merkel PA, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. Ann Intern Med. 1997;126:866–73.
3. Chikazawa H, Nishiya K, Matsumori A, Hashimoto K. Immunoglobulin isotypes of anti-myeloperoxidase and anti-lactoferrin antibodies in patients with collagen diseases. J Clin Immunol. 2000;20:279–86.
4. Venkataseshan VS, Grishman E. Other collagen disease relapsing polychondritis, acute rheumatic fever, and polymyositis/dermatomyositis. In: Grishman E, Churg J, Needle MA, Venkataseshan VS, editors. The kidney in collagen vascular diseases. New York; Raven Press; 1993. p. 189–211.
5. http://www.nanbyou.or.jp/english/index.htm (2011). Accessed 18 March 2011
6. Sontheimer RD. Cutaneous features of clinical dermatomyositis and amyopathic dermatomyositis. Curr Opin Rheumatol. 1999;11:475–82.
7. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol. 2002;46:626–36.
8. Kushihata S, Hirabayashi A, Yorioka N. ANCA-related glomerulonephritis during dermatomyositis. Jpn J Nephrol. 1999;41:567 (Japanese abstract).
9. Iwabuchi M, Arakawa M, Hanakama M, Sasaki Y. MPO-ANCA related glomerulonephritis at ten years after dermatomyositis. Jpn J Nephrol. 2003;45:534 (Japanese abstract).
10. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2005;52:1571–6.
11. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2009;60:2193–200.
12. Hoshino K, Muro Y, Sugiura K, Tomita Y, Nakashima R, Mimori T. Anti-MDA5 and anti-TIF1γ antibodies have clinical significance for patients with dermatomyositis. Rheumatology. 2010;49:1726–33.

13. Gunawardena H, Wedderburn LR, Chinoy H, Betteridge ZE, North J, Ollier WER, et al. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. Arthritis Rheum. 2009;60:1807–14.
14. Oddis CV, Fertig N, Goel A, Espada G, Confalone Gregorian M, et al. Clinical and serological characterization of the anti-MJ antibody in childhood myositis. Arthritis Rheum. 1997;40(Suppl 9):S139 (abstract).
15. Espada G, Confalone Gregorian M, Ortiz Z, Fertig N, Londino AV, Oddis CV, et al. Serum autoantibodies in juvenile idiopathic inflammatory myopathies (IIM) in a cohort of Argentine patients. Arthritis Rheum. 1997;40(Suppl 9):S140 (abstract).