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CASE REPORT

Diffuse proliferative glomerulonephritis associated with dermatomyositis with nephrotic syndrome

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Abstract We described a 44-year-old man developing dermatomyositis (DM) and nephrotic syndrome (NS). Renal biopsy revealed diffuse proliferative glomerulonephritis (DPGN) with depositions of immunoglobulin and complements. A combination therapy of steroid and cyclophosphamide (CTX) was found very effective for the patient. Chronic glomerulonephritis is rare in DM. In our review of related literature, membranous glomerulonephritis (MN) is the main type of glomerular lesion, another type is mesangial proliferative glomerulonephritis (mesPGN). Here we reported a case of DM associated with DPGN developing NS, which was not found in existing literature. Although glomerulonephritis is uncommon in patients with DM, renal pathology is not as simplex as previously thought, and treatment with steroid or/and cytotoxic drugs is favorable for prognosis.

Keywords Dermatomyositis · Glomerulonephritis · Nephrotic syndrome · Treatment

Introduction

Dermatomyositis (DM) is an autoimmune disease with proximal muscle involvement and typical skin lesion. Five criteria have been put to help the diagnosis of DM. These criteria refer to a progressive, proximal and symmetrical weakness, an increased concentration of muscle enzymes, an abnormal electromyogram accompanied with an abnormal muscle biopsy result and finally a characteristic cutaneous lesion [1]. Nonmuscular and nondermatologic manifestations of DM may take several forms, including pulmonary, cardiac and alimentary tract involvement. In contrast to other autoimmune diseases such as systemic lupus erythematosus (SLE), sjogren syndrome (SS) or systemic sclerosis (SSc), DM seldom cause renal damage. One manifestation of renal involvement is acute tubular necrosis caused by myoglobulinemia and myoglobulinuria. Another is chronic glomerulonephritis [2]. Herein we report a patient who concurrently developed DM and glomerulonephritis with a rare pathological type. In addition, we discussed the association of DM with glomerulonephritis and treatment strategy for this condition.

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Case report

A 44-year-old male presented in May 2007 complaining of having papules and macules over the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and elbow joints. He also had myalgia in both his lower limbs as well as arthralgia in shoulder, elbow and wrist joints. After meloxicam therapy (15 mg/day for 35 days) in a local hospital, his myalgia and arthralgia improved slightly. However, the rash aggravated. In July 2007, He developed edema and proximal muscle weakness in both upper and lower limbs, which impair specific tasks such as getting up from a sitting position and reaching overhead or combing the hair. One month later, violaceous rash appeared on his face, trunk, neck and scalp. He also had dysphagia and occasionally aspirate oral contents. He was then referred to our hospital on 17 August.

On admission, his temperature was 37°C, pulse 75/min, and blood pressure 120/75 mmHg. Physical examination

revealed heliotrope rash on his upper eyelids, cheeks, scalp and trunk, pitting edema of lower extremities, macules over bilateral MCP, PIP and elbow joints suggesting Gottron's lesion. The muscle strength of neck muscles, deltoid muscles, femoral muscles was grade II, grade III, grade II, respectively. Arthritis was not found.

Laboratory studies performed at admission showed mild anemia with red blood cell count of 2.31×10^{12}/L and hemoglobin of 99 g/L. Blood platelets and white blood cell count were normal. The creatine phosphokinase (CPK), aminotransferase (AST), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH) increased up to 3,039, 254, 271, 476, 619 IU/L, respectively. Serum albumin level was low (16.5 g/L). Serum creatinine and urea nitrogen were within normal limits. Hyperlipidemia was confirmed with the help of increased blood level of triglyceride (2.46 mmol/L), low-density lipoprotein (3.86 mmol/L) and very low-density lipoprotein (0.66 mmol/L). The serum myoglobin level was normal, and myoglobinuria was not noted. All auto-antibodies examined were negative. Complements C_3, C_4 in serum decreased to 0.45 and 0.09 g/L, respectively. Urinalysis suggested scores of 4+ for protein, and the urinary sediment contained five red cells, 8–13 white cells, and no cast per highpower field. The urinary protein excretion level was 3.88 g/24 h. Electromyographies of the deltoid and rectus femoris muscle showed myogenic patterns with polyphasic potentials and increased insertional activity and fibrillation. An open biopsy of the right deltoid muscle revealed necrosis and regeneration of fibers, and infiltration of lymphocytes in endomysium and perimysium. On the basis of these data, he was diagnosed as having DM and NS. A percutaneous renal biopsy was performed on the tenth day of admission. One of 18 glomeruli obtained showed global sclerosis under light microscopy. 12 of them showed hyperplasia of mesangium, endothelium and epithelium. Basement membrane thickened irregularly, and part of glomeruli were infiltrated by neutrophils (Fig. 2a). With Masson staining, Fuchsins-

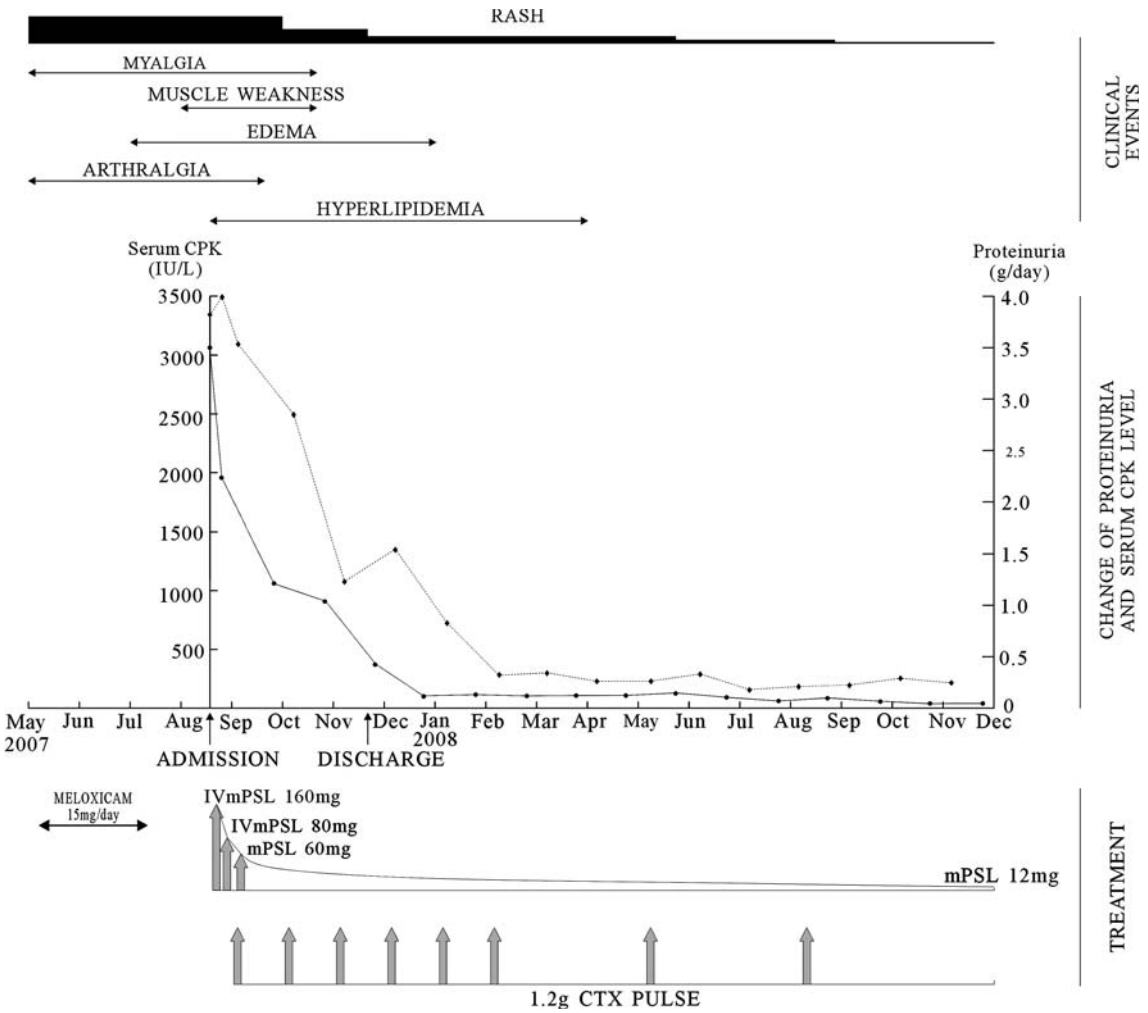

Fig. 1 Clinical course. In coordinate system, *solid line* shows changes of serum CPK level. *Broken line* shows changes of proteinuria. *IVmPSL* intravenous methylprednisolone, *CTX* cyclophosphamide

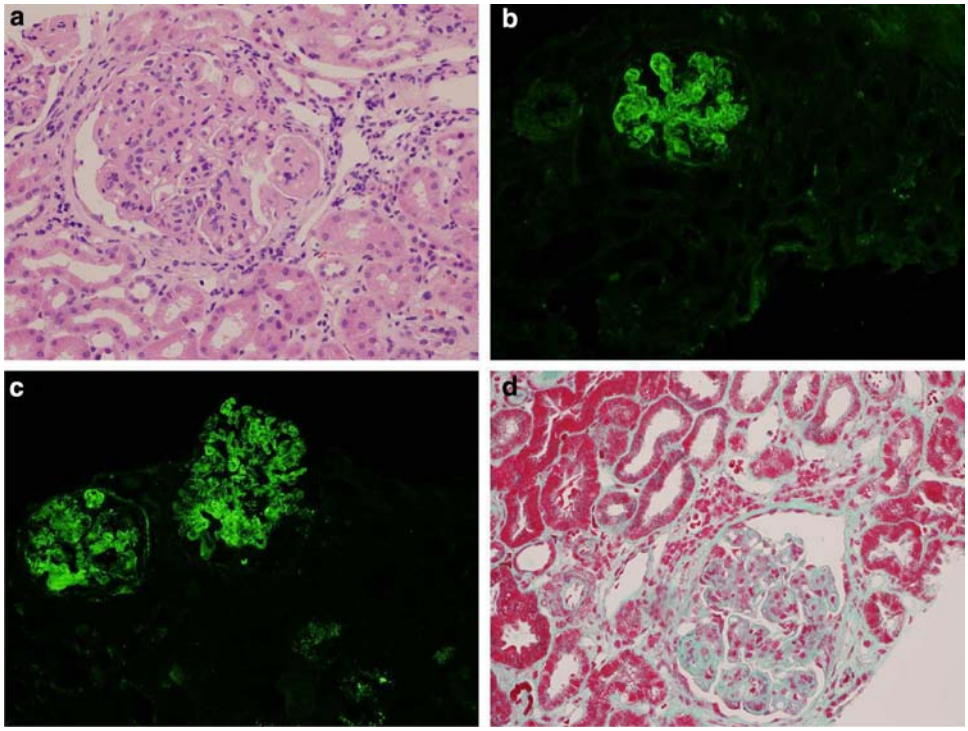

Fig. 2 Renal pathology. **a** Light microscopy revealing hyperplasia of mesangium, endothelium and epithelium, and thickening of basement membrane (PASM; ×400). **b**, **c** Direct immunofluorescence staining showing proliferative deposits of IgG and C_3 both in mesangium and capillary wall (×200). **d** Masson staining showing Fuchsins-addicting deposits under epithelium, endothelium and within basement membrane (×400)

addicting deposits were detected under epithelium, endothelium and within basement membrane (Fig. 2d). Tubules showed mild degeneration, with protein casts in individual lumens. Part of interstitium was infiltrated by lymphocytes. The Immunofluorescent microscopy revealed five glomeruli with 1 + IgG and 2 + C_3/C_{1q} both in mesangium and capillary wall (Fig. 2b, c). These findings led to the diagnosis of diffuse proliferative glomerulonephritis (DPGN) with depositions of immune complexes.

From the fifth day of admission, we administered 160 mg/day intravenous methylprednisolone (IVmPSL) for 5 days, CPK level decreased to 1598 IL/L, myalgia and muscle weakness improved slightly. We administrated a second course of 80 mg/day IVmPSL for 10 days. His muscle enzymes levels gradually decreased, while proteinuria remained the same level (3.52 g/day). Thus, 1.2 g/month intravenous cyclophosphamide (CTX) was started to treat glomerulonephritis, and followed by 60 mg/day oral mPSL for one and a half-month. After 8 weeks of steroid therapy, the serum levels of CPK, as well as other muscle enzymes recovered to the normal range. Myalgia and muscle weakness disappeared. The skin rash discolored, with scaly lesion over the MCP, PIP and elbow joints. The patient was discharged on 19 November 2007. Decrement of mPSL dosage started. Moreover, the amount of proteinuria decreased to 0.35 g/day after 6 months of pulse CTX therapy. Then CTX was administrated every 3 months intravenously at the same dosage and stopped in August 2008. He was further followed up to December 2008. Exacerbation was not noted. Figure 1 summarises the clinical course of this patient.

Discussion

Renal involvement in DM is uncommon. Similar to polymyositis (PM) that is congeneric with DM, two reasons contribute to renal damage. One is tubular disorder caused by myoglobulinemia and myoglobulinuria following acute rhabdomyolysis. Another is chronic glomerulonephritis, which is more uncommon than tubular lesion [2].

To date, only seven cases of pathology-proven glomerulonephritis associated with DM, including one child, have been reported [3–9]. Table 1 summarises the clinical features of these patients. Four of them suffered from DM and glomerulonephritis concurrently, and the rest three had glomerulonephritis 1.5, 2, 9 years after the diagnosis of DM, respectively. All adult patients had varying degree of proteinuria with urine protein > 1 g/day. Percutaneous renal biopsy revealed MN in five patients and mesPGN in two. Nearly all had positive immunofluorescence findings for immunoglobulin and complements. Unlike DM, however, most PM patients with glomerulonephritis had a pathological diagnosis of mesPGN, others were diagnosed as MN, focal glomerulonephritis (FGS), Crescentic glomerulonephritis or Lipoid nephrosis. Moreover, majority of PM had no depositions of immunoglobulin and complements in kidneys [10–15]. This phenomenon suggests that DM and PM may have different immunopathological mechanisms.

Table 1 Clinical features of eight patients with dermatomyositis with glomerulonephritis

Case	1	2	3	4	5	6	7	This patient
Reference	Fukui et al. [3]	Moriyama et al. [4]	Makino et al. [5]	Picco et al. [6]	Akashi et al. [7]	Yen et al. [8]	Soylu et al. [9]	
Age/sex	37/M	46/F	35/M	16/M	43/F	26/F	10/M	44/M
Onset	Concurrent	Concurrent	2 years after DM	Concurrent	9 years after DM	1.5 years after DM	Concurrent	Concurrent
Proteinuria (g/day)	2.5	1.0	2.4	2.5	9.3	5.1	ND	3.9
Pathological findings	MN (with IgG, IgA)	MN (with IgG)	MN (with IgG, IgA, C_3, C_{1q})	MesPGN (with IgM, C_3)	MN (with IgG, C_3)	MesPGN (with IgA, C_3)	MN (with IgA, IgG, C_{1q})	DPGN (with IgG, C_3, C_{1q})
Treatment	Steroid	Steroid	Steroid	Steroid AZA	Steroid	Steroid AZA	Steroid	Steroid CTX
Outcome	Improved	Improved	Improved	Improved	Improved	Improved	Improved	Improved

DM dermatomyositis, *MN* membranous glomerulonephritis, *mesPGN* mesangial proliferative glomerulonephritis, *DPGN* diffuse proliferative glomerulonephritis, *AZA* azathioprine, *CTX* cyclophosphamide, *ND* not described

In our patient, what attracted us most were his pathological findings as DPGN and clinical course as NS, which have not been noted in literature. Generally thinking, DPGN is commonly seen in lupus nephritis (LN) and seldom seen in other autoimmune diseases, especially in DM. Kilani reported a patient with overlap syndrome (SLE + DM) had DPGN. He attributed this pathological finding to LN [16]. It is interesting to note that we had no concrete evidence of SLE during a long-term follow up in our patient. This strongly indicated that DPGN was associated with DM. In addition, immunopathological mechanism similar to SLE in a certain degree may elucidate the coexistence of DM and DPGN. DM is believed to be the result of a humorally mediated immune process, in which complement is activated, and complement deposits attack the microvascular endothelium in muscles and deplete muscle capillaries, in turn, leads to characteristic myopathological changes. Thus, it is not surprising that this process occurs in other organs, including the lungs, heart, gastrointestinal tract and kidneys [17]. When kidneys are involved, the complement mediated reaction is quite similar to that in LN, and may attack the glomerular membrane and break the protective mechanism of capillaries. In DM, the serum levels of complements are almost in normal range. In our patient, however, complements C_3, C_4 decreased remarkablely, suggesting a violent immunologic process, in which immune complex consumed complements in peripheral blood and invaded mesangium, basement membrane and endothelium in an extensive way. As a result, renal lesion in this patient appeared to be diffused and led to the diagnosis of DPGN. However, possibility of coexistence of latent SLE cannot be ruled out yet. In fact, Characteristic manifestation of SLE may show up after the onset of DM. Due to similar treatment both in DM and SLE, steroid or CTX therapy may cover the clinical and laboratory evidence of SLE. Therefore, this patient needs a further follow-up.

All patients in literature accepted steroid therapy. Two of seven accepted cytotoxic drugs. As a whole, they survived and had a favorable outcome [3–9]. Glomerulonephritis in our patient responded poorly to steroid, indicating an individual difference in steroid control of glomerulonephritis. Application of cytotoxic drugs in early stage, such as CTX pulse in this patient, is helpful for prognosis.

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