CASE REPORT

Anti-glomerular basement membrane disease accompanied by systemic lupus erythematosus presenting central nervous system involvement

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Abstract We report a case of rapidly progressive glomerulonephritis caused by anti-glomerular basement membrane (GBM) disease accompanied by systemic lupus erythematosus (SLE) presenting central nervous system involvement in a 32-year-old Japanese male. He was admitted to our hospital because of a 3-week history of fever and rapidly failing renal function requiring hemodialysis (HD). Laboratory tests showed anti-GBM antibody elevation with a value of 16,385 units/ml. On day 85, he had generalized tonic-clonic seizure. Brain magnetic resonance T2 Flair imaging showed multiple high intensity lesions in a broad area. We made a diagnosis of central nervous system involvement in SLE based on positivity for antinuclear and anti-DNA antibodies, hypocomplementemia, and discoid skin rash. After combined therapy consisting of plasma exchange, HD, and steroid pulse, the patient made a good recovery without any residual neurological sequelae, though kidney dysfunction requiring maintenance HD remained. Anti-GBM antibody finally became undetectable on the 144th hospital day.

Keywords Rapidly progressive glomerulonephritis · Anti-glomerular basement membrane disease · Systemic lupus erythematosus

Introduction

Coexistence of anti-glomerular basement membrane (GBM) disease and systemic lupus erythematosus (SLE) is a rare entity. We present a case of rapidly progressive glomerulonephritis caused by anti-GBM disease accompanied by SLE presenting central nervous system involvement.

Case report

A 32-year-old Japanese male was admitted to our hospital with a 3-week history of fever and rapidly failing renal function requiring hemodialysis (HD). He had a history of acute pericarditis with high fever, abnormal ECG change and no signs of viral infection 5 years ago. He had recovered by receiving only nonsteroidal anti-inflammatory drug (NSAID). At that time, laboratory tests had showed the positivity of antinuclear antibody ($\times 320$, homogenous, speckled, and nucleolar pattern). On admission, laboratory tests showed anti-GBM antibody elevation with a value of 16,385 units/ml (Table 1). There were no urinalysis data because of anuria. The patient's C-reactive protein concentration was elevated (16.45 mg/dl). An immunological test also showed that the patient was positive for antinuclear antibody ($\times 640$, homogenous pattern) and anti-double stranded DNA antibody (14.9 International Units/ml). Anti-Sm and anti-cardiolipin antibodies, lupus anticoagulant were negative. The direct coombs test was positive. PA-IgG was slightly elevated (41.4 ng/ 10^7 PL). A physical examination revealed no significant abnormalities. Computed tomography scanning showed no pulmonary bleeding, atrophy in the kidney, or hydronephrosis (Fig. 1). The renal biopsy obtained 12 glomeruli. Histological examination of glomeruli showed 0 % of global sclerosis, 92 % (11/12) of crescent and formation of

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Table 1 Laboratory tests

(CBC)		BUN	57.6 mg/dl	Anti-GBM	16,385 U/ml
WBC	11,000/ μ l	Cr	12.4 mg/dl	MPO-ANCA	(–)
RBC	315×10^4 / μ l	UA	6.4 mg/dl	PR3-ANCA	(–)
Hb	8.9 g/dl	Na	130 mEq/l	ANA	640 (homogeneous)
Plt	22.5×10^4 / μ l	K	4.5 mEq/l	Anti-DNA (ds)	14.9 IU/ml
		Cl	99 mEq/l	Direct coombs	(+)
		Ca	7.1 mg/dl	Anti-Sm	(–)
		CRP	16.45 mg/dl	Anti-cardiolipin	(–)
		HbA1c	6.0 %	Lupus anticoagulant	(–)
(Biochemistry)				PA-IgG	41.4 ng/ 10^7 PL
TP	5.6 g/dl	(Immunity)			
Alb	1.8 g/dl	IgG	1836 mg/dl		
T-Bil	0.5 mg/dl	IgA	293 mg/dl		
AST	34 IU/l	IgM	52 mg/dl		
ALT	33 IU/l	C3	105 mg/dl		
LDH	165 IU/l	C4	16.8 mg/dl		
T-chol	102 mg/dl	CH50	31 U/ml		
TG	99 mg/dl	Cryoglobulin	(–)

Fig. 1 Computed tomography scanning showed pleural fluid and no pulmonary bleeding (a), atrophy in the kidney or hydronephrosis (b)

granuloma. There were also prominent tubulointerstitial damages. Immunohistochemistry showed linear deposition of IgG on the GBM. Anti-IgA, IgM, C4, C1q staining were

negative, and anti-C3 staining was weakly positive in glomeruli. On the other hands, the immunostaining in the tubular basement membrane was negative for IgG, IgM, IgA, C3, C4 and C1q. Electron microscopic study showed foot process fusion and wrinkling of the GBM without accumulation of electron-dense deposits (Fig. 2). We made a diagnosis of rapidly progressive glomerulonephritis (RPGN) caused by anti-GBM disease and initiated intravenous methylprednisolone pulse therapy following oral corticosteroid administration and plasma exchange. The patient had blood coagulation during hemodialysis, and had arteriovenous fistula thrombosis 1 week after the initiation of hemodialysis using heparin as anticoagulant. Because of the high level of heparin-induced thrombocytopenia (HIT) antibody, we diagnosed him as HIT. Therefore, we had to switch the anticoagulant from heparin to argatroban. The anti-GBM antibody level gradually decreased. On the 85th hospital day, however, he had generalized tonic-clonic seizure suddenly. There were no premonitory signs such as high fever and headache. Laboratory data showed thrombocytopenia (3.3×10^4 / μ l) and hypokalemia (3.1 mEq/l). C-reactive protein and white blood cell were not elevated. Brain magnetic resonance T2 Flair imaging showed multiple high intensity lesions in a broad area (Fig. 3a). Hypocomplementemia and discoid skin rash (Fig. 4) were also shown. The cerebrospinal fluids indicated that the pressure was 33 cmH₂O and <1 cells, protein was 87 mg/dl, glucose was 51 mg/dl. The culture of fluids was negative. We made a diagnosis of central nervous system involvement in SLE based on positivity for both antinuclear and anti-DNA antibodies, hypocomplementemia, a history of pericarditis, and discoid skin rash. We resumed methylprednisolone pulse therapy and plasma exchange. We did not use cyclophosphamide because he did not want to lose

Fig. 2 Histological examination of a kidney biopsy specimen showed cellular crescents and formation of granuloma (*arrow*) (**a**, PAS staining) with linear deposition of IgG (**b**, immunofluorescence staining). Electron microscopic study showed foot process fusion and wrinkling of the GBM without accumulation of electron-dense deposits (**c**)

his reproductive function. He did not have a recurrence of seizure and his neurological abnormal findings rapidly improved. The high intensity lesions on brain MRI had almost disappeared on the 112th hospital day (Fig. 3b). He generally had a good recovery, though kidney dysfunction requiring

Fig. 3 Findings of head MRI on the day of generation of tonic-clonic seizure (**a**). T2 flair image showed multiple high intensity areas. After combined methylprednisolone pulse therapy and plasma exchange, the abnormal findings improved (**b**)

Fig. 4 The picture of discoid skin rash on the 85th hospital day

maintenance HD remained. Plasma exchange was performed 24 times over a period of 4 months. Anti-GBM antibody finally became undetectable on the 144th hospital day (Fig. 5).

Discussion

Cases of anti-GBM disease accompanied by SLE are seldom confirmed. There have been only a few cases in Japan. In those cases, it was assumed that the precedence of lupus nephritis exposed GBM antigens and caused secondary production of anti-GBM antibody. The diagnosis of SLE

Fig. 5 Clinical course

was based on a history of noninfectious pericarditis, positivity of antinuclear and anti-dsDNA antibodies, generated seizure, and discoid skin, despite lack of typical symptoms, such as malar rash, photosensitivity, or arthritis. Because of preceding pericarditis, we speculated that SLE preceded anti-GBM disease in our case. Since formation of granuloma was shown by histological examination, we first considered RPGN associated with anti-neutrophil cytoplasmic antibodies (ANCA). However, because ANCA was negative both by ELISA and by indirect immunofluorescence, we regarded granuloma as a nonspecific finding. According to a report from China, the eight percent of 157 patients with SLE were positive for anti-GBM antibody and all of those patients had nephritis. In that study, only two cases showed neuropsychiatric manifestation [1]. It has been reported that the DNA allele in anti-GBM disease or SLE showed HLA-DRB1*15:01 in Japanese patients [2]. Interestingly, there was one report of identical twins having anti-GBM nephritis and SLE, respectively, and both had homozygotes in HLA-DRB1*15:01 [3]. However, our patient's allele showed HLA-DRB1 08:03:03/09:01:02, not 15:01. The common mechanism of anti-GBM disease and SLE has remained unknown, but kallikrein gene abnormalities in the pathogenesis of each disease were suggested by results of in vitro and genome-wide association studies [4]. It has also been shown that anti-GBM disease and lupus nephritis did not occur in kallikrein gene-transduced models [5]. In conclusion, we experienced a case of anti-GBM disease accompanied by SLE presenting central nervous system involvement. Combination therapy

consisting of plasma exchange, HD, and steroid pulse therapy was effective.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient.

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