Successful treatment of severe crescentic lupus nephritis by multi-target therapy using tacrolimus and mycophenolate mofetil

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Abstract Treatment of severe lupus nephritis (LN) has been controversial, and according to recent guidelines and recommendations, cyclophosphamide still remains a first-line therapy. Herein, we present the case of a 37-year-old female patient who developed rapidly progressive glomerulonephritis, which was histologically diagnosed as class IV + V LN, with a large number of cellular to fibrocellular crescents (62 % of glomeruli). Although the patient was considered to have the most severe form of LN, complete remission was achieved within 6 months by multi-target therapy using tacrolimus and mycophenolate mofetil combined with methylprednisolone pulse therapy. Our experience suggests that multi-target therapy could be a potential treatment option for patients with severe crescentic LN.

Keywords Crescentic lupus nephritis · Multi-target therapy · Mycophenolate mofetil · Lupus nephritis · Tacrolimus

Introduction

Based on the results of several randomized controlled trials in the last decade, recent guidelines and recommendations have identified mycophenolate mofetil (MMF) and cyclophosphamide (CYC) as the immunosuppressive agents of

first choice for the induction or initial therapy of active proliferative LN (class III or IV) [1–4]. On the other hand, the treatment of severe crescentic LN still remains controversial, although CYC is widely used despite the lack of firm evidence [5].

Several years ago, Bao et al. [6] reported the efficacy and safety of multi-target therapy using tacrolimus (TAC) and MMF for induction therapy of class IV + V LN, which is often resistant to conventional CYC therapy. They conducted a randomized controlled study and reported that a high complete remission rate was achieved with multi-target therapy as compared to intravenous CYC (IVCY) therapy. The complete remission rates obtained with multi-target therapy vs. IVCY were 50 vs. 5 % at 6 months and 65 vs. 15 % at 9 months. Recently, we also demonstrated that multi-target therapy was effective in inducing early remission and in yielding a high remission rate in patients with active class III to V LN, including those with mixed membranous and proliferative LN [7].

Here, we present in detail the case of a patient with LN who was enrolled in a retrospective study of multi-target therapy reported previously [7]. Although the patient had crescentic class IV + V LN and showed rapid deterioration of renal function, complete remission was achieved within 6 months by multi-target therapy combined with methylprednisolone (mPSL) pulse therapy.

Case report

A 37-year-old female with a 24-year history of systemic lupus erythematosus (SLE) was admitted to our hospital in September 2011 with nephrotic syndrome and rapidly progressive renal dysfunction. She had been diagnosed as having SLE in 1987, based on the presence of a malar rash,

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photosensitivity, joint pain, leukopenia and seropositivity for antinuclear antibody (ANA) and anti-double-strand (ds) DNA antibody and was under treatment with glucocorticoids. She had experienced a flare and was receiving treatment with oral CYC (50 mg/day), followed by azathioprine (AZA 50 mg/day) for some length of time. One year before her admission in 2011, the dose of prednisolone (PSL) had been increased from 10 to 25 mg/day and TAC (3 mg/day) had been added due to the detection of decreased CH50 levels and increased anti-dsDNA antibody

titers. Although partial response was obtained, the serological activity increased again following reduction of the PSL dose to 10 mg/day. In addition, increase of the serum creatinine (Cr) was also observed from 0.60 mg/dl at 4 months before admission to 1.10 mg/dl at 2 weeks before admission, associated with massive proteinuria.

At admission, the patient's body temperature was 37.3 °C and blood pressure was 144/95 mmHg. She had facial puffiness and edema of the lower extremities. The laboratory data were as follows: hemoglobin level 10.0 g/

Fig. 1 Renal pathology. **a**, **b** Light-microscopic findings showing severe endocapillary proliferation and crescents (indicated by *arrows*, **a** periodic acid-Schiff staining, original magnification $\times 100$, **b** hematoxylin–eosin staining $\times 400$). **c** Immunofluorescence staining for C1q. Fine granular stainings are observed, mainly along the glomerular capillary walls (original magnification $\times 400$). **d**, **e** Electron-microscopic findings showing both subepithelial (indicated by *arrowheads*) and subendothelial deposits (indicated by *arrows*) (original magnification, **d** $\times 2,500$, **e** $\times 15,000$)

dl, white blood cell count 7,200/ μ l, lymphocytes 960/ μ l, platelets 74,000/ μ l, serum total protein 4.7 g/dl, serum albumin 1.5 g/dl, serum Cr 1.36 mg/dl, estimated glomerular filtration rate (eGFR) 36.3 ml/min/1.73 m², serum C-reactive protein (CRP) 0.81 mg/dl, antinuclear antibody 1:40, anti-dsDNA antibody 86 IU/ml (normal, 0–12), anti-Sm antibody 72.5 U/ml (normal, negative), serum CH50 10.8 U/ml (normal, 30.0–46.0), serum C3 41.0 mg/dl (normal, 65–135), and serum C4 5.4 mg/dl (normal, 13–35). Serum tests for anti-myeloperoxidase antibody, anti-proteinase 3 antibody and anti-glomerular basement membrane antibody were negative. The urinary protein excretion was 10.8 g/g Cr. Examination of the urinary sediment showed more than 200 red blood cells (RBCs) per high-power field, together with oval fat bodies, RBC casts and granular casts. X-ray and ultrasound examinations revealed no evidence of pleural/pericardial effusion or ascites.

On the day after admission, a renal biopsy was performed. Thirteen glomeruli were obtained and severe endocapillary proliferation was observed in all the glomeruli. Mainly cellular and some fibrocellular crescents were also observed in 8 out of the 13 glomeruli, together with focal tubulointerstitial infiltration (Fig. 1a, b). Immunofluorescence staining showed diffuse granular deposits of IgG, IgA, IgM, C3, C4 and C1q along the glomerular basement

membrane (Fig. 1c). Electron-microscopic examination revealed both subepithelial and subendothelial deposits and segmental spike formation (Fig. 1d, e). Based on the findings, the patient was diagnosed as having class IV-G (A) + V LN with severe crescent formation.

Intravenous mPSL pulse therapy (500 mg/day, 3 days; 2 times with a 1-week interval between the pulses) was administered, followed by oral PSL (45 mg/day; 1 mg/kg/day) and MMF (1,000 mg/day) therapy. The dose of MMF was determined according to the original protocol of multi-target therapy by Bao et al. [6]. Administration of TAC (3 mg/day) was continued. As shown in Fig. 2, the serum Cr peaked to 1.83 mg/dl at 10 days after the initiation of the mPSL pulse therapy, followed by a gradual decrease. Reduction of proteinuria was also observed. However, 3 weeks after the mPSL pulse therapy, the patient developed pancytopenia. Because the cytomegalovirus (CMV) pp65 antigenemia test was positive (10 cells/150,000 WBC), the dose of MMF was reduced and the drug was discontinued, and ganciclovir was administered until the CMV antigenemia became negative. Subsequently, MMF was reintroduced at 0.5 g/day (Fig. 2).

Complete remission was achieved (urinary protein excretion <0.5 g/g Cr and urinary RBC <5 cells/hpf) at 6 months after the initiation of the induction therapy, together with improvement of the renal function,

Fig. 2 Clinical course after admission. *mPSL* methylprednisolone, *PSL* prednisolone, *TAC* tacrolimus, *MMF* mycophenolate mofetil, *AZA* azathioprine, *GCV* ganciclovir, *CMV* cytomegalovirus, *LN* lupus nephritis, *U-Pro* urinary protein, *anti-dsDNA* anti-double-strand DNA antibody

normalization of CH50 levels and decreased levels of anti-dsDNA antibody. MMF was subsequently switched to AZA (50 mg/day). In April 2014, the patient was receiving maintenance therapy with PSL, TAC and AZA, and remained in complete remission: urinary protein 0.12 g/g Cr, urinary RBC 3 cells/hpf, serum Cr 0.62 mg/dl, and eGFR 83.9 ml/min/1.73 m².

Discussion

Although the definition of severe LN is not yet well established, rapidly progressive glomerulonephritis and LN with crescentic necrotic lesions are considered as the most severe forms of LN [8]. Indeed, several studies have reported the association of crescent formation with poor renal outcomes [9, 10]. The patient reported here showed rapidly progressive glomerulonephritis, which was histologically diagnosed as class IV + V LN, with a large number of cellular to fibrocellular crescents (62 % of glomeruli). Therefore, the patient was considered as having the most severe form of LN.

For the induction therapy of active proliferative LN, both MMF and CYC are suggested as immunosuppressant agents of first choice in recently published guidelines and recommendations [1–4]. However, according to some guidelines/recommendations, CYC rather than MMF is “preferable” for the treatment of severe LN [2, 3]. In addition, most physicians prefer to use CYC for severe forms of LN, such as those with crescent formation or rapid deteriorating renal function [5, 8]. One of the plausible reasons for choosing CYC is that data on the use of MMF for severe LN are still limited as compared to those on the use of CYC, which has a long history of clinical trials and clinical treatment for LN. For example, one of the NIH clinical trials demonstrated that long-course CYC therapy can prevent deterioration of renal function more effectively than mPSL pulse therapy in patients with severe LN [11].

However, although the use of CYC for severe LN is supported by the results of clinical trials and physicians’ clinical experiences, a number of systemic reviews and meta-analyses have reported a high incidence of amenorrhea and a high risk of development of hemorrhagic cystitis and/or transitional cell carcinoma of the bladder in patients receiving treatment with CYC [8]. In addition, CYC is not a satisfactory treatment agent for severe crescentic LN. Yu et al. [9] reported that patients with crescentic class IV LN, which they defined as being represented by crescent formation in more than 50 % of glomeruli, had lower complete remission rates and poorer renal outcomes than patients with LN without crescents, although most of them were treated with CYC.

Our patient developed the complication of pancytopenia associated with CMV infection. In general, MMF is reported to be associated with a lower risk of infections and leukopenia than IVCY [12, 13]. However, some researchers have pointed out that MMF possibly increases the risk of CMV infection in patients who have undergone renal transplantation [14]. Indeed, in a previous study conducted by us, 6 out of 16 (37.5 %) LN patients developed the complication of CMV viremia during the early phase of multi-target therapy [7]. Two out of the 6 patients with positive CMV antigenemia also had CMV-related complications: pancytopenia in the patient presented in this report, and gastric ulcer in another patient. Although multi-target therapy was generally well tolerated, it is necessary to pay close attention to the risk of CMV infection.

In summary, we have reported a patient with severe crescentic class IV + V LN, in whom early complete remission was obtained by multi-target therapy using TAC and MMF. Although occurrence of infections, including CMV infection, should be carefully monitored for, multi-target therapy using TAC and MMF in combination with mPSL pulse therapy could represent an effective therapeutic option for patients with severe crescentic LN.

Conflict of interest K. Hiromura has received honoraria for lectures and research grants from Astellas Pharma Inc and honoraria for lectures from Chugai Pharmaceutical, Co., Ltd. H. Ikeuchi has received research grants from Chugai Pharmaceutical, Co., Ltd. A. Maeshima has received research grants from Astellas Pharma Inc. Y. Nojima has received honoraria for lectures and research grants from Astellas Pharma Inc and research grants from Chugai Pharmaceutical, Co., Ltd.

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