Rheumatol Int (2009) 29:821–824
DOI 10.1007/s00296-008-0826-y

CASE REPORT

Hemolytic uremic syndrome with ischemic glomerulonephropathy and obliterative vasculopathy in a systemic sclerosis patient treated with cyclosporine-A

Wei-Sheng Chen · An-Hang Young · Hon-Pin Wang · De-Feng Huang

Received: 10 April 2008 / Accepted: 12 December 2008 / Published online: 21 January 2009

Abstract Hemolytic uremic syndrome (HUS) is not a commonly reported complication in post-transplantation patients treated with cyclosporine-A (CSA), and is extremely rare in systemic sclerosis (SSc) patients treated with this drug. CSA may contribute to the development of chronic ischemic glomerulonephropathy and vasculopathy, features not easily distinguished from SSc-related nephropathy. Here, we describe a 41-year-old Chinese man with diffuse-type SSc treated with CSA who developed thrombocytopenia, acute renal failure and hemolytic anemia and was diagnosed with HUS. Renal function and thrombocytopenia improved gradually after intensive treatment of plasma exchange (PE) and high-dose steroid therapy. After PE, renal biopsy showed ischemic glomerulonephropathy and obliterative vasculopathy. This case illustrates that PE can improve the hematological disorders and characteristic renal changes of HUS in SSc patients treated with CSA. However, this therapy may not be effective in normalizing serum creatinine level in SSc patients once CSA has triggered the normal kidney to develop glomerulonephropathy and vasculopathy with ischemic and sclerotic changes.

W.-S. Chen · H.-P. Wang · D.-F. Huang (✉)
Division of Allergy, Immunology, and Rheumatology,
Department of Medicine, Taipei Veterans General Hospital,
201, Sec2, Shih-Pai Road, Taipei 11217, Taiwan
e-mail: dfhuang@vghtpe.gov.tw; curtis625@msn.com

A.-H. Young · D.-F. Huang
Division of Allergy, Immunology, and Rheumatology,
Department of Medicine, National Yang-Ming University,
Taipei, Taiwan

D.-F. Huang
Division of Allergy, Immunology, and Rheumatology,
Department of Medicine, Taipei-Medical University,
Taipei, Taiwan

Keywords Hemolytic uremic syndrome · Systemic sclerosis · Cyclosporine-A

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread obliterative vasculopathy and excessive collagen deposition in the skin and visceral organs [1]. In autopsy studies, about 60–80% of SSc patients had renal involvement [2], however, most renal involvement was either subtle or without clinical manifestations. About 10–20% of SSc patients will develop a renal crisis resulting in malignant hypertension, acute renal failure, microangiopathic anemia or thrombocytopenia, in which the causes can be the disease itself, infection or drugs.

Cyclosporine-A (CSA) has been used to prevent post-renal transplantation rejection and to treat skin sclerosis or renal damage in SSc patients [3]. CSA nephrotoxicity is divided into acute and chronic categories. Acute CSA nephrotoxicity is usually reversible with cessation of therapy, while the chronic form is usually irreversible, eventually progressing to end-stage renal disease.

Thrombotic microangiopathy includes hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenia purpura (TTP), a rare complication in post-transplantation patients treated with CSA. Only nine SSc patients with TTP and two with HUS have been reported [4, 5]. Data on the consequent renal pathological findings after CSA treatment in SSc patients are very limited. Here, we report a SSc patient treated with CSA who developed HUS. The renal pathological change caused by CSA is also discussed, as well as the role of plasma exchange (PE) in the treatment of HUS in SSc patients treated with CSA.

Case report

Systemic sclerosis was diagnosed in this 41-year-old male patient in July 2005 based on the appearance of sclerodactyly, Raynaud's phenomenon, proximal scleroderma involving the upper limbs, trunk and face, and Scl-70 antibody. He had no history of infection, exposure to traditional herbal medicines, NSAIDs or other potentially nephrotoxic agents. He was treated with D-penicillamine (300 mg/day) for 3 months. Because the involved skin became tighter and thicker very quickly, the dose of D-penicillamine was increased to 450 mg/day and pulse methylprednisolone therapy (750 mg/day for 3 days each month) for a 2-month period, beginning in September 2005. Because of persistence of symptoms, the treatment was shifted to cyclosporine [3.5 mg (kg day)] alone from December 2005 until January 2006. Throughout the course, the serum creatinine level, complete blood count and urinalysis were all within normal limits.

On 21 January 2006, the patient was admitted because of progressive general weakness. Physical examination was unremarkable except for the typical skin changes of diffuse-type SSc, tachycardia (105/min), and hypertension (158/83 mmHg). Complete blood count revealed leucocytosis (WBC 14,160/mm^3), anemia (Hgb 11.0 mg/dL) severe thrombocytopenia (platelets 52,000/mm^3), and an increase blood reticulocytes (6.2%, normal < 1.5). Many fragmented RBCs were found in the peripheral blood smear. Serum haptoglobin level was decreased (<13 mg/dL, normal > 30) but direct and indirect Coombs tests were negative. Proteinuria (0.6 gm/day) with microscopic hematuria and granular casts were noted in the urinalysis. Serum SMAC tests were normal except for elevated creatinine (3.6 mg/dL, normal < 1.2), lactate dehydrogenase (LDH) (918 μL/L, normal < 213), and bilirubin (direct/total: 0.4/1.7 mg/dL, normal < 0.3/1.6). The autoantibody profile was: Scl-70(+), Sm (−), RNP (−), SSA (−), SSB (−), ANCA (−), anticardiolipin Ab (−), and lupus anticoagulant (−). Prothrombin time and activated partial thromboplastin time were normal. Renal biopsy was not performed because of prolonged bleeding time, although bilateral renal size was normal. Chest X-ray showed mild interstitial infiltration in the bilateral lower lung fields without cardiomegaly or signs of pulmonary arterial hypertension.

After admission, renal function rapidly deteriorated and blood pressure rose continuously to 170/100 mmHg. Therefore, aggressive treatment with PE using fresh frozen plasma (2.88 L/each course) for a total of 14 courses was started on the 4th hospital day. Methylprednisolone [1 mg (kg day)] initially, tapered as the disease stabilized) and nifidepine were given simultaneously. Renal function and thrombocytopenia improved gradually thereafter. The levels of LDH, serum creatinine, and the platelet count during the entire clinical course are depicted in Fig. 1. As the serum creatinine level was persistently elevated (3.7 mg/dL), renal biopsy was performed on the 38th hospital day (6 days after PE). The two main biopsy findings were as follows: (1) diffuse vessel wall thickening of the renal arteries and arterioles, where intimal fibrosis, medial layer hypertrophy and endothelial thickening were found; (2) diffuse global ischemic changes of the glomeruli, in which the glomerular tuft was collapsed, and capillary walls and lumens were segmentally obliterated (Fig. 2). Immunofluorescence studies revealed no evidence of IgG, IgA, IgM, C1q, C3 and C4 deposition in renal tissues. All renal pathological findings were compatible with chronic CSA nephrotoxicity or chronic renal involvement of SSc. The characteristic nephropathological changes of HUS, such as glomerular thrombi, were not found on electromicroscopy which was possibly attributable to the effectiveness of plasma exchange therapy.

Discussion

This patient developed acute hemolytic anemia, thrombocytopenia, and acute renal failure only 4 weeks after starting CSA 3.5 mg/kg treatment, responsible for the condition. HUS associated with CSA was suspected based on clinical manifestations. HUS was initially described by Gasser et al. in 1955. When HUS occurs in the presence of SSc, it may mimic a scleroderma renal crisis (SRC). As the treatment of HUS is different from that of SRC, failure to make the correct diagnosis may delay life-saving therapy. High-dose plasma infusion or PE was reported as effective treatment for TTP/HUS [6]. Our patient had clinical features consistent with SRC, but the dramatic clinical improvement after PE strongly suggests that our patient had HUS rather than SRC.

The association between CSA and thrombotic microangiopathy (TMA) was first suggested by Shulman et al.

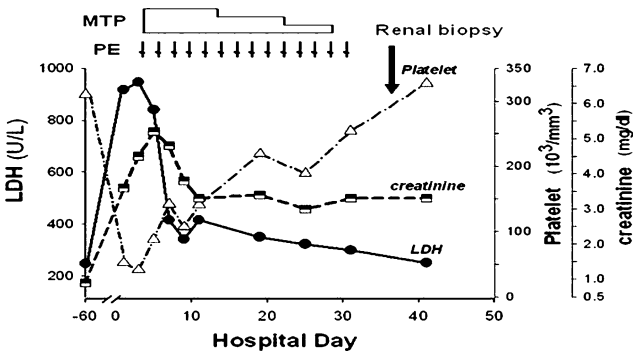

Fig. 1 Serum level of creatinine, LDH and blood platelet counts gradually improved after plasma exchange. *PE* plasma exchange, *MTP* methylprednisolone, *LDH* lactate dehydrogenase

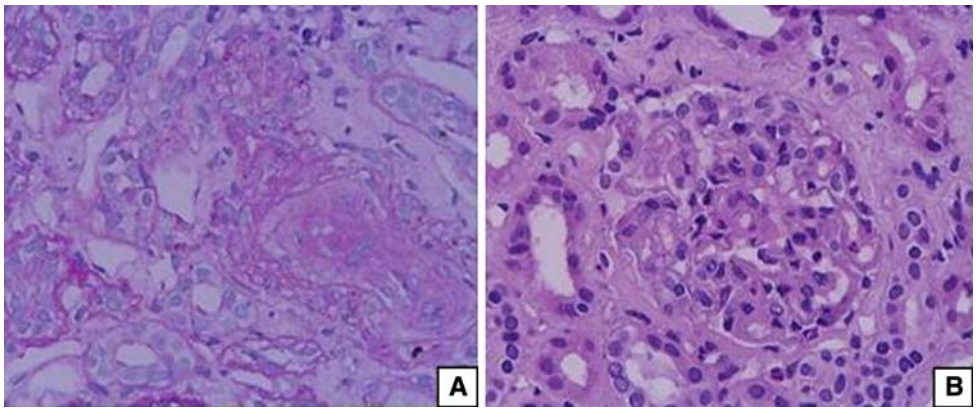

Fig. 2 Representative section of the renal biopsy specimen (**a**) diffuse vessel wall thickening of the renal arteries and arterioles (**b**) diffuse global ischemic changes of the glomeruli (HE stain ×400)

[7]. They described three cases of a rapidly fatal syndrome in bone marrow transplant recipients treated with CSA. TMA is a rare but well-recognized syndrome of acute CSA toxicity in transplant recipients. CSA-induced TTP-HUS in association with SSc has been rarely reported [4, 5, 8].

Acute CSA nephrotoxicity is usually reversible with cessation of therapy or dose reduction [9]. No specific pathologic changes are induced acutely by CSA, however, vascular lesions similar to those in HUS are sometimes found. On the other hand, chronic CSA nephrotoxicity is manifested by renal insufficiency due to glomerular and vascular disease, abnormalities in tubular function, and increase in blood pressure [10]. The risk of chronic renal insufficiency (CRI) continues to increase over time. About 20% of non-renal transplant recipients treated with CSA developed CRI during a follow-up of 3–5 years.

Zachariae et al. [5] reported a SSc patient with normal renal biopsy before CSA treatment who developed HUS. A second biopsy after 21 days of CSA revealed thickened arteriole walls and thrombi in the lumen. Four months later, the arterial changes found in the autopsy were of the type well known from the chronic visceral form of SSc. They considered that the acute phase of visceral scleroderma evolved possibly due to the CSA treatment, initially with severe microangiopathy which eventually led to severe arterial changes characteristic of chronic visceral scleroderma.

Renal biopsy in patients with chronic CSA nephrotoxicity revealed obliterative arteriolopathy, ischemic collapse of the glomeruli, vascularization of the tubules, and focal areas of tubular atrophy and interstitial fibrosis [11]. These findings are similar to changes that take place in the chronic sclerotic kidney. In our patient, renal biopsy showed ischemic glomerulonephropathy and obliterative vasculopathy. These findings, however, do not definitively distinguish chronic CSA nephrotoxicity from chronic sclerotic renal involvement. These renal changes are seen in both low-dose and higher dose CSA therapy, although they seem to occur earlier and last longer with higher doses. The risk factors for CSA nephrotoxicity in SSc patients with renal failure are middle-aged female, diffuse-type SSc, and a rapidly progressive disease course. Our interpretation is that short-term low-dose CSA use in SSc patients may cause chronic CSA nephrotoxicity changes or accelerate irreversible chronic scleroderma changes in the abnormal kidney.

In conclusion, whether there is a “safe” chronic dose of CSA that is effective, but does not cause progressive renal dysfunction remains unclear because of the lack data from well-controlled clinical trials. However, in specific types of patients, such as those with SSc, especially diffuse type, middle-dose and short-term CSA use may lead to progressive renal failure. Close monitoring and care are necessary, and PE may be an effective therapy in the acute stage of HUS in SSc patients.

References

1. Claman HN, Giorno RC, Seibold JR (1991) Endothelial and fibroblastic activation in scleroderma. The myth of the “uninvolved skin”. Arthritis Rheum 34:1495–1501
2. Shapiro A, Medsger TA Jr (1988) Diseases of kidney, 4th edn. Little Brown, Boston
3. Filaci G, Cutolo M, Basso M, Murdaca G, Derchi L, Gianrossi R (2001) Long-term treatment of patients affected by systemic sclerosis with cyclosporin A. Rheumatology (Oxford) 40:1431–1432
4. Manadan AM, Harris C, Block JA (2005) Thrombotic thrombocytopenic purpura in the setting of systemic sclerosis. Semin Arthritis Rheum 34:683–688
5. Zachariae H, Hansen HE, Olsen TS (1992) Hemolytic uremic syndrome in a patient with systemic sclerosis treated with cyclosporin A. Acta Derm Venereol 72:307–309
6. Coppo P, Bussel A, Charrier S, Adrie C, Galicier L, Boulanger E (2003) High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. Medicine (Baltimore) 82:27–38
7. Shulman H, Striker G, Deeg HJ, Kennedy M, Storb R, Thomas ED (1981) Nephrotoxicity of cyclosporin A after allogeneic marrow transplantation: glomerular thromboses and tubular injury. N Engl J Med 305:1392–1395

8. Ruiz JC, Val F, de Francisco AL, de Bonis E, Zubimendi JA, Prieto M (1991) Progressive systemic sclerosis and renal transplantation: a contraindication to ciclosporin. Nephron 59:330–332
9. Lamas S (2005) Cellular mechanisms of vascular injury mediated by calcineurin inhibitors. Kidney Int 68:898–907
10. Kahan BD (1989) Cyclosporine. N Engl J Med 321:1725–1738
11. Bertani T, Ferrazzi P, Schieppati A, Ruggenenti P, Gamba A, Parenzan L (1991) Nature and extent of glomerular injury induced by cyclosporine in heart transplant patients. Kidney Int 40:243–250