

Hemolytic Uremic Syndrome in a Patient with Systemic Sclerosis Treated with Cyclosporin A

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The case is presented of a 48-year-old female suffering from diffuse cutaneous systemic sclerosis (diffuse scleroderma) since 8 years, who went into renal failure as part of hemolytic uremic syndrome following 3 weeks' treatment with 3.8 mg/kg cyclosporin A. Hemolytic uremic syndrome has previously been described in transplant patients receiving cyclosporin A. There are also four cases reported in the literature of renal failure developing in middle aged females with diffuse cutaneous systemic sclerosis after short-term use of low dosage cyclosporin A treatment. It is suggested, that it may be wise not to use cyclosporin A to this category of patients, in which it can not be ruled out, that even a low dose therapy may trigger the rapid onset of scleroderma renal crisis or as in our case provoke hemolytic uremic syndrome.

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Cyclosporin A (CsA), a potent immunosuppressive agent has been claimed to improve severe progressive systemic sclerosis (PSS) (1-6). The drug, however, displays a number of side-effects of which nephrotoxicity and hypertension are considered the most serious (7). Hemolytic uremic syndrome (HUS), which includes anaemia, thrombocytopenia, erythrocyte morphological abnormalities, increased number of reticulocytes, bone marrow hyperplasia, and renal failure have been reported taking place de novo in renal transplant recipients immunosuppressed with CsA (8). Acute renal failure has also been reported in PSS treated with CsA, but it has not been clear whether this was due to treatment or to progression of the disease (2, 5, 9). We present the case of a patient with severe diffuse PSS who developed HUS after only 3 weeks' treatment with CsA.

CASE REPORT

A forty-eight-year-old female who had diffuse scleroderma for 8 years. Previous treatment with penicillamine from 1983 to 1988 had produced a moderate effect. But after this therapy was discontinued elsewhere, the disease progressed, and treatment with prednisone and methotrexate was given without effect. Due to very severe progression for the last two years methotrexate was discontinued and CsA was started with 3.8 mg/kg. At this time there was symmetrical diffuse involvement of the whole skin of the trunk and extremities with only few lesions of hands and feet, but with pronounced livedo vasculitis on the lower legs together with minor ulcerations. The patient had a decreased passage through esophagus and a tendency to diarrhoea. She had a normal lung function and normal kidney function judged by a normal glomerular filtration rate and a serum creatinine of 87 µmol/l and no proteinuria. A pre-CsA kidney biopsy was considered normal. Her blood pressure (BP) was 120/90.

CsA was administered in two daily dosages (100 + 150 mg) together with nifedipine 10-20 mg and an unchanged prednisone dosage of 10 mg daily. After two weeks' treatment, there were no complaints and blood pressure and serum creatinine remained stable. After four weeks BP had increased to 180/110 and serum creatinine to 177 µmol/l. A proteinuria of 1.0 g/l was discovered and CSA treatment discontinued. One week later BP was still elevated, serum creatinine had increased to 201 µmol/l, thrombocytopenia (64×10^9) and microscopic hematuria had developed. Because of HUS with rapidly deteriorating renal function she was transferred to the department of Nephrology where chronic intermittent dialysis was initiated and total anuria developed within one week. The initial course was complicated by gastrointestinal bleeding from a duodenal ulcer which was effectively treated by electrocoagulation and omeprazol.

A renal biopsy was done 21 days after first sign of renal involvement had appeared.

Signs of haemolysis and thrombocytopenia disappeared within three weeks after start of dialysis. The patient's condition stabilized temporarily but renal failure with total anuria persisted. After 4½ month on dialysis death occurred because of a perforated duodenal ulcer and diffuse peritonitis.

PATHOLOGY

The first renal biopsy performed just before the beginning of CsA therapy showed a minor degree of interstitial fibrosis and some arterioles with moderate hyaline change, but appeared otherwise normal.

The second renal biopsy performed 21 days after the onset of renal involvement consisted of 2 mm medulla and 4 mm cortical tissue.

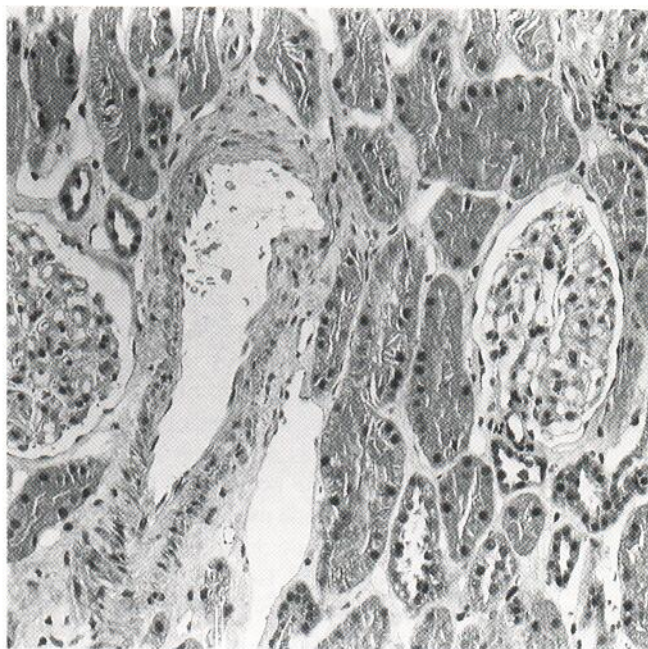


Fig. 1. Renal biopsy performed before cyclosporin treatment. Note the normal structure, particularly the artery. PAS staining, $\times 150$.

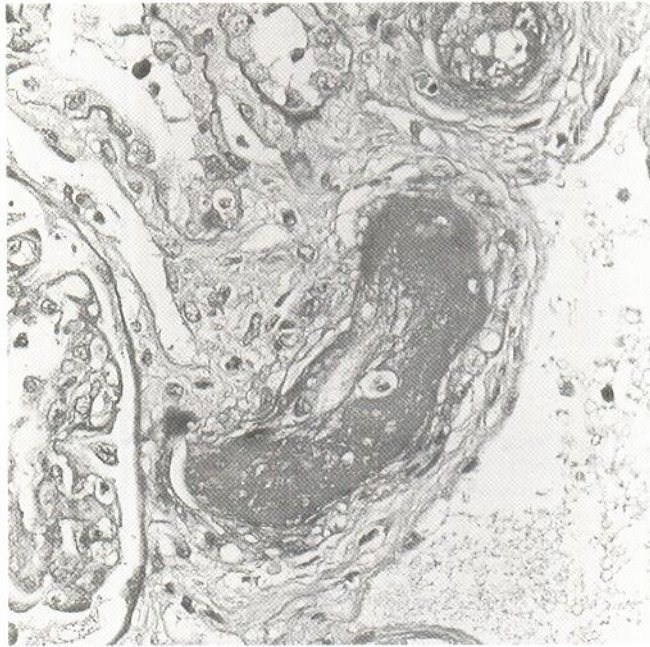


Fig. 2. The second biopsy after 21 days of cyclosporin treatment, during acute renal failure. Arterioles with multilayered, thickened walls and lumen obstructed by thrombi. PAS $\times 300$.

While the medullary part of the biopsy was preserved, most of the cortex showed necrosis of tubular epithelium sparing only a narrow zone close to the medulla. The arterioles were dilated and were occluded by thrombi. Their walls had an onionlike multilayering and had fibrin deposits. Some glomeruli showed ischemic collapse of the tuft, others had thrombosis of some capillary loops. One of them contained an epithelial crescent. A part of one medium sized artery with edematous intimal thickening was present at the edge of the biopsy. The histological diagnosis was thrombotic microangiopathy of the type known from HUS. The necroses were interpreted as indicating bilateral cortical necrosis (focal or complete).

Autopsy. A perforated ulcer was found in the duodenum. There was diffuse peritonitis. The kidneys were moderately reduced in size, smooth, with scattered coarse scars. The cortex was narrowed to 3–5 mm. Microscopically there was moderate interstitial fibrosis and tubular atrophy. Many glomeruli showed ischemic sclerosis of the tuft but no recent capillary thrombosis. In some areas all glomeruli were sclerotic. The arteries showed severe concentric intimal fibrosis with extreme narrowing of their lumina.

DISCUSSION

Our patient developed acute hemolytic anaemia, thrombocytopenia, and acute renal failure only 3 weeks after initiation of CsA 3.8 mg/kg indicating that CsA was responsible to the condition. The renal biopsy performed after the onset of renal insufficiency showed a picture of microangiopathy which has been described in HUS as well as associated to a number of conditions, among them also the acute form of progressive systemic sclerosis (10). Thrombotic microangiopathy has also been described in cyclosporin-treated patients with renal, hepatic and bone marrow transplants. The necrosis present in the second biopsy from our patient led to the assumption of bilateral cortical necrosis. If this has been the case, it must have been of the partial, focal type since the autopsy specimen did not show strong diffuse tubular atrophy. The arterial changes

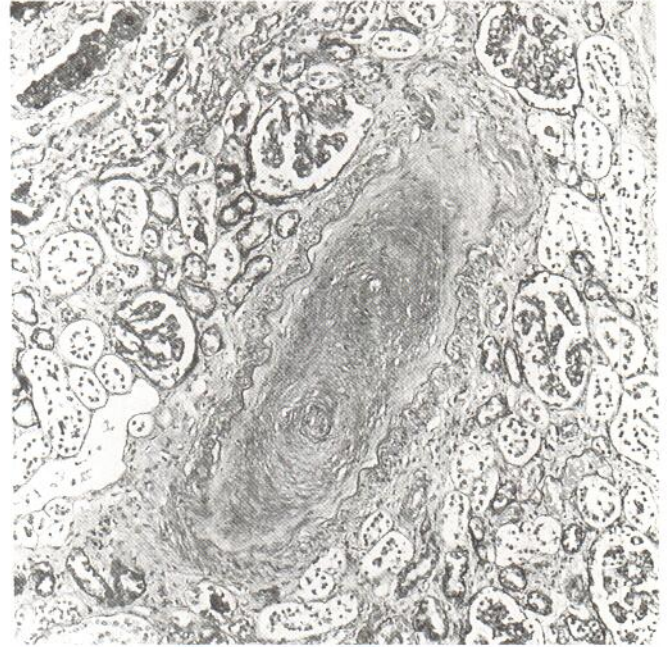


Fig. 3. The kidney at autopsy. Medium-sized artery with concentric, fibrous intimal thickening almost totally occluding the lumen. PAS $\times 90$.

found in the autopsy specimen were of the type well known from the chronic visceral form of progressive systemic sclerosis. Our interpretation of these findings is that an acute phase of visceral scleroderma evolved possibly due to the cyclosporin-treatment, initially with severe microangiopathy which eventually led to severe arterial changes characteristic of chronic visceral scleroderma. Cortical necrosis, which must have been patchy, played probably a minor role in the renal insufficiency.

Patients with a high risk of renal failure from PSS are mainly middle aged females with a disease history of approximately 2 to 3 years. A rapid increase in the generalized cutaneous sclerosis may precede the renal failure (11). Although our patient had a PSS history of 8 years, she had only severely progressed for the last 2 years and therefore still should be considered belonging to the risk group.

The previous reports (2, 5, 7) on renal failure following CsA in PSS also all concern the risk group of middle aged females suffering from diffuse scleroderma (diffuse cutaneous systemic sclerosis). In all four patients low dosage therapy was used and the renal failure occurred after a few months of treatment. Two patients, however, were treated with NSAID's simultaneously, which may increase toxicity of CsA. This was not the case in our patient. A renal biopsy was performed in one of these patients showing recent thrombotic microangiopathic lesions, ischemic glomeruli, moderate tubular atrophy, and interstitial fibrosis. No pretreatment kidney biopsies were reported and no histories of HUS were disclosed.

The nephrotoxicity of our patient should not be confused with the low grade morphological changes of arteriolar hyalinosis and interstitial fibrosis previously reported by us to follow low dosage CsA in PSS (1). These latter findings are similar to changes taking place in psoriatic patients treated

with the same low dosage CsA for approximately one year (12). The clinical relevance of these minor changes is still unknown, and in our opinion they do not exclude the use of CsA in severe psoriasis or in aggressive PSS outside the risk group, when found necessary. We do, however, find it is prudent not to use CsA in female patients with diffuse PSS as long as it can not be ruled out, that CsA even in a low dose regime may trigger the rapid onset of a renal crisis. It is also important to state, that CsA should not be combined with NSAID's in PSS treated with CsA.

HUS has also been found in other conditions i.e. in CsA-treated patients who underwent bone-marrow transplantation (13). The pathogenesis of the CsA induced HUS is unknown. Leithner and coworkers (12) proposed that CsA precipitates HUS by inhibiting prostacyclin synthesis by vascular tissue. The reduced PGI₂ should lead to endothelial cell damage, capillary thrombosis and vessel wall necrosis. It has also been suggested that this CsA reaction is idiosyncratic and not dose related (8). In our case CsA was immediately discontinued after diagnosis. But renal failure progressed to total anuria necessitating chronic dialysis. The patient eventually died after 4½ months on dialysis from a perforated duodenal ulcer.

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