Case Report

An unusual evolution of the systemic capillary leak syndrome

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Introduction

Systemic capillary leak syndrome (SCLS) is characterized by sudden shock with diffuse oedema sparing the lungs [1]. Currently, about 50 cases have been reported with a 5-year survival of 25% [2,3].

For the first time, we describe a case of SCLS evolving over 20 years and culminating in a late and fatal myeloma with amyloidosis.

Case

A 33-year-old black male, was referred to our department in 1981 for the following symptoms consistent with typical SCLS: several episodes of shock with generalized oedema; diffuse pain; and transient anuria. A monoclonal gammapathy of undetermined significance (MGUS) was discovered at that time. Three years later, he had minimal proteinuria (monoclonal component). Femoral artery superficialization was performed to obtain a permanent and easy vascular access, and the patient was treated during subsequent crises by colloid or gelatin fluids. Prevention of these crises was attempted unsuccessfully with corticosteroids, theophylline, cyclophosphamide, cyclosporin A, plasma exchanges, and naftazone. Beginning in 1986, transient diabetes mellitus occurred during the crises. Because of the presumably auto-immune mechanism common to both the SCLS and the episodes of diabetes mellitus, the patient began treatment with intravenous polyvalent immunoglobulins. These reduced the intensity of his crises, with only abdominal pain, moderate hypotension and weight gain. In 1991, the patient developed permanent diabetes mellitus and, beginning in 1999, diabetic retinopathy, progressive neuropathy and nephropathy.

In May 2000, the patient had acute renal failure and persistent proteinuria, and a renal biopsy was performed. Optical examination showed osmotic nephrosis-like lesions in the podocytes and most tubules, but no amyloidosis. On immunofluorescence, some polyclonal depositions were seen in glomeruli as well as tubular basement membranes. Electronmicroscopy showed basal thickening, without fibrillar or granular deposition, and mesangial expansion, suggesting an early diabetic nephropathy. The patient recovered renal function after this episode. However, he presented more frequent crises, weight loss, thoracic pain and, finally, worsening cardiac function. A pericardial effusion was drained. Pericardial biopsy showed no amyloidosis despite evidence revealed by echocardiography. A bone marrow aspiration showed 80% abnormal plasmocytes, confirming the diagnosis of myeloma. M-component serum level was 18 g/l. Humeral lacunae were seen on an X-ray. Cutaneous and salivary biopsies revealed AL amyloidosis.

In April 2001, treatment was begun with melphalan and prednisone. However, the patient died after two treatment courses from cardiac and hepatic amyloidosis.

Discussion

The SCLS is a rare but fatal disease first described by Clarkson et al. [1]. Crises are heralded by abdominal pain, nausea, and vertigo, followed rapidly by severe shock and generalized oedema. Normal blood pressure is restored by intravenous fluid administration. The end of the crisis is characterized by rapid polyuria. A monoclonal gammapathy, the only laboratory anomaly between crises, has been described for all but two of the reported cases [2,4,5]. The differential diagnosis of SCLS includes C1 esterase inhibitor deficiency, adrenal disease or myeloma. In many of the reported cases, death occurred during severe shock because of lack of a vascular access [1,2]. Two patients died during the early stages of disease from myeloma [5]. Numerous therapies have been unsuccessfully tried for prophylaxis, including theophylline, terbuvatine,
corticosteroids, prostacycline, gingko biloba, indomethacin, spironolactone, cyclosporin A and plasma exchanges [2,3].

The pathophysiology of SCLS is still unclear. Leukotriene B4 (LTB4) plays a central role in capillary permeability. We found, in vitro, an increase in LTB4 generation in our patient during crises, reflecting activation of the 5-lipoxygenase pathway in blood leukocytes [4]. However, the triggering factor that would act in vivo upon 5-lipoxygenase activity in SCLS remains unknown. Additionally, treatment of our patient with an anti-leukotriene (naftazone) failed to prevent disease recurrence. Although capillary permeability can be increased by a number of circulating factors, including histamine, bradykinin, complement-derived anaphylatoxins, C5a and C3a, Atkinson [5] has found that complement, kinins, prostaglandin, coagulation factors, histamine and serotonin are all normal in patients with SCLS. A secondary SCLS has been induced by injection with IL-2 and IFN β and has been described in graft vs host disease and infection, suggesting a role for cytokines in the pathogenesis of SCLS [6,7]. However, cyclosporin A, which decreases IL-2 production, did not prevent crises in two patients, including ours [2].

This case is the longest reported evolution of SCLS and the only one with AL amyloidosis. retrospectively, the most important therapeutic intervention was obtaining reliable vascular access. Undoubtedly, patient instruction also played an important role in this long survival period; the patient was instructed to return to the hospital at the onset of abdominal pain, which, for him as well as for most patients, was the initial manifestation of a crisis [1].

Although we found no effective pre-emptive therapy, intravenous immunoglobulins appeared to be efficacious in reducing crisis intensity and duration. In 1984 Sultan et al. [8] successfully treated two patients who had auto-antibodies to factor VIII with polyvalent immunoglobulins thought to contain anti-idiotypic antibodies. The monoclonal gammapathy in the majority of SCLS patients, as well as the intermittent diabetes mellitus described in our patient, suggests an auto-immune mechanism in the aetiology of SCLS. However, no immunofixation of paraprotein on endothelial cells or on muscle vascular walls, and no direct toxicity on cultured endothelial cells could be demonstrated [5,11,12]. Furthermore, plasmapheresis has been ineffective as therapy [2,5]. Thus, the mechanism of action for the clinical benefits we observed in our patient after administration of intravenous immunoglobulins remains unclear.

Of all reported cases, our patient is the first to have developed a stage III myeloma with amyloidosis and to die from general amyloidosis. A monoclonal component has been described in almost all cases of SCLS, and three patients developed stage I myeloma [9]. Given the fact that 40% of patients with MGUS develop myeloma after 25 years [11], survival was probably too short in most other cases of SCLS to see the development of myeloma or of concomitant amyloidosis. As discussed above, the case history we describe strongly suggests a role for a paraprotein in the pathophysiology of SCLS. Beermann et al. [12] treated one patient who had stage I multiple myeloma and SCLS with melphalan and prednisone and noted a decrease in the severity of shocks over 3 years. It may be necessary to initiate treatment with melphalan and prednisone during the early phase to control SCLS and MGUS evolution.

Renal failure in this patient was probably multifactorial: functional renal insufficiency during episodes of shock, repeated colloid infusions, diabetes (manifested by proteinuria and retinopathy), amyloidosis. Renal biopsy found an osmotic nephrosis-like kidney. Although biopsy did not show any diabetic nodules, electron microscopy showed thickened basement membranes. Interestingly, this thickness was also found in the glomerular capillary of another patient with SCLS and on the muscle vascular basal membrane of two other patients [1,10]. This is probably a consequence of a hyperpermeability syndrome as much as of diabetes. As noted above, the patient also had salivary and cutaneous amyloidosis and died from cardiac and hepatic amyloidosis. It is likely that amyloid deposition developed in the kidney. Additionally, some Ig deposition, due a monoclonal component or to the administration of intravenous immunoglobulins, was found on immunofluorescence and could have contributed to renal failure.

In conclusion, we describe for the first time a case of SCLS evolving over a 20-year period. This unusually long survival period was probably due to patient instruction, rapid reanimation and early administration of polyvalent immunoglobulins. Additionally, this is the first description of SCLS with a very late transformation from MGUS to myeloma associated with amyloidosis AL. The patient died from amyloidosis and not from shock. A monoclonal component could play a role in the development of SCLS, and early treatment with myeloma chemotherapy may lessen the signs and severity of shock and prevent a late evolution to myeloma.

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