An unusual rash and end-stage renal failure

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CASE REPORT

A 55-year-old man was admitted to hospital with a 2-week history of increasing dyspnoea and peripheral oedema. He gave a 5-year history of intermittent purpuric rash on both legs, with recurrent ulceration at the right lateral malleolus, and arthralgia.

Examination revealed hypertension (180/90mmHg), peripheral and pulmonary oedema. He was oliguric. There was a painless purpuric rash on the right lower limb and both thighs, but no cardiac murmurs or stigmata of bacterial endocarditis. Investigations showed renal impairment (urea 28.9mM, creatinine 303mM), proteinuria 3.1g/24h with microscopic haematuria (50 erythrocytes/μl), and a serum albumin level of 29g/litre. His liver function test and auto-antibody profile (including antinuclear antibody) were normal, so were his immunoglobulins (Ig) and serum protein electrophoresis. Renal ultrasound and venous doppler were normal. Repeated blood cultures were sterile, and echocardiography showed no evidence of vegetation. Renal biopsy revealed proliferative glomerulonephritis with mesangiocapillary changes, with weak immunofluorescence staining for C3 in mesangium and glomerular capillary walls. Serum C3 was normal and C4 undetectable, in keeping with type 1 mesangiocapillary glomerulonephritis. Rheumatoid factor was strongly positive (titre 1 in 640), and cryoglobulins of IgG and IgM types were found in the serum, consistent with type II (mixed) cryoglobulinaemia. Hepatitis B surface antigen and hepatitis C virus antibody were not detected. A bone marrow aspirate was hypocellular but reactive, with a block in iron utilization, and no evidence of lymphoproliferative disease.

His fluid overload was controlled with ultrafiltration, and immunosuppression (prednisolone 60 mg/day, cyclophosphamide 1.5 mg/kg/day) started. His renal function stabilized (serum creatinine 250 mM), but proteinuria persisted (8 g/24h, serum albumin 24 g/litre). Antihypertensive therapy was commenced. His nephrotic syndrome proved resistant to sodium restriction, diuretics and angiotensin-converting enzyme inhibition; he was re-admitted twice with fluid retention requiring ultrafiltration, complicated by recurrent cellulitis in both legs. Plasma exchange (ten sessions with 3 litres each time) was added subsequently as an adjunct but did not improve the situation with declining creatinine clearance, severe hypertension, and progressive malnutrition requiring dialysis. His condition improved greatly with dialysis, and he is now established on dialysis, with healed leg ulcers, and no other clinical manifestations of cryoglobulinaemia. He remains well on haemodialysis, but serum cryoglobulinaemia persists. Renal transplantation is not being considered at present.

INTRODUCTION

The clinical syndrome of mixed cryoglobulinaemia was first described in 1966 by Meltzer et al. There are three types of cryoglobulinaemia according to Brouet's classification (Brouet et al, 1974). Type I cryoglobulins are entirely monoclonal. Type II is composed of a polyclonal immunoglobulin G (IgG) bound to another globulin, a monoclonal anti-IgG rheumatoid factor, while type III cryoglobulins are composed entirely of polyclonal immunoglobulins (IgM rheumatoid factor and polyclonal IgG). Its aetiology is unknown but there is close association with hepatitis C virus. This article describes an unusual case of cryoglobulinaemia which presented with renal failure and highlights the importance of recognizing the condition.

DISCUSSION

Essential (mixed) cryoglobulinaemia is a rare cause of glomerulonephritis, in which diagnostic delay is common. Purpuric, vasculitic rash affecting the lower limbs is the usual presenting feature, often preceding evidence of renal involvement by several years; nonetheless, 20–70% of patients have evidence of renal disease at diagnosis (Frankel et al, 1992; Monti et al, 1995). The prognosis for renal function is regarded as generally favourable, with end-stage renal failure described in <10% of patients after 10 years (D'Amico et al, 1989). Progression of renal disease is variable, however, with one-third of patients having remission of symptoms and 20% having nephrotic or nephritic flare up during the course of the disease. It is unusual for renal function to deteriorate as quickly as described in this case.

Arthralgia is reported in up to 75% of cases but arthritis and deformity is uncommon. Liver involvement is also very common, particularly in patients with hepatitis C virus and cryoglobulinaemia. However, it was only found in 11% of patients with cryoglobulinaemia in the absence of hepatitis C virus (Ramos-Casals et al, 1998). Close, but not universal, associations between hepatitis C virus and cryoglobulinaemia led D'Amico (1995) to propose the existence of a 'hepatitis C virus-associated glomerulonephritis'.

Sinico et al (1995) reported a 91% rate of hepatitis C virus positivity in patients with mixed essential cryoglobulinaemia. Hepatitis C virus subtype 1b correlated significantly with signs of chronic hepatitis and the presence of peripheral neuropathy. The most frequent causes of death are systemic vasculitis, liver disease, renal impairment, cardiovascular and lymphoproliferative

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disease. This patient did not have any liver involvement and his hepatitis C serology was negative despite the severity of his disease.

It is very important to look for underlying disease as 60–75% of all cryoglobulinaemias are found in patients with other identifiable illnesses. This includes malignant paraproteinaemias in type I cryoglobulinaemia (multiple myeloma, Waldenstrom's macroglobulinaemia, lymphoproliferative disease), infections in type II cryoglobulinaemia (endocarditis, hepatitis C, hepatitis B, human immunodeficiency virus infection, Epstein–Barr, cytomegalovirus), and autoimmune disorders in type III cryoglobulinaemia (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, scleroderma). The risk of non-Hodgkin's lymphoma is also increased in patients with chronic hepatitis C infection with co-existing mixed cryoglobulinaemia (Rasul et al, 1999).

Anecdotal evidence supports the use of immunosuppression for both renal and extrarenal manifestations. Interferon is useful in patients with hepatitis C virus-related cryoglobulinaemia but the sustained response was found to be higher in the non-cryoglobulinaemic group (Adinolfi et al, 1997). Whether the therapeutic role of interferon in this situation (hepatitis C virus-negative) will differ from its place in hepatitis C virus-associated liver disease is still undefined.

CONCLUSION

Although a rare condition, cryoglobulinaemia is important as early diagnosis and treatment can often ensure favourable outcome both in terms of morbidity and mortality. Doctors should be aware that an unexplained purpuric leg ulcer can be a presenting feature of mixed essential cryoglobulinaemia. The associated underlying disease should always be looked for and treated accordingly. HM

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