Late onset Raynaud's phenomenon, hypertension, deteriorating renal function, and a fit in a middle aged woman

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A 55 year old woman was admitted to hospital with a 10 minute grand mal seizure that had resolved spontaneously. She had felt generally unwell for the previous four days, principally with severe headaches. She had a three year history of Raynaud's phenomenon associated initially with sclerodactyly and this hardening of the skin (scleroderma) had progressed to involve most of her body. Mild gastro-oesophageal reflux and general malaise were also noted during follow up in the rheumatology clinic. Recent investigations had shown antinuclear antibody positive, titre 1/320, but the extractable nuclear antigen SCL 70 and anticentromere antibodies were negative. Lung function tests, a high resolution computed tomogram of the thorax and renal function had been essentially normal (baseline serum creatinine 70 $\mu\text{mol/l}$ (normal <115), creatinine clearance 95 ml/min (normal range 110–150), and urinalysis repeatedly negative for protein). Her current medication included naproxen, naftidrofuryl oxalate, and omeprazole. Two years previously she had been noted to be hypertensive and started on an angiotensin converting enzyme (ACE) inhibitor but this was stopped 18 months before this admission due to symptoms of postural hypotension. It was noted at her last clinic visit, two months before this admission, that her blood pressure had been raised at 160/100 mm Hg.

On examination the patient was disorientated in time and place but responded to verbal commands. There was a bilateral extensor plantar response, but no other neurological signs. Her blood pressure was raised at 174/107

mm Hg, she also had mild peripheral oedema, a raised jugular venous pressure at 7 cm, and a loud second heart sound. Sclerodactyly and hardening of the skin proximal to the elbows and knees and around the face was noted.

Inpatient investigations were as follows: computed tomography of the brain was normal; urea concentration was 7.5 mmol/l (3.0–8.5), creatinine 101 $\mu\text{mol/l}$, potassium 4.2 mmol/l (3.5–5.0), sodium 139 mmol/l (136–144), and adjusted calcium 2.55 mmol/l (2.18–2.62). A blood film was reported as normal. Urinalysis revealed proteinuria and culture and microscopy was unremarkable. The electrocardiogram was normal and echocardiography demonstrated a small pericardial effusion with no evidence of left ventricular hypertrophy.

The next day she was fully orientated, but complained of headaches and feeling generally unwell. Despite treatment with a calcium channel blocker (amlodipine 10 mg once daily) over the next three days her blood pressure remained high (160/100–203/136 mm Hg). During this period her renal function deteriorated (24 hour creatinine clearance 30 ml/min, 24 hour urinary protein 2.4 g, urea 9.5 mmol/l, and creatinine 196 $\mu\text{mol/l}$). Fundoscopy revealed grade III hypertensive changes.

Questions

- (1) What is the underlying diagnosis?
- (2) What is the cause of her fit, hypertension, and deteriorating renal function?
- (3) What is the treatment?

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Answers

QUESTION 1

The underlying clinical diagnosis is diffuse scleroderma.

Raynaud's phenomenon developing in a middle aged woman is very suggestive of systemic sclerosis. Systemic sclerosis is subdivided principally into two groups, diffuse and limited scleroderma. Diffuse scleroderma is present if there is skin thickening present proximal to the elbows and knees and involving the trunk and face. It is therefore a clinical diagnosis rather than a serological diagnosis. Antinuclear antibodies are present in the sera of over 90% of diffuse scleroderma patients, but these antibodies are not specific to diffuse scleroderma and are present in a range of other diseases. Only 20%–40% of diffuse scleroderma patients have serum antibody reactive with an extractable nuclear antigen termed SCL 70 (antitopoisomerase I), an antibody specific to systemic sclerosis. A further 5%–10% of diffuse scleroderma patients are positive for anticentromere antibodies. Diffuse scleroderma is particularly associated with both renal involvement and progressive pulmonary fibrosis.

Limited scleroderma is associated with less extensive skin changes often involving only the hands and face, and is always limited to the skin distal to the elbows and knees. This is considered to be a more "benign disease", but is occasionally associated with primary pulmonary hypertension and is often associated with severe gastro-oesophageal reflux, intractable Raynaud's phenomenon, and is strongly associated with anticentromere antibodies (50%–90%).¹

QUESTION 2

The clinical presentation is characteristic of scleroderma renal crisis (SRC).

Scleroderma renal crisis is associated with the development of accelerated malignant hypertension, the rapid development of hypertensive retinopathy, fits, renal failure, and occasionally microangiopathic haemolytic anaemia with fragmented red cells noted on the blood film.

QUESTION 3

Prompt control of the blood pressure specifically with an ACE inhibitor. Additionally illoprost, a vasodilatory prostacyclin analogue is used.

Discussion

It is critical to make the diagnosis of SRC promptly as renal function can deteriorate rapidly resulting in complete loss of function. Before the use of ACE inhibitor therapy SRC was fatal or required permanent dialysis in almost all cases, although the prognosis for patients treated with an ACE inhibitor is far more favourable, with 60% of patients not requiring permanent dialysis.²

Scleroderma renal crisis is precipitated by functional vasospasm "renal Raynaud's phenomenon" superimposed on pre-existing renal

Learning points

- Scleroderma renal crisis (SRC).
- SRC is associated with diffuse rapidly progressive diffuse scleroderma and occurs in 20% of such cases.
- SRC is associated with malignant hypertension, renal failure, grand mal seizures, and microangiopathic haemolytic anaemia.
- Raised serum concentrations of renin as a consequence of a renal arteriolar vasospasm precipitate the clinical features seen in SRC.
- Treatment with an ACE inhibitor prevents renal failure and death.

arteriolar fibrotic change. This process triggers the release of renin and markedly raised plasma levels of renin activity are observed in the majority of diffuse scleroderma patients at the onset of SRC.³ Consequently the renin-angiotensin system is activated and a vicious circle ensues with angiotensin II causing further vasoconstriction resulting in worsening cortical ischaemia. The accelerated hypertension damages the renal arteriolar media, further worsening renal perfusion with the eventual development of cortical necrosis and renal failure. Renal crisis can therefore be managed more effectively when the hypertension is aggressively controlled with ACE inhibition. Prophylactic use of ACE inhibitors to prevent SRC is now used widely, however there are several cases of SRC occurring despite concurrent ACE inhibition.⁴

Microangiopathic haemolysis can occur in SRC and is the result of extrarenal vascular injury secondary to intimal disruption and fibrin deposition. Anaemia develops as a result of intravascular haemolysis with peripheral blood smears demonstrating fragmented red cells, decreasing fibrinogen levels, and fibrin degradation products.

Scleroderma renal crisis develops in 20% of diffuse scleroderma patients with the majority (70%) of such cases occurring within three years of the initial diagnosis.⁵ It is particularly associated with rapidly progressive skin changes as demonstrated in this case and observed almost exclusively in diffuse as opposed to limited scleroderma.⁶ Particular drugs used to treat other complications of scleroderma such as cyclosporin and corticosteroids are associated with precipitating scleroderma renal crisis whereas penicillamine has been observed to have a protective effect, but plays no part in the acute management of the disease.⁴ The patient described here responded to ACE inhibition, with good blood pressure control. A five day course of intravenous illoprost was also given and the decline in renal function was reversed. At a recent clinic appointment she was well with a blood pressure of 110/60 mm Hg and a serum creatinine of 170 $\mu\text{mol/l}$.

In summary it is essential that SRC is recognised and treated effectively with ACE

inhibition to prevent the inevitable consequences of permanent dialysis and a one year mortality rate of 90%.

Final diagnosis

Diffuse scleroderma with associated scleroderma renal crisis.

- 1 Tan EM, Rodnan GP, Garcia I, *et al.* Diversity of antinuclear antibodies in progressive systemic sclerosis. Anti-centromere antibody and its relationship to CREST syndrome. *Arthritis Rheum* 1980;23:617–25.
- 2 Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. *Intern Med* 2000;133:600–3.
- 3 Kovalchik MT, Guggenheim SJ, Silverman MH, *et al.* The kidney in progressive systemic sclerosis. A prospective study. *Ann Intern Med* 1978;89:881–7.
- 4 Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998;41:1613–9.
- 5 Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000;43:2437–44.
- 6 Steen VD, Medsger TA Jr, Osial TA. Factors predicting development of renal involvement in progressive systemic sclerosis. *Am J Med* 1984;76:779–86.