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CORE TRAINING FOR DOCTORS

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Scleroderma renal crisis

Introduction

Systemic sclerosis is an autoimmune connective tissue disorder characterized by endothelial cell injury, vascular hyperreactivity, obliterative microvasculopathy and excess collagen deposition, particularly within the dermis of the skin. *Table 1* outlines the various terms that are used to describe the extent and location of sclerosis. Limited cutaneous and diffuse cutaneous are the two main forms that exist.

Complications affecting viscera are the main cause of reduced life expectancy and a spectrum of renal involvement is recognized, from asymptomatic proteinuria or relatively mild reduction in renal function on the one hand, to scleroderma renal crisis, representing the most severe vascular complication, that still carries a very significant morbidity and mortality. Rarely, systemic sclerosis is associated with glomerulonephritis and other causes of renal impairment, which should not be overlooked. This article outlines what you need to know about scleroderma renal crisis.

Scleroderma renal crisis

Scleroderma renal crisis is a life-threatening complication of systemic sclerosis which, although it has significantly reduced in incidence over the last few decades to approximately 5–10% (Walker et al, 2007), still carries a significant risk of death or end-stage renal disease. Studies from the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database suggest a lower prevalence (5% of diffuse scleroderma and 2% of limited) (Walker et al, 2007).

The clinical presentation can be obvious or obscure, hence diagnostic criteria have been proposed (*Table 2*) (Traub et al, 1983). The key feature is a rapidly progressive oligouric or anuric acute kidney injury (≥30% reduction in estimated glomerular filtration rate) and/or significant systemic hypertension (>150/85 mmHg) with no explanation other than systemic sclerosis (Traub et al, 1983; Walker et al, 2007). Despite better validated diagnostic criteria for acute kidney injury (e.g. Kidney Disease: improving global outcomes Acute Kidney Injury; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012), in routine practice estimated glomerular filtration rate offers an accessible and

Table 1. Terminology

Term	Definition
Scleroderma	Tightness, thickening and non-pitting induration of skin
Sclerodactyly	Skin changes in the hands and feet as for scleroderma distal to the metacarpophalangeal or metatarsophalangeal joints
Proximal scleroderma	Changes as for scleroderma proximal to the metacarpophalangeal or metatarsophalangeal joints
Diffuse cutaneous scleroderma	Truncal and acral skin involvement. Presence of tendon friction rubs. Onset of skin changes (puffy or hidebound) within 1 year of onset of Raynaud's phenomenon – skin involvement may precede onset of vascular symptoms
Limited cutaneous scleroderma	Skin sclerosis distal to the wrists (or ankles), over the face and neck. Often longstanding Raynaud's phenomenon

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important investigation in the identification of scleroderma renal crisis.

The routine use of angiotensin-converting enzyme inhibitors has greatly reduced the mortality (from 76% to less than 15%) of scleroderma renal crisis and its early and aggressive institution has been linked to its reduced incidence (Steen et al, 1990). In fact, where scleroderma renal crisis had previously been a leading cause of death in systemic sclerosis patients, other organ involvement, particularly lung disease (pulmonary hypertension and pulmonary fibrosis), is now the major cause of death (Steen and Medsger, 2007). However, scleroderma renal crisis remains a vitally important finding as early diagnosis allows prompt therapeutic intervention and improved outcome.

Risk factors for scleroderma renal crisis

Several factors increase the risk of scleroderma renal crisis in patients with systemic sclerosis, including certain autoantibody profiles (*Table 3*) (Steen, 2003). Scleroderma renal crisis occurs relatively early (usually within 4 years of diagnosis) in the course of rapidly progressive diffuse cutaneous systemic sclerosis. Treatment with corticosteroids (>15 mg per day) and/or ciclosporin can also precipitate scleroderma renal crisis, although the exact mechanism is not fully understood.

The presence of anti-RNA-polymerase III antibodies, detected by enzyme-linked immunosorbent assay (ELISA), has a strong association with the development of scleroderma renal crisis, whereas the presence of anti-topoisomerase, anti-centromere or anti-U3RNP antibodies does not predict its development. In addition, specific human leucocyte antigen (HLA) subsets HLA DRB1*0407 and HLA-DRB1*1304 are independent risk factors for the development of scleroderma renal crisis (Nguyen et al, 2011).

Presentation

Known systemic sclerosis patients undergoing scleroderma renal crisis classically present with acute kidney injury associated with rapidly progressive and severe 'accelerated' hypertension. Progressive dyspnoea and hypoxia, tachyarrhythmias and/or symptoms of hypertensive encephalopathy including headache, confusion, visual disturbances, cortical blindness and seizures may all occur. In 25% of cases, scleroderma renal crisis is the first presentation of systemic sclerosis.

Fundoscopy may reveal papilloedema, and urinanalysis and urine microscopy will usually demonstrate proteinuria. Phase contrast microscopy will be helpful in differentiating scleroderma renal crisis and proliferative glomerular disease that may be seen in the scleroderma spectrum. History may reveal a precipitating cause such as recent high-dose corticosteroids or give a clue to duration, e.g. a recent diagnosis of anaemia. Profound peripheral vasoconstriction may result in extreme digital hypoperfusion and dry gangrene and so during a full-blown scleroderma renal crisis the limbs have been described as feeling 'like marble'.

Pathogenesis

The pathogenesis of scleroderma renal crisis is not fully understood, but the pathological changes within renal vessels are well reported. Initial endothelial cell injury propagates platelet aggregation and adhesion, intimal thickening and proliferation within interlobular and arcuate arterial walls, and increased vascular permeability promotes collagen and fibrin deposition (Steen, 2003). Small vessel thrombotic microangiopathy manifests as myxoid inti-

Table 2. Renal crisis classification

Definition of scleroderma renal crisis	New onset of blood pressure >150/85 mmHg obtained at least twice over a 24-hour period
	Documented decrease in the renal function as defined by a decrement of >30% in the calculated glomerular filtration rate
Corroborative features	Microangiopathic haemolytic anaemia
	Hypertensive retinopathy
	New onset of urinary red blood cells (other causes having been excluded)
	Flash pulmonary oedema
	Oligouria or anuria
	Typical renal biopsy features

Table 3. Investigations in scleroderma renal crisis

Routine investigation	Specific indication	
Biochemistry	Renal function	Quantify renal impairment, acute kidney injury
	Liver function and lactate dehydrogenase	Useful in monitoring progress of haemolysis
	Haptoglobins	Reduced during microangiopathic haemolytic anaemia
	Plasma renin	May be 10–100 x normal range (rarely used in practice)
Haematology	Full blood count and reticulocytes	Anaemia and thrombocytopaenia indicative of microangiopathic haemolytic anaemia
	Red blood cell film	Fragmented red blood cells, reticulocytosis
Immunology	Autoantibody profile	Confirms diagnosis of systemic sclerosis and may highlight patients at increased risk of developing scleroderma renal crisis, e.g. anti RNA III polymerase antibodies
	Anti-topoisomerase (Scl-70)	
	Anti-RNA III polymerase	
	Anti-centromere	
Urinalysis	Urine protein:creatinine ratio	Usually <2.5 g/24 h
	Microscopy	Confirm glomerular bleeding – dysmorphic red blood cells, 5–100 cells/high power field, granular casts
Cardiology	Echocardiography	Assess ventricular function, non-invasive assessment of pulmonary arterial systolic pressure, exclude pericardial effusions

mal changes and microvascular thrombi occur. Overall reduction in kidney cortical perfusion resulting from these vessel changes, as well as 'vasospasm', drives increased renin secretion associated with juxtaglomerular apparatus hyperplasia. This likely fuels the malignant hypertension seen in scleroderma renal crisis (Steen, 2003). Sheer stresses within the vessels may also perpetuate the intravascular haemolytic events. *Figure 1* shows typical histological features in scleroderma renal crisis.

Although such vascular changes are typically seen in renal biopsies performed following scleroderma renal crisis, similar vascular pathology may be present in patients with accelerated hypertension from other causes. It appears likely that the triggers for scleroderma renal crisis are multi-factorial, where vascular changes, progressive reduction in renal blood flow and hyperreninaemia in response to ischaemia are all aggravated by a precipitating cause or causes. Factors that worsen renal haemodynamics, and thus tip the balance in favour of scleroderma renal crisis, may include pregnancy, congestive cardiac failure and acute changes in both intravascular volume and body temperature as well as the use of non-steroidal anti-inflammatory drugs or corticosteroids (Steen, 2003).

Investigations

The diagnosis includes demonstrating acute kidney injury in the context of accelerated hypertension while identifying associated complications. Urinalysis and microscopy may detect proteinuria and microscopic haematuria, and dysmorphic red blood cells may be seen on subsequent microscopy. Proteinuria can be quantified by random protein:creatinine ratio (typically <2.5 g/24 hours).

In addition to routine blood tests, indices of microscopic haemolytic anaemia including lactate dehydrogenase should be tested and blood film performed in all cases to detect both thrombocytopenia and the presence of normochromic fragmented red cells. Haptoglobin levels usually fall in the presence of free circulating haemoglobin and can occasionally be a useful adjunctive test. The degree of uraemia and life-threatening hyperkalaemia must be established without delay. Serum autoantibody profiles are interesting but unlikely to affect the acute management.

Chest radiograph and electrocardiography should be performed in all patients and there should be a low threshold for requesting an echocardiogram to assess ventricular function and look for pericardial effusions that are often present and occasionally compromising. *Table 3* summarizes the relevant investigations.

Management

The primary aim of therapy in scleroderma renal crisis is to control blood pressure, but the rate of reduction has to be carefully considered along with the choice of agent. Short-acting angiotensin-converting enzyme inhibitors (e.g. captopril) are useful (if available) before introducing longer-acting agents so that blood pressure can be titrated more precisely in the early days following presentation. Intravenous therapy is often combined with angiotensin-converting enzyme inhibition. Nitrates are acceptable but iloprost infusions (5 ng/kg/min), titrated to achieve 10–15 mmHg systolic blood pressure reduction in the first 24 hours, offer additional theoretical advantages especially in cases of severe microangiopathic haemolytic anaemia.

Intermittent forms of renal replacement therapy to manage complications of acute kidney injury and fluid overload may need to be undertaken, but continuous veno-venous haemofiltration or peritoneal dialysis may be preferrable in the acute setting when small changes in intravascular volume can alter clinical state dramatically. Early involvement with critical care is highly recommended. Measurements of systemic vascular resistance are particularly useful (if available) as vasodilator therapy can be titrated against systemic vascular resistance to reduce blood pressure and cardiac after-load and gain control of the acute scleroderma renal crisis.

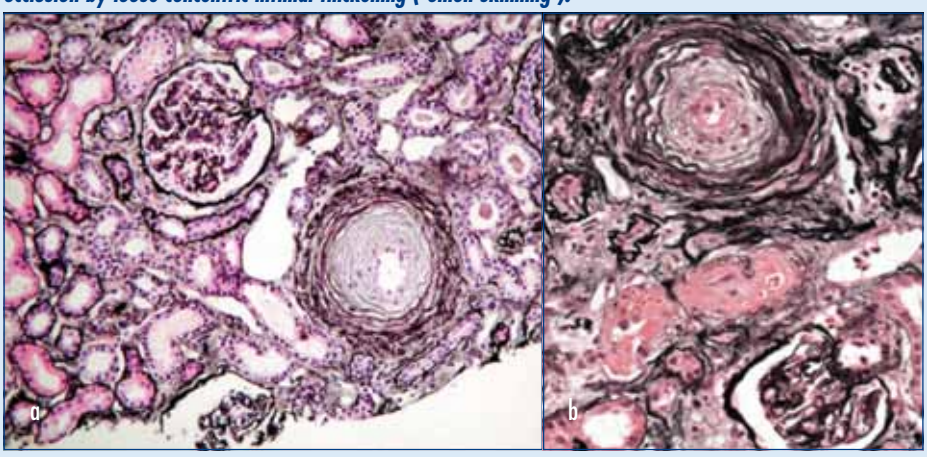
Prognosis

Historically, scleroderma renal crisis was almost universally fatal. There are early reports of occasional patients surviving following nephrectomy to control hypertension followed by maintenance dialysis. The advent of angiotensin-converting enzyme inhibitors in the 1970s revolutionized the acute management of hypertensive renal crisis. Even so, many patients still end up requiring renal replacement therapy. However, recovery of renal function is relatively common and has been reported following both maintenance haemodialysis and peritoneal dialysis. Although a significant proportion of patients demonstrate such recovery within the first 12 months, vascular remodelling and improvement in renal function can occur up to 3 years after scleroderma renal crisis (Penn et al, 2007).

Early diagnosis of scleroderma renal crisis and blood pressure control can avert the need for renal replacement therapy. It is important to appreciate that the serum creatinine level in such patients usually continues to rise for a number of days despite adequate blood pressure control, with plateauing, before falling slowly as renal function improves.

Identifying patients at increased risk of developing scleroderma renal crisis is important and prompt control of blood pressure using angiotensin-converting

Figure 1. Severe acute small vessel vasculopathy. (a) and (b) (silver stain) show shrunken collapsed glomeruli with wrinkling of basement membranes, particularly (b). Interlobular arteries show virtual occlusion by loose concentric intimal thickening ('onion skinning').



enzyme inhibitors should be instituted in all patients who develop scleroderma renal crisis. Angiotensin-converting enzyme inhibitors should also be continued in patients who survive a scleroderma renal crisis, particularly in those requiring maintenance renal replacement therapy, as continued angiotensin-converting enzyme inhibition is associated with an improved chance of recovering independent renal function (Steen and Medsger, 2000). Consideration of renal transplant can be delayed even up to 2 years until it is certain that late renal recovery has been excluded.

Endothelin receptor blockers

Evidence is growing for the role of dysregulation of the endothelin system in patients with scleroderma renal crisis. Three isoforms of endothelin exist (ET-1, ET-2 and ET-3), all of which have potent vasoconstrictive properties and have homology to sarafotoxins found in snake venom (Mayes, 2003). The level of ET-1 production is increased in systemic sclerosis and regulated at a genetic level. However, the presence of angiotensin II, hypoxia and shear stress all significantly increase ET-1 production significantly, augmenting vasoconstriction. In addition, specific ET-B receptor polymorphisms have been linked to scleroderma renal crisis and ET-1 expression has been shown to be upregulated. Endothelin receptor blockers have therefore been proposed as a target for therapy in addition to angiotensin-converting enzyme inhibitors in scleroderma renal crisis.

In a single small open-label trial, six patients (within 6 weeks of confirmed scleroderma renal crisis) received bosentan (endothelin receptor blocker) for 1 month at 62.5 mg and then subsequently 5 months at 125 mg for a total of 6 months. The therapy was well tolerated in this small group but overall mortality was not significantly different from standard therapy (Penn et al, 2009).

Prophylactic angiotensin-converting enzyme inhibitors

The prophylactic use of angiotensin-converting enzyme inhibitors in patients with systemic sclerosis remains controversial. There is currently a lack of evidence advocating administration of prophylactic angiotensin-converting enzyme inhibitors and some reports have highlighted unfavourable outcomes and increased risk of requiring long-term renal replacement therapy. It has been speculated that angiotensin-converting enzyme inhibitor therapy may actually mask hypertension thus leading to patients presenting with delayed or 'normotensive' scleroderma renal crisis, which carries a poorer prognosis (Penn et al, 2009). However, it is now widely recommended that patients should monitor their home blood pressure readings and that there should be a low threshold for the introduction of angiotensin-converting enzyme inhibitor therapy in those patients at risk of developing scleroderma renal crisis (*Table 3*).

Conclusions

Scleroderma renal crisis is a life-threatening complication of systemic sclerosis, the management of which has been revolutionized over the last few decades with the prompt and early use of angiotensin-converting enzyme inhibitors as well as dialysis and supportive care. Patients who develop rapidly progressive oligouric or anuric acute kidney injury and/or rapidly progressive hypertension with no explanation other than systemic sclerosis must therefore be swiftly identified and managed with rheumatology, nephrology and critical care services in order to optimize outcome.

Regular assessment of blood pressure is mandated in all new systemic sclerosis patients as early recognition of scleroderma renal crisis may reduce mortality and the need for dialysis. Autoantibody profiling may help identify those at particular risk of scleroderma renal crisis. The use of prophylactic angiotensin-converting enzyme inhibitors has not yet been established as beneficial in preventing scleroderma renal crisis but they have a very clear role in managing the acute crisis and in encouraging recovery of renal function even when dialysis is established. Careful control of blood pressure, systemic vascular resistance and optimizing intravascular volume as well as advanced supportive care has improved short-term survival, yet morbidity and mortality is still relatively high. **BJHM**

Figure 1 *is reproduced courtesy of Professor AJ Howie, Department of Histopathology, Royal Free Hospital, London.*

Conflict of interest: none.

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KEY POINTS

- Angiotensin-converting enzyme inhibitors are first-line therapy for the treatment and management of scleroderma renal crisis.
- All new systemic sclerosis patients should have regular blood pressure checks and a high index of suspicion maintained so that prompt interventions can be taken if scleroderma renal crisis develops. A diagnosis of scleroderma renal crisis should be considered in all patients who present with accelerated hypertension.
- Native renal function in scleroderma renal crisis patients may improve even after many months of renal replacement therapy. Continuation of angiotensin-converting enzyme inhibitors has been shown to improve the chances of discontinuing dialysis.