Seminars in Arthritis and Rheumatism 44 (2015) 687–694

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Scleroderma renal crisis

Nilanjana Bose, MD, Andres Chiesa-Vottero, MD, Soumya Chatterjee, MD, MS, FRCP*

Department of Rheumatic and Immunologic Diseases, Orthopaedic and Rheumatologic Institute, Cleveland Clinic, 9500 Euclid Ave, Desk A50, Cleveland, OH 44195

ARTICLE INFO

Keywords:
Scleroderma renal crisis
Scleroderma
Systemic sclerosis
Angiotensin-converting enzyme inhibitor

ABSTRACT

Objectives: To discuss the pathophysiology, risk factors, clinical manifestations, diagnosis, treatment, prevention, and outcomes of scleroderma renal crisis (SRC), a serious yet potentially treatable complication of scleroderma (systemic sclerosis).
Methods: A PubMed search for articles published up until April 2014 was conducted using the following keywords: scleroderma, systemic sclerosis, scleroderma renal crisis, renal, treatment, and prognosis. Literature was carefully reviewed, and different risk factors, treatment options, prognostic factors, and survival data were assessed.
Results: SRC occurs in about 10% of all patients with scleroderma. It is characterized by malignant hypertension and progressive renal failure. Around 10% of SRC cases may present with normal blood pressure, termed normotensive renal crisis. The etiopathogenesis is presumed to be a series of insults to the kidneys resulting in endothelial injury, intimal proliferation, and narrowing of renal arterioles leading to decreased blood flow, hyperplasia of the juxtaglomerular apparatus, hyperreninemia, and accelerated hypertension. Risk factors include rapid skin thickening, use of certain medications such corticosteroids or cyclosporine, new-onset microangiopathic hemolytic anemia and/or thrombocytopenia, cardiac complications (pericardial effusion, congestive heart failure, and/or arrhythmias), large joint contractures, and presence of anti-RNA polymerase III antibody. Since the 1970s, with the advent of angiotensin-converting enzyme (ACE) inhibitors, mortality associated with SRC decreased from 76% to $<10\%$. Some patients may progress to end-stage renal disease and need dialysis. Renal transplantation has improved survival, though SRC may recur in transplanted kidneys.
Conclusions: More than 60 years after its initial description, SRC still remains an important cause of morbidity and mortality in scleroderma. Since the advent of ACE inhibitors, the prognosis of SRC has improved substantially. Prompt diagnosis and treatment may help prevent adverse outcomes and improve survival.

Introduction

Scleroderma or systemic sclerosis (SSc) is a rare autoimmune disease that predominantly affects women of childbearing age. This condition causes fibrosis in the skin and subcutaneous tissue and frequently involves the internal organs such as heart, lungs, kidneys, and gastrointestinal tract. Scleroderma can have 3 main phenotypes: limited disease, diffuse disease, and overlap syndrome. Limited scleroderma (formerly CREST syndrome) is associated with skin thickening limited to the areas distal to the elbows and knees with less internal organ involvement; however, patients have a higher incidence of pulmonary arterial hypertension. Diffuse scleroderma manifests with Raynaud phenomenon, puffy hands, fatigue, arthralgias, and palpable tendon friction rubs and progresses to diffuse skin thickening extending beyond the elbows and knees and involving the proximal extremities and the trunk. These patients are also more prone to develop widespread fibrosis of the internal organs. Overlap syndrome can be seen in patients presenting with features of scleroderma, lupus, myositis, or inflammatory arthritis.

Current reviews estimate the incidence of scleroderma to range between 10 and 43 per million per year and the prevalence to be around 56–341 per million [1]. Domsic et al. [2] have proposed the use of the "skin-thickness progression rate" (STPR) as a tool for monitoring and treating these patients. They found that mortality at 2 years is strongly associated with age >55 years [odds ratio (OR) $=$ 2.57], cardiac involvement (OR $=$ 2.27), tendon friction rubs (OR $=$ 2.13), gastrointestinal involvement (OR $=$ 1.83), and rapid STPR (OR $=$ 1.74), along with other factors such as male

Drs. Bose and Chatterjee had full access to all of the data in the study, and they both take responsibility for the integrity and accuracy of the data.

* Corresponding author.
E-mail address: chattes@ccf.org (S. Chatterjee).

http://dx.doi.org/10.1016/j.semarthrit.2014.12.001
0049-0172/

gender (OR = 1.60) and anti-RNA polymerase III antibody (OR = 0.61) [2]. Currently, the leading causes of death in scleroderma are pulmonary fibrosis and pulmonary arterial hypertension.

Scleroderma renal crisis (SRC) has remained one of the most dreaded complications of scleroderma. It is regarded as a medical emergency. The cumulative incidence ranges between 10% and 19% [3,4]. However, since the 1970s, with the introduction of angiotensin-converting enzyme (ACE) inhibitors, the mortality and morbidity from SRC have decreased significantly. The 10-year survival among scleroderma patients has improved from 52% to 65% and survival among SRC patients from $<10\%$ to 65% [5].

Methods

A PubMed search for articles published up until April 2014 was conducted using the following keywords: scleroderma, systemic sclerosis, scleroderma renal crisis, renal, treatment, and prognosis. Articles published in English were reviewed, which included original research (limited to humans), case series, case reports, and review articles. The literature was carefully reviewed and pathophysiology, risk factors, treatment options, diagnostic modalities, prognostic factors, data on renal transplantation, prevention, outcomes, and survival data were assessed. Conclusions were based on the data from available literature sources and the authors' personal experiences.

Results and discussion

Historical perspective

In 1863, Auspitz [6] first reported renal involvement in scleroderma in a young locksmith with skin tightness who died of progressive uremia; however, no association was made between the 2 conditions at that time. At the turn of the century, Osler elucidated that patients with scleroderma succumb to "nephritis" [7]. Masugi and Ya-Shu [8] in 1938 and Talbott et al. [9] in 1939 described intimal hyperplasia and fibrinoid degeneration in renal interlobular arteries. In 1945, Goetz [10] coined the term "progressive systemic sclerosis" (PSS) to describe changes in the skin and renal vessels. Finally, in 1952, Moore and Sheehan [11] identified the specific renal lesions when they described 3 patients with scleroderma who died of uremia and had histopathologic changes in the kidneys; they coined the term "scleroderma renal crisis" to describe this entity of malignant hypertension and renal failure.

Definition

A universally accepted gold standard definition of SRC does not exist. An expert panel led by Steen et al. [12] suggested that the following clinical parameters need to be satisfied for the diagnosis of SRC: (a) systolic blood pressure (SBP) $\geq$ 140 mmHg, (b) diastolic blood pressure (DBP) $\geq$ 90 mmHg, (c) rise in SBP $\geq$ 30 mmHg, (d) rise in DBP $\geq$ 20 mmHg, (e) increase in serum creatinine by $\geq 50\%$ over baseline or serum creatinine $>120\%$ of upper limit of normal for the local laboratory, (f) proteinuria $\geq 2+$ by dipstick and confirmed by spot urine protein : creatinine ratio $\geq$ upper limit of normal, (g) hematuria $\geq 2+$ on dipstick or ≥ 10 red blood cells/high power of field (in the absence of menstruation), (h) platelet count $<100{,}000/\text{mm}^3$, and (i) hemolysis (evidenced by schistocytes or other RBC fragments on peripheral blood smear or elevated reticulocyte count). To this list of diagnostic criteria, the "International Scleroderma Renal Crisis Survey" (ISRCS) investigators also added another criterion: presence of hypertensive encephalopathy [13]. SRC can occur in around 10% of patients with scleroderma [3]; up to 10–25% of patients with diffuse scleroderma may develop SRC as compared to a minority (1–2%) of patients with limited disease [3,14]. Recent estimates suggest around 4.2% of patients with diffuse SSc and 1.1% of those with limited SSc develop this complication [15]. Rarely, SRC can be the initial manifestation of scleroderma.

The incidence of SRC has been decreasing over the years. Most patients with diffuse scleroderma develop SRC within the first 4 years of their disease, though late recurrences have been documented too; most patients are African American and are male [3].

Seasonal variation in SRC

Traub et al. reviewed 68 patients with SRC between 1955 and 1981; clinical evidence of SRC first appeared in winter and fall months in 43 cases versus 25 cases in spring and summer months ($p < 0.005$) [16]. However, this seasonal variation has not been substantiated in other studies.

Pathogenesis

Pathogenesis of SRC has not been clearly elucidated. It has been postulated that a series of insults affect the renal vasculature leading to this condition (Fig. 1). Initially, there is injury to the endothelial cells with intimal thickening and proliferation in the arcuate and interlobular arteries [17].There is a notable absence of inflammatory cells (lymphocytes and monocytes) in the renal vasculature. Platelet factors are released causing increased vascular permeability, fibrin deposition, and collagen formation, which lead to further luminal narrowing. Narrowed renal arterioles decrease renal cortical blood flow. In addition, episodic renal vasospasm or "renal Raynaud" may also contribute to decreased blood flow [18]. Decreased renal blood flow causes hyperplasia of the juxtaglomerular apparatus and release of renin. However, hyperreninemia and exaggerated renin response to cold challenge have been demonstrated in patients without SRC [19], and hence may not be predictive of SRC. A large prospective study looking at 57 patients also noted that isolated increases in plasma renin activity did not predict SRC [20].

Renal pathology

All diseases associated with thrombotic microangiopathy are characterized by endothelial injury and thrombus formation. The pathologic findings involve glomeruli and vessels, can be divided into acute and chronic lesions, and do not distinguish multiple disease entities associated with thrombotic microangiopathy. *Acute glomerular changes* include intracapillary fibrin thrombi, endothelial swelling and detachment from the underlying glomerular basement membrane, and red blood cell fragmentation. *Chronic glomerular changes* comprise a membranoproliferative pattern, mesangiolysis, segmental glomerular scars, organizing thrombi, glomerular ischemic changes, and sub-endothelial electron-lucent material. *Acute vascular changes* encompass intravascular fibrin thrombi and mucoid intimal edema. *Chronic vascular changes* entail vessel-wall sclerosis and intraluminal organizing thrombi [21].

In scleroderma, there is prominent small vessel involvement which predominates over glomerular changes. Intravascular thrombi (Fig. 2A) and mucoid intimal edema (Fig. 2B) may be seen. Small vessel thrombi are more abundant than glomerular thrombi (unlike the pathology seen in hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura) [22]. A review of 17 renal biopsies with SRC revealed that vascular thrombosis,