REVIEW

Renal Impairment in Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) represents a connective tissue disease, characterized by progressive fibrosis of the skin and internal organs, microvascular abnormalities, and alterations in cellular and humoral immunity. Renal impairment is a relatively common feature in patients with systemic sclerosis. It can take various clinicopathological forms, of which the most specific and severe manifestation is represented by scleroderma renal crisis. This presentation is characterized by acute onset of moderate to malignant hypertension and acute kidney injury. Although some progress has been made in management of scleroderma renal crisis with the introduction of angiotensin-converting enzyme inhibitors therapy, a large population of patients still presents a poor outcome, with up to 50 percent needing renal replacement therapy. Further understanding of disease pathogenesis may lead to improvement in patient's outcome and survival.

Keywords: scleroderma renal crisis, angiotensin-converting enzyme inhibitors, end-stage kidney disease.

Introduction

Systemic sclerosis (SSc) represents a rare, chronic connective tissue disease, characterized by progressive fibrosis of the skin and internal organs, microvascular abnormalities, and alterations in cellular and humoral immunity [1].

Systemic sclerosis can be classified by clinical presentation and visceral involvement in localized scleroderma, in which the fibrosis is limited to the skin, and systemic sclerosis, which also involves the internal organs [1,2]. The spectrum of localized scleroderma includes morphea, linear scleroderma and en coup de sabre. The major subsets of systemic sclerosis include limited cutaneous systemic sclerosis (lcSSc), diffuse cutaneous systemic sclerosis (dcSSc) and systemic sclerosis sine scleroderma. The

difference between the latter is based on the extent of skin involvement. Limited cutaneous systemic sclerosis involves skin sclerosis distal to the knees and elbows, whereas diffuse cutaneous systemic sclerosis is characterized by skin thickening proximal to the knees and elbows. SSc sine scleroderma is a rare subset in which patients develop vascular and serological features of SSc but have no detectable skin involvement [1].

Systemic sclerosis is a multisystem disease. The major organ impairment involves the skin, blood vessels, lungs, heart, kidneys, musculoskeletal system, and the gastrointestinal tract. The cutaneous manifestations include skin thickening and fibrosis, telangiectasia, digital tip ulcers, calcinosis cutis and Raynaud phenomenon [3]. Pulmonary involvement is present in more than 80 percent of patients with SSc and is divided in two major manifestations, represented by interstitial lung disease (fibrosis alveolitis) and pulmonary vascular disease, which leads to pulmonary arterial hypertension [3,4]. The cardiac involvement is common in SSc, but might be entirely asymptomatic. SSc can affect all anatomical heart structures, including pericardium, myocardium, and the conduction system [4, 5]. Gastrointestinal involvement is also very common in patients with SSc. The complications that can occur are represented by gastroesophageal reflux, gastroparesis, gastric antral vascular ectasia, mucosal ulcerations, sphincter dysfunction and primary biliary cholangitis [3,6]. Musculoskeletal system involvement is also a common feature of SSc. The manifestations are diverse and include arthritis, tendinitis, tendon friction rubs, joint contractures, and myopathy [3,4].

Renal involvement in systemic sclerosis

Renal involvement represents one of the most significant consequences of arterial lesion and vasospasm, that can remain subclinical until the late stages of disease progression [7]. It is a relatively common feature in patients with systemic sclerosis, affirmation derived from necroptic studies, which demonstrated that approximately 60-80 percent of patients with dcSSc have occult renal disfunction [8]. In addition, another study found that approximately 50 percent of asymptomatic patients have microalbuminuria, hypertension, or an elevated level of serum creatinine [9]. Impaired kidney function in SSc is associated with worse patient outcomes [10].

Spectrum of renal impairment in systemic sclerosis

The most specific and severe form of renal impairment in systemic sclerosis is scleroderma renal crisis (SRC). Other kidney manifestations include antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, antiphospholipid-associated nephropathy, isolated reduced glomerular filtration rate, high intrarenal arterial stiffness, and proteinuria [7]. Additional causes of kidney disfunction include prerenal disease (heart failure, diuretics, pulmonary hypertension), chronic hypertension, drug toxicity (cyclosporine, nonsteroidal anti-inflammatory drugs) and glomerulonephritis [11].

Scleroderma renal crisis

Scleroderma renal crisis is characterized by acute onset of renal failure, defined by reduction of more than 30 percent of estimated glomerular filtration rate, associated with abrupt onset of moderate to marked hypertension [7]. This manifestation occurs in 5 to 20% of patients with diffuse cutaneous SSc and only in 1 to 2% of patients with limited cutaneous SSc [12,13]. Scleroderma renal crisis represents one of the leading causes of mortality in patients with systemic sclerosis (~ 11%). The prevalence of SRC is estimated at 2.4% [14].

Scleroderma renal crisis is a complication that usually develops in the early stages of the disease and may even be the initial manifestation of SSc. In a study which

comprised a series of 110 cases, SRC occurred at a median duration of 7.5 months after the first non-Raynaud manifestation of the disease [12].

Pathogenesis of scleroderma renal crisis

The pathogenesis of scleroderma renal crisis is still not completely understood, but a few genetic and environmental factors have been identified. Several genetic studies have concluded that there is a strong correlation between certain MHC classes, in particular HLA (human leukocyte antigen)-DRB1*0407 and HLA-DRB1*1304 and SRC [15].

The injury of endothelial cells, which determines intimal thickening and proliferation of the renal interlobular and arcuate arteries, is thought to be the primary pathogenic process. In addition to these structural changes, episodic vasospasm contributes to renal hypoperfusion, increased activation of renin-angiotensin system and juxtaglomerular hyperplasia. These alterations, along with the renal overexpression of endothelin-1 receptors, determine vasoconstriction and renal ischemia, which contributes to accelerated hypertension [7].

Clinical manifestations of scleroderma renal crisis

The clinical presentation of patients with SRC is variable. They usually present signs and symptoms generally associated with acute onset of moderate to malignant hypertension, such as hypertensive encephalopathy, hypertensive retinopathy, congestive heart failure, pericardial effusion, or arrhythmias [16]. In addition, as in other forms of acute kidney injury, patients may present with oliguria or with uremic symptoms [17]. It is important to note that in approximately 10 percent of patients, SRC occurs in the absence of hypertension. However, these patients have blood pressure values that are higher compared to their baseline values. Unfortunately, these patients have a worse kidney outcome, higher mortality rates and an earlier need for renal replacement therapy than patients with SRC who have hypertension. This can be partly attributed to delayed diagnosis leading to subclinical kidney injury and thrombotic microangiopathy [18].

Risk factors for developing scleroderma renal crisis

Several risk factors for developing scleroderma renal crisis have been identified. Diffuse skin involvement is the most important risk factor, especially if it is rapidly progressive [12,13]. In addition, the presence of tendon friction rubs and large joint contractures, which is a frequent occurrence in patients with dcSSc is associated with a marked risk for SRC [19]. Another known risk factor for developing SRC is prior use of glucocorticoids, particularly in moderate- to high-doses (≥15 mg/day of prednisone or equivalent) [12]. The risk for SRC can also pe predicted by the presence or absence of certain autoantibodies. Several studies concluded that the presence of anti-RNA polymerase III autoantibodies significantly increased the risk of SRC. The anti-centromere antibodies, specific for lcSSc, are seen much less common in SRC and their presence correlates with a lower risk for SRC [12,20]. Several reports suggest that cyclosporine, a renal vasoconstrictor, represents a potential risk factor for developing SRC [21]. Other potential risk factors for developing SRC include new-onset anemia and new cardio-vascular events [22].

Pathology of scleroderma renal crisis

The major histopathological findings in the kidney are localized in the interlobular, arcuate arteries and the glomeruli. The primary characteristic is intimal thickening and proliferation, which leads to obliteration of the vascular lumen, with concentric "onion-skin" hypertrophy [22].

Renal biopsy does not definitively establish the diagnosis of SRC because it cannot distinguish between the thrombotic microangiopathy caused by SRC and the similar histopathological changes found in malignant hypertension nephrosclerosis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), radiation nephritis, chronic kidney transplant rejection, and the antiphospholipid antibody syndrome [22]. Although the histologic findings are not specific, renal biopsy may be useful by providing prognostic information. In a study which reviewed 17 kidney biopsies from patients with SRC, the presence of severe glomerular ischemic collapse and a greater number of thrombosed blood vessels correlated with persistent kidney failure or death [23].

Diagnosis of scleroderma renal crisis

The diagnosis of scleroderma renal crisis is based upon the specific findings in high-risk patients with SSc. However, it is important to note that acute kidney injury is not always due to SRC in patients with SSC, therefor other potential causes for kidney disease must be excluded.

Although there is no generally validated definition of SRC, an international, multidisciplinary panel of experts from 16 countries identified a core set of items that characterize SRC using consensus methodology. The final core classification defined blood pressure parameters and required the presence of at least one associated feature for the diagnosis of SRC.

Hypertension was defined as >140/90 mmHg or a rise in systolic blood pressure >30 mmHg or in diastolic blood pressure >20 mmHg.

The associated manifestations in this definition included the following: acute kidney injury defined by the KDIGO criteria, microangiopathic hemolytic anemia and thrombocytopenia, organ dysfunction (hypertensive retinopathy, hypertensive encephalopathy, acute heart failure, acute pericarditis) and histopathological findings in kidney biopsy consistent with SRC [24].

Screening for scleroderma renal crisis

Blood pressure should be measured on a regular basis in all patients with SSc. High-risk patients should monitor their blood pressure daily. For other patients a biweekly measurement should suffice.

Patients with a basal blood pressure <120/70 mmHg, which present a persistent rise of 20 mmHg in systolic blood pressure and/or a persistent rise of 10 mmHg in diastolic blood pressure, should be further investigated for SRC. Also, patients on antihypertensive treatment which present persistent blood pressure >150/90 mmHg which doesn't respond to dose adjustment, should be further evaluated for SRC.

Patients with SSc should measure their serum creatinine level every three months. An elevation in this serum marker should raise concern of impending SRC [12].

Treatment options for scleroderma renal crisis

The key to proper management of SRC is effective and prompt blood pressure control. Studies have shown that if left untreated, SRC can determine rapid deterioration of renal function within a period of less than one month, with death occurring within one year [25]. Early detection is crucial because the success of antihypertensive treatment depends on its initiation before irreversible kidney injury has occurred. The EULAR recommends angiotensin-converting enzyme inhibitors (ACE-I) as first-line treatment, with captopril being the preferred therapeutic agent because of its rapid onset and short duration of action, which allows a better dose titration [22]. Several studies have compared the efficacy of different antihypertensive agents for treating SRC. The results have shown that ACE-I are associated with greater efficacy in maintaining normal blood pressure values, better preservation of kidney function, and

significantly higher survival rate in patients with SRC. In addition, ACE-I efficacy has been proven even for patients with end-stage kidney disease [12,26]. If proper blood pressure control is not achieved at the maximum tolerated doses of ACE-I, other antihypertensive drugs should be initiated, preferably a dihydropyridine calcium channel blocker, such as amlodipine [22]. Angiotensin II receptor blockers (ARBs) might be expected to be a good alternative for patients with ACE-I intolerance, but their efficacy has yet to be proven. If necessary, other antihypertensive agents can be added, such as diuretics or alpha blockers. Beta blockers should be avoided because of the risk of aggravating vasospasm in patients with SSc. In severe cases of SRC, endothelin-1 receptor antagonists (such as bosentan) or renin antagonists can be used, however there is limited data regarding their long-term efficacy and safety [22]. Eculizumab, a humanized recombinant monoclonal antibody directed against complement component 5, can be used as a rescue therapy in SRC. However, limited evidence is available regarding safety and efficacy of complement inhibitors in patients with SRC [7, 22].

Scleroderma renal crisis and end-stage kidney disease

Despite proper treatment, permanent dialysis may be needed for approximately 20 to 50 percent of SRC patients. A study from the United States Renal Data System (USRDS) revealed that survival on dialysis in patients with SRC is worse than in other forms of ESKD [27]. With proper ACE-I treatment, up to half of the cases requiring renal replacement therapy can eventually discontinue dialysis, but this may take up to 18 months since the initial SRC, therefor decisions regarding renal transplantation do not need to be made immediately following an episode of SRC [22].

Kidney transplantation offers superior survival rates in SSc compared with long-term dialysis. However, renal transplantation is not always possible in patients with SRC, mainly due to the severity of the extrarenal manifestations of SSc [22].

Conclusions

Renal impairment is a relatively common occurrence in patients with SSc. The spectrum of kidney involvement includes a variety of abnormalities, of which the most specific and life-threatening presentation is scleroderma renal crisis. Patients with SRC typically present with hypertension, but there is a subgroup of patients with normal blood pressure values at presentation, which have a poorer renal prognosis and higher mortality rates than the patients with hypertensive SRC. Early diagnosis and aggressive treatment with ACE-I represents the key management of SRC. Unfortunately, despite proper treatment, approximately 20 to 50 percent of patients with SRC progress to end-stage renal disease. However, a significant proportion recovers sufficient kidney function to discontinue renal replacement therapy. In patient with SSc there is a strong association between renal impairment and patients' outcomes, therefor active screening should be performed to identify patients at risk of developing SRC.

Author Contributions:

A.C. conceived the original draft preparation. A.C., A.M., and O.P. were responsible for conception and design of the review. VA.I., and O.P. were responsible for the data acquisition. VA.I, A.M., and O.P. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. A.C., A.M., VA.I., and O.P. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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