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Overview of Scleroderma Renal Crisis - A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Scleroderma renal crisis is a life-threatening condition. It usually starts with a sudden onset of severe hypertension, followed by renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anemia. Renal ischemia, hyperplasia of the juxtaglomerular apparatus, activation of the renin-angiotensin-aldosterone system (RAAS), and an increase in blood pressure are caused by decreased blood flow caused by structural changes in

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the blood vessels as well as renal vasospasm ("Raynaud's phenomenon"). This overview discusses the evaluation, diagnosis, and treatment of scleroderma renal crisis, emphasizing the importance of early detection of disease, strong correlation of corticosteroids intake and the disease incidence, and best approach of such cases.

Keywords: Scleroderma renal; renal; renal failure; encephalopathy; hypertension.

1. INTRODUCTION

Scleroderma renal crisis is a life-threatening condition. It usually starts with a sudden onset of severe hypertension, followed by renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anaemia [1]. Scleroderma is a rare multisystem immunological disease that affects one to two people out of every 100,000 people. Immune activation, autoantibody synthesis, fibroblast dysfunction, extracellular matrix deposition, and vasculopathy are all symptoms of this condition. On the basis of the level of skin involvement, people with scleroderma are divided into two subsets: limited and diffuse. These clinical characteristics, in combination with autoantibody profiles, can help predict clinical outcomes. Renal illness, particularly scleroderma renal crisis (SRC), is linked to a higher risk of death in scleroderma patients [2- 9].

Atypical presentations, such as systemic sclerosis sans scleroderma and/or the presence of uncommon antibodies, can delay the diagnosis of this disease in some patients [10].

SRC is a thrombotic microangiopathy with substantial small vessel involvement showing as myxoid intimal alterations, thrombi, onion skin lesions, and/or fibrointimal sclerosis on histologic examination. Renal biopsies are useful for verifying the clinical diagnosis, removing overlapping/superimposed disorders that could cause acute renal failure in Scleroderma patients, forecasting the clinical outcome, and optimizing patient care [11].

The use of angiotensin-converting enzyme inhibitors (ACE-I) to treat SRC has been appropriately synonymous with a favourable outcome over the past three decades, and has transformed the trend of SRC mortality. Despite this, SRC is still one of the top four reasons of death among Scleroderma patients [12].

SRC is still a major source of morbidity and mortality in scleroderma more than 60 years after it was first described. The prognosis for SRC has significantly improved after the introduction of ACE medications. Prompt diagnosis and treatment can help patients avoid negative outcomes and live longer [13].

2. INCIDENCE AND PROGNOSIS

SRC is becoming less common, possibly due to vigorous early treatment with angiotensin-converting enzyme inhibitors (ACEi). SRC, on the other hand, affects about 10% of people with diffuse scleroderma and 2% of patients with circumscribed illness in the United States. The Scleroderma Trials and Research (EUSTAR) database of the European League Against Rheumatism (EULAR) suggests a lower prevalence (5 percent of diffuse scleroderma and 2% of confined scleroderma), and a retrospective cohort study from Japan revealed a prevalence of 3.2 percent. Geographic variances in autoantibody profiles, notably anti-RNA polymerase III anti-bodies, are most likely to blame for these disparities in prevalence [2].

SRC affects roughly ten percent of all scleroderma patients. Malignant hypertension and gradual renal failure are the hallmarks of this condition. Around 10% of SRC patients will have normal blood pressure, which is referred to as normotensive renal crisis [13].

Scleroderma is an independent predictor of mortality in the dialysis population, but it is also an independent predictor of renal recovery, according to retrospective investigations of patients with SRC who require dialysis. Renal functional recovery rates in the scleroderma population vary by geography, with rates as low as 10% in Australia and as high as 34–38 percent [2].

Renal transplant survival rates are comparable to those reported in individuals with lupus and other connective tissue illnesses who receive kidney transplants. Renal transplant survival rates in the scleroderma population were 53% for deceased donor allografts and 100% for live donor allografts, according to the ANZDATA registry [2].

Females are more commonly affected by SRC than males. This could be due to the fact that the female population has a higher prevalence of Scleroderma . Skin thickening that progresses quickly in patients with Scleroderma, as well as excessive corticosteroid doses, are risk factors for the development of SRC. However, SRC has been reported in rare occasions as a result of topical steroid usage. Older age and male sex have been proposed as negative prognostic variables in patients with SRC who had normal or modestly increased blood pressures. Due to delayed diagnosis, the poor prognosis in normotensive SRC patients may represent continuous subclinical renal injury leading to severe irreversible loss of the renal parenchyma [11].

3. ETIOLOGY

Patients with diffuse scleroderma (10% to 25%) experience the most cases of scleroderma renal crisis, compared to just 1% to 2% of patients with confined disease. Scleroderma renal crisis frequently develops early in the course of scleroderma, with up to 75% of cases appearing within the first 4 years of diagnosis, and the median duration of scleroderma at the time of diagnosis of scleroderma renal crisis being 8 months [1].

Diffuse skin involvement, especially with rapid progression, the presence of anti-RNA polymerase III antibod-ies, corticosteroid therapy in doses greater than 15 mg per day, tendon friction rubs, new onset anaemia, pericarditis, and congestive heart failure are all risk factors for scleroderma renal crisis [1,14- 18].

Corticosteroid medication has been related to SRC, with 60 percent of patients receiving corticosteroids before to presentation. Many SRC patients had a recent history of high-dose corticosteroid treatment (e.g. prednisolone or equivalent at >15 mg/day), according to Steen and Medsger [19- 22].

The clinical features of SRC's initiation and progression point due to sudden onset of severe stress, such as a cold or an autoimmune insult to susceptible arteries and arterioles. Renal injury becomes self-perpetuating when renin activity is exceedingly high, causing an increase in blood pressure and further renal and systemic vascular damage [23].

4. PATHOPHYSIOLOGY

The pathophysiology of scleroderma renal crises remains unknown. In the early phases of endothelial cell injury, structural changes in blood arteries (intimal thickening and proliferation, fibrin deposition) occur. Renal ischemia, hyperplasia of the juxtaglomerular apparatus, activation of the renin-angiotensin-aldosterone system (RAAS), and an increase in blood pressure are caused by decreased blood flow caused by structural changes in the blood vessels as well as renal vasospasm ("Raynaud's phenomenon"). The essential increase in blood pressure damages renal blood vessels even more, setting off a vicious cycle that eventually leads to malignant hypertension [1].

T helper lymphocyte type-2 (TH-2) activation, cytokine production (especially Il-4, IL-13, and IL-17), and excess collagen buildup have all been linked to Scleroderma, which may play a role in the development of vasculopathy [11].

SRC induces a proliferative obliterative vasculopathy with concentric ‘onion peel' constriction of arterioles and glomerular ischemia. There are no inflammatory or immunological deposits in the glomeruli. These pathologic findings, together with the presence of significant hyperreninemia, suggest that altered juxtaglomerular apparatus perfusion, which causes renin-driven hypertension, could be a driver of SRC. Autopsy investigations, on the other hand, show renal vascular abnormalities in some people who do not have clinical indications of SRC. Furthermore, some individuals demonstrate physiologic evidence of episodic renal vasospasm (‘renal Raynaud's phenomenon'), which, while correlating with baseline and cold-induced renin levels, does not predict the development of SRC [2].

Antiendothelial cell antibodies, which can cause endothelial cell death , have also been found in up to 85 percent of Scleroderma patients . Endothelin-1, a protein involved in blood vessel constriction, and its receptor, endothelin-B, were found to be overexpressed in the small vessels of two SRC patients. In addition, the C4d complement degradation product, which is thought to be an immunologic marker of antibody-mediated rejection in renal allografts, has been found in native renal biopsies from a fraction of SRC patients [11].

In the pathophysiology of SRC, activation of the renin–angiotensin–aldosterone pathway appears to be crucial. There is evidence of juxtaglomerular apparatus hyperplasia, and high-dose ACEi can usually control blood pressure. Unfortunately, an increased plasma renin level does not indicate the onset of SRC [24,25,26].

5. SYMPTOMS AND RISK FACTORS

A quick and severe elevation in systemic blood pressure (although normotensive SRC has been described) and abrupt renal failure, with or without considerable microangiopathic hemolytic anaemia or thrombocytopenia, are common features of SRC. Headache, blurred vision, and dyspnea are common symptoms of SRC [11].

When it comes to risk factors, Rapid skin thickening, the use of certain medications like corticosteroids or cyclosporine, new-onset microangiopathic hemolytic anaemia and/or thrombocytopenia, cardiac complications (pericardial effusion, congestive heart failure, and/or arrhythmias), large joint contractures, and anti-RNA polymerase III antibody are all risk factors.

6. DIAGNOSIS

Since SRC can cause acute renal failure, a large increase in serum creatinine and a significant decrease in glomerular filtration rate would be expected (GFR). The median blood creatinine value in SRC patients at presentation was 200 mmol/l (2.3 mg/dl) in most cases [11].

In 43% of instances, thrombotic microangiopathy is discovered. In one-third of SRC patients, anti-RNA-polymerase III antibodies are detected. If SRC appears with characteristic symptoms, a renal biopsy is not required. In atypical forms, however, it can assist define prognosis and guide treatment. [24].

Eearly detection of Scleroderma is critical Because diagnosis of SRC may precede diagnosis of Scleroderma in up to 20% of patients. In other cases, there is no evidence of skin sclerosis at the time SRC develops [27]. Headaches, hypertensive retinopathy with visual abnormalities, encephalopathy, seizures, fever, and general malaise are all symptoms of SRC. Water and salt retention due to massive overload and oliguria are also prominent causes of pulmonary oedema. If you have arrythmia, myocarditis, or pericarditis, you may have a worse prognosis [19].

A number of differential diagnoses should be evaluated in the case of acute renal failure in a patient with Scleroderma. Malignant hypertension can accompany renal arterial stenosis. Hypovolemia might be mistaken for SRC. Dehydration, third space sequestration in the case of gut involvement and intestinal paresis, diuretics, NSAIDs, heart failure, and/or arrhythmia are all potential triggers [24].

7. LABORATORY FINDINGS

At the time of presentation, serum creatinine levels can be significantly elevated. Even after blood pressure is under control, it can rise for several days. Mild proteinuria (0.5 to 2.5 g/l) is usually detected on urinalysis. In the vast majority of instances, microscopic hematuria, commonly identified with a dipstick, corresponds to hemoglobinuria. In 43 percent of individuals with SRC, thrombotic microangiopathy develops, which is characterised by hemolytic anaemia and thrombocytopenia. Thrombocytopenia is usually mild, with counts of over 50,000/mm3 in the majority of cases, and returns to normal after blood pressure is controlled [24].

ANAs are seen in nearly all Scleroderma patients, and there is a clear link between SRC and an ANA speckled pattern positive status, which is found in 60% of SRC patients. Patients with Scleroderma -specific ARA (I and III) , which are detectable in 59 percent of SRC patients, had much higher rates of severe cutaneous and renal illness. Anti-fibrillarin or anti-U3-RNP antibodies (AFA) can also be used to detect young children who are at risk of developing Scleroderma internal organ symptoms, such as SRC . Patients with anti-centromere antibodies or anti-topoisomerase 1 antibodies, on the other hand, are less likely to develop renal illness [19,28,29,30].

Anti-nuclear antibodies (abs) are a frequent type of antibody. Anti-topoisomerase antibodies, which are detected in 30% of individuals with diffuse Scleroderma, are not predictive of the development of this symptom. Anti-RNA polymerase III abs, which are nearly exclusively found in diffuse Scleroderma, identify patients who are at risk. SRC will develop in 33 percent of these patients [24].

8. TREATMENT

In the etiology of scleroderma renal crises, RAAS activation is critical. Furthermore, the use of angiotensin-converting enzyme inhibitors (ACEIs) in this condition has reduced 1-year mortality to 24% from 85% prior to their use. As a result, the current strategy is to use ACEIs to quickly drop blood pressure and then maintain it [1].

This treatment has enhanced survival, reduced the need for dialysis, and allowed patients to stop dialysis after 6 to 18 months. The best outcome will be achieved with early diagnosis and aggressive beginning of ACE inhibitor therapy [24].

Captopril (D3-mercapto-2-methylpropionyl-L-proline) blocks peptidyl dipeptide hydrolase, which prevents angiotensin I from being converted to angiotensin II. It is ideal as first-line therapy because of its short half-life, which allows for easy titration. The goal is to reduce the SBP by 20 mmHg per 24 hours and the DBP by 10 mmHg per 24 hours until the blood pressure is within normal ranges while avoiding hypotension [2].

Additional treatment medications are needed to treat SRC that is resistant to ACE-I. Combining ACE-I with endothelin receptor blockers and complement component-targeting drugs has recently sparked interest. In high-risk patients, prophylactic use of ACE-I had little benefit [12].

Calcium channel blockers may be effective in patients who aren't getting enough blood pressure relief from ACE inhibitor medication alone. Iloprost given intravenously may also aid in the reversal of microvascular abnormalities. If pulmonary oedema is present, further oral hypotensive medications (e.g. labetalol) and nitrate infusion might be administered as needed. If there is significant thrombotic microangiopathy, plasma exchange may be considered. Intermittent haemodialysis or continuous venous–venous haemofiltration are used to support renal function [19]. Patients with SRC and microangiopathy, as well as those who are intolerant to ACE medications, appear to benefit from plasma exchange [31].

8.1 Renal Transplantation

Patients with SRC benefit from renal transplantation. Scleroderma patients with end-stage renal failure (ESRF) who receive a transplant had a better prognosis than those who are waiting for a transplant. However, because of the relatively high rates of renal functional recovery, it is normally recommended to wait until patients have been dialysis dependent for at least two years before undergoing transplantation [2].

9. CONCLUSION

Scleroderma Renal Crisis without doubt is one of the most dangerous cases, due its life-threatening case, luckily due to recent development in angiotensin converting enzymes inhibitors (ACEs) prognosis of this disease has rapidly improved, they have improved the survivability rate and reduced the need of dialysis and renal transplantation. Renal transplantation may still be need in some of the worst cases, but also recently there have been also multiple other drugs under development and testing, usage of additional agents such calcium inhibitors, Iloprost, and other hypertensive agents may be helful, we hope for better improvement of the treatment options for such cases. Corticosteroid seems to have correlation to incidence of the disease according to different studies, that's why it's recommended to use it only as necessary and if does by the minimum dosage required as high dosage seems to be cause of the disease. Early detection of systematic sclerosis (Scleroderma) is also critical Because diagnosis of SRC may precede diagnosis of Scleroderma in up to 20% of patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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