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Case Report

Scleroderma renal crisis triggered by ibuprofen: Insights on complement-directed therapy

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Abstract

Scleroderma renal crisis is a severe complication of systemic sclerosis with a poor prognosis. Therefore, identifying precipitating factors is essential. Among known risk factors, only few are reversible. On the contrary, anti-C5 therapy appears effective, at least in some cases. We describe a 59-year-old man with diffuse cutaneous systemic sclerosis who developed life-threatening scleroderma renal crisis following ibuprofen administration. Despite aggressive management, he did not improve. Renal biopsy have displayed features of thrombotic microangiopathy but no complement deposition. We then discuss the pathomechanism of scleroderma renal crisis that could drive eculizumab treatment since some renal biopsies exhibit complement deposits and others do not.

Keywords

Scleroderma renal crisis, complement, non-steroidal anti-inflammatory drug, eculizumab, renal pathology, scleroderma renal crisis

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Introduction

Scleroderma renal crisis (SRC) is a severe complication of systemic sclerosis associated with poor prognosis. Risk factors for further onset of SRC include anti-RNA polymerase III autoantibodies, tendon frictions rub, synovitis, and glucocorticoid therapy. SRC may develop without known risk factors, which means undisclosed precipitating factors exist. On the contrary, eculizumab represented a promising therapy for SRC patients. However, its effectiveness remains inconstant. Here we present a case of SRC induced by ibuprofen and whose pathomechanisms may help tailoring the treatment of SRC.

Case report

A 59-year-old man was transferred to the intensive care unit (ICU) for respiratory distress and rapidly progressive renal failure. He was admitted to hospital 5 days earlier because of malaise and fatigue over the last 15 days. Blood pressure was normal. On hospital admission, laboratory tests revealed hemoglobin 71 g/L, platelet count 116 G/L, C-reactive protein (CRP) 56 mg/L (N < 5), and creatinine 2.68 mg/dL. Ibuprofen was discontinued. Subsequent analyses indicated worsening of kidney function within 3 days.

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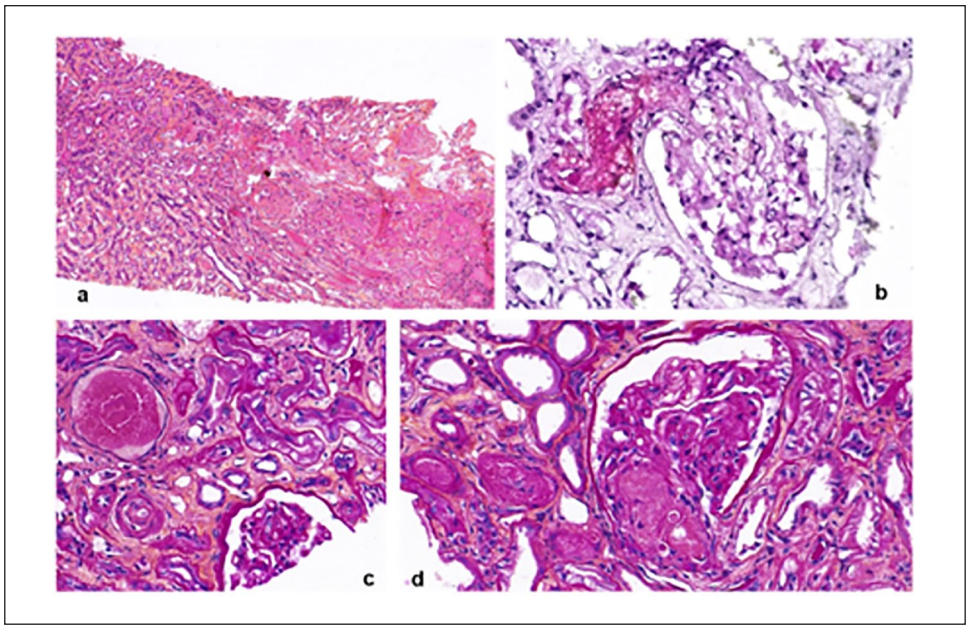

Figure 1. (a) Renal pathology of SRC: on low-power field, biopsy displays cortical necrosis on the right part of biopsy sample: HE × 10. (b) Fibrinoid necrosis of an arteriole emerging from the vascular pole of a glomerulus with shrinking flocculus: HE × 40. (c) Typical features of arteriolar wall thickening with intimal proliferation and narrowing of the vascular lumen: PAS × 40. (d) Another ischemic glomerulus with focal mesangiolysis: PAS × 40.

He was on hydroxychloroquin, indacaterol, and pantoprazole. His past medical record included chronic obstructive pulmonary disease, gastric ulcer, and diffuse cutaneous systemic sclerosis with anti-topoisomerase autoantibodies and anti-polymyositis/scleroderma (PM/Scl) autoantibodies which was diagnosed 3 years earlier. Besides cutaneous involvement, few lung infiltrates were noticed. He was then lost to follow-up.

One month before the ongoing admission, he had been hospitalized within the division of cardiology for pleuropericarditis. A workup, including mainly virus, bacteria, and mycobacterium tuberculosis, was performed which remained negative. He was then prescribed a 3 weeks course of ibuprofen plus colchicine. At that time, creatinine was 0.68 mg/dL.

Following his admission on ICU, laboratory tests have displayed hemoglobin 84 g/L, platelets 127 G/L, lactate dehydrogenase (LDH) 794 IU/L, haptoglobin < 10 g/dL, schizocytes count 17‰ (N < 10‰), and creatinine 4.34 mg/dL. These were consistent with microangiopathic hemolytic anemia (MAHA). Urinalysis showed microscopic hematuria, leukocyturia, and protein-to-creatinine ratio of 2.22. ADAMTS13 levels at 25% ruled out thrombocytopenic thrombopenic purpura. Complement pathway study showed normal factor B, factor Bb at 0.263 mg/dL (N < 0.153), and FBb/FB ratio of 2.35 (N < 1.07). Serum C5b-9 was normal. A gene panel study for atypical hemolytic uremic syndrome (aHUS) did not reveal any pathogenic variant.

Alongside with angiotensin conversion enzyme inhibitors (captopril), plasma exchanges were started daily until renal biopsy was carried out 1 week later.

Light microscopic examination showed (Figure 1) endothelial cells swelling within the glomerulus. Mesangiolysis foci were also present. Arterioles walls were thickened with intimal proliferation and disclosed fibrinoid necrosis. Immunofluorescence (IF) study was free of deposits. This was consistent with SRC.

Within the 1 week, there was no significant improvement of MAHA parameters. Renal function did not improve too (Table 1).

Hypoxia worsened and the patient required mechanical ventilation. Plasma exchanges were continued on alternate day. Finally, the patient deceased due to multiple organ failure.

Conclusion

The clinical feature of this patient was characterized by diffuse cutaneous systemic sclerosis with anti-topoisomerase and anti-PM/Scl antibodies. He developed normotensive SRC. There was neither proteinuria nor pre-existing renal disease. He took ibuprofen for 1 month prior to SRC onset. Non-steroidal anti-inflammatory drug (NSAID) inhibits prostacyclin synthesis. Renal prostacyclin regulates renal blood flow and renin secretion. A marked increase of renin levels at the time of SRC has been demonstrated. As a consequence, angiotensin II through its receptor constitutes one of the most crucial pathways in vascular smooth muscle cell proliferation. Prostacyclin signaling is essential to oppose vasoconstrictor pathways.[1,2] This case suggests that whenever it is suppressed by NSAID, this may precipitate acute vasculopathy.

Table 1. Selected renal and thrombotic microangiopathic biomarkers during the course of SRC.

	Day 1 PlEx started	Day 8 At biopsy	Day 14 PlEx stopped	Normal range
Creatinine (mg/dL)	4.34	CVVHDF	CVVHDF	0.7–1.20
Hemoglobin (g/L)	74	94	92	13–17
Platelets (G/L)	127	116	125	150–450
Schizocytes (‰)	17	12	15	<10
LDH (U/L)	796	327	371	<192
Haptoglobin (mg/dL)	<10	64	146	30–200
C3 (g/L)	0.83			0.8–1.64
C4 (g/L)	0.16			0.10–0.40
sC5-b9 (mg/L)	63			<314

SRC: scleroderma renal crisis; PlEx: plasma exchange; CVVHDF: continuous veno-venous hemodiafiltration; LDH: lactate dehydrogenase.

Renal biopsy exhibited classic findings of SRC. Neither complement nor immunoglobulin (Ig) deposition was observed. Plasma exchanges worked poorly, which suggests the lack of significant involvement of antibody-mediated SRC. The acute vasculopathy of SRC is the final step of a process where autoantibodies-mediated response, complement cascade, and proinflammatory vasoconstrictors factors interact. C5b-9 deposition includes both classical and alternate pathways activation. Taken alone, the latter does not predict response to anti-C5 therapy.[3] At least in one patient who responded to anti-C5 therapy, renal biopsy disclosed C3 and C5b-9 deposition alongside with C4d staining, which meant an active antibody-mediated process.[4] This suggests that anti-C5 therapy in SRC tends to be more effective with strong classical and alternate pathway activation, while lack of complement or Ig deposition results in poor response. This highlights the role of the triggering event initiating acute vasculopathy and the balance of the different processes leading to SRC. An ischemic insult mediated by NSAID would give poor response to anti-C5 therapy compared to the effectiveness that may result in case of immunological insult. Thus, renal biopsy might help tailoring patients who are best suited for anti-C5 therapy.

In conclusion, we describe the first-ever-reported SRC-induced NSAIDs-induced SRC. Its pathology findings suggested the ineffectiveness of eculizumab. It also provides along with already-described SRC cases a clue to select patients where eculizumab would be effective. In line with renal pathology, we hypothesize that two different subtypes of SRC exist depending on the triggering event: either toxic/ischemic or immunological insult. Finally, because of its over-the-counter use, NSAID administration should be carefully checked in SRC patients.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: the editor/editorial board member of *Journal of Scleroderma and Related Disorders* is an author of this paper; therefore, the peer-review process was managed by alternative members of the board, and the submitting editor/board member had no involvement in the decision-making process.

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Supplemental material

Supplemental material for this article is available online.

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