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CASE REPORT

IgA Nephropathy and Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE): A Case Report

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Abstract

IgA nephropathy (IgAN) remains the most frequent glomerular disease worldwide, with a broad spectrum of clinical and histological presentations. It has been associated with many secondary causes. The remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is an autoimmune disorder characterized by swelling in the extremities and negative autoimmune serological tests. The primary treatment for this condition involves the use of immunosuppressive therapy. Although several triggers have been identified, the exact cause of this condition is still unknown. We report a case of a 53-year-old man who presented with acute exacerbation of chronic kidney disease, whose etiological study revealed advanced IgAN, associated with pleural and pericardial effusions. Even with volume optimization and dialysis intensification, the pericardial effusion worsened, despite the resolving pleural effusion. Upper arm arthralgias were developed afterward. An extensive study ruled out other causes and the hypothesis of RS3PE syndrome was considered. Glucocorticoid (GC) therapy was instituted for 6 months with clinical improvement and no recurrence at 2 years follow-up. The complexity of this case shows the importance of considering a wider diagnosis for the complaints of arthralgias and volume overload, reinforcing the importance of clinical awareness for other concurrent conditions, whose treatment may be lifesaving.

Keywords IgA nephropathy · RS3PE syndrome · Case report

Introduction

IgA nephropathy (IgAN) is the most common glomerular disease worldwide, with a very extensive spectrum of clinical and histological presentations [1, 2]. Patients with IgAN may present with near-normal histology to severe crescentic glomerulonephritis, which clinically may be shown as asymptomatic hematuria to nephrotic syndrome [1].

There are many systemic conditions associated with secondary IgAN—gastrointestinal and liver disorders, viral and chronic infections, respiratory diseases, neoplasms, and autoimmune disorders—although the disease mechanisms are not clear, they seem to be the same as for primary IgAN [3]. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome was first described in 1985 by McCarthy et al. [4] as the sudden onset of bilateral symmetrical synovitis and seronegative inflammation with symmetrical pitting edema. To our knowledge, IgAN associated with RS3PE syndrome has not been described so far.

Case Report

We report a case of a 53-year-old man who presented with acute exacerbation of chronic kidney disease, associated with pleural and pericardial effusions, with the need for dialysis due to volume overload. A recurrent pericardial effusion and new-onset arthralgias suggested an overlapping diagnosis. A clinical diagram is provided in Fig. 1.

A 53-year-old man presented to the emergency department with shortness of breath, anasarca, and hypertension. He had a history of non-controlled hypertension, alcohol

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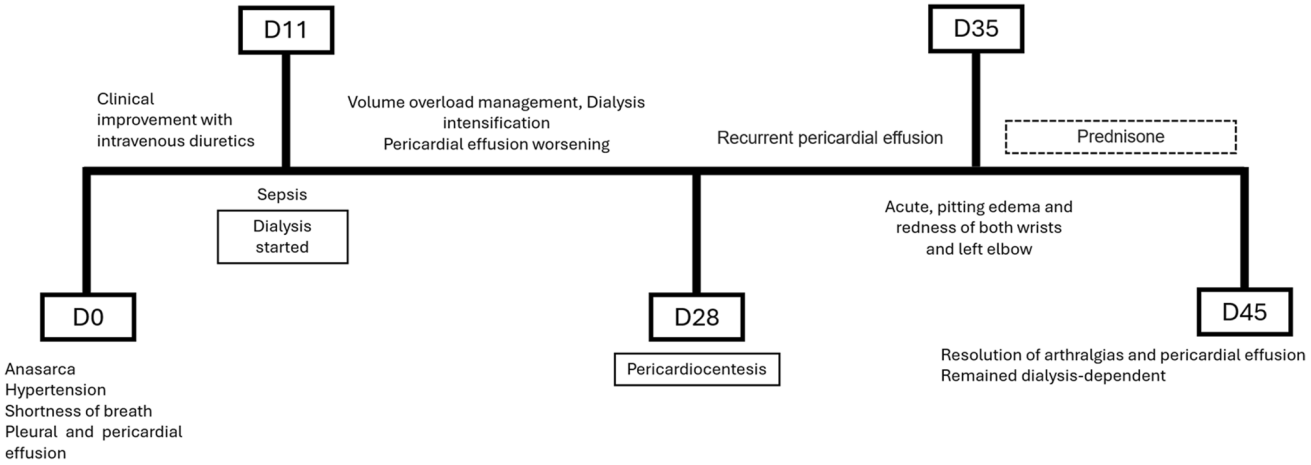

Fig. 1 Clinical diagram of the patient's evolution during hospitalization, with the most important findings, procedures, and pharmacological interventions

abuse (120 g per day), and previous hepatitis A. He had no history of chronic kidney disease and was not taking any medication.

On admission, his blood pressure was 163/103 mmHg, and pulse oximetry 96% at rest without an oxygen supply. He had reduced breath sounds on both sides and bilateral tender pitting edema up to the hip.

Blood tests revealed anemia (hemoglobin 8.2 g/dL), kidney dysfunction (creatinine 4.28 mg/dL, with no known previous creatinine; blood urea nitrogen (BUN) 72.8 mg/dL), low serum albumin (2.3 g/L), low bicarbonate (11.7 mmol/L), hyperkalemia (6.25 mmo/L), and increased N-terminal prohormone of brain natriuretic peptide (>35,000 ng/L).

The initial urinary protein-creatinine ratio (UPCR) was 2740 mg/g. Urinary sediment was remarkable for extensive dysmorphic hematuria (with >5% acanthocytes and erythrocytic casts) (Fig. 2). The kidney ultrasound revealed normal-sized kidneys and excluded obstruction.

A thoracic CT scan showed pericardial and pulmonary effusions.

The nephrological workup showed that immunoglobulin-A levels were increased (667 mg/dL), whereas the other relevant serological tests (related infectious, auto-immune, and neoplastic causes for kidney disease) were ruled out.

Kidney biopsy showed 6 glomeruli, including 1 globally sclerotic. The others revealed endocapillary hypercellularity, double-contours on glomerular basement membrane (GBM), and podocyte hypertrophy (Fig. 3). Subendothelial deposits were found in 2 glomeruli. The interstitium had 60% of fibrosis and lipidic protein reabsorption was found in the proximal tubules. Immunofluorescence was revealed on 4 glomeruli for immunoglobulin A (IgA) (2+), κ (1+) and λ (3+) light chain, and C3 (2+) deposition in the glomerular mesangium (Fig. 3). These findings endorsed the IgA nephropathy diagnosis, accounting for M0E1S0T2-C0, according to Oxford Classification.

Initial medical management included intravenous diuretics with good clinical response but worsening

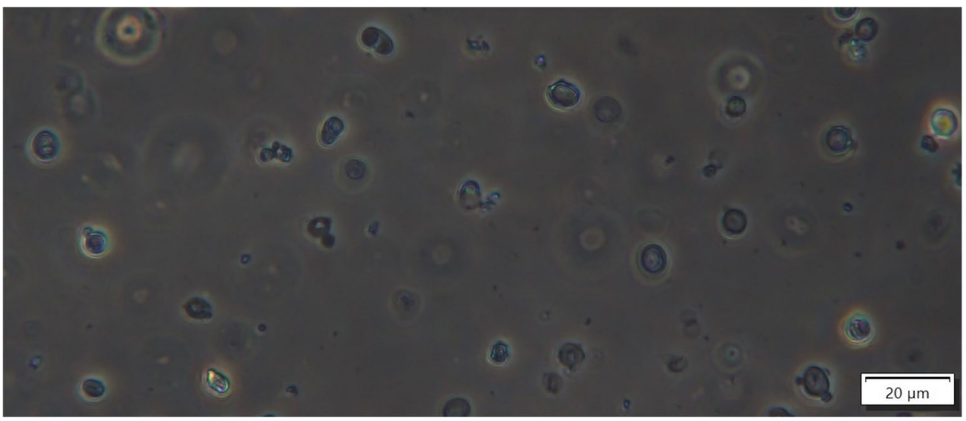

Fig. 2 Dysmophic red blood cells, under phase contrast (×400)

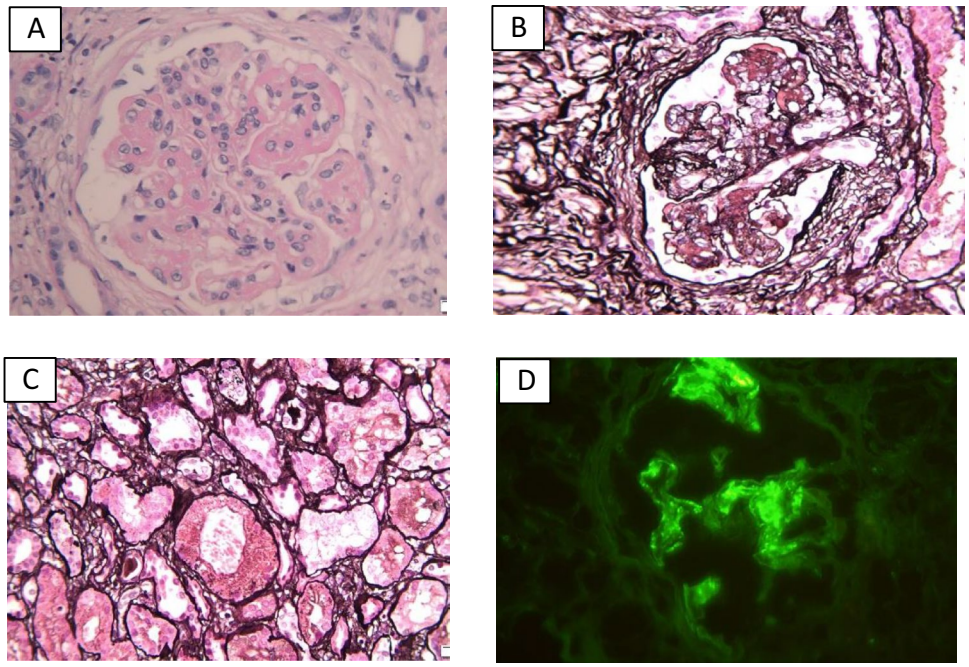

Fig. 3 Kidney biopsy findings. **A** Light microscopy shows mesangial hypercellularity and endocapillary hypercellularity (periodic acid–Schiff). **B** Endocapillary hypercellularity and subendothelial deposits are observed in the basement membrane (silver stain). **C** Tubular atrophy and tubular edema (silver stain). **D** Immunofluorescence staining for IgA shows mesangial and parietal staining

pericardial effusion. Intercurrent urinary sepsis caused the further worsening of kidney function with the need for dialysis.

Despite the intensification of ultrafiltration and dialysis, pericardiocentesis was necessary to avoid cardiac tamponade. The cytological analysis of the pericardial effusion excluded the neoplastic and infectious causes. Pleural effusion was resolved by this time.

One week after the pericardiocentesis, the patient had recurrent pericardial effusion alongside new symptoms of acute, pitting edema and redness of both wrists and left elbow. The joint ultrasound confirmed synovitis. The laboratory results showed elevated C-reactive protein (CPR) (7.4 mg/L) and an extensive autoimmune (antinuclear antibody, extractable nuclear antigen, DNA double-stranded antibodies), infectious, and malignant workup was performed excluding these causes.

Prednisone was started at 20 mg (0.3 mg/kg) for 5 days with remission of arthralgias. Relapse occurred at 48h after discontinuation of prednisone. So, the diagnosis of R3SPE syndrome was considered and prednisone was restarted. After restarting prednisone, there was sustained improvement in pericardial effusion and joint complaints.

The patient was discharged home on prednisone taper after the resolution of arthralgias and pericardial effusion. Prednisone therapy was stopped about 6 months after and the patient remains free of recurrent symptoms at 2 years of follow-up.

Despite the normal-sized kidneys and less than 80% of interstitial fibrosis supporting a more favorable renal prognosis, the patient remained dialysis dependent for persistent volume overload refractory to diuretic therapy and dietary fluid restriction.

Discussion

We report a case of a 53-year-old man presenting with anasarca, hypertension, hypoalbuminemia, subnephrotic proteinuria, and dysmorphic hematuria.

The histology showed advanced IgAN with a predominance of mesangial deposits, as well as endovascular proliferation and subendothelial deposits favoring secondary causes [1].

Considering the IgAN diagnosis, the patient had heavy drinking habits, although no clinical signs of chronic hepatic disease were found and abdominal ultrasound did not show hepatic alterations. No further potential secondary cause could be ascertained.

The clinical evolution led to dialysis, mostly due to refractory volume management overload. Even after ultrafiltration optimization, the pericardial effusion worsened and was associated with new-onset arthralgias that responded well to GC therapy. These findings endorsed the hypothesis of an overlapping diagnosis. The negativity for auto-antibodies including rheumatoid factors, with the previous criteria described, allowed the diagnosis of RS3PE syndrome [5].

Considering these findings, in our case, IgAN preceded RS3PE, resulting in recurrent pericardial effusion and arthralgias.

This is a rare condition characterized by symmetrical polyarthritis with acute onset of pitting edema, involving mostly

hands and feet, that usually responds well to low doses of prednisolone and has a good prognosis [6, 7].

This syndrome is more frequent in elderly males and is usually associated with neoplasms (lung, prostate, ovary, endometrium, breast, bladder, gastrointestinal, and hematological), autoimmune diseases, and neurodegenerative disorders [5, 7]. In our case, an extensive study was performed, including CT-scan and endoscopic exams, and all the above systemic conditions were excluded.

The pathophysiology of RSE3P syndrome relies on the increase of the vascular endothelial growth factor (VEGF) that is responsible for hypervascularity and increase of the vascular permeability, contributing to the development of pitting edema, which improves very quickly after GC treatment [8, 9].

A few case reports demonstrated the association of RS3PE syndrome in hemodialysis (HD) patients, although the serological identification of VEGF has not been shown in this population [10, 11].

This important differential diagnosis can be easily underdiagnosed as the accumulation of extracellular fluid and arthritis phenomena in hemodialysis patients is most often due to amyloidosis, chronic inflammation, and volume overload [8, 10]. This association was reported in literature only in long-standing HD patients (9 and 23 years after dialysis) [10, 11], whereas our patient developed the symptoms just after a few weeks.

Regarding CKD and R3SPE syndrome association, only one case reported an association with diabetic nephropathy [11], and our case report suggests an association with IgAN.

The pleural and pericardial effusions are unusual complications in RS3PE syndrome. Yanamoto et al. [5] report a case of 74-year-old Japanese women with idiopathic RS3PE syndrome where pleural and pericardial effusion were evident. An additional five case reports documented the same association, with most of them revealing no identifiable cause and only one related to angioimmunoblastic T-cell lymphoma [5].

This case enhances the need to clarify the physiopathological mechanisms of these two clinical entities and how they may be related to bring a causality between them. This case report may be an important tool for further investigation in this field in the future.

Conclusions

The complexity of this case shows a link between IgAN and RS3PE, reinforcing the importance of considering a wider diagnosis for the complaints of arthralgias and volume overload. Pericardial effusion was a discernible finding in our patient, which motivated an active intervention due to the risk of cardiac tamponade and improved significantly after corticosteroid therapy, further supporting the diagnosis of RS3PE syndrome.

This case report describes a diagnostic approach to the RS3PE syndrome, emphasizing clinical features that should be considered in the CKD population. The early recognition of RS3PE was demanding, reinforcing the need for appropriate management to achieve better clinical outcomes in similar cases.

Author Contribution JD: conception, drafting, final approval, and funding acquisition. CM: critically revising and adding important intellectual content.

All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Declarations

Ethics Approval Ethics approval was not required since this report describes a case from routine clinical practice.

Consent to Participate Consent to participate was not required since this report describes a case from routine clinical practice.

Consent for Publication Written informed consent was obtained from the patient for publication of this case report.

Competing Interests The authors declare no competing interests.

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