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Case Report

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An Overlap of Anticoagulant-Related and IgA Nephropathy: A Case Report

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Abstract
Introduction: Anticoagulant-related nephropathy (ARN) is an increasingly recognized cause of acute kidney injury (AKI), initially associated with warfarin use. Supratherapeutic warfarin levels were implicated in kidney toxicity. With the widespread adoption of direct oral anticoagulants (DOACs), it becomes imperative to understand their potential risk for ARN and its clinical presentation. ***Case Presentation:*** We report a case of a 64-year-old male prescribed DOAC for paroxysmal atrial fibrillation management, presenting with heart failure and worsening AKI. Hematuria and mild proteinuria were also observed. Despite management attempts, AKI persisted, prompting a kidney biopsy. Histopathological examination revealed acute tubular injury with numerous intratubular red blood cell casts consistent with ARN. Additionally, findings indicative of IgA nephropathy (IgAN), including mesangial hypercellularity and IgA dominant deposition, were noted. ***Conclusion:*** This case underscores the emerging risk of ARN associated with DOACs and emphasizes the potential exacerbation of ARN in the presence of underlying glomerular diseases such as IgAN. Clinicians should maintain a high index of suspicion for ARN in patients on anticoagulation therapy, particularly DOACs, who present with AKI and urinary abnormalities, as early recognition and intervention are crucial in preventing further renal damage.

Introduction

Anticoagulant-related-nephropathy (ARN) was first described as a complication of warfarin therapy in 2009 and recognized as a cause of acute kidney injury (AKI) [1]. Subsequently, 5/6 nephrectomy animal models described detailed histopathological findings in rats receiving supratherapeutic doses of dabigatran similar to those seen previously with warfarin [2]. This suggested a non-vitamin K dependent pathogenesis of ARN, and in 2017 a case report was published that not only suggested for the first time that Factor Xa inhibitors can induce ARN, it also reported characteristic biopsy data supporting ARN in a patient receiving apixaban [1, 3]. Over the past decade, the lexicon has thus evolved from warfarin-related nephropathy to ARN. With the rising use of direct oral anticoagulants (DOACs), an improved

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understanding of ARN including associated risk factors will help manage this subpopulation and their complications. Herein, we describe a case of a patient treated with DOAC who subsequently developed ARN superimposed on an underlying glomerulonephropathy.

Case Presentation

The patient is a 64-year-old Hispanic male with a history of paroxysmal atrial fibrillation who was hospitalized for decompensated heart failure and AKI. His medical history included obesity, obstructive sleep apnea, diastolic heart failure, and diabetes mellitus. His home medications comprised of pravastatin, dapagliflozin, enalapril, rivaroxaban, and metformin.

Upon admission, the patient's creatinine level was elevated to 2.65 mg/dL from his baseline of 0.83 mg/dL. The AKI was attributed to heart failure and subsequent diuresis where he was discharged with a creatinine of 2.95 mg/dL. However, an outpatient creatinine measurement showed a rise to 3.35 mg/dL which prompted another admission.

The patient had been on rivaroxaban 20 mg daily for paroxysmal atrial fibrillation which was initiated 7 months prior to the hospitalization. After he was discharged from his first hospitalization on dose-reduced 15 mg daily rivaroxaban, he started to experience gross hematuria, hematochezia, and epistaxis. He underwent cystoscopy and colonoscopy with both tests being unremarkable. A decision was made to change his DOAC from rivaroxaban to apixaban 5 mg twice daily to decrease his bleeding risk. A graphic representation of the patient's serum creatinine with use of different DOACs over time can be seen in Figure 1.

On his second admission for chief complaint of shortness of breath, an aPTT was 29 s (laboratory reference aPTT 21–35 s) and apixaban dose was reduced to 2.5 mg daily on day 3. On day 5, apixaban was discontinued in favor or initiation of argatroban continuous infusion with aPTT monitoring with a target of 40–75 s. Argatroban was initiated due to its direct and rapid thrombin inhibition, providing precise control over coagulation, and allowing for targeted aPTT management while minimizing bleeding risks. Blood urea nitrogen remained persistently elevated in the 50 s mg/dL throughout all the creatinine fluctuations. Enalapril was discontinued and not restarted throughout hospitalization.

Bilateral renal ultrasonography revealed kidneys with normal dimensions and parenchymal echogenicity, without any signs of obstruction or hydronephrosis. A renal Doppler ultrasound was not performed. Urinalysis upon this admission showed microscopic hematuria reported as red blood cells (RBCs) "Too Many to Count" with large hemoglobinuria and moderate proteinuria. Previous urinalysis had illustrated moderate proteinuria and this classification is generally interpreted based on the degree of protein excretion: <150 mg/24 h is normal, and 150–500 mg/24 h is considered moderate proteinuria. There was no eosinophilia. Anti-myeloperoxidase, anti-proteinase-3, and the anti-glomerular basement membrane antibodies were of low titers. The antinuclear antibody-screening test was negative. Rheumatoid factor, complement C3, C4, and total immunoglobulin levels were all normal. Serum and urine protein electrophoresis with immunofixation were without monoclonal antibody spike. Serologies for hepatitis viruses A, B, and C were not detected.

Given the hematuria and persistently elevated creatinine, a kidney biopsy was performed following brief discontinuation of the argatroban infusion. The biopsy revealed glomeruli demonstrating diffuse and nodular mesangial sclerosis with segmental mesangial hypercellularity (Fig. 2a). Diffuse acute tubular injury was seen associated with numerous intratubular RBCs as well as RBC casts (Fig. 2b). Mild interstitial fibrosis and moderate arteriosclerosis were present. Moderate mesangial deposits of IgA were seen on IF (Fig. 2c). C3, kappa, and lambda light chains were present in a similar pattern. By EM, the glomerular basement membranes were mildly thickened. There was severe foot process effacement. The mesangial matrix was moderately increased and contained electron dense deposits (Fig. 2d). The final pathologic diagnosis was anticoagulant-induced acute tubular injury, nodular diabetic glomerulosclerosis, and IgA nephropathy (IgAN). MEST-C score: M1 E0 S1 T0 C0.

Post-Biopsy Course

In the post-biopsy course, argatroban was discontinued, and the patient remained off systemic anticoagulation. Approximately 1 year after hospitalization, a subsequent urinalysis revealed mild proteinuria with a measured value of 20 mg/dL. To provide context, normal values for a random urine sample typically range from 0 to 14 mg/dL. Additionally, trace hemoglobin was noted, but it is crucial to highlight that this did not indicate the presence of hematuria. Notably, the serum creatinine had improved to 1.33 mg/dL 1 year after the kidney biopsy. The patient's preadmission proteinuria was considered moderate, and this classification is generally interpreted based on the degree of protein excretion: <150 mg/24 h is normal, and 150–500 mg/24 h is considered moderate proteinuria.

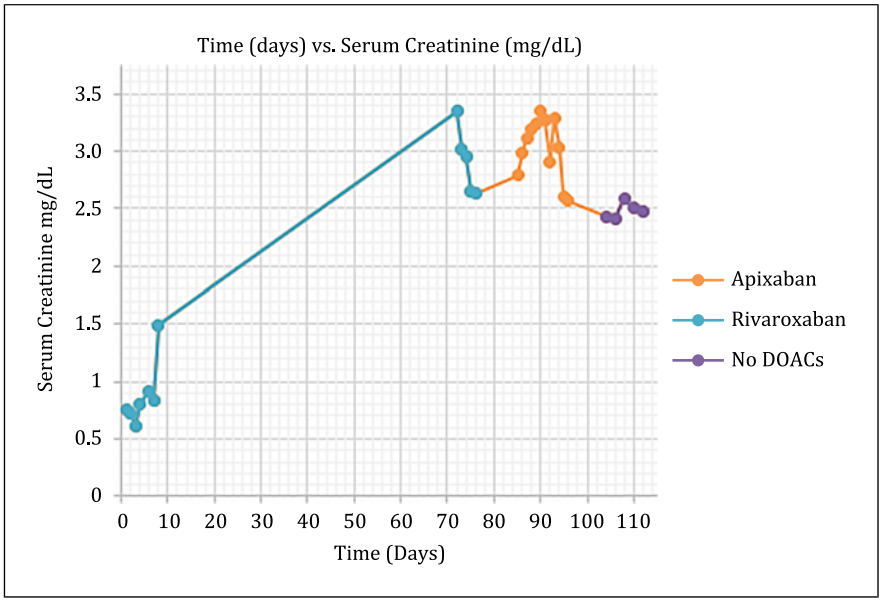

Fig. 1. Time (days) versus serum creatinine in mg/dL: this is a graphic representation of the patient's serum creatinine and use of different DOACs. The first few days in the graph incorporate data from the first hospitalization. Throughout this time course, the patient had been on rivaroxaban until the end of his second hospitalization. His second hospitalization ended on day 76; it was at this time where a decision was made to transition his rivaroxaban to apixaban. The patient returned to the current hospitalization on day 85 on the graph. One year after the kidney biopsy, during which the DOAC medications were discontinued, the serum creatinine decreased to 1.33 mg/dL.

Discussion

As a relatively newly recognized clinical entity, the consensus definition of ARN is in flux, and its study has piqued the interest of clinical nephrologists, renal pathologists, and other renal professionals who care for patients with an indication for systemic anticoagulation. One obstacle to histopathological study is the reluctance to perform kidney biopsies among patients who need systemic anticoagulation. For this reason, ARN is a clinical diagnosis, but its unique histopathological findings have caused some researchers to propose a clinicpathologic flow chart for ARN that includes biopsy data [4]. Certainly, when clinically suspected and when a patient has other comorbid causes of AKI, renal biopsy can be invaluable in ruling in or ruling out the diagnosis of ARN; biopsy data remain crucial for diagnosing ARN, even though physicians often hesitate to perform kidney biopsies in anticoagulated patients due to concerns about bleeding risk [5].

ARN typically does not develop in normal kidneys but rather in patients with an underlying glomerular disease, with IgAN being the most frequently associated glomerular disease [6]. Kock et al. [5] recommend a systematic approach to screening for ARN by first assessing patients' risk levels based upon their underlying kidney function. Even before starting anticoagulant therapy, it is important to evaluate kidney function and conduct urine tests to check for hematuria or AKI. For high-risk patients, such as those with underling CKD or glomerular disease, they advise monthly monitoring of serum creatinine and INR levels, along with urine dipstick tests while on DOACs [5]. For low-risk individuals, monitoring serum creatinine and urine dipstick tests over 3 months is usually sufficient. If alternative diagnoses are found, ARN is less likely; if not, a kidney biopsy after stabilizing the patient's condition may be needed to confirm ARN.

The pathophysiology involves endothelial damage that is presumed to be partly due to preexisting glomerular filtration barrier damage (such as from IgAN) and partly due to reduced thrombin, which is critical for maintaining endothelial cell integrity through proteinase-activated receptor signaling [7, 8]. This progressively worsening endothelial injury and disruption of the glomerular filtration barrier lead to chronic hemorrhage, accumulation of RBCs in renal tubules, and tubular damage [9], all of which are critical findings in the diagnosis.

Initially, the cause of our patient's worsening AKI was ambiguous, considering his various comorbidities including diabetes, obesity, and acute decompensated congestive heart failure. Upon examining the histopathological analysis, both diabetic nephropathy and IgAN were identified concurrently. The observed mild mesangial hypercellularity and segmental glomerular sclerosis suggest that diabetic nephropathy is likely a primary factor in the patient's chronic kidney disease. This complicates Oxford scoring as these findings align with both diabetic nephropathy and IgAN. Importantly, it is crucial to highlight that IgAN significantly contributes to the exacerbation of hematuria, a feature not commonly observed in cases of diabetic nephropathy.

Investigations for other causative factors or triggers were unrevealing. Dapagliflozin was considered as a

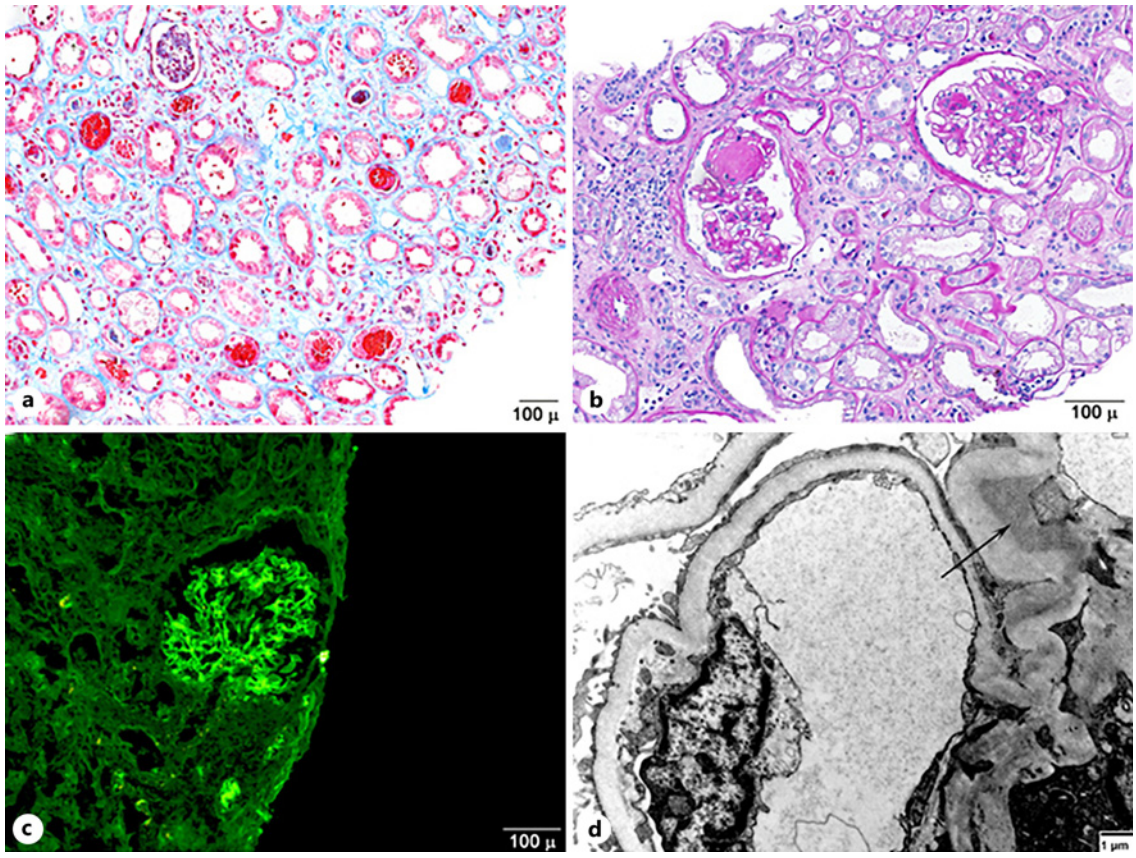

Fig. 2. Kidney biopsy. **a** Diffuse tubular injury with RBCs in many tubules, flattening of lining epithelium, loss of brush borders and interstitial edema (Trichrome stain, ×100). **b** Diffuse and nodular glomerulosclerosis and tubular injury (Periodic-acid Schiff Reagent, ×200). **c** Mesangial IgA deposits (fluorescein-conjugated, antihuman IgA, original magnification, ×200). **d** Mesangial deposits (arrow) and thick glomerular basement membranes (unstained, original magnification, ×10,000). MEST-C: M1 E0 S1T0 C0.

possible culprit but deemed unlikely due to the absence of AKI following its initiation. Additionally, there were no documented instances of hypotension, which would be expected with dapagliflozin-induced AKI. Patient had been on a stable dose of enalapril with no hemodynamic changes and thus ACE inhibitor induced AKI was less likely. Additionally, despite limited research data on the existence of a concentration-dependent effect due to variability in individual levels of DOACs, we anticipate and encourage further investigations in this area. Future studies addressing this matter could provide valuable insights into the potential implications of concentration-dependent effects, contributing to a more comprehensive understanding of anticoagulant therapy.

Management of patients with ARN secondary to DOACs currently involves discontinuing the DOAC and providing supportive care [10]. In the absence of a proven reversal agent, no additional therapy has a consensus recommendation. In cases of ARN in the setting of IgAN, use of immunosuppressive therapy has been suggested; however, this treatment rarely leads to complete recovery [10]. The role of steroids in treatment of IgAN is still relatively uncertain, and a thorough risk-benefit analysis should always precede their initiation [11]. Further research is needed to establish an ideal treatment for ARN with underlying IgAN. As more cases are recognized through enhanced monitoring and kidney biopsies, real world outcomes with the various management options can be evaluated.

Conclusion

ARN is a relatively recently recognized entity. The direct factor Xa inhibitors apixaban and rivaroxaban are two known causative agents. While these two medications

are widely utilized, there may be a lack of awareness of their nephrotoxic potential. Kidney function tests and urinalysis should be performed before initiation of anticoagulants and closely trended afterward, especially in the setting of known or suspected chronic renal disease. This patient's biopsy exhibited histopathological findings of ARN in the setting of IgAN. Our case illustrates the value of kidney biopsy to elucidate the cause of AKI and underlying glomerular disease that may have increased the risk for ARN.

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Statement of Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was reviewed and approved by HCA Healthcare, Approval No. 8282. Written informed consent was obtained from the patient for publication of the details of medical case and any accompanying images.

Conflict of Interest Statement

In compliance with the ICMJE uniform disclosure form, all authors declare that there are no conflicts of interest or competing interests associated with this work.

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This work was supported by HCA Healthcare and/or an HCA Healthcare affiliated entity. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

Mercedes Galloway M.D. took the lead in composing the case report, conducted data interpretation and analysis, and played a pivotal role in clinically interpreting the patient's medical history. Dr. Galloway was primarily responsible for writing the majority of the paper. John J. Sim M.D. assumed a crucial role in organizing and meticulously editing the manuscript to ensure clarity, making vital revisions that significantly improved the overall quality of the report. Andrew Slater M.D. contributed to the collection and analysis of patient data, with a specific focus on the detailed explanation of ARN within the introduction section. Dr. Slater also actively participated in composing portions of the case presentation. Christopher Bray M.D. PhD provided guidance for writing and offered critical insights for the clinical interpretation of the case. Dr. Bray also contributed to the revision process. Daniel Bishev M.D. assisted in data collection and analysis, particularly in relation to laboratory findings and discussion segment. Patrick Walker M.D., as the pathologist, conducted the histopathological analysis and provided valuable insights into the interpretation of pathological findings.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author Mercedes Galloway.

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