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Case report: rivaroxaban related nephropathy

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ABSTRACT

The characteristics of direct oral anticoagulants (DOACs) make them more appealing for prevention of thromboembolic events than vitamin K antagonists (VKA). Despite that, both classes have been a recognized as a cause of anticoagulant related nephropathy (ARN). Herein we describe a case of a 72-year-old man, with chronic kidney disease (CKD), medicated with rivaroxaban, who presented with acute kidney injury (AKI) and microscopic hematuria. The kidney biopsy revealed anticoagulant related-nephropathy. Rivaroxaban was suspended, the patient showed improvement of renal function and apixaban was prescribed. This case emphasizes the need for careful monitoring of serum creatinine when these drugs are prescribed, especially in high risk groups.

Case Report

Implication for health policy/practice/research/medical education:
This report highlights the importance of awareness of anticoagulant related nephropathy, especially in patients with risk factors and that it should be suspected whenever eGFR is impaired in a patient taking DOAC.

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Introduction

Since their appearance, direct oral anticoagulants (DOACs) have been increasingly used to prevent thromboembolic events due to their advantages when compared with vitamin K antagonists (VKA). They have a quicker onset and offset effect, therefore a predictable pharmacokinetic profile and routine coagulation evaluation is unnecessary (1,2).

However, two types of kidney injury have been identified. The first one is tubular interstitial nephritis, most likely a secondary immune reaction (3,4) and the second is known as anticoagulant related nephropathy (ARN), primarily called warfarin related nephropathy (3,5).

Rivaroxaban is an active direct factor Xa inhibitor, it was approved for clinical use in 2012, including treatment of deep vein thrombosis and prevention of venous thromboembolism, stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF). The first case of ARN was reported in 2017 by Oliveira et al (6).

Herein, we report a case of a patient with CKD, who was treated with rivaroxaban and presented with acute kidney injury (AKI) due to ARN.

Case Presentation

A 72-year-old man presented to the emergency department with fever, cough and dyspnea, with no urinary tract symptoms, namely dysuria, gross hematuria or oliguria. He had a past medical history of hypertension, heart failure, AF and CKD of unknown cause (serum creatinine 2.6 mg/dL, estimated glomerular filtration rate [eGFR] using Chronic Kidney Disease Epidemiology Collaboration Equation – CKD-EPI – of 24 mL/min/1.73 m^2), without previous nephrology consultation. His daily medication comprised rivaroxaban 20 mg/d for three years and switched to 15 mg accordingly to eGFR for one month, enalapril 20 mg/d, lercanidipine 20 mg/d,

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bisoprolol 5 mg/d, furosemide 40 mg/d, alopurinol 100 mg/d and digoxin 0.25 mg/d.

At admission, he presented with a blood pressure of 162/112 mm Hg, a pulse rate of 100 beats/min, a peripheral oxygen saturation of 99% and a tympanic temperature of 38.5°C. The patient had crackles in both lung bases at pulmonary auscultation and swollen lower limbs with pitting edema. Further physical examination was unremarkable.

Laboratory assessment showed: AKI with serum creatinine of 4.4 mg/dL and blood urea nitrogen level of 100 mg/dL; acidosis by hyperchloremic metabolic acidosis; hyperkalemia (serum potassium of 6.9 mmol/L); white cell count of 13.20 × 10^9/L, with normal neutrophils and eosinophils, hemoglobin of 9.2 g/dL and C-reactive protein of 9.72 mg/dL; B-type natriuretic peptide of 1884 mg/dL; prothrombin time 17,6 seconds with international normalized ratio of 1,50.

Urinalysis revealed erythrocyturia (10183/µL) and 24h urine analysis a proteinuria of 1.04 g. The autoimmune screening was negative, including antinuclear antibodies, anti-neutrophil cytoplasmatic antibodies, rheumatoid factor and anti-glomerular basement membrane antibodies. Complement levels were normal. Immunoglobulin (Ig) A, IgG and IgM were normal. Serum and urinary proteins electrophoresis and immunofixation showed no monoclonal component. Additionally the serologies for human immunodeficiency virus, hepatitis B and C virus were negative. Urine culture and blood cultures were sterile.

Renal ultrasound revealed normal-sized kidneys with reasonable corticomedullar differentiation. The chest X-ray showed diffuse infiltrates, compatible with pulmonary edema.

Enalapril was promptly stopped, rivaroxaban was switched to enoxaparin 1 mg/kg/d, amoxicillin clavulanate was started for respiratory infection and diuretic for congestive heart failure, as well as medical therapy for hyperkalemia. The patient evolved with resolution of the acid-base and electrolytic disorders, congestive heart failure and respiratory infection. Nevertheless there was no improvement of AKI, therefore a renal biopsy was conducted. The biopsy specimen contained 12 glomeruli and the findings were: one glomerulus with segmental sclerosis lesion; various glomeruli with presence of erythrocytes in the urinary space; areas of interstitial hemorrhage (Figure 1); striped fibrosis occupying 70% of the cortex, with chronic inflammatory infiltrate; tubular atrophy; several tubules filled with erythrocyte cylinders (Figure 2). Moreover, medium and large caliber arteries with fibrotic hypertrophy of the severe intima. Immunofluorescence without immune deposits. These histological findings led to the diagnosis of focal and segmental glomerulosclerosis (FSGS) and ARN.
The patient was discharged with improved renal function (serum creatinine 2.4 mg/dL).

Rivaroxaban was discontinued and switched to apixaban 5 mg twice daily. One month later, he had serum creatinine of 1.9 mg/dL. He started hemodialysis 2 years later.

Discussion

VKA as warfarin and acenocoumarol have some unfavorable characteristics, namely drug and food interactions, especially important in the CKD population who has a very strict diet, making DOACs a safer and very appealing alternative for prevention of thromboembolic events (1,2, 7). Nevertheless, kidney injury has been described for both pharmacological classes. Recently, Harel et al had compared the risk of AKI in elderly patients with AF with newly prescribed DOAC (dabigatran, rivaroxaban, or apixaban) versus warfarin and concluded that the former were associated with a lower risk of AKI. (8)

The pathophysiology of ARN is complex. There is disruption of the glomerular barrier caused by a reduction of an endothelial trophic factor, causing intraglomerular haemorrhage and tubular obstruction by red blood cell

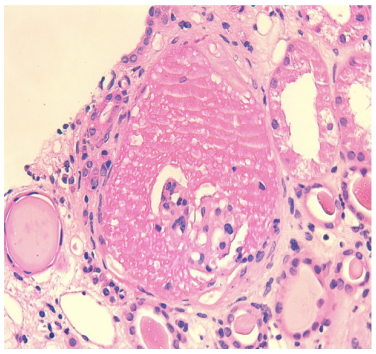

Figure 1. Masson trichrome staining (×200); tubules filled with red blood cells casts; areas of interstitial hemorrhage; tubular atrophy; banded fibrosis.

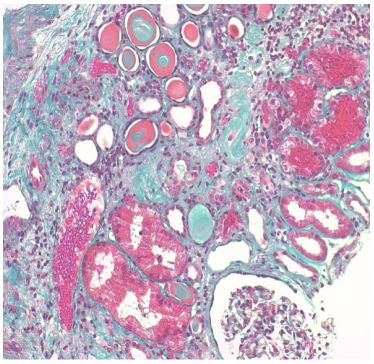

Figure 2. Hematoxylin-Eosin staining (×400); presence of erythrocytes in the urinary space of the glomerulus.

casts (RBCC) (3,6). The oxidative stress perpetuates the injury (6). Histological findings include interstitial hemorrhage, occlusive RBCC, and acute tubular necrosis (5).

Rivaroxaban has a significant renal metabolism and clearance and for that reason doses should be reduced for creatinine clearance (CrCl) <50 mL/min and are contra-indicated for CrCl under 15 mL/min. In patients with kidney impairment, the rivaroxaban effect may be enhanced in presence of other medications which have renal clearance (9). Likewise, CKD patients not only can have progression of kidney disease but also they share a higher risk of developing AKI, making them more susceptible of over coagulation and consequently ARN.

So far, the known risk factors for ARN are pre-existing CKD, advanced age, body weight, diabetic nephropathy, arterial hypertension, glomerulonephritis and heart failure (6,10,11). The main preventive measure is the adjustment of anticoagulant dose, particularly in CKD patients.

This patient had multiple risk factors, as CKD caused by glomerulonephritis, arterial hypertension and heart failure.

The patient started rivaroxaban three years ago. At that time his serum creatinine was 1 mg/dL (eGFR CKD EPI of 76 mL/min/1.73 m^2) that increased to 1.3 mg/dL on the subsequent year (eGFR CKD EPI of 59 mL/min/1.73 m^2). He lost follow-up for two years and returned to doctor's appointment with a laboratory test result from two months ago showing a serum creatinine of 2.6 mg/dL (eGFR CKD EPI 24 mL/min/1.73 m^2). Therefore, rivaroxaban dose was reduced to 15 mg/d. The next evaluation was at the emergency department, as described previously. Since there was a considerable time lag between serum creatinine assessments and rivaroxaban adjustment, it is unclear whether the renal function was further aggravated in the meantime. In addition, congestive heart failure, respiratory infection and enalapril have also contributed to AKI, resulting in a supratherapeutic dose of rivaroxaban and ARN.

There are two other cases of ARN reported in the literature (6,12). In both cases the renal outcome was poor, with the two patients starting chronic hemodialysis, three weeks and three months after the diagnosis (6,12). Despite the fact that our patient had improvement of renal function after rivaroxaban was discontinued, there was a progression to end-stage renal disease, probably due to FSGS and accentuated fibrosis.

Conclusion

In conclusion, this case highlights the importance of awareness of ARN, especially in patients with risk factors and should be suspected whenever eGFR is impaired in a patient taking DOAC, especially in presence of marked hematuria. Thus as it has already been recommended, renal function monitoring is necessary for patients on DOAC.

Authors' contribution

LLC is the first and main author. She prepared, wrote and review this manuscript. AR and RP contributed to the writing of the manuscript. CL, TS, SL and AS made contributions to critical revision of the article and final approval of the version to be published. HV and MG made contributions in selection of the most representative images and provided assistance in morphopathological matters. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient has for publication of this report. In addition ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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