Anticoagulant-related nephropathy: An atypical case with two episodes

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ABSTRACT

Anticoagulant-related nephropathy (ARN) is a cause of acute kidney injury (AKI) that may occur due to excessive anticoagulation with warfarin or other anticoagulants, such as direct oral anticoagulants (DOACS). ARN is under recognized as a cause of AKI and the mechanism of ARN is not well understood. Glomerular hemorrhage, tubular epithelial cell injury and tubular obstruction by red blood cell casts are characteristic pathological findings. ARN is associated with a poor renal prognosis, with a greater likelihood of chronic kidney disease and a high risk of mortality. We describe a case with a 70-year-old man who presented with 2 episodes of ARN: the first associated with rivaroxaban and the second with warfarin. On the first admission, he presented with AKI KDIGO stage 3 and consequent need for dialysis induction. Despite chronicity features present in the kidney biopsy, our patient recovered kidney function. In the second episode, he suffered a progressive worsening of renal dysfunction after warfarin initiation. The rapid recognition of the pathology and warfarin suspension allowed improvement in kidney function. Anticoagulants are increasingly being used by patients with renal disease. This case report emphasizes the need to monitor kidney function, as well as urine sediment in patients that initiate anticoagulant medication, and the importance of early recognition of clinical signs of this entity.

Keywords: Anticoagulant-related nephropathy. Acute kidney injury. Anticoagulants. Warfarin. Rivaroxaban.

Nefropatía por anticoagulantes: un caso atípico con dos episodios

La nefropatía por anticoagulantes es una causa de insuficiencia renal aguda (IRA) que puede ocurrir debido a anticoagulación excesiva con warfarina u otros anticoagulantes, como los anticoagulantes orales directos (ACOD). La nefropatía por anticoagulantes está poco reconocida como causa de IRA y su mecanismo no está claro. La hemorragia glomerular, la lesión de las células epiteliales tubulares y la obstrucción tubular por cilindros de glóbulos rojos son hallazgos patológicos característicos. La nefropatía por anticoagulantes se asocia a un mal pronóstico renal, con mayor probabilidad de enfermedad renal crónica y alto riesgo de mortalidad. Describimos el caso de un hombre de 70 años que presentó 2 episodios de nefropatía por anticoagulantes: el primero asociado a rivaroxabán y el segundo a warfarina. En el primer ingreso presentó IRA KDIGO estadio 3 y consecuente necesidad de diálisis. A pesar de las características de cronicidad presentes en la biopsia renal, nuestro paciente recuperó la función renal. En el segundo episodio, sufrió un empeoramiento progresivo de la disfunción renal tras el inicio de la warfarina. El rápido reconocimiento de la patología y la suspensión de warfarina permitieron mejorar la función renal. Los pacientes con enfermedad renal utilizan cada vez más anticoagulantes. Este caso hace hincapié en la necesidad de controlar la función renal, así como el sedimento urinario en pacientes que inician medicación anticoagulante, y la importancia del reconocimiento temprano de los signos clínicos de esta entidad.

Palabras clave: *Nefropatía por anticoagulantes. Insuficiencia renal aguda. Anticoagulantes. Warfarina. Rivaroxabán.*

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INTRODUCTION

Anticoagulant-related nephropathy (ARN) is a cause of acute kidney injury (AKI) that may occur due to excessive anticoagulation with warfarin or other anticoagulants, such as direct oral anticoagulants (DOACs)[1]. ARN was first described by Brodsky et al. in 9 patients with AKI, hematuria, and warfarin overdose, so the primary name of this entity was warfarin-related nephropathy[2].

ARN is under recognized as a cause of AKI and the true incidence is difficult to determine in the absence of kidney biopsy. It is estimated that 20-30% of patients taking warfarin have ARN, but the frequency varies significantly between studies[1-4]. Data about DOACs is still scarce, although emerging in recent years due to massive use of these medications[3,5].

ARN mechanism is poorly understood[3,5]. In addition to obstruction of the renal tubules by red blood cells, other mechanisms seem to be involved, such as oxidative stress to renal tubules, inhibition of mesangial cells growth through blockage of growth arrest-specific gene 6, PAR-1 inhibition with increased susceptibility to endothelial injury, reduction in protein C concentration and impaired endothelial protein C receptor signaling[3,6].

Age, arterial hypertension, diabetes mellitus, obesity, heart failure, and pre-existing kidney disease, including glomerular diseases, were all found as independent risk factors for ARN[2,3,7,8].

The characteristic pathologic findings are glomerular hemorrhage, tubular epithelial cell injury and tubular obstruction by red blood cell casts.

Data associated with warfarin-related nephropathy reveal a worse kidney prognosis, with a greater likelihood of chronic kidney disease (CKD) and a high mortality risk[3,7].

Clinical reports of ARN caused by two different classes of anticoagulants are scant. In this case the authors describe two episodes of ARN, caused by rivaroxaban and warfarin, which occurred several years apart.

CASE REPORT

We present the case of a 70-year-old Caucasian man, with a past history of hypertension, bilateral hip prothesis, pulmonary thromboembolism (PTE) during the postoperative period of the second hip surgery, and recurrence of PTE 4 months after oral anticoagulation suspension. His daily medication included perindopril 4 mg id and rivaroxaban 20 mg id since the second PTE episode. He had normal kidney function in the previous month, with a serum creatinine (SCr) of 0.8 mg/dL (95 ml/min/1.73 m² - CKD EPI Creatinine).

He was admitted in the Nephrology Department due to fatigue, anorexia, vomiting, decreased urinary output and macroscopic hematuria. On admission, he presented with an arterial blood pressure of 140/80 mmHg and an otherwise normal physical examination. The laboratory admission results (Table 1) showed alteration in kidney function, with AKI stage 3 according to the KDIGO classification (SCr 21.6 mg/dL, urea 343 mg/dL), metabolic acidosis (with a normal anion gap), hyperkalemia and elevation of inflammatory parameters. Urinalysis revealed erythrocyturia and a proteinuria-creatinuria ratio (PCR) of 3.1 g/g. Kidney ultrasound showed enlarged kidneys (140 mm), with preserved corticomedullary differentiation, without hydronephrosis. He started hemodialysis due to oliguria and uremic syndrome. The analytical study for kidney disease was inconclusive (Table 1) and other causes of AKI have been ruled out as pre-renal or nephrotoxic causes. A kidney biopsy was performed: the sample had 12 glomeruli, 9 with global sclerosis, 2 with cellular crescents with intraglomerular hemorrhage and segmental endocapillary hypercellularity; 80% of interstitial fibrosis and tubular atrophy, associated with interstitial hemorrhage and red blood cells' casts; the arteries showed no changes; immunofluorescence examination showed C3 parietal granular deposition and electronic microscopy revealed subepithelial "humps". These histologic changes suggest ARN and infection-related glomerulonephritis (IRGN) (fig. 1).

Based on the histological findings, anticoagulation was suspended, and the patient started targeted antibiotic therapy, according with antibiotic sensitivity test, for *Klebsiella pneumoniae* isolated on a urine culture. The patient evolved with progressive improvement of kidney function. Three months later, hemodialysis was suspended, maintaining a SCr of 2.5 mg/dL. Given the high thrombotic risk, he was medicated with enoxaparin, which the patient did not comply with.

Five years later, he was readmitted due to bilateral PTE. He started enoxaparin on therapeutic dose, that was switched to warfarin a week later. On admission, he presented a SCr of 1.59 mg/dL. Three days after warfarin initiation, kidney function progressively worsened (maximum SCr of 4.8 mg/dL), with erythrocyturia and PCR 1.7 g/g. At his point, the patient had supratherapeutic levels of warfarin (INR 5). Kidney ultrasound showed signs of CKD, with no other alterations. Warfarin was discontinued, and enoxaparin was initiated, with a progressive improvement in kidney function (*nadir* of Cr 3.4 mg/dL). He maintained preserved diuresis and stable kidney function under enoxaparin.

The etiological study for thrombotic events revealed a genetic mutation (MTHR 677C>T and 1298A>C in heterozygosity, PAI-1 5G/4G in heterozygosity), and an antithrombin III of 64%. Therefore, due to a high thrombotic risk, enoxaparin was maintained at a dose of 1.5 mg/kg/day.

DISCUSSION AND CONCLUSION

Vitamin K antagonists (VKA), such as warfarin and acenocoumarol, have been widely used in long-term anticoagulation. However, VKA have some disadvantages such as numerous drug interactions and require regular laboratory monitoring, which could be associated with decreased therapeutic compliance[8,9].

Table 1. Laboratory results

Laboratory analysis	Results
Admission	
Hemoglobin	11.0 g/dL
White blood cell and platelet count	Normal
Serum creatinine	21.6 mg/dL
Serum urea	343 mg/dL
Serum potassium	8.6 mmol/L
INR and activated partial thromboplastin time (aPTT)	Normal (0.9 and 24.4 seconds respectively)
C-reactive protein	10 mg/dL
Random urine analysis	Proteinuria (+); sediment with pyuria and red blood cells (++), with dysmorphic red blood cells
Arterial blood gas	Metabolic acidemia - pH 7.09, pCO_2 17.9 mm Hg, pO_2 108 mm Hg, HCO_3^- 8.5 mmol/L, lactate 0.9 mmol/L
Investigation	
Random urine analysis (second sample)	Minor proteinuria (50 mg/dL); sediment with dysmorphic red blood cells (65 cells/ low power field)
Blood and urine cultures	Negatives
Antistreptolysin-O test	Negative
Peripheral blood smear	Normal
Immunoglobulins and light chains dosing; free light-chain ratio	Normal
Serum immunofixation	No monoclonal component
Antinuclear antibody	Negative
Extractable nuclear antigen antibodies	Negative
Anti-neutrophil cytoplasmic antibody	Negative
Anti-glomerular basement membrane antibody	Negative
Anticardiolipin antibodies	Negative
Cryoglobulins	Negative
Anti-dsDNA antibody	Negative
C3 complement level C4 complement level	Decreased (82 mg/dL) Normal (39 mg/dl)
Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) serologic tests	Negative

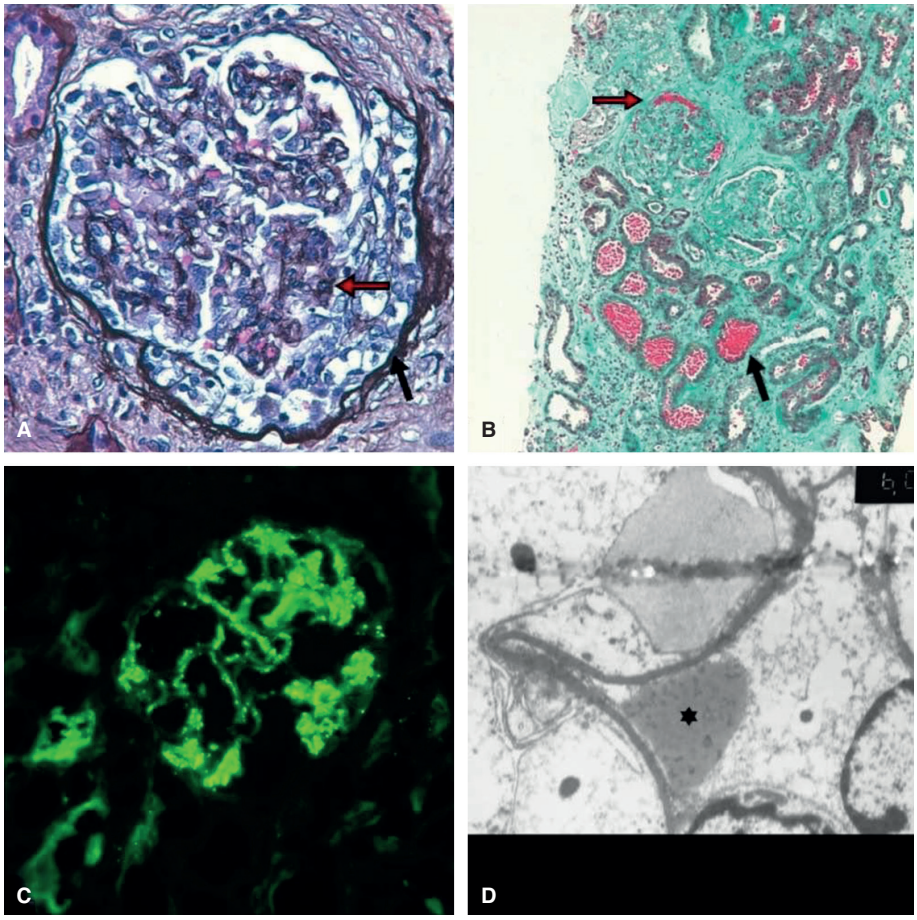

Figure 1. **A)** Silver stain (magnification × 400), on light microscopy (LM): cellular crescent (black arrow) and endocapillary hypercellularity (red arrow); **B)** Masson Trichrome stain (magnification × 100), on LM: extensive interstitial fibrosis and tubular atrophy, red blood cells' casts (black arrow) and glomerular hemorrhage (red arrow); **C)** Immunofluorescence: glomerular C3 granular deposition; **D)** Electronic microscopy (magnification × 6000): subepithelial *"hump"* (*).

DOACs changed this reality: they don´t require regular monitoring of coagulation and their pharmacokinetic profile is more predictable, which may be associated with a greater therapeutic adherence by patients[7,9]. Several clinical trials have shown non-inferiority of DOACs as compared to VKA, and no significant differences regarding major bleeding[9,10]. Currently, we have four drugs approved: a thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).

ARN is a cause of AKI in patients receiving anticoagulants, even without any signs of coagulopathy and active bleeding[3,11]. This has primarily been reported after the use of warfarin, however cases have also been described associated with acenocoumarol and with the use of DOACs[3,7,8]. In a recent review, VKAs were responsible for approximately 37% of ARN cases, whereas DOACs for about 5-14% of them. Within the DOACs, dabigatran was associated with more renal side effects (4.6%), compared to rivaroxaban (3.5%), apixaban (2%) and edoxaban (1.7%)[3,7,12].

The pathophysiology of ARN is still poorly understood, but is related to glomerular hemorrhage and occlusive red blood cells casts, with acute glomerular and tubular injuries[13,14]. On kidney biopsy, the presence of occlusive RBC casts, acute tubular necrosis and interstitial hemorrhage are typical histological features of ARN[1,15].

Most ARN cases evolve as severe forms of AKI, with most patients requiring hemodialysis on admission[7]. Kidney prognosis is worse in patients with previous CKD, especially those with higher degrees of glomerulosclerosis and tubulointerstitial fibrosis[16].

There are no prospective studies that indicate the best treatment for ARN[7]. Corticosteroids may potentially suppress the inflammatory response following glomerular hemorrhage and tubular obstruction in the kidney[7,12]. The beneficial effects of N-acetylcysteine and prednisone in improving kidney function have been observed in experimental models and in some case reports[3,7,17].

Our patient was at a high risk of development of ARN, considering his advanced age, medical history of arterial hypertension and absence of regular evaluation of kidney function.

He had 2 episodes of ARN. The first episode, associated with rivaroxaban, presenting at the same time an IRGN; the patient evolved with transitory need of dialysis, but, despite biopsy features of chronicity, he recovered kidney function; also, urinary sediment and C3 level returned to normal range, reflecting the resolution of the "nephritic process". The second episode was associated with warfarin, with supratherapeutic levels of warfarin (INR 5), with a maximum SCr of 4.8 mg/dL. Kidney biopsy was not performed at this time; the rapid recognition of the pathology and the consequent suspension of warfarin led to an improvement in kidney function, without the need for renal replacement therapy.

In conclusion, due to confounding factors and the risk of performing a kidney biopsy in these patients, ARN is probably underdiagnosed. The number of patients taking anticoagulants with AKI is increasing, especially with DOACs. This case report highlights the necessity for monitoring kidney function, as well as urine sediment in patients who begin oral anti-coagulation medication, especially those with pre-existing kidney disease. An early recognition is crucial, with drug suspension being the best hypothesis for kidney recovery.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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