Acenocoumarol induced anticoagulant-related nephropathy with newly diagnosed IgA nephropathy: A repeat biopsy case report

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Abstract

Anticoagulant-related nephropathy (ARN) is an underestimated cause of acute kidney injury (AKI) with poor renal and overall prognosis. Pathogenesis is not fully elucidated yet, although AKI is probably resulting from glomerular hemorrhage and most commonly has been described in patients with glomerular lesions, that alter the glomerular permeability, and conditions with glomerular hyperfiltration. Herein, we describe a case with a 58-year-old man who presented with macroscopic hematuria and AKI, and recently taking acenocoumarol for aortic valve replacement. The first renal biopsy showed red cell casts in the renal tubules, one glomerular crescent formation in the glomeruli with mild immunoglobulin A deposition, and severe interstitial inflammation. Based on these findings, the patient was diagnosed with acenocoumarol induced ARN with newly diagnosed IgA nephropathy and switched to tinzaparin with a short course of corticosteroids. Renal improvement in ARN is usually partial and is delayed, as confirmed by a second biopsy in our patient after six months.

Introduction

Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that may be caused by excessive anticoagulation with warfarin and other anticoagulants [1]. A decade ago, Brodsky et al. described this new clinicopathologic entity as “warfarin-related nephropathy” [2]. The characteristic pathologic findings are the glomerular hemorrhage, the tubular epithelial cell injury, and the obstruction of renal tubules by red blood cell casts, whereas these casts do not contain Tamm-Horsfall protein. However, the glomeruli are not usually involved [2]. The main predisposing features seemed to be excessive anticoagulation (in the first 3 months of warfarin use), older age, diabetes mellitus, obesity, heart failure, and pre-existing kidney disease, including glomerular diseases. In most patients with ARN, the serum creatinine stabilizes or improves slightly within the first few weeks after correction of the warfarin coagulopathy. However, some patients may have little or no recovery of kidney function [2].

Case Presentation

A 58-year-old Caucasian man presented at the emergency room complaining of 10 days of painful macroscopic hematuria. His medical history included diabetes, hypertension, and obesity. Furthermore, 2 months ago he underwent aortic valve replacement with a mechanical valve and he began taking acenocoumarol (vitamin K antagonist) as an anticoagulant agent.

The laboratory results at the time of admission are detailed in Table 1. The patient presented with AKI stage 3 (according to the KDIGO classification) and the renal ultrasound showed normal-sized kidneys. 2 months ago, renal function was normal with serum creatinine 0.9 mg/dL (0.72-1.25). Coagulation test results revealed prothrombin time (PT) and activated thromboplastin time (aPTT) values of 19.2 and 40.1, respectively, with an international normalized ratio (INR) 3.5.

Table 1
Laboratory results on admission

Laboratory test	Patient result	Reference range
Creatinine, mg/dL	5.9	0.72-1.25
Urea, mg/dL	101	18-55
Sodium, mmol/L	140	136-145
Potassium, mmol/L	3.5	3.5-5.1
Glucose, mg/dL	170	70-105
Calcium, mg/dL	8.1	8.4-10.2
Albumin, g/dL	3.6	3.5-5
AST, U/L	13	5-34
ALT, U/L	10	0-55
LDH. U/L	302	125-220
Bilirubin, total, mg/dL	0.4	0.2-1.2
CRP, mg/L	50	0-5
WBC count, x10e3/uL	79.36	5.2-12.4
Platelet count, x10e3/uL	413	130-400
Hemoglobin, g/dL	10.1	12-18
Urine tests		
pH	6	5.5-6.5
Specific gravity	1007	1015-1028
RBC/ HPF	>200	0-2
WBC/ HPF	8-10	0-5
Protein, mg/dL	150	0-20

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, Lactate Dehydrogenase; CRP, C-reactive protein; WBC, white blood cells; RBC, red blood cells; HPF, high power field

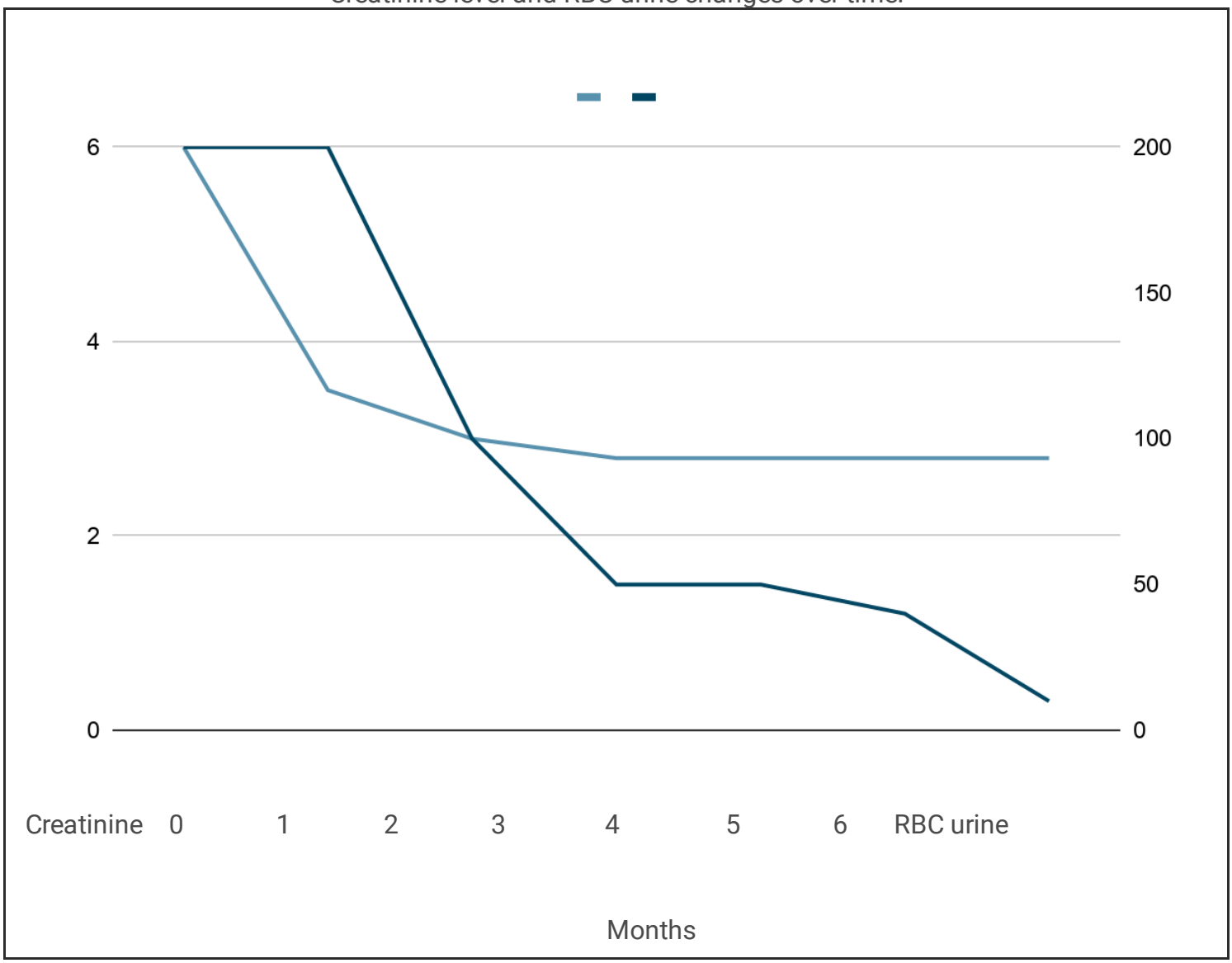
The patient denied previous episodes of macroscopic hematuria in the past or kidney family history. He also denied recent episodes of respiratory or gastrointestinal infection. A phase-contrast microscopic examination of the urinary sediment revealed numerous red blood cells, including several dysmorphic erythrocytes and 24-h urinary protein excretion presented 2.5g/day. In addition, serologic testing for hepatitis B, hepatitis C, and HIV were negative. Serum complement for **C3 192mg/dL** (75-180), **C4 55.8mg/dL** (10-40), IgA 238mg/dL (70-400), IgG 930mg/dL (700-1600), IgM 96 mg/dL (40-230),

antinuclear antibody, anti-double-stranded DNA and antineutrophil cytoplasmic antibodies were negative. Severe infections including endocarditis, abscess, and respiratory infections were excluded by blood cultures, transesophageal cardiac ultrasound, and PET scan.

After the PT-INR had normalized, a renal biopsy was performed. The biopsy specimen contained 10 glomeruli with mild mesangial hypercellularity and 1/10 (10%) glomeruli with cellular crescent form. The interstitial renal tissue was filtered with inflammatory cells, mainly lymphocytes, with the presence of acute tubular necrosis and occlusive red blood cell casts. The immunofluorescence revealed mesangial deposits of **IgA (2+)** and **C3 (1+)**, and no IgM, IgG, C1q, C4, k, and λ light chains.

Based on these histological findings, the patient was diagnosed with acute kidney injury associated with anticoagulant-related nephropathy in the presence of IgA nephropathy. Firstly, he was managed with normal saline infusion, and then pos prednisolone 1mg/Kg/daily was added to his treatment, particularly due to the severe interstitial nephritis, with a gradual reduction in 4 months. The patient was discharged home on the 20th day with serum creatinine 3.5 mg/dL and acenocoumarol was replaced by tinzaparin. After 3 months, although his urine continued to present microscopic hematuria (50-60 red blood cells per high-power field), renal function was improved further and proteinuria was beginning to decrease (Table 2).

Table 2
Creatinine level and RBC urine changes over time.



At 6 months the patient presented stable serum creatinine 2.6mg/dL and a second kidney biopsy was performed to determine the chronicity/activity index. The biopsy specimen contained 10 glomeruli with mild mesangial hypercellularity and without crescent form. The interstitial fibrosis was extended with minimal inflammation, while the acute tubular injury was yet present without the previous occlusive red blood cell casts. Now, the immunofluorescence was negative.

After 1 year, the patient presents persistent microscopic hematuria but the renal function is further improving (creatinine 2mg/dL).

Discussion

This case report highlights an unusual cause of AKI “anticoagulant-related nephropathy” [ARN], which is an underdiagnosed entity, for the reason that kidney biopsies have difficulties in patients who receive anticoagulant treatment, because of concerns related to the risk of thrombosis or bleeding. This entity constitutes a severe form of AKI (all cases stage 3 according to KDIGO classification), with the majority of patients requiring hemodialysis on admission. Recently Imperio et al. [3] suggested a clinicopathologic pathway towards the true diagnosis of ARN with the proposed clinical and histological criteria.

It has been reported the description of ARN with the use of all classes of vitamin K antagonists as well as novel oral anticoagulants. We report here a case of ARN with recent onset of acenocoumarol use (2 months), associated with newly diagnosed IgA nephropathy, because of moderate IgA staining on kidney biopsy, and sub-nephrotic range proteinuria. According to the literature, IgA nephropathy is quite often related to ARN (Table 3), although only 1 case has been described to be induced by acenocoumarol [8], as in our patient. The glomerular permeability alteration is essential for RBC leak to occur during periods of over-anticoagulation and can be related to IgA nephropathy, thin glomerular basement membrane, and nephrosclerosis, resulting in ARN [10].

Table 3
Anticoagulant-related nephropathy associated with IgA nephropathy

Ref	Age/Sex	Anticoagulant therapy	INR	Cre (mg/dL)	IgA IF	crescents	recovery
Gois et al [8]	84/M	acenocoumarol	2.03	4.68	3+	(-)	Partial
Ishii et al [6]	55/M	warfarin	3.75	9.01	1+	(+)	Partial
Moeckel et al [5]	67/M	dabigatran	1.6	5.5	2+/3+	(-)	Partial
Escoli et al [4]	69/F	dabigatran	2.3	8	1+	(-)	Partial
Ng et al [7]	56/F	warfarin	4.95	3.6	No data	(-)	Partial
Golbin L et al [10]	76	fluindione	2.51	3.6	1+	(-)	Partial
Golbin L et al [10]	73	fluindione	3.8	3.5	2+	(-)	Partial
Golbin L et al [10]	90	fluindione	3.39	6.6	2+	(-)	Died
Golbin L et al [10]	78	warfarin	4.5	HD	3+	(-)	Partial
Golbin L et al [10]	69	warfarin	2.7	HD	2+	(-)	Not recovery
Kalaitzidis et al [11]	78	dabigatran	1.9	6.8	3+	(-)	Total
Ikeda et al [9]	67/F	dabigatran	2.47	3.67	1+	(-)	Total
Brodsky et al [12]	62 ± 14 n=14/41 IgAN	Warfarin, apixaban, heparin,	5.6± 6	4.33± 1.99	No data	(-)	No data
Brodsky et al [2]	38/F	warfarin	3.9	0.9	2+	(-)	Total
Brodsky et al [2]	82/F	warfarin	2.8	4.5	1+	(-)	Total

One study showed that only a few patients (<1.5%) with IgA nephropathy presented AKI [13]. Most episodes were triggered by respiratory infections and all the patients had a histomorphological pattern of focal proliferative glomerulonephritis with strong mesangial deposits IgA by IF, and 8–33% incidence of

extra capillary crescents, and a 7–16% incidence of glomerulosclerosis. In addition, several studies have shown a positive correlation between the percentage of glomeruli affected by the crescent formation and the severity of initial and subsequent renal failure. Therefore, we consider that the cause of AKI was anticoagulant-related nephropathy rather than IgA nephropathy because there was no history of prior infection and the presence of numerous RBC tubular casts could not be explained just by these glomerular findings (the mild mesangial proliferation, as well as the deposits of IgA by immunofluorescence).

Our patient exhibited more other extraordinary characteristics, including crescent formation. This is the second case to show crescentic form in the glomeruli associated with anti-coagulopathy nephropathy and IgA nephropathy [6]. Golbin L et al also described in 3/13 patients with ARN crescents formations, no one with IgA nephropathy [10]. However, the mechanism of glomerular crescent formation in patients with ARN is not elucidated yet and it is required further investigation.

The steroids may be useful in mitigating the onset of interstitial fibrosis as a consequence of ARN. Specifically, in our patient, our decision to introduce corticosteroid treatment was based mainly on clinical judgment and the extensiveness of pathohistological abnormalities (crescent form), as well as on the intensity of acute tubulointerstitial nephritis. While early steroid administration was reported to accelerate recovery of AKI after gross hematuria in IgA nephropathy [14], the use of prednisolone in ARN is not strongly supported in experimental models and is limited to a single prior case report [15]. Finally, AKI recurrence could happen after the initiation of the same anticoagulant agent or switching to another. [10].

It is remarkable that this is the first case study associated with ARN with a repeat kidney biopsy. As pathogenesis and renal outcome in ARN is not clearly defined, the second renal biopsy informs us that the acute renal tubular injury maybe persists after six months, therefore renal recovery, if it is possible to happen, is considerably delayed.

Consequently, this case demonstrates that ARN is a possible cause of AKI in a patient without previous etiology and recent use of anticoagulant therapy, accompanied by microscopic or gross hematuria. Although treatment options are limited, corticosteroids may potentially suppress the inflammatory response following glomerular hemorrhage and tubular obstruction in the kidney. Considering the poor renal prognosis of ARN, it highlights the necessity for close vigilance of renal function, as well as, urine sediment in patients, who begin on anticoagulation, especially with pre-existing renal diseases, including glomerulopathies and those with glomerular hyperfiltration.

Declarations

Funding

None

Conflict of Interests

There are no conflicts of interest.

Ethics approval

The patient provided informed consent for publication of the case report.

Consent to participate

Not applicable

Consent for publication

None

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

AC wrote the final manuscript whose final version was approved by all the authors; DK, AG actively participated in the treatment of the described patient; HG performed the histopathological analysis; DP supervised the findings of work

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Figures

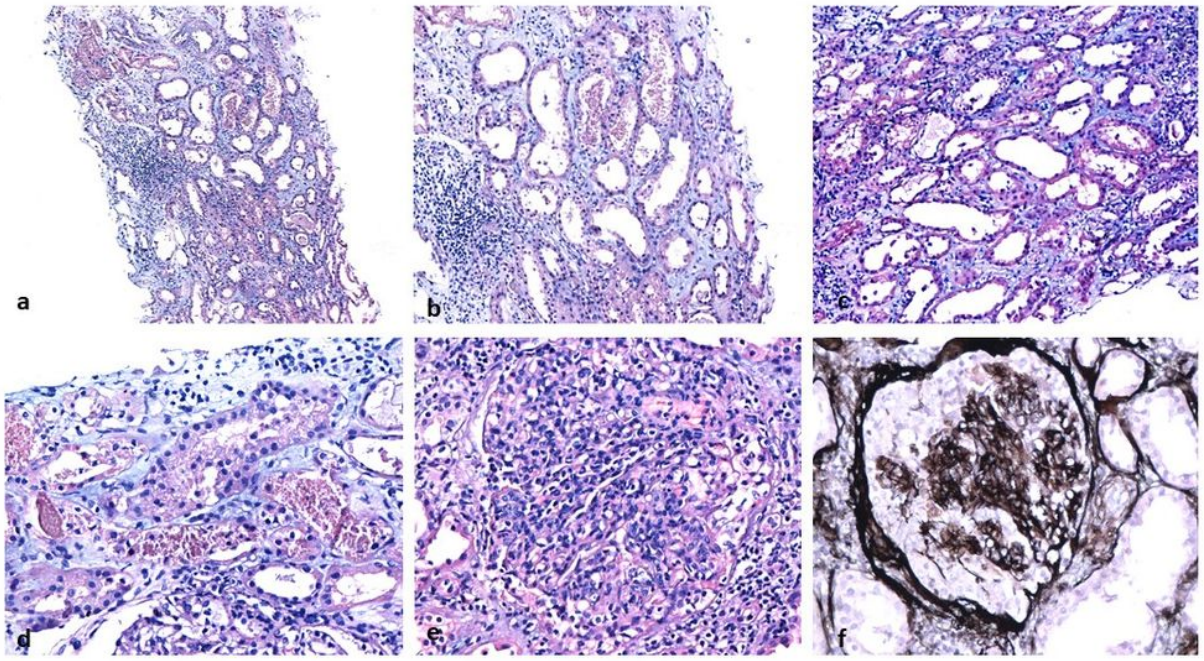

Figure 1

a,b,c, d Acute tubular injury with red blood cell casts, severe interstitial edema, and inflammation (Hematoxylin and eosin, original magnification x200, x400). e. A glomerulus with mesangial expansion and cellular crescent formation (Hematoxylin and eosin, original magnification x400). f. A glomerulus with mesangial expansion and cellular crescent formation (Masson's trichrome stain, original magnification x400)

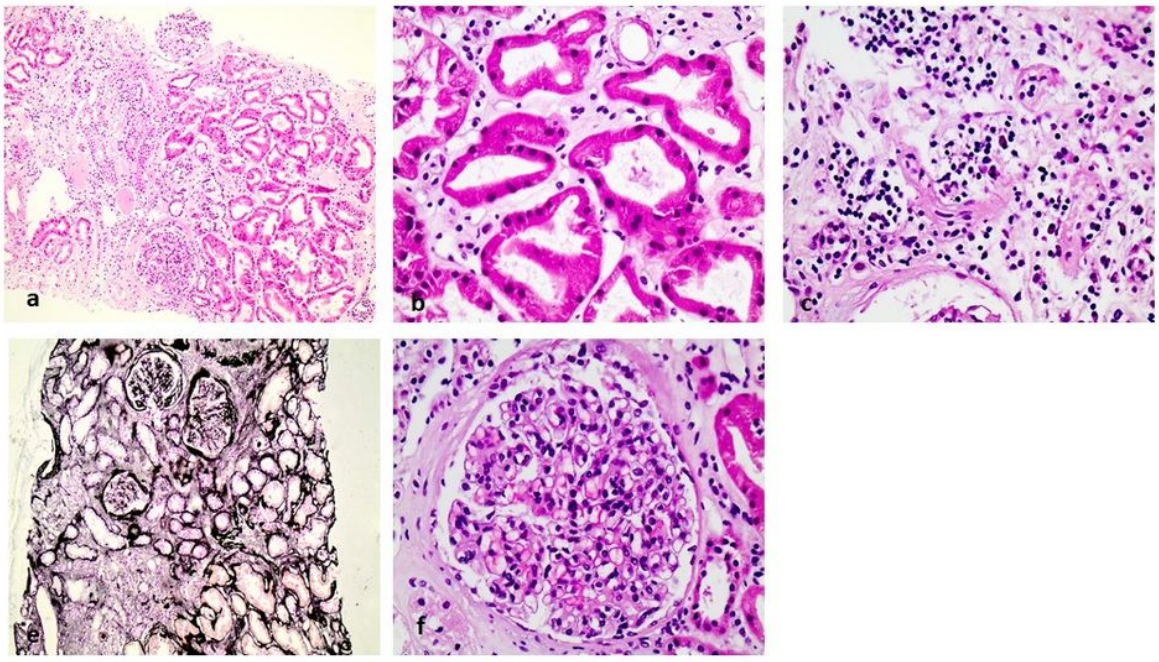

Figure 2

a,b,c Acute tubular injury without red blood cell casts and interstitial fibrosis. (Hematoxylin and eosin, original magnification x200, x400). d. Acute tubular injury and interstitial fibrosis (Masson's trichrome stain, original magnification x200). f. A glomerulus with mild mesangial expansion (Hematoxylin and eosin, original magnification x400)

Supplementary Files

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