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Anticoagulant-Related Nephropathy in a Renal Transplant Recipient

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INTRODUCTION

Anticoagulant-related nephropathy (ARN) classically presents with hematuria followed by acute kidney injury (AKI) during a period of over-anticoagulation with supratherapeutic international normalized ratio (INR). The corresponding renal histology is acute tubular injury (ATI) associated with red blood cells (RBCs) within the Bowman space and obstructive tubular RBC casts.[1] It has been observed that ARN is more common among patients with chronic kidney disease (CKD), and it was shown to accelerate CKD progression and increase mortality.[2–4] Therapeutic options other than withholding the anticoagulant and reversing its effect are limited. *N*-acetyl cysteine and steroids have shown some benefit in experimental settings, with anecdotal evidence of success in patients.[5]

Anticoagulant-related nephropathy was first described by Atb *et al*. in a patient taking warfarin with thin basement membrane disease.[6] Subsequently, 2 cases of ARN with underlying IgA nephropathy[7] and systemic lupus erythematosus[8] were reported. Brodsky *et al*. coined the term "warfarin-related nephropathy" in a clinicopathological study of 9 patients.[1] Since its original description in patients taking warfarin, this entity has been reported in patients taking all classes of vitamin K antagonists (warfarin, acenocoumarol, fluindione),[9] thrombin inhibitors (dabigatran),[S1] factor Xa inhibitors (apixaban, rivaroxaban),[S2] and dual antiplatelet therapy, and in coagulopathies unrelated to medication.[S3]

Anticoagulant-related nephropathy, which is well described in native biopsy results, has not yet been reported in the published literature in a transplant kidney, except in abstract form.[S4] We provide a detailed case report of a patient developing biopsy-proven ARN in the kidney allograft, and discuss possible pathogenetic mechanisms.

CASE PRESENTATION

A 61-year-old man, 8 years post−renal transplantation, presented with a 1-day history of dysuria and graft pain. On examination, he was febrile with a blood pressure of 153/79 mm Hg. Blood investigations showed neutrophil leucocytosis (white cell count 21.9×10^9/l) and raised C-reactive protein (135 mg/l). Serum creatinine (sCr) was 224 μmol/l (baseline 210−230 μmol/l) and INR was 2.5. Urinalysis showed 3+ protein, 3+ blood, 1+ leukocytes, and positive nitrites. Transplant kidney ultrasound showed a globally well-perfused, unobstructed kidney. Intravenous fluids and empirical treatment with temocillin and vancomycin were commenced for urosepsis, which was confirmed by positive urine culture for *Escherichia coli*.

The patient had been on warfarin for 20 years following metallic mitral valve replacement. Although he had a history of gout and a ureteric calculus, the cause for end-stage renal failure was uncertain. He had undergone renal transplantation 8 years prior, from a deceased donor following cardiac death. He had received alemtuzumab induction followed by tacrolimus monotherapy maintenance immunosuppression.

The patient had undergone 3 allograft biopsies from the time of the transplantation until the current admission. Initially, the immediate post-transplantation period was complicated by a postoperative bleed and suboptimal graft function. An allograft biopsy on day 20 post-transplantation showed acute tubular injury

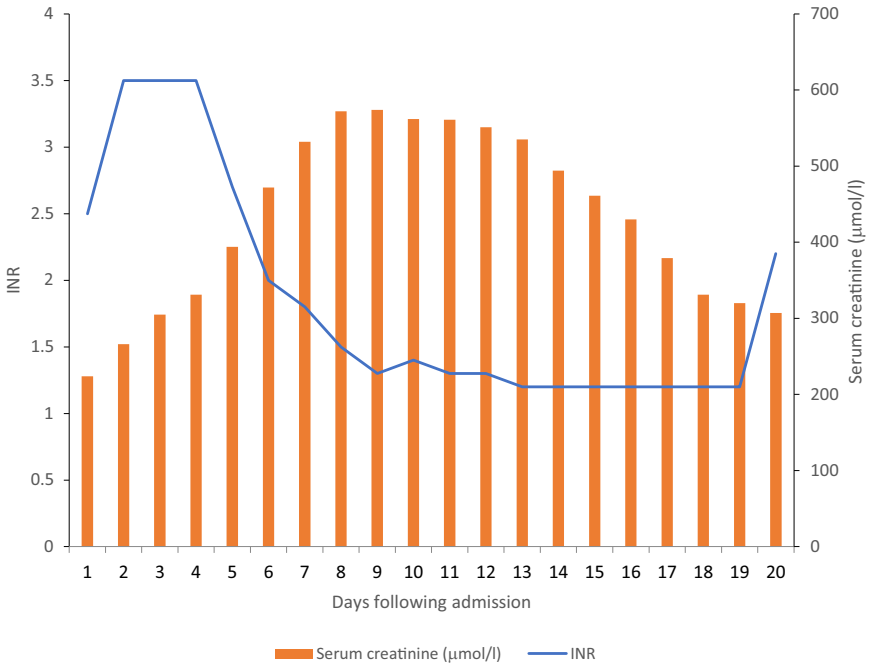

Figure 1. Progressive change in serum creatinine and international normalized ratio (INR) following admission.

with <5% scarring, with mild arterial intimal thickening. An increase in sCr prompted a second biopsy 2 years post-transplantation, which showed 15% cortical scarring with nodular arteriolar hyaline and mild arterial intimal thickening without evidence of rejection. The patient's sCr continued to rise during the third year post-transplantation, and a renal biopsy showed acute T-cell–mediated rejection (Banff 1b). He was treated with alemtuzumab and steroids. His renal function remained stable (sCr 210–230 μmol/l) under regular clinic follow-up for the next 5 years. Post-transplantation, he had been investigated for intermittent hematuria for which no urological cause had been found.

During the current admission, following initiation of antibiotics, from day 2 onward he developed acute kidney injury on chronic kidney disease. His sCr rose to 570 μmol/l. His INR was above therapeutic range at 3.5 (Figure 1). Warfarin was suspended, and he was commenced on heparin i.v. infusion in preparation for an allograft biopsy.

The renal biopsy (Figure 2) showed severe acute tubular injury and widespread RBC casts occluding the tubules with hemosiderin within tubular epithelial cells. Moderate interstitial inflammation was present, with foci of lymphocytic tubulitis and a few neutrophil casts. Cortical scarring was estimated at 30%. Moderate arteriolar hyalinosis and mild intimal thickening were present. C4d and SV40 immunostains were negative. Immunofluorescence for IgG, IgA, IgM, C3, C1q, kappa, and lambda light chains were negative on protease-digested paraffin-embedded tissue. Electron microscopy showed dysmorphic RBCs in tubules (Figure 3). The findings were in keeping with ARN, with evidence of resolving urinary tract infection and features of acute T-cell–mediated rejection (Banff 1b).

The patient was treated with 2 weeks of i.v. antibiotics. His immunosuppression was not augmented in view of the concomitant infection, the burden of immunosuppression, and on the basis of frailty. He was started on acenocoumarol, aiming for an INR of 2 to 3. His renal function returned to baseline (Figure 1), and inflammatory markers normalized. Four months after discharge from the hospital, his renal function remains stable.

DISCUSSION

A sequence of events has been proposed in the pathophysiology of ARN. In susceptible individuals, glomerular RBC leakage into the Bowman space and tubules during periods of over-anticoagulation causes tubular RBC cast formation and tubular epithelial cell injury resulting in AKI.

It appears that an underlying glomerular permeability alteration is essential for RBC leak to occur during periods of over-anticoagulation. This susceptibility to glomerular RBC leak can be related to a range of underlying kidney pathologies, including IgA nephropathy and other glomerulonephritides, thin glomerular basement membranes, and nephrosclerosis. A summary of the clinicopathological characteristics of all published ARN reports to date is provided in Table 1. Animal studies suggest that thrombin

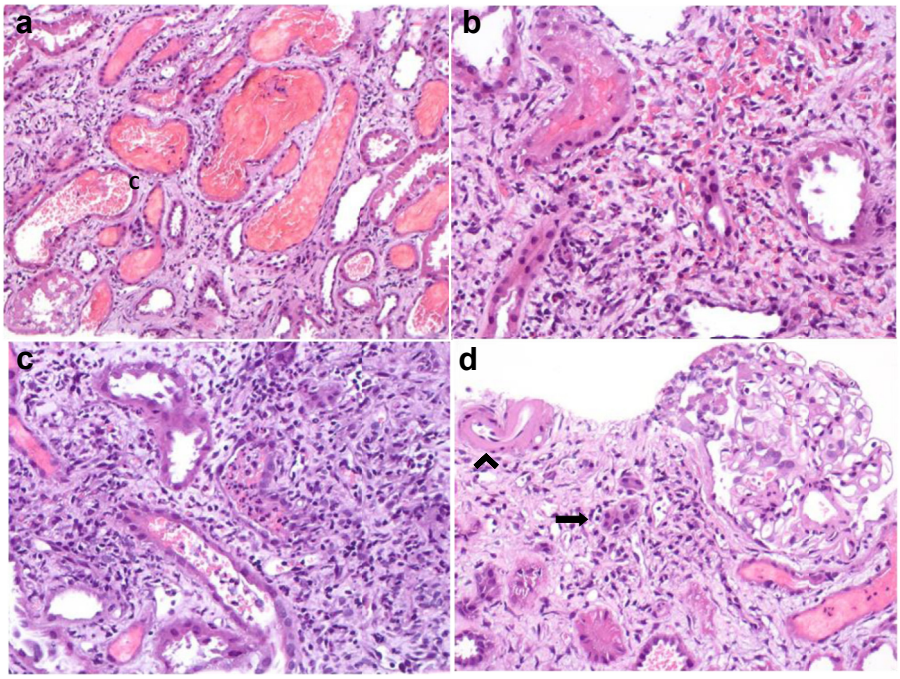

Figure 2. Representative post-transplantation kidney biopsy findings. Representative post-transplantation kidney biopsy findings. (a) Widespread occlusive red blood cell casts and acute tubular injury (hematoxylin and eosin [H&E], original magnification ×100). (b) Severe interstitial edema, hemorrhage, and inflammation (H&E, original magnification ×200). (c) Neutrophil casts within tubules (H&E, original magnification ×200). (d) A glomerulus showing mild segmental mesangial expansion. There is lymphocytic tubulitis (arrow). The arterioles show moderate hyaline arteriolosclerosis (arrowhead) (H&E, original magnification ×200).

inhibition can contribute to susceptibility of glomerular hemorrhage through inhibition of protease-activated receptor 1, which plays a role in maintaining the endothelial barrier intact.[S5] Interestingly inhibition of thrombin is common to all drugs implicated in ARN.

Two possible mechanisms have been proposed to explain the AKI: tubular obstruction by RBC casts, and heme toxicity.[9] A study of kidneys with glomerular diseases that had macrohematuria-associated renal damage failed to show retrodiffusion of Tamm Horsfall protein into the Bowman space. This argues against tubular occlusion as the cause of renal impairment.[S6] Hemoglobin released from intratubular degradation of RBCs is reabsorbed by the proximal tubular epithelium and further degraded within the tubular lumina. Free hemoglobin within tubules promotes lipid peroxidation. Intracellular hemoglobin, heme, and/or iron generate reactive oxygen species, resulting in activation of caspases, which in turn trigger apoptosis and

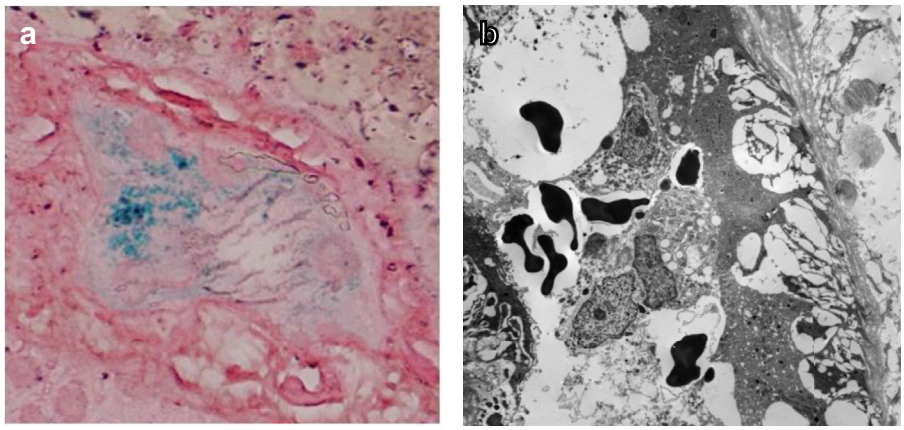

Figure 3. Hemosiderin deposition within tubular epithelial cell cytoplasm and dysmorphic red blood cells within damaged tubules on ultrastructural examination. (a) Hemosiderin deposition within tubular epithelial cell cytoplasm; a biomarker of local release of catalytic iron which results in cell injury. (Perl stain, original magnification ×400). (b) Dysmorphic red blood cells within damaged tubules on ultrastructural examination (electron microscopy, original magnification ×2500).

Table 1. Summary of clinical characteristics, management, and outcomes of previously published biopsy-proven cases of anticoagulation-related nephropathy

Patient no.	Age, yr	Sex	Anticoagulant	Indication	Presentation	INR	sCr, mg/dl	Baseline sCr	Underlying kidney disease	Management	Outcome	First author (year) reference
1	59	M	Warfarin	DVT	Gross hematuria, flank pain	3.6	8.4	1.0	Thin basement membrane disease	HD	sCr 1.3 mg/dl at 6 mo	Abt (2000)[6]
2	59	F	Phen-Procoumon	DVT	Gross hematuria, edema, dyspnea	3.2	12.4	Normal	IgAN	Phen-procoumon stopped, HD, steroids	Recovery	August (2002)[7]
3	27	F	Warfarin	APLS, PTE	-	8	3.1	1 - 0.6	ICGN (SLE)	Vitamin K, prednisolone, azathioprin	Recovery (sCr 0.75 mg/dl at 2.5 yr); no recurrence.	Kabir (2004)[8]
4-12	61.6±19	M:5 F:4	Warfarin	-	Hematuria (n = 9), proteinuria (n = 6), eosinophilurea (n = 1)	4.3±1.9	4.3 ± 2.3	1.3±0.8	IgAN (n = 2), IgAN/DN (n = 1) ICGN (SLE) (n = 1), ICGN (IgG) (n = 1), FSGS (n = 1), HTNS (n = 2)	-	Recovery (n = 4), HD (n = 3), death (n = 1), CKD (n = 1), recurrence (n = 1), no recurrence (n = 8)	Brodsky (2009)[1]
13	51	F	Aceno-coumarol	AF, CVR	Gross hematuria	6.2	8.6	0.8	IgAN	Switched to enoxaparin steroids	sCr remained increased (1.3 mg/dl); recurrence (1)	Cleary (2010)[S12]
14	48	M	Warfarin	CVR	Gross hematuria	>3	2	-	IgAN	-	-	Brodsky (2012)[2]
15	67	M	Dabigatran	AF	Gross hematuria	1.6	5.5	1.0	IgAN	Switched to warfarin	CKD (sCr 1.8 mg/dl at 3 mo); no recurrence	Meckel (2013)[S1]
16	74	M	Warfarin	AF, CVR	Gross hematuria	4.62	3.5	1.8	ICGN (IgG)	Vitamin K, continued warfarin	HD dependent	Santos (2013)[S13]
17	61	F	Warfarin	DVT	AKI (diarrhea)	5	6.6	Normal	ICGN (IgG)	-	-	Brodsky (2014)[S14]
18	41	F	Warfarin		Hematuria	27	6.7	1	None	-	-	Brodsky (2014)[S14]
19	73	M	Warfarin	AF	Worsening sCr	2	8.2	1.3	HTNS, secondary FSGS	$NaHCO_3$ (no response), followed by steroids	CKD (4.4 mg/dl at 3 mo)	Di Maso (2014)[S15]
20	56	M	Warfarin	CVR	Gross hematuria, AKI	-	-	-	-	Warfarin withheld, vitamin K	Dialysis independent	Larpparisuth (2014)[S17]
21	69	F	Dabigatran	AF	Oliguria, nausea, and vomiting	2.3	8	1.5	IgAN	Dabigatran stopped, HD/i.v. fluids	CKD (sCr 1.9 mg/dl at 2 wk)	Escoli (2015)[S16]
22	56	M	Warfarin	CVR	Gross hematuria, Vomiting	6.08	11.5	1.4	FSGS	Warfarin stopped, vitamin K, HD	CKD (sCr 4.95 mg/dl at 1 yr)	Larpparisuth (2015)[S17]
23	56	F	Warfarin	AF, CVR	AKI	5	3.58	0.8	ICGN (NOS)	Warfarin switched to LMWH and restarted after 5 days of prednisolone	CKD (sCr 3 mg/dl)	Ng (2016)[S18]
24	33	M	Warfarin	PTE	Hematuria, proteinuria	5.3	2.6	0.9	None	Warfarin withheld	Recovered kidney function	Mendonca (2017)[S19]
25	84	M	Aceno-coumarol	AF	Gross hematuria	2.1	4.68	1.0	IgAN	Acenocoumarol stopped; bridged with enoxaparin	CKD (sCr 1.7 mg/dl at 7 mo)	Gois (2017)[S20]
26	83	M	warfarin	PM	Hematuria AKI	1.4	2.41	0.96	Urothelial carcinoma of renal pelvis	Warfarin stopped	CKD (sCr 1.66 mg/dl at 3 mo)	Nagasako (2017)[S21]
27	78	F	Dabigatran	AF	Gross hematuria	1.9	6.8	1-1.1	IgAN	Dabigatran stopped	Recovery (1.1 mg at 1 yr)	Kalaitzidis (2017)[S22]
28-40	69.3±13	-	Fluindione (n = 7), aceno-coumarol (n = 2), warfarin (4)	-	-	5.7 ± 3	HD (n = 6), 492.7 ±1 91.2 µmol/l	eGFR 77.8 ±25 ml/min	IgAN (n = 5), IgAN + DN (n = 1), HSP (n = 1), PIGN (n = 1), ICGN (IgG κ) (n = 1), HTNS (n = 3), not identified (n = 1)	Fluindione switched to warfarin (n = 6), fluindione continued (n = 1), aceno-coumarol stopped (1), acenocoumarol continued (1), warfarin continued (1), warfarin stopped (2)	Recovery (n = 1), partial improvement eGFR at 1 yr 28–59 ml/min (n = 9), HD dependent at 1 yr (n = 1), died (n = 2), recurrences (n = 2), no recurrences (n = 9), not known (n = 1)	Golbin (2017)[9]

(Continued on following page)

Table 1. (Continued) Summary of clinical characteristics, management, and outcomes of previously published biopsy-proven cases of anticoagulation-related nephropathy

Patient no.	Age, yr	Sex	Anticoagulant	Indication	Presentation	INR	sCr, mg/dl	Baseline sCr	Underlying kidney disease	Management	Outcome	First author (year) reference
41	82	F	Riva-roxaban	AF	Gross hematuria	2.3	5.0	1	HTNS, chronic TIN	Rivaroxaban stopped and bridged with enoxaparin *N*-acetyl cysteine	HD dependent; no recurrences.	Olivera (2017)[S23]
42	82	F	Apixaban	AF	Oliguria, microscopic hematuria, AKI	-	8.52	3.26	Focal and segmental necrotizing and crescentic GN (active)	Apixaban stopped, LMW heparin, steroids	HD dependent	Brodsky (2017)[S24]
43	55	M	Warfarin	CVR	Gross hematuria	3.75	9.01	0.76	IgAN (active)	Warfarin stopped, heparin	CKD (sCr 1.43 mg/dl at 18 mo)	Ishii (2018)[S25]
44	50	F	Aceno-coumarol	CVR	Gross hematuria, vomiting	4.7	4.7	0.9	TIN	Switched to warfarin steroids	Recovery	Golla (2018)[S26]
45	82	M	Dlopidogrel, aspirin	IHD	Gross hematuria, AKI	1.22	5.9	-	GN (monoclonal IgG3 kappa), renal tumor, lymphoma	Antiplatelet therapy discontinued, HD, chemo	HD dependent	Krátká (2018)[S27]
46	81	F	Dabigatran	AF	Edema	-	9	1	ICGN (resolving PIGN) (inactive)	Dabigatran stopped, HD	HD dependent	Sharfuddin (2018)[S28]
47	61	M	Dabigatran	AF	Gross hematuria	4.09.	4.72	0.98	IgAN (inactive)	Dabigatran stopped, vitamin K, HD	Recovery	Li (2019)[S29]
48	70	M	Warfarin	TIPS PVT	Hematuria	8.7	8.6		IgAN (inactive)	HD	CKD (sCr 2.5 mg/dl)	Li (2019)[S30]
49	61	M	Warfarin	AF, CVR	Hematuria, AKI	3.52	6.8	2.03	Focal and segmental necrotizing and crescentic GN (active)	Prednisone, HD	-	Rawala (2019)[S31]
50	67	F	Dabigatran	DVT	Gross hematuria, AKI	2.47	3.67	0.5	IgAN (inactive)	Dabigatran stopped	Recovery; no recurrence	Ikeda (2019)[S32]
51	62	M	Warfarin	AF	Hematuria	5.4	5.35	1.2	None	Warfarin withheld, LMWH, steroids, *N*-acetyl cystein	CKD (sCr 1.3 at 3 mo)	Yadav (2019)[S33]
52-92	62 ± 14 n=41	M:26 F: 15	Warfarin (n = 28), heparin (n = 4), apixaban (n = 2), clopidogrel,and aspirin (n = 1), coagulopathy (n = 6)	AF 20, DVT 8, APLS 2	Hematuria	5.6 ± 6	4.33 ± 1.99	1.25 ± 0.40	IgAN (n = 14), ICGN–IgG (n = 5), ICGN–SLE (n = 3), ICGN–MGN (n = 1), PICGN (n = 8), FSGS (n = 4), DN (n = 2), FGN (n = 1), C3 GM (n = 1), glomerulomegaly (n = 2)	-	-	Brodsky (2019)[S3]

AF, atrial fibrillation; AKI, acute kidney injury; APLS, antiphospholipid syndrome; chemo, chemotherapy; CKD, chronic kidney disease; CVR, cardiac valve replacement; DN, diabetic nephropathy; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; F, female; FGN, DVT, deep venous thrombosis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HD, hemodialysis; ICGN, immune-complex glomerulonephritis; IgAN, IgA nephropathy; IHD, intermittent hemodialysis; LMWH, low-molecular-weight heparin; M, male; MGN, membranous glomerulonephritis; PIGN, post-infectious glomerulonephritis; PICGN, pauci-immune crescentic glomerulonephritis; PM, pacemaker; PTE, pulmonary thromboembolism; PVT, portal vein thrombosis; sCr, serum creatinine; SLE, systemic lupus erythematosus; TIN, tubulointerstitial nephritis; TIPS, transjugular intrahepatic portosystemic shunt.

mitochondrial damage and upregulate vascular adhesion molecules and proinflammatory/profibrotic cytokines.[S7] An experimental model has shown that treatment with antioxidants (N-acetylcysteines) can prevent AKI in rats with 5/6 nephrectomy and warfarin-induced over-anticoagulation without a change in glomerular hematuria or RBC cast formation,[S8] supporting further the role of heme-induced oxidative damage as the cause of AKI.

It is likely that ARN in an allograft is mechanistically similar to ARN in a native kidney. Overall risk factors for the development of ARN in a native kidney include older age, chronic kidney disease, diabetes, hypertension, cardiovascular disease, heart failure, drugs (aspirin, angiotensin-converting enzyme inhibitors, calcium channel blockers), thin and thick basement membranes, low serum basal albumin, high serum aspartate aminotransferase (AST), hematuria, urinary infection, hypotension, hypovolemia, coagulopathy, rapid normalization of INR, and gene polymorphisms affecting warfarin metabolism.[4,S9] Many of these risk factors are common in transplant patients, as discussed below.

Reduced Nephron Mass/Chronic Kidney Disease

In experimental studies, ARN occurred in rats with 5/6 nephrectomy but not in controls,[S10] suggesting that underlying reduction in nephron mass plays a role in its pathogenesis. In the current case, the kidney biopsy showed 30% tubulointerstitial scarring, causing reduced nephron mass.

Cardiovascular Disease

In our case, there was moderate arteriolar hyaline and mild intimal thickening. Many transplanted kidneys, especially from deceased donors, have significant vascular pathology, which may increase susceptibility to ARN. The presence of arteriovenous fistulas in allografts could cause regional hemodynamic changes in the kidney, which could, in theory, add to this susceptibility.

Drugs

Antibiotics are a common group of drugs that interact with vitamin K antagonists. Temocillin could have potentiated the anticoagulant effect of warfarin in our patient. In this patient, the presence of focal tubulitis with moderate inflammation amounted to acute T-cell–mediated rejection (Banff 1b). The presence of concomitant tubulointerstitial nephritis contributes to tubular injury and exacerbates hypoxia-induced tubular injury. The differential diagnoses include drug-induced and infectious acute tubulointerstitial nephritis, which cannot be excluded.

Table 2. Teaching points

- Anticoagulant-related nephropathy (ARN) presents with acute kidney injury (AKI) as a result of glomerular bleeding on a background of over-anticoagulation.
- Since the original description of ARN in patients taking warfarin, it has been reported with use of all classes of vitamin K antagonists as well as novel oral anticoagulants.
- The main histopathological findings include acute tubular injury associated with red blood cells (RBCs) within the Bowman space and obstructive tubular RBC casts.
- ARN can occur in the kidney allograft but is rare.
- An underlying glomerular disease is commonly seen in kidney biopsy specimens with ARN.
- Given the limited management options and the poor renal and overall prognosis of ARN in native kidneys, as well as the challenges of performing a renal biopsy, renal transplant patients on anticoagulation should be judiciously monitored with the aim of early detection and prevention of anticoagulant-related renal damage.

Infection

The presence of occasional neutrophil casts in our case is likely due to the resolving urosepsis, which is a risk factor for ARN.

Performing a renal biopsy in anticoagulated patients can be a challenge for the nephrologist because of the increased risk of bleeding and/or the risk of thrombosis when anticoagulation is withheld. Studies in the native kidney setting have suggested that an increase in sCr closely following an increase in INR >3 is adequate for the diagnosis of ARN in the absence of any other etiology, even without histological confirmation.[S11] However, this case illustrates that renal biopsy gives additional information and is at times essential for diagnosis in clinical practice. This is especially pertinent in the case of a transplant, for which causes of AKI and their therapeutic implications are diverse.

It is interesting to note that this patient has had several episodes of macroscopic hematuria during the post-transplantation period, for which a urological cause had been excluded. It has not been possible to ascertain retrospectively whether any of these episodes were associated with an increase in INR or an impairment in renal function. However, the possibility that macroscopic hematuria can be precipitated by episodes of over-anticoagulation, which can result in subclinical renal damage, must be considered. This may have contributed to the progression of scarring in the patient's post-transplantation biopsy specimens, along with other insults such as calcineurin inhibiter toxicity and T-cell–mediated rejection.

Currently, there are no prospective studies on the management of ARN. The approach taken in previous case reports and case series are individualized to the patient, with variable outcomes (Table 1). The optimal approach to remove or reduce the impact of the inciting agent is a management dilemma. It is further compounded in patients with mechanical heart valves such as our patient, in whom anticoagulation cannot be permanently stopped.

Finally, we do not know the cause of renal failure in this patient or whether warfarin had any role in the development or the aggravation of renal damage in his native kidney. Meta-analysis of retrospective population studies on outpatients on warfarin anticoagulation estimate the prevalence of ARN at 20.4% and suggest that it is likely underdiagnosed in clinical practice.[4] The prevalence is greater among high-risk groups and the presence of CKD doubles the risk of developing ARN.[2,3]

Our literature review demonstrates that the current case is the first published report of ARN in a renal transplant recipient. The presence of ARN in native kidney biopsy specimens has been published in case reports and case series (Table 1). Warfarin was the most commonly implicated anticoagulant, followed by dabigatran, apixaban, and rivaroxaban. The most common presentation pattern was AKI or AKI on CKD with macroscopic or microscopic hematuria. As with the current case, an underlying kidney pathology was present in the majority of reports, with IgA nephropathy being the predominant glomerular disease (n=34), followed by immune-complex GN (n=27) and FSGS or nephrosclerosis (n=12). Selection bias in the decision to biopsy is clearly the major limitation in this review of case reports and case series. In addition, it is acknowledged that recognising ARN in the kidney biopsy could be challenging in view of the presence of underling kidney pathologies. Renal outcomes varied; however, recovery of renal function was only observed in 11 out of 51 cases which had available data. Of note, only in a minority of cases excessive overanticoagulation was present, confirming the initial observations by Brodsky *et al* in their landmark study, where moderate over-anticoagulation was sufficient to cause AKI.[1]

Judging from the literature pertaining to native kidneys, one could extrapolate that it is possible that ARN may be under-diagnosed among transplant patients. We therefore have undertaken a retrospective study reviewing the histopathology of all allograft biopsies from transplant recipients on long term anticoagulation (warfarin, apixaban, rivaroxaban) in our institute for a period of 10 years (2006-2016) with a minimum of 2 years follow up. There were 126 allograft biopsies from 40 patients; only the index case had features of ARN. This limited data suggests that ARN has not been under-diagnosed in the post-transplant setting. However, the indications for these biopsies vary and we do not have data on the level of anticoagulation at the time of biopsy. Prospective studies on large cohorts of post-transplant patients on anticoagulation need to be carried out in order to get an accurate understanding of the incidence and prevalence of ARN among the transplant population.

This case illustrates that the occurrence of ARN in a renal allograft can pose diagnostic and management challenges to the transplant physician. Renal biopsy was useful in this situation and should be considered on a case by case basis after careful consideration of risks compared to benefits, especially if the cause of AKI is not apparent or if supportive measures fail to improve AKI. Considering the limited therapeutic options and the poor renal and overall prognosis of ARN in the non-transplant population, it is imperative that post-transplant patients on anticoagulation are closely monitored with the aim of prevention and early detection of over-anticoagulation (Table 2).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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