Warfarin-related Nephropathy

Abstract

Warfarin-related nephropathy also referred to as anticoagulant-related nephropathy (ACRN) is a type of acute kidney injury (AKI) that may be caused by excessive anticoagulation with warfarin and other anticoagulants. Despite the well-described histological entity, the clinical course and approach to ACRN in patients requiring life-long anticoagulation are however not well described in the literature. We report a 50-year-old Indian woman who was on prolonged anticoagulant therapy post-mitral valve replacement. She presented with AKI, and renal biopsy was suggestive of ACRN. Steroids were given and her creatinine levels reached within the normal range in 2 weeks. A presumptive diagnosis of ACRN should be made if a severe warfarin coagulopathy is present and if other causes of AKI have been excluded, in patients with chronic anticoagulant therapy. Renal function should be monitored regularly in patients who are on anticoagulant therapy.

Keywords: *Acute kidney injury, anticoagulant-related nephropathy, corticosteroids, mitral valve replacement, warfarin*

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Introduction

Acute kidney injury (AKI) resulting from glomerular hemorrhage has been described in patients with underlying kidney disease in the absence[1-3] and presence[4,5] of coagulopathy (international normalized ratio [INR] of 6–9 range). More recently, AKI has been described among patients without underlying kidney disease and with more modest elevations of INR.[6] The recognition of a characteristic histologic lesion that was associated with the clinical presentation of otherwise unexplained AKI in the setting of over-anticoagulation led to the term "anticoagulant-related nephropathy." We report a case of AKI with biopsy-proven anticoagulant-related nephropathy (ACRN) in a patient with mechanical heart valve where the anticoagulant therapy cannot be withheld.

Case Report

A 50-year-old Indian female, who underwent mitral valve replacement for chronic rheumatic heart disease with severe mitral stenosis with left atrial appendicular clot, was on tablet acenocoumarol (Acitrom) 1 mg, tablet Ecosprin (aspirin) 75 mg, tablet Lanoxin (digoxin) 0.125 mg post mitral valve replacement for 2 years. She was on regular follow-up every 2 months and the dose of acenocoumarol was increased to 2 mg after 6 months. Her creatinine levels were within normal limits and INR within the therapeutic range. She had sudden abdominal distension with fever 1 year later and was diagnosed to have small bowel obstruction for which laparotomy with adhesiolysis was done. Tablet acenocoumarol 1 mg was started again postoperatively, which was increased to 2 mg in the next 6 months. Her creatinine levels were 0.9 and INR was within the therapeutic range. She had been on regular follow-up and was asymptomatic for a period of 1 year. She presented to us with the complaints of multiple episodes of non projectile, non-bilious vomiting following food intake and persistent high-colored urine for the past 1 month. There was no history of exertional dyspnea, chest pain, palpitations, and skin rashes. The patient did not complain of decreased urine output, dysuria, or pyuria. She was not a known diabetic or hypertensive. There was no significant past history with similar complaints. On physical examination, she was well nourished and moderately built, no evidence of pallor, pulse rate was 80 beats/min, and blood pressure was 110/60 mmHg. The patient had epigastric tenderness on abdominal palpation. Serum creatinine was 4.7 mg/dl, a 4-fold increase from her serum creatinine levels 6 months

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back, and INR was 4.70 (out of the therapeutic range) with dysmorphic red blood cells (RBCs) and casts in the urine. The provisional diagnosis of AKI in the background of anticoagulation was made and investigated further.

The autoimmune markers including anti-dsDNA antibodies, ANCA, and antinuclear antibodies were negative. The ultrasonography showed bilateral normal sized kidneys. Non-contrast computerized tomography confirmed bilateral normal-sized kidneys with no calculi, hydronephrosis, or retroperitoneal fibrosis. Renal biopsy was planned after switching over to heparin and achieving the therapeutic INR. Post biopsy, she was switched over to warfarin, and the target INR of 2 was achieved. The histology suggested acute tubulointerstitial nephritis with RBC casts [Figure 1] and the immunofluorescence studies were negative. The patient was started on steroids. All the clinical investigations are shown in Table 1.

Discussion

The diagnosis of ACRN should be suspected among patients who present with AKI in the setting of excessive anticoagulation and hematuria. A definitive diagnosis is made by renal biopsy. Incidence of AKI in the largest cohort of warfarin using patients was 20.5% overall and 33% in patients with a history of chronic kidney disease (CKD). Moderate or severe coagulopathy induced by warfarin or other anticoagulants, especially if INR >4 and CKD, is the strongest risk factor for ACRN, and in these cases, prognosis is also worse than those without CKD. Other independent predictors of AKI risk in these patients were age, diabetes mellitus, heart failure, hypertension, and glomerulonephritis particularly with nephrotic syndrome.[6-8] Kidney biopsy in a subset of these patients showed obstruction of the renal tubule by RBC casts, and this appears to be the dominant mechanism of AKI.[6]

The initiating event in the pathogenesis of ACRN appears to be glomerular hemorrhage, caused by excessive anticoagulation due to warfarin or other anticoagulants.[9] Glomerular hemorrhage results in the formation of obstructing RBC casts within the renal tubules. Obstructing intraluminal RBC casts are the most conspicuous histologic feature of ACRN in the tissue obtained from patients who have undergone biopsy[10] and in animal models.[11] The major histologic feature of ACRN is the obstruction of renal tubules (mainly distal) by RBC casts [Figure 1].[10] Even though disruption of the glomerular filtration barrier is the main pathophysiological event, the molecular mechanism is poorly determined. Proteinase-activated receptors which are activated by thrombin have trophic effect on endothelium; however, its role in the pathogenesis of ACRN is yet to be determined.[12] The glomeruli show little or no abnormalities by immunofluorescence, light, or electron microscopy.

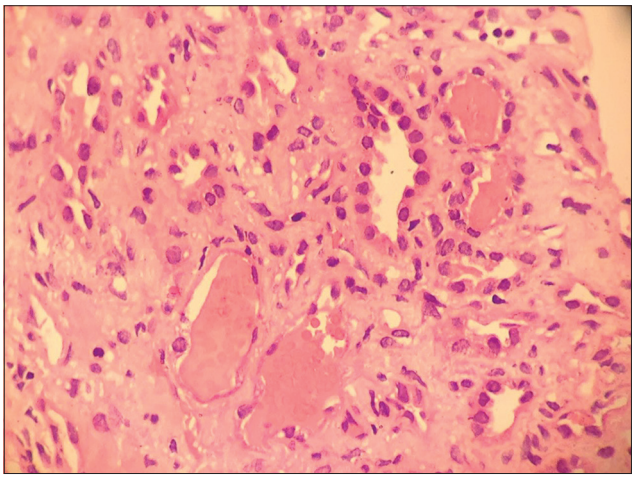

Figure 1: Renal biopsy findings: tubules show intraluminal red cell casts. Interstitium shows infiltrate of lymphocytes and neutrophils

The management of warfarin-related nephropathy (WRN) in patients requiring prolonged anticoagulation poses a management dilemma. Alternative to warfarin, other anticoagulants such as dabigatran (direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (direct-activated factor X inhibitors) are being increasingly used. However, their renal safety is not established. In the literature, two cases of dabigatran-related nephropathy were reported.[13,14] Although RE-LY study showed that dabigatran was associated with smaller reductions in glomerular filtration rate compared to warfarin, its clinical significance is not clear, and most importantly, this study excluded those patients with estimated GFR (eGFR) of <30 ml/min, which is the strongest risk factor for ACRN.[15]

Brodsky *et al*. published a data of 9 patients of WRN. A total of 3 patients had complete renal recovery and 6 patients had partial/no renal recovery. All the three patients who recovered had normal eGFR 3 months before biopsy, and in the remaining 6 patients, eGFR was lower than normal. In our case, patient had normal baseline serum creatinine (0.9 mg/dl) before increasing warfarin dose, probably this could be the reason for complete renal recovery.[10]

The role of steroids is not clear in WRN. The anti-inflammatory effect of steroids may be useful in mitigating the onset of interstitial fibrosis as a consequence of WRN. Temporary interruption of anticoagulation may ameliorate glomerular bleeding and result in stabilization of the renal function.[16] We administered steroids in the present case and it should be tested in the future studies.

Conclusion

Among patients who develop AKI and are on chronic anticoagulant therapy, a presumptive diagnosis of ACRN should be made if a severe coagulopathy is present and if other causes of AKI have been excluded. Renal biopsy may be warranted in different clinical setting. The most

Table 1: Laboratory findings according to clinical phase and time

	September 2014 (MVR)	2nd admission (may 2015)	Present admission (November 05, 2016)	Heparin switch over (November 10, 2016)	Initiation of steroids (November 12, 16)	At discharge (November 26, 2016)
Hb (g/dl)	12	11	10.2	9	9.4	10
TC (cells/mm^3)	8000	7000	4700	5200	4900	12,200
Platelets (lakhs/mm^3)	2.3	2	2.2	3	3	2.8
Blood urea (mg/dl)	30	60	120	124	132	22
Creatinine (mg/dl)	1.1	0.9	4.60	6.10	7.6	1.1
Bilirubin (mg/dl)	0.98	1.1	0.4	0.6	0.8	1.1
CUE						
ALB	1 + Grading of protenuria	1+	3+		2+	2+
RBC	Nil	1-2	Plenty dysmorphic RBCs		15-20	5-6
Pus cells	1-2	2-3	2-4		3-6	3-4
PT (s)	12	15	52	16.20	20.0	22
INR	1.5	2.1	4.70	1.5	2	2.1
APTT (s)	28	36	49.50	29.10	28.20	30
ANA/dsDNA			Negative	-		
ANCA	-	-	Negative	-	-	-
C3/C4	-	-	Normal	-	-	-

MVR: Mitral valve replacement, ANCA: Antineutrophil cytoplasmic antibodies, RBC: Red blood cell, Hb: Hemoglobin, TC: Total count, PT: Physical therapy, INR: International normalized ratio, APTT: Activated partial thromboplastin time, ANA: Antinuclear antibody, CUE: Complete urine examination, ALB: albumin

important measure to prevent ACRN is proper adjustment of the anticoagulant dose, especially in the CKD patients, who are more vulnerable to ACRN.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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