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Frequently Missed, Never Dismissed: Anticoagulant-Related Nephropathy

—Case Presentation and Review of the Literature

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Abstract

We reported here a case of anticoagulant-related nephropathy (ARN) in an elderly patient with background history of chronic kidney disease (CKD-stage 4, with an estimated glomerular filtration rate (eGFR) of <24 ml/min). He presented with an acute kidney injury on background of chronic kidney disease (AKI/CKD) with eGFR of 9 ml/min and serum creatinine of 6.0 mg/dl.

Keywords

Acute Kidney Injury, Anticoagulant-Related Nephropathy, Warfarin-Related Nephropathy, Corticosteroids, eGFR, Chronic Kidney Disease

1. Introduction

Anticoagulant-related nephropathy (ARN), also known as Warfarin-related Nephropathy (WRN) is an acute kidney injury which may be caused by excessive anticoagulation with warfarin or other anticoagulants [1] [2]. ARN has been associated with irreversible kidney injury with increased morbidity and mortality. The term anticoagulant-related nephropathy is more inclusive than warfarin-related nephropathy (WRN), because other anticoagulant can incite and cause the acute kidney injury.

The patient had gross hematuria at the time of presentation to the hospital. His bassline serum creatinine was 2.6 mg/dl with eGFR of 24 ml/min. There was no evidence of pre-renal or post-renal causes to account for his acute kidney dysfunction.

2. Case History

An 81-year-old Caucasian male, nursing home resident. He has history of qua-

driplegia, chronic kidney disease stage-4 with an estimated GFR of 24 ml/min, hypertension, hyperuricemia, atrial fibrillation on warfarin 5 mg per day. He is morbidly obese with lower extremities chronic lymphedema.

He is on regular follow-up with his cardiologist with stable INR. This time he is admitted to the hospital with low grade fever and altered mental status. He was diagnosed with pneumonia.

His lab work-up in the emergency department (ED) is shown in Table 1.

On physical examination: The patient is encephalopathic, obese and with significant shortness of breath. He is placed on bilevel positive pressure ventilation (BIPAP) to help in the acute decompensation of cardio-respiratory status. Cardiovascular examination revealed atrial fibrillation with rapid ventricular rate. There is no murmur or rubs. Lung examinations revealed that the patient is using the accessory muscles of respiration with increased work of breathing. Auscultation of the lungs showed widespread crackles in both lung fields. Abdomen is distended with no rebound tenderness. Foley catheter was in place with gross hematuria in the urine bag. Lower extremities showed bilateral 2 - 3+ pitting edema with breakdown of the skin with blisters.

Management consisted of intra-venous isotonic fluid resuscitation with broad spectrum antibiotics.

His hospital course showed some improvement in physical examination as well as biochemically in the in the BUN and creatinine, 79 and 5.3 mg/dl by the 2nd hospital day. His INR had decreased to 1.8 with stopping of the warfarin and vitamin K supplementation.

Non-enhanced CT scan of the abdomen revealed normal sized kidneys with no evidence of obstruction. On the fourth hospital day his kidney function stabilized with BUN and creatinine of 74 and 5.0 mg/dl and urine output of 600 ml/day.

Despite fluid resuscitation and conservative management no further improvement in kidney function had occurred. The decision was made following a long discussion with him and his family to start renal replacement therapy by the 5th hospital days.

3. Discussion

The diagnosis of ARN should be entertained in any patient with AKI in the setting

Table 1. Shows some of his biochemical data.

Character	value
INR	9.3
Serum creatinine	6.0 mg/dl
BUN	90 mg/dl
Total CO_2	17 mEq/L
Albumen	2.9 g/L
Total protein	6.4 g/L
Alkaline phosphatase	121 units
eGFR	9 ml/min

of excessive anticoagulation and hematuria. The definitive diagnosis is made by kidney biopsy which is not always done because of the risks of bleeding and or thromboembolism if the anticoagulant had to stop for renal biopsy.

It is estimated that the incidence of AKI in patients on anticoagulant was 20.5% overall and 33% in patients with a history of chronic kidney disease [3]. The strongest risk factor for ARN is an INR of >4 and CKD. Other predictor factors for ARN were age, diabetes mellitus, heart failure, hypertension, and glomerular diseases, particularly the nephrotic syndrome [4] [5] [6].

Kidney biopsy in ARN frequently showed obstruction of renal tubules by RBC casts, and little in the way of inflammation in the distal tubules of the kidneys [7] [8]. Disruption of the glomerular filtration barriers is thought to be the main pathophysiological events. The mechanism is poorly understood.

The glomeruli showed little or no abnormalities by immunofluorescence, light, or electron microscopy.

The pathogenesis and diagnosis of ARN is based on the histological analysis of kidney tissues obtained by kidney biopsy and the extrapolation of information obtained from the experimental animal models for ARN [7] [8] [9] [10]. The most prominent features on biopsy are;

- Glomerular hemorrhage
- Obstruction of the renal tubules by red blood cells casts
- Tubular epithelial cell injury

Glomerular hemorrhage results from over coagulation with the formation of tubular obstruction by RBC casts are the main and consistent histological features of ARN [9] [10] [11]. However, the number of obstructed tubules by RBC casts observed on microscopy do not appear sufficient to explain the decrease in GFR. Only small percentage of tubules are completely obstructed by RBC casts on histology [4] [5] [11], which can be explained by misrepresentation of the obstructed tubules on histology because of the small sample size that is usually examined under the microscopy. This can be a plausible explanation of the discrepancy between the clinical and the histological pictures.

Brodsky *et al.* published a data on 9 patients with WRN. A total of 3 patients had complete kidney recovery and 6 patients had partial/to no kidney recovery. All the 3 patients who recovered kidney function had normal estimated glomerular filtration rate (eGFR) before the incident and no history of CKD [7].

The management of ARN in patients requiring anticoagulation poses dilemma. Alternative to warfarin like dabigatran (direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (direct-activated factor X inhibitors) are being used but are also plagued with the occurrences of ARN [12] [13]. A reduced kidney function with an eGFR of <30 ml/min poses the greatest risk for ARN [14].

The role of steroids is not clear in ARN. The anti-inflammatory effects of steroids may be useful in mitigating the interstitial fibrosis sometimes induced in ARN. Temporary interruption of anticoagulation may ameliorate glomerular bleeding with stabilization of the renal function [15]. However, patient with sig-

nificant reduction in kidney function frequently end-up on renal replacement therapy [16].

Back to our patient, despite a conservative management over an extended period of time, the decision was made to place him on renal replacement therapy, in the form of hemodialysis, for fluid and electrolyte management. He remained dialysis dependent.

4. Conclusion

Patients who develop AKI in the setting of chronic anticoagulation therapy with high INR, a presumptive diagnosis of ARN should be entertained as a possibility if other causes of AKI have been excluded. Renal biopsy is the definitive way to diagnose ARN but it is not always practical or possible to carry out. The most important measure to prevent ARN is proper adjustment of anticoagulation dose, especially in patients with CKD who are more susceptible to the development of ARN.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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