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Hussam Al Hennawi
Thomas Jefferson University

Muhammad Shan Ul Abedin

Rui Song
Thomas Jefferson University

Majid Khan
Thomas Jefferson University

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CASE REPORT

Biopsy-Proven Anticoagulant-Related Nephropathy: A Case Report and Review of the Literature

Hussam Al Hennawi, MD[1]; Muhammad Shan Ul Abedin, MD[1]; Rui Song, MD[1]; and Majid Khan, MD[1]

[1]Jefferson Abington Hospital, Abington, Pennsylvania

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Corresponding Author
Hussam Al Hennawi, MD; e-mail, Hussam.AlHennawi@jefferson.edu.

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Abstract
Anticoagulant-related nephropathy is a type of acute kidney injury that may follow warfarin and other anticoagulants. Anticoagulant-related nephropathy has been shown to be associated with irreversible kidney injury and increased risk for morbidity. Accurate diagnosis and management remain to be challenging. We describe a case of a 62-year-old man with significant cardiac history who presented with impaired kidney function associated with supratherapeutic international normalized ratio. Kidney biopsy findings suggested anticoagulant-related nephropathy.

Background
The adverse effects of warfarin in patients with chronic kidney disease (CKD) were first observed in the 1970s and early 1980s, as warfarin was a component of the Melbourne cocktail, which comprises dipyridamole, cyclophosphamide, and warfarin. As professor Kincaid Smith was experimenting with the role of anticoagulant (warfarin) for treating glomerulopathies, mainly IgA nephritis, she noted more glomerular bleeding, evidenced by erythrocyte counts in the treatment compared with the control group (1). This was followed by a case series in 2009 describing patients on warfarin with unexplained acute kidney injury (AKI) with microscopic or gross hematuria (2). Given the association between vitamin K antagonists and hematuria-predominant AKI, it was then found that newly emerging direct-acting oral anticoagulants (DOACs), antiplatelet agents, and hemorrhagic states also may predispose to similar findings (3, 4).

Histologic hallmarks of anticoagulant-related nephropathy (ARN) are characterized by glomerular hemorrhage and acute tubular injury with profuse red blood cells and casts (5). Case series and reports have described the histopathologic changes in patients with ARN, whereby most patients had underlying kidney disease. IgA-predominant immune complexes were present in 30% to 40% of patients with ARN, of whom most were on warfarin (2). Risk factors include overanticoagulation, older age, and underlying nephropathy. The prognosis of patients with ARN remains poor, with most patients achieving partial kidney function or continuing to be on dialysis (2, 6).

The clinical outcome of patients with ARN who require permanent anticoagulation in mechanical heart valves remains uncertain.

Objective
This report highlights the clinical course of a patient with a mechanical aortic valve who developed ARN and the challenges associated with switching to a different anticoagulant agent.

Case Presentation
A 62-year-old White man with a significant history of Asperger disorder, CKD (baseline creatinine of 1.7 mg/dL), atrial fibrillation, rheumatic heart disease, mechanical aortic valve replacement on warfarin, aortic root replacement, and nonischemic cardiomyopathy status post implantable

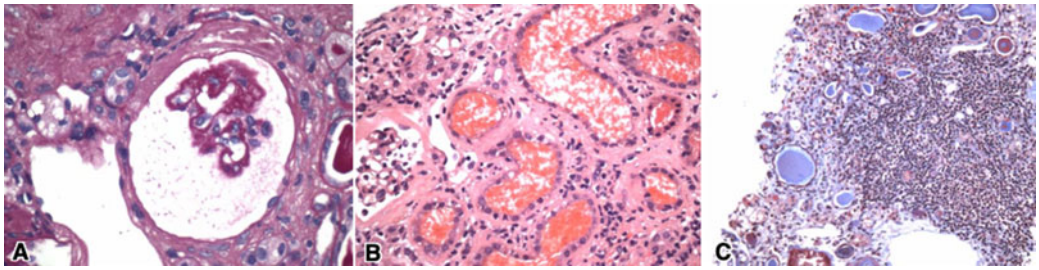

Figure 1. **Hematoxylin–eosin-, Periodic acid–Schiff-, trichrome-, and Jones Methenamine Silver Stain–stained sections show ischemic glomerulus (A), erythrocyte casts (B), and moderate patchy tubular atrophy and interstitial fibrosis affecting 50% of the cortical area accompanied by a patchy, focally dense mononuclear inflammatory cell infiltrate (C). Proximal tubules show patchy degenerative and regenerative changes, including loss of apical brush border, nuclear enlargement, and prominent nucleoli. Focal endocrine-type tubular atrophy is noted in the subcapsular region. (A: magnification ×400; B: magnification ×400; C: magnification ×200.)**

cardioverter defibrillator insertion presented to the emergency department due to epistaxis. International normalized ratio (INR) was found in the supratherapeutic range (5.8).

His medications include aspirin 81 mg, carvedilol 12.5 mg, furosemide 40 mg, pantoprazole 40 mg, simvastatin 20 mg, and warfarin 2 mg. There were no recent changes in medications. On physical examination, he had a slow nosebleed with otherwise normal vital signs.

Of note, the patient initially presented to the hospital 6 months previously with a creatinine (Cr) level of 2.4 mg/dL and 1.9 mg/dL on discharge. Peak INR was 5.1, which decreased to 1.2 after treatment with vitamin K and holding warfarin. Extensive work-up for AKI with hematuria including antineutrophil cytoplasmic antibody, serum complements, and serum/urine protein electrophoresis were within normal ranges. Warfarin was restarted on discharge with a heparin bridge and plan for a kidney biopsy if kidney function worsens in the future.

Laboratory results on current presentation were significant for a Cr level of 4.3 mg/dL. Work-up including urinalysis showed 2+ protein; 2+ blood; negative leukocyte esterase, greater than 182/high-power field erythrocytes; 32/high-power field white blood cells, and urine protein/creatinine ratio of 0.92 mg/g. Antinuclear antibodies and glomerular basement membrane antibody were within normal ranges. Results of ultrasonography showed stable bilateral renal cortical cysts with no evidence of kidney stones and hydronephrosis. Warfarin was held given a supratherapeutic range, and a kidney biopsy was obtained for further evaluation. Histology and immunofluorescence findings supported the diagnosis of IgA nephropathy (MEST-C [i.e., mesangial and endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy, and the presence of crescents] score M0E0S0T2C0) complicated by ARN given supratherapeutic INR (Figure 1). Warfarin was restarted on discharge, and close monitoring of INR was considered necessary.

Five months later, he developed AKI on CKD with an INR of 3.9 on admission requiring intermittent hemodialysis. Warfarin was permanently held per the patient's request, with a noticeable kidney function improvement with no further hemodialysis requirement. His Cr ranged between 1.7 and 2 mg/dL for the next 6 months. Due to the high risk for stroke, given mechanical valve and atrial fibrillation without warfarin, a collaborative team approach coordinated the decision to initiate apixaban 2.5 mg twice daily while acknowledging the less effectiveness compared with warfarin in mechanical heart valves. His Cr has been followed closely and is stable to date.

Discussion

ARN is a form of AKI caused by excessive anticoagulation with warfarin or other anticoagulants. CKD and glomerulonephritis are risk factors, particularly with nephrotic syndrome. According to a study by Brodsky and colleagues (7), ARN occurred in 33% of the CKD cohort and 16.5% of the non-CKD cohort. This study also showed an increase in the progression of CKD in patients with ARN (8). Moreover, 85% of ARN cases have underlying IgA nephropathy (9). Incidence of ARN might be overestimated, given lack of biopsy evidence, whereas the actual incidence could be underestimated, given that kidney biopsies are not widely performed with a supratherapeutic INR (7, 8, 10).

The temporal relationship between an elevated INR to ARN remains unclear, but INR greater than 3 was mainly observed with possible persistence of nephropathy after normalization of INR (8, 11). Most observational studies suggested AKI in the setting of ARN tends to occur in an average of 8 weeks after starting warfarin (4). Diagnosis is established by kidney biopsy demonstrating obstructing intraluminal erythrocyte casts. Notably, ARN shares many clinical and histologic features with IgAN, including hematuria, glomerular hemorrhage, and erythrocyte casts. IgA-predominant immune complexes were present in 30% to 40% of patients with ARN, of whom most were on warfarin (4). Distinguishing these diseases is based primarily on patient's history and characteristic histologic findings. Immunofluorescence will reveal a diffuse mesangial granular pattern of IgA deposits in IgAN. In our case, immunofluorescence findings were suggestive of an underlying IgA nephropathy, the tubular injury with erythrocyte casts in the setting of supratherapeutic INR suggested ARN, which is in line with the literature findings.

Holding or decreasing the dose anticoagulation to restore INR normalization can be effective. Nevertheless, this poses a dilemma in patients who need lifelong anticoagulation. In patients on warfarin, it may be appropriate to switch to DOACs (12), but it can be challenging in cases like mechanical heart valves. Similarly, switching to another DOAC or lowering the dose can be possible options. The use of glucocorticoids in the treatment of ARN has been suggested but is unproven (9). Our patient also has paroxysmal atrial fibrillation, complicating mechanical aortic valve. Although DOACs are less effective in mechanical valves, they could decrease the risk for stroke from paroxysmal arrythmias. We believe that a multidisciplinary approach with the patient's participation is very important for an effective treatment option.

Conclusions

ARN is an uncommon clinical entity that may have been overlooked in patients presenting with AKI while on anticoagulation. A high clinical index of suspicion may provide early treatment and prevent further deterioration of kidney function. This case adds to the controversy regarding anticoagulation considerations in patients requiring life-long management.

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