Acute Kidney Injury During Warfarin Therapy Associated With Obstructive Tubular Red Blood Cell Casts: A Report of 9 Cases

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Acute kidney injury (AKI) during warfarin therapy usually is hemodynamic secondary to massive blood loss. Here, we report pathological findings in kidney biopsy specimens from 9 patients with warfarin overdose, hematuria, and AKI. Kidney biopsy specimens from patients on warfarin therapy with AKI were identified in our database within a 5-year period. Each kidney biopsy specimen was evaluated by using semiquantitative morphometric techniques, and medical history was reviewed for conditions explaining AKI. Biopsy specimens with morphological findings of active glomerulonephritis and active inflammatory lesions were excluded from the study. Biopsy specimens from 9 patients were selected. At presentation with AKI, each patient had an abnormal international normalized ratio (mean 4.4 ± 0.7 IU) and increased serum creatinine level (mean, 4.3 ± 0.8 mg/dL). Morphologically, each biopsy specimen showed evidence of acute tubular injury and glomerular hemorrhage: red blood cells (RBCs) in Bowman space and numerous occlusive RBC casts in tubules. Each biopsy specimen showed chronic kidney injury. Six of 9 patients did not recover from AKI. These data suggest that warfarin therapy can result in AKI by causing glomerular hemorrhage and renal tubular obstruction by RBC casts. Our experience suggests that this may be a potentially serious complication of warfarin therapy, especially in older patients with underlying chronic kidney injury.

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INDEX WORDS: Warfarin; occlusive red blood cell (RBC) casts; glomerular hemorrhage; renal pathology; acute kidney injury.

Warfarin (Coumadin; Bristol-Meyers Squibb, Princeton, NJ) treatment is widely used in patients with different disorders to prevent thrombosis. Several adverse effects of warfarin overdose on kidney function have been described, including hemorrhage, vasculitis, interstitial nephritis, and hematuria.[1,2] A recent publication showed correlation between the severity of chronic kidney disease and warfarin-associated hemorrhagic complications.[3]

It has been suggested that warfarin can cause acute kidney injury (AKI) by inducing glomerular hematuria with subsequent widespread tubular obstruction. This was first reported in a patient with severe warfarin coagulopathy and glomerular basement membrane (GBM) nephropathy.[4] We presented a similar syndrome in a patient with inactive systemic lupus erythematosus, but abnormally thick GBM.[5] Our work extends these observations by using retrospective and prospective analysis of our kidney biopsy files to identify patients with unexplained AKI while on warfarin therapy. We hypothesize that in susceptible individuals, warfarin can cause marked glomerular hematuria, resulting in tubular obstruction by red blood cell (RBC) casts and clinical symptoms of AKI.

CASE REPORTS

We searched the kidney biopsy files at the Department of Pathology, The Ohio State University Medical Center, Columbus, OH, for a 5-year period. We focused on biopsy specimens from patients who presented with unexplained AKI and hematuria while on warfarin therapy. We identified 2,801 native kidney biopsy specimens. Of these, 61 biopsy specimens were from patients on warfarin treatment (according to clinical information provided). AKI was noted in the clinical history for 35 biopsies. Only patients without pathological findings of acute/active glomerulonephritis were

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included in the study. Using these selection criteria, we identified 11 biopsy specimens from 9 patients.

The number of RBCs and RBC casts in tubules was evaluated by using a semiquantitative morphometric technique, as described previously.[6] GBM thickness was measured as described earlier.[7] Kidney biopsy specimens were stained with antibodies against CD10, cytokeratin AE1/AE3, and Tamm-Horsfall protein to identify proximal and distal tubules and the thick ascending loop of Henle, respectively. By performing Tamm-Horsfall protein staining, we also wanted to see whether RBC casts contain this important cast-forming protein.

Clinical data are listed in Table 1. No hydronephrosis was noted by means of ultrasound in any of our patients. Warfarin treatment was stopped and the international normalized ratio was normalized in all patients before the kidney biopsy (through the use of vitamin K or fresh frozen plasma).

Histological findings are listed in Table 2. No active proliferative glomerular lesions were seen in any biopsy specimens. All biopsy specimens had RBCs within the tubular lumina (in 6.4% ± 0.7% of tubules) with formation of occlusive RBC casts (in 11.5% ± 2.3% of tubules; Table 2; Fig 1A). RBCs also were seen in numerous Bowman spaces (Fig 1B). The occlusive RBC casts were localized mostly to distal nephron segments and did not contain Tamm-Horsfall protein (Fig 1B and C). Dysmorphic RBCs were present in several tubules (Fig 1D).

An underlying kidney disease was evident in all patients. Five patients had mild glomerular immune complex deposits. Focal segmental glomerular sclerosis was noted in 1 patient, and 2 patients had predominantly interstitial findings (Table 2).

Clinically, many patients did not recover from the AKI after normalization of international normalized ratio. Four patients remained on dialysis therapy; 1 of them later died. One patient had no improvement in kidney function 2 months after biopsy, but he is not on dialysis therapy.

DISCUSSION

In the present study, we summarize pathological findings in kidney biopsy specimens obtained from patients on warfarin treatment who developed unexplained AKI. We identified RBCs in Bowman space, RBCs in tubules, and occlusive RBC casts predominantly in distal nephron segments. In addition, all patients had underlying chronic kidney injury, but no active proliferative glomerular lesions.

The association of hematuria with warfarin treatment in the absence of acute kidney disease has been reported previously.[9,10] In 1964, Reilly et al[11] found hematuria in 35 of 200 patients receiving warfarin. However, no significant correlation between plasma prothrombin level and occult blood in urine was found.[11] The possibility of an increased risk of hematuria in patients receiving combined therapy with warfarin and nonsteroidal anti-inflammatory drugs has been proposed more than 30 years ago.[12,13] We had previously reported a case of warfarin-associated hematuria with AKI in a patient with systemic lupus erythematosus and no active lupus nephritis, but with thickened GBM.[5] In the present study, we expand these observations and present detailed kidney biopsy findings in patients with unexplained AKI while on warfarin therapy.

One may argue that the presence of RBCs in tubules is a common morphological finding in small biopsy specimens and is related to the biopsy procedure itself. We analyzed this scenario and concluded that in our study, the presence of RBCs in tubules is not a biopsy artifact for the following reasons: (1) we did not notice the presence of RBCs around the edges of the biopsy specimen; (2) RBCs were present overwhelmingly within the nephron, but not in the interstitium; (3) all our biopsy specimens contained not only RBCs in tubules, but also occlusive RBC casts; (4) the tubular epithelium frequently was flattened/compressed by the RBC casts; (5) the distribution of RBCs and casts in biopsy specimens was not uniform; they were localized mainly in distal nephron segments; (6) light and electron microscopy showed dysmorphic RBCs in tubules; and (7) in a previous study, we analyzed tubular RBCs in biopsy specimens from patients with minimal change disease to assess the extent to which the trauma of the biopsy can result in blood in the tubules. We found that the biopsy itself can account for only about 1% of tubules containing blood.[7] Our present study shows a much greater percentage of tubules with blood, including obstructing casts.

We found that the incidence of unexplained AKI in patients on warfarin therapy is low; in our study, it was less than 1% of our native kidney biopsy material. However, some patients may be overlooked because a detailed clinical history often is not available for a pathologist. After we started to pay attention to this problem, we specifically inquired whether a patient with unexplained AKI and RBC casts was on warfarin treatment and his or her coagulation results were abnormal. We identified more than 30% of cases within the last 7 months.

Several pathogenetic mechanisms of gross hematuria in patients on warfarin treatment have been proposed. The formation of microscopic