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Review Article

GESDAV

Warfarin-related nephropathy and beyond. What renal pathologists need to suspect in a kidney biopsy?

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ABSTRACT

We have recently described a new clinical syndrome in patients receiving warfarin for anticoagulation therapy. First, we identified that warfarin therapy can result in acute kidney injury (AKI) by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts in some patients. This syndrome has been named warfarin-related nephropathy (WRN), and patients with chronic kidney disease appear to be particularly susceptible. We defined WRN as an acute increase in international normalized ratio (INR) to >3.0, followed by evidence of AKI (defined as a sustained increase in serum creatinine of ≥0.3 mg/dl) within a week of the INR increase. We believe that anticoagulant-related kidney injury should be suspected in a patient on anticoagulation therapy, if there is a disproportion between the number of RBC tubular casts, acute tubular necrosis and the degree of underlying kidney lesion (such as glomerular immune complex depositions, glomerular basement membrane thickness abnormalities etc.) in kidney biopsy. Detailed evaluation of coagulation data and medications is recommended for all patients with RBC casts and AKI.

KEY WORDS: Drug, kidney, injury, nephropathy, toxicity

INTRODUCTION

We have recently described a new clinical syndrome in patients receiving warfarin for anticoagulation therapy. First, we identified that warfarin therapy can result in acute kidney injury (AKI) by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts in some patients [1]. All these patients had and an underlying kidney disease. Later we found that out of 103 patients with chronic kidney disease (CKD), 37% of patients with an international normalized ratio (INR) >3.0 had a coincidentally AKI, which was defined as an increase in serum creatinine (SC) ≥0.3 mg/dl[2]. These patients had accelerated progression of CKD, as compared to patients without AKI [2]. This syndrome has been named warfarin-related nephropathy (WRN), and patients with CKD appear to be particularly susceptible. The consecutive analysis of more than 15,000 patients treated with warfarin at The Ohio State University Medical Center showed that 4059 of those had INR >3.0 and approximately 20% of these patients also had an increase in SC ≥0.3 mg/dl associated with INR >3.0 (WRN group). The WRN group had a 1-year mortality rate of 31% versus 18.9% in non-WRN group ($P < 0.001$), and a 5 years mortality rate of 42%, when compared to 27% for the non-WRN group ($P < 0.001$). For both WRN and non-WRN groups, the 5 years mortality rate was consistently higher in those with CKD compared with those with non-CKD (50.1% vs. 37.0% for the WRN cohort; 39.7% vs. 24.5% for the non-WRN cohort; $P < 0.0001$) [3].

We defined WRN as an acute increase in INR to >3.0, followed by evidence of AKI (defined as a sustained increase in SC of ≥0.3 mg/dl) within a week of the INR increase. The AKI cannot be explained by any other factors, and the kidney biopsy demonstrates extensive glomerular hemorrhage with tubular obstruction by RBCs [1]. Beyond AKI, WRN is a significant risk factor for mortality within the first 2 months of diagnosis, and it accelerates the progression of CKD [2,3].

We believe that WRN is a significant public health problem because more than 2 million people in the USA are started on warfarin therapy annually. Among CKD patients experiencing an increase in INR above 3.0, WRN was seen in 33-37% of the patients [2,3], demonstrating that WRN is common. Since our first publications, several other groups have described WRN in patients on warfarin therapy [4,5]. Their data confirmed our observations, including a high incidence of WRN. The main conclusions from published data are:

- The risk of AKI occurs at an INR threshold of >3; AKI risk is not a function of the level of INR beyond 3
- The kidney biopsy findings in those with AKI and INR >3 are consistent with catastrophic glomerular hemorrhage causing tubular injury
- An abnormally elevated INR is not sufficient by itself to cause WRN; we postulate that WRN occurs in the setting of pre-existing glomerular damage (that may not have been clinically known/diagnosed) coupled with

over-anticoagulation. Normal patients who develop WRN likely have undiagnosed CKD/glomerular injury

- When specifically analyzed, WRN is associated with progression of CKD and an increased risk of subacute mortality
- The true incidence of WRN is difficult to determine from the mainly retrospective studies published thus far, but it appears to be high. The only prospective study [5] suggests an incidence of 60%, at least in the elderly population examined
- Over 26 million people in the USA have CKD, and anticoagulation therapy is common in CKD patients [6,7]. Furthermore, warfarin is difficult to titrate in CKD, and this difficulty in maintaining the target INR increases the risk of over-anticoagulation, which is the cause of WRN [8,9]. It is interesting that WRN seen in patients without known CKD [3], may actually represent WRN in patients with sub-clinical CKD, which would put an even larger number of patients at risk. Adding to this public health problem is emerging evidence that WRN is only a subset of a broader syndrome we have named anticoagulant-related nephropathy, in which other, and possibly all currently used anticoagulants may cause AKI. Indeed, AKI associated with dabigatran (direct thrombin inhibitor) use has been reported [10-12] and recently demonstrated by us in experimental animals [13]. In addition, anticoagulants may aggravate an underlying kidney disease and induce hematuria and AKI [14].

There is a challenge for a renal pathologist to recognize WRN in kidney biopsy. Renal pathologists often do not recognize WRN because of an underlying kidney disease. Acute tubular injury and RBC casts are usually associated with those conditions. In our first description of WRN, a variety of underlying kidney disease was found [Table 1] [1].

No guidelines are established yet to diagnose WRN. Here are several recent examples from our practice, when WRN was diagnosed:

Case 1

The first case is about a 61-year-old Caucasian female with recently diagnosed diabetes mellitus. Baseline SC was normal. She presented to the hospital after episodes of diarrhea with SC of 3.2 mg/dl. She developed deep vein thrombosis, and she was started on warfarin therapy. Her INR was as high as 5. SC increased up to 6.6 mg/dl within 2 weeks after initiation of warfarin therapy. Serologies showed positive ANA (1:640), but the complement levels were normal. Kidney biopsy findings by light microscopy included numerous RBC casts and acute tubular necrosis (ATN) [Figure 1a]. The glomeruli were unremarkable [Figure 1b]. Immunofluorescence showed mild smudgy staining for IgG [Figure 1c]. Electron microscopy showed scattered small electron-dense immune-type complex deposits [Figure 1d]. There was a disproportion between the number of RBC casts, the degree of ATN and relatively small immune complex deposits in the absence of proliferative glomerular lesions or cellular crescents.

Case 2

The second case we present here is a 41-year-old Caucasian female with a history of aortic bifurcation thrombosis, she underwent a graft placement and started on warfarin therapy. Her INR was as high as 27. Baseline SC was 1.0 mg/dl but

Table 1: Demographics, laboratory data, and morphologic findings in patients with WRN

Patient	Demographics and laboratory data						Morphological findings								Outcome
	Age	Gender	Race	Maximal INR, IU	SC change from baseline, mg/dl	Urinalysis	# of GI	% of sclerotic GI	IntInf	ATN	IFTA	RBC casts, %	Immunofluorescence	GBM thickness, nm*	
1	27	F	AA	8.0	2.5	3+hematuria, 1+proteinuria	19	11	1+	1+	1+	2.8	1+mesangial IgG, IgM, C1q, C3	560±120	Renal function recovery
2	76	F	W	7.0	2.5	2+hematuria	20	55	1+	3+	3+	20.9	Non-specific	350±63	Dialysis
3	61	M	W	2.0	1.8	2+hematuria, 3+proteinuria	3	0	+/–	2+	2+	4.4	Non-specific	357±101	Dialysis, expired
4	80	M	W	5.2	2.6	2+hematuria, 2+proteinuria	23	17	1+	3+	1+ to 2+	16.8	1+mesangial IgA	429±85	Dialysis
5	38	F	W	3.9	1.3	1+hematuria, 1+proteinuria	12	0	0	1+	0	2.3	1+mesangial IgA	277±73	Renal function recovery
6	63	M	W	3.7	1.5	2+hematuria, RBC casts	21	14	0	1+	1+	16.3	Non-specific	430±99	Partial renal function recovery
7	82	F	W	2.8	3.4	1+hematuria	6	17	1+	2+ to 3+	1+	17.8	1+mesangial IgA	289±76	Renal function recovery
8	73	M	W	3.0	3.9	2+hematuria, 3+proteinuria	14	36	2+	3+	2+	10.9	Non-specific	310±89	Dialysis
9	55	M	W	3.8	8.3	1+hematuria, 1+proteinuria	11	19	+/–	3+	1+	11.4	1+mesangial IgG, C1q, C3	343±148	Renal function recovery

*The mean GBM thickness established in our laboratory for males 373±56 nm and for females 351±40 nm; #Combined with frozen tissue. ATN: Acute tubular necrosis, GBM: Glomerular basement membrane, GI: Glomeruli, RBC: Red blood cell, IntInf: Interstitial inflammation, IFTA: Interstitial fibrosis and tubular atrophy, WRN: Warfarin-related nephropathy, SC: Serum creatinine, M: Male, F: Female. Morphological findings were scored semiquantitatively using the following criteria: 0−: Absent, 1+: Mild, 2+: Moderate, 3+: Prominent. If changes were minimal but not absent, the score of ±was applied

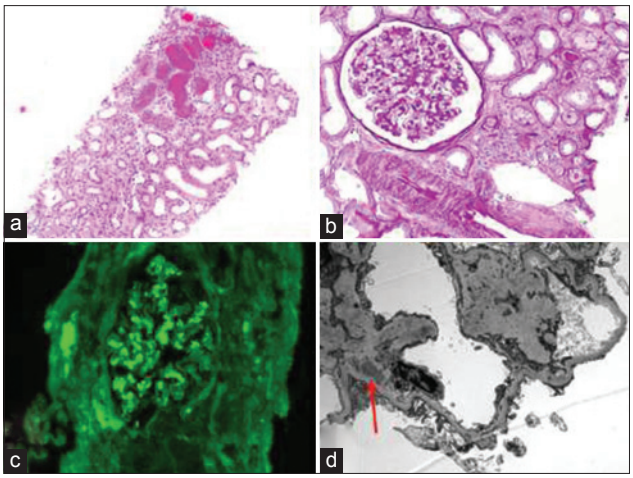

Figure 1: Light microscopy, immunofluorescence and electron microscopy in a patient with suspicious warfarin-related nephropathy (Case 1). (a) Light microscopy shows numerous red blood cell casts in the tubules and acute tubular necrosis (H and E, ×40). (b) Glomeruli are unremarkable by light microscopy (Periodic acid-Schif, ×200). (c) Direct immunofluorescence with an antibody to IgG shows mild mesangial staining (×200). (d) Electron microscopy shows scattered mesangial electron dense immune-type deposits (arrow) (Magnification)

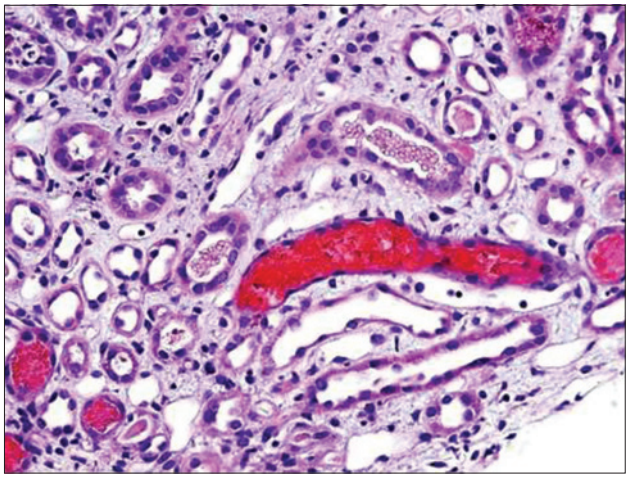

Figure 2: Light microscopy in a patient with suspicious warfarin-related nephropathy (Case 2). Light microscopy shows numerous red blood cell casts in the tubules and acute tubular necrosis (H and E, ×200)

increased to 6.7 mg/dl shortly after the high INR. Urinalysis showed hematuria with RBC casts. Her serologies (ANA, ANCA) were negative and complement levels normal. In a kidney biopsy, immunofluorescence did not show positive staining. Electron microscopy showed normal glomerular basement membrane (GBM) thickness. However, by light microscopy there were numerous tubular RBC casts and ATN [Figure 2].

It is not clear whether other anticoagulant, including new oral drugs, can induce AKI. A case of dabigatran-induced AKI has been reported [10]. We had a kidney biopsy from a patient on heparin therapy, where we seen numerous RBC casts and ATN as well. We believe that anticoagulant-related kidney injury should be suspected in a patient on anticoagulation therapy, if there is a disproportion between the number of RBC tubular casts, ATN and the degree of underlying kidney lesion (such as glomerular immune complex depositions, GBM thickness abnormalities etc.) in kidney biopsy. Detailed evaluation of coagulation data and medications is recommended for all patients with RBC casts and AKI.

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