Haematuria and Acute Kidney Injury Associated with Warfarin Anticoagulation

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Abstract

Bleeding is a common complication of warfarin anticoagulation and not uncommonly affects the kidney and urinary tract. This review explores the potential causes of haematuria and acute kidney injury in patients receiving warfarin treatment. It covers urological aspects as well as the recently described warfarin-related nephropathy and other less common causes of kidney injury related to warfarin treatment.

Keywords: Warfarin; Warfarin-related nephropathy; Haematuria; Acute kidney injury; Chronic kidney disease

Background

The use of warfarin to treat glomerulonephritis and various renal diseases was practiced in many countries in the 1970s and early 1980s [1-5]. However, the pendulum may have swung the other way in recent years, with concern that warfarin may be detrimental to the kidneys in the long term. There is interest in the development of acute kidney injury (AKI) associated with warfarin therapy and possible poor outcomes in susceptible groups.

Warfarin is an oral anticoagulant which inhibits vitamin K dependent γ-carboxylation of clotting factors II, VII, IX and X. The main indications for warfarin are treating and preventing thromboembolism. Although effective, warfarin use is potentially complicated by supratherapeutic anticoagulation (overanticoagulation). Warfarin is strongly protein bound, mainly to albumin. Albumin is a negative acute phase reactant and many illnesses reduce serum albumin. Warfarin is mainly metabolised by the CYP-2CP microsomal liver enzymes, which may be affected by a number of medications. Thus, medication interactions and medical conditions may predispose patients to supratherapeutic anticoagulation. The prothrombin time, standardised as the International normalized ratio (INR) is used to monitor warfarin anticoagulation. Warfarin reversal may be achieved by administering vitamin K.

Haemorrhage is the main complication of concern with warfarin therapy. The top three sites of bleeding are the oropharynx, soft tissue, gastrointestinal and urinary tract [6]. In one study, the average annual frequency of major bleeding was 3%, with 15% of major bleeding originating from the urinary tract. However, there is a wide variation in bleeding figures, depending on the INR target, patient characteristics and definitions used. Patients with chronic kidney disease (CKD) have an increased risk of overanticoagulation as they spent less time in the therapeutic range, required frequent dose adjustments and had higher bleeding risk [7,8].

Briefly, AKI is typically considered by mechanism as prerenal, intrinsic (intrarenal), and postrenal (obstructive); all of which may be involved in warfarin-treated patients. This review explores the possible causes of haematuria and AKI which may be attributed to a complication of anticoagulation with warfarin.

Urological Considerations

Urinary tract bleeding in the setting of warfarin anticoagulation commonly presents as haematuria. Bleeding from the kidney may be retroperitoneal, intraluminal or intrarenal [9]. Intrarenal bleeding may be suburothelial, intraparenchymal, subcapsular, perinephric or pararenal [10,11]. Intrarenal and intraluminal bleeding uncommonly leads to obstructive urethropy and postrenal AKI. Shock from massive retroperitoneal bleeding or kidney rupture may lead to prerenal AKI but are also uncommon.

Haematuria and suburothelial bleeding

Decades ago, the source of haematuria in anticoagulated patients was a mystery. Dajani, in a letter to the New England Journal of Medicine in 1977 wrote "I have looked in vain for a description of the mechanism of hematuria in patients on anticoagulants [12]". He subsequently described a patient who presented with macroscopic haematuria following warfarin overanticoagulation. The patient had a nephrectomy due to the concern of a malignant cyst on the pyelogram. Microscopic examination of the kidney showed multiple foci of haemorrhage in the pelvicalyceal wall, ranging from subepithelial haemorrhage to rupture of the epithelium and frank leaks into the urinary channels. In addition to this histopathological description, numerous radiological reports have demonstrated bleeding within the pelvicalyceal system related to anticoagulation [9,13-18]. The suburothelial haematoma in the renal pelvis may mimic a tumour, the so-called Antopol-Goldman lesion [19,20]. The majority of such patients with pelvicalyceal bleeding present with macroscopic haematuria and flank or back pain. These patients have often ended up with unnecessary nephrectomies as radiological studies were unable to exclude transitional cell carcinoma.

In a recent study by Gayer et al. [21], seven patients with coagulopathy and spontaneous suburothelial haemorrhage diagnosed by CT were analysed. Six patients had abdominal or flank pain, and 5/6 had macroscopic haematuria. One patient had painless haematuria. Five of the patients had supratherapeutic warfarin anticoagulation.

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defined pathologies (13%). Of those with microscopic haematuria cystis (8%), renal infarct from atrial fibrillation (8%) and other less including calculi (21%), malignancy (17%), radiation or haemorrhagic sonography, CT and retrograde pyelogram as required. Two-thirds patients were evaluated with an IVP and cystoscopy, with additional excluded and the majority had macroscopic haematuria (87%). These urological examination compared with patients who have haematuria anticoagulation (46% of cohort) were more likely to have a normal yield a 71% diagnosis of underlying urinary tract abnormalities, most commonly stone disease, prostate abnormalities, bladder tumours and haemorrhagic cystitis. Tumours were found in 16% of the cohort. Others, utilising more comprehensive assessments, found varying rates had an INR >4.0. However, the nature of the haematuria was not stated. to the primary concern of malignancy. Some studies show no underlying lesions when utilising diagnostic imaging alone. In a retrospective study of CT scans in warfarin-treated patients, Danaci et al. found no underlying lesion in 7 patients with haematuria, intra-renal or retroperitoneal haemorrhage [18]. Six of those patients had an INR >4.0. However, the nature of the haematuria was not stated. Others, utilising more comprehensive assessments, found varying rates of renal tract abnormalities and malignant lesions.

Haematuria and obstructive uropathy

It appears that in some cases, suburothelial bleeding involving the ureters may lead to obstructive uropathy. This was well illustrated in a report by Kollo et al. which described a patient with oliguric AKI following overanticoagulation with warfarin [22]. She had microscopic haematuria and bilateral hydronephrosis on ultrasound. Unenhanced CT showed hyperdense thickening of the renal pelvis and ureters, with narrowing of the lumen. Anticoagulation was reversed with vitamin K which resulted in prompt diuresis and resolution of AKI. Subsequent contrast enhanced CT demonstrated intraluminal defects in the pelvicalyceal system and both ureters. These cases suggest that correction of anticoagulation may reverse the AKI associated with partial or subtotal ureteric obstruction from suburothelial bleeding.

Haematuria and renal tract pathology

The detection of haematuria often raises the question of underlying renal tract pathology, with the primary concern of malignancy. Some studies show no underlying lesions when utilising diagnostic imaging alone. In a retrospective study of CT scans in warfarin-treated patients, Danaci et al. found no underlying lesion in 7 patients with haematuria, intra-renal or retroperitoneal haemorrhage [18]. Six of those patients had an INR >4.0. However, the nature of the haematuria was not stated. Others, utilising more comprehensive assessments, found varying rates of renal tract abnormalities and malignant lesions.

Cutino et al. retrospectively examined the sources of macroscopic haematuria in a cohort of 24 warfarin-treated patients with therapeutic anticoagulation, who were assessed with intravenous pyelogram (IVP) supplemented by cystoscopy [23]. In combination, IVP and cystoscopy yielded a 71% diagnosis of underlying urinary tract abnormalities, most commonly stone disease, prostate abnormalities, bladder tumours and haemorrhagic cystitis. Tumours were found in 16% of the cohort.

Avidor et al. retrospectively analysed 24 patients on warfarin with macroscopic haematuria [24]. After evaluation with cystoscopy (88%), IVP (54%) or ultrasound (38%), 62% of the cohort on warfarin had an underlying urological disorder. The majority of bleeding was due to the prostate, bladder neck lesions and stones. Tumours were found in 24%, mostly in the lower urinary tract. Patients with suprathrapeutic anticoagulation (46% of cohort) were more likely to have a normal urological examination compared with patients who have haematuria in the therapeutic range (55% vs. 23%).

Schuster et al. examined 29 patients with haematuria while receiving warfarin anticoagulation [25]. Patients with overanticoagulation were excluded and the majority had macroscopic haematuria (87%). These patients were evaluated with an IVP and cystoscopy, with additional sonography, CT and retrograde pyelogram as required. Two-thirds of patients with macroscopic haematuria had underlying pathology, including calculi (21%), malignancy (17%), radiation or haemorrhagic cysts (8%), renal infarct from atrial fibrillation (8%) and other less defined pathologies (13%). Of those with microscopic haematuria (17% of cohort), 3 had posterior urethritis, one had calculi, and one was normal.

Van Savage and Fried prospectively assessed 30 patients with new onset haematuria while on warfarin or heparin therapy [26]. Majority had macroscopic haematuria (80%), while microscopic haematuria (20%) had to be present on two or more urinalysis. The prothrombin time and partial thromboplastin time were within therapeutic range. Majority of haematuria was due to stone disease, prostate hypertrophy or prostatitis, and cystitis; with 57% of lesions detected in the lower urinary tract. These authors found malignancy in 7% of patients with macroscopic haematuria and none in those with microscopic haematuria.

In a nested case-control study of 565 patients receiving outpatient treatment, Landefeld et al. assessed bleeding outcomes in patients recently commenced on warfarin [27]. Major or minor haematuria occurred in 13.8% of the cohort. Notably, the definition of minor bleeding included macroscopic haematuria. Excluding patients with previously known renal tract lesions, major and minor haematuria, important remediable lesions were detected in 33%, including stones and malignancy (22% of cohort with haematuria). Previously undiagnosed lesions were more likely detected if bleeding occurred at lower prothrombin time ratio and when prothrombin time was not elevated at the time of bleeding.

In a 2 year prospective study, Culclasure et al. performed regular urinalysis on 243 patients receiving long-term warfarin anticoagulation and compared the findings to an age and sex-matched control group not receiving anticoagulation [28]. During the study, all haematuria was microscopic and there was no difference in the incidence of haematuria between the two groups, which was 0.05 and 0.08 per 100 patient-months, respectively. Further evaluation was initiated after a second episode of haematuria. An underlying abnormality was found in 84% of warfarin-treated patients. However, half of the abnormalities were related to urinary tract infection. Stones, tumours and papillary necrosis were found in 15.6%, with malignancy accounting for only 6.3% of abnormalities (similar to control patients). In their analysis, the level of anticoagulation did not appear to correlate with haematuria. However, only 1-2% of their cohort had an INR >5.0 and it was not possible to separate out patients whose INR was >3.0 from those with an INR >2.7 but <3.0. Finally, the data was analysed as patient-months and not as individual patients.

There are several factors to consider when deciding to pursue further investigations. Urinary tract infections, trauma and instrumentation should be excluded initially. In urological studies, there appears to be higher likelihood of an underlying lesion when haematuria is macroscopic. However, there are limitations to these studies. There is paucity of data on outcomes with microscopic haematuria, which may be due to a selection bias with urologic studies due to referral patterns, as reflected in the high rates of macroscopic relative to microscopic haematuria in these reports. Patients with high INR are less likely to receive an adequate diagnostic evaluation compared to those with therapeutic INR [29]. The variable rate of detection of occult lesions may also reflect the different diagnostic approaches, ranging from comprehensive tests (CT, IVP and cystoscopy) to single imaging. It may also reflect the heterogeneity of patients studied, with regards to variable INRs and diagnosis of haematuria.

It is unclear if the risk of detecting an occult lesion is different if haematuria occurred within the therapeutic range of warfarin anticoagulation as suggested by Avidor et al. [24] and Landefeld et al.
Can these patients be safely dismissed? The prospective study by Culcasure et al. suggests that such an association does not exist [28]. Currently, the criteria for initiating a work-up for an underlying lesion are not universal and the role of comprehensive testing is even less clear. However, these findings should lower one's threshold for conducting further investigations: macroscopic haematuria, persistent microscopic haematuria, and haematuria with a therapeutic level of warfarin anticoagulation. It also appears that diagnostic imaging alone is unlikely to be sufficient to exclude occult pathology.

### Warfarin-related Nephropathy

Today, we are still learning about the origins of haematuria in anticoagulated patients in light of the recently described warfarin-related nephropathy (WRN). It basically refers to glomerular leakage of red blood cells resulting in tubular injury and AKI, either by mechanical obstruction of tubules with red cell casts or toxicity of breakdown products of the red cell. The occurrence of this entity adds a new dimension to the evaluation of haematuria in anticoagulated patients. Is it possible that previously undetermined causes of haematuria were due to WRN and these unaccounted cases of haematuria represented glomerular bleeding? The majority of the older studies in this field have not systematically evaluated erythrocyte morphology.

### Evidence for warfarin-related nephropathy

Case reports have noted the association of haematuria and AKI in patients who were anticoagulated with warfarin. Renal biopsy would demonstrate tubular red blood cells and casts associated with acute tubular injury. These early cases were reported in patients with underlying diseases such as systemic lupus erythematosus and thin basement membrane disease [20,30]. The diagnosis of WRN was first suggested by Brodsky et al., who performed a retrospective analysis of biopsy specimens from 9 patients who presented with unexplained AKI and haematuria while on warfarin therapy [31]. All biopsies demonstrated tubular red blood cells and obstructive red cell casts to some degree. Red blood cells were seen in Bowman's space in some glomeruli in 4 of the 9 patients. No active proliferative glomerular lesions were seen although all patients had some form of underlying chronic disease such as systemic lupus erythematosus, IgA nephropathy, focal segmental glomerulosclerosis and nephrosclerosis. Many patients did not recover from AKI.

Brodsky et al. subsequently performed a retrospective analysis of the association of serum creatinine and INR levels in warfarin-treated patients with CKD [32]. After screening a cohort of 148 patients with stage 2-4 CKD at their institution, 49 patients were suitable for analysis. These patients had an episode of INR >3.0, serum creatinine performed within one week and had serum creatinines available for one year prior and one year after this episode of anticoagulation. Medical records were studied to determine if there was a condition which was likely to explain AKI, which was defined as an increase in serum creatinine of ≥ 0.3 mg/dl. They found that 37% of these patients experienced an unexplained increase in creatinine ≥ 0.3 mg/dl following an INR >3.0 (Group 1). Compared to patients without an increase in creatinine after INR >3.0 (Group 2), Group 1 patients had persistently elevated creatinine at follow up. Of note, there were a higher proportion of African-Americans in Group 1. There was a trend towards more diabetics in Group 1 (44.4% vs. 25.8%, p=0.18) and more recent initiation of warfarin (33.3% vs. 12.9%, p=0.087). There was no difference in medication use, other comorbidities, blood pressure or age. The mean INR values were 4.9 ± 3.1 and 4.2 ± 1.3 in Group 1 and Group 2, respectively. Searching the medical records revealed only 50% of patients in both groups had haematuria at the time of INR >3.0. The authors concluded that overanticoagulation was a risk factor for accelerated progression of CKD for a subset of patients diagnosed with AKI. However, they were not able to correlate the detection of haematuria with the elevated creatinine in this study. They were also not able to distinguish the main factors separating Group 1 and Group 2 patients.

The next study by Brodsky et al. examined the impact of supratherapeutic INRs on patients without CKD [33]. In this article, they coined the term warfarin-related nephropathy using the definition previously described [32], which is an acute increase in serum creatinine of >0.3 mg/dl within 1 week of an INR >3.0. This definition is somewhat arbitrary but would be in keeping with the Acute Kidney Injury Network (AKIN) criteria for AKI [34]. After screening a retrospective cohort of 15,258 patients who initiated warfarin over a 5 year period, they identified 4006 patients with sufficient information for a diagnosis of WRN. Of this final cohort, 20.5% were deemed to have presumptive WRN. By 3 months after the onset of WRN, the mean serum creatinine in the WRN group was higher than non-WRN patients (1.80 ± 1.24 vs. 1.13 ± 0.67 mg/dl, P < 0.001). Some of the difference was explained by a higher baseline serum creatinine in the WRN group. Both CKD and no-CKD patients developed WRN but the risk was higher with CKD patients compared to no-CKD patients (33% vs. 16%). The WRN cohort also recovered better from AKI, with their eGFR (CKD-EPI equation) returning to pre-WRN baseline at 3 months. Only a partial recovery was noted in CKD patients.

In this study, haematuria was assessed by urine dipstick only. There was no difference in dipstick haematuria before, during or after documentation of an INR >3.0 in this cohort. From a medication perspective, aspirin use was associated with an increased risk of WRN (35% vs. 28%, p = 0.001). The baseline risk factors for WRN identified were age, diabetes mellitus, hypertension and cardiovascular disease. Finally, the 5-year Kaplan-Meier survival rate was significantly lower in WRN compared with no-WRN patients (58% vs. 73%, P <0.001). The hazard for death was highest in the first weeks after documenting an INR >3.0, with a hazard ratio of around 3.0 for WRN vs. no-WRN patients. The one year mortality was 18.9% without WRN and 33.2% with WRN (increased risk of 65%).

The main limitations of this study was the presumptive nature of the WRN diagnosis, as medical records were not checked for other causes of AKI such as hypovolaemia, medication use and the like. A large number of medications can acutely increase INR as an interaction with warfarin. Furthermore, some medications such as trimethoprim-sulfamethoxazole can elevate both INR and creatinine [35], and may easily confound the observations. It is also possible that concurrent illness such as decompensated heart failure, along with diuretic use could lead to renal impairment and supratherapeutic INR [36]. A possible selection bias may exist as patients who were ill or unstable were more likely to have blood tests performed and patients with no cause to check their creatinine were missed in the analysis [37]. Thus, the quoted prevalence may be higher than reality. This is a valid concern as only 26% of the 15,258 patients in the study had suitable data. The accuracy of medical coding is also a known limiting factor in these studies. Finally, the criteria used to diagnose WRN are arbitrary and the sensitivity and specificity is not tested. It is highly likely that proper validation is not possible, given the fact it is not possible or necessary to perform universal biopsies in such patients. Without a gold standard to which this definition can be tested, we are left with a best guess or best fit solution.

### Potential Implications

To summarise, WRN has been linked to acceleration of CKD...
and increased mortality, with CKD patients having double the risk of non-CKD patients [30,33]. As mentioned, a number of older clinical trials have included anticoagulation as part of the treatment strategy for various forms of glomerulonephritis. The question now raised is whether or not WRN could have confounded the results of these trials. One such example is the use of cyclophosphamide for IgA nephropathy, where patients were coadministered warfarin and dipyridamole in the treatment arm [38]. It may be prudent to factor in the possibility of WRN into any trial involving warfarin anticoagulation where renal function is an outcome of interest. One way to accomplish this may be to compare the episodes or duration of anticoagulation in all treatment arms and to ensure they are comparable.

Currently, the data does not support the use of haematuria as a surrogate for the presence of WRN. The potential risks identified from these retrospective studies suggest that the net benefit of warfarin therapy may be reduced in some patients. How one identifies these patients in the risk-benefit assessment remains unresolved. This is particularly relevant to those whose target INR is >3.0, such as patients with mechanical heart valves.

Prospective Studies

One published study has examined the impact of overanticoagulation on AKI and haematuria [29]. In this observational study, 243 eligible patients were screened and 150 patients receiving warfarin anticoagulation were included. Compared to previous studies, this cohort consisted of predominantly elderly patients (mean age 80 years) on long term warfarin treatment who were acutely admitted to hospital. Over 50% of patients presented with an INR >3.0 and recent antibiotic exposure was the main risk factor for supratherapeutic anticoagulation. In this cohort, the risk of haematuria was only evident with an INR >4.0 but no association with AKI was found when using either RIFLE or AKIN criteria. The prevalence of haematuria was 25% which was predominantly microscopic, which is consistent with a previous prospective study [28]. Glomerular haematuria comprised only 29% of the positive cases with the rest demonstrating non-glomerular (40%) or indeterminate morphology (31%). Patients with glomerular haematuria had a higher mean INR than those with non-glomerular haematuria (4.84 ± 2.06 vs. 3.38 ± 0.89, P = 0.04). Furthermore, an INR >5.0 was associated with a significant risk of glomerular haematuria (relative risk = 3.87). Only 15% of haematuria positive cases persisted at follow up 4-6 weeks later. Admission with heart failure was the predominant risk factor for persistent renal dysfunction at follow up.

This study demonstrated that transient haematuria does occur with acute overanticoagulation and both glomerular and urothelial bleeding occurs. However, no direct risk of overanticoagulation on AKI was detected. The elderly cohort may limit generalisability of the results to younger patients with less comorbidity. Other limitations include the lack of baseline urinalysis for comparison, short follow-up and lack of definitive urological diagnosis.

Animal Model

To further study WRN, animal models are logical. Nothing would be simpler than giving rat poison to rats. The 5/6-nephrectomy rat model of nephron reduction has been used to mimic WRN by treatment with Brodifacoum [39]. In this model, toxic levels of anticoagulation were achieved with prothrombin times over 10-fold from baseline by day 3 and all animals died by day 4. Morphologically, red cells were observed in Bowman's space, along with red cells and red cell casts in the tubules of rats treated with Brodifacoum 8 weeks after 5/6-nephrectomy. Serum creatinine increased in 5/6-nephrectomy rats given Brodifacoum 8 weeks after surgery but not in control rats. Brodifacoum treatment was associated with increased apoptosis of glomerular endothelial cells and tubular epithelial cells. It is proposed that glomerular endothelial damage may contribute to the pathogenesis of WRN, and this may be systemic rather than limited to the kidney. However, one issue with this model is the development of spontaneous progressive haematuria in the absence of anticoagulation. This aspect of the 5/6-nephrectomy model is not represented in most humans. The second difference pertains to the relationship between the degree of INR elevation above normal and the risk of WRN. This relationship existed in the animal model but not in the human data previously analysed.

Due to the limitations of the Brodifacoum model, a follow-up study utilising warfarin anticoagulation in 5/6-nephrectomy rats was performed, with the intention of assessing the dose-response relationship of warfarin and serum creatinine [40]. In this study, anticoagulation was gradual and the authors demonstrated a dose-dependent increase in prothrombin time and serum creatinine. Increasing warfarin dose also increased haematuria and similar morphological findings of acute tubular injury associated with red cell casts in the tubules was noted. Furthermore, treatment with vitamin K was able to prevent the changes in serum creatinine and tubular injury. A single episode of WRN was insufficient to affect progression of CKD, suggesting that repetitive insults would be required.

Mechanism of injury

Which cells or processes within the kidney are affected by warfarin? Some interest has been shown with growth arrest-specific gene 6 (gas6). The product of gas6 is a vitamin K-dependent growth factor which acts in an autocrine fashion on mesangial cells and vascular smooth muscle cells [41-44]. Warfarin may have an anti-mitogenic effect on these cells and result in alterations in glomerular haemodynamics and filtration. Studies have also suggested that Gas6, through its receptor Axl mediates apoptosis of endothelium and vascular smooth muscle induced by hydrogen peroxide [45]. It is also known that the gas6 product is responsible for endothelial cell survival in experimental studies of cultured human umbilical vein endothelial cells [46-48]. For this to fit with the observational data on WRN there must be a threshold or critical exposure level to warfarin which seems to trigger the effect. It also means that the effect may not be limited to the kidney.

Unanswered questions

It is still arguable as to what degree of anticoagulation carries the risk of haematuria and AKI. A threshold INR of 3.0 has been set as the definition of WRN by Brodsky. Their retrospective human studies indicated that the risk did not increase in proportion to INR elevation above 3.0. This is in contradistinction to their animal studies demonstrating a correlation with INR and serum creatinine in warfarin-treated rats. Furthermore, the mean INR in their human cohorts were >4.0. The available prospective study suggests that an INR >4.0 is associated with an increased risk of haematuria but not AKI when prerenal and postrenal factors have been accounted for. Even less is known for non-glomerular bleeding.

Another interesting question is whether the duration of supratherapeutic anticoagulation is relevant to the risk of haematuria or AKI. A previous study of macroscopic haematuria in IgA nephropathy suggested that persistent renal dysfunction was more likely in patients with haematuria >10 days, baseline CKD and age >50 years [49]. This question has not been adequately assessed in recent studies. The 5/6-nephrectomy model suggests that a single episode of WRN is...
unlikely to lead to progression of CKD, implying that repeated insults are required.

Lastly, how does haematuria fit into the equation as a predictive marker for WRN or AKI? In available prospective studies, macroscopic haematuria is uncommon compared with microscopic haematuria. Should we fine-tune our assessment to include red blood cell morphology to distinguish glomerular leak from urothelial haemorrhage? The potential impact of anticoagulants other than warfarin in the pathogenesis of WRN is also unknown. Is WRN unique to vitamin K antagonists?

Miscellaneous Disorders

Cholesterol embolism

A handful of reports describe spontaneous cholesterol embolism occurring soon after initiating warfarin therapy [50-52]. These have been referred to as blue or purple-toe syndrome. These studies suggest that emboli originate from aortic and pelvic arterial plaques. Renal failure due to cholesterol emboli may also occur [52]. The prevalence of this disorder is unknown.

Vascular calcification

Warfarin use is associated with coronary and femoral artery calcification [53-55]. There may be an effect of vitamin K antagonists on inhibiting matrix Gla protein, as mice deficient in matrix Gla develop spontaneous arterial calcification [56]. The potential impact on vascular disease in the kidneys has not been studied.

Allergic interstitial nephritis and vasculitis

Volpi et al. described a case of tubulointerstitial nephritis due to warfarin sodium [57]. The patient developed macroscopic haematuria with oliguric AKI after 25 days of treatment with diltiazem, nitroglycerin and warfarin for a myocardial infarct. Renal biopsy showed tubulointerstitial nephritis but also noted mesangial hypercellularity with IgA and C3 deposition. The prothrombin times were not reported but the patient was receiving 20 mg daily of warfarin. Tubular injury with cellular casts was noted. Withdrawal of warfarin and steroid treatment normalised renal function in 45 days. Kapoor and Bekaii-Saab described a patient who presented with AKI, purplish macular rash and a INR of 9.9 [58]. The patient had microscopic haematuria and eosinophiluria. Renal biopsy showed acute tubular necrosis, IgA nephropathy and interstitial nephritis with eosinophils. Skin biopsy demonstrated a leukocytoclastic vasculitis with dense eosinophils. He had been on warfarin for 2 months and sertraline for 9 months.

One might speculate as to whether WRN was partially responsible for AKI in these cases. However, the mesangial IgA deposits remained unexplained or may represent coincidental IgA nephropathy which predisposed these patients to haematuria. Isolated maculopapular rash associated with warfarin and other coumarin derivatives have also been reported [59,60]. Currently, the association of warfarin with allergic interstitial nephritis remains weak. If a true cause-effect relationship exists, interstitial nephritis due to warfarin seems extremely rare.

Summary

Haematuria in warfarin-treated patients may result from glomerular leak or urothelial haemorrhage. Red cell morphological analysis may be useful to distinguish between the two but could be indeterminate in a third of cases. Overanticoagulation (INR >3.0) is associated with AKI but robust prospective data is lacking. Obstructive uropathy may occur in some cases of suburothelial haemorrhage in the renal pelvis or proximal ureter. The risk of occult lesions may be higher with macroscopic haematuria, occurrence of haematuria within the therapeutic range of warfarin, and persistent abnormal urinalysis. Larger, prospective studies are needed to clarify the actual risk of AKI related to overanticoagulation. Ideally, a better correlation between haematuria and AKI should be demonstrated to confirm the pathogenesis of WRN as related to glomerular bleeding.

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