

Case Report

Warfarin Related Nephropathy: The First Case Report in Thailand

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Warfarin is the most prescribed oral anticoagulant. Adverse renal effect from warfarin therapy are uncommon and Thailand is not acquainted. Warfarin-related nephropathy (WRN) is a newly recognized complication of warfarin treatment, especially in patients with chronic kidney disease. The authors hereby report a 56-year-old man who developed gross hematuria and severe acute kidney injury (AKI) necessitating hemodialysis, following supra-therapeutic INR level. Renal pathology revealed extensive intratubular obstruction with red blood cell casts. From the literature, there were only twelve case reports of WRN, which were confirmed by renal histopathology. Renal survival of this condition was unsatisfactory. However, our patient was dialysis-independent after vitamin K treatment and temporary warfarin discontinuation. To the best of our knowledge, this is the first case report of biopsy-proven WRN in Thailand.

Keywords: Warfarin, Warfarin related nephropathy, Acute kidney injury, Intratubular hemorrhage, Gross hematuria, Anticoagulants

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Since an initial introduction to clinical practice in 1954, warfarin has become the most prescribed oral anticoagulant in the world. The most common side effect of warfarin is bleeding which is associated with supra-therapeutic dosage. Adverse renal effects from warfarin therapy are uncommon. Various renal complications of warfarin therapy have been reported, including pre-renal acute kidney injury (AKI) or ischemic acute tubular necrosis secondary to massive hemorrhage, atheroembolic renal disease, obstructive uropathy from renal hematoma⁽¹⁾ and acute interstitial nephritis with leukocytoclastic vasculitis⁽²⁾.

In 2009, another distinct AKI syndrome associated with warfarin overdose was addressed. Brodsky SV et al reported nine patients who developed AKI resulting from intratubular red blood cell (RBC) casts obstruction⁽³⁾. Five of the nine patients experienced unfavorable renal outcome. This clinical entity was termed as “warfarin-related nephropathy” (WRN). Here, we report on a patient who developed gross hematuria and AKI necessitating hemodialysis

following supra-therapeutic INR level. Renal pathology revealed intratubular obstruction with RBC casts without evidence of active glomerulonephritis.

Case Report

A 56-year-old man with well-controlled essential hypertension, presented with gross hematuria for 2 weeks. Two years ago, he developed *Streptococcus suis* endocarditis with severe mitral and aortic regurgitation. He underwent mitral valvuloplasty and aortic valve replacement with St. Jude prosthesis. Intravenous penicillin G sodium was given for four weeks. Warfarin had been started after the operation. At that time, he also experienced AKI with nephritis urine sediment and a low-complement C3 level. Cause of AKI was presumably endocarditis associated glomerulonephritis. Renal failure was resolved after completion of treatment. His blood urea nitrogen and serum creatinine at discharge were 17 and 1.4 mg/dl, respectively, which remained stable during the follow-up period. Urinalysis revealed no red blood cells (RBC) and urine protein per creatinine ratio (UPCR) was 1.1 g/g creatinine. He had excellent compliance and international normalized ratio (INR) was within acceptable range (range, 2.33 to 2.48 IU).

Three weeks before the admission, he attended regular follow-up with a cardiovascular

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surgeon; the INR had increased to 6.08 IU. Warfarin dosage was reduced by 25 percent and INR was repeated the next week. Two weeks before, his INR level decreased to 3.63 IU but he noted that his urine became bloody throughout the voiding. He also had anorexia, fatigue and occasional nausea and vomiting for 3-4 days. His BUN and serum creatinine were 96.5 mg/dl and 11.5 mg/dl, respectively. Warfarin dosage was further reduced by 24 percent and he was referred to a nephrologist. There was no clinical evidence of hypovolemia, infection and drug abuse. He did not have a previous history of rash, arthralgia, arthritis or hemoptysis. Beside warfarin, other medications consisted of amlodipine and atenolol.

At admission, his blood pressure was 147/90 mmHg. He was afebrile but looked weak and anemic. A physical examination revealed mild puffy eyelids and mild pitting edema of both legs. Valve click was detected at aortic valve area without murmur. Urinalysis revealed bloody appearance with numerous dysmorphic RBCs and RBC casts. Dipstick urine protein was 2+ and UPCR was 1.8 g/g creatinine. Serum complement C3 was mildly decreased (73.8 mg/dl; normal range 83-177 mg/dl) while C4 was normal (34 mg/dl; normal range 15-45 mg/dl). Renal ultrasonography found normal size and echogenicity of both kidneys without evidence of hydronephrosis. He underwent renal biopsy for definite diagnosis after prompt correction of abnormal coagulation.

Renal pathology

The biopsy tissues contained renal medulla and cortex with 27 glomeruli. Nine glomeruli were globally sclerotic and five glomeruli were segmental sclerosis. No evidence of crescentic formation or endocapillary proliferation was observed. The mesangium showed no increase in cells and matrix. RBC casts were seen in numerous distended renal tubules, which had characteristic of diffuse tubular injury. Tubular atrophy and interstitial fibrosis was demonstrated in 60% of renal parenchyma. There was no interstitial hemorrhage or inflammation. Hyalinosis of arterioles and moderate to severe intimal fibrosis of intralobular arteries was also found (Fig. 1, 2). The immunofluorescence study showed no significant immunoglobulin or complement staining. Electron microscopic study revealed occasional medium-sized mesangial deposits. No subepithelial or endothelial deposition was observed.

Management and outcome

Warfarin was stopped and oral vitamin K was given to correct over anticoagulation. Prothrombin time and INR after receiving vitamin K was 15 seconds and 1.2 IU, respectively. Hemodialysis was initiated due to presence of uremic symptoms. Warfarin was carefully reinstated on day 6th of admission. INR level was kept in the range of 2-2.5 IU. His urine became clear on day 10 of admission.

He had been put on hemodialysis for 10 weeks before recovery of renal function was documented. After this event, he had excellent compliance and his INR was within acceptable range. His renal function

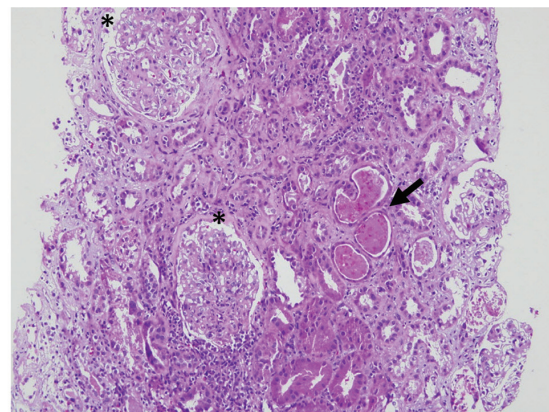


Fig. 1 Glomeruli (*) showed no increased in cell and matrix, no crescentic formation. Intratubular obstruction with RBC casts was revealed in many tubules, accompanied with evidence of tubular cell injury (arrow). Interstitial fibrosis is seen in some area.

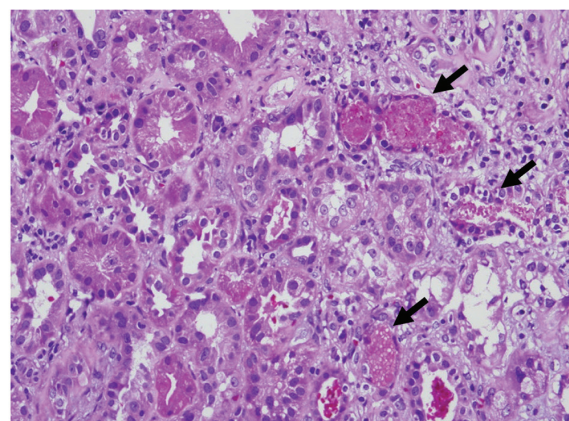


Fig. 2 Focused on tubule, there was evidence of acute tubular injury and RBC obstruction in the tubules (arrow).

gradually improved throughout follow-up time. At one year after AKI, his serum BUN and creatinine were 50.4 and 4.95 mg/dl, respectively, independent of renal replacement therapy.

Discussion

Acute kidney injury is a considerable and potentially treatable condition. Recognition of AKI etiology has a pivotal role in determination of appropriate management. Gross hematuria is one of the well-known adverse events of warfarin and may alert clinicians to the presence of focal urinary tract lesion such as cancer⁽⁴⁾. However, WRN is new clinical entity of AKI that indicate importance of macroscopic hematuria was related with the over anticoagulation.

In 2009, Brodsky SV et al reported the crucial case series of warfarin associated- intratubular obstruction with RBC casts⁽³⁾. They reviewed patients who underwent renal biopsies over a 5-year period at a single center and focused on who ever presented with unexplained AKI and hematuria during warfarin therapy. Out of 2,801 biopsy specimens, renal tissues from nine patients who developed AKI without evidence of active glomerulonephritis were included. All nine patients had underlying renal disease and three patients had baseline estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m². At presentation of AKI, INR level ranged from 2.8-8.0 IU. Renal pathology of all specimens showed numerous erythrocytes within Bowman spaces and renal tubules. Tubular lumen contained RBCs and RBC casts in 6.4±0.7% and 11.5±2.3% of tubules, respectively. The occlusive casts were mostly located in distal tubular segments and did not have Tamm-Horsfall protein. Dysmorphic RBCs were observed in many tubules by electron microscopy technique.

From these findings, Brodsky et al proposed that warfarin overdose associated with AKI and hematuria occurred in only patients with underlying kidney disease, including both glomerular lesion and tubulointerstitial disease. They also reviewed previous reports from literature and found two AKI cases, which had extensive intratubular RBC obstruction related with supra-therapeutic level of warfarin^(5,6). After this case series, there were only a few published case reports with same histopathological characteristics^(7,8).

The authors hereby report a case that had a similar context to previous studies. Our patient had chronic kidney disease (CKD) stage III with baseline eGFR of 51 ml/min. From histopathology, the

etiology of CKD most likely was focal segmental glomerulosclerosis secondary to long standing hypertension and previous endocarditis associated glomerulonephritis. The authors did not reveal endocapillary proliferation and crescentic formation. Presence of focal glomerulosclerosis was not a reasonable cause of deterioration of renal function and severe intratubular erythrocyte obstruction. Occasional medium-sized mesangial deposits, which are found in EM, should derive from the resolving process of infection associated with glomerulonephritis. Our case developed macroscopic hematuria and AKI after the episode of supra-therapeutic INR levels. Renal pathology of our patient also revealed the same pathological findings as in antecedent studies. The authors summarized fundamental data of all case reports with pathognomonic histological findings in the literature, including those of our patient as shown in Table 1. However, we could not access one report which is published in Japanese⁽⁸⁾.

Regarding pathogenesis of WRN, the relationship between gross hematuria and AKI should be deciphered. The most creditable cause of numerous RBCs obstructed in renal tubules is severe glomerular hemorrhage. The explanation is that RBCs are glomerular in origin, and is based on demonstration of numerous dysmorphic RBCs in urine specimen and in kidney tissue by mean of electron microscopy, and that there are no other obvious sites of hemorrhage in urinary tract. Similar to WRN, AKI secondary to intratubular RBC cast obstruction is a well-known complication of IgA nephropathy⁽⁹⁾ and necrotizing glomerulonephritis⁽¹⁰⁾. Tubular obstruction can lead to back flux of intratubular fluid into glomeruli and generate interstitial edema by increasing interstitial fluid pressure. In addition, acute tubular necrosis is a common concomitant finding in this condition. Hemoglobin toxicity may be another crucial factor of tubular injury⁽¹¹⁾.

Renal outcome of this phenomenon was unfavorable. From previous 11 patients^(3,5,7), 6 patients subsequently developed end stage renal disease. In our case, after recognition of this condition, we immediately corrected abnormal coagulopathy. Even with AKI severity, our case was dialysis-independent at last and his renal function gradually improved at 1-year follow-up time. However, when compared to baseline results, his eGFR declined to less than 15 ml/min/1.73 m² (CKD stage 5).

After 2009, Brodsky et al have continued to study this clinical entity further. They conducted a

Table 1. Summary of fundamental clinical characteristics of all reported patients with warfarin associated AKI

Patient No.	Reporter (reference No.)	Age/ gender	Underlying renal disease	Baseline eGFR (ml/min/1.73 m ²)	SCr at biopsy (mg/dl)	INR level	Urinalysis
1	Abt et al. ⁽⁵⁾	59/M	Thin basement membrane disease	82	8.4	3.60	Hematuria, protein 3, RBC cast
2	Brodsky et al. ⁽³⁾	27/F	SLE with LN class II	154	3.1	8.00	Gross hematuria, protein 1
3	Brodsky et al. ⁽³⁾	73/M	Moderate interstitial fibrosis	26	6.5	3.00	Hematuria, protein 3
4	Brodsky et al. ⁽³⁾	61/M	Nephrosclerosis	23	4.8	2.00	Hematuria, proteinuria 3.4 g/24 hour
5	Brodsky et al. ⁽³⁾	76/F	FSGS	65	3.4	7.00	Hematuria
6	Brodsky et al. ⁽³⁾	38/F	Mesangial IgA deposits	100	0.9	3.90	Hematuria, protein 0.9 g/24 hour
7	Brodsky et al. ⁽³⁾	82/F	Mesangial IgA deposits	51	4.5	2.80	Hematuria
8	Brodsky et al. ⁽³⁾	80/M	Diabetic nephropathy and mesangial IgA deposits	68	3.9	5.20	Hematuria, proteinuria
9	Brodsky et al. ⁽³⁾	63/M	Mild to moderate nephrosclerosis	80	2.5	3.70	Hematuria, RBC cast
10	Brodsky et al. ⁽³⁾	55/M	Mesangial IgG deposit	107	9.1	3.80	Hematuria, proteinuria
11	Santos et al. ⁽⁷⁾	74/M	Diffuse mesangial proliferation	SCr 1.8 mg/dl	3.5	4.62	Hematuria, proteinuria
12	Our patient	56/M	FSGS	70.8	11.5	6.08	Gross hematuria, proteinuria 1.8 g/gCr

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; SCr = serum creatinine; INR = international normalized ratio; SLE = systemic lupus erythematosus; LN = lupus nephritis; FSGS = focal segmental glomerulosclerosis; RBC = red blood cell; M = male; F = female

large retrospective study in patients with warfarin therapy. The new clinical diagnosis, ‘warfarin-related nephropathy (WRN)’ was proposed which is defined by ‘an increase in serum creatinine ≥ 0.3 mg/dl within 1 week after the INR exceeded 3.0 with no record of bleeding’. The results showed association between supra-therapeutic INR level and development of a WRN⁽¹²⁾. CKD is the major risk factor. This form of AKI also worsened CKD progression and increased mortality rate. However, there was no renal biopsy result and limited clinical data to consider any other potential cause or mechanism of AKI.

In conclusion, our case report confirms the existence of WRN. To establish diagnosis, renal biopsy should be considered in patients who have received warfarin with unexplained AKI. However, risk of anticoagulant reversal must be of concern. Early diagnosis with prompt correction of supra-therapeutic INR level with vitamin K is mandatory for treatment of warfarin-associated AKI.

What is already known on this topic?

WRN is the newly recognized AKI syndrome caused by intratubular RBC casts obstruction from warfarin overdose. Until now, there are 12 patients with WRN proven by renal histopathology in literature. Most of case reports originated from western country. Renal survival of WRN is unsatisfactory.

What this study adds?

This case report confirmed the existence of WRN, especially in Asian population. Prompt correction of abnormal coagulation after early recognition of this clinical entity may be crucial to improve the renal outcome.

Potential conflicts of interest

None.

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ภาวะไตวายเฉียบพลันจากยารวาร์ฟาริน: รายงานผู้ป่วยรายแรกในประเทศไทย

นัฐสิทธิ์ ลาภปริสุทธิ, บุญยฤทธิ์ ชื่นสุขน, รัตนา ขวนะสุนทรพจน์, สมเกียรติ วสุวิญญกุล, เกรียงศักดิ์ วารีแสงทิพย์

วาร์ฟารินเป็นยาต้านการแข็งตัวของเลือดที่ใช้อย่างแพร่หลาย ภาวะแทรกซ้อนทางไตจากยานี้พบได้น้อยและยังไม่เป็นที่รู้จักดีในประเทศไทย ในช่วง 3-4 ปีนี้มีรายงานกลุ่มผู้ป่วยที่เกิดภาวะไตวายเฉียบพลัน เนื่องจากมีลิ่มเลือดอุดตันท่อไตสัมพันธ์กับภาวะที่มีการแข็งตัวของเลือดลดลงอย่างมากจากยารวาร์ฟาริน โดยภาวะนี้พบได้เฉพาะในผู้ป่วยที่มีโรคไตเสื่อมเรื้อรังอยู่เดิม ผู้นิพนธ์ได้รายงานผู้ป่วยที่มาพบแพทย์ด้วยอาการปัสสาวะเป็นเลือด และเกิดภาวะไตวายเฉียบพลันขึ้นสัมพันธ์กับการแข็งตัวของเลือดที่ลดลงอย่างมากจากยารวาร์ฟาริน การตรวจทางพยาธิวิทยาของชิ้นเนื้อไตพบเม็ดเลือดแดงเกาะกลุ่มอุดตันอยู่เต็มท่อไต จากรายงานกลุ่มผู้ป่วยในต่างประเทศพบว่าอัตราการอยู่รอดของไตในภาวะนี้ไม่ดี แต่ผู้ป่วยในรายงานนี้พบว่าไตสามารถกลับมาทำงาน และผู้ป่วยหยุดฟอกเลือดล้างไตได้หลังได้รับยาวิตามินเคโดยเร็วหลังสงสัยภาวะนี้ รายงานนี้ยังได้ทบทวนถึงรายงานผู้ป่วยภาวะนี้ทั้งหมด ปัจจัยเสี่ยงของการเกิดโรค และพยาธิสรีรวิทยาของโรคด้วย
