CASE REPORT

Rivaroxaban-related acute kidney injury in a patient with IgA vasculitis

Yoshihiko Fujino,¹ Chisato Takahashi,¹ Kensuke Mitsumoto,¹ Takashi Uzu²¹Nephrology, Nippon Life Hospital, Osaka, Japan
²Nephrology and Blood Purification, Nippon Life Hospital, Osaka, Japan

Correspondence to

Dr Takashi Uzu,
takuzu@belle.shiga-med.ac.jp

Accepted 14 January 2019

SUMMARY

Anticoagulants have recently been recognised as a cause of acute kidney injury (AKI). We describe the case of a 75-year-old man with IgA vasculitis and atrial fibrillation treated with rivaroxaban, who presented with macroscopic haematuria and an acute decline in renal function. Two months before referral, he noted palpable purpuric lesions and was diagnosed with IgA vasculitis based on skin biopsy findings; the skin lesion disappeared following treatment with a steroid external preparation. Renal biopsy revealed glomerular haemorrhage and red blood cell casts. Although rivaroxaban was withdrawn, his kidney function worsened and he was started on haemodialysis. His renal function did not recover. To the best of our knowledge, this is the first case of direct oral anticoagulant (DOAC)-related AKI in systemic vasculitis. During DOAC therapy, close monitoring of a patient's urinalysis results and their renal function may be required for patients with systemic vasculitis to avoid AKI.

BACKGROUND

Anticoagulation is approved for prevention of stroke in patients with atrial fibrillation (AF). However, such therapy is associated with an increased risk of bleeding. In addition, recent case reports^{1–3} and case series^{4,5} have shown that anticoagulation therapy with warfarin is associated with an increased risk of acute kidney injury (AKI) in AF patients, especially those with chronic kidney disease (CKD).⁵ Based on the renal biopsy findings, Brodsky *et al* demonstrated glomerular haemorrhage and renal tubular obstruction by red blood cell (RBC) casts in patients with AKI associated with warfarin therapy.^{4,5} Direct oral anticoagulants (DOACs), which directly inhibit key proteases (factors IIa or Xa), were increasingly used instead of warfarin. In addition to warfarin, it has been reported that a factor IIa inhibitor, dabigatran, can cause AKI and that CKD patients with reduced estimated glomerular filtration rate (eGFR) level (<30 mL/min/1.73 m²) and dabigatran users tended to have a higher risk of AKI in comparison to warfarin users.⁶ However, the knowledge on Xa inhibitor-related AKI is limited. In addition, to the best of our knowledge, there have been no reported cases of DOAC-related AKI in systemic vasculitis.

We herein report the case of an elderly man with AF and IgA vasculitis who was undergoing treatment with rivaroxaban (a Xa inhibitor), who presented with AKI. A renal biopsy demonstrated macroscopic haematuria, glomerular haemorrhage

and renal tubular obstruction by RBC casts. We also review the relevant literature.

CASE PRESENTATION

A 75-year-old man was referred to our department with macroscopic haematuria and an elevated serum creatinine level (4.12 mg/dL). He had a 10-year history of hypertension and diabetes mellitus. His medical history also included percutaneous coronary intervention of the left circumflex artery, which had been performed 8 years previously, and cerebral infarction, which had occurred 3 years previously. He was treated with verapamil (40 mg, two times per day), metformin (500 mg, daily), and pilsicainide (50 mg, two times per day). He had also been treated with rivaroxaban (10 mg) for more than 3 years for AF. Two months prior to the patient's referral, he noted palpable purpuric lesions over both lower limbs with microscopic haematuria and trace proteinuria and was diagnosed with IgA vasculitis based on the skin biopsy findings. No prior infectious disease was noted before he presented with purpura. Microscopic haematuria and trace proteinuria were also found. The skin lesion was treated with an external steroid preparation. One month prior to the patient's referral, although the purpura had disappeared, microscopic haematuria and trace proteinuria were found. At that time his serum creatinine level was 1.13 mg/dL. On the initial presentation after referral to our department, physical examination revealed a blood pressure of 158/106 mm Hg and bilateral pitting oedema on his lower legs. His purpuric skin lesions had disappeared and brown pigmented skin lesions were seen.

INVESTIGATIONS

At referral, laboratory analysis revealed the following results: total protein, 6.2 g/dL; serum albumin, 2.8 g/dL; total cholesterol, 177 mg/dL; serum creatinine, 4.31 mg/dL; blood urea nitrogen, 64 mg/dL; haemoglobin, 139 g/L; white cell count, 9130 × 10⁹/L; and platelet count, 217 000/μL. His eGFR was 11.4 mL/min/1.73 m². A serological test showed a C reactive protein level of 0.76 mg/dL. Immunological tests revealed that the patient was negative for antinuclear antibodies, myeloperoxidase antineutrophil cytoplasmic antibody and proteinase-3 antineutrophil cytoplasmic antibodies. The patient had normal serum complement values and an elevated IgA titer (511 mg/dL). Urinalysis showed nephrotic-range proteinuria

© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Fujino Y, Takahashi C, Mitsumoto K, *et al*. *BMJ Case Rep* 2019;**12**:e227756. doi:10.1136/bcr-2018-227756

Figure 1 Focal and segmental mesangial cell proliferation and glomerular haemorrhage (Masson trichrome staining $\times 400$).

(protein-creatinine ratio, 6.9 g/g) and macroscopic haematuria. RBC casts, renal tubular epithelial cell casts and granular casts were found in his urine sediment. Because his renal function was rapidly declining and macroscopic haematuria and heavy proteinuria persisted, a renal biopsy was performed. We identified 10 glomeruli by light microscopy. Light microscopy demonstrated an increased mesangial matrix with mesangial cell proliferation (figure 1). Global sclerosis was found in one of the glomeruli and fibro-cellular crescent was noted in another. Immunofluorescence microscopy demonstrated mild diffuse staining of IgA (figure 2) and complement 3 (C3) in the mesangial area of the glomeruli. The results of IgG, IgM, C1q and C4 staining were negative. In addition, glomerular haemorrhage with renal tubular obstruction by RBC casts were observed (figure 3). The degrees of interstitial fibrosis and tubular atrophy were moderate ($<50\%$) and RBC and/or RBC cast were found in almost 10% of tubules. Electron microscopy was not performed. Including the skin biopsy, these findings indicated that he had IgA vasculitis.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of AKI and macroscopic haematuria.

1. Postrenal diseases (stones, genitourinary malignancy).

Figure 2 Immunofluorescence microscopy demonstrating mesangial deposits of IgA ($\times 400$).

Figure 3 Red blood cell casts and acute tubular necrosis (Masson trichrome staining ($\times 400$)).

2. Acute tubular Injury (myoglobin, haemolysis, toxins).
3. Rapidly progressive glomerulonephritis/crescentic glomerulonephritis.
4. Small vessel vasculitis.
5. Anticoagulant related kidney injury.

TREATMENT

Because his eGFR was reduced to 11.4 mL/min/1.73 m², metformin was withdrawn and insulin aspart with linagliptin (a dipeptidyl peptidase-4 inhibitor) was started. Although rivaroxaban was also withheld, his macroscopic haematuria remained, his kidney function worsened, and his serum creatinine and blood urea nitrogen levels increased to 5.73 mg/dL and 97.7 mg/dL, respectively. In addition, the patient had symptoms of uraemia (nausea and anorexia) with uncontrollable pleural effusion. He was started on haemodialysis at 3 weeks after admission.

OUTCOME AND FOLLOW-UP

His renal function did not recover. Haemodialysis provided regularly three times per week for him.

DISCUSSION

The most common clinical indications for anticoagulant drugs are stroke prevention in non-valvular AF. It is estimated that 0.6%–1.6% individuals in the Japanese population suffer from AF.⁷ DOACs, which include the thrombin inhibitor dabigatran and the anti-Xa agents rivaroxaban, apixaban and edoxaban, do not require laboratory testing for dose adjustment and are used in ordinary clinical practice in many countries. In Japan a community-based prospective survey of AF patients showed that the prevalence of DOAC use gradually increased following their release 2011.⁸ It has recently been reported that excessive anticoagulation with warfarin (prothrombin time/international normalised ratio >3) can result in AKI by causing glomerular haemorrhage and renal tubular obstruction by RBC casts—a condition named warfarin-related nephropathy.^{4,5}

DOAC-associated AKI is also being increasingly recognised, especially in association with dabigatran. Recently, it was also reported that the onset of AKI was associated with anticoagulant therapy with apixaban, an Xa inhibitor.⁹ These findings indicate that all classes anticoagulant can induce AKI, especially in patients with CKD. Although a retrospective cohort analysis

showed that DOACs may be associated with a lower risk of adverse renal outcomes than warfarin,¹⁰ it was reported that in comparison to warfarin, DOACs were associated with a higher risk of AKI among patients with eGFR of <30 mL/min/1.73 m².¹¹ Thus, patients with CKD who receive DOACs may have a high risk of developing AKI.

The present patient had IgA vasculitis with trace proteinuria and microhaematuria. In addition, purpuric skin lesions disappeared and no recurrence was observed. Thus, the AKI with heavy proteinuria and macroscopic haematuria was not directly caused by IgA vasculitis; rather, it occurred as a result of anticoagulation with rivaroxaban. In addition, the deterioration of the renal function likely exacerbated the renal effects by elevating the serum levels of rivaroxaban.

Brodsky *et al*⁴ was the first to describe warfarin-related nephropathy through kidney biopsy in patients with warfarin overdose, haematuria and AKI, and each of their biopsy specimens demonstrated evidence of acute tubular injury, glomerular haemorrhage and renal tubular obstruction by RBC casts. To the best of our knowledge, three cases of AKI in patients with IgA nephropathy have been reported,^{1–3} but none of those cases involved IgA vasculitis. In both the reported cases of AKI in patients with IgA nephropathy and the present case, macroscopic haematuria, AKI, glomerular haemorrhage and renal tubular obstruction by RBC casts were also observed. Ryan *et al* investigated the effects of dabigatran on the kidney in an animal model and found that dabigatran caused AKI, which involved RBC casts and acute tubular injury, in 5/6 nephrectomy model rats.¹² Thus, the mechanisms, which are the same mechanisms as warfarin—including glomerular endothelial cell damage, interstitial nephritis and atheroembolism—may contribute to the development of DOAC-related AKI.

Anticoagulant-related AKI is a newly recognised clinical entity that should be suspected in patients with macroscopic haematuria and an increased decline in their renal function during treatment with warfarin or DOACs, especially in patients with CKD. Because the decline in renal function is a risk factor for excessive bleeding in patients treated with DOACs, to avoid AKI, close monitoring of renal function and adjustments to pharmacotherapy are required for patients with CKD and/or systemic vasculitis.

Patient's perspective

Bloody urine is common in patients presenting with urinary tract infections and renal stones. These problems usually cause pain. If you are treated with an oral anticoagulant, painless bloody urine may signal a rapid decline in the kidney function (acute kidney injury).

Learning points

- Oral anticoagulant drugs, warfarin or direct oral anticoagulants (DOACs), can cause acute kidney injury (AKI). Anticoagulant-related AKI should be considered in the differential diagnosis of patients presenting with an acute deterioration in their renal function and macroscopic haematuria during oral anticoagulant treatment.
- During DOAC therapy, close monitoring of the renal function and adjustments to pharmacotherapy are required, especially in patients with chronic kidney disease and/or systemic vasculitis.

Contributors YF, CT, KM and TU treated the patients. YF, CT and KM collected data. YF and TU drafted the report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Moeckel GW, Luciano RL, Brewster UC. Warfarin-related nephropathy in a patient with mild IgA nephropathy on dabigatran and aspirin. *Clin Kidney J* 2013;6:507–9.
- 2 Jansky L, Mukkamala P, Jebakumar D, *et al*. Acute kidney injury and undiagnosed immunoglobulin A nephropathy after dabigatran therapy. *Proc* 2018;31:321–3.
- 3 Ishii H, Hirai K, Yanai K, *et al*. Warfarin-related nephropathy with acute kidney injury in a patient with immunoglobulin A nephropathy. *CEN Case Rep* 2018;7:198–203.
- 4 Brodsky SV, Satoskar A, Chen J, *et al*. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis* 2009;54:1121–6.
- 5 Brodsky SV, Nadasdy T, Rovin BH, *et al*. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011;80:181–9.
- 6 Chan YH, Yeh YH, See LC, *et al*. Acute Kidney Injury in Asians With Atrial Fibrillation Treated With Dabigatran or Warfarin. *J Am Coll Cardiol* 2016;68:2272–83.
- 7 Kodani E, Atarashi H. Prevalence of atrial fibrillation in Asia and the world. *J Arrhythm* 2012;28:330–7.
- 8 Yamashita Y, Uozumi R, Hamatani Y, *et al*. Current status and outcomes of direct oral anticoagulant use in real-world atrial fibrillation patients – Fushimi AF Registry. *Circ J* 2017;81:1278–85.
- 9 Brodsky SV, Mhaskar NS, Thiruveedi S, *et al*. Acute kidney injury aggravated by treatment initiation with apixaban: Another twist of anticoagulant-related nephropathy. *Kidney Res Clin Pract* 2017;36:387–92.
- 10 Dörks M, Jobski K, Herget-Rosenthal S, *et al*. Mortality and acute kidney injury in asians with atrial fibrillation treated with Dabigatran or Warfarin. *J Am Coll Cardiol* 2017;69:2471.
- 11 Yao X, Tangri N, Gersh BJ, *et al*. Renal outcomes in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2017;70:2621–32.
- 12 Ryan M, Ware K, Qamri Z, *et al*. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. *Nephrol Dial Transplant* 2014;29:2228–34.

Copyright 2019 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow