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CASE REPORT

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Tranexamic acid-induced acute bilateral renal cortical necrosis in a young trauma patient: a case report and literature review

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Abstract

Background Tranexamic acid is an anti-fibrinolytic drug recommended in the setting of post-partum hemorrhage and non-obstetrical massive bleeding. Its putative role in the pathogenesis of renal cortical necrosis is unclear and has been rarely reported.

Case presentation We report the case of a young woman who developed anuric acute kidney injury upon administration of tranexamic acid in the setting of mild traumatic hemorrhage. Early contrast-enhanced computed tomography revealed diffuse defects of cortical enhancement in both kidneys, consistent with the diagnosis of acute bilateral renal cortical necrosis. Biological tests did not detect hallmarks of thrombotic microangiopathy or disseminated intravascular coagulation and testing for acquired thrombophilic disorders were negative. The patient remained dialysis-dependent for two months and then partially recovered renal function to an estimated glomerular filtration rate of 40 ml/min/1.73 m^2.

Conclusions This case illustrates the potential prothrombotic effect of tranexamic acid administered in the context of non-obstetric acute bleeding and the importance of re-considering its prescription in the presence of concomitant estrogenic impregnation in order to alleviate the risk of occurrence of renal cortical necrosis. It also addresses the predictive value of kidney imaging for the severity of renal cortical necrosis and subsequent renal recovery.

Keywords Acute kidney injury, Renal cortical necrosis, Tranexamic acid, Oral contraceptive, Kidney imaging, Case report

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Background

Renal cortical necrosis (RCN) is a rare but severe cause of acute kidney injury (AKI). It is characterized by the ischemic necrosis of the renal cortex, resulting from the acute reduction in renal arterial perfusion sparing the medulla. According to published studies, 30 to 50% of patients affected with RCN may progress to end-stage renal disease (ESRD) [1, 2, 3]. To this day, this clinical entity remains more prevalent in low-income countries, where it accounts for up to 3 to 7% of all cases of AKI, against 2% in high-income countries [1, 4, 5]. RCN usually occurs secondarily to systemic disorders that may jointly reduce renal perfusion through three main mechanisms: microvascular thrombosis induced by endothelial injury or activation, vasospasm and/or severe hypovolemia [6]. Firstly, obstetric causes commonly include post-partum hemorrhage (PPH), septic abortion and puerperal sepsis and account for 50 to 70% of all cases of RCN [1, 2, 6], especially in developing countries where pregnancy-related care remains deficient. Besides, most reported non-obstetric causes include thrombotic microangiopathy (TMA), disseminated intravascular coagulation (DIC), snakebite, acute pancreatitis, extensive burns, trauma or non-trauma related massive hemorrhage, septic shock, genetic and acquired thrombophilias [1, 6].

Tranexamic acid (TXA) is a well-known anti-fibrinolytic drug, currently recommended for the prevention and treatment of massive bleeding in various clinical situations [7]. Indeed, randomized controlled trials have shown significant improvement in mortality and life-threatening bleeding related to PPH [8], high-risk surgical procedures [9] and trauma situations [10], with rare renal adverse events. The risk of venous or arterial thrombosis was not increased in both surgical and non-surgical patients receiving TXA according recent meta-analyses [11, 12]. Nonetheless, a limited number of cases of non-obstetric related RCN following use of TXA has been reported [13, 14, 15, 16], pinpointing a possible causative effect of TXA in the pathogenesis of RCN. Here, we report a case of acute bilateral RCN developed upon administration of TXA in the setting of trauma-related hemorrhage in a young woman. In the discussion part, we then establish a literature review of reported cases of TXA-induced RCN and discuss the pathogenic contribution of TXA in the occurrence of RCN.

Case presentation

A 24-year-old Caucasian woman was admitted to the intensive care unit of the University Hospital of Montpellier in June 2023 for high-energy trauma following a car accident. She had no medical history, in particular no previous obstetrical event, no family history of TMA or thrombophilia, and her only medication was a hormonal oral contraception.

On pre-hospital admission, blood pressure was around 100/60 mmHg and pulse rate was elevated at 120 bpm. Physical examination revealed diffuse abdominal pain without contracture, while no signs of peripheral hypoperfusion or external bleeding were noted. Isotonic saline solution and 1 g of TXA (Exacyl®) were rapidly administered, and the patient was placed under mechanical ventilation support.

At intensive care unit admission, blood pressure acutely dropped to 81/55 mmHg, prompting the introduction of norepinephrine up to 0.4 mg/hour, which rapidly normalized the hemodynamic status. Initial laboratory tests notably showed: hemoglobin = 10.3 g/dl, platelet count = 163 G/l, prothrombin time = 76%, activated partial thromboplastin time ratio = 1.12, fibrinogen = 1.4 g/l, moderate hyperlactatemia of 2.2 mmol/l and a normal serum creatinine level of 0.9 mg/dl. Contrast-enhanced computed tomography (CECT) detected multiple fractures, a large liver laceration associated with mild perihepatic and pelvic hemoperitoneum, without active arterial hemorrhage. Renal perfusion was preserved as well as kidney size and corticomedullary differentiation (Fig. 1A). Initial management consisted of vascular filling and a massive transfusion protocol including a total of 5 packed red blood cells, 7 fresh-frozen plasma, 1 platelet concentrate, a four-factor human prothrombin complex concentrate (PCC) 25 IU/kg and 3 g of fibrinogen. The patient also received TXA at a loading dose of 600 mg infused for one hour, followed by a maintenance dose of 1 g for 8 h. She then underwent complex orthopedic surgery at day 8, with no complication. Forty-eight hours after admission, she developed anuric AKI with a peak serum creatinine level of 5.1 mg/dl (Fig. 2), prompting the initiation of hemodialysis. A second CECT found a bilateral non-enhancement of the renal cortex, compatible with the diagnosis of diffuse acute bilateral RCN (Fig. 2B). Some cortical territories remained perfused though, notably in the subcapsular and juxta-medullary regions (Fig. 1B). Of note, there was no CT sign of urinary obstruction and no active bleeding. Hemodynamics remained stable, with low norepinephrine dose requirements of less than 0.5 mg/hour, and hemoglobin level remained normal at 12 g/dl, ruling out any hemorrhagic shock (Fig. 2). Platelet count progressively dropped to 47 G/L at 24 h following admission but then rapidly normalized, whereas hemostasis parameters (prothrombin time, activated partial thromboplastin time ratio, fibrinogen; Fig. 3) were not altered, thereby excluding diagnosis of DIC. While LDH level rapidly rose from 1313 (10 N) to 3466 IU/L (16 N), reticulocyte count and haptoglobin level were measured once at 95 G/L and 1.64 g/l, respectively, and no schistocytes were detected on blood smear, ruling out TMA. Pregnancy test, antiphospholipid and ANCA antibodies were negative. Anti-DNA antibodies

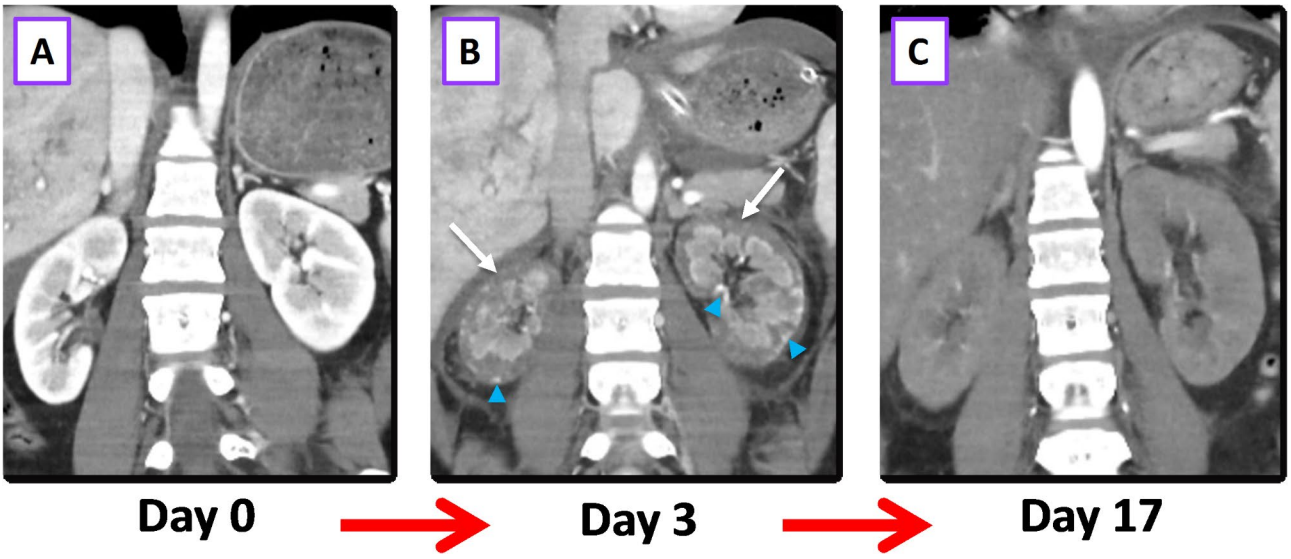

Fig. 1 Contrast-enhanced computed tomography (coronal images). (**A**) At admission: normal kidney enhancement and preserved cortico-medullary differentiation. (**B**) At day 3: association of diffuse hypoattenuating cortical enhancement (white arrows) with intact medullary enhancement in both kidneys corresponding to the "*reverse rim sign*" and consistent with bilateral acute renal cortical necrosis. Of note, perfusion of subcapsular and juxta-medullary regions seemed preserved within the cortex (blue arrowheads). (**C**) At day 17: bilateral and complete corticomedullary dedifferentiation probably indicative of progressive renal reperfusion of the cortex

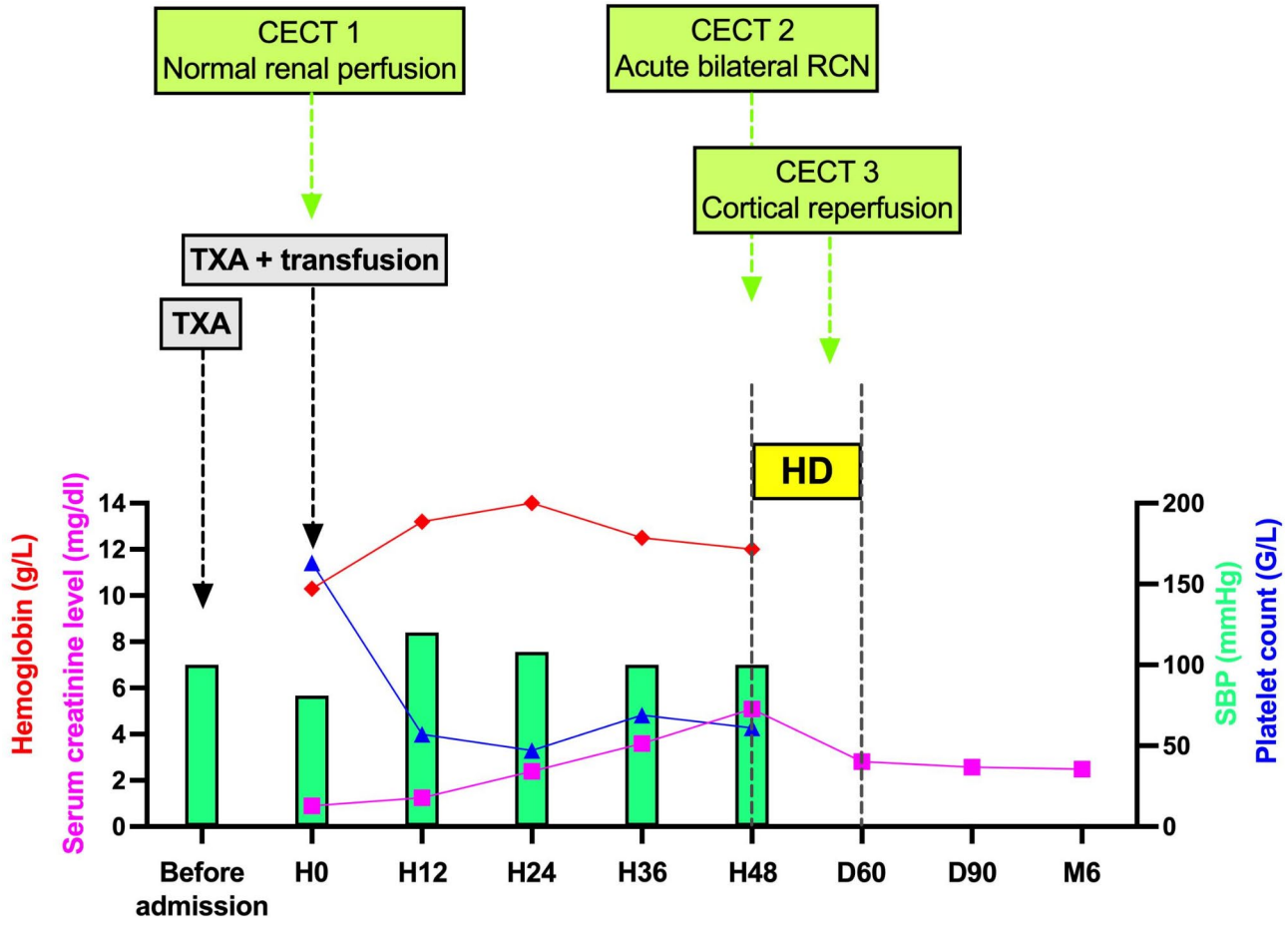

Fig. 2 Evolution of serum creatinine level, hemoglobin, platelets and systolic blood pressure (SBP) during follow-up. Timing of tranexamic acid (TXA) administration and transfusion, results of performed contrast-enhanced computed tomographies (CECT) and timing of hemodialysis (HD) are indicated

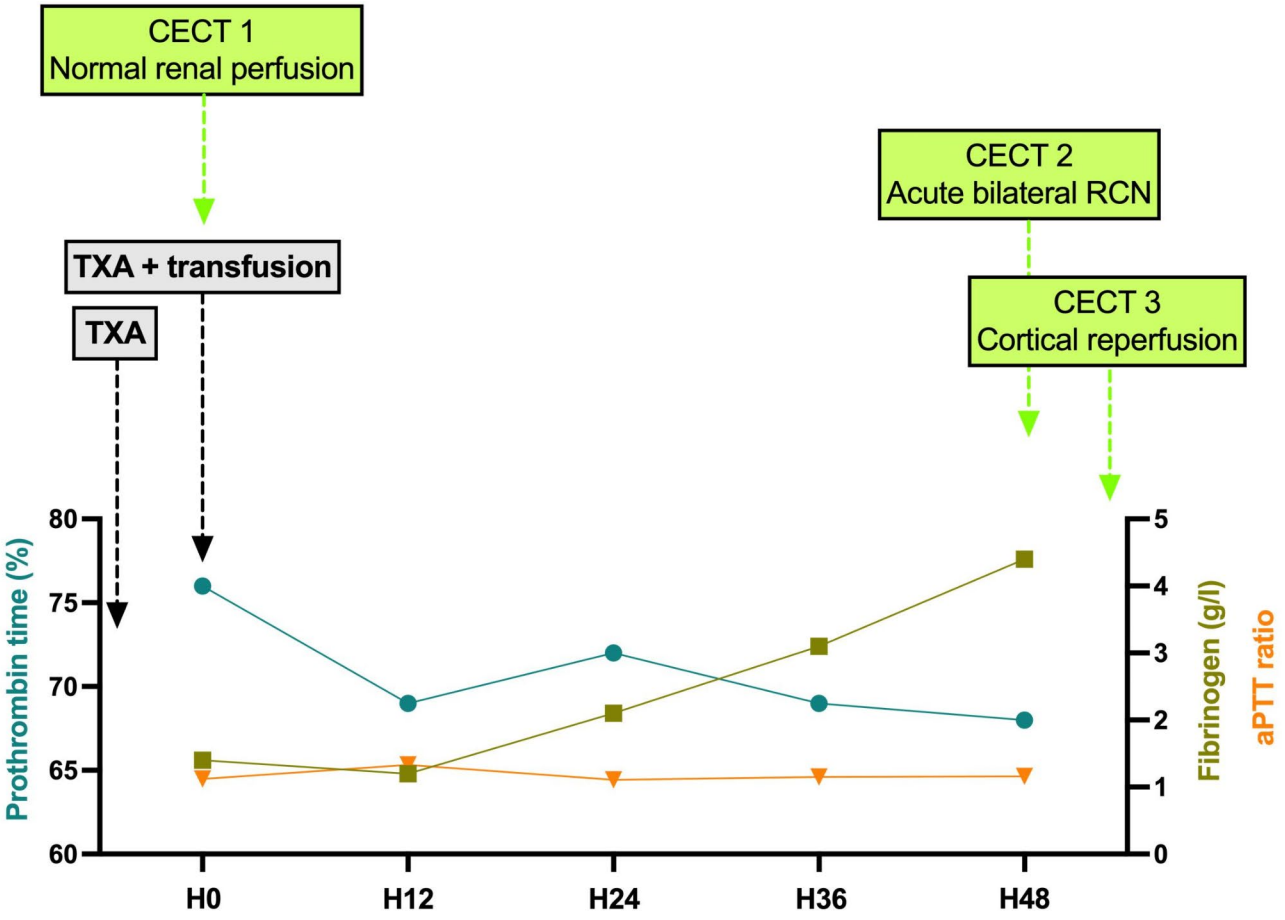

Fig. 3 Evolution of homeostasis parameters in the first 48 h following admission: prothrombin time, activated partial thromboplastin time (aPTT) ratio and fibrinogen. Timing of tranexamic acid (TXA) administration and transfusion as well as the results of performed contrast-enhanced computed tomographies (CECT) are indicated

were titrated at 1/160 with no specificity. Serum levels of complement fraction C3 and C4 were normal. Testing for acquired thrombophilia (antithrombin III, protein S and C activity) was negative and testing for hereditary thrombophilia was not performed.

The patient was then transferred to the nephrology critical care unit, where she remained dialysis-dependent. A control CECT performed at day 17 revealed a modified renal profile with a cortico-medullary dedifferentiation appearance after contrast administration, probably indicative of cortical reperfusion (Fig. 1C). Diuresis gradually increased from day 16 upon diuretic therapy while kidney function only started to recover after two months, so that hemodialysis could be discontinued (Fig. 2). At one year, the patient stabilized at an estimated glomerular filtration rate (eGFR) of 40 ml/min/1.73 m^2 without medication and is now followed in our nephrology department.

Discussion and conclusions

We describe an unusual case of non-obstetric TXA-induced bilateral RCN in the aftermath of traumatic hemorrhage.

Based on (existing) literature data, the direct pathogenic effect of TXA in the development of RCN remains debated, particularly when used in the setting of severe acute bleeding which represents a potential confounding risk factor for RCN primarily through the reduction of renal blood flow [1, 6]. In our case, the identification of TXA as a causative factor was supported by 2 points. Firstly, the initial bleeding appeared relatively mild: hemodynamics remained stable throughout the hospitalization with transient requirement and low-dose of catecholamine support therapy, no active hemorrhage was detected on initial CT-scans and hemoglobin level remained above 10 g/dl. Second, differential diagnosis of DIC and TMA were clearly ruled out.

To date, only five cases of non-obstetric related RCN associated with TXA treatment were previously published between 1999 and 2017 [13, 14, 15, 16, 17]: their

Table 1 Cases of non-obstetric bilateral renal cortical necrosis related to tranexamic acid administration reported in the literature

	Koo, et al. (14)	Levin, et al. (15)	Odabas, et al. (16)	Park, et al. (17)	Ko, et al. (13)
Age (yr) / Sex	37 / M	24 / F	21 / M	49 / M	82 / F
Indication of TXA	Hemoptysis complicating post-tuberculosis bronchiectasis	Hemorrhagic diathesis complicating acute promyelocytic leukemia	Epistaxis complicating hemophilia A	Traumatic hemothorax	Hematemesis following endoscopic papillectomy
Hemodynamic instability	No	NR	No	No	No
Cumulative dose of TXA (g)	15	NR	12	NR	12
Duration until AKI onset (d)	6	2	3	1	4
Anuria	Yes	Yes	Yes	Yes	Yes
Requirement of RRT	Yes	Yes	Yes	Yes	Yes
Duration until onset of RRT (d)	NR	5	9	NR	4
Recovery of renal function	Yes	No	NR	Yes	No
Time to renal recovery (wk)	3		NR	32	
Death	No	No	No	No	No

yr, year; d, day; wk, week; M, Male; F, Female; NR, non reported; TXA, tranexamic acid; AKI, acute kidney injury; RRT, renal replacement therapy

data are detailed in Table 1. Similarly to our case, hemodynamic status was stable in all patients despite active bleeding at initial presentation. Patients promptly developed anuric AKI in a median time of 3 (1.5-5) days and all of them required hemodialysis in a median time of 5 [4, 5, 6, 7, 8, 9] days following TXA administration. Two patients remained dialysis-dependent and two other patients partially recovered their renal function within a median time of 17.5 (3–32) weeks. No death was reported. Though these observations support the pathogenic effect of TXA, they need to be confronted to the results of large-scale randomized controlled trials showing the use of TXA did not increase the rate of AKI in patients presenting with PPH [8] as well as in patients with or at risk of significant bleeding following non-cardiac surgery [9] or trauma [10].

Nevertheless, not all patients treated with TXA in the context of bleeding develop RCN, strongly suggesting the involvement of other contributory factors. We hypothesize that hormonal-based contraception may have, in part, favored the development of RCN in our patient, as it is classically established to favor thromboembolic events. RCN occurred upon administration of 2.6 g of TXA, a much lower dose than that found in our literature review (average dose 13 g; Table 1). However, no clear association between hormonal contraceptives, or more generally estrogenic impregnation, and RCN has been found in the literature. A recent meta-analysis did not show increased thrombotic risk either in the context of pharmacologic or physiological estrogenic state related to PPH [18]. In contrast, a single case has reported acute myocardial infarction in a women under combined treatment with TXA and oral contraceptive [19]. Although no specific case of RCN has been described with concomitant use of antifibrinolytics and estrogens, it is currently recommended to prescribe TXA with caution in women with hormonal contraception [20].

Importantly, we could not definitely rule out the contributory role of concomitant administration of fibrinogen and PCC at admission in the development of AKI in our patient [21]. A retrospective study of bleeding patients following cardiac surgery found an increased incidence of AKI when treated with PCC compared to fresh-frozen plasma, probably through a hypovolemic rather than microthrombotic mechanism, but no case of RCN has ever been reported in this context [21, 22].

Beyond the role of TXA in the occurrence of RCN, our case also highlights the severity of this entity and the importance of identifying predictive factors of initial renal replacement therapy requirement and future renal recovery. In a retrospective French study reporting 18 adult cases of obstetric RCN following PPH, the mean duration of TXA maintenance was significantly increased up to 7.1 h in patients with an eGFR inferior to 15 ml/min/1.73 m^2 at 6 months as compared to the higher eGFR group, while loading and cumulative doses of TXA were similar regardless of residual kidney function [2]. These findings contrast with our patient who experienced partial renal recovery despite a total 9 h of TXA administration and need to be confirmed in other cases of non-obstetric related RCN.

The predictive contribution of kidney imaging is an additional interesting point raised by our case. Indeed, both scannographic presentation and evolution may provide relevant prognosis information for RCN severity. First, the presence of a few spots of subcapsular and juxta-medullary enhancement at initial diagnosis indicated a preserved perfusion in these cortical regions [23]. From a pathophysiological point of view, it can be explained by the existence of local anastomoses between the distal end of interlobular arteries and digestive

microvessels capable of vascularizing the subcapsular cortex, and by the greater caliber of the interlobular arteries at their origin, sparing the deepest cortex from ischemic necrosis. Besides, correlation between the diffuse or patchy extension of RCN and renal outcome remains unclear [24]. Our patient was successfully weaned from dialysis and partially recovered a renal function despite diffuse RCN, in contrast with a higher prevalence of diffuse lesions among patients with low residual eGFR in a previous study [2]. While the presence of the "reverse rim sign" at day 3 was clearly pathognomonic of acute bilateral RCN [5, 13, 14, 23, 25], the delayed appearance of a complete corticomedullary dedifferentiation is not fully understood. We speculate that this pattern likely reflects a phenomenon of cortical reperfusion following the initial phase of ischemic necrosis, thereby predicting subsequent renal recovery. Because of AKI, CECT is rarely repeated in the course of RCN. As previously suggested [24], better radiological characterization of renal pattern using MRI at initial presentation and during follow-up may be relevant not only for the assessment of the severity of RCN but also for helping clinicians to predict renal recovery.

In conclusion, we report an additional case of non-obstetric TXA-induced bilateral RCN in a young woman, probably precipitated by concomitant hormonal contraception. The rapid occurrence of RCN following low doses of TXA combined with mild bleeding and the absence of DIC or TMA criteria collectively reinforce the imputability of TXA. Hence, our case may incite the need to assess the risk-benefit ratio of its administration, especially in the context of non-obstetric and mild hemorrhage. Lastly, initial and repetitive kidney imaging during follow-up may provide predictive patterns for RCN severity and subsequent renal recovery, warranting further studies.

Abbreviations

AKI	Acute kidney injury
CECT	Contrast-enhanced computed tomography
DIC	Disseminated intravascular coagulation
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
PCC	Prothrombin complex concentrate
PPH	Post-partum hemorrhage
RCN	Renal cortical necrosis
TMA	Thrombotic microangiopathy
TXA	Tranexamic acid

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Author contributions

All authors were involved in diagnosis, management and follow-up of the patient in Lapeyronie Hospital. J.B. and M.M. designed the study, wrote the manuscript and performed the figures; M.Q-D., I.M., L.C. and J-E.S. revised the manuscript. All authors have contributed, read and approved the final manuscript.

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Data availability

If required, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

No ethics approval was required as this is a case report. The authors declare that they obtained written consent from the patient reported in this article.

Consent for publication

Written informed consent was obtained from the patient for publication of their clinical and clinical images.

Competing interests

The authors declare no competing interests.

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