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Case Series

Not an innocent bystander – case series of tranexamic acid induced cortical necrosis

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ABSTRACT

Acute cortical necrosis accounts for <2% of all acute kidney injuries. Pregnancy complications, viperine snake bites, haemolytic uremic syndrome, shock, and severe pancreatitis are all linked to it. There are relatively few case reports of acute cortical necrosis secondary to tranexamic acid, which is utilised in the treatment of acute bleeding because of its antifibrinolytic actions. Acute cortical necrosis is very infrequently brought on by medicines. Here, we present a group of three instances, each of which experienced the onset of oligo-anuria soon after receiving tranexamic acid. Cortical necrosis was demonstrated by contrast computed tomography (CT) and renal biopsy. While the third patient had patchy cortical necrosis and had partially recovered renal functions, the other two patients both had total acute cortical necrosis and are still reliant on dialysis. This case series demonstrates the need for clinicians to be cautious while using tranexamic acid and to be aware of the possibility of abrupt renal cortical necrosis following its administration.

Keywords: Tranexamic acid, Cortical necrosis, Kidney injury

INTRODUCTION

Tranexamic acid (TXA) is a synthetic lysine amino acid derivative which reduces the dissolution of haemostatic fibrin by plasmin. TXA is a drug frequently used in various disciplines such as cardiology, neurosurgery and obstetrics and gynaecology as a haemostatic agent and "fibrin sealant".[1] While it is generally considered safe and effective when used appropriately, there have been rare reports of cortical necrosis associated with the use of TXA.

Kidney cortex necrosis is a relatively rare cause of acute kidney injury and is characterized by complete or partial destruction of the renal cortex, but sparing of the medulla. This can lead to acute kidney injury and even permanent kidney damage. The exact mechanism by which TXA can cause cortical necrosis is not fully understood, but it is believed to be related to the drug's effect on the blood clotting system and the resulting disruption of blood flow to the kidneys. We discuss three cases with acute cortical necrosis following administration of TXA.

CASE SERIES

Case 1

Patient A was a 39-year-old female with no comorbidities had lumbar radiculopathy treated with a micro-lumbar discectomy on the right side (MRI spine: L5-S1 disc herniation). There was no evidence of hemodynamic instability. She was given amikacin before the operation. She was given 1g of intravenous paracetamol and 1g of intravenous TXA after surgery. Later within 48 hours of surgery she had anuria. During the process, there are no extra triggering conditions documented. Her creatinine level rose to 4.7 mg/dl on post-operative day one and 6.7 mg/dl on day three, necessitating hemodialysis for pulmonary edema and acidosis. Her LDH level was 4195 U/L, and she had neither anaemia or thrombocytopenia. Her peripheral blood smear revealed no schistocytes or

fragmented RBCs. Haptoglobin levels were also reported to be normal. Coagulation parameters checked after surgery, PT/INR and aptt were normal. Her plasmic score was 3, and her complement and ADAMTS-13 levels were both normal. She had a kidney biopsy, which revealed cortical necrosis as illustrated in Figure 1. Six months later she continues to be on maintenance hemodialysis and is being worked up for renal transplant.

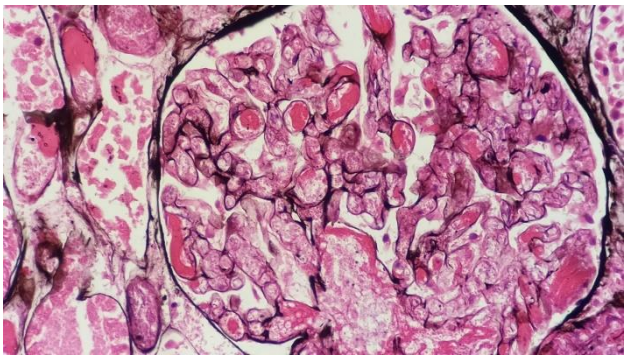

Figure 1: Renal biopsy on Jones-methenamine silver stain showing ghost glomeruli suggestive of acute cortical necrosis (X 200).

Case 2

Patient B was a 42-year-old female with no comorbidities. She underwent a hysterectomy because of irregular uterine bleeding. She had intra-operative bleeding that required one PRBC transfusion and one gram of TXA. No intraoperative hypotension was seen. Anuria was detected after surgery with first 36 hours. Her creatinine level rose to 3 mg/dl on post-operative day two necessitating hemodialysis for pulmonary edoema and acidosis. Her LDH level was 2068 U/L, and she had no features of thrombotic microangiopathy. Her platelets, coagulation parameters PT/INR, aPTT, haptoglobin were normal. Her d-dimer and fibrinogen levels were normal, normal complement and ADAMTS-13 activity. Peripheral smear did not show any schistocytes. A contrast CT abdomen was conducted, as shown in Figure 2. Three months after the surgery, she is still anuric and on dialysis.

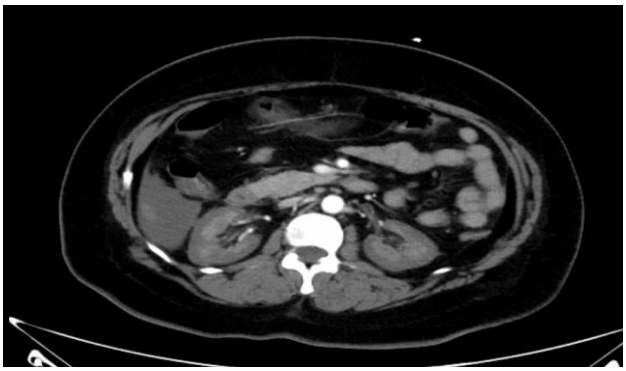

Figure 2: Relative hypo-enhancement of the renal cortex and normal enhancement of the renal medulla (reverse rim sign).

Case 3

Patient C was a post renal transplant recipient 41-year-old female, with native kidney disease being IgA nephropathy, 5 years post-transplant, who underwent dilatation and curettage in view of menorrhagia. She Received paracetamol and 1g of tranexamic acid post operatively. Noted to be anuric after the procedure within 24 hours. Her laboratory reports are depicted in Table 1. Patient had anemia which could be due to blood loss and thrombocytopenia which showed a rising trend. Work up for hemolytic uremic syndrome was negative as shown in Table 1. Perfusion scan showed diminished perfusion to kidneys with suboptimal cortical tracer extraction (delayed cortical peaking time) with prolonged intra renal transit of tracer Renal biopsy done showed patchy cortical necrosis with diffuse intravascular thrombosis involving arterioles and glomerular capillaries. She remained dialysis dependent for 3 weeks and subsequently had partial recovery of creatinine to 1.8 mg/dl.

Table 1: Lab reports of patient C.

Pre-op	POD 0 (28/05/22)	POD 1 (30/05/22)
Hb	8.9	7.7
TC	14580	18600
PLT	75000	1,22,000
Creat 1.1	8.2	Dialyzed
TB	8.9	
DB	14580	
AST	75000	
ALT	8.2	
ALP	8.9	
LDH	3314	2548

Blood culture: no growth, INR: 1.07/APTT: 23.6, FDP–8 mcg/ml, haptoglobin: 60 mg/dl, retics: 1.9%, Coombs negative, D-dimer–0.5, ADAMTS 13 levels–normal, anti-factor H antibody–negative, peripheral smear–no schistocytes, tacrolimus level–5.5 ng/ml

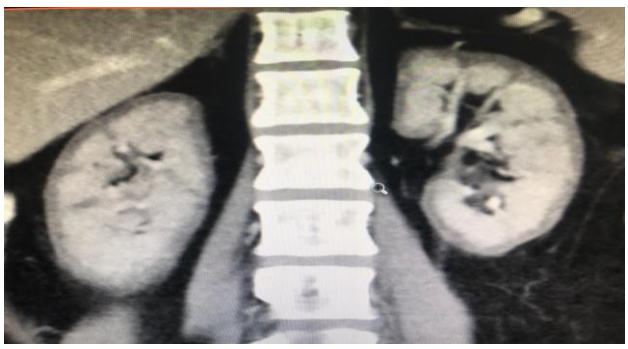

Figure 3: CECT showing reverse rim sign.

DISCUSSION

Acute cortical necrosis accounts for less than 2% of all causes of renal failure, with a substantial proportion progressing to CKD. Obstetrical, severe hypotension,

hemorrhage, disseminated intravascular coagulation (DIC), pancreatitis, snake bite, hemolytic uremic syndrome (HUS), allograft rejection, and alcohol poisoning are all common causes. Renal cortical necrosis (RCN) is characterized by patchy or diffuse ischemic destruction of all the elements of renal cortex resulting from significantly diminished renal arterial perfusion due to vascular spasm and microvascular injury.

TXA is a synthetic lysine amino acid derivative that inhibits fibrinolysis by reversibly blocking lysine binding sites on plasminogen, preventing plasmin from engaging with lysine residues on the fibrin polymer and inducing fibrin breakdown. TXA is broadly distributed in the intracellular and extracellular compartments and is primarily eliminated unaltered in the urine. It can be taken orally or intravenously. It is generally well tolerated, but there have been isolated cases of significant side effects. In a few case reports, TXA has been linked to acute renal cortical necrosis (ACN). The reasons for this are unknown, but they include fibrinolysis inhibition and endothelial injury.[1] TXA is also known to induce renal artery vasoconstriction in a dose dependant manner primarily mediated by endothelin-1.[1] Koo et al documented a 37-year-old man who had haemoptysis as a result of post-TB bronchiectasis.[2] He got oligo-anuria after receiving 3 g TXA for three days. ACN was discovered via CT scan and kidney biopsies. He was on dialysis for two weeks and only made a partial recovery. Our patients received a dosage of 1 gram which precipitated cortical necrosis. Odabas et al reported on a 21-year-old male with haemophilia A and epistaxis.[3] He was given 3 g of TXA each day for four days and presented three days later with oligo-anuria and azotaemia. He needed HD, and CECT revealed cerebral necrosis. Ko et al reported on an 82-year-old female who received 13.5 g TXA for bleeding after an endoscopic papillectomy for a tumour in the ampulla of Vater.[4] She developed oligo-anuric AKI and was treated with haemodialysis for over 6 months. Sung et al documented a 49-year-old lady who had haemoptysis owing to bronchiectasis and was treated with TXA for three days.[5] She had anuria and azotaemia four days later. ACN was confirmed by a CECT scan. Six months after her initial presentation, she was still on haemodialysis. In 2013, a French periodic safety update report (PSUR) cautioned of an unusually high rate of unexplained renal failure following the treatment of TXA in combination with other medications for severe postpartum haemorrhage.[6] Another French study documented 18 occurrences of renal cortical necrosis in women who had received TXA for post-partum haemorrhage. [7] At 6 months following delivery, none of the 18 patients had recovered normal renal function, and eight (44%) were on dialysis. The only risk factor related with poorer kidney outcomes was the length of tranexamic acid intake and its dosage.[8] Stämpfli et al documented 29 examples of renal vascular and ischemic alterations caused by TXA in their "Vigibase" journal. Similarly, as previously stated, we recorded three cases of cortical necrosis following TXA administration.[8] Two patients remained on dialysis, while one made a partial recovery. The dosage of TXA in all the three cases was 1000 mg and the onset of renal dysfunction was within 24-48 hours.

CONCLUSION

Our experience clearly indicates that antifibrinolytic drugs can produce acute cortical necrosis in an otherwise normal kidney and we must be aware of this potentially dangerous complication of this drug.

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