# Drug-Induced Thrombotic Microangiopathy Resulting in ESRD

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## INTRODUCTION

Thrombotic microangiopathy (TMA) is a pathologic term used to describe small vessel injury, manifesting clinically as microangiopathic anemia, thrombocytopenia, and target organ damage including kidney injury. The classical TMA syndromes are ADAMTS13 deficiency–associated thrombotic thrombocytopenia (TTP) and the Shiga toxin–mediated hemolytic uremic syndrome. Other primary TMA syndromes include drug-induced TMA (DITMA), complement-mediated TMA, and rare hereditary disorders of hemostasis and vitamin B12 metabolism. In addition to the primary syndromes, various systemic conditions can manifest with TMA. These include malignant hypertension, malignancies, pregnancy-associated conditions such as pre-eclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, infections, autoimmune diseases, and stem cell or solid organ transplants. Patients may present with symptoms related to anemia, thrombocytopenia, or evidence of end-organ involvement including neurological symptoms, skin rash, and renal failure. A peripheral blood smear is an essential first step to establish evidence of microangiopathic anemia. Once microangiopathic anemia and thrombocytopenia have been confirmed, a primary systemic condition should be excluded. If no systemic condition is identified, a diagnosis of primary TMA syndrome should be sought. DITMA are acquired from specific drug exposures and result from dose-dependent drug toxicity or immune-mediated mechanisms. Quinine is the most common cause of immune-mediated DITMA.[1,2] Here we report a case of TMA associated with sulfamethoxazole-trimethoprim (SMX-TMP) in a previously healthy man.

## CASE PRESENTATION

A 62-year-old man was transferred to our hospital for acute renal failure in the setting of new onset anemia, thrombocytopenia, and hyperkalemia. His past medical history included prostate cancer treated with radical prostatectomy 3 years ago. He had been in his usual state of health until 2 weeks before admission when he presented to a community hospital with new rash on his left ankle. Initial evaluation revealed hemoglobin was 12.8 g/dl, hematocrit was 40.3, white blood cell count was 25,500/mm$^3$, platelet count was 200,000/mm$^3$, and creatinine was 1.0. Electrolytes were within normal limits, and his C-reactive protein was elevated to 38.5. He was treated with cephalexin for suspected cellulitis, but then switched to i.v. ampicillin/sulbactam for poor response and persistent leukocytosis (77% neutrophils). Eventually, a skin biopsy of the left ankle plaque was performed, and it revealed findings of epidermal necrosis, dermal inflammation, and absence of vasculitis or neoplastic changes. This raised concern for Sweet's syndrome. He was discharged on prednisone 80 mg daily and SMX-TMP for Pneumocystis carinii prophylaxis. Additional workup at this time included a computed tomography scan of his chest, abdomen, and pelvis, which did not reveal any evidence of malignancy. A transthoracic echocardiogram revealed a moderate pericardial effusion without any hemodynamic compromise. This was attributed to a possible viral etiology and was to be followed up as an outpatient.

One week after discharge, he returned to the community hospital for malaise, chills, nausea, vomiting, diarrhea, and decreased amount of ''brown-colored'' urine. Initial evaluation revealed anemia, thrombocytopenia, acute renal failure, and hyperkalemia.

**Table 1.** Laboratory evaluation 1 week before current hospital admission, at the time of admission, and at hospital day 2 and day 15

| Test | Reference | 1 wk prior | On admission | Day 2 | Day 15 |
|---|---|---|---|---|---|
| **Hematology** | | | | | |
| WBC count | 4–10 K/µl | 18.4 | 27.3 | 47.3 | 29.1 |
| Hemoglobin | 13.7–17.5 g/dl | 11.4 | 8.6 | 8.2 | 9.9 |
| Hematocrit | 40%–51% | 35.8 | 26.3 | 25.4 | 33.3 |
| Platelet count | 150–400 K/µl | 180 | 56 | 150 | 157 |
| % Neutrophils | 345–71 | 90.4 | 82 | | |
| % Lymphocytes | 19–53 | 4.1 | 1 | | |
| % Monocytes | 5–13 | 3.9 | 6 | | |
| % Eosinophils | 1–7 | 0 | 0 | | |
| % Basophils | 0–1 | 0.2 | 0 | | |
| ESR | <20 mm/h | 31 | | | |
| CRP | <3 mg/l | 38.5 | | | |
| Ferritin | 30–400 ng/ml | | 1567 | | |
| LDH | 94–250 IU/l | | 1723 | 1323 | 520 |
| Haptoglobin | 30–200 mg/dl | | <10 | <10 | 55 |
| **Coagulation profile** | | | | | |
| Fibrinogen | 180–400 mg/dl | | 155 | 248 | |
| PT | 9.4–12.5 s | | 17.2 | | 12.1 |
| PTT | 25–36.5 s | | 28.3 | | 29.9 |
| INR | 0.9–1.1 | | 1.6 | | 1.1 |
| **Chemistries** | | | | | |
| Sodium | 135–147 mEq/l | 141 | 134 | 140 | 136 |
| Potassium | 3.5–5.4 mEq/l | 4.0 | 7.1 | 5.1 | 4.2 |
| Chloride | 96–108 mEq/l | 110 | 94 | 96 | 96 |
| Bicarbonate | 22–32 mEq/l | 28 | 12 | 21 | 26 |
| Anion gap | 10–18 mEq/l | 4 | 28 | 23 | 14 |
| BUN | 6–20 mg/dl | 22 | 176 | 77 | 66 |
| Creatinine | 0.5–1.2 mg/dl | 0.97 | 6.6 | 3.6 | 5.7 |
| AST | 0–40 IU/l | 53 | 112 | 182 | 42 |
| ALT | 0–40 IU/l | 68 | 75 | 105 | 28 |
| Alk phos | 40–130 IU/l | 51 | 120 | 45 | 68 |
| Total bilirubin | 0–1.5 mg/dl | 0.7 | 5.4 | | |
| Indirect bilirubin | 0–1.2 mg/dl | | 1.6 | | |
| Lactate | 0.5–2 mmol/l | | 4.6 | | |
| **Autoimmune panel** | | | | | |
| ANA | Negative | Negative | Negative | | |
| ANCA | Negative | | Negative | | |
| dsDNA | Negative | | Negative | | |
| C3 | 90–180 mg/dl | | 67 | | 86 |
| C4 | 10–40 mg/dl | | 9 | | 16 |
| Rheumatoid factor | <14 IU/ml | <10 | <14 | | |
| SPEP | | | No monoclonal Ig | | |
| Free kappa | 3.3–19.4 mg/l | | 43.1 | | |
| Free lambda | 5.7–26.3 mg/l | | 33.6 | | |
| Free K/L ratio | 0.26–1.65 | | 1.3 | | |
| **Special tests** | | | | | |
| ADAMTS13 activity | >67% | | 31% | | |
| Cryoglobulin | Negative | | 0.5% (negative on repeat) | | |
| MMA | 87–318 nmol/l | | 519 | | |
| Vitamin B12 | 240–900 pg/ml | | 1523 | | |
| B2GP1 Ab (IgA/M/G) | <9 | | <9 | | |
| Cardiolipin Ab (IgG/M) | Negative | | Negative | | |
| **Infectious panel** | | | | | |
| Anaplasma phagocytophilum Ab | Negative | | Negative | | |
| Lyme Ab | Negative | Negative | Negative | | |
| Hepatitis B | Negative | | sAb+/sAg−/cAb− | | |
| Hepatitis C Ab | Negative | | Negative | | |
| CMV Ab | Negative | | IgG+/IgM− | | |
| EBV | Negative | | IgG+/EBNA+/IgM− | | |

*(Continued on next page)*

**Table 1.** (Continued) Laboratory evaluation 1 week before current hospital admission, at the time of admission, and at hospital day 2 and day 15

| Test | Reference | 1 wk prior | On admission | Day 2 | Day 15 |
| --- | --- | --- | --- | --- | --- |
| HIV Ab | Negative | Negative | Negative | | |
| HCV Ab | Negative | | Negative | | |
| HSV 1 Ab | Negative | | IgG+/IgM− | | |
| HSV 2 Ab | Negative | | IgG−/IgM− | | |
| Blood cultures | Negative | | Negative | | |

ALT, alanine transaminase; ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate transaminase; BUN, blood urea nitrogen; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HCV, hepatitis C virus; HSV, herpes simplex virus; INR, international normalized ratio; K/L, kappa:lambda ratio; LDH, lactate dehydrogenase; MMA, methylmalonic acid; PT, prothrombin time; PTT, partial thromboplastin time; SPEP, serum protein electrophoresis; WBC, white blood cell.

Laboratory values are detailed in Table 1. Given concern for TTP, he was transferred to our hospital for potential plasmapheresis.

On arrival, he was afebrile. His vital signs were blood pressure 80/54 mm Hg, heart rate 110/min, respiratory rate 20/min, and oxygen saturation of 99% on room air. On examination, he was anasarcic, alert, oriented, and conversant. Pupils were equally round and reactive to light bilaterally; extraocular movements were intact. Neck was supple without any lymphadenopathy, thyromegaly, or carotid bruit. Heart sounds S1, S2 were regular without any murmurs or rubs. Lungs were clear to auscultation bilaterally. Abdominal examination revealed minimal bowel sounds with a soft and diffusely tender abdomen. No organomegaly was noted. Skin examination was notable for small 2–3 cm necrotic ulcers on both feet, worse on the medial side of the left ankle. There was no purulent or bloody drainage for these ulcers. Neurologically, his motor strength was 5/5 in all 4 extremities, sensations to light touch and pain were intact, facial expressions were symmetrical with normal neck movements, and shoulder shrugs. Speech was fluent. Asterixis was noted. Initial labs are given in Table 1. Electrocardiogram showed widened QRS. An urgent peripheral smear revealed schistocytes (Figure 1). SMX-TMP and prednisone were stopped. Emergent hemodialysis was first performed, followed by plasmapheresis. A broad infectious and autoimmune workup were obtained (Table 1). ADAMTS13 activity was low at 31% but did not meet criteria for continuing plasmapheresis. His platelet counts recovered completely by hospital day 2, although he continued to have worsening leukocytosis, anemia, and dialysis-dependent anuric renal failure (initially continuous veno-venous hemodiafiltration due to hypotension). Methylprednisolone 40 mg every 24 hours was restarted on day 2. On day 4, he underwent coronary angiography, right heart catheterization, and endomyocardial biopsy for newly reduced ejection fraction 30%–35% (compared with 55%–60% 2 weeks ago) and elevated troponin. On the same day, he also underwent a bone marrow biopsy, for persistent leukocytosis, which did not show any neoplastic process. The endomyocardial biopsy revealed mild cardiomyocyte hypertrophy but otherwise no evidence of myocarditis or infiltration.

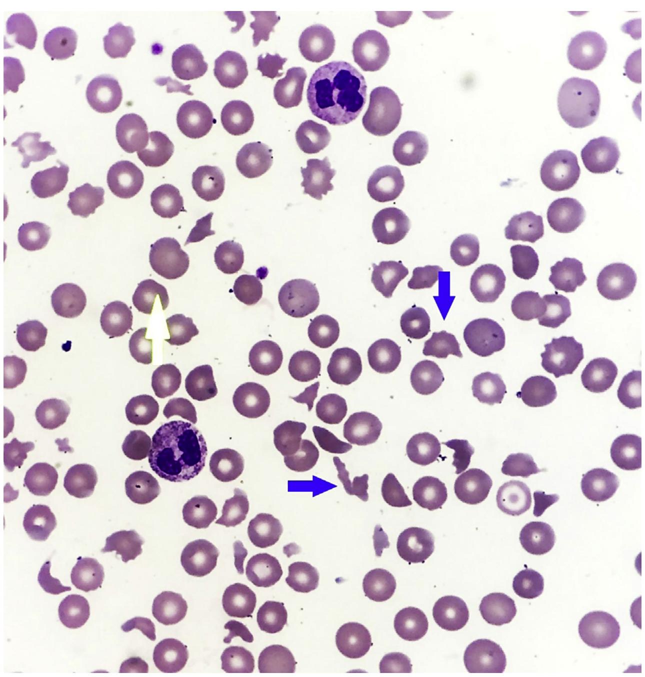

**Figure 1.** Peripheral blood smear. The yellow arrow is pointing at a normal-appearing red blood cell and blue arrows point at schistocytes.

Hospital course was further complicated by intermittent need for intensive care unit and continuous veno-venous hemodialysis for renal replacement due to persistent hypotension. His hemodynamics gradually improved, and a repeat echocardiogram on day 8 revealed improvement in left ventricular ejection fraction to 41% and reduction in the pericardial effusion. Renal biopsy was performed on day 15 for prognostic purposes because the patient remained anuric and dialysis dependent. The renal biopsy showed a diffuse TMA pattern involving glomeruli and arterioles with associated extensive tubular and focally interstitial necrosis (Figure 2). The patient was discharged to an acute rehabilitation facility and continues to be dialysis-dependent 6 months after discharge. In the interim, he has also been started on mycophenolate mofetil as a steroid-sparing agent for an undifferentiated systemic inflammatory syndrome in lieu of persistently elevated C-reactive protein.

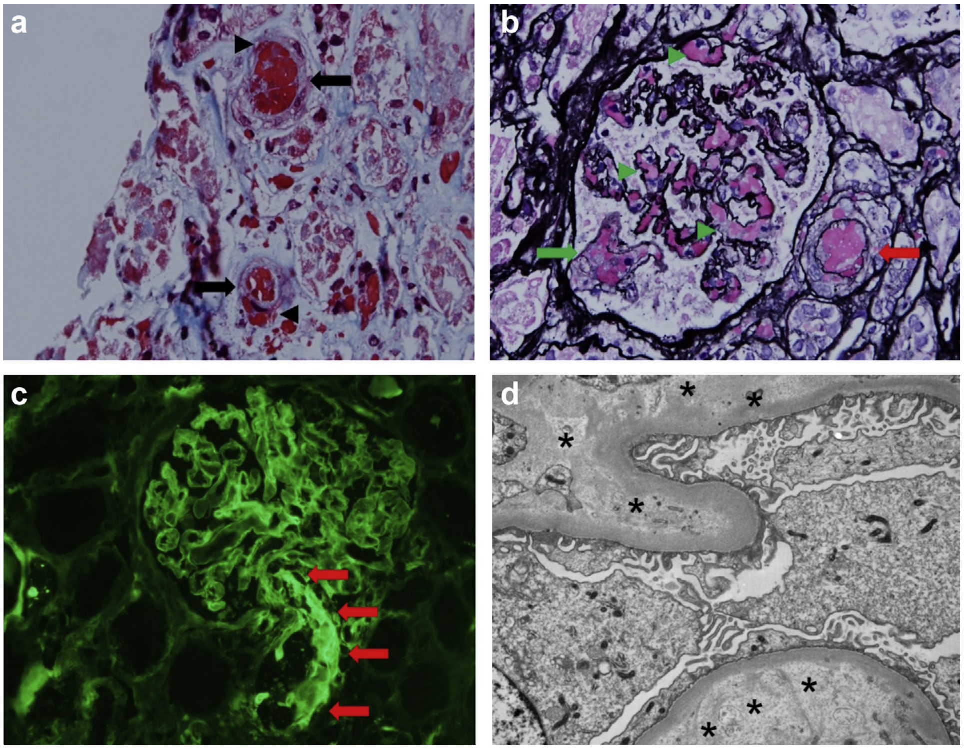


**Figure 2.** Renal biopsy. (a) Arterioles contain fibrin thrombi (arrows) and intramural fragmented red blood cells or schistocytes (arrow heads). Tubular injury is seen diffusely. Masson trichrome stain, original magnification ×200. (b) Glomeruli contain fibrin thrombi (arrowheads) and show mesangiolysis (green arrow). The glomerular basement membrane shows diffuse ischemic changes. An arteriole contains an intraluminal fibrin thrombus (red arrow). Jones silver stain, original magnification ×200. (c) Arterioles and glomeruli contain abundant fibrin thrombi (red arrows). Direct immunofluorescence antifibrin, original magnification ×200. (d) Glomerular basement membranes show marked subendothelial lucency and flocculent material (asterisks), consistent with endothelial injury/thrombotic microangiopathy pattern. Electron microscopy, original magnification ×10,000.

## DISCUSSION

TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia. The former is diagnosed by the presence of schistocytes on a peripheral blood smear and markers of hemolysis including elevated lactate dehydrogenase, elevated indirect bilirubin, and haptoglobin typically less than 10. The pathologic mechanisms include endothelial cell injury, leading to formation of platelet microthrombi in the microvasculature, which shear red blood corpuscles as they traverse narrowed capillaries. Glomerular capillaries are particularly susceptible to involvement by TMAs. Once TMA is suspected, it is important to rule out TTP, which results from an ADAMTS13 deficiency or acquired inhibitory antibodies. In TTP, ADAMTS13 activity is severely reduced (<10%). Plasma exchange should be initiated pending results to replenish ADAMTS13 and remove inhibitory antibodies in addition to the large von-Willebrand factor multimers. Hemolytic uremic syndrome is another primary TMA syndrome that is caused by Shiga toxin–producing

**Table 2.** Teaching points

| |
|---|
| TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia. |
| Glomerular capillaries are often involved in TMAs. |
| DITMA is rare, and 90% is associated with quinine. |
| Mechanisms of DITMA include immune-mediated, which involves drug-dependent antibodies targeting host cells, or direct dose-dependent drug toxicity. |
| Management involves discontinuation of the offending drug and supportive treatment. |
| Renal recovery is expected, but up to 57% patients can progress to chronic kidney disease. |

DITMA, drug-induced thrombotic microangiopathy; TMA, thrombotic microangiopathy.

**Table 3.** Mechanisms of drug-induced thrombotic microangiopathy

| Mechanism | Immune-mediated | Direct drug toxicity |
|---|---|---|
| Pathophysiology | Exposure to offending drug → formation of drug-dependent antibodies to platelets, neutrophils, complement factors, endothelial cells → microvascular injury → thrombosis and platelet consumption | Exposure to offending drug → direct endothelial cell injury → thrombosis and platelet consumption |
| Diagnosis | Acute onset anemia, thrombocytopenia, thrombosis, and acute kidney injury usually triggered by first contact with the drug | Acute kidney injury and systemic features on initial or prolonged exposure to the drug |
| Common examples | Quinine, oxaliplatin, quetiapine, and gemcitabine | Cyclosporine, tacrolimus, sirolimus, interferons, bevacizumab, gemcitabine, and mitomycin |

organisms such as *Escherichia coli* O157:H7, O104:H4, O111 and *Shigella dysenteriae*. Other primary TMA syndromes include complement-mediated TMA, DITMA, and rare hereditary disorders of coagulation (thrombomodulin, plasminogen, diacylglycerol kinase epsilon) and cobalamin metabolism (methylmalonic aciduria and homocystinuria type C gene).[3] The fundamental role of the complement system in various TMA syndromes is now recognized, and testing for complement pathway components and presence of inhibitors is available. Treatment for some disorders with anticomplement agents such as eculizumab has led to further progress.[4]

DITMA is rare. As per the Oklahoma TTP/hemolytic uremic syndrome registry, of all 487 patients with suspected TTP/hemolytic uremic syndrome referred for plasma exchange, only 23 (5%) had definite or probable evidence for a causal association with a candidate drug.[2] Almost 90% of these cases were associated with quinine (Table 2). Mechanisms of DITMA include immune mediated, which involves drug-dependent antibodies targeting host cells, or direct dose-dependent drug toxicity (Table 3). The criteria to determine causality of the drug-induced thrombocytopenia were described by George *et al*. in 1998.[5] A definite causal relationship requires that 4 criteria be met: (i) therapy with the candidate drug preceded thrombocytopenia and recovery of platelet count was complete and sustained after the drug was discontinued, (ii) the candidate drug was the only drug used before thrombocytopenia or other drugs were continued or reintroduced after discontinuation of the offending drug with a sustained normal platelet count, (iii) other causes of thrombocytopenia were excluded, and (iv) re-exposure to the candidate drug led to recurrent thrombocytopenia. Although this definition was evaluated for drug-induced thrombocytopenia, it should hold true for immune-mediated DITMA because pathogenesis involves drug-dependent antibodies attacking not just platelets but also endothelial cells and possibly organ tissues directly. Although testing for specific drug-dependent antibodies has been performed for research purposes, it does not change clinical management. Management involves discontinuation of the offending drug and supportive treatment. Renal recovery is expected but a case series reported chronic renal failure in 57% patients with quinine-associated DITMA.[6]

In our patient, SMX-TMP met criteria 1 through 3, suggesting "probable" causality.[5] This drug did not need to be reintroduced in our patient, and therefore criterion 4 was not assessed. The mechanism of drug injury in our case appears to be immune mediated. This is supported by the hypocomplementemia, rapid development of symptoms (within days of exposure), progressive anemia, thrombocytopenia, anuric renal failure within days of exposure, and the rapid recovery of platelets after discontinuation of SMX-TMP. Alternatively, dose-mediated drug toxicity usually presents with subacute renal failure in the setting of prolonged exposure to a candidate drug.[7] To our knowledge, only 3 case reports of SMX-TMP–associated TTP have been published so far.[8,9,S1] Lichtin *et al*.'s[8] case series focused on plasmapheresis and did not include specific details about the patient. Martin *et al*.'s[9] patient had normal ADAMTS13 activity, no renal dysfunction, and no tissue diagnosis. Bapani *et al*.'s[S1] report demonstrated SMX-TMP–associated TTP with ADAMTS13 activity less than 5% but only met the first criteria for causality as described above. None of these cases had tissue evidence of TMA, and none resulted in any long-term renal disease. Our case is the only reported case of SMX-TMP–induced TMA with histopathologic diagnosis and resultant end-stage renal disease. The exact reason for the lack of renal recovery and persistently elevated inflammatory markers remains elusive. Some authors suggest the role of the complement system in DITMA, with the drug exposure serving as a "second-hit" over an underlying genetic defect.[4] Further studies are warranted to better understand the exact mechanisms of DITMA and elucidate risk factors so that at-risk individuals can be identified before prescribing potentially offending medications.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Supplementary Reference.**

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