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Drug-induced thrombotic microangiopathy associated with eltrombopag

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ABSTRACT

Drug-induced thrombotic microangiopathy due to an immune reaction is idiosyncratic and not dose-dependent. The classic example is quinine-dependent antibodies resulting in thrombotic microangiopathy due to activation of endothelial cells. Eltrombopag is a thrombopoietin-receptor agonist indicated in resistant chronic immune thrombocytopenia (ITP). This is the first report of full-blown biopsy-proven thrombotic microangiopathy with acute kidney injury (AKI) and nephrotic syndrome (NS) in a patient with chronic ITP who was initiated on eltrombopag therapy.

Introduction and background

There are multiple types of thrombotic microangiopathy (TMA) syndromes. All these syndromes can be life-threatening and are characterized by thrombocytopenia, microangiopathic hemolytic anemia, and target organ damage (such as AKI, and neurological manifestations), Table 1. [1]. TMA syndromes can be hereditary such as thrombotic thrombocytopenic purpura (TTP) due to ADAMTS13 mutations, or complement-mediated TMA due to mutations in C3, CD46, complement factor H (CFH), complement factor B (CFB), or other alternative complement pathways genes; or acquired such as, Shiga-toxin-mediated TMA, immune-mediated drug-induced TMA (DITMA) due to an immune reaction by drug-dependent antibody (the classic example is quinine), non-immune drug-induced TMA due to a toxic effect such as vascular endothelial growth factor (VEGF) inhibition due to sunitinib, or complement-mediated TMA due to antibodies (such as anti-factor H antibodies) [2]. Differentiating immune and non-immune DITMA is not always possible. Note that both TTP and complement-mediated TMA can be either hereditary or acquired.

Eltrombopag is a thrombopoietin-receptor agonist indicated in resistant chronic ITP. This is the first report of full-blown biopsy-proven TMA with AKI and NS in a patient with chronic ITP patient who was started on eltrombopag.

Case presentation

A 65-year-old woman with corticosteroid and intravenous immunoglobulin G (IVIG) resistant chronic ITP presented with confusion, lethargy, worsening thrombocytopenia, fever, and AKI. Eltrombopag was started 4 days prior to presentation. Past medical history is significant for CVA, dyslipidemia, and left nephrectomy due to a kidney abscess. Admission medications included atorvastatin, apixaban, gabapentin, and eltrombopag 50 mg orally daily. Physical examination was remarkable for a temperature 38.1°C, blood pressure 110/51 mmHg, and lethargy. Skin examination was unremarkable. She did not have family history of blood disorders.

Three weeks earlier, creatinine was 0.84 mg/dl, and platelets 84,000 $\times 10^9$/L. On admission, Creatinine was 5.22 mg/dl, and platelets 50,000 $\times 10^9$/L. LDH was 1,193 U/L, and blood smear showed many schistocytes (3 %-4 % of RBCs). Urine albumin-to-creatinine ratio was 6510 mg/g. Hyperlipidemia and hypoalbuminemia were noted. She tested negative for COV-SARS-2. Blood and urine cultures, and direct Coombs test were negative. Anticardiolipin antibodies, prothrombin time (PT), activated partial thromboplastin time (aPTT), vitamin B12 level, hepatitis B and C, and connective tissue disorders serologies (C3, C4, CH-50, ANA, DS DNA, rheumatoid factor, SS-A, SS-B, and ANCA) were unremarkable. Pre- therapeutic plasma exchange (TPE) ADAMTS13 activity was normal (86.4 %, reference range >66.8 %). Genetic testing for atypical hemolytic-uremic syndrome was not done. Versiti Blood Center of Wisconsin did not identify eltrombopag-dependent, platelet-reactive antibodies. The laboratory findings are summarized in Table 2.

Eltrombopag was discontinued, IV corticosteroids, TPE, and hemodialysis (HD) were started on admission. A renal biopsy was done on hospital day 8 and it showed focal cortical necrosis, focal acute tubular necrosis, ischemic changes in the glomerular capillary loops, and focal arteriolar fibrin thrombi with red blood cell fragmentation (Figs. 1 and 2). The patient did not experience complications related to kidney biopsy.

Clinical condition improved significantly after 7 daily TPE sessions with normalization of platelets count and mental status. After cessation of TPE, her platelets count returned gradually to around 80,000 $\times$ 10^9/L, her prior baseline was 60,000 $\times$ 10^9/L - 80,000 $\times$ 10^9/L. Corticosteroids were tapered off and discontinued at discharge. Two months after

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Table 1
Types of TMA syndromes.

Hereditary TMA syndromes
TTP due to ADAMTS13 gene mutations
Complement-mediated TMA due to mutations in C3, CD46, CFH, CFB, or other alternative complement pathways genes
Acquired TMA syndromes
ADAMTS13 deficiency due to autoantibodies
Shiga-toxin-mediated TMA
Complement-mediated TMA due to antibodies (such as anti-factor H antibodies).
Drug-induced TMA [DITMA] (immune-mediated) due to drug-dependent antibodies (example: quinine): idiosyncratic, not dose dependent, sudden
Drug-induced TMA [DITMA] (toxic, non-immune-mediated) such as vascular endothelial growth factor (VEGF) inhibition due to bevacizumab: dose-dependent, direct injury to tissues, no drug-dependent antibodies.

Table 2
Summary of laboratory tests.

Laboratory test	3 weeks pre-admission	Day 1 (admission)	Day 7	Day 12 (discharge)	2 months	10 months
Hemoglobin (g/dl)	9.3	8.9	7.6	7.8	8.8	11.8
Platelets 10^9/L	84	50	155	135	81	59
BUN (mg/dl)	18	70	63	96	29	46
Creatinine (mg/dl)	0.84	5.22	5.75	7.53	1.89	2.3
Potassium (mEq/L)	3.9	6.0	4.6	5.4	4.2	4.0
LDH (normal:135–225 U/L)	298	1193	301	291	257	
Urine-albumin-creatinine ratio (normal: <30 mg/g)		6510				530

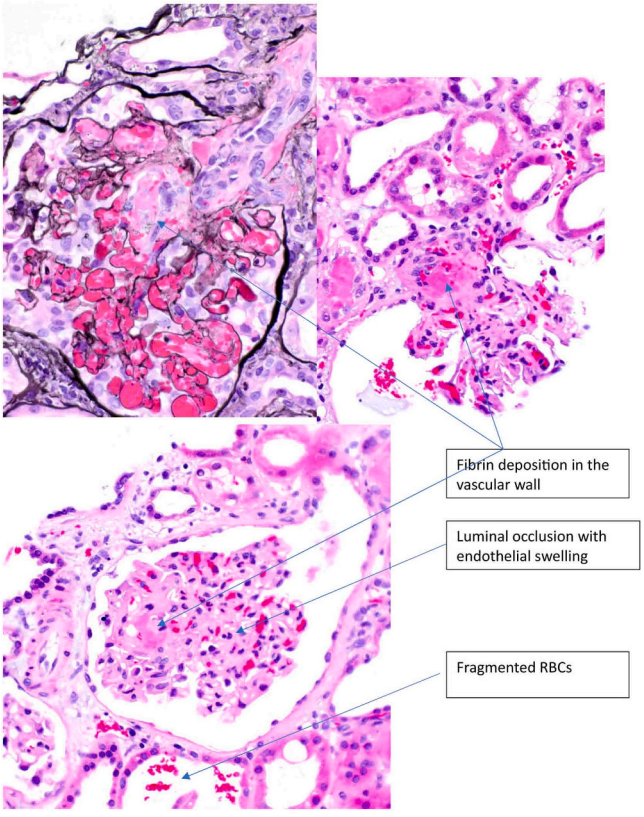

Fig. 1. There is arteriolar hyalinosis, fibrin thrombi, luminal closure, and red blood cells fragmentation.

initial presentation creatinine was 1.89 mg/dl, urine volume 1650 ml/24 h, creatinine clearance 25 ml/min, and she was taken off HD. Ten months after the initial presentation, the patient remains off HD with a creatinine 2.3 mg/dl (stage 4 CKD), and chronic thrombocytopenia on ongoing maintenance IVIG treatment.

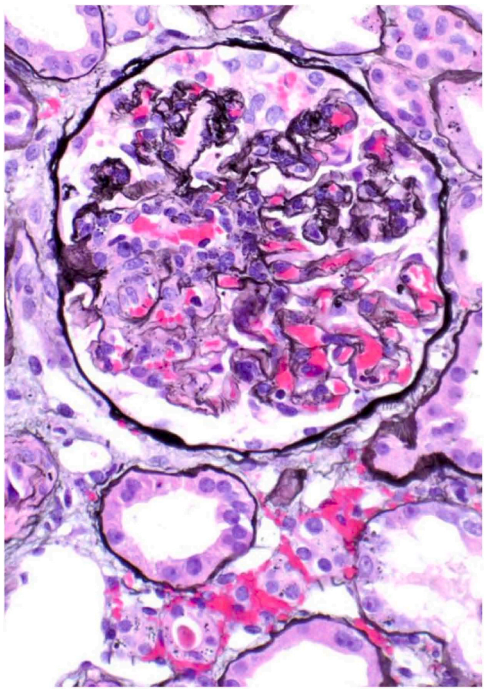

Fig. 2. The glomerulus shows congestion and ischemic changes, including contraction of glomerular capillary tuft and red blood cell fragmentation. There is no endocapillary hypercellularity or crescent formation.

Discussion

There are four reports of eltrombopag-associated AKI, one was renal limited TMA, two presented with AKI and NS, and another in a patient with antiphospholipid syndrome [3–6].

Bali et al. reported a case of AKI and biopsy-proven TMA in a 64-year-old woman with chronic ITP after ten weeks of treatment with eltrombopag [3]. She was started on HD and corticosteroids. Treatment with eltrombopag was discontinued. ADAMTS13 was normal. She received TPE daily for 5 days, then on alternate days for 2 weeks. After 2

weeks TPE and HD were discontinued, and her creatinine improved to 2.15 mg/dl.

Ghosh et al. reported a case of AKI and NS in a 77-year-old man with chronic ITP six weeks after initiating treatment with eltrombopag [4]. A renal biopsy was not done. The patient was started on high-dose prednisolone. By week 24, his creatinine went back to baseline, NS went into remission, and he was weaned off prednisolone.

Teng et al. reported a case of biopsy proven focal segmental glomerulosclerosis (FSGS), NS, and AKI in a 46-year-old woman after receiving seven doses of eltrombopag [5]. The patient required HD which was discontinued after 44 days.

Sperati et al. reported a case of AKI associated with eltrombopag in a 54-year-old man with antiphospholipid syndrome [6]. His renal function returned to baseline after cessation of treatment with eltrombopag. He did not develop NS. A renal biopsy was not done.

In our case, Naranjo adverse drug reaction probability scale showed a score of 7 or a probable relationship between eltrombopag and TMA [7]. A negative test for drug-dependent antibody does not exclude the drug as a potential trigger for TMA [8]. Causation cannot be proven in our case or in the other four ones. None of the above four cases tested for drug-dependent antibody, and only two did a kidney biopsy of which only one showed TMA.

The kidney biopsy in this patient confirmed the diagnosis of TMA. It is not required in every case of DITMA; however, the presence of nephrotic range proteinuria made a stronger case for performing a diagnostic renal biopsy.

Our case is unique because TMA occurred in a patient with existing thrombocytopenia due to ITP. The patient had the classic pentad for TMA (thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological manifestations, and AKI). TMA was seen on the kidney biopsy, and drug-dependent antibody testing was done.

Drug-induced TMA (DITMA) due to an immune reaction is uncommon, idiosyncratic, and is not dose-dependent. This form of TMA is diagnostically challenging because diagnostic laboratory tests require a specialized laboratory [9]. One must exclude other causes of TMA including ADAMTS13 deficiency. In our case Versiti Blood Center of Wisconsin did not identify eltrombopag-dependent, platelet-reactive antibodies in this patient. Lack of antibody does not indicate the safety of the suspected drug [8]. Given the severity of the presentation, reintroduction of eltrombopag will be completely avoided in this patient. In this patient, other causes of TMA were excluded based on the laboratory testing described above.

Drug-dependent antibodies may exist in the body due to a prior sensitization. The classic example is quinine-dependent antibodies resulting in TMA due to activation of endothelial cells. The drug-dependent antibodies can only bind their intended target (such as endothelial cells, platelets, or neutrophils), when the offending drug is present [8]. This may trigger thrombi formation. Symptoms onset is sudden and severe usually resulting in AKI. Neurological, gastrointestinal, and cardiac manifestations are characteristic as well. Patients have negative direct antiglobulin test; normal PT, aPTT, and ADAMTS13 activity (>20 %).

Many drugs have been implicated in DITMA, but sufficient evidence exists regarding quinine, gemcitabine, sulfisoxazole, trimethoprim-sulfamethoxazole, oxaliplatin, adalimumab, and quetiapine [10]. Although the mainstay of treatment is drug withdrawal and supportive care, therapeutic TPE was performed in this case due to initial uncertainty of the diagnosis, and the severity of the presentation. This is often the case in DITMA. Immunosuppressive medications are not indicated; however, corticosteroids are often used until the diagnosis is ascertained. Hypertension, chronic kidney disease (CKD), and end-stage kidney disease (ESKD) are known sequelae for DITMA [10].

Conclusion

The optimal management for drug-induced TMA is unclear. Current recommendations are based on a limited number of heterogeneous case reports. More research is needed in this area. Drug cessation, supportive care, corticosteroids, TPE, and renal replacement therapy are considerations in the management drug-induced TMA. A diagnostic kidney biopsy and testing for drug-dependent antibodies may aid the diagnosis. All the above should be considered on a case-by-case basis and is left to the best judgement of the treating clinicians.

CRediT authorship contribution statement

Mohammad Tinawi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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