



Immune Thrombotic Microangiopathy: An Unusual Complication of Novel Anticancer Therapy

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Abstract

Keywords

- acquired TTP
- oncology
- plasmapheresis
- thrombotic microangiopathy
- trastuzumab-emtansine

Thrombotic microangiopathy (TMA) and thrombotic thrombocytopenic purpura (TTP) are rare potentially life-threatening complications in the oncology setting. The rapid approval of new drugs in oncology brings challenges since these can cause TMA/TTP by unexpected mechanisms. Additionally, confounding factors in oncology patients like sepsis and coagulopathy make recognition of TMA difficult.

Trastuzumab–emtansine (TDM1) is a HER2-targeted antibody–drug conjugate. The antibody is the anti-HER2 IgG1 trastuzumab, and the cytotoxin emtansine (DM1) is a microtubule inhibitor. TTP has not been reported with TDM1 therapy previously. Here, we discuss a patient with breast cancer who developed immune-mediated TMA/acquired TTP after her therapy was switched from trastuzumab to TDM1 and was treated successfully with plasmapheresis and rituximab.

Brief Report

Our patient was diagnosed with locally advanced invasive ductal carcinoma left breast (estrogen and progesterone receptor negative, HER2/neu over-expressed). Treatment was started with four cycles of neoadjuvant chemotherapy (paclitaxel–carboplatin–trastuzumab), followed by modified radical mastectomy for poor disease response. After surgery, four cycles of chemotherapy (epirubicin–cyclophosphamide) were delivered concomitantly with trastuzumab and pertuzumab, followed by radiation therapy to the left chest wall and axilla (45 Gy). While the patient was continuing trastuzumab + pertuzumab every 3 weeks, a follow-up positron emission tomography/computed tomography revealed pulmonary metastases. The subsequent therapeutic line consisted of 3-weekly TDM1 (trastuzumab–emtansine).

Progressively worsening anemia (Hb 8.9 g/dL) and thrombocytopenia (platelet count $38 \times 10^9/\mu\text{L}$) were identified prior to the 11th cycle of TDM1. Further investigations showed reticulocytosis, increased indirect bilirubin

and lactate dehydrogenase (LDH), low serum haptoglobin (0.08 g/L), and 2.8% schistocytes on peripheral smear. There were no neurological signs, renal dysfunction, or fever. Bone marrow aspirate and biopsy, Coombs test, and fibrinogen were normal. Screening for connective tissue disorders was unremarkable, and viral serologies (human immunodeficiency virus, hepatitis viruses, cytomegalovirus) were negative. ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) level was requested and plasma exchange (PEX) and methyl prednisone were started based on high probability of thrombotic microangiopathy (TMA). This led to a notable improvement in platelet count and hemoglobin level after four sessions, and PEX was discontinued after a week (**► Fig. 1**). Meanwhile, lab results revealed a very low ADAMTS-13 activity (<0.01 IU/mL) with normal antigen level. Inhibitory antibody to ADAMTS-13 was detected (39.9 U/mL). A provisional diagnosis of acquired thrombotic thrombocytopenic purpura (TTP) was made (likely TDM1-induced in the absence of any other identifiable etiology).

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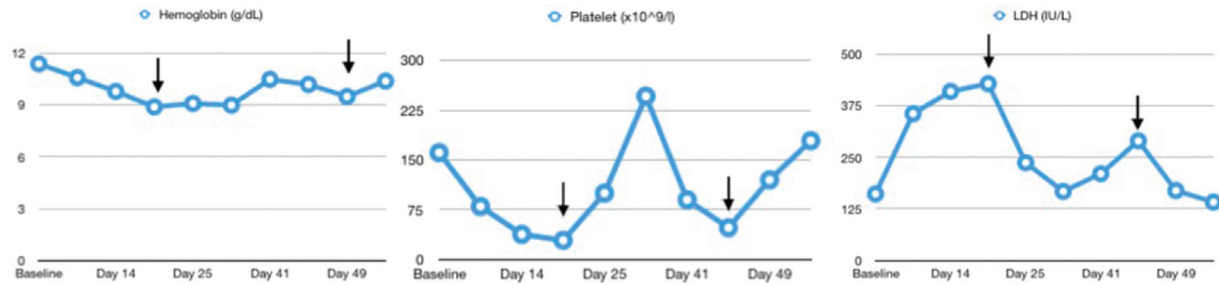


Fig. 1 Time course of hemoglobin, platelet, and LDH (at initial presentation and at recurrence). The two arrows indicate times of initiation of PEX. LDH, lactate dehydrogenase; PEX, plasma exchange.

While on follow-up, features of TTP reappeared within 3 weeks in the form of thrombocytopenia, anemia, and rising LDH. PEX was resumed, resulting in rapid hematological response within three sessions (►Fig. 1). In view of recurrence, it was decided to add rituximab while PEX was being tapered. ADAMTS-13 and haptoglobin levels normalized after 2 weeks of PEX, and to prevent future recurrence of TTP, maintenance rituximab was delivered at 2-monthly intervals for three doses. From an oncological perspective, it was decided not to expose the patient to TDM1 anymore, and a new line of treatment incorporating trastuzumab and vinorelbine was initiated, which she tolerated well.

Discussion

The hallmark of TMA is microangiopathic hemolytic anemia and thrombocytopenia; our patient had a subtype of TMA resembling acquired TTP, as immune-mediated mechanisms involving antibodies against ADAMTS-13 were involved in the pathogenesis. Acute renal failure, fever, and neurological involvement can be associated but are not required for diagnosis. As seen in our patient, the presentation can be subtle and mimic chemo-toxicity. Oncology patients develop anemia, thrombocytopenia, and renal dysfunction due to myriad reasons (sepsis, disseminated intravascular coagulation, chemo-toxicity, etc.). Consequently, a high level of suspicion is needed for diagnosis.¹

Many mechanisms of TMA have been described with anticancer drugs. Immune-mediated TMA or acquired TTP can arise due to development of antibodies against ADAMTS-13 (which cleaves von Willebrand factor multimers), resulting in microthrombi formation and endothelial damage.¹ TMA in this scenario usually occurs in a delayed manner (as was seen in our patient), the median time being 8 months after initiating the agent. Another mechanism involves direct endothelial toxicity, which can occur within days after initiation of the drug or in a dose-dependent manner with slower progression of hemolysis and renal dysfunction.¹ Drugs that interfere with endothelial homeostasis, like vascular endothelial growth factor inhibitors or tyrosine kinase inhibitors, have been reported to cause TMA.² Likewise, drugs containing monoclonal immu-

noglobulins may act as TMA triggers through direct injury to endothelial cells or indirect mechanisms like auto-antibody production.² Sudden onset of symptoms or rapid recurrence, as seen in our patient, should prompt consideration of an immune mechanism. Trastuzumab (in combination with docetaxel) has been implicated in TMA in case reports, where it is not possible to attribute the TMA specifically to trastuzumab.^{3–5} Our patient was on trastuzumab for a year, and TMA occurred only after she was switched to TDM1. Moreover, she did not develop recurrence of TMA after re-challenge with trastuzumab, suggesting that the cytotoxic emtansine component was the likely culprit here.

Management of chemotherapy-induced TMA is complex, since mechanisms differ or are often unknown with newer drugs. Only a subset of patients with TMA has immunological mechanisms, which can respond to plasmapheresis and rituximab.¹ Discontinuation of the precipitating drug and screening for ADAMTS-13 is important. In many centers, there is often a delay before ADAMTS-13 levels are available; hence, the initial treatment should be a trial of PEX, as this is a hematological emergency with high mortality if untreated. The optimal duration of rituximab therapy in drug-induced TTP and the optimal treatment strategy in non-immune-mediated TMA are unknown and are potential areas for further research.

Conclusion

Clinicians should be aware that TMA may be a complication of newer anticancer therapy. Mild anemia and thrombocytopenia may be the only clue to diagnosis, and peripheral blood film screening for microangiopathic hemolysis is an important aid in diagnosis. Early initiation of treatment and discontinuation of the incriminated drug can improve outcomes and decrease long-term morbidity.

Novelty Statement

1. What is the new aspect of your work?

This is the first report of immune-mediated thrombotic microangiopathy (TMA) in association with trastuzumab–emtansine (TDM1) therapy and is a pointer to the unusual side effects of newer anticancer drugs.

2. What is the central finding of your work?

Trastuzumab-emptansine can cause immune-TMA through anti-ADAMTS-13 antibodies, which respond well to plasmapheresis and rituximab. Since only a minority of cancer-associated TMA is immune-mediated, ADAMTS-13 testing is crucial to identify the subset of patients who can respond to plasmapheresis and rituximab.

3. What is the specific clinical relevance of your work?

Novel anticancer agents can cause TMA by unexpected mechanisms. Since there are many confounding factors in oncology patients (like anemia, thrombocytopenia, and renal dysfunction from other causes), a high threshold of suspicion is needed for diagnosis. Delay in diagnosis and treatment can increase the morbidity and mortality associated with this potentially fatal condition.

Authors' Contributions

S.P.M. and T.Y. wrote the manuscript; L.K.A. and S.M.A. provided valuable inputs and reviewed the manuscript. All the authors have approved the manuscript and consented to its publication.

Patient Consent

Patient consent was obtained.

Conflict of interest

None declared.

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