International Journal of Advances in Medicine
Kandari S et al. Int J Adv Med. 2025 May;12(3):308-310
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20251081

Case Report

A case report of thrombotic microangiopathy in a patient with advanced pancreatic carcinoma: an emerging, rare, and serious complication

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Received: 27 January 2025
Accepted: 10 March 2025

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ABSTRACT

Thrombotic microangiopathies are characterized by microangiopathic hemolytic anemia and end-organ damage following endothelial injury. The chemotherapeutic agents used in malignancy are one of the important causes of secondary TMA. Both malignancy and TMA are associated with significant morbidity and mortality. Timely recognition of both can result in early target-specific treatment initiation and better outcomes for both diseases. Here, we present a case of TMA in a patient with stage 4 pancreatic carcinoma being treated with Gemcitabine presented with acute kidney disease with new-onset hypertension, edematous illness, and anemia. The patient was Hemodialysis dependent and was treated with steroids, plasma exchange, and rituximab. The patient remained HD dependent 6 months post-treatment and was declared ESRD. Highlighting the importance of early recognition and timely treatment initiation.

Keywords: Thrombotic microangiopathy, Gemcitabine induced-TMA, Acute kidney disease, Plasmapheresis, Chemotherapy-associated complication

INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinic-pathologic diagnosis following endothelial injury, characterized by the triad of thrombocytopenia, microangiopathic hemolytic anemia, and end-organ damage. Its etiopathogenesis and clinical manifestations are diverse, the most common being acute kidney injury (AKI).

Broadly, TMAs are divided into two types primary and secondary. Secondary TMAs are more prevalent, 94%, out of which malignancies and drugs constitute a significant proportion, 19% and 26%, respectively.[2] Malignancies associated with TMA are mostly adenocarcinomas and hematological malignancies. Drugs-induced TMA (Di-TMA) is commonly seen with ticlopidine, sunitinib, bevacizumab, mitomycin, and Gemcitabine (G-TMA).[3] It is challenging to differentiate TMA as a direct effect of malignancy or chemotherapy-related clinically.

CASE REPORT

A 54-year-old male diagnosed with BRCA 2 positive pancreatic adenocarcinoma with liver and lymph node metastasis was started on chemotherapy with Paclitaxel and Gemcitabine and was being followed up in the oncology unit. Family history was positive for adenocarcinoma breast in the younger sister and adenocarcinoma lung in the mother. After six months of treatment, the patient had a complete resolution of liver metastasis on PET-CT.

During that time, the baseline renal functions were normal. Following the seventh cycle of the same chemotherapeutic agents, the patient developed nausea, vomiting, and loss of appetite, followed by edematous illness and decreased urine output. The patient had these symptoms for 2 weeks, which she initially thought likely to be chemotherapy-related. However, suddenly, at night, the patient had

shortness of breath more on lying, for which the patient consulted a local physician, where she was found to have grade 2 systemic hypertension, pallor, grade 3 bilateral pitting edema with a serum creatinine of 5.2 mg/dl with severe metabolic acidosis. Urine routine examination was positive for RBC cast and grade 2 proteinuria. A lung grey scan was indicative of a bilateral B profile. Bilateral kidneys were of normal size with raised preserved CMD and normal echogenicity.

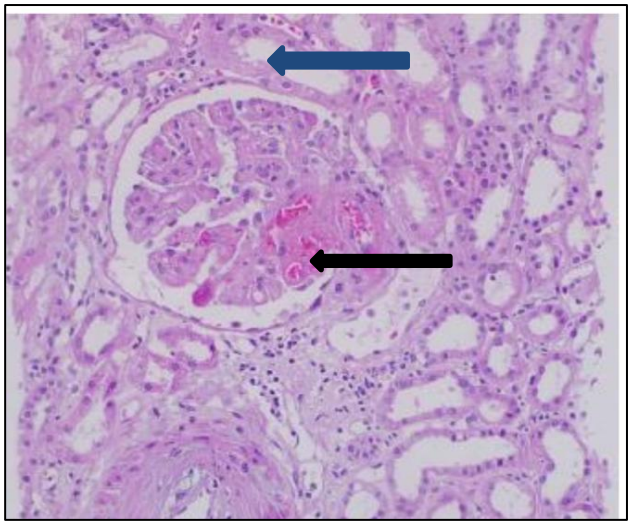

Figure 1: The biopsy revealed one glomerulus showing mesangiolysis and ischemic changes. Intracapillary thrombi were identified, while no crescents or tuft necrosis were observed. The tubules showed cytoplasmic vacuolar changes (Blue arrow) and minimal tubular atrophy and interstitial fibrosis. A few arteries and arterioles displayed luminal thrombotic occlusion (Black arrow) in the vascular compartment, consistent with thrombotic microangiopathy (TMA).

A possibility of acute kidney disease was kept, and urgent Hemodialysis was initiated. During admission, the patient was anuric and had worsening anemia and thrombocytopenia (platelet count was normal at presentation), normal C3 and C4 complements, low haptoglobin, raised LDH and reticulocytosis with schistocytes in PBF. The PLASMIC score was less than 4, with no neurological symptoms. Still, the patient was advised for ADAMTS13, but it could not be done due to affordability issues. The possibility of thrombotic microangiopathy was kept, and differentials were discussed based on the clinical status and investigations.

The patients' cumulative Gemcitabine dose was 38 grams, with a relatively low tumor burden; provisionally, a diagnosis of Gemcitabine-induced TMA (Gi-TMA) was kept. Tumor-induced TMA (Ti-TMA) was kept as a close differential. The points against Ti-TMA diagnosis were the low tumor burden, the absence of a global thrombotic phenomenon, and the patient was on an improving trend post-chemotherapy. The patient was started on high-dose steroids and plasma exchange (PLEX). The renal biopsy indicated ischemic changes, including mesangiolysis, wrinklings, and secondary sclerosis of capillary tufts with Intra-capillary thrombi with vessel wall fibrinoid necrosis and luminal thrombotic occlusion. Following steroids and PLEX, the patient had transient improvement in thrombocytopenia, improving LDH and decreasing reticulocytosis.

However, the patient was still anuric and HD dependent. As the culprit drug was stopped already and due to the non-availability of drug-dependent antibodies for Gemcitabine, the possibility of immune complex-mediated endothelial damage cannot be ruled out. The patient was given a trial of rituximab 375 mg/m^2 for 2 doses at 2 weeks apart. A tunneled HD catheter was placed in the right IJV, and HD was continued through the same. On regular follow-up visits, the patient had persistently advanced creatinimia and no improvement in urine output and was still HD dependent. The patient was declared ESRD.

DISCUSSION

The term TMA was first introduced in 1952 by Symmers for the systemic vascular lesions seen in thrombotic thrombocytopenic purpura (TTP) and later on the hemolytic uremic syndrome.[4] Gemcitabine is one of the most commonly reported drugs causing TMA, with an incidence of 0.25-0.4% of patients receiving the drug, and it is dose-dependent. However, the first case of G-TMA was noted in 1994 during its phase 2 trials for pancreatic cancers. However, the clinical presentation is quite variable but mostly progressive and fatal even after discontinuation of the drug. With the ongoing uptrend of target cancer agent use, TMA is an emerging and potentially serious complication.[5]

Pathogenesis is bimodal, as immune and non-immune mechanisms play a role in endothelial damage, causing widespread thrombus/fibrin formation, platelet aggregation, and end-organ damage. Non-immune mechanisms include direct endothelial damage and loss of vascular endothelial-derived growth factor (VEGF) support by using anti-VEGF drugs like sunitinib and bevacizumab.[6,7]

In our case, the patient had already received a cumulative dose of 38 grams over 7 months, and 2 weeks following the last dose, the patient started having symptoms of nausea, vomiting, and decreased urine output. This usually is the most common timeline seen in G-TMA.[5] However, the patient and his treating physician thought this to be chemotherapy-related until he had shortness of breath and advanced creatininemia, following which he consulted a nephrologist, and this time delay could have caused loss of renal tissue. The patient was worked up, and a possibility of TMA was kept and treatment initiated.

However, the patient never recovered from his illness following PLEX. In contrast, in the case reported by

Murugapandian et al, the patient had a partial renal recovery with the use of rituximab following plasma exchange in a patient with ovarian carcinoma presenting with G-TMA. However, late response to plasma exchange could also not be ruled.[8] Mild forms of G-TMA in advanced pancreatic carcinoma with complete remission following withdrawal of Gemcitabine only without any plasma exchange or rituximab have been documented in some case series.[9]

CONCLUSION

Targeted chemotherapeutic regimens are being used more in clinical practice. The rising incidence of the associated chemotherapeutic side effects must also be considered. Keeping vigilance for them always on every clinical visit, especially renal involvement in the form of TMA, which contributes to both morbidity and mortality in the longer run. Even after a timely diagnosis, the patient's prognosis can vary.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kandari S, Singh A, Puri R, Cheriyan A, Kaur S. A case report of thrombotic microangiopathy in a patient with advanced pancreatic carcinoma: an emerging, rare, and serious complication. Int J Adv Med 2025;12:308-10.