

Gemcitabine-Induced Thrombotic Microangiopathy: A Case Report

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Abstract

Case Report

We report the case of a 69-year-old woman with metastatic lung adenocarcinoma who developed severe thrombotic microangiopathy (TMA) only seven days after receiving her first dose of gemcitabine. The patient had pre-existing stage 3a chronic kidney disease and previous exposure to bevacizumab, which may have increased her susceptibility to endothelial injury. She presented with profound thrombocytopenia, hemolytic anemia, severe acute kidney injury, proteinuria, and microscopic hematuria. Although the schistocyte count was below the conventional diagnostic threshold, elevated lactate dehydrogenase, markedly decreased haptoglobin, and a negative Coombs test supported the diagnosis of microangiopathic hemolysis. Thrombotic thrombocytopenic purpura was excluded by a normal ADAMTS13 activity level, while complement investigations were unremarkable. Renal biopsy confirmed TMA with characteristic glomerular and arteriolar lesions, supporting gemcitabine-induced TMA after exclusion of alternative causes. Gemcitabine was immediately and permanently discontinued, and the patient was managed with hemodialysis without plasma exchange or complement-targeted therapy, resulting in a favorable clinical and renal outcome. This case highlights the exceptionally early onset of gemcitabine-induced TMA, demonstrating that this complication can occur after the first administration and is not necessarily related to cumulative drug exposure. It also emphasizes that significant schistocytosis may be absent and should not exclude the diagnosis when other clinical and laboratory findings are suggestive. Early recognition, prompt withdrawal of gemcitabine, and appropriate supportive treatment remain essential to improving outcomes.

Keywords: Gemcitabine-induced thrombotic microangiopathy, acute kidney injury, chronic kidney disease, microangiopathic hemolytic anemia, thrombocytopenia, drug-induced nephrotoxicity, endothelial dysfunction, renal biopsy, hemodialysis, bevacizumab exposure.

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INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinicobiological syndrome characterized by mechanical hemolytic anemia, consumptive thrombocytopenia, and thrombotic microangiopathic lesions affecting the microcirculation of various organs, particularly the kidneys and central nervous system. Histologically, it is characterized by the formation of fibrin-platelet thrombi within capillaries and arterioles, resulting in tissue ischemia.

Among drug-related etiologies, gemcitabine is a major causative agent. As a deoxycytidine nucleoside analogue, it is widely used in the treatment of non-small cell lung cancer, pancreatic cancer, bladder cancer, and breast cancer. Its cumulative nephrotoxicity may manifest as TMA, a complication first described in 1994, whose actual incidence remains underestimated and ranges from 0.015% to 1.4% across different series [1].

The risk may be increased in patients with pre-existing chronic kidney disease (CKD), cardiovascular comorbidities, or previous exposure to nephrotoxic chemotherapy. The underlying pathogenic mechanisms involve endothelial dysfunction, abnormal platelet activation, and complement dysregulation, ultimately leading to intravascular microthrombus formation.

We report the case of a 69-year-old woman who developed severe TMA after her very first course of gemcitabine, in the setting of an underlying oncological condition associated with increased vulnerability and pre-existing CKD. We also discuss the pathophysiological mechanisms, diagnostic criteria, and current therapeutic approaches in light of the available literature.

CASE PRESENTATION

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A 69-year-old woman was being followed for metastatic lung adenocarcinoma with bone involvement, diagnosed six months earlier. She had initially received six cycles of chemotherapy consisting of pemetrexed at a dose of 700 mg per cycle and bevacizumab. Her clinical course was complicated by stage 3a CKD, with a baseline estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m² according to the MDRD equation.

One month after her last chemotherapy cycle, the patient developed tumor progression, characterized by an increase in both the size and number of metastatic lesions. In response to this progression, second-line palliative chemotherapy with gemcitabine was initiated at a dose of 1,400 mg.

Seven days after administration of this first cycle, when the patient presented for her second cycle, she exhibited clinical deterioration with fever, fatigue, and dyspnea, suggesting a pulmonary infectious syndrome. Laboratory investigations revealed severe leukopenia, with a white blood cell count of 50/mm³, normochromic normocytic anemia with a hemoglobin level of 6.4 g/dL, and thrombocytopenia with a platelet count of 5,000/mm³.

Inflammatory markers were markedly elevated, with a C-reactive protein (CRP) level of 400 mg/L and a procalcitonin level of 2.6 ng/mL, indicating a high risk of sepsis. Transaminase levels were mildly elevated, whereas serological tests for viral hepatitis and human immunodeficiency virus (HIV) were negative. Urinalysis revealed proteinuria of 1 g/24 h and microscopic hematuria, without leukocyturia.

Hematological and biochemical investigations also demonstrated elevated lactate dehydrogenase (LDH) levels of 1,501 IU/L, a markedly decreased haptoglobin level of less than 0.01 g/L, and a negative direct antiglobulin test (Coombs test). Peripheral blood smear examination revealed fewer than 1.5% schistocytes.

Renal function was severely impaired, with a serum creatinine level of 69 mg/L, corresponding to an estimated GFR of 7.6 mL/min/1.73 m² according to the MDRD equation. These findings were suggestive of thrombotic microangiopathy.

Given the diagnosis of TMA associated with neurological involvement, thrombotic thrombocytopenic purpura (TTP) was initially ruled out by an ADAMTS13 activity level of 121%. Complement investigations, including C3, C4, CH50, factors I and H, membrane cofactor protein (MCP), and anti-factor H antibodies, were within normal limits. The clinical presentation was consistent with probable gemcitabine-induced TMA in the context of a severe pulmonary infectious syndrome.

A kidney biopsy was performed and confirmed the presence of thrombotic microangiopathy, with characteristic lesions affecting the glomerular microvasculature. Ultimately, a drug-induced etiology related to gemcitabine was established.

Gemcitabine was immediately discontinued. The patient's clinical course was favorable under hemodialysis, with progressive improvement in serum creatinine levels and no need for plasma exchange or monoclonal antibody therapy.

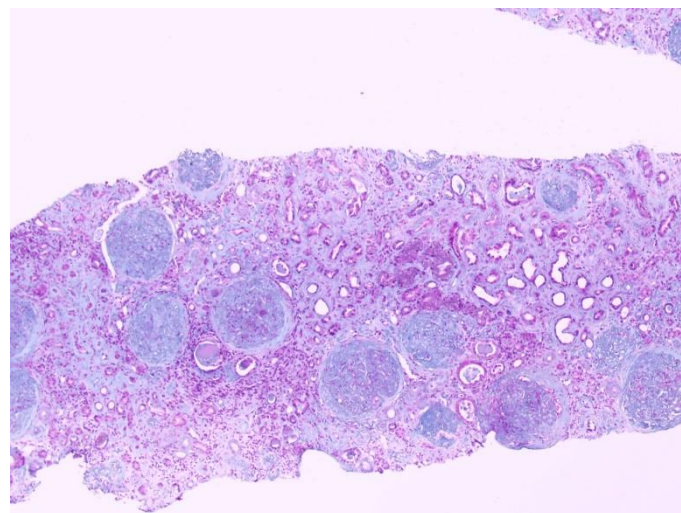


Figure 1: Masson's trichrome staining at low magnification showing thrombosed blood vessels associated with tubular atrophy

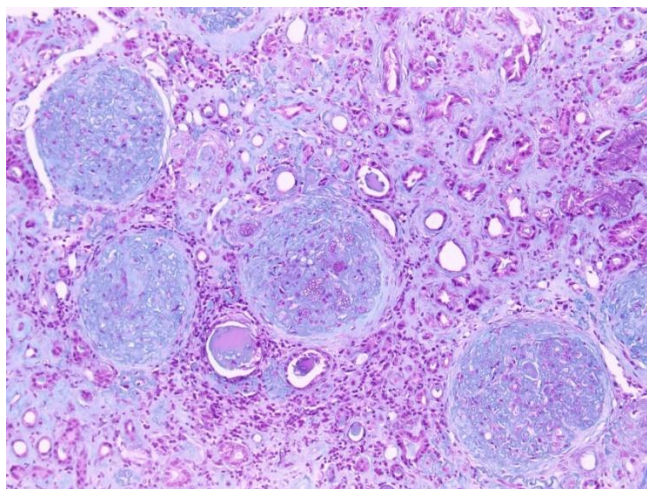


Figure 2: Thrombotic microangiopathy showing vascular luminal obliteration

DISCUSSION

The most distinctive feature of our case is the occurrence of TMA as early as seven days after the first and only administration of gemcitabine, at a dose of 1,400 mg. This is an exceptionally short interval compared with the available literature. In the French cohort reported by Daviet *et al.*, [2], the median time to onset was 210 days, with a median cumulative dose of 12,941 mg/m². Similarly, the Japanese pharmacovigilance analysis conducted by Takigawa *et al.*, [3] reported a median time to onset of 161 days, with most cases occurring between five and eight months after treatment initiation.

This discrepancy may be explained by the pathophysiological classification of drug-induced TMA, which traditionally distinguishes between dose-dependent, cumulative toxicity, most frequently reported with gemcitabine, and an immunologically mediated idiosyncratic reaction that may occur after the first few exposures, irrespective of the administered dose [4]. Furthermore, the Weibull shape parameter analysis performed by the same investigators [3] demonstrated that gemcitabine-induced TMA does not necessarily follow a dose-dependent pattern. This finding is consistent with the hypothesis of an early-onset mechanism in our patient.

Two patient-specific vulnerability factors may also account for this early presentation. First, pre-existing CKD, with an eGFR of 45 mL/min/1.73 m² according to the MDRD equation, represented an underlying condition of renal vulnerability. Gemcitabine-induced TMA predominantly manifests as renal involvement in the vast majority of cases. Second, previous exposure to bevacizumab may have played an important role. Anti-VEGF therapies exert direct endothelial toxicity by persistently inhibiting circulating VEGF, which is essential for maintaining the integrity of the fenestrated glomerular endothelium. This previous exposure may have lowered the patient's threshold for subsequent gemcitabine-induced endothelial injury,

suggesting a potential toxic interaction between antiangiogenic agents and cytotoxic drugs, as described in the literature on cancer-associated TMA.

From a laboratory standpoint, the patient exhibited the cardinal features of TMA, with severe renal impairment (eGFR of 7.6 mL/min/1.73 m²), proteinuria, and microscopic hematuria. However, the schistocyte count was low (<1.5%), below the threshold generally considered diagnostically significant [5]. This illustrates a well-recognized diagnostic challenge, as chemotherapy-induced hematological abnormalities, particularly leukopenia and thrombocytopenia, may obscure or attenuate the typical manifestations of mechanical hemolysis.

Bertin *et al.*, [6] reported a similar case, with a schistocyte count of only 1.5% despite undetectable haptoglobin levels and severe biopsy-confirmed renal impairment. This observation highlights that a schistocyte count below the conventional threshold should not lead to the exclusion of TMA when the overall clinical and laboratory presentation remains strongly suggestive.

The diagnostic approach relied on the sequential exclusion of the main differential diagnoses. TTP was definitively ruled out by a normal ADAMTS13 activity level of 121%. This test must be performed urgently because patients presenting with thrombocytopenia associated with microangiopathy are often treated empirically with plasma exchange while awaiting the results.

Atypical hemolytic uremic syndrome was considered unlikely given the entirely normal complement assessment, including C3, C4, CH50, factors I and H, MCP, and anti-factor H antibodies. Although secondary activation of the alternative complement pathway, with excessive formation of the membrane attack complex, has been described in some cases of gemcitabine-induced TMA [7], the absence of abnormalities in complement regulatory proteins in our

patient is consistent with direct endothelial toxicity rather than constitutional complement dysregulation.

The kidney biopsy confirmed the diagnosis, demonstrating thickening of the glomerular capillary walls, duplication of the glomerular basement membranes, arteriolar fibrinoid necrosis, and intraluminal thrombi. The biopsy was particularly valuable because the low schistocyte count and concomitant infectious syndrome could otherwise have led to the misdiagnosis of a purely sepsis-related complication of chemotherapy.

Management was primarily based on the immediate and permanent discontinuation of gemcitabine, which is universally regarded as the cornerstone of treatment. Unlike TTP, gemcitabine-induced TMA responds inconsistently to plasma exchange; therefore, routine plasma exchange is not recommended in the absence of clinical suspicion of TTP.

The favorable outcome observed in our patient with hemodialysis alone, without plasma exchange or monoclonal antibody therapy, contrasts with the generally poor prognosis associated with this complication. In the French cohort reported by Daviet *et al.*, [2], complete remission was achieved in only 42.1% of cases, while 54.7% of patients died. The favorable outcome in our patient may be attributable to early diagnosis and immediate withdrawal of the causative drug, before the development of irreversible endothelial injury.

Several alternative therapeutic strategies have been proposed for refractory cases. Rituximab, whose efficacy has been reported in certain cases resistant to plasma exchange, has been used in selected patients; however, its mechanism of action in this setting remains hypothetical [8].

Eculizumab, a terminal complement inhibitor, has also been proposed for selected refractory cases, particularly when complement activation is suspected or documented. Van den Eeckhaut *et al.*, [9] reported that, following failure of gemcitabine withdrawal, corticosteroid therapy, and plasma exchange, eculizumab enabled transfusions to be discontinued within one week and dialysis to be stopped within one month.

In our patient, the absence of any complement abnormalities did not support the use of this treatment. The spontaneous favorable outcome with renal replacement therapy alone underscores the importance of early withdrawal of the causative drug and supportive care in the management of this complication.

CONCLUSION

This case illustrates an exceptionally early presentation of gemcitabine-induced TMA, occurring after the first treatment cycle in a patient with specific vulnerability factors, including pre-existing CKD and previous exposure to bevacizumab. It suggests that this complication does not necessarily follow a strictly cumulative dose-dependent pattern and may occur unpredictably after the first administrations.

Whenever acute kidney injury, hemolytic anemia, and thrombocytopenia occur in a patient receiving gemcitabine, TMA should be suspected without delay, even in the absence of marked schistocytosis.

Kidney biopsy remains an important diagnostic tool in atypical presentations, allowing histological confirmation and exclusion of alternative diagnoses.

Finally, the favorable outcome achieved with supportive care alone emphasizes that early diagnosis and immediate discontinuation of treatment remain the key determinants of prognosis. These findings also highlight the need to strengthen routine laboratory monitoring in all patients receiving gemcitabine, particularly those with multiple cumulative risk factors.

REFERENCES

- Lai-Tiong F, Duval Y, Krabansky F. Gemcitabine-associated thrombotic microangiopathy in a patient with lung cancer: a case report. *Oncol Lett*. 2017;13(3):1201–1203.
- Daviet F, Rouby F, Poullin P, Moussi-Franès J, Sallée M, Burtey S, *et al.*, Thrombotic microangiopathy associated with gemcitabine use: presentation and outcome in a national French retrospective cohort. *Br J Clin Pharmacol*. 2019;85(2):403–412.
- Takigawa M, Tanaka H, Washiashi H, Onoda T, Ishigami A, Ishii T. Time to onset of gemcitabine-induced thrombotic microangiopathy in a Japanese population: a case series and large-scale pharmacovigilance analysis. *Cancer Diagn Progn*. 2023;3(1):115–123.
- Chatzikonstantinou T, Gavriilaki M, Anagnostopoulos A, Gavriilaki E. An update in drug-induced thrombotic microangiopathy. *Front Med (Lausanne)*. 2020;7:212.
- Zini G, d'Onofrio G, Briggs C, Erber W, Jou JM, Lee SH, *et al.*, International Council for Standardization in Haematology (ICSH). ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes. *Int J Lab Hematol*. 2012;34(2):107–116.
- Bertin L, Gauthier M, Boullenger F, Brocheriou I, Chevallier R, Mary F, *et al.*, Thrombotic microangiopathy after long-lasting treatment by gemcitabine: description, evolution and treatment of a rare case. *J Med Cases*. 2024;15(10):272–277.

- Grall M, Daviet F, Jourde Chiche N, Provot F, Presne C, Coindre JP, *et al.*, Eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre. *BMC Nephrol.* 2021;22:267.
- Murugapandian S, Bijin B, Mansour I, Daheshpour S, Pillai BG, Thajudeen B, Salahudeen AK. Improvement in gemcitabine-induced thrombotic microangiopathy with rituximab in a patient with ovarian cancer: mechanistic considerations. *Case Rep Nephrol Dial.* 2015;5(2):160–167.
- Van den Eeckhaut L, Hannon H, Schurgers M, Monsaert E, Claes K. Gemcitabine-induced thrombotic microangiopathy treated with eculizumab: a case report. *J Gastrointest Oncol.* 2022;13(6):3314–3320.
- Humphreys BD, Sharman JP, Henderson JM, Clark JW, Marks PW, *et al.*, Gemcitabine-associated thrombotic microangiopathy. *Cancer.* 2004;100(12):2664–2670. doi:10.1002/cncr.20290.
- Arnadottir M, Benediktsson T, Hrafnkelsson J. The cumulative incidence of gemcitabine-induced thrombotic microangiopathy. *Acta Oncol.* 2007;46(4):545–546. doi:10.1080/02841860600975268.