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Case Report

A case of gemcitabine-induced thrombotic microangiopathy in a urothelial tumor patient with a single kidney

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Abstract

Thrombotic microangiopathy (TMA) is a rare complication of gemcitabine treatment. A 55-year-old man with a history of urothelial cancer underwent right ureteronephrectomy and palliative chemotherapy. The patient presented with dyspnea, generalized edema with foamy urine, and new-onset hypertension with acute kidney injury (AKI). Although AKI with oliguria was evident, thrombocytopenia and hemolytic anemia were not overt. To determine the cause of rapidly progressive azotemia, kidney biopsy was performed despite a single kidney and revealed chronic TMA. Microangiopathic hemolytic anemia and thrombocytopenia developed after renal biopsy. Diagnosed as gemcitabine-induced TMA, gemcitabine cessation and active treatment including steroids, plasmapheresis, and rituximab were carried out, but the patient's condition progressed to a dialysis-dependent state. Gemcitabine-induced TMA is often difficult to diagnose because of its variable clinical course. Therefore, heightened awareness of this potentially lethal complication of gemcitabine is essential; renal biopsy may be helpful.

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Introduction

Gemcitabine is a nucleoside analogue of cytarabine, first approved by the US Food and Drug Administration in 1996. Its use has increased because of relatively mild complications. Currently, in combination with other chemotherapeutic agents, gemcitabine is included among first-line treatments in some adjuvant and palliative settings for non–small cell lung, ovarian, breast, and pancreatic cancers. In urothelial tumors, gemcitabine with cisplatin showed equal efficacy and less toxicity in elderly patients and currently, is a first-line regimen in advanced stages.

Thrombocytopenia and anemia are the most common complications of gemcitabine-induced myelosuppression. Mild proteinuria, microscopic hematuria, and elevated levels of blood urea nitrogen (BUN) and creatinine (Cr) can occur after gemcitabine treatment but are rarely of clinical significance. Nevertheless, gemcitabine-induced thrombotic microangiopathy (TMA) has been reported in a few cases and it can lead to persistent kidney failure with poor prognosis. The first case was reported in 1994; the currently known incidence of gemcitabine-induced TMA is 0.015–1.4% [1,2]. The combination therapies with other chemotherapeutic agents including carboplatin, cisplatin, vinorelbine, tegafur, and docetaxel may increase the risk of TMA as discussed in previous studies [3,4].

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There have been reports that gemcitabine-induced TMA occurred in patients with urothelial cancer, but none of these included a nephrectomy case [5–7]. We report the case of gemcitabine-induced TMA in a patient with a single-kidney urothelial cancer, who eventually needed kidney biopsy for diagnosis.

Case report

A 55-year-old man, who had undergone palliative chemotherapy for urothelial carcinoma, was referred to nephrology for dyspnea and generalized edema for a month. One year previously, he was diagnosed with urothelial carcinoma when he visited a clinic on account of right flank pain. He received one cycle of neoadjuvant chemotherapy with gemcitabine/cisplatin but did not continue because of elevation of the liver enzyme level. After the neoadjuvant chemotherapy, thrombocytopenia developed (92,000/mm^3), but the thrombocyte count returned to a normal level within 1 week. The final pathologic staging after right nephroureterectomy was T3Nx. Pathologic findings of the non–tumor-involved kidney tissue showed a normal glomerulus without significant tubular damage. At the time of surgery, his renal function was within the normal range. BUN and serum Cr (sCr) levels were 15 mg/dL and 1.2 mg/dL, respectively. Three months after surgery, multiple lymph node metastases were found on positron emission tomography, after completion of four cycles of palliative gemcitabine/cisplatin over 3 months. In each cycle, 35 mg/m^2 of cisplatin and 1,500 mg/m^2 of gemcitabine were injected. Cumulative doses of cisplatin and gemcitabine were 294 mg and 18,354 mg, respectively, including neoadjuvant and palliative chemotherapy.

The patient was hospitalized with dyspnea on exertion and generalized edema, developing during the final month of chemotherapy. He had gained 10 kg in 1 month and also reported foamy urine. He did not have a history of hypertension, but his blood pressure was elevated up to 164/110 mmHg. Daily urine output had decreased to less than 500 mL/day, and lower extremity pitting edema was prominent. The white blood cell count was 4,303/mm^3, the hemoglobin level was 9.1 g/dL, and the platelet count was 133,000/mm^3. BUN and sCr levels were elevated to 42 mg/dL and 3.4 mg/dL, respectively. Serologic test results were within the normal range, except for fluorescent antinuclear antibody titer positive at 1:40. Urinalysis showed 2+ albuminuria and microscopic hematuria. The spot urine protein-to-Cr ratio (g/g) was 15.32, and the albumin-to-Cr ratio (g/g) was 9.375. Shifting bilateral pleural effusions were found on chest radiography. On renal ultrasonography and abdominal computed tomography, the single left kidney measured 10.3 cm, without evidence of hydronephrosis. Interval decrease of multiple lymph node metastases was seen. On hospital day 3, hemodialysis was started because of worsening dyspnea and progressive azotemia. To differentiate the cause of rapidly progressive renal failure, we performed a kidney biopsy despite his single kidney.

After the biopsy, anemia and thrombocytopenia worsened, with a hemoglobin level of 7.9 mg/dL and a platelet count of 98,000/mm^3. Additional laboratory results were compatible with microangiopathic hemolytic anemia (MAHA), including decreased haptoglobin (8 mg/dL) and elevated plasma hemoglobin (10.5 mg/dL) levels, increased lactic acid dehydrogenase (533 IU/L) levels, and schistocytes on peripheral blood smears (Fig. 1). Ultimately, we demonstrated chronic TMA involvement of the kidney with endothelial hypercellularity and a tram-track appearance, combined with acute tubulitis from the kidney biopsy (Fig. 2).

The patient underwent steroid and rituximab therapy, with 16 sessions of plasmapheresis; however, his kidney failure did not recover, and he progressed to a dialysis-dependent state. Bone marrow biopsy was performed to check for an occult cause of refractory TMA, even after the intensive treatments, but did not show any abnormality. After 5 weeks of the treatments, thrombocytopenia began to recover, but urothelial carcinoma metastases progressed, and the patient is currently on second-line palliative chemotherapy with weekly taxol. The patient's clinical course and laboratory parameters are shown in Fig. 3.

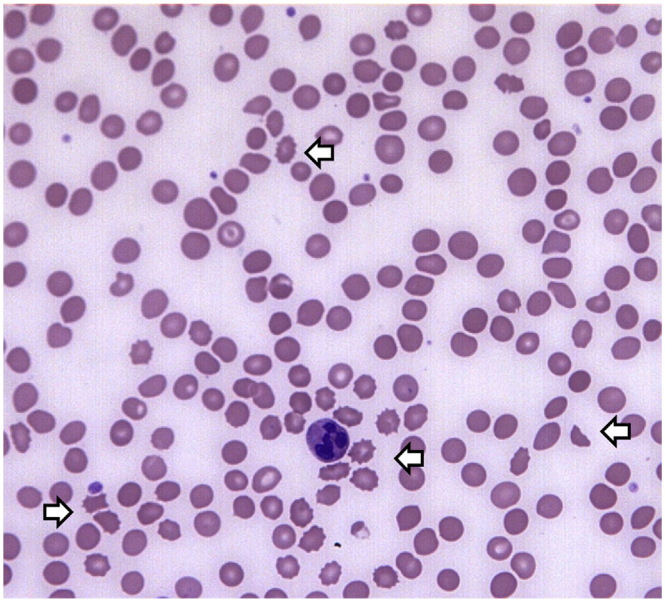

Figure 1. Peripheral blood smear. The arrows indicate schistocytes.

Discussion

TMA is a spectrum of diseases that includes thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, characterized by glomerular microvascular endothelial injury. Anemia and thrombocytopenia occur as a result of MAHA, and other organs are often injured. In the kidney, TMA appears as endocapillary cell swelling, fibrin thrombi, platelet plugs, arterial intimal fibrosis, and membranoproliferation. Many chemotherapeutic agents, including mitomycin, bleomycin, cisplatin, and 5-fluorouracil, can induce TMA, but the precise pathophysiology is unknown. Since its initial use, a few cases of gemcitabine-induced TMA have been reported.

The incidence of gemcitabine-induced TMA varies between 0.015% (based on clinical trials) and 0.41% (from a single-center study) [1,2]. Gemcitabine-induced TMA can occur at a cumulative dose of 2,450 mg/m^2 and within 3 months after the first chemotherapy cycle, but the risk of occurrence seems to increase when the cumulative dose approaches 20,000 mg/m^2 and more than 18 doses are administered [8]. Although kidney biopsy is necessary for confirmation, clinical manifestations, such as MAHA and thrombocytopenia with acute kidney injury (AKI),

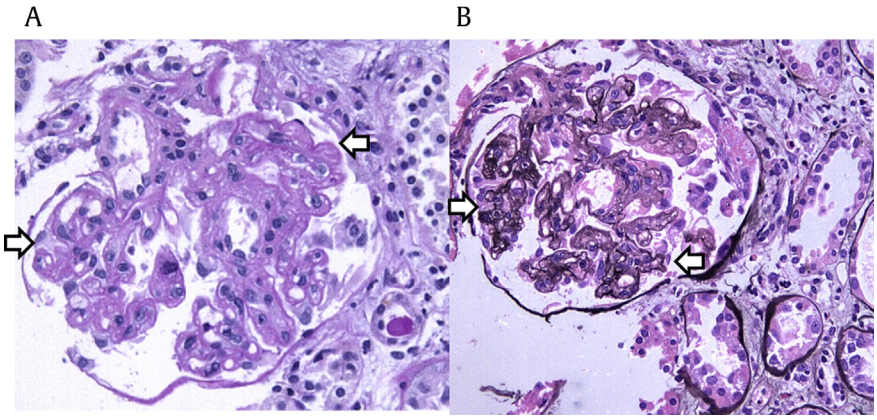

Figure 2. Light microscopy of renal biopsy. The arrows indicate endothelial hypercellularity with a tram-track appearance. Stains used were hematoxylin and eosin (A) and methenamine silver (B), with 400× magnification for both.

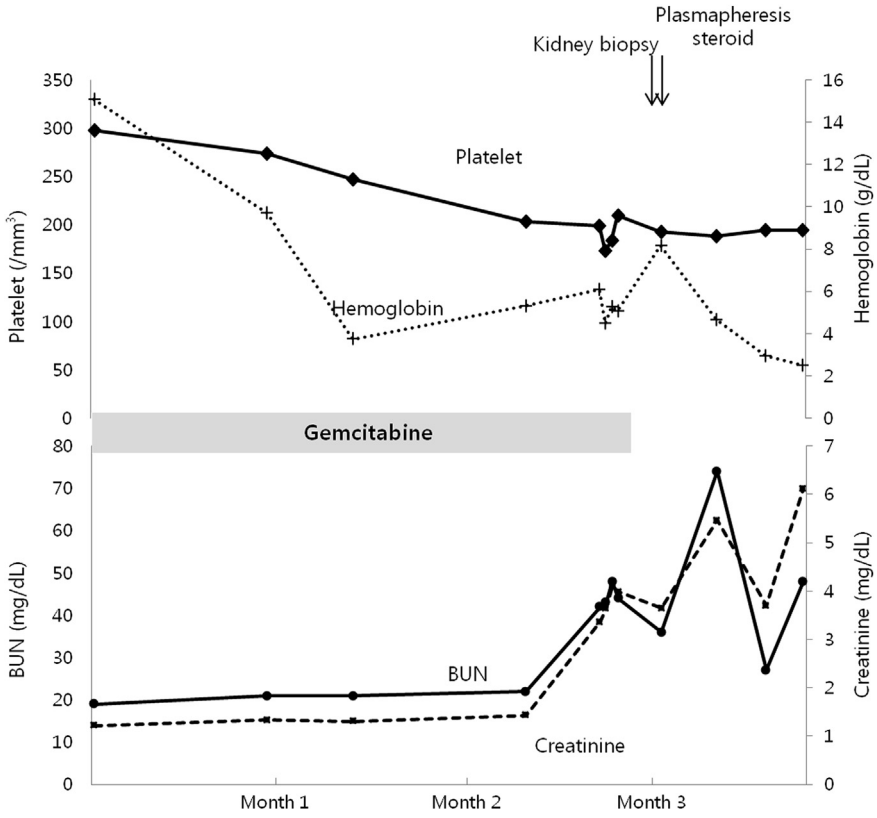

Figure 3. Clinical course and laboratory data. BUN, blood urea nitrogen.

are sufficient for diagnosis in most cases. New or exacerbation of hypertension and proteinuria may appear before clinical manifestations. Neurologic and respiratory symptoms are often associated with gemcitabine-induced TMA [9]. Discontinuation of gemcitabine and plasmapheresis with steroids is the primary therapy for TMA. In some patients, dialysis is needed for AKI. Recently, rituximab treatment showed benefit in cases refractory to plasmapheresis and steroid therapy [9,10].

For diagnosis of chemotherapy-induced TMA, various factors need to be considered when thrombocytopenia with AKI occurs during palliative treatment. Thrombocytopenia and anemia can occur with myelosuppression, and chemotherapy-induced tubulopathy and microangiopathy caused by disseminated cancer can induce AKI. Early diagnosis and proper management are important to improve prognosis and enable further cancer treatment, but differential diagnosis is often difficult based on clinical manifestations. In addition, the variable time course of gemcitabine-induced TMA presentation makes diagnosis more complicated.

In our case, gemcitabine-induced TMA presented acutely on a chronic course. From the patient's history, foamy urine with dyspnea and generalized edema appeared at least 1 month before admission, which was 7 months after the initial gemcitabine dose, and 3 months after the start of palliative therapy.

The sCr level was only slightly elevated by 2 weeks after initial symptoms. Although AKI was overt, with oliguria at the time of the admission, thrombocytopenia and MAHA were not evident. For correct diagnosis and management, kidney biopsy was inevitable, despite the single kidney. Kidney pathology showed chronic TMA features. In this patient, thrombocytopenia and anemia recovered slowly, eventually requiring maintenance dialysis, even after active treatments including plasmapheresis and steroids. During the treatment of TMA, the cancer progressed, which suggested a poor prognosis.

This case highlights the importance of following blood pressure and urinalysis for new-onset hypertension and proteinuria for early diagnosis, when treating with gemcitabine. In patients with urothelial cancer, urinalysis with Cr testing should be performed routinely, with the caveat that various conditions can affect the result, including postoperative changes, tumor progression, and chemotherapy complications, as in this case. A high index of suspicion is required for early diagnosis, and biochemical tests associated with hemolysis should be considered.

In conclusion, we report a case of chronic TMA induced by gemcitabine that required kidney biopsy for diagnosis in a patient with a single kidney. Usually, TMA can be differentially diagnosed from MAHA features, thrombocytopenia, and other clinical manifestations, but sometimes, kidney biopsy is eventually needed to differentiate other causes. We should be aware of the importance of careful monitoring in renal function and be suspicious about TMA in patients with urothelial cancer with palliative gemcitabine treatments as in this case.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

[1] Fung MC, Storniolo AM, Nguyen B, Arning M, Brookfield W, Vigil J: A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. *Cancer* 85:2023–2032, 1999

[2] Muller S, Schutt P, Bojko P, Nowrousian MR, Hense J, Seeber S, Moritz T: Hemolytic uremic syndrome following prolonged gemcitabine therapy: report of four cases from a single institution. *Ann Hematol* 84:110–114, 2005

[3] Dasanu CA: Gemcitabine: vascular toxicity and prothrombotic potential. *Expert Opin Drug Saf* 7:703–716, 2008

[4] Zupancic M, Shah PC, Shah-Khan F: Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol* 8:634–641, 2007

[5] Teixeira L, Debourdeau P, Zammit C, Estival JL, Pavic M, Colle B: Gemcitabine-induced thrombotic microangiopathy. *Presse Med* 31: 740–742, 2002

[6] Moya-Horno I, Querol Ninerola R, Bonfill Abella T, Dalmau Portulas E, Gallardo-Diaz E, Saigi Grau E, Pericay Pijaume C: Haemolytic uraemic syndrome associated with gemcitabine. *Clin Transl Oncol* 12:381–383, 2010

[7] Thomas JG, Sethi S, Norby SM: Chronic thrombotic microangiopathy secondary to chemotherapy for urothelial carcinoma in a patient with a history of Wegener granulomatosis. *Am J Kidney Dis* 57:799–802, 2011

[8] Zupancic M, Shah PC, Shah-Khan F: Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol* 8:634–641, 2007

[9] Bharthuar A, Egloff L, Becker J, George M, Lohr JW, Deeb G, Iyer RV: Rituximab-based therapy for gemcitabine-induced hemolytic uremic syndrome in a patient with metastatic pancreatic adenocarcinoma: a case report. *Cancer Chemother Pharmacol* 64:177–181, 2009

[10] Gourley BL, Mesa H, Gupta P: Rapid and complete resolution of chemotherapy-induced thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) with rituximab. *Cancer Chemother Pharmacol* 65:1001–1004, 2010