*Case Report*

# Thrombotic Microangiopathy Associated with Gemcitabine: A Case Report

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Many etiologies have resulted in thrombotic microangiopathy [TMA], amongst which are antineoplastic chemotherapies. Gemcitabine-related thrombotic microangiopathy [TMA] has rarely been described, but it is a life-threatening complication. However, only a few case reports have been conducted in Thailand. A 52-year-old male who was diagnosed with cholangiocarcinoma and was treated with surgery and gemcitabine. After that, he developed acute kidney injury, generalized edema, and hemolytic anemia. The kidney biopsy revealed three renal pathologies in this patient that included lupus nephritis class V, chronic thrombotic microangiopathy, and drug-induced acute interstitial nephritis. A review of the medical record of the patient plus a comparison with the literature was conducted. The patient was treated with permanently stop gemcitabine, prednisolone, anti-hypertensive drugs and blood transfusion. His renal function and hemolytic anemia improved in one month later.

***Keywords:*** Thrombotic microangiopathy, TMA, Gemcitabine

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Thrombotic microangiopathy [TMA] is a group of disorders characterized by mechanical hemolytic anemia with thrombocytopenia and an ischemic organic lesion of potentially fatal importance affecting mostly the kidneys and the brain with histologically a disseminated and occlusive microvasculopathy(1). TMA is a rare condition and it occurs from many etiologies.

Gemcitabine is a nucleoside analog of cytarabine and widely used anticancer drug. The main adverse effects include myelosuppression, skin rashes, and □u-like symptom. TMA is a rare desirable effect. The incidence of gemcitabine-induced TMA varies between 0.015% and 0.41%(2). The authors report a patient with gemcitabine-induced TMA who presented with anemia, thrombocytopenia, and acute renal failure and generalized edema.

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## Case Report

A 52-year-old male without any prior medical history was diagnosed with cholangiocarcinoma. He underwent surgery (Right hepatectomy with cholecystectomy) and received adjuvant chemothe rapy with gemcitabine (1,000 mg/m$^2$ on Days 1, 8, and 15 every four weeks). During the fifth cycle, he developed anemia (Hematocrit 38% → 26.9%) and leukocyte- poor blood was administered. Gemcitabine dose was decreased by 25%. At the first day of the sixth cycle, the patient developed generalized edema, a decreased hematocrit level (Hct.27% → 24.6%), a new onset hypertension (BP 160/90 mmHg), thrombocy topenia (Platelet 88,000 /mm$^3$) and acute renal failure (serum creatinine 1.0 mg/dl ≥1.4 mg/dl). The chemotherapy was stopped, and the patient was admitted to work up. (Cumulative doses of gemcitabine

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was 24,079 mg)

Further investigations revealed the microangiopathic hemolytic anemia [MAHA] blood picture (Figure 1), a normal coagulogram, reticulocyte count of 1.41%, LDH level of 603, and a negative direct Coomb's test. Proteinuria (Urine protein 1+ and 24 hours of urine with a total protein of 231 mg) and microscopic hematuria (RBC 20 to 30 without dysmorphic RBC) were noted. Complementary factors were within the normal ranges. Moreover, a CT of the whole abdomen did not show any signs of obstruction or renal stones, no recurrent tumors at the surgical bed or thrombosis of the inferior vena cava. Thrombotic microangiopathy [TMA] from gemcitabine or chronic disseminated intravascular coagulopathy was the differential diagnosis. His blood test revealed ANA 1: 640 of the coarse speckled type, and high-titer positive Anti-dsDNA (274 IU/ml). Kidney biopsy was made and the histopathological diagnosis was Lupus nephritis class V, chronic thrombotic microangiopathy, and acute drug-induced interstitial nephritis (AIN) (Figure 2, 3). In addition, antiphospholipid syndrome workup was done, but the result was negative. Gemcitabine was permanently discontinued. He was treated with prednisolone (1 mg/kg/day for 2 weeks then taper off in 1 month) due to AIN, anti-hypertensive drugs, and gave a blood transfusion. Subsequently, the renal function and CBC were back to baseline after one month.

## Discussion

The primary TMA syndromes include thrombotic thrombocytopenic purpura (TTP: hereditary or acquired), Shiga toxin-mediated HUS (hemolytic-uremic syndrome [ST-HUS]), drug-induced TMA (DITMA) syndromes, complement-mediated TMA (hereditary or acquired), and rare hereditary disorders of vitamin B12 metabolism or factors involved in hemostasis[3]. The clinical features included microangiopathic hemolytic anemia, thrombocytopenia, and organ injury[4]. Thus, TMA syndromes require urgent management directed at the pathophysiology, as there is a variety of conditions that can cause TMA.

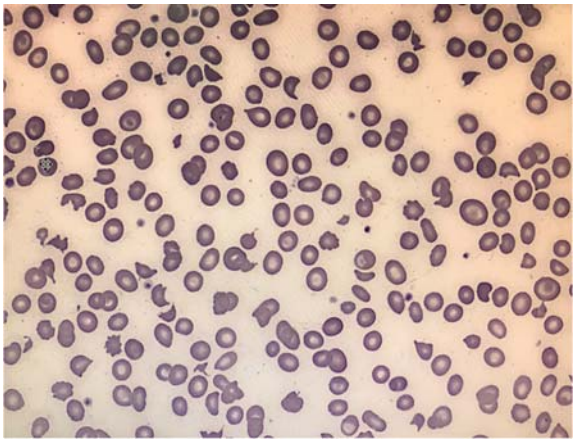

**Figure 1.** Peripheral blood smear: MAHA blood picture.

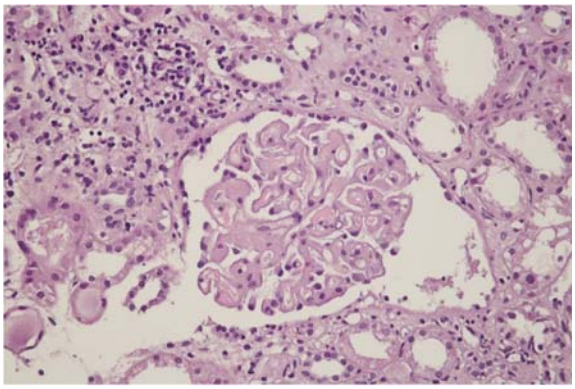

**Figure 2.** The glomerular capillary wall is moderately thickening, and there is mild mesangial matrix expansion. The adjacent periglomerular tubulo-interstitium shows moderate mononuclear cell infiltration and a flattened renal tubular epithelium (H&E, x400).

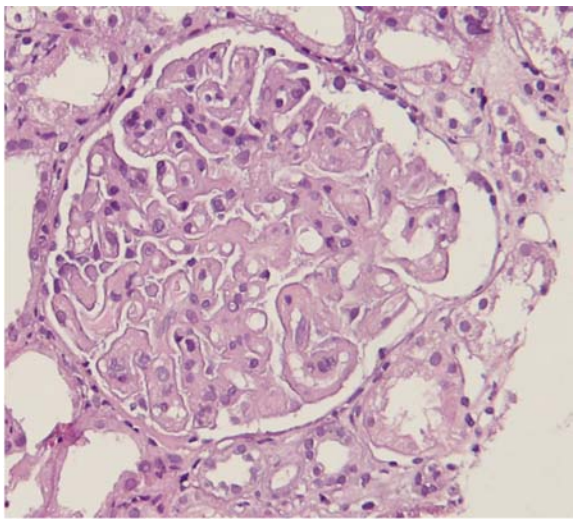

**Figure 3.** The glomerular capillary wall is globally thickening, and there is segmental mesangial proliferation (H&E, x400).

**Table 1.** Summary of the previous case and the treatment

| Authors, Year | Age, Gender | Malignancies | Adam 13 | Duration of the Onset | Accumulative Gemcitabine Dose | Treatment | Result |
|---|---|---|---|---|---|---|---|
| Fung et al, 1998[2] (Review 12 pts.) | 43 to 73, both sexes | NSCLC, gastric, pancreatic, biliary tract | - | Median duration 5.8 mo. | Median cumulative dose 18,252 mg | - Discontinued<br>- Steroid<br>- Plasma exchange<br>- Dialysis | - |
| Carlos et al, 1999[11] | 65, male | Pancreatic adenocarcinoma | - | 8 mo. | - | - Discontinued | Improve in 4 mo. |
| | 67, female | Pancreatic adenocarcinoma | - | 12 mo. | - | - Discontinued<br>- Steroid 1 wk. | Improve in 2 mo. |
| Karl Lhottaa et al, 1999[12] | 23, male | Pancreatic adenocarcinoma | - | 7 mo. | 38,400 mg | - Discontinued<br>- Steroid (Fail)<br>- Dialysis | Improve in 6 mo. |
| | 58, female | Cholangiocarcinoma | - | 8 mo. | 28,800 mg | - Discontinued<br>- Dialysis | Not improve, cont. dialysis |
| Sai et al, 2005[13] | 72, male | Pancreatic adenocarcinoma | - | 4 mo. | - | - Discontinued<br>- Dialysis | Not improve, cont. dialysis |
| Finkenwirth et al, 2009[14] | 67, male | Pancreatic adenocarcinoma | Normal | 5 cycles | 19,000 mg | - Discontinued<br>- Plasma exchange | Improve in 1 mo. |
| Robinson et al, 2010[15] | | Duodenal adenocarcinoma | - | 7 mo. | 29,716 mg | - Discontinued<br>- High dose of steroid (Fail)<br>- Plasma exchange<br>- Splenectomy | Improve in 3 mo. |
| Starck et al, 2013[16] | 45, male | Duodenal | Normal | 5 mo. | 13,000 mg/m$^2$ | - Discontinued<br>- High dose of steroid<br>- Plasma exchange (Fail)<br>- Rituximab (Fail)<br>- Eculizumab<br>- Dialysis | Improve in 2.5 mo. |
| Al Ustwani et al., 2013[17] | 75, male | Squamous cell cancer of the lung | Normal | 3 mo. | 11,100 mg | - Discontinued<br>- Eculizumab | Improve in 5 mo. |
| | 70, male | Pancreatic adenocarcinoma | Normal | 18 mo. | 99,540 mg | - Discontinued<br>- Steroid<br>- Eculizumab | Improve in 4 mo. |
| | 73, female | Cholangiocarcinoma | - | 24 cycles | - | - Discontinued<br>- Eculizumab | Died in 4 mo. |

**Table 1.** Cont.

| Authors, Year | Age, Gender | Malignancies | Adam 13 | Duration of the Onset | Accumulative Gemcitabine Dose | Treatment | Result |
|---|---|---|---|---|---|---|---|
| | 69, male | Squamous cell cancer of the lung | Normal | 3 mo. | - | - Discontinued<br>- Plasma exchange (not improve)<br>- Eculizumab | Improve in 2.5 mo. |
| Murugapandian et al., 2015[18] | 74, female | Ovary | Normal | 4 mo. | 9,460 mg | - Discontinued<br>- Plasma exchange<br>- Rituximab | Improve in 2 mo. |
| Lai-Tiong et al., 2017[19] Not improve, | 63, male | | NSCLC | Normal | 4 mo. | - | - Discontinued |
| | | | | | | - Dialysis | cont. dialysis |

In this case report, the clinical manifestations of TMA occurred for six months after the initial administration of gemcitabine. The patient had three renal pathologies that included LN class V, chronic TMA, and drug-induced AIN.

Three hypotheses were formulated. First, the patient had previous inactive LN class V, but after being treated with gemcitabine, he developed TMA and AIN. This can cause an acute onset of a MAHA blood picture, proteinuria and hypertension while a blood test showed him being ANA and anti-dsDNA positive. The mechanism may have come from adverse drug reactions; such as, non-dose related idiosyncratic, immunologic reactions or toxic effects that are dependent on the dosage and timing[5].

The second hypothesis was the patient did not have any renal disease until the dispensing of gemcitabine. This drug caused LN class V, TMA, and AIN. However, anti-dsDNA was not commonly positive in drug-induced lupus (<5%)[6]. A few case reports of gemcitabine-induced SLE have revealed cutaneous manifestations; such as, subacute cutaneous lupus erythematosus or purpura, which rarely involves a major organ[7,8]. There was no case report of gemcitabine induce lupus nephritis.

The third hypothesis, TMA was caused by LN class V with or without the antiphospholipid syndrome. However, most of the reports of gemcitabine-induced lupus nephritis do not associate with lupus nephritis class V. Song et al reported that TMA was associated with LN class IV or LN class IV-V more than LN class V alone (91.7% and 8.3%, respectively)[9]. Chen et al also revealed mostly TMA were found in SLE associated with LN class II-IV (90.9%).In addition, it was mentioned that TMA associated with lupus nephritis often occurs with other clinical signs of *active lupus*[10]. However, the patient did not have any involvement of other organs and the complements were found to be in a normal range.

The treatments for TMA associated with gemcitabine (Table 1) were supportive care with or without systemic steroid, plasma exchange, anti-complement therapy (e.g. eculizumab) or additional therapies.

In this patient, the most likely cause was gemcitabine-induced TMA. Therefore, supportive care and avoidance of medication may be the only beneficial form of management. Because the kidney pathology did not only show chronic TMA but also showed AIN and LN class V, a short course of prednisolone 1 MKD, which was reduced over a period of four weeks was

given to him. The indication was the renal function did not improve after gemcitabine. For LN class V, there was minimal proteinuria, so the treatment was only minimized proteinuria with ACEI or CCB with no immunosuppressives. One month later, his kidney function, anemia, and thrombocytopenia had improved and returned to the baseline value. He remained diseased free from the tumor in the last CT scan.

## Conclusion

Clinicians should be aware of thrombotic microangiopathy in the patient receiving gemcitabine with anemia and acute kidney injury. When in doubt, a kidney biopsy is essential to distinguish TMA from other causes of acute kidney injury.

## What is already known on this topic?

Gemcitabine is one of the drugs-induced TMA. This condition can cause life-threatening complication.

## What this study adds?

The Clinicians should be aware the thrombotic microangiopathy in the cancer patient who treats with gemcitabine. Although it seems a rare condition, this disorder is potentially fatal. The early detection is improving outcome. If in doubt, a kidney biopsy is an essential option.

## Potential conflicts of interest

The authors declare no conflict of interest.

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