Thrombotic microangiopathy after long lasting treatment by Gemcitabine: description, evolution and treatment of a rare case report

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Case Report

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Abstract

Background: Thrombotic microangiopathy is an uncommon but severe complication that may occur in cancer patients under Gemcitabine chemotherapy. Gemcitabine induced thrombotic microangiopathy can clinically and biologically present as atypical hemolytic uremic syndrome, with activation of the complement pathway asking the question of the use of Eculizumab.

Case presentation: We describe here the case of a patient suffering from metastatic cholangiocarcinoma treated by Gemcitabine for 4 years leading to remission of the underlying neoplasia. Despite an impressive response to therapy, she developed thrombopenia, regenerative anemia and acute kidney injury leading to the suspicion then diagnosis based on renal biopsy of a very late Gemcitabine associated thrombotic microangiopathy. Spontaneous evolution after treatment interruption was favorable without dialysis requirement. However, in this case where Gemcitabine is the only chemotherapy remaining for a mortal underlying condition, we discussed re-initiation of Gemcitabine under Eculizumab treatment.

Conclusions: This atypical case of thrombotic microangiopathy illustrates the importance of recognizing, even belatedly, this rare but serious complication of chemotherapy. It asks the question of resumption of discontinued chemotherapy notably under Eculizumab cover, in this population with high risk of cancer progression.

Background

Thrombotic microangiopathy (TMA) is defined by hemolytic anemia, peripheral thrombopenia and various organ injury due to ischemia after capillary thrombosis (1). The kidney is one of the most impacted organs with clinical presentation of oligo-anuric acute kidney failure of vascular origin.

Two main etiologies of TMA in adulthood population are: 1/ thrombotic thrombocytopenic purpura (TTP) presenting with prevalent neurological disorders and deficit of ADAMTS 13 activity and 2/ atypical hemolytic uremic syndrome (aHUS) characterized by quantitative or qualitative abnormalities in regulatory proteins of the complement alternative pathway. Typical HUS due to capillary endothelium alteration by infectious mechanism is less frequent than in children. Others conditions can be associated with TMA and needed to be investigated, including various infections, connective tissue disorder, malignant tumors and drug exposure as chemotherapies.

Gemcitabine is one of the usual agents implicated in secondary TMA with frequent severe renal involvement and poor prognosis (2). The management of Gemcitabine TMA is not codified.

We reported here a case of histologically proven TMA with isolated kidney acute failure in a woman suffering from cholangiocarcinoma under long lasting Gemcitabine chemotherapy.

Case Presentation
On May 2022, 55 years old woman was admitted to our nephrology department for suspicion of TMA.

Patient’s medical history included intracerebral hemorrhage due to aneurysmal rupture in 2011 complicated by chronic epilepsy, type two diabetes mellitus under insulin therapy with chronic kidney disease stage 3A (DFG = 44 mL/min/1.73m²), hypertension, chronic psychosis. She has developed in 2018 a cholangiocarcinoma (histologically proven) with liver and lymph nodes metastasis, put under chemotherapy including Gemcitabine and platinum salt agent (GEMOX) all the 21 days until march 2022 then Gemcitabine alone. At the moment of hospitalization, she had 37 cures of Gemcitabine 1000mg/m2 (cumulated dose of 37 g/m²).

She consulted in April 2022 for global fatigue. At the entrance, clinical examination revealed general psychomotor slowing, no other clinical sign was noted. She had normal blood oxygenation, apyrexia and high blood pressure at 200/80 mmHg. Standard biology revealed regenerative anemia (hemoglobinemia 7,3g/dL and reticulocytes 115 000/mm³) with schizocytes (1,5 %), indosable haptoglobin, thrombopenia (125 000/mm3) and organic acute kidney injury with serum creatinine level at 880 µmol/L, urea fractional excretion 54 %, no glomerular range proteinuria (70 mg/mmol) and microscopic hematuria. Renal echography showed two normally cortico-medullary differentiated kidneys of 11,8 and 11,2 cm, without hydronephrosis. Renal biopsy (figure 1) confirmed the diagnosis with lesions of chronic TMA including double contour appearance of the glomerular basement membranes and swelling and detachment of glomerular endothelial cells associated to acute tubular necrosis.

In front of TMA with neurological impairment, PTT was first excluded with ADAMTS 13 level of 121 % and cerebral Magnetic Resonance Imaging (MRI) showing no Posterior-reversible encephalopathy syndrome (PRES). HUS was then investigated, the patient did not report any episode of diarrhea, fever, urinary symptoms. Hemocultures were sterile, cytobacteriological examination of urines (CBEU) did not show leukocytosis or bacteria, no Shiga-Toxin producing Escherichia Coli (STEC) analysis could be performed (no stool culture). Complement biological investigation (C3, C4, CH50, protein I, protein H, MCP, Factor-H antibody negative) was normal, no genetic analysis was performed (on expert opinion).

Other causes of secondary TMA were ruled out: negatives plasmatic B-Human Chorionic Gonadotropin, no autoimmunity was found (no antinuclear antibodies (ANA), neither lupus anticoagulant, B2GP1 antibody nor anticardiolipin antibody), hepatitis and Human Immunodeficiency Virus serologies were negatives.

Neoplastic causes were excluded after thoracic-abdominal-pelvic computed tomography-scan and liver MRI showing remission of cholangiocarcinoma and no sign of new tumoral disease.

We finally consider as diagnosis of exclusion an iatrogenic cause of TMA due to gemcitabine. The evolution was spontaneously favorable with progressive amelioration of serum creatinine level without dialysis necessity. However, a chronic kidney disease persists, with last creatinine level 22 mg/l, and glomerular filtration rate of 28 ml/min/1.73 m².


Discussion

We described here a rare case of TMA under Gemcitabine (G-TMA) treatment in a long survival case of cholangiocarcinoma. In TMA following the curse of neoplasia it is helpful to differentiate 1/ paraneoplastic TMA and 2/ drugs induced TMA (15% of Acute Kidney Injury in cancer)(2). Iatrogenic TMA includes TMA under anti-vascular epithelial growth factor (VEGF) and TMA post-chemotherapy. Two major chemotherapies are concerned: Mitomycin C and Gemcitabine, both dose-depending.

The incidence of G-TMA has been reported between 0,015% and 2,2% (3). Average timing reported after introduction of Gemcitabine is 6 months and cumulated dosage of 31,2g/m2 (9–48 g/m2) (4). As in our case, severe acute renal failure is one of the main symptoms reported (58% stage 3 AKI), usually associated with hypertension and edemas. Although 56% of cases can biologically resolve after Gemcitabine discontinuation(5), G-TMA prognostic can be severe with 25% of cases presenting chronic renal insufficiency and a high-rate mortality at 4 months (60%) (2) principally due to neoplastic progression after chemotherapy discontinuation.

Until a recent study of Grall and al in 2021 (4), the treatment of G-TMA has not been well codified apart from permanent discontinuation of Gemcitabine and supportive cares. Plasma exchanges and corticosteroids are generally tried with poor efficacy reported at the contrary of TTP. Although underlying pathophysiological mechanisms involved are not known and no complement alternative pathway-related abnormalities have been described in G-TMA (4, 6, 7), clinical presentation and normal ADAMTS 13 level are reminiscent of aHUS. Which is supported in the study of Grall and al (4), by the deposits of C5b9 (membrane attack complex) found along the glomerular and tubular membrane and in the capillary wall on immunofluorescence in kidney biopsy. In this context, Eculizumab, a monoclonal antibody directed against complement protein C5 used in aHUS, has been used and seemed efficient in numerous case reports of G-TMA (5, 8–15). The observational retrospective study of Grall and al (4) reported 12 cases of G-TMA treated by Eculizumab after Gemcitabine discontinuation with a median of 4 injections and 900 mg/injection. 83% of patients had a hematological response and 84% achieved a complete (17%) or partial (67%) renal response without exacerbation or relapse after Eculizumab discontinuation.

Spontaneous recovery of our patient after Gemcitabine discontinuation did not indicate the treatment of Eculizumab in the active phase of G-TMA. However, the continuation of treatment of metastatic cholangiocarcinoma in recovery under Gemcitabine appears to be a vital question. In reported cases, discontinuation of chemotherapy in acute phase of G-TMA is noted as important as specific G-TMA treatment (4, 6, 7). However, the survival rate also depends of underlying disease with 5 / 6 deaths during follow-up due to progression of the underlying disease in the series of Grall and al (4). Number of cases of Gemcitabine re-initiation is few (15–18) and with variable outcomes (stability, second TMA episode, underlying disease progression). After a multidisciplinary meeting of experts on our patient’s file, if Gemcitabine is the only possibility and needs to be perform to maintain recovery, it could be done under maintenance treatment with Eculizumab 1200 mg every 2 weeks. We think that larger studies should be
performed addressing the question of whether or not Gemcitabine and Eculizumab can both be used safely after G-TMA.

**Conclusion**

Here, we report an atypical case of TMA after a very long treatment of Gemcitabine in a patient suffering from metastatic cholangiocarcinoma with favorable spontaneous evolution after discontinuation of Gemcitabine. The question of whether or not Eculizumab add to Gemcitabine treatment can be used after a first TMA episode in this population at-risk of cancer progression and mortality without other possible chemotherapy needs to be addressed in larger studies.

**Abbreviations**

TMA : Thrombotic Microangiopathy

TTP : Trombotic Thrombocytopenic Purpura

aHUS / HUS : atypical Hemolytic Uremic Syndrome / Hemolytic Uremic Syndrome

MRI : Magnetic Resonance Imaging

PRES : Posterior-reversible encephalopathy syndrome

ANA : Antinuclear Antibodies

STEC : Shiga-Toxin producing Escherichia Coli

CBEU : Cytobacteriological Examination of Urines

G-TMA : Thrombotic Microangiopathy under Gemcitabine

VEGF : Vascular Epithelial Growth Factor

**Declarations**

- *Ethics approval*: Not applicable
- *Consent for publication*: Consent obtained (institutional consent form).
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References


**Figures**
Figure 1

Renal biopsies in TMA due to Gemcitabine

(A) ischemic glomerulus with floculus retraction

(B) doubling of glomerular basement membrane
(C) glomerular mesangiolysis