Gemcitabine-induced thrombotic microangiopathy with nephrotic syndrome

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Abstract

We encountered a case of gemcitabine (GEM)-induced secondary thrombotic microangiopathy (TMA) with nephrotic syndrome. Advanced pancreatic cancer with liver metastasis had originally been diagnosed. Renal biopsy showed focal reduplication of the glomerular basement membrane, endothelial cell swelling, and narrowed capillary lumens with fragmented erythrocytes and fibrin deposition, compatible with TMA. Regular monitoring of renal function during GEM treatment and discontinuation of treatment if acute kidney injury (AKI) might occur is crucial, because AKI combined with TMA is life-threatening.

Keywords Thrombotic microangiopathy · Gemcitabine · AKI · Nephrotic syndrome

Introduction

Thrombotic microangiopathy (TMA) is a rare but serious disease with pathologic features including widening of the subendothelial space with detachment of endothelial cells from the glomerular basement membrane, intraluminal thrombi, glomerular mesangiolysis, thickening of the vessel wall, and microvascular obstruction. Clinically, TMA includes thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *Escherichia coli* (STEC)–hemolytic uremic syndrome (HUS), atypical HUS (aHUS), and secondary TMA.

Gemcitabine (GEM) is a nucleoside analog used against various cancers, including pancreatic cancer, breast cancer, ovarian cancer, non-small cell lung cancer, and bladder cancer. The major side effects of GEM are myelosuppression, mild liver dysfunction, respiratory failure, gastrointestinal symptoms, and elevation of blood pressure. In addition, cases of GEM-associated secondary TMA have been reported [1].

Here we report a case of GEM-induced acute kidney injury (AKI) accompanied by nephrotic syndrome, hemolytic anemia and thrombocytopenia. Since few reports have described the nephrotic range of proteinuria in GEM-induced secondary TMA, renal biopsy was performed to clarify pathological changes such as severe endothelial cell injury in the present case.

Case report

A 46-year-old woman was hospitalized with severe cough, systemic edema, hypoventilation (SpO₂ 93%) and high blood pressure (175/108 mmHg). Four days after admission, she was transferred from the Department of Surgery to the Department of Nephrology for the treatment of AKI. Advanced pancreatic cancer with liver metastasis had originally been diagnosed before this admission, and administration of GEM was started at another local clinic. The dose of GEM was started at 400 mg/day and increased to 600 mg/day. She received a total 11,000 mg of GEM over the course of 8 months. She had no medical history of renal disease before GEM therapy was started, at which point she had normal kidney function (serum creatinine 0.53 mg/dL) and no proteinuria.

The major laboratory findings on admission are shown in (Table 1). Electrocardiography showed no abnormalities, with a heart rate of 86 beats/min. Chest X-ray disclosed

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Table 1 Laboratory findings on admission

TP	5.0	g/dl	Ca	8.1	mg/dl	Blood gas analysis (shunt)	
<i>Alb</i>	2.9	<i>g/dl</i>	P	5.2	mg/dl	pH	7.362
T-bil	1.7	mg/dl	CRP	10.42	mg/dl	<i>HCO₃</i>	20.9 mmol/L
AST	47	U/L	WBC	6420	/μl	<i>BE</i>	−3.5 mmol/L
LDH	1172	U/L	<i>Hb</i>	6.5	<i>g/dl</i>	<i>HPT</i>	10.8 mg/dl
CK	101	U/L	<i>Ht</i>	20.7	%	Coombs test	Neg
BUN	24.9	mg/dl	MCV	101.0	Pg	<i>Fe</i>	57 μg/dl
Cr	1.54	mg/dl	<i>Plt</i>	6.1	× 10 ⁴ /μl	TSAT	30.6 %
UA	2.7	mg/dl	PT	11.7	s	FER	217.1 ng/ml
<i>Na</i>	142	<i>mEq/L</i>	APTT	24.0	s	ret RBC	1.6 %
<i>K</i>	4.2	<i>mEq/L</i>	Fib	237.6	mg/dl	Fecal oc bld	Neg
<i>Cl</i>	109	<i>mEq/L</i>	ATIII	93.1	%	Eosino	Neg
HbA _{1c}	3.6	%	IgG	771.8	mg/dl	U blood	3+
P,C-ANCA	Neg		IgA	157.1	mg/dl	Urinary sediment	
CA19-9	25.6	U/ml	IgM	74.1	mg/dl	RBC 50–99/HPF, WBC 50–99/HPF, Granular cast (+)	
DUPAN	96	U/ml	T-IgE	226.0	IU/ml	U Pro	7.83 g/day
						U β ₂ MG	662 μg/L

Bold indicates a value higher than the normal reference range. Italic indicates a value lower than the normal reference range

a cardiothoracic ratio of 46% and mild bilateral pleural effusion.

Taken together, AKI accompanied by nephrotic syndrome (NS), hemolytic anemia and thrombocytopenia were confirmed on admission. Neither fever nor neurological symptoms were observed. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADTAMTS13) activity was 63.1% (normal reference > 70%) and ADAMTS13 inhibitor screening yielded negative results. GEM-induced TMA was considered the most probable diagnosis, and GEM was therefore, discontinued. Drug lymphocyte stimulation testing for GEM yielded an indeterminate (+/−) result. The patient was treated with rest and protein restriction to conservatively improve AKI, resulting in amelioration of thrombocytopenia and kidney dysfunction (Fig. 1). Because GEM-induced TMA seldom presents with NS [2, 3], renal biopsy was performed after red blood cell transfusion.

Biopsy specimens included 31 glomeruli and 2 of them showed global sclerosis in light microscopy (Fig. 2). No segmental sclerosis was found in any glomerulus. Glomeruli showed diffuse global changes of endocapillary proliferation and endothelial cell swelling. Moreover, segmental double-layered basement membranes were diffusely identified. Mesangial proliferation (lobulation), crescent formation and epithelial proliferation were not found. No deposition was identified in PAM-Masson stain. Several renal tubules were atrophic, and lymphoplasmacytes and a few eosinophils focally and mildly infiltrated the interstitium. Immunofluorescence staining showed IgG(−), IgA(−), IgM(periphery+), C1q(−), C3(periphery+), and C4(−). In

Fig. 1 Clinical course. The patient initially presented with proteinuria (about 8 g/day), which gradually decreased. As serum creatinine (sCr) increased unexpectedly on day 7, renal biopsy was performed to assess the cause of AKI. *Hb* hemoglobin, *Plt* platelet count, *U Pro* urinary protein, *RCC* red cell concentrate transfused

electron microscopy, glomeruli showed endocapillary cell proliferation and endothelial swelling with mild increase of mesangial matrix. In subendothelial and paramesangial areas, there were lots of heterogeneous dense materials, probably exudation as well as filamentous materials, namely fibrin deposition. Capillary lumens were narrowed and hardly identified. Foot processes were preserved and slight swelling of epithelial cells were identified. These renal biopsy findings were compatible with TMA. Proteinuria gradually ameliorated with supportive therapy. The patient was discharged 36 days after admission, and kidney

Fig. 2 Renal biopsy findings. **a** Periodic acid–Schiff staining. The glomerulus shows thickening of the glomerular capillary walls. **b** Periodic acid methenamine silver (PAM)/Masson staining. Focal reduplication of the glomerular basement membranes with fragmented erythrocytes is seen. **c** Periodic acid–Schiff staining. Focal lymphocyte infiltration is clearly apparent in the interstitial tissue. **d**

Immunofluorescence microscopy. Non-specific positive IgM are seen in the subendothelial and mesangial areas, corresponding to deposits. **e** Electron micrograph of a glomerular basement membrane. Fibrins are clearly recognizable in the capillary loop. **f** Endothelial cell swollen with electron-dense deposition at the subendothelial area, indicating severe endothelial cell injury

function eventually normalized (estimated glomerular filtration rate > 70 ml/min/1.73 m²) by the 3-month follow-up. Urinary protein gradually decreased after discharge. It was 3.64 g/day just after discharge, and 0.87 g/day 1 month later. Urinary protein finally decreased to 0.54 g/day at 3 months follow-up.

Discussion

TMA is a pathophysiological disease with: (1) microangiopathic hemolytic anemia (MAHA); (2) consumptive thrombocytopenia; and (3) organ injury with platelet-induced microvascular occlusion. The concept of TMA generally includes TTP, STEC-HUS, aHUS, and secondary TMA, although no international consensus has yet been determined [4, 5].

HUS is a thrombotic disease characterized by the triad of: (1) microangiopathic hemolytic anemia; (2) thrombocytopenia; and (3) AKI. The classic form of HUS, also known as diarrhea-positive (D+) HUS, is a disease of infants and children caused by STEC. This form represents 90% of all HUS. Stool culture to detect STEC helps diagnosis. TTP is generally diagnosed with significant reduction of ADAMTS13 activity ($< 10\%$) [6]. However, 5–12% of HUS is aHUS,

formerly known as diarrhea-negative (D–) HUS; this form is related to complement dysregulation. Not only complement factor H, but also C3, factor B, complement factor I, CD46, and others have been reported as dysregulated in aHUS [7].

Secondary TMA has been associated with a variety of triggers, including bacterial and viral infections, drugs, malignancy, maternity, and systemic disease. Drug-induced secondary TMA is caused by chemotherapeutic agents such as mitomycin C, cisplatin, and GEM. The present patient had a history of malignancy treated with GEM, compatible with secondary TMA.

Among TMA, STEC-HUS and aHUS are known as the major causes of kidney injury. Malignancy-related secondary TMA has generally been reported with gastric, lung, ovarian, breast, and prostate cancer [8]. This patient presented with proteinuria (7.8 g/day; nephrotic range) and urinary protein selectivity was low (> 0.2). GEM-induced TMA appears quite rare (0.25–0.4% among patients using GEM) [9]. Phase 2 trials of GEM reported World Health Organization grade 1–2 proteinuria in 58% of patients [1, 10]. Only a small number of reports have described the nephrotic range of proteinuria in GEM-induced TMA according to the literature [1–3]. To the best of our knowledge, only one report has described NS during GEM treatment, although renal biopsy showed membranous nephropathy rather than TMA

[11]. Therefore, we cannot deny that TMA in the present case might have been complicated or triggered by some other glomerular disease which often causes NS, such as membranous nephropathy and focal segmental glomerulosclerosis though no typical findings of these diseases were disclosed by renal biopsy. A recent report detected excretion of podocytes in urine among 2 cases with TMA and advanced cancer that rapidly developed AKI and NS [12]. This indicates that severe endothelial cell dysfunction during the acute phase of glomerular TMA can lead to podocyte loss. In the present case, endothelial cells were swollen and electron-dense deposits were seen in the subendothelial area, indicating severe endothelial cell injury that might have led to some podocyte injury (Fig. 2f).

Another reason to perform renal biopsy was that in the present case, AKI was found with rapid elevation of serum creatinine levels from the normal range. AKI might rapidly progress to irreversible end-stage renal disease and fatal multiple-organ failure in several days. We therefore, considered renal biopsy as necessary in this patient after treating anemia and thrombocytopenia with blood transfusion. Findings from renal biopsy specimen were compatible with TMA, mildly complicated by interstitial nephritis (Fig. 2c).

GEM can result in direct injury to the endothelium and cause TMA [13]. The detailed mechanisms remain unclear, but prostacyclin has been suggested to decrease the secretion of von Willebrand factor, subsequent platelet aggregation and endothelial cell injury [9]. Because AKI is life-threatening and expected to increase in aging societies with the use of anti-cancer agents [14, 15], the risk of TMA with GEM has been noted in the United States' Food and Drug Administration (FDA)-approved information to evaluate renal function. Onset of TMA has been reported to occur after 5–8 months of treatment [9]. Newly onset hypertension after GEM treatment have been reported as common clinical symptom of GEM–TMA. The present case also showed elevated blood pressure. Discontinuation of GEM, anti-hypertensive therapy, plasma exchange, and dialysis have been suggested as treatments for GEM-induced TMA [1].

Conclusion

Here we have reported a very rare case of biopsy-confirmed GEM-induced TMA with NS. Monitoring blood pressure and renal function is crucial when administering GEM, because TMA combined with AKI obviously represents an emergency.

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Compliance with ethical standards

Conflict of interest Authors have declared that no conflict of interest exists for this work.

Ethical statement All of the treatment and the examination followed the guideline laid down in the Declaration of Helsinki.

Informed consent Informed consent for the treatment and the renal biopsy was obtained from the patient.

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