A Case of Hemolytic Uremic Syndrome in a Pancreatic Cancer Patient Treated with Gemcitabine

Joon Hyung Jhi, Dong Uk Kim, Dong Hoon Baek, Guen Am Song

Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

Introduction: Hemolytic uremic syndrome (HUS) is a rare disorder characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. HUS arises from a wide spectrum of conditions, and chemotherapeutic agents have been reported to be associated with HUS, including Mitomycin, Cisplatin, Bleomycin, and Gemcitabine.

Case: A 58-year-old male with a history of mild hypertension underwent chemotherapy for Stage III adenocarcinoma of the pancreas in September 2012. He received twelve cycles of erlotinib plus gemcitabine (cumulative dose, 60 g). His baseline creatinine was 1.13 mg/dL. Surveillance laboratory data during the twelfth infusion were significant for an increased creatinine to 3.15 mg/dL with elevated LDH 1042. His creatinine peaked at 6.77 mg/dL. Admission laboratory data revealed hemoglobin of 7.4 g/dL, platelet count of 46,000, low haptoglobin level and new onset proteinuria. Concomitantly, the patient's blood pressure increased from a baseline of 120/80 to 170/100 mmHg with non-cardiogenic pulmonary edema. Renal biopsy revealed segmental capillary thrombosis of glomeruli, and fibrin thrombi with obliteration of arteriole. His condition improved with symptomatic, corticosteroid treatments and hemodialysis. Plasmapheresis was not performed. Gemcitabine treatment was discontinued. He chose hormonal therapy and he remained definitively free of TMA stigmata. However, oliguria was prolonged over 3 months, and he was under hemodialysis.

Conclusion: Although it seems rare, a high index of suspicion for HUS is essential when pancreatic cancer patient is treated with gemcitabine, especially with prolonged therapy.

Case presentation

- Age/Gender: 58/M
- C/C: General weakness
- P/I: 2012년 9월, pancreatic cancer 진단받고, 2013년 8월 2일까지 11차례 gemcitabine, erlotinib 병합 치료를 받았으며, 8월 29일 12차 투여 중에 심한 전신 무력감을 호소함.
- P/Hx: gout, hypertension

  2012. 09. **pancreatic cancer (adenocarcinoma, T4N1M0, stage III)**

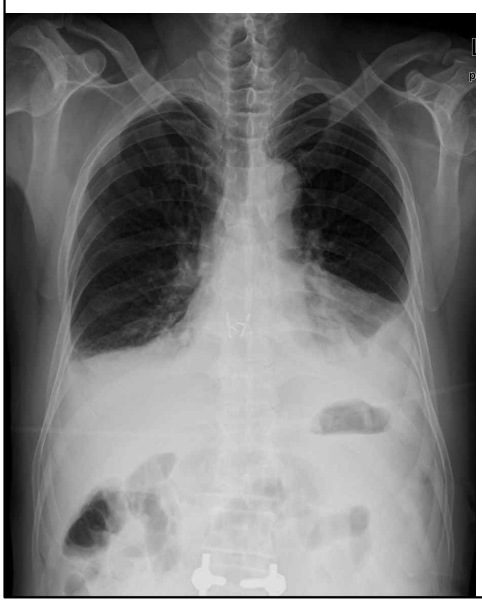
  2012. 09. 18.-2013. 08. 29. **1-12 Gemzar-Tarceva 100%**

Date	Gemcitabine 1g/m^2, Erlotinib 100 mg qd
2012.09.18	1-1 pGem-Tarceva
2012.10.19	1-2 pGem-Tarceva
2012.11.19	1-3 pGem-Tarceva
2012.12.17	1-4 pGem-Tarceva
2013.01.14	1-5 pGem-Tarceva
2013.02.18	1-6 pGem-Tarceva
2013.03.18	1-7 pGem-Tarceva
2013.04.15	1-8 pGem-Tarceva
2013.05.13	1-9 pGem-Tarceva
2013.06.14	1-10 pGem-Tarceva
2013.07.19	1-11 pGem-Tarceva
2013.08.16	1-12 pGem-Tarceva 100% D1
2013.08.29	1-12 pGem-Tarceva 100% D8
Gemcitabine: 누적 용량(약 60,000 mg), 투여기간(11개월)	

Case presentation (2013. 09. 09)

- **V/S**
  - **170/100 mmHg** - 82 /min - 20 /min -36.7℃
- **ROS**
  - Chronic ill-looking appearance
  - Cough / Sputum : (-/-), Dyspnea (-)
  - Chest pain (-), Palpitation (-)
- **P/Ex**
  - **Anemic conjunctiva(+),** anicteric sclera
  - CBS /s^{r}, RHB /s^{m}
  - Bowel sound : normoactive
  - Tenderness/RT (-/-)
  - **Generalized edema (+)**
  - Skin rash (-)

Radiologic findings (2013. 09. 09)



Chest PA

- Both pleural effusion

ECG

- Normal sinus rhythm

Transthoracic Echocardiography

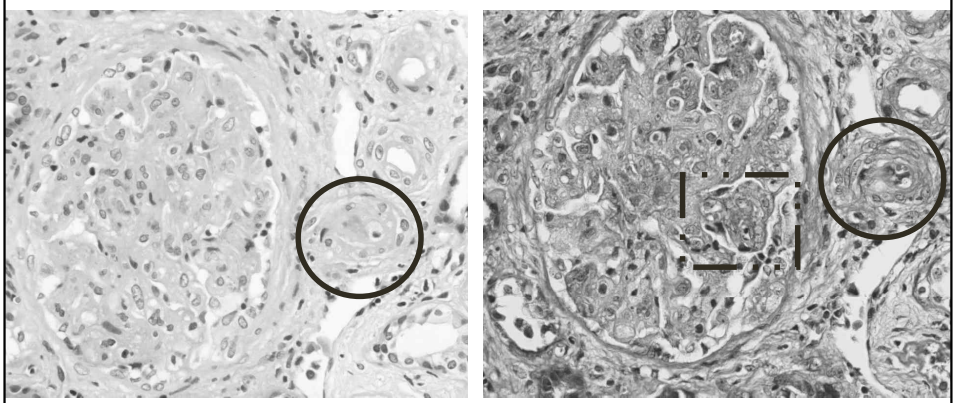
- EF 58%
- Small pericardial effusion without hemodynamic significance
- Degenerative mild MR and LAE

Lab findings (2013. 09. 09)

CBC with PBS consultation		
WBC	7580	/uL
Neut #	4460	/uL
Hb	7.4	g/dL
PLT	46	10E3/uL
Reticount	0.35	%
Electrolyte		
Na	138.4	mmol/L
K	3.90	mmol/L
Others		
CRP	2.14	mg/dL
PT INR	1.04	
aPTT	36.3	sec
Haptoglobin	1	mg/dL
Fibrinogen	231.1	mg/dL
Indirect, direct coombs test	negative	

LFT/RFT		
AST	51	IU/L
ALT	39	IU/L
ALP	89	IU/L
LDH	1042	IU/L
T.Bil	1.35	mg/dL
D.Bil	0.55	mg/dL
T.Protein	5.8	g/dL
Alb	3.2	g/dL
BUN	37.0	mg/dL
Cr	3.15	mg/dL
T.Chol	174	mg/dL
Uric acid	9.1	mg/dL
Ca	8.1	mg/dL
P	4.6	mg/dL
Urine		
Pro/Cr ratio	413.69	mg/g

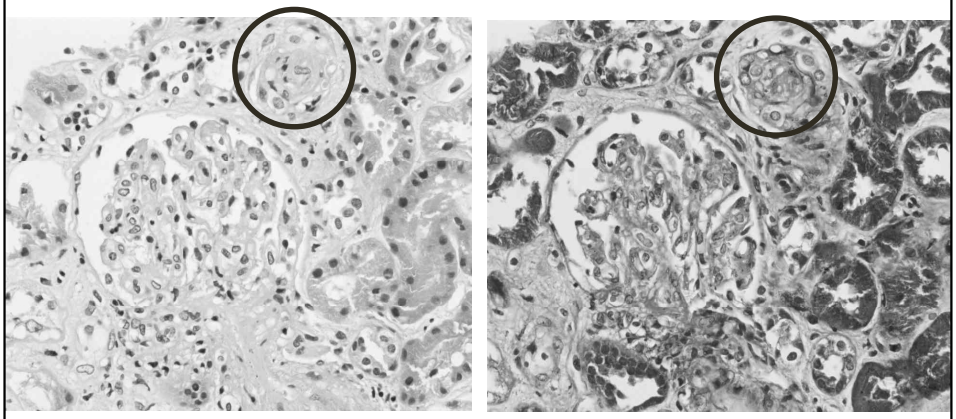
Kidney needle biopsy



: segmental capillary thrombosis of glomeruli

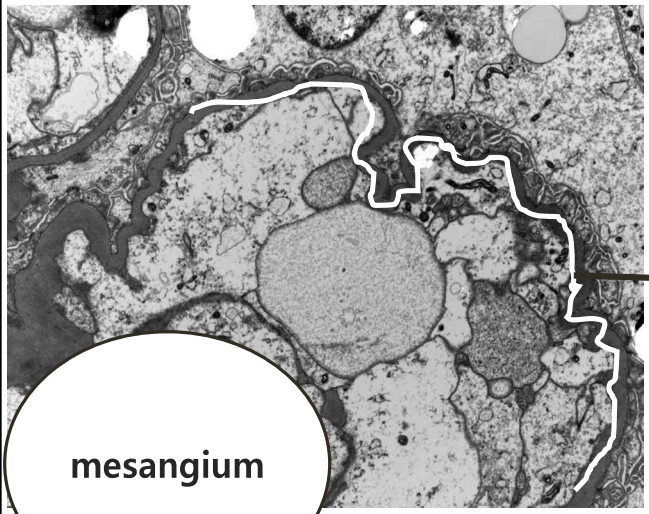
: Fibrin thrombi with obliteration of arteriole

Kidney needle biopsy

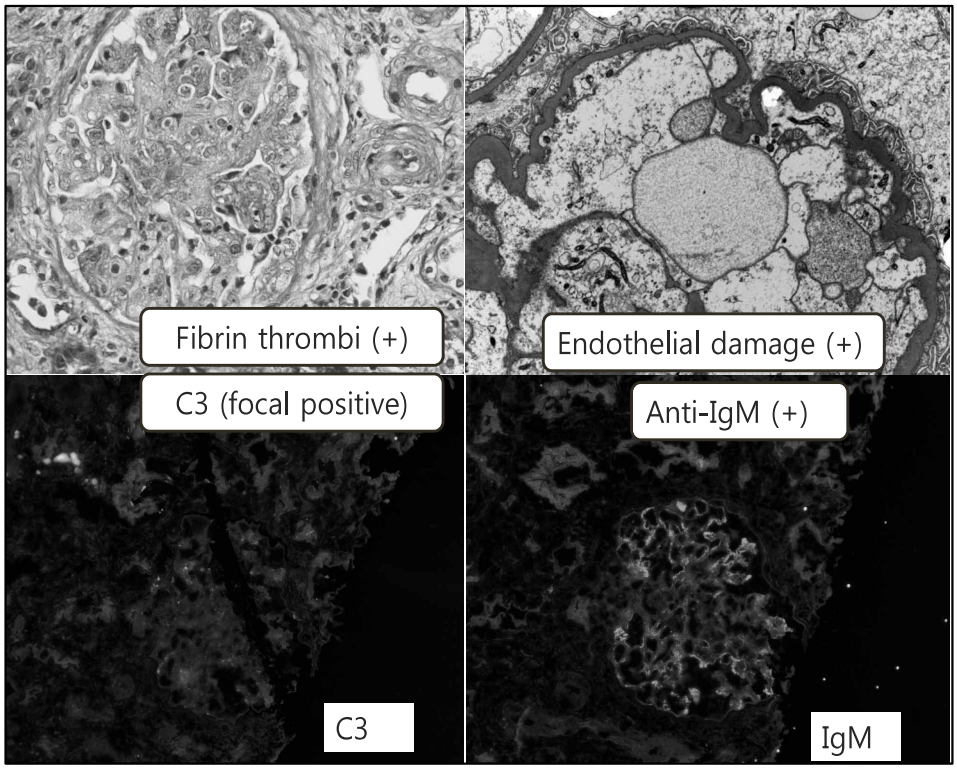


: Fibrin thrombi with obliteration of arteriole

Kidney needle biopsy



ELECTRON MICROSCOPY (X8000)
: wrinkled GBM and swollen endothelial cell



- **Diagnosis**

  Gemcitabine-induced hemolytic uremic syndrome

- **Treatment**

  1. Gemcitabine 중단

  2. Corticosteroid

Progression

	Baseline	9/9	9/17	9/26	10/4	10/14	10/25	11/25
PLT	344K	55K	115K	232K	312K	289K	322K	294K
LDH	272	1042	680	684	477	310	310	332

Gemcitabine 중단
PDS 60mg 시작

Hemodialysis 시작
(Oliguria, Cr: 6.77)

Hemodialysis 유지

Gemcitabine induced thrombotic microangiopathy (TMA)

Chemotherapy-associated renal dysfunction

Vaibhav Sahni, Devasmita Choudhury and Ziauddin Ahmed

Sahni, V. *et al. Nat. Rev. Nephrol.* **5**, 450–462 (2009);

Gemcitabine-induced thrombotic microangiopathy

Nephrol Dial Transplant (2006)

Agent	Dose adjustment required when eGFR 10–50 ml/min (%)	Dose adjustment required when eGFR <10 ml/min (%)	Evidence level[a]
Cisplatin	75	50, but avoid if possible	A
Carboplatin	Approximately 50 (AUC-based dose adjustment)	Approximately 25 (AUC-based dose adjustment)	A
Chlorambucil	75	50	D
Ifosfamide	100	75	B
Cyclophosphamide	100	75	B
Daunorubicin	100	100	D
Doxorubicin	100	100	D
Epirubicin	100	100	D
Carmustine	75 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	D
Lomustine	70 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Semustine	70 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Streptozocin	75	50	D
Mitomycin C	100	75	B
Mithramycin	75	50	B
Azacitidine	100	100	B
Gemcitabine			B
Cytarabine	100	100	D
Methotrexate	50	Avoid	A
Pentostatin	60 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Fludarabine	75	50	D
Cladribine	75	50	D
5-Fluorouracil	100	100	D
Melphalan	75	50	B
Paclitaxel	100	100	A
Vincristine	100	100	B
Vinblastine	100	100	B

Drug	Renal toxicity	Mechanism	Possible preventive strategies	Treatment/s
Cisplatin	ARF; tubular damage; renal concentration defect; polyuria; hypomagnesemia;[12] rarely HUS	Toxic damage to the S3 segment of proximal tubule,[14] loop of Henle, and distal tubules	Volume infusion;[13,21] amifostine[33]	Avoid further use; volume infusion; magnesium repletion; supportive management; dialysis for uremia
Ifosfamide	Subclinical tubular damage in most patients;[60] type 1 RTA; Fanconi syndrome;[60,63] severe electrolyte depletion; nephrogenic diabetes insipidus; reversible ARF; rarely CKD	Proximal tubular damage by metabolites such as chloracetaldehyde; total dose-related toxicity	Limit total dose;[66] Mesna (questionable benefit);[67] avoid concomitant cisplatin	Bicarbonate; phosphate; electrolyte repletion
Cyclophosph				self-limiting
	Hyponatremia	Hyponatremia: increased ADH effect[72]		
Nitrosoureas	Slowly progressive, dose-related, irreversible renal failure, most commonly with streptozocin[78,79]	Glomerular sclerosis and chronic tubulointerstitial nephritis[81]	Volume infusion; avoid high doses	Electrolyte supplementation;, supportive management; dialysis for uremia
Mitomycin C	TTP and HUS often presents as ARF; more common if total dose >60 mg[86]	Thrombotic microangiopathic lesions; glomerular infarction[85]	No established preventive measures	Plasmapheresis;[87] *Staphylococcus* A column immunoadsorption[88]
Mithramycin	High doses can lead to tubular injury and ATN[90]	Unclear—probably direct toxicity	Dose modification (clear data not available)	Supportive measures
Azacitidine	Mild subclinical tubular dysfunction (70% of patients); symptomatic proximal tubular damage[92]	Tubular damage	No established preventive measures	Bicarbonate and electrolyte supplementation
Gemcitabine	Rare incidence of HUS (0.015%)[93]	Microangiopathy	No established preventive measures	Supportive measures
Methotrexate	Nonoliguric renal failure with high dose therapy (1.8%)[96]	Precipitation of methotrexate and 7-hydroxymethotrexate into renal tubules	Volume infusion; alkalinization with sodium bicarbonate; leucovorin rescue[97]	Supportive measures; high-flux dialysis to reduce methotrexate levels;[98] carboxypeptidase-G2 rapid excretion of methotrexate[99]
Pentostatin	Transient elevation of creatinine[99]	Unclear mechanism but might be dose-related[100]	Volume infusion[4]	Supportive
Interleukin 2	Prerenal ARF—completely reversible in most patients	Plasma depletion by capillary leak[102]	No established preventive measures	Volume infusion
Interferon α	Proteinuria (15–20% of treated individuals),[108] usually reversible; rarely nephrotic syndrome;[109] mild, reversible ARF	Minimal-change disease; ATN	No established preventive measures	Supportive measures
Bevacizumab	Proteinuria; rarely, nephrotic syndrome[123]	Immune-complex-mediated focal proliferative glomerulonephritis	No established preventive measures	Supportive measures
Cetuximab	Hypomagnesemia[32]	Magnesium channel TRPM6 deactivation by	No established preventive measures	Magnesium supplementation

thrombotic microangiopathy (TMA)

- **TMA**
  - Microvascular occlusive disorder characterized by predominantly platelet thrombi in the renal and/or systemic circulations

- **Clinical triad**
  - Renal failure (>1.5 mg/dl)
  - Thrombocytopenia (<120*10^9/l)
  - Microangiopathic hemolytic anemia

    (normal fibrinogen, >1 + schistocytes, >1.5* LDH and/or low serum haptoglobin)

- **Incidence**
  - in 2003 the gemcitabine product information from Eli Lilly reported an incidence rate of 0.25% (6 of 2,429 patients) for clinical trials
- **Time course between gemcitabine therapy and the development of HUS**
  - Gemcitabine-associated HUS developed after an estimated median cumulative dose range from 2,450 to 48,000 mg/m^2
  - The median duration of cytotoxic therapy was 5.8 months, with a median of 17.5 doses and cumulative therapy of 18,252 mg/m^2

- **Symptoms**
  - worsening of anemia
  - Thrombocytopenia
  - increments of LDH or serum creatinine
  - elevated blood pressure
  - Proteinuria
  - dyspnea
  - neurological signs

- gradual progression, and indicates the importance of a screening for suggestive anomalies(complete blood count, serum creatinine and urine dipstick) before each cycle of gemcitabine treatment

- **Haematological findings**
  - Delayed: because anaemia and thrombocytopenia may be attributed to myelotoxicity of the anticancer agents
  - PBS should be screened for the presence of fragmented red blood cells
  - increased levels of LDH are observed frequently in tumour patients ➔ marked increase in LDH suggest the potential development of HUS

- **Renal findings**
  - Increase serum creatinine, mild PU, microscopic HU
  - Full or partial recovery of renal function occurred in 66% of patients
  - 24% progressed to end-stage renal failure needing dialysis
  - definitive diagnosis theoretically depends on a renal biopsy
    - ➔ glomerular and/or arteriolar fibrin deposits
    - ➔ demonstrated using immunofluorescence techniques

- **Outcome**
  - prognosis for HUS associated with malignancy is rather poor
  - General HUS: mortality rates of 10–20%
  - CTx. Induced HUS: mortality rates of 40–90%

- **Treatments**
  - Aspirin, dipyridamole and corticosteroids
  - Glucocorticoids and plasma infusion may be used in the initial management
  - plasma exchange is the mainstay of treatment
  - improvement of haematological parameters has been reported relatively frequently with plasma exchange therapy, whereas renal function only rarely responds.