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Hemolytic uremic syndrome (HUS) as a rare complication of induction chemotherapy for acute myeloid leukemia (AML) without maturation

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ABSTRACT

A 75-year-old male was diagnosed with acute myeloid leukemia without maturation and was treated with combination chemotherapy. After the first remission-induction therapy, he reached complete remission. About one month after the first induction therapy, he was diagnosed with a complication of chemotherapy-related HUS (C-HUS). He gradually recovered from the C-HUS after the initiation of a plasma exchange.

In conclusion, it seems that the anti-leukemic drugs might play an important role in the development of chemotherapy C-HUS.

Key words : acute leukemia, chemotherapy-related HUS, thrombomodulin

CASE REPORT

A 75-year-old male was admitted to the hospital in November 2002 with high-grade fever (above 38℃), cough, hypoxia, and progressive general lassitude. Laboratory findings showed the following: hemoglobin level, 5.9 g/dl; leukocytes, 31,890/μl with 79.5% blast; platelet count, 26,000/μl; and reticulocytes, 0.877%. There were no morphological abnormalities of the red blood cells at that time. Other significant laboratory findings included serum lactic dehydrogenase (LDH) 1,107 IU/l; blood urea nitrogen (BUN), 35 mg/dl; creatinine, 1.6 mg/dl; and C-reactive protein, 6.2 mg/dl. A bone marrow aspiration was performed. His bone marrow yielded over 90% of blast without differentiation and with myeloperoxidase and surface marker following CD13, CD33 and HLA-DR were positive. He was diagnosed with acute myeloid leukemia without maturation.

He received one cycle of remission-induction therapy with 25 mg/m^2 daunorubicin (DNR) on days 1-3 and 200 mg/m^2 behenoyl-ara-C (BHAC) on days 1-7. Sulfamethoxazole/trimethoprim (ST), ciprofloxacin hydrochloride

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Table 1. Summary of laboratory data

	NOv.05,02	Dec.17	Jan.05,03	Jan.15	Feb.10	Feb.21
WBC (/μl)/blast (%)	31,890/79.5	6,010/0	1,300/0	1,250/0	4,290/0	6,770/0
Hb (g/dl)	5.9	7.2	8.3	7.2	7.5	6.4
Plt ($x10^4$/μl)	2.6	5.1	5.0	3.8	4.7	8.4
T.Bil (mg/dl)	0.2	0.3	0.9	1.2	0.6	0.5
LDH (IU/l)	1,397	1,996	1,412	2,410	1,243	784
BUN/ Crea (mg/dl)	35/1.6	118/7.2	55/3.9	91/4.0	64/3.0	20/1.6
Proteinuria/Hematuria	(+)/(−)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)
RBC fragmentation	(−)	(+)	(+)	(+)	(+)	(+)
vWF activity (%)			294	317	478	367
TM (FU/ml)		26.5	29.5	24.1	26.5	13.7

(CFPX), and itraconazole (ITCZ) were administered for prophylaxis of an opportunistic infection from day 1. On day 30 after the first chemotherapy, his bone marrow achieved complete remission, and his hemopoiesis slowly recovered.

In the middle of December, hypertension and oliguric started to be gradually noted, although there were no remarkable respiratory symptoms, including sore throat, cough, dyspnea, or abdominal symptoms such as nausea, vomiting, and diarrhea. Urinalysis presented hematuria and mild proteinuria. Anemia and thrombocytopenia then progressed. Although fragmented erythrocytes and schistocytes were noted on the peripheral blood smear, there were no morphological abnormalities of leukocytes. Direct and indirect Coombs tests were negative. Acute renal failure was very severe, with disturbing values of 118 mg/dl BUN and 7.20 mg/dl creatinine. Other significant laboratory values included serum 1,996 IU/l LDH and 6.3 mg/dl C-reactive protein, but the unconjugated billirubin was almost normal. The prothrombin time and activated prothrombin time were both normal, although fibrinogen was slightly increased (400 mg/dl) with normal fibrin degradation products. In spite of the fact that there was no evidence of disseminated intravascular coagulation (DIC), Thrombomodulin (TM), which is associated with endothelial cell damage and the activation of the von Willebrand factor, increased remarkably, as shown in Table 1. As oliguria developed into anuria, the patient demonstrated moderate irritability and drowsiness. We thought that these findings indicated thrombotic microangiopathy (TMA), such as hemolytic hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Continuous hemodialysis and plasma exchange were started; simultaneously, we investigated von Willebrand factor cleaving protease activation (vWF-CP), which was lost in TTP. In addition, his blood culture was negative and stool culture grew *E.coli*, which was not the O157 strain and was negative for verotoxin. However, his vWF-CP activation remained at 52%. Therefore, chemotherapy-related HUS was diagnosed.

After 12 days of hemodialysis and plasma exchange, the BUN, creatinine, LDH, and TM

levels decreased, and the patient experienced renal failure, although his neurological symptoms improved temporarily in the middle of January.

However, the patient's respiratory condition worsened gradually in late February. We diagnosed pneumonia with congestive heart failure. Although oxygen therapy, antibiotics, and diuretics were started with other supportive therapies, he died three months after admission.

DISCUSSION

We presented a patient with HUS that developed after induction chemotherapy for AML. TMA includes HUS, and TTP is a common complication in patients with cancer. Chemotherapy-related HUS (C-HUS) has a tendency to occur as a complication in patients who have achieved a partial or complete response to therapy for carcinoma as gastric cancer and is closely associated with the usage of MMC and 5-FU [1].

However, a few cases of patients developing C-HUS after treatment for acute leukemia have been reported [2, 3]. This patient maintained vWF-CP activation of 52% beside he had severe renal failure and hemolytic anemia with fragmented erythrocytes. We made a diagnosis of C-HUS according to clinical features and laboratory findings.

The patient's TM levels were very high. Mori et al reported that TM levels were significantly higher in patients of HUS who died than in patients who survived [4]. It seems that TM levels may reflect the severity of C-HUS in a patient.

After the start of hemodialysis and plasma exchange, the abnormal findings due to C-HUS gradually improved. Although C-HUS is rare at the onset, during, and after induction chemotherapy for acute leukemia, it can be a fatal complication. We emphasize that quick diagnoses for C-HUS are necessary so that therapies, such as hemodialysis or plasma exchange, can be started as soon as possible.

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