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Successful treatment with intravenous colistin of sepsis caused by metallo-beta-lactamase-producing multidrug-resistant *Pseudomonas aeruginosa* in a patient with acute myeloid leukemia

Hitoshi Hanamoto, Keigo Sano, Ryousuke Fujiwara, Keiko Yamazaki, Hideo Yagi, Kazuo Tsubaki

Department of Hematology, Nara Hospital, Kinki University School of Medicine

Abstract

In recent years, multidrug-resistant *Pseudomonas aeruginosa* (MDRP) has been detected in patients undergoing chemotherapy for hematological malignancies. MDRP can cause life-threatening infections such as sepsis and pneumonia, being a major concern for physicians and patients. Here, we report the case of a patient with acute myeloid leukemia (AML; FAB classification M2) who developed septic shock from MDRP infection during leukopenia induced by the first cycle of consolidation therapy, and in whom the combination of colistin administration and steroid pulse therapy promptly improved the septic shock symptoms and cleared MDRP from the blood. Although a transient nephrotoxic effect was observed, it subsided rapidly on discontinuation of treatment. MDRP in stool samples fell to undetectable levels following oral doses of polymyxin B sulfate. The patient could continue consolidation chemotherapy and has remained in remission.

Key words: colistin, MDRP, AML, sepsis

Introduction

Multidrug-resistant *Pseudomonas aeruginosa* (MDRP) has acquired resistance to at least three classes of antibiotics, carbapenems, fluoroquinolones and aminoglycosides. MDRP infection is designated as Category 5, for which reporting is mandatory by sentinel facilities. MDRP often fails to respond to a wide range of antibiotics besides the above; therefore, serious MDRP infections such as sepsis may result in a poor clinical outcome due to the lack of effective therapies. It is especially life-threatening for patients who are undergoing intense chemotherapy leading to a decrease in the number of white blood cells (particularly neutrophils). In recent years, the number of MDRP infections has been increasing[1,2] and physicians are becoming more concerned about the lack of established therapies.[3] Colistin has been used to treat MDRP infections in the US and Europe[4]; however, it is not commercially available in Japan, which makes it difficult for physicians to use it for therapy. In our hospital, colistin is available in order to control MDRP infections under the management of the Infection Control Team (ICT). We report here a case of MDRP-induced sepsis that developed during consolidation chemotherapy for acute myeloid leukemia (AML), which was successfully treated with prompt colistin administration, causing no adverse effects.

Case report

Patient: 51-year-old man
Chief Complaint: General fatigue, shortness of breath

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History of Present Illness : The patient developed general fatigue and shortness of breath in April 2011 and visited the nearest clinic. Laboratory examination at that time showed white blood cells (WBC) 13,600/uL, red blood cells 2, 320,000/uL, hemoglobin (Hb) 8.4 g/dL, hematocrit 25% and platelets (Plt) 62,000/uL revealing an increase in white blood cells, anemia and thrombocytopenia. He was referred to our hospital for further evaluation on May 2, 2011 and was admitted on May 6, 2011 due to the presence of leukemic cells in the peripheral blood.

Past Medical History : None

Physical Examination : Body temperature 36.7°C, blood pressure 102/60 mmHg, pulse 66 (regular). Conjunctiva pallor was noted. Scleral icterus was absent. Respiratory sounds were normal with no murmurs. Abdomen was flat with no signs of tenderness or hepatosplenomegaly. No neurological abnormalities were found. No swollen lower extremities or superficial lymph nodes were observed.
Laboratory Examination : Table 1
Progress : Fig. 1

On May 9 (Day 3) after admission, laboratory tests showed an increasing level of CRP (2.4 mg/dl), suggesting the presence of infection ; therefore, administration of IPM (0.5 g x 2/day) and AMK (200 mg x 2/day) along with GRNX (400 mg/day) and ITCZ (200 mg/day) was initiated for intestinal antisepsis. On May 10, the patient was diagnosed with acute myeloid leukemia (FAB classification M2) by bone marrow biopsy, and remission induction therapy was initiated using the JALSG AML201 protocol (Ara-C 100 mg/m² x 7 and DNR 50 mg/m² x 5) following insertion of a central venous catheter (PICC). On May 18 (Day 8), the white blood cell count dropped to 810/uL (net 46%). Since the patient also developed diarrhea and fever, possible signs of pseudomembranous colitis, VCM (0.5 g x 4/day) was added to the regimen. On May 19, IPM was replaced with MEPM (0.5 g x 2/day). On May 20, the patient developed a high temperature and we reinitiated administration of AMK (200 mg x 2/day), which has been discontinued, and added intravenous immunoglobulin (5 g/day x 3). The fever fell on May 23, and on June 1, a general improvement in the condition and an increase in the white cell count to 1420/uL (net 13%) were observed. On June 7, laboratory tests showed WBC 4650/uL (net 45%), Hb 8.4 g/dL and Plt 1,077,00/uL, indicating further improvement of hematopoiesis, and remission

Table 1 Laboratory data

WBC	10500/μl	T-Bil	0.2 mg/dl	BM	
stab	0%	AST	15 U/L	NCC	48.2x10^4/μl
seg	32%	ALT	18 U/L	MgK	35/μl
lympo	13%	ALP	306 U/L	Blast	28.8
mono	3%	LDH	368 U/L	Auel body	+
myelo	26%	BUN	15 mg/dl	PO	+
Blast	23%	CRN	0.9 mg/dl		
Hb	9.3 g/dl	UA	6.3 mg/dl	Surface marker in BM	
Plt	57000/μl	TP	7.7 g/dl	CD7	−
		ALB	3.4 g/dl	CD14	−
PT-INR	1.11	CRP	3.76 mg/dl	CD16	−
APTT	23.6 sec	Na	137 mEq/L	CD13	+
FIB	545 mg/dl	K	4.1 mEq/L	CD33	+
FDP	3.6 μg/ml	Cl	107 mEq/L	CD56	+
AT-3	112.7%	Ca	8.4 mg/dl	CD34	+
				HLA-DR	+

Karyotype
45,X,-Y,t(8;17;21)(q22;q21;q22) 5/20

WT-1mRNA 12000 copy/μgRNA
AML/MTG8 mRNA 540000 copy/μgRNA
FISH AML1/ETO 184/200

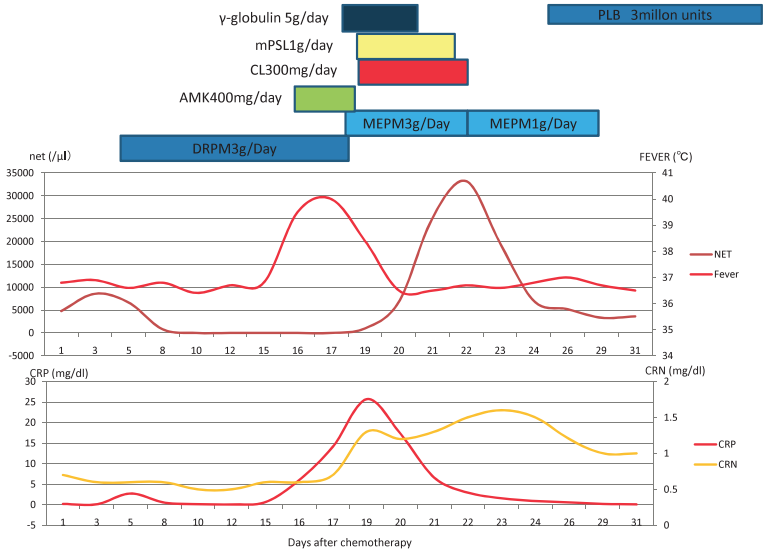

Fig. 1 Clinical course
Clinical course including Fever, net, CRP and CRN.
AMK : amikacin sulfate, MEPM : meropenem hydrate, DRPM : doripenem hydrate
PLB : polymixin B sulfate, CL : colistin, mPSL : methylprednisolone sodium succinate
net : neutrophil, CRP : C-reactive protein

was confirmed by bone marrow examination on June 8 (AML1/ETO negative by FISH, WT-1 negative by PCR). Although the patient experienced prolonged diarrhea during the period of leukopenia, only Candida was positive in stool cultures. As the white cell count recovered, subjective symptoms including diarrhea also improved. Nevertheless, laboratory screening on June 4 revealed the presence of MDRP in stool cultures (Table 2). Since the amount of MDRP was very small (20 counts) and diarrhea was resolving, it was determined to be an asymptomatic carrier state. Subsequently, we initiated consolidation therapy with high-dose cytarabine (Ara-C 2,000 mg/day x 5) through PICC on June 13 based on the detection of AML1/ETO-positive cells and the characteristics of CBF AML. On June 17 (Day 4), DRPM (1 g x 3/day) was given seeing that CRP had increased to 2.74. As diarrhea was noted at the same time, VCM (0.5 g x 4/day) was also added. On June 17, stool cultures showed positive for MRSA (3+). On June 20 (Day 7), the patient experienced a decrease in WBC to 870/uL (net 94%), declining blood pressure and worsening diarrhea, which were managed by adding more intravenous fluid. On June 28, DRPM was replaced with MEPM (3 g/day) and AML (400 mg/day) was added as the patient developed a high fever. On June 28, a blood culture test preliminarily showed positive for Gram-negative bacilli, giving a diagnosis of sepsis, and we added G-CSF to the regimen. On July 1, the peripheral blood culture report showed the presence of MDRP, revealing that the patient had

Table 2 Susceptibility testing results of *Pseudomonas aeruginosa*

Antimicrobial agent	MIC	Sensitivity
ampicillin	>32	R
piperacillin	>128	R
cefazolin	>64	R
cefotaxime	>64	R
caftazidime	>64	R
cefepime	>64	R
cefmetazole	>64	R
azithromycin	16	I
imipenem	>16	R
meropenem	>16	R
amikacin	>64	R
gentamicin	>16	R
minocycline	>16	R
fosfomycin	>256	R
sulfamethoxazole/trimethoprim	>320	R
lomehloxiacin	>8	R
ciproxacin	>4	R

gone into MDRP-induced septic shock. Since the symptoms worsened severely, showing BP 80/40, we administered with steroid pulse therapy (mPSL 500 mg/day) and catecholamine on July 1. Antithrombin III was also administered as the laboratory test showed Fib 569 mg/dL, FDP 9.5 ug/mL and AT-3 79%, possibly indicating DIC. When we chose antibiotics we considered that MDRP might still be partially sensitive to monobactams or gentamicin.[5] However, as we did not find either prompt recovery of the white cell count or sensitivity to these drugs, we administered colistin (CL) with written consent

obtained after we, together with the ICT chief physician, provided the patient and his wife with sufficient detailed information. CL was given at a dose of 150 mg x 2/day from July 1 to July 4. The combination of CL and steroid pulse therapy promptly reduced the fever and improved the septic shock symptoms. The patient eventually survived the crisis, and hematopoiesis and general conditions were restored and MDRP was found to have cleared on July 2. Although the patient experienced mildly decreased renal function during treatment with CL, it was restored to normal on termination of treatment and no deterioration was noted afterwards. On the other hand, stool cultures tested positive for MDRP for some time. There are some reports that PL-B is effect to MDRP.[6,7] For this reason, we replaced GRNX with PL-B (3,000,000 units/day) for intestinal antisepsis, which cleared MDRP in the stool on July 25. Administration of PL-B for antisepsis was continued afterwards and chemotherapy was continued on without interruption.

Discussion

Development of sepsis during chemotherapy is a potentially fatal complication. Increasing frequency of multidrug-resistant organisms isolated from patients undergoing chemotherapy has become a serious problem in recent years. MDRP is particularly life-threatening with a high mortality rate, and requires control measures to prevent nosocomial infections.[8] Antibiotics that are effective against MDRP are not currently available in Japan, making the management of MDRP infections very difficult. CL is effective against MDRP and is frequently used for treatment in the US and Europe. CL is a polypeptide antibiotic that kills the bacteria by disrupting membrane integrity and demonstrates excellent activity against Gram-negative bacilli, including *Pseudomonas aeruginosa, Acinetobacter, Escherichia coli and Klebsiella pneumoniae*. Gram-negative bacteria that are CL-resistant include Serratia and Proteus. Synergistic effects of CL used in combination with other antibiotics have been reported, which suggests that combination therapy may hold promise for more effective treatment. There are also increasing reports of successful treatment against MDRP with the appropriate combination of antibiotics that have been optimized by reviewing the culture results of the BC plates.[9] It has been shown that the response rate of CL for MDRP is 58%-74%.[10] In addition, a study in Japan by Kaneyama et al. revealed that 3.6% among 139 *Pseudomonas aeruginosa* strains isolated from the blood was CL-resistant, suggesting that CL would be a fairly effective drug choice. In the US, CL is given by intravenous injection at a dose of 2.5-5 mg/kg divided into two to four equal doses. CL is eliminated by the kidneys and may require dose adjustment for patients with renal disease.[11] In our protocol, CL is given twice at a dose of 150 mg, which corresponds to 5 mg/kg. The main toxicities of CL are nephrotoxicity and neurotoxicity. It has been thought that approximately 20% of patients would experience nephrotoxicity ; however, Reina reported that the appearance of nephrotoxic effects is rare.[12] Since nephrotoxicity develops in a dose-dependent manner, the drug dose as well as the amount of intravenous fluid should be adjusted according to the renal function. Nonetheless, the nephrotoxic effects appear to be transient and subside on discontinuation of treatment. As the development of nephrotoxicity is common during the early days of treatment, close monitoring of renal function from the early stage is considered to be essential. In our case, the patient first showed abnormal renal function due to the development of septic shock prior to CL administration, and a gradual worsening of symptoms was observed during the early days of treatment with CL. However, the patient subsequently showed signs of recovery, enabling prompt termination of CL, which led to a rapid improvement of symptoms (Fig. 1). I contrast, neurotoxicity was not observed. During remission, MDRP was isolated from stool cultures, suggesting the possibility of non-nosocomial transmission. Meanwhile, the growth of MDRP might have been accelerated with the use of GRNX for intestinal antisepsis and of carbapenems during febrile neutropenia.[13] In our hospital, the ICT unit imports CL and maintains it in stock for immediate availability in case of emergency. For this reason, it was possible to provide CL promptly to the patient under the surveillance of the ICT. Without CL the patient might not have survived the septic shock that developed during leukopenia induced by chemotherapy, confirming the importance of the structure in which the ICT works closely and makes CL available for urgent use. Moreover, it might be more effective to use PL-B for intestinal

antisepsis when MDRP is isolated from stool samples as the use of PL-B in our case after the development of sepsis reduced MDRP in stool to an undetectable level, enabling a high dose of cytarabine administration subsequently as scheduled. Ideally, combination drugs have to be optimized using the BC plate method. However, this is unavailable in our hospital; thus, we empirically chose carbapenems in combination with CL. Administration of CL should have contributed at least to the stabilization of symptoms until recovery of the white cell count, which is the primary cure for MDRP-induced sepsis. In addition to prompt treatment for MDRP infections, it is important that every effort should be made to prevent MDRP spreading. It is also recommended to have CL in stock for prompt and appropriate use.

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