Therapy-related myelodysplastic syndrome following cyclophosphamide pulse and/or methotrexate therapy in a patient with systemic lupus erythematosus.

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[Case Report]

THERAPY-RELATED MYELODYSPLASTIC SYNDROME FOLLOWING CYCLOPHOSPHAMIDE PULSE AND/OR METHOTREXATE THERAPY IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract : A 27-year-old woman exhibited progressive pancytopenia during cyclophosphamide pulse therapy for lupus nephritis and low-dose methotrexate therapy for severe arthralgia. Bone marrow aspiration revealed highly abnormal cell morphology, indicating therapy-related myelodysplastic syndrome. Pancytopenia and bone marrow cell morphology improved 3 months after discontinuation of cyclophosphamide. It is necessary to promptly examine bone marrow cell morphology and chromosomal aberration in cases with connective tissue diseases complicated by sudden cytopenia during immunosuppressive therapy with chemotherapeutic agents.

Key words : cyclophosphamide, therapy-related myelodysplastic syndrome, systemic lupus erythematosus

INTRODUCTION

Two types of myelodysplastic syndrome (MDS) are known : primary MDS of unknown cause ; and therapy-related MDS (T-MDS) that follows administration of antitumor drugs or radiation. T-MDS frequently develops in patients with hematopoietic neoplasms who have received large amounts of antitumor drugs[1,2)], although T-MDS has also been reported in cases with connective tissue diseases[2-4)]. T-MDS is generally resistant to therapy and has poor prognosis[1,2)]. It is often accompanied by chromosomal aberrations[1,2)], and few cases achieve spontaneous remission. Here, we report a rare case of systemic lupus erythematosus that transiently revealed bone marrow cell morphology compatible with MDS during immunosuppressive therapy with cyclophosphamide (CYC) and/or methotrexate (MTX).

CASE REPORT

In 1991, a 16-year old woman exhibited high fever, butterfly rash and photosensitivity, and was diagnosed with systemic lupus erythematosus (SLE) at a local clinic. She was treated with prednisolone (PSL), but continued to have relapses and was referred to our department in 1997 (at age 22 years).

In September 1997, renal biopsy was performed as her urine protein became positive, and she was diagnosed with lupus nephritis (WHO IIIB). She received methyl-PSL pulse therapy followed by CYC pulse therapy (total dose, 3,400 mg) but proteinuria continued. In addition, methotrexate (MTX) at 4 mg/week (total dose, 768 mg) was administered due to high fever and arthralgia, and the amount of PSL was then decreased gradually.

Proteinuria again developed in February 2002. In June, a second renal biopsy was performed, and she was diagnosed with lupus nephritis (WHO IVC). After receiving CYC pulse therapy for 3 months

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(monthly dose, 750 mg/month ; total dose, 2,250 mg), proteinuria decreased. However, from the end of August, a high fever of 39°C or more appeared once per week, and anemia progressed simultaneously. The patient was admitted to our department in September 2002 (at age 27 years).

On admission, her palpebral conjunctiva was anemic, and subcutaneous hematoma was observed in the right lower leg. Superficial lymph nodes were not palpable. Laboratory tests revealed an increased erythrocyte sedimentation rate of 41 mm in 1 hour, and a white blood cell count of 9,400/μl (11% Band ; 64% Seg ; 5% Ly ; 11% Mo ; 5% Eo ; 2% Myelo ; 1% Meta), decreased hemoglobin of 6.0 g/dl, and platelet count of $11.9\times10^4/\mu$l. Total protein was 5.4 g/dl, LDH was 330 U/L, Crea was 1.0 mg/dl, and CRP was 1.5 mg/dl. Levels of C3, C4, and CH50 were normal. Anti-DNA antibodies were negative. Urinalysis showed no proteinuria (Table 1). Microbes were not identified on culture of blood, sputum, and urine. Because pancytopenia had progressed (white blood cells, 2,600/μl ; hemoglobin, 5.3 g/dl ; platelets $2.9\times10^4/\mu$l), bone marrow aspiration was performed. She was subsequently diagnosed with MDS and refractory anemia with excess blasts (RAEB-1) (Figures 1A-1C) based on the WHO classification[5]. Slightly hypercellularity of bone marrow was noted in the biopsied sample, but no chromosomal aberrations were present. T-MDS was suspected because bone marrow cell morphology was highly abnormal and had developed during CYC pulse and low-dose

Table 1. Laboratory Findings at Presentation

Peripheral blood		Blood chemistry					
WBC	9,400/μl	TP	5.4	g/dl	C_3	99	mg/dl
Ne	75%	Alb	3.4	g/dl	C_4	21	mg/dl
Eo	5%	AST	55	IU/l	CRP	1.5	mg/dl
Ba	1%	ALT	28	IU/l	Coombs' test	(−)	
Ly	5%	LDH	330	IU/l	ANA	×320 Sp, CE	
Mo	11%	γ-GTP	68	IU/l	a-DNA Ab	5.0>	IU/ml
Myelo	2%	TB	0.6	mg/dl	a-Sm Ab	(−)	
Meta	1%	TTT	1.0	mg/dl	a-RNP Ab	93.2	IU/ml
RBC	$1.71\times10^6/\mu$l	ZTT	2.4	mg/dl	a-CL Ab	(−)	
Hb	6.0 g/dl	BUN	15	mg/dl	CH50	47.7	U/ml
MCV	107.3 fl	Creatinine	1.0	mg/dl	PAIgG	64.8	ng/10^7
MCH	35.3 pg	UA	10.1	mg/dl			
MCHC	32.9%	β2M	4.29	μg/dl	Virological results		
Plt	11.9×10^4/μl	T-Chol	139	mg/dl	EBVEA-IgM (IF)	10>	
Ret	11.1‰	TG	303	mg/dl	EBVEA-IgG (IF)	(+)40	
		Na	142	mEq/l	EBNA (IF)	indeterminable	
ESR	41 mm/h	K	4.1	mEq/l	CMV antigen	0/0	
		Cl	107	mEq/l	HSV1 Ab (NT)	(−)	
Urinalysis		Fe	114	μg/dl	HSV2 Ab (NT)	(−)	
pH 5.5		UIBC	225	μg/dl	Parvovirus B 19 IgM	(−)	
SG 1.018		Ft	254	ng/dl	HZVIgM (EIA)	(−)	
Protein (±), blood (−)		$Vt.B_{12}$	210	pg/ml	HZVIgG (EIA)	(+)	
RBC 1-4/1		Foric acid	1.8	ng/ml	Rubella IgM (EIA)	(−)	
WBC 20-29/1					Rubella IgG (EIA)	(+)	
protein 0.05 g/day		Serology			Mumps IgM (EIA)	(−)	
		IgG	691	mg/dl	Mumps IgG (EIA)	(+)	
		IgA	108	mg/dl	HIV-1/2 Ab (CLIA)	(−)	
		IgM	28	mg/dl			
		γ-glob	0.6	g/dl			

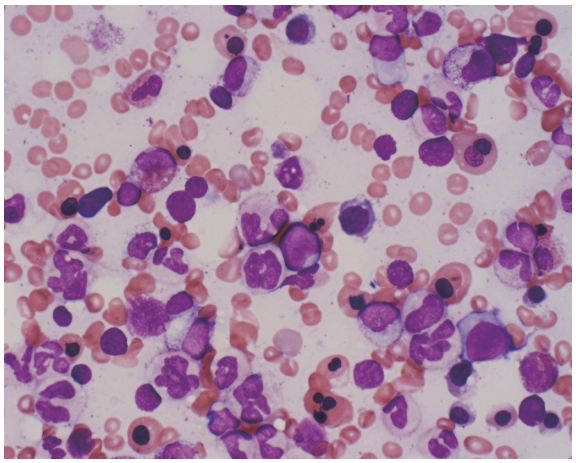

Fig. 1A.

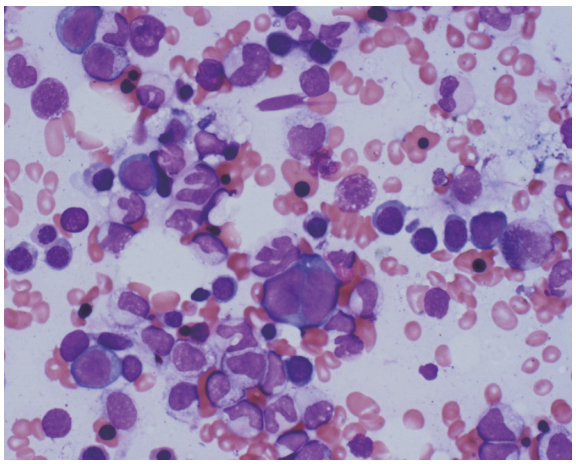

Fig. 1B.

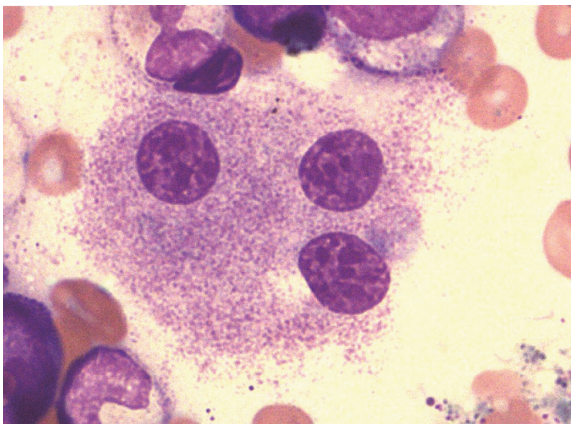

Fig. 1C.

Fig. 1. Bone marrow aspirate shows abnormal morphologic changes in multilineage blood cells.
(A-B) Twenty-four percent of erythroblasts exhibit dysplastic features including multiple nuclei, nuclear fragmentation, and megaloblastic changes. The proportion of myeloblasts was also increased (5.2% in total bone marrow cells ; 7.6% in non-erythroid cells), although pseudo-Pelger-Huet anomaly is rare.
(C) Morphologic abnormalities such as multiple small nuclei are observed in 10% of megakaryocytes.
May-Giemsa stain. Original magnification, ×200(A,B), × 1,000(C)

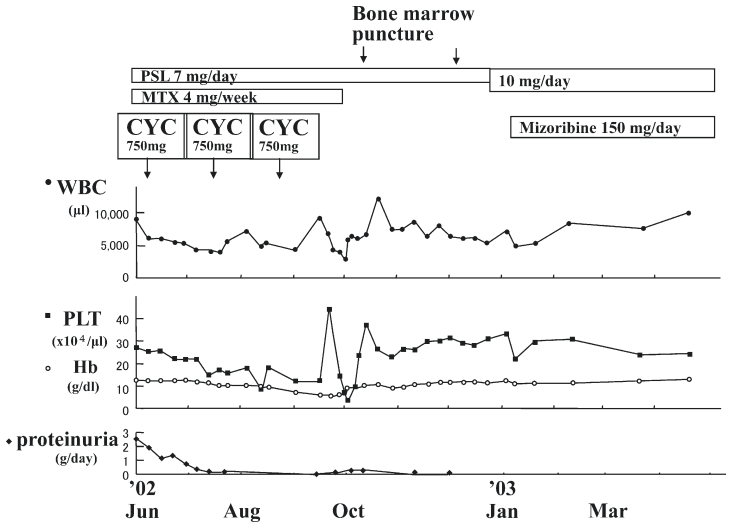

Fig. 2. Clinical course of the present case.
PSL : prednisolone
MTX : methotrexate
CYC : cyclophosphamide

MTX therapy. Administration of CYC and MTX was discontinued, and concentrated red cells were transfused due to severe anemia. Fever declined gradually and pancytopenia improved accordingly. Three months later, bone marrow aspiration revealed improved cell morphology. Clinical course is shown in Figure 2.

DISCUSSION

Drugs, chemicals, viral infection, or radiation can cause acquired bone marrow failure syndromes. In this case, pancytopenia associated with myelodysplasia developed during CYC and pulse therapy for lupus nephritis and low-dose MTX therapy. Bone marrow cell morphology similar to those of RAEB indicated T-MDS, as the patient repeatedly received the alkylating agent CYC.

T-MDS is a myeloid disorder that is seen after chemotherapy or radiotherapy. Approximately half of patients with T-MDS have a history of hematopoietic malignancies, including malignant lymphoma, myeloma and macroglobulinemia[1,2], and the other half have various cancers, although there have also been reports of cases with nonneoplastic disorders, including collagen diseases such as SLE, Behçet's syndrome, and rheumatoid arthritis (RA)[2-4,6-13] (Table 2).

Drugs for chemotherapy, particularly alkylating agents such as melpharan and CYC are more likely to induce T-MDS[14,15]. Alkylating agents are known to decrease hematopoetic potential for pluripotent stem cells and cause bone marrow hypoplasia. It has been suggested that T-MDS develops based on hematopoietic stem cells injured by chemotherapeutic agents during convalescesce from

Table 2. Clinical & pathologic features in patients with connective tissue disease complicated with MDS or AML after chemotherapy

Age	Diagnosis	Medication			Myeloid disorder	Cytogenetics	Outcome
		Type	Cumulative dose, g	Duration, years			
32	SLE	Cytoxan	NA	NA	AML M4Eo	Inv16	remission
23	SLE	AZA	52	0.8	AMML	NA	died
31	SLE	AZA	273	6	SMML	NA	died
24	SLE	AZA	40	0.75	AML	NA	died
67	SLE	CYC	4	1	AML M2	NA	died
32	SLE	CYC/AZA	27/30	0.8/2	AML M4Eo	Inv16, (p13,q22)	remission
44	SLE	CYC/AZA	1.7/37	0.16/2	MDS→AML M2	Monosomy 7	died
41	SLE	CYC/AZA	5.4/89	0.5/7	AML M4	Monosomy 7	remission
40	SLE	AZA	300	6	AML M6	7q(22)-	remission
29	SLE	AZA	55	0.5+0.5	AML	NA	died
50	SLE	CYC/AZA	120/50	4/1.5	AML M5b	NA	died
51	Behçet	CHL	NA	NA	RAEB-T→AML M2	NA	NA
46	Behçet	CHL	NA	NA	AML M2	5q,-3,7,12,20	remission
57	WG	CYC	109	2	MDS-NOS	5q-	died
64	WG	CYC	112.5	3	RAEB-T	7q-	died
75	WG	CYC	120	2	RAEB-T	Monosomy	living
36	TA	CYC	91.2	2	MDS-NOS	7q-	living
72	PM	CHL	6.5	3	RAEB	5q-	died
46	GP	CYC	110	3	MDS-NOS	Monosomy	died

SLE=systemic lupus erythematosus ; WG=Wegener's granulomatosis ;
TA=Takayasu arteritis ; PM=polymyositis ; GP=Goodpasture's syndrome ;
AZA=azathioprine ; CYC=cyclophosphamide ; CHL=chlorambucil ;
AML=acute myeloid leukemia ;
RAEB-T=refractory anemia with excess blasts in transformation ;
MDS-NOS=MDS not otherwise subclassified
AMML=acute myelomonocytic leukemia ; SMML=subacute myelomonocytic leukemia
NA=not available

bone marrow hypoplasia.

Approximately 30% of cases showing T-MDS develop to therapy-induced acute myeloid leukemia (T-AML) each year[2], and the condition is often resistant to therapy[1,2]. WHO classifications are difficult to apply to T-MDS, as morphological abnormalities in the three blood cell lines are severe. In addition, chromosomal aberrations are seen in 80-90% of cases ; abnormal chromosome 5 (5q-) or chromosome 7 (-7) is seen in 50-80%[1,2].

The relative risk of T-MDS and T-AML development by cytostatic agents is 100 times or more that of primary diseases[16] ; this is presumed to be dependent on total dose[17]. Total dose of CYC in this case was 5,650 mg, which did not reach the 20,000 mg considered to influence the relative risk of CYC. Furthermore, bone marrow cell morphology improved 3 months after discontinuation of CYC, and no chromosomal aberrations were seen. For these reasons, a diagnosis of typical T-MDS was not confirmed.

Michels *et al*. suggested that there are three stages of therapy-related panmyelosis : (1) pancytopenia associated with myelodysplastic changes in which the marrow blast count is frequently <5% ; (2) frank MDS ; and (3) overt AML[2]. It is possible that this case was in the early stages of T-MDS/T-AML, although long-lasting spontaneous improvement is extremely rare in MDS patients[18].

The patient had been receiving MTX at a dose of 4 mg/week for the treatment of severe arthritis. MTX suppresses DNA sysnthesis by inhibiting dihydrofolate reductase, and its chromosome-breaking effect leads to damage in bone marrow cells[19]. There have been several reports and case series in which hematological malignancies have developed in autoimmune diseases receiving MTX[4,20-25]. In particular, there have been case reports of lymphomas and lymphoproliferative disorders (LPDs), developing during MTX therapy for autoimmune diseases, and spontaneously regressing shortly after discontinuation of treatment. Such LPDs are considered to be MTX-associated LPDs, and are recognized by the WHO among the immunodeficiency-associated LPDs[26]. Although rarely described, MDS have been reported patients with autoimmune diseases after MTX therapy[27-29]. Moreover, a relationship between the use of MTX and T-MDS has not been demonstrated[30-33]. However, it is possible that combined therapy with MTX and CYC influenced the development of T-MDS in this case.

There have only been two case reports on complicating SLE and MDS[34,35], and in those cases, MDS developed before SLE, and one showed chromosomal aberrations[35]. In this case, it was difficult to infer whether MDS was related to SLE.

Some viruses, including HIV, are known to induce hematopoietic failure, such as in MDS. It has been reported that parvovirus B 19 infection elicits transient MDS-like bone marrow findings[36,37], and these cases resulted in spontaneous improvement without treatment. In this case, there was no evidence of viral infection by HIV, parvovirus, cytomegalovirus or EB virus. However, an unknown infection cannot be excluded as a cause of hematopoietic failure, as the patient had high fever before the occurrence of pancytopenia.

Consequently, it is noteworthy that the hematopoietic failure in this case was in the early stages of T-MDS induced by CYC and/or MTX. Alkylating agents are frequently administrated to patients with connective tissue diseases, and cytopenia is one of the most common side effects of the drug. It is thus necessary to promptly examine bone marrow cell morphology and chromosomal aberrations in cases with sudden cytopenia during immunosuppressive therapy with chemotherapeutic agents.

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