CASE REPORT

Acute myeloid leukemia developed through myeloproliferative features during immunosuppressive therapy for juvenile idiopathic arthritis

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Abstract : A 17-year-old male with thrombocytosis and exacerbation of arthralgia during intensified immunosuppressive therapy with tocilizumab, prednisolone, and methotrexate for juvenile idiopathic arthritis (JIA) was referred to our department. Bone marrow examination revealed myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U). Peripheral myeloblasts disappeared temporarily after discontinuation of tocilizumab but progressed to acute myeloid leukemia six months after the development of MDS/MPN-U. The patient sustained complete remission after unrelated bone marrow stem cell transplantation, followed by chemotherapy. The arthralgia also improved after chemotherapy. The possibility of developing malignancies during immunosuppressive therapy in patients with JIA should be considered. J. Med. Invest. 71 : 335-339, August, 2024

Keywords **:** *juvenile idiopathic arthritis, acute myeloid leukemia, myelodysplastic syndrome, tocilizumab, myeloproliferative neoplasm*

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for at least six weeks, with a reported frequency of 10–15 cases per 100,000 children in Japan (1). The incidence of malignancy may increase during the clinical course of JIA (2) ; however, its epidemiology in Japan remains unclear. We report a case of acute myeloid leukemia (AML) arising from a myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U), that developed two years after the initiation of immunosuppressive therapy for systemic JIA.

CASE REPORT

A 17-year-old male was referred to our department with thrombocytosis and myeloblasts in the peripheral blood. The patient had a history of JIA for two years. When he developed JIA with persistent fever and arthralgia, his hemoglobin level was 6.2 g/dl, white blood cell count was 8.2×10^9/L, platelet count was 359×10^9/L and the level of serum matrix metalloprotease-3 (MMP-3) was at 374.7 ng/mL. His hemoglobin level was stable around 13.0–13.5 g/dl, white blood cell count was $4.2–9.9 \times 10^9$/L, and the platelet count was $146–243 \times 10^9$/L, before development of hematological disease. JIA was controlled with prednisolone, methotrexate, and adalimumab ; however, adalimumab was switched to tocilizumab due to exacerbation of arthralgia four months before visiting our department.

Physical examination revealed no joint swelling. Complete blood examination revealed a hemoglobin level of 12.3 g/dL, white blood cell count of 2.7×10^9/L and myeloblasts were 4.5% (Table 1). The platelet count increased to 704×10^9/L, while kidney and liver function were normal. MMP-3 levels were slightly elevated at 171 ng/mL. Bone marrow examination revealed a hypercellular marrow (Figure 1A) with myelodysplastic changes, such as pseudo-Pelger–Huet anomaly (Figure 1B) and micro-megakaryocytes (Figure 1C) along with an increase in megakaryocytes (Table 1). The proportion of myeloblasts increased to 11.2% of all nucleated cells (Figure 1D, Table 1). Myeloblasts were positive for CD13, 33, and 34, HLA-DR, and CD117 and negative for CD3 and 19, by flow cytometry. The karyotype was 45, XY, with a deletion of chromosome 7. The Philadelphia chromosome or the *JAK2* V617F mutation was not detected and *WT1* mRNA was 5,100 copies/μg RNA in the bone marrow. Based on these findings, the patient was diagnosed with MDS/MPN-U according to World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, 2017.

After discontinuation of tocilizumab, the platelet count gradually decreased to the normal range, and peripheral myeloblasts disappeared over the next four months (Figure 2). However, soon after, blood tests showed increased peripheral white blood cells and myeloblast counts of up to 20.5% (Figure 2). The patient was diagnosed with acute myeloid leukemia with myelodysplasia-related changes (AML-MRC), according to the WHO classification of tumors of hematopoietic and lymphoid tissues, 2017. The cellularity of the bone marrow was reduced and megakaryocytes were decreased. However, the morphological features of myeloblasts did not change. In addition to monosomy 7, the bone marrow karyotype revealed trisomy eight.

Induction therapy with idarubicin and cytarabine failed to achieve hematological remission. After reinduction therapy

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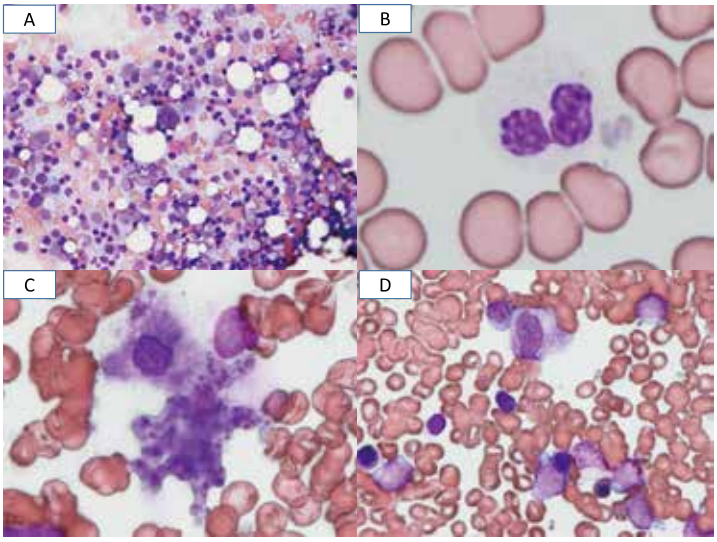

Figure1. Bone marrow examination when tocilizumab was discontinued.
Figure 1A. Hyper-cellular marrow (×100).
Figure 1B. Pseudo-Pelger nuclear anomaly was observed in the neutrophils (×400).
Figure 1C. Dysplastic megakaryocyte (micro-megakaryocyte) with agglutinated platelets (×400).
Figure 1D. Myeloblasts with high nucleus/cytoplasm ratio and clear nucleolus. Auer rods were not observed (×200).

Table 1. Results of laboratory examination at the time of referrals

Blood cell count			Blood chemistry			Bone marrow aspiration		
WBC	2.7×10^{9}	/L	GOT	17	U/L	Nucleic cells	29.8×10^{4}	/μL
myeloblast	4.5	%	GPT	12	U/L	Megakaryocytes	319	/μL
promyelocyte	0.0	%	ALP	262	U/L	Erythroid	37.0	%
myelocyte	0.0	%	γ-GT	12	U/L	Proerythroblast	1.2	%
metamyelocyte	0.0	%	LDH	276	U/L	Baso.erythroblast	1.4	%
band	1.0	%	BUN	10.0	mg/dL	Poly. erythroblast	32.6	%
seg	62.5	%	Cre	0.71	mg/dL	Ortho. erythroblast	1.8	%
basophill	0.0	%	TP	6.5	g/dL	Myeloid	37.2	%
eosinophill	0.5	%	TSH	0.95	μg/mL	Myeloblast	11.2	%
monocyte	0.0	%	Free T3	3.4	pg/mL	Promyelocyte	0.2	%
lymphocyte	31.5	%	Free T4	1.18	ng/dL	Myelocyte	2.2	%
RBC	3.56×10^{12}	/L				Metamyelocyte	1.2	%
Hb	12.3	g/dL	Serological test			Stab.	4.4	%
Hct	37.4	%	CRP	<0.05	mg/dL	Seg.	11.4	%
MCV	105.0	fL	IgG	991	mg/dL	eosinophil	5.8	%
PLT	704×10^{9}	/L	IgA	67	mg/dL	Basophil	0.8	%
Reticulocyte	823×10^{9}	/L	IgM	94	mg/dL	Monocyte	1.8	%
			MMP-3	171.0	ng/mL	Lymphocyte	20.6	%
			sIL-2 receptor	208.0	U/mL	Macrophage	0.4	%
			HIV Ag/Ab	(-)		Megakaryocyte	3.0	%
			HBs Ag	(-)		Plasma cell	0	%
			HBs Ab	(-)		M/E ratio	1.01	
			HBc Ab	(-)		Karyotype	45, XY, -7	
			HTLV-1 Ab	(-)		*JAK2* p.V617F	(-)	
			EBVCA IgG	<10x		*WT1* mRNA	5,100copies	/μgRNA
			EBVCA IgM	<10x				
			EBEA IgG	<10x				
			EB-EBNA	<10x				

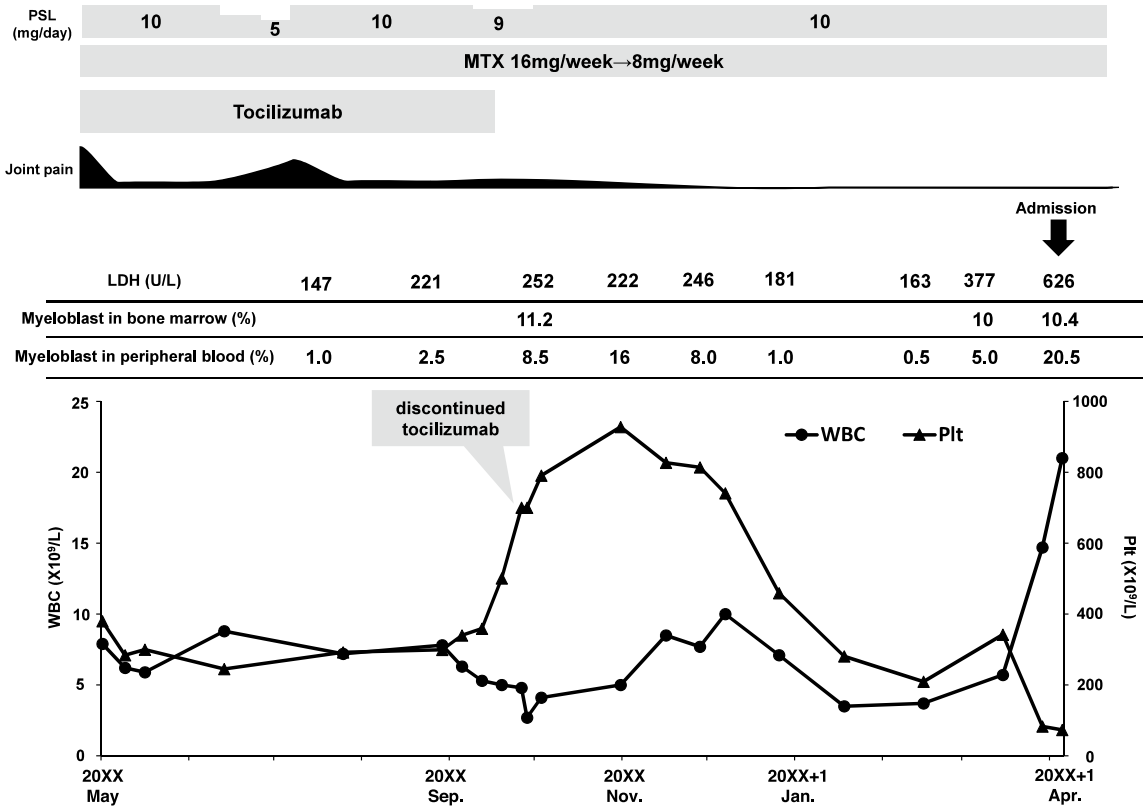

Figure2. Clinical course
Two months after adding tocilizumab for exacerbation of arthralgia, myeloblasts appeared in the peripheral blood. Two more months later, platelets increased rapidly. After discontinuing tocilizumab, the platelet and myeloblast counts decreased almost to the normal range. However, seven months after cessation of tocilizumab, the white blood cell count rapidly increased, and the platelet count decreased. AML eventually developed, three years after onset of JIA. MTX ; methotrexate, PSL ; prednisolone, Plt ; platelet count, WBC ; white blood cell count

with cytosine arabinoside, aclarubicin, and granulocyte-colony-stimulating factor, a combination regimen of cytosine arabinoside and etoposide was administered as consolidation therapy. However, these treatments also failed to achieve hematological remission, and *WT1* mRNA was 9,200 copies/μgRNA in the bone marrow after consolidation therapy. Unrelated bone marrow stem cell transplantation from an HLA-matched donor was performed, followed by myeloablative conditioning with tacrolimus and short-term methotrexate as Graft-versus-Host disease (GVHD) prophylaxis. The granulocytes were engrafted for 15 days. Donor-recipient chimerism was defined as complete donor type 28 days after transplantation. While tapering the tacrolimus dose, the patient developed acute bilateral extensive pulmonary abnormal shadows and required intensive care, including intubation. He was diagnosed with pulmonary graft-versus-host disease 60 days after transplantation and achieved immediate remission with corticosteroids. The patient was discharged 216 days after transplantation. Arthralgia disappeared after transplantation (MMP-3 levels was 81.0 ng/mL), but the patient required low-dose prednisolone for chronic GVHD of the skin. There was no evidence of relapse for more than five years after transplantation.

DISCUSSION

We report a case of AML-MRC arising from MDS/MPN-U two years after the initiation of immunosuppressive therapy for JIA. We performed unrelated bone marrow stem cell transplantation, followed by chemotherapy.

JIA is a chronic arthritis of unknown etiology, and its classification was proposed by the Pediatric Standing Committee of the International League (3). JIA is classified into seven categories that eventuate as two types, according to clinical symptoms : systemic JIA and others (4). The incidence of each type of JIA has been reported, and systemic JIA was found more frequently in Japan, 41.7–50%, than in Europe and the United States, 5-15% (1).

The development of malignancies during the treatment of JIA has attracted attention in other countries. In Sweden, 9,027 patients with JIA (mean age, nine years) were followed up for 131,144 person-years. Sixty malignancies developed during the observation period, and the relative risk for all malignancies compared with the general population was 2.3 (95% confidence intervals [CI] : 1.2–4.4) in patients with JIA identified in 1987 ; however, the relative risk for lymphoproliferative disease was 4.2 (95% CI : 1.7–10.7) (5). In the United States, 3,605 biologic-naïve patients with JIA with a mean age of 11 years were

followed up, and the relative risk for development of malignancy was 2.8 (95% CI : 0.9–8.3), compared to matched controls (6). In Taiwan, 2,892 patients with JIA were followed up, and the relative risk of malignancy in both methotrexate- and anti-tumor necrosis factor (TNF) biologic-naïve children with JIA was 2.75 (95% CI : 1.75–4.32) during 16,114.16 patient-years. The incidence rate ratio for leukemia was 7.38 (95% CI : 2.50–22.75) (7). In Germany, 3,691 patients with JIA were followed-up for 60,075 person-years, and malignancy was reported in 47 patients, including 11 patients with melanoma. The standardized incidence ratio (SIR) for females was 1.19 (95% CI : 0.77–1.60), but the SIR for melanoma was 3.21 (95% CI : 1.60–5.73) in females (8). Another study was performed with 3,695 patients with JIA over 13,198 observation person-years. Nine patients developed malignancy, including six lymphoid malignancies, and the relative risk was 6.3 for all malignancies, and 8.0 for leukemia or lymphoma (9). However, no significant increase in malignancy risk has been observed in Canada (2, 10). Taken together, malignancy risk should be considered during the treatment of patients with JIA.

MDS is a common disease in adults, but is relatively rare in children. It has been reported that MDS in children has a higher frequency of monosomy 7 chromosomal abnormality, *RAS* gene mutation, germline gene mutation, and a lower frequency of mutation of splicing factor than adult MDS, indicating a different pathogenesis between adult and childhood MDS (11). Moreover, our patient developed MDS with myeloproliferative features. Juvenile myelomonocytic leukemia (JMML) is a distinctive disease with both MDS and myeloproliferative disease ; however, our case did not show an increase in monocytes, and the ratio of myeloblasts was greater than 20% ; therefore, our case did not meet the JMML criteria (12). Systemic symptoms, such as arthritis and fever, preceded the development of AML-MRC by three years, suggesting a different pathogenesis from that of JMML.

MDS/MPN-U developed soon after the exacerbation of arthritis and intensified immunosuppressive therapy. In addition, after the discontinuation of tocilizumab, myeloblasts in the peripheral blood decreased rapidly. A component of the aggravation of joint pain could be arthritis induced by paraneoplastic mechanisms because hematological malignancy developed in a relatively short period after modification of the immunosuppressive treatment. In fact, a case that required leukemia as the differential diagnosis of arthralgia has been reported (13). In childhood, administration of adalimumab or tocilizumab has been reported to be safe and feasible in patients with JIA (14, 15). However, in Turkey, 1,023 patients with JIA (656 patients were treated with biologic agents) with a mean age of 16.7 ± 5.6 years were followed up for 9.9 ± 5.0 years. In this follow up period, one patient who was treated with etanercept and tocilizumab developed a hematologic malignancy and the SIR was 2.5 (95% CI : 0.9–8.3), compared to the patients treated with non-biologic agents (16). It is unclear whether there is a direct association between the development of malignancy and immunosuppressive therapy including MTX ; however, the possibility of the development of malignancy should be considered during immunosuppressive therapy, especially during treatment with biologic agents for JIA.

In conclusion, we described a case of AML-MRC originating from MDS/MPN-U during immunosuppressive therapy for JIA. Further pathophysiological analyses are warranted to understand the etiology of JIA and malignancy.

COMPETING INTERESTS

The authors declare no conflicts of interest associated with this manuscript.

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