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Case Study

Therapy-Related Myeloid Neoplasm in Methotrexate-Associated Lymphoproliferative Disease in a Rheumatoid Arthritis Patient

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Methotrexate (MTX) has been reported as one of the most potent drugs causing other iatrogenic immunodeficiency-associated lymphoproliferative diseases (OIIA-LPDs). Recently, we experienced a rare case of OIIA-LPDs in a rheumatoid arthritis (RA) patient; a 58-year-old female patient developed high fever and night sweats during MTX and infliximab administration, and the discontinuation of these drugs led to prompt improvement of such symptoms. However, lymphadenopathies and increased serum lactate dehydrogenase levels were observed, and Hodgkin lymphoma-mixed cellularity was diagnosed by bone marrow (BM) examination. ABVD therapy were then administered, resulting in complete remission. After 2 years of ABVD therapy, anemia and thrombocytopenia with monocytosis gradually developed during tocilizumab therapy. BM examination indicated an increased number of monocytes and blasts with multilineage dysplasia, and an abnormal karyotype, inv(11)(p15q22), was detected, suggesting therapy-related myeloid neoplasm (acute myeloid leukemia/myelodysplastic syndrome). Supportive care including hydroxyurea and transfusions was provided; however, following a sudden and marked increase in the white blood cell count, the patient died within a day because of multiple organ failure. To the best of our knowledge, this is the first report of a patient with OIIA-LPDs-RA who developed a therapy-related myeloid neoplasm. 〔*J Clin Exp Hematop 54(2) : 137-141, 2014*〕

Keywords: rheumatoid arthritis, methotrexate, other iatrogenic immunodeficiency-associated lymphoproliferative diseases, therapy-related myeloid neoplasm, therapy-related acute myeloid leukemia/myelodysplastic syndrome

INTRODUCTION

The category "other iatrogenic immunodeficiency-associated lymphoproliferative diseases" (OIIA-LPDs), as defined by the 4th edition of the WHO classification, comprises autoimmune diseases or conditions other than allograft/autograft transplantation that are caused by immunosuppressive medications.[1] Methotrexate (MTX) is one of the most potent drugs for treating rheumatoid arthritis (RA) and is now regarded as the first-line medication.[2] Recent studies have revealed that LPDs occasionally occur in patients receiving MTX therapy as well as in patients receiving tumor necrotizing factor-α antagonists, including infliximab, adalimumab, and etanercept.[3,4] In a previous report, we described 23 patients with OIIA-LPDs-RA and proposed 3 specific groups: the first was defined as "regression occurrence after MTX withdrawal," the second as "remaining LPD even after MTX withdrawal," and the third as "LPD development after discontinuing MTX" (other-mediated-LDP).[5] During the clinical course, an MTX-RA patient with Hodgkin lymphoma (HL) who belonged to the other-mediated-LDP group developed therapy-related acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) after ABVD therapy (adriamycin, bleomycin, vinblastine, and dacarbazine).

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CASE REPORT

A 58-year-old female had been suffering from RA for 20 years and had been administered various medications such as

nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). MTX was detected as the most effective drug in this patient and thus was administered for 15 years in combination with other medications such as NSAIDs, prednisolone (PSL), salazosulfapyridine, and infliximab. Although these medications resulted in stable RA activity, B symptoms such as a high fever and night sweats appeared suddenly. The findings of an increased serum C-reactive protein (CRP) level and splenomegaly revealed by computer tomography and gallium scan suggested the presence of OIIA-LPD. The anti-RA drugs, including MTX, were discontinued, resulting in rapid improvement in 3 weeks; however, RA activity flared (Fig. 1). Although tacrolimus was simultaneously administered as well, B symptoms such as high fever and general malaise appeared again after 7 months. The patient's laboratory data at this time (second admission) are presented in Table 1. Serum CRP and serum soluble interleukin-2 receptor (sIL-2R) levels were increased at 8.4 mg/dL and 9,580 U/mL, respectively. Computer tomography indicated mild hepatosplenomegaly and lymphadenopathies, whereas bone marrow (BM) examination revealed $CD15^{+}CD30^{+}CD20^{-}PAX\text{-}5^{+}EBER^{+}$ lymphoma cell invasion with a normal karyotype, leading to the diagnosis of Hodgkin lymphoma (HL)-mixed cellularity (Fig. 2). After 2 cycles of ABVD therapy, severe cytopenia developed, with chemotherapy being suspended because of severe panniculitis of her leg. This severe infection took 8 months to ameliorate, and 4 additional cycles of ABVD were administered (a total of 6 cycles), resulting in complete remission, with RA activity being well controlled by PSL (5 mg/day) administration (Fig. 1).

Active synovitis developed 10 months after the completion of chemotherapy, and the anti-interleukin 6 antibody, tocilizumab, was prescribed to relieve RA activity. Fourteen months after the initiation of tocilizumab therapy, she developed interstitial pneumonitis, and increased PSL dose (20 mg/day) resulted in rapid improvement (Fig. 1). However, concurrently, mild monocytosis in the peripheral blood along with decreased red blood cell and platelet counts was observed. BM examination revealed a hypercellular marrow (nuclear cell count, 401,000 cells/μL) with marked monocytosis and monoblasts (20% and 27.8%, respectively) and multilineage dysplasia, including hypogranulation of neutrophils, macrocytosis and poikilocytosis of erythrocytes, and micro-

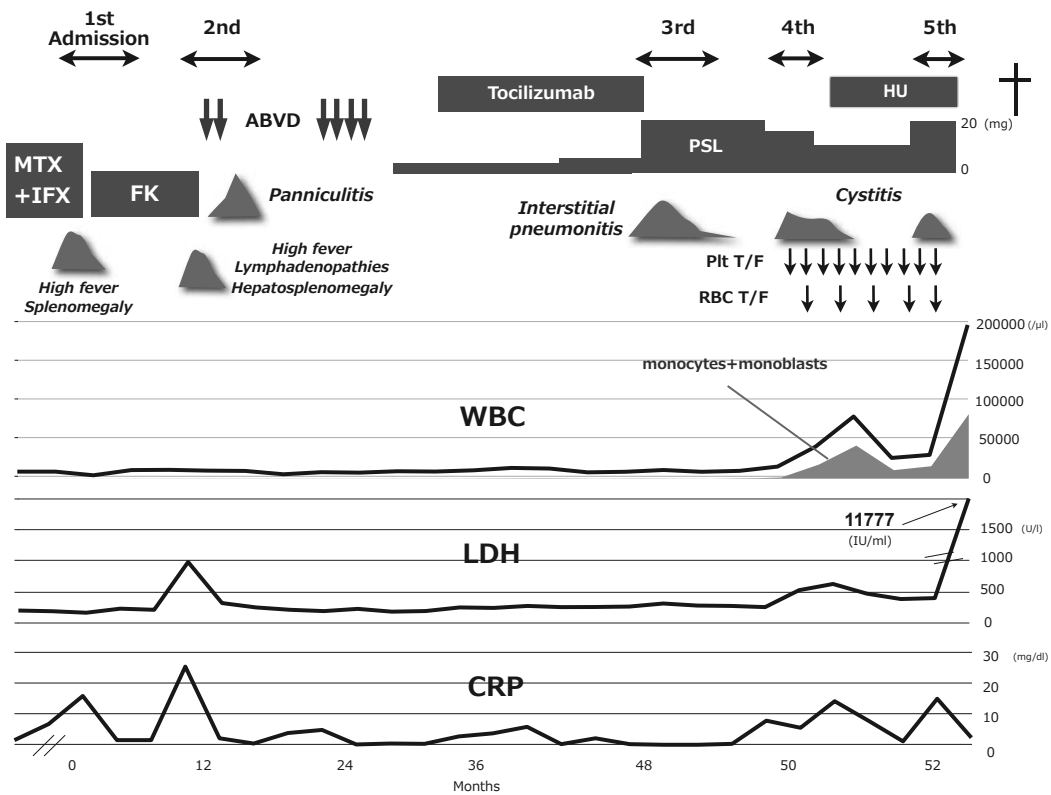

Fig. 1. Graph of the clinical course. A detailed description of the clinical course is provided in the case report. WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; MTX, methotrexate; IFX, infliximab; FK, tacrolimus; PSL, prednisolone; ABVD, combination therapy of adriamycin, bleomycin, vinblastine, and dacarbazine; HU, hydroxyurea; RBC, red blood cell; Plt, platelet; T/F, transfusion.

Table 1. Laboratory data

At the time of second admission				At the time of fifth admission			
WBC	4,800/μL	TP	6.4 g/dL	WBC	323,000/μL	TP	6.4 g/dL
Blast	0%	Alb	2.2 g/dL	Blast	1.0%	Alb	3.2 g/dL
Pro	0%	AST	27 U/L	Pro	1.0%	AST	9 U/L
Myelo	0%	ALT	27 U/L	Myelo	1.0%	ALT	7 U/L
Meta	0%	LDH	207 U/L	Meta	4.0%	LDH	266 U/L
Band	2.0%	BUN	11 mg/dL	Band	7.0%	BUN	15 mg/dL
Seg	83.0%	Cr	0.63 mg/dL	Seg	32.0%	Cr	0.51 mg/dL
Mono	11.0%	Na	134 mEq/L	Mono	45.0%	Na	144 mg/dL
Lymph	4.0%	K	4.0 mEq/L	Lymph	10.0%	K	3.8 mEq/L
RBC	354 × 10^4/μL	Cl	94 mEq/L	RBC	176 × 10^4/μL	Cl	101 mEq/L
Hb	9.0 g/dL	T-Bil	1.1 mg/dL	Hb	5.8 g/dL	T-Bil	0.9 mg/dL
Ht	26.9%	CRP	8.4 mg/dL	Ht	16.6%	CRP	6.4 mg/dL
Plt	20.9 × 10^4/μL	IgG	1,085 mg/dL	Plt	2.4 × 10^4/μL	IgG	1,041 mg/dL
Ret	0.8%	IgA	343.4 mg/dL	Ret	8.4%	IgA	329 mg/dL
APTT	29.3%	IgM	54.7 mg/dL	APTT	41.5%	IgM	103 mg/dL
PT	74%	sIL2R	9,580 U/L	PT	41%	sIL-2R	635 U/L
Fib	626 mg/dL	Ferritin	950 mg/dL	Fib	358 mg/dL	Ferritin	767 mg/dL

Pro, promyelocyte; Myelo, myelocyte; Meta, metamyelocyte; Seg, Segmented; Lymph, lymphocyte; Plt, platelet; Ret, reticulocyte; Fib, fibrinogen; sIL2R, soluble interleukin-2 receptor

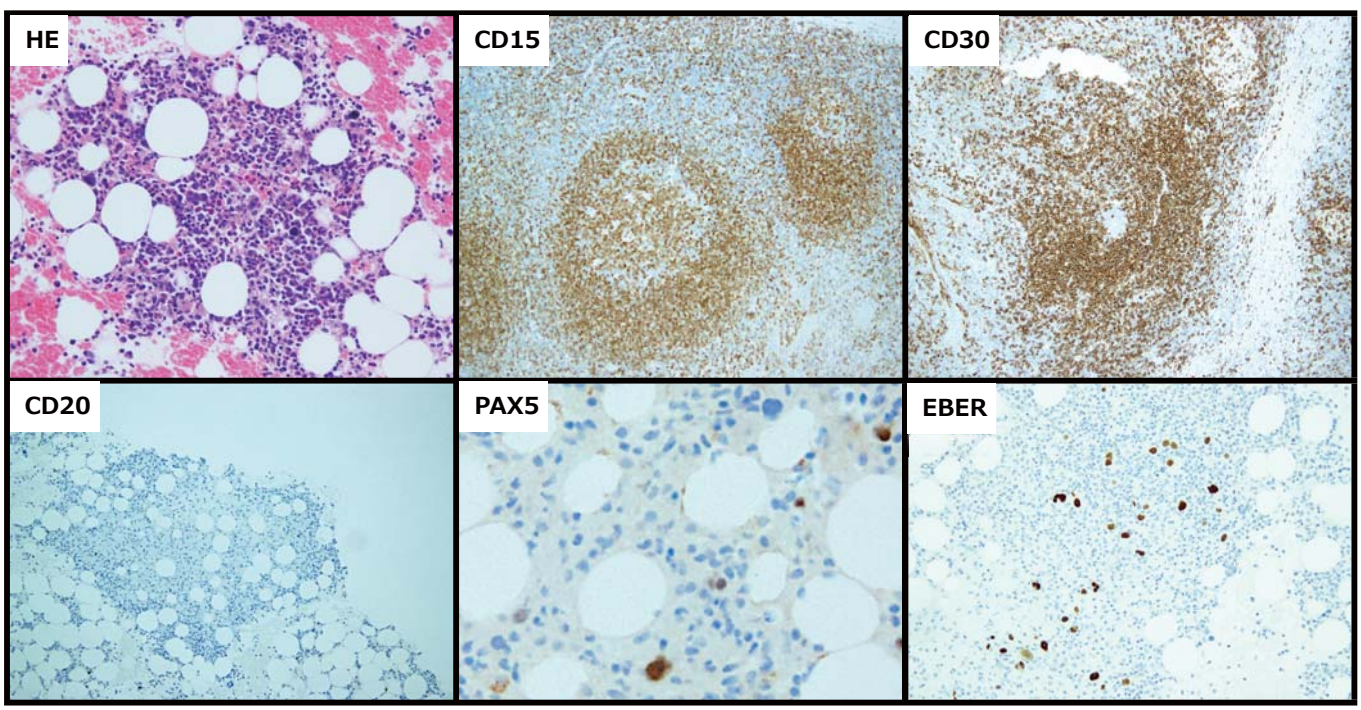

Fig. 2. Morphology of the bone marrow (BM) sample collected at the second admission. BM sample stained with hematoxylin & eosin (HE) revealing infiltration of lymphoma cells. Expression of CD15, CD30, and PAX-5, but not CD20, can be observed in these cells. Furthermore, *in situ* hybridization analyses for EBER are positive (original magnification: × 400, PAX-5: × 800). The diagnosis of Hodgkin lymphoma-mixed cellularity was made.

megakaryoctyes (Fig. 3). The phenotype of the monoblasts indicated $CD13^+$, $CD14^+$, $CD33^+$, $HLA\text{-}DR^+$, $CD34^-$, and $CD56^-$, and the karyotype was 46XX, inv(11)(p15q22). Taken together, these findings suggested the presence of t-AML/MDS. Because of the poor performance status and at the patient's request, intensive chemotherapy was not considered. Good disease control was achieved for 2 months by hydroxyurea (500-1,000 mg/day) administration. However, exacerbation of cystitis recurred, resulting in admission for the fifth time. Laboratory data at this time are shown in Table

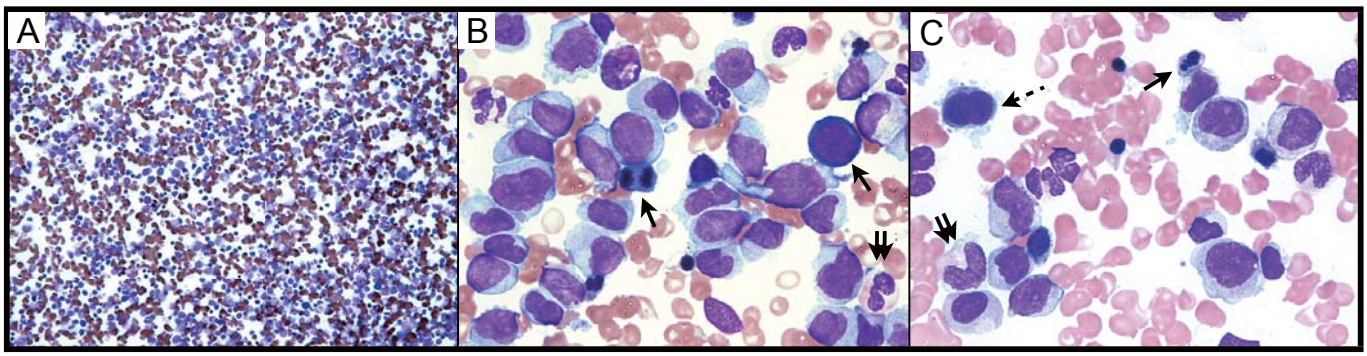

Fig. 3. Morphology of the bone marrow (BM) sample collected at the time of development of monocytosis. (***3A-3C***) May-Giemsa staining. BM reveals a hypercellular appearance, with marked mature and immature monocytes. The phenotype of these cells was $CD13^{+(dim)}$, $CD14^{+(dim)}$, $CD33^{+}$, DR^{+}, $CD34^{-}$, and $CD56^{-}$, and the karyotype was 46XX, inv(11)(p15q22) (20/20) (data not shown). The *arrows* indicate dysplasia in the erythroid (*single arrows*), myeloid series (*double arrows*), and megakaryocytes (*dotted arrow*) (*3A*, original magnification, × 200: *3B* & *3C*, original magnification, × 800), which is consistent with the diagnosis of therapy-related myeloid neoplasm (therapy-related acute myeloid leukemia/myelodysplastic syndrome).

1. Although the condition of the patient improved somewhat after admission, she developed rapid onset of shock with high fever, suggesting septic shock. While a relatively stable state was obtained with antibiotic administration, marked and rapid increases in white blood cell count (195,000 cells/μL) and serum lactate dehydrogenase level (11,777 IU/L) were observed. Severe acidosis (pH6.905) and multiple organ failure with severe disseminated intravascular coagulation developed exponentially, and the patient died within a day. Permission to perform an autopsy could not be obtained from her family.

DISCUSSION

We here reported a rare case of t-AML/MDS with MTX-associated LPD in a patient with RA. In a previous study, we focused on OIIA-LPDs in patients with RA and proposed 3 specific clinical patterns.[5] The presented clinical pattern was thought to fall into the "other-mediated-LDP" group as the patient developed LPD after discontinuing MTX. The clinical features in our patient were typical of the "other-mediated-LDP" classification because she revealed the HL phenotype, B symptoms, and high serum levels of lactate dehydrogenase, CRP, and sIL-2R at the time of LDP development.[5]

Therapy-related myeloid neoplasm (TRMN) including t-AML/MDS is commonly mediated by cytotoxic agents such as alkylating agents, ionizing radiation therapy, topoisomerase II inhibitors, antimetabolites, and/or antitubulin agents.[1,6] Losses or deletions in chromosome 7 and/or 5 are typical characteristics of alkylating agent-induced t-AML, whereas development of t-AML with balanced translocations in the chromosome bands, such as 11q23 and 21q22, has been related to previous therapy with drugs such as targeting DNA-topoisomerase.

On the other hand, it has been demonstrated that RA itself is associated with a significantly increased risk of the development of leukemia.[7,8] In addition, it has also been well documented that t-AML/MDS has rarely been observed in patients with HL who receive ABVD therapy, whereas it has often been observed in patients receiving c-MOPP therapy.[9] For instance, no cases of t-MDS/AML (therapy-related myelodysplastic/myeloproliferative neoplasms) were observed in the ABVD arm of a randomized trial conducted in Italy that compared ABVD with BEACOPP in untreated patients with advanced-stage HL.[10] In addition, Delwail *et al*. conducted a retrospective analysis of patients treated between 1972 and 1998 with either ABVD (n = 462) or MOPP (n = 373) followed by high-dose irradiation, and 37 patients were documented with t-AML/MDS in all patients, although none of those treated with ABVD alone developed TRMN.[11] Furthermore, we reported the coexistence of acute myeloid leukemia with t-AML/MDS multilineage dysplasia and Epstein-Barr virus-associated T-cell LPD in a patient with RA in a previous study.[12]

In the presented case, the patient received ABVD therapy containing DNA-topoisomerase II, and the abnormal translocation of inv(11)(p15q22), resulting from the fusion of NUP98 on chromosome 11p15 and DDX10 on chromosome 11q22, was detected. This abnormality has been reported in patients with de novo AML and in those with TRMN,[13,14] so the developing TRMN of this patient was suggested to be mediated by the cytotoxic agents. To confirm additional influences other than by chemotherapies, such as by RA itself, and the severe immunosuppressive state mediated by anti-RA medications, it will be necessary to investigate a greater number of patients with OIIA-LPDs-RA.

DISCLOSURE STATEMENT

The authors state that they have no conflicts of interest.

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