Successful Treatment of Therapy-related Acute Promyelocytic Leukemia with All-trans-retinoic acid Following Epirubicin for Hepatocellular Carcinoma and Docetaxel and Pembrolizumab Therapies for Lung Carcinoma: A Triple Malignancy Case

Rikio SUZUKI, Hidetsugu KAWAI, Daisuke FURUYA, Hibiki AKASHI, Yoshiaki OGAWA, Hiroshi KAWADA and Kiyoshi ANDO

Department of Hematology/Oncology, Tokai University School of Medicine

(Received March 3, 2020; Accepted April 22, 2020)

A 69-year-old man was referred to the hematology department for the evaluation of pancytopenia. He had been treated with radiation and epirubicin for hepatocellular carcinoma, and with docetaxel and pembrolizumab for lung adenocarcinoma. Bone marrow smears exhibited markedly increased promyelocytes, and polymerase chain reaction (PCR) study demonstrated chimeric fusion genes of *PML-RARA*. He was diagnosed with therapy-related acute promyelocytic leukemia (t-APL) and treated with all trans-retinoic acid (ATRA). After 30 days of ATRA treatment, complete hematological response was achieved. To the best of our knowledge, this case represents the first description of successfully treated t-APL diagnosed after treatment with pembrolizumab.

Key words: acute promyelocytic leukemia, pembrolizumab, docetaxel, adenocarcinoma, hepatocellular carcinoma

INTRODUCTION

Acute promyelocytic leukemia (APL) is a rare form of acute myeloid leukemia (AML), accounting for 10–15% of AML cases [1, 2]. APL is driven by an oncogenic balanced chromosomal translocation t(15; 17) (q22; q12) fusing the promyelocytic leukemia (*PML*) and retinoic acid receptor alpha (*RARA*) genes [1, 3]. The resulting PML/RARA fusion protein causes a specific differentiation block in the promyelocyte stage [4]. Induction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) represents a major advance in the treatment of APL and is regarded as the mainstay of molecularly targeted therapy, leading to dramatic improvements in the prognosis of APL [5, 6].

Therapy-related APL (t-APL) accounts for up to 12% of all APL cases, with incidence gradually increasing over time due to the increased use of chemotherapeutic agents and radiotherapy [7–12]. Most reports have found that t-APL demonstrates a remission rate of generally about 70%, comparable to the treatment of de novo APL with ATRA- and anthracycline-based regimens [7, 8, 12–14]. However, less evidence has been accumulated regarding the associations of taxanes (paclitaxel and docetaxel) or immune checkpoint inhibitors (ICI; nivolumab and pembrolizumab) with t-APL.

Here we present the first description of a patient with triple malignancy (t-APL, lung carcinoma, and hepatocellular carcinoma after treatment with docetaxel and pembrolizumab) successfully treated with ATRA.

CASE REPORT

A 69-year-old man was diagnosed with hepatitis C-induced hepatocellular carcinoma (HCC) in 2008. He underwent surgery, but then relapsed. Radiofrequency ablation was performed in 2015 and 2016, and transcatheter arterial chemoembolization with epirubicin was also performed in 2018. However, the lesion remained, and he was followed-up without treatment (Fig. 1A). He was diagnosed with lung adenocarcinoma (cT4N2M1a, Stage IV, EGFR (-), EML4-ALK (-), programmed death-ligand 1 (PD-L1) > 50%) from bronchoscopic biopsy of the right hilar tumor in May 2017. Since invasion of the superior vena cava was observed (Fig. 1B), the patient was initially treated with radiotherapy. As purpura nephritis was also observed, steroid pulse therapy was administered, followed by eight cycles of docetaxel treatment. Next, he was treated with seven cycles of pembrolizumab, but interstitial pneumonia appeared (Fig. 1C), possibly due to pembrolizumab or induced by radiation, and pembrolizumab was thus discontinued. Prednisolone therapy was therefore started for interstitial pneumonia. In December 2018, the patient complained of dizziness and was admitted to our hospital under a diagnosis of duodenal ulcer bleeding. Because pancytopenia and blasts were identified in the blood test, he was introduced to the hematology department for detailed examination (Table 1; Fig. 2A). Bone marrow

Rikio SUZUKI, Department of Hematology/Oncology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-92-4511 E-mail: Rikio_Suzuki@tsc.u-tokai.ac.jp

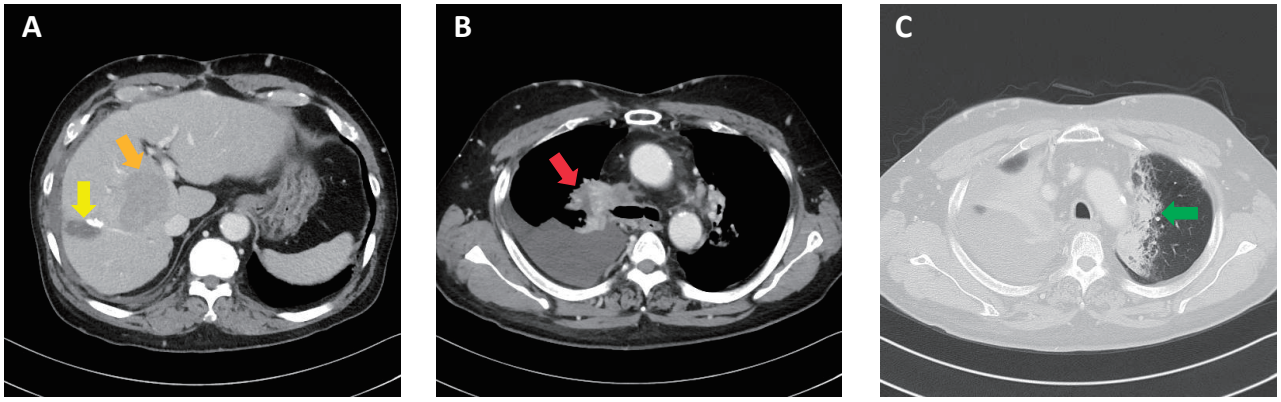

Fig. 1 Computed tomography images on admission.
A. Hepatocellular carcinoma (HCC). Yellow arrow indicates HCC lesion after transcatheter arterial chemoembolization. Orange arrow indicates new HCC lesion.
B. Lung adenocarcinoma. Red arrow indicates invasion of the superior vena cava.
C. Interstitial pneumonia. Green arrow indicates radiation- or drug-induced interstitial pneumonia.

examination revealed 37.5% promyelocytes, and he was transferred to the hematology department under a diagnosis of APL (Table 2; Fig. 2B). Active treatment for HCC and lung adenocarcinoma is difficult, but for APL, prognosis may be extended by several months if ATRA induction therapy proves successful. The patient was therefore started on ATRA induction therapy in December 2018. The clinical course is shown in Figure 3. At the beginning of treatment, DIC was detected by differentiation induction therapy and supportive therapy centered on blood transfusion was provided, but blood cells eventually recovered smoothly. Bone marrow testing performed in January 2019 confirmed hematological complete remission (myeloblasts, 0.4%; promyelocytes, 1.9%), but positive results from *PML-RARA* mRNA testing. Originally, we planned to consolidate using cytarabine (Ara-C) or an anthracycline anticancer agent, but because uncontrolled lung adenocarcinoma and HCC were coexisting, he was discharged from our hospital in January 2019, with no consolidation therapy planned and ATRA maintenance therapy planned as outpatient treatment. For lung adenocarcinoma and HCC, the course was followed without treatment. Thereafter, one course of maintenance therapy with ATRA was implemented from the end of January 2019, and bone marrow examination performed in the outpatient clinic in April 2019 showed maintenance of hematological remission (myeloblasts, 0.9%; promyelocytes, 0.7%), but results of the *PML-RARA* mRNA test remained positive. From mid-May 2019, respiratory distress increased and made outpatient visits impossible, and lung adenocarcinoma worsened. He died from the progression of lung adenocarcinoma in June 2019. For APL, hematological remission appeared to have been maintained until the end.

DISCUSSION

The incidence of t-APL is apparently rising due to the increased use of chemotherapeutic agents centering on topoisomerase II inhibitors [7, 8, 13]. A recent report suggested that translocation breakpoints in APL occurring after exposure to topoisomerase II inhibitors such as mitoxantrone, etoposide and doxorubicin were clustered in a "hot spot" region within *PML* intron 6 (bcr1) and *RARA* and were confirmed to be common cleavage sites of mitoxantrone-induced cleavage by topoisomerase II [15]. Moreover, recurrent breakpoints identified in epirubicine-related APL were also found in these preferential sites of topoisomerase II-induced DNA damage [11]. On the other hand, exposure to radiation is associated with enhancement of leukemogenic effects [16–18]. Reactive oxygen species (ROS) induced by radiation increase the frequency of DNA double-strand breaks (DSBs) [16, 19]. DSBs are potentially associated with the formation of chromosomal rearrangements leading to radiation-induced leukemias [16, 20]. In this case, leukemogenesis appeared to be enhanced by the synergistic effects of radiotherapeutic and chemotherapeutic agents, including docetaxel and epirubicin.

To date, many reports have investigated therapy-related leukemia after taxane treatment, and the combination of paclitaxel and platinum preparations [21]. However, very few reports have examined docetaxel [22], which shows significant anti-tumor activities against various cancers, mainly via: 1) inhibition of the function of microtubules; and 2) changes in mitochondria-dependent pathways [23–27]. Docetaxel shows higher affinity for microtubules than paclitaxel, and may phosphorylate bcl-2 more potently, leading to its activation and apoptosis [26, 28, 29]. Taxane-associated leukemia is relatively likely to show an M4 subtype, and no specific chromosomal abnormalities have been reported [21]. In particular, since pancytopenia progressed after using docetaxel, that agent was considered key to the leukemogenesis in this case. Although no cases of APL have been reported in docetaxel-reported leukemia, the translocation point was almost the same as in other t-APL cases. In the present case, remission induction therapy with Ara-C or an anthracycline-based therapy was judged as too difficult due to the frail condition of the patient, and remission induction therapy was thus performed using ATRA alone. Complete hematological remission was successfully obtained. Conventional ATRA-based induction therapy was considered an effective treatment option for t-APL after docetaxel treatment. Docetaxel is still the mainstay of anti-cancer chemotherapeutic regimens in the field of lung cancer and gynecological cancer [30, 31], and the frequency of usage may further increase in the future. This case is believed to

Table 1 Laboratory data
Complete blood count, biochemistry, and coagulation data.

CBC		Chemistry		Coagulation	
WBC	700 /μL	TP	5.9 g/dL	PT	14.1 seconds
Seg	47.0%	Alb	3.1 g/dL	APTT	28 seconds
Stab	1.0%	T-Bil	1.4 mg/dL	Fib	376 mg/dL
Lym	49.0%	AST	54 U/L	FDP	17.4 mg/mL
Mo	2.0%	ALT	76 U/L	D-dimer	4.1 mg/mL
Eo	0%	ALP	328 U/L		
Ba	0%	LDH	270 U/L		
Others	1.0%	γ-GTP	288 U/L		
RBC	257 × 10^4/μL	UA	6.5 mg/dL		
Hb	7.7 g/dL	Glu	130 mg/dL		
Ht	23.0%	BUN	42 mg/dL		
MCV	89.5 fL	Cre	1.09 mg/dL		
MCH	30.0 pg	Na	139 mEq/L		
MCHC	33.5%	K	4.3 mEq/L		
Ret	33 ‰	Cl	106 mEq/L		
PLT	1.9 × 10^4/μL	Ca	8.9 mg/dL		
		CRP	1.68 mg/dL		
		Ferritin	128 ng/ml		

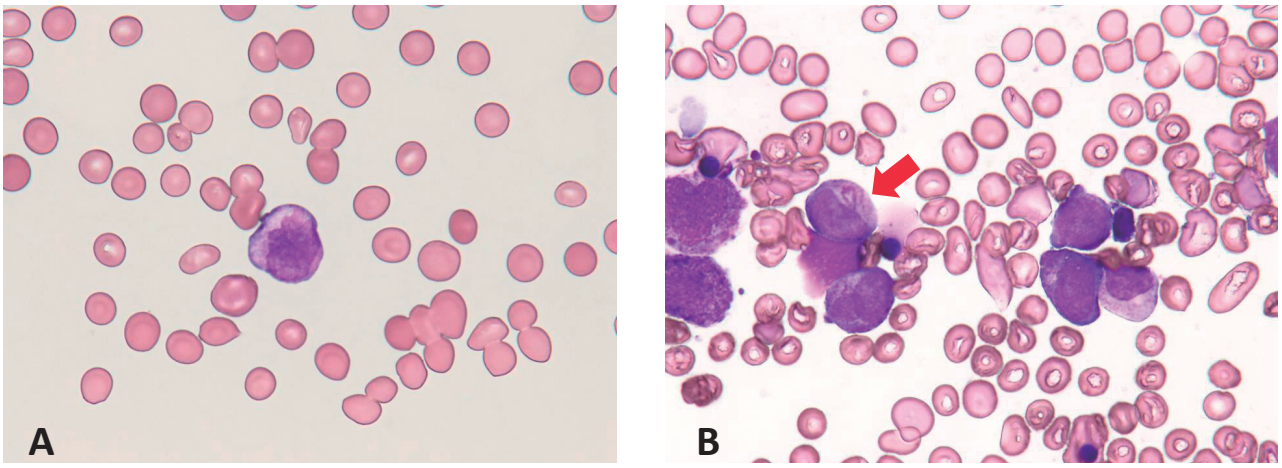

Fig. 2 Peripheral blood and bone marrow examination at diagnosis.
A. Peripheral blood examination.
B. Bone marrow examination. Red arrow indicates a faggot cell, which contains Auer rods in the cytoplasm.

offer important insights.

Pembrolizumab is a full-length human immunoglobulin G4 monoclonal antibody directed against programmed cell death 1 (PD1), and is currently in wide use as a treatment for several solid tumors and hematological malignancies. The binding of PD-1 to PD-L1 induces tolerance between tumor cells and the host immune system and escape from the host immune system, and finally promotes tumor progression [32]. Inhibition of PD-1/PD-L1 binding by pembrolizumab activates T lymphocytes, and shows significant anti-tumor effects against various cancers [33]. Importantly, the PD-1/PD-L1 pathway becomes dysregulated, leading to immune escape for AML [34, 35]. As a result, AML can be considered a promising target for ICI. However, ICI including pembrolizumab alone or in combination with chemotherapeutic agents have shown less impressive results for AML than for solid tumors such as melanoma or lung cancer [36, 37], probably due to the low immunogenicity of AML compared to other solid immunogenic cancers, such as melanoma and lung cancers [38, 39], or an immunosuppressive tumor microenvironment [40]. In the future, if more optimal partners with pembrolizumab and the optimal timing of administration can be determined, further improvements in the prognosis of AML may be expected. Few reports have examined the efficacy of pembrolizumab in APL patients. In this case, pembrolizumab was administered for lung cancer, but had to be discontinued by the 7th course due to the risk of drug-induced interstitial pneumonia. The rapid decrease in platelets after discontinuation of pembrolizumab suggests that pembrolizumab suppressed the overt t-APL, but t-APL may have worsened after its discontinuation. These observations suggest that pembrolizumab may offer an effective treatment option in t-APL. The prognosis of APL has dramatically improved with the advent of ATRA and ATO [5, 6], but combined use with pembrolizumab may lead to deeper CR, and finally cure of t-APL.

In conclusion, this is the first report to describe therapy-related APL diagnosed after treatment with docetaxel and pembrolizumab. In addition, ATRA and pembrolizumab may represent important options in

Table 2 Laboratory data
Results of bone marrow examination.

NCC	$7.2 \times 10^4/\mu L$	Flow cytometry analysis	
MgK	$< 15/\mu L$	CD13	88.1%
Myelogram		CD33	88.2%
Blast	0.0%	CD117	68.2%
Prom	37.5%	MPO	93.1%
Mye	2.2%	CD71	86.9%
Meta	0.6%	CD38	67.5%
Stab	1.2%		
Seg	3.4%	G-banding	
Eo	0.8%	N/A	
Ba	0.0%		
Mo	0.2%	PML-RARa RT-PCR	
Macrophage	0.0%	bcr1 (+)	
Lybl	0.0%		
Ly	12.1%		
Plasma	0.4%		
Mast cell	0.0%		
Others	0.0%		
Pro-Er	0.0%		
Baso-Er	0.8%		
Poly-Er	28.9%		
Ortho-Er	11.9%		
M/E	1.1		

Fig. 3 Clinical course.
WBC, white blood cell; PLT, platelet; CR, complete remission; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; DTX, docetaxel; RCC, red cell concentrate; PC, platelet concentrate; FFP, fresh-frozen plasma.

the treatment of t-APL.

AUTHORSHIP

R.S. and K.A. analyzed the clinical status of the patient, analyzed the data, and prepared the manuscript. H.K., D.F., H.A., Y.K., Y.O., and H.K. analyzed the data.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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