Patient with Refractory Multiple Myeloma Developing Eosinophilia after Lenalidomide Treatment and Lung Cancer 9 Months Later: Case Report and Review of the Literature

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Abstract A 78-year-old man was diagnosed as having advanced symptomatic IgG multiple myeloma in June 2008. Melphalan-prednisolone therapy was effective, however, relapse occurred in January 2011 after 21 courses of melphalan-prednisolone therapy. Addition of bortezomib and dexamethasone led to partial remission, but the treatment needed to be discontinued due to autonomic dysfunction. Combined therapy with lenalidomide and dexamethasone was started in May 2012, which resulted in partial remission. The patient had a persistently elevated eosinophil count (2,350/ μ L) and increased serum IL-6 level. Pleuritis carcinomatosa developed in January 2013. Lenalidomide was discontinued, which was followed by rapid improvement of the eosinophilia. The patient died of respiratory failure in March 2013. There have been only five reported cases of eosinophilia caused by lenalidomide used for the treatment of multiple myeloma. In these cases, lenalidomide has been speculated to activate cytotoxic T cells to control the plasmacytoma. It would be of interest, therefore, that eosinophilia could serve as a new indicator.

Keywords Multiple myeloma · Lenalidomide · Eosinophilia · IL-6 · Second primary cancer

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Introduction

Eosinophilia during treatment with lenalidomide is rare, with only 19 cases reported to date [1–11]. Of these, only five patients were under treatment with the drug for multiple myeloma. Lenalidomide-induced eosinophilia tends to be more common in Japanese, but its prognosis and outcome are unknown. The present patient developed eosinophilia and hyperinterleukinemia-6 immediately after the start of treatment with lenalidomide. The eosinophilia persisted, with partial remission maintained for 9 months under treatment with lenalidomide. Richter et al. [12] reported that lenalidomide, which exerts antitumor activity, activates natural killer (NK)/T cells, thereby inducing eosinophilia. Eosinophilia could be an indicator of a good therapeutic response to lenalidomide. Actually, the three patients for whom the prognosis of multiple myeloma has been reported showed a therapeutic effect no worse than that during the plateau phase.

Case Report

A 78-year-old Japanese man presented with the chief complaints of cough and sputum production. His medical history included tonsillectomy for tonsillar hypertrophy, taxis for inguinal hernia, atrial fibrillation and hypertension. He had no significant family or social history.

The patient visited our department in June 2008 complaining of persistent low back pain since March. Examination revealed conjunctival pallor. The laboratory findings at admission are shown in Table 1. Results of detailed examination of the bone marrow and other tests (Fig. 1) led to the diagnosis of IgG κ multiple myeloma, Durie-Salmon stage IIIB, International Staging System stage 3. His

Table 1 Laboratory findings at the initial examination

Blood count	
WBC	2,400/ μ L↓ (4,000–8,000)
Neut	53.0 %
Ly	31.0 %
Mono	11.0 %↑ (4.0–7.0 %)
Eo	5.0 %
RBC	2,300,000/ μ L↓ (410–530)
Hb	8.2 g/dL↓ (14.0–18.0)
MCV	102.9 fL↑ (84.0–99.0)
MCH	35.7 pg
PLT	136,000/ μ L↓ (15.0–35.0)
Coagulation	
PT activity	51 %↓ (70–100 %)
PT-INR	1.56
APTT	33.4 s
Fbg	200 mg/dL
FDP	≤5.0 μ g/mL
DD	0.79 μ g/mL
Biochemistry	
TP	12.5 g/dL↑ (6.7–8.3)
ALB	1.6 g/dL↓ (3.9–4.9)
BUN	50 mg/dL↑ (8–22)
CREA	2.60 mg/dL↑ (0.61–1.04)
UA	10.2 mg/dL↑ (2.0–8.0)
Na	129 mM/L↓ (138–146)
Cl	104 mM/L
K	3.9 mM/L
Ca	12.0 mg/dL↑ (8.7–10.3)
T-Bil	0.2 mg/dL
AST	22 IU/L
ALT	17 IU/L
LDH	103 IU/L↓ (119–229)
ALP	354 IU/L
CRP	0.4 mg/dL↑ (0.0–0.3)
β 2MG	18.2 mg/L↑ (1.0–1.9)
Immune serum	
IgG	9,065 mg/dL↑ (870–1,700)
IgA	10 mg/dL↓ (110–410)
IgM	≤5 mg/dL↓ (33–190)
IgD	≤0.6 mg/dL↓ (0–9.0)
Immunoelectrophoresis	
Serum IgG- κ	Positive
Urinary BJP- κ	Positive
Urinalysis	Protein (±)
Bone marrow examination	Dry tap

clinical course was as shown in Fig. 2. After the start of melphalan-prednisolone (MP) therapy, the serum monoclonal (M)-protein decreased and the clinical course was favorable.

However, the serum M-protein increased again (IgG, 4,895 mg/dL) in January 2011 after 21 courses of MP therapy.

His medication was changed to intravenous bortezomib injection at 1.3 mg/m² (5-week cycles of weekly injections) and oral dexamethasone at 20 mg/day (on the day of intravenous injection of bortezomib and the following day) in February 2011. The serum M-protein decreased (IgG 2,020 mg/dL) and partial remission was achieved. However, in September 2011, autonomic dysfunction (reduction in blood pressure and presyncope) became prominent during the fourth course of treatment, and bortezomib was discontinued as this was considered to be an adverse reaction of bortezomib.

In the same month, the patient's medication was changed to thalidomide, and the autonomic dysfunction disappeared. The dose of thalidomide was increased to 300 mg/day, but the patient's condition deteriorated (IgG 4,895 mg/dL). After the start of treatment with thalidomide, the eosinophil count increased transiently to 840/ μ L, but then decreased subsequently to 300/ μ L. In May 2012, the medication was changed again to 10 mg/day of lenalidomide (each course consisting of 21 days of oral treatment followed by 7 days of rest). The M-protein peak decreased rapidly (IgG 1,516 mg/dL), however, the eosinophil count increased markedly to 2,350/ μ L. The clinical course was favorable, with no clinical symptoms or organ dysfunction, therefore, the treatment with lenalidomide was continued. No increase of the serum IL-5, which is said to be associated with eosinophilia, was observed (1.4 pg/mL; reference value, ≤3.9 pg/mL). No increase of the serum interferon (IFN) γ (0.1 IU/mL), interleukin (IL)-1 β (9 pg/mL), IL-2 (1.3 U/mL) or IL-3 (2.9 pg/mL) was observed either, however, the IL-6 was elevated to 17.8 pg/mL (reference value, ≤4.0 pg/mL).

In June 2012, a chest X-ray showed no abnormalities. In January 2013, the cough and sputum developed. Massive right pleural effusion was found (Fig. 3a), and examination of the pleural fluid led to the diagnosis of pleuritis carcinomatosa associated with lung adenocarcinoma. Lenalidomide was effective, and no myeloma cells were seen in the pleural fluid, suggesting that the patient had developed a second primary cancer after treatment with melphalan or lenalidomide. ¹⁸F-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG–PET–CT) showed diffuse thickening of the right pleura and FDG accumulation in the region of branching of the right truncus intermedius into the middle and lower lobe bronchi, suggesting that the lung tumor was the primary focus (Fig. 3a).

In late January, lenalidomide was discontinued, which was followed by rapid decrease of the eosinophil count, but the multiple myeloma relapsed (IgG 2,256 mg/dL). In February, the patient was admitted to our department,

Fig. 1 Bone marrow biopsy. **a** HE staining ($\times 600$) showed many plasma cells with unclear intranuclear findings and unevenly distributed nuclei. **b** IgG ($\times 600$) was positive. **c** IgA ($\times 600$) was negative. **d** κ ($\times 600$) was positive. **e** λ ($\times 600$) was negative. **f** CD138 ($\times 600$) was positive

however, the pleural effusion was uncontrollable. In March 2013, the patient died of respiratory failure due to pleuritis carcinomatosa.

Discussion

Our patient reported here developed eosinophilia immediately after the start of treatment with lenalidomide, which resolved immediately after completion of the treatment, suggesting that the eosinophilia was caused by lenalidomide. Eosinophilia developing during treatment with lenalidomide is rare (Tables 2, 3). However, the serum IL-5, a cytokine that is known to be associated with eosinophilia, did not increase. In addition, the serum levels of granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-3 also did not increase, while the serum IL-6 increased. Richter et al. [12] reported that lenalidomide activates NK/T cells, thereby inducing eosinophilia.

The MM-017 ($n = 15$) [1] and MDS-007 ($n = 11$) [2] studies, which are clinical studies conducted on Japanese patients, found one and five cases of lenalidomide-induced eosinophilia, respectively. However, among clinical studies conducted in countries other than Japan, the MDS-001 study ($n = 43$) [6] and a pilot study of concurrent lenalidomide and radiotherapy for glioblastoma multiforme ($n = 23$) [7] found three cases and one case, respectively, of lenalidomide-induced eosinophilia, whereas the MM-009/010 ($n = 353$) [3, 4] and MDS-004 ($n = 69$) [5]

studies found no such cases. Studies other than clinical studies have also reported lenalidomide-induced eosinophilia: 5 cases in the special drug use-results survey involving 2,449 patients who had received lenalidomide from July 2010 to February 2013 in Japan [8] and four cases from case reports (Table 3). These case reports showed that eosinophilia occurred in the early stage of treatment, that is, 2 weeks to 1 month after the start of lenalidomide or during the second cycle. In addition, in three patients for whom the prognosis of myeloma has been reported, the prognosis was no worse than that during the plateau phase, suggesting that the prognosis of myeloma is relatively good. The incidence of eosinophilia varies greatly among reports, however, only a total of 19 patients have been reported (Tables 2, 3). Of these, 12 patients were Japanese; thus, lenalidomide-induced eosinophilia tended to be more common in Japanese patients. However, the prognosis and outcome of eosinophilia remains unknown, except in the three cases (not available in one case) shown in Table 3.

In the MDS-001 study ($n = 43$) [6], which involved patients with myelodysplastic syndrome (MDS), 24 patients (56 %) showed hematologic responses, and 2 of the 3 patients who developed eosinophilia showed hematologic improvement. However, the prognosis and outcome of these patients remain unknown. In the present patient also, eosinophilia developed immediately after the start of treatment with lenalidomide (Day 7) and the serum M protein decreased rapidly, consistent with partial remission.

Fig. 2 Clinical course. **a** MP therapy led to a reduction in the serum M-protein and partial remission, however, the serum M-protein increased again after the 21st course of MP therapy. The medication was changed to intravenous injection of bortezomib in February 2011. This was followed by a decrease again of the serum M-protein and partial remission. **b** Serious autonomic dysfunction developed during the fourth course of bortezomib, and bortezomib was discontinued. The medication was changed to thalidomide, and the autonomic dysfunction disappeared, however, thalidomide proved ineffective. After treatment with thalidomide, the eosinophil count increased slightly. The medication was changed to 10 mg/day lenalidomide, and the serum M-protein decreased rapidly. The eosinophil count and the serum IL-6 increased. In January 2013, the patient was diagnosed as having developed pleuritis carcinomatosa, and the lenalidomide was discontinued. The eosinophilia resolved, however, the multiple myeloma relapsed and the serum IL-6 increased. In March, the patient died of respiratory failure due to pleuritis carcinomatosa

In addition, the patient continued to have eosinophilia and partial remission was maintained for 9 months under treatment with lenalidomide. The serum IL-6 also increased during this period. In the three cases shown in Table 3, the myeloma was no worse than that during the plateau phase, suggesting that the eosinophilia and hyper-interleukinemia-6 could be indicators of a good therapeutic response to lenalidomide, mediated via immune activation. Richter et al. [12] reported that lenalidomide induces eosinophilia through the activation of NK/T cells. In addition, there are reports that human eosinophils produce IL-6 [13] and that many patients with myeloma show increase of the serum IL-6 during treatment with lenalidomide [14]. However, there is also a report of the serum IL-

Fig. 3 **a** Chest X-ray showing massive right pleural effusion. **b** FDG-PET-CT showing diffuse thickening of the right pleura and FDG accumulation in the region of branching of the right truncus intermedius into the middle and lower lobe bronchi, suggesting that the lung tumor was the primary focus

X-P

FDG PET CT

Table 2 Reports of eosinophilia caused by lenalidomide

	Background	Total number of patients (<i>n</i>)	Eosinophilia (<i>n</i>)	Incidence (%)	References
MM-017	Japan	15	1	6.7	[1]
MDS-007	Japan	11	5	45.5	[2]
MM-009/010	Outside Japan	353	0	0	[3, 4]
MDS-004	Outside Japan	69	0	0	[5]
MDS-001	Outside Japan	43	3	7.0	[6]
A pilot study of concurrent lenalidomide and radiotherapy for glioblastoma multiforme	Outside Japan	23	1	4.3	[7]
Special drug use-results survey MM/MDS	Japan	2,449	5	0.2	[8]
	Japan/ outside Japan	2,475/488	11/4	0.4/0.8	

Table 3 Case reports of eosinophilia caused by lenalidomide

Case	Age	Sex	Previous treatment	Dose of Rev (mg/day)	Rev treatment period	Eosinophil count n/μL (%)	Therapeutic effect on MM	Complication	Treatment for eosinophilia	Treatment for the complication	Outcome of eosinophilia	Death	Outcome of MM complication	References
1	78	Male	MP Bor Thal	10	Ca. 1 month	2,350	PR	Lung cancer	Discontinuation of Rev	Pleurodesis	Improved			This case
2	78	Female	N.A	25	Ca. 1 month	3,000	No relapse	DRESS	Discontinuation of Rev	Discontinuation of Rev	Improved	Improved	No relapse	[9]
3	62	Female	Thal DEXA HDMEL/ Auto	25	2 cycles	(4-6 %)	N.A	Pulmonary toxicity	Discontinuation of Rev	Discontinuation of Rev	N.A	Improved	N.A	[10]
4	66	Male	VAD Thal DEXA HDMEL/ Auto	25	2nd week	(20 %)	Plateau phase	Hyper sensitivity pneumonitis	Discontinuation of Rev	Discontinuation of Rev	N.A	Improved	Plateau phase	[11]

Rev lenalidomide, MM multiple myeloma, MP melphalan prednisolone, Bor bortezomib, Thal thalidomide DEXA dexamethasone, HDMEL/Auto high dose melphalan/auto peripheral blood stem cell transplant, VAD vincristine doxorubicin dexamethasone, N.A not available, PR partial remission, DRESS drug reaction with eosinophilia and systemic symptoms syndrome, PSL prednisolone

6 promoting an increase of myeloma cells [15], and it is necessary to perform careful long-term follow-up studies to obtain definitive results. Actually, in the present patient, the serum IL-6 also increased after discontinuation of lenalidomide and decrease in the serum eosinophil count. There are no large-scale studies showing the prognosis and outcomes of patients who developed eosinophilia or hyperinterleukinemia-6 during treatment with lenalidomide, and it is necessary to perform the analysis on a larger number of patients in the future.

There have been reports of the risk of second primary cancer following treatment with lenalidomide in both newly diagnosed [16–18] and relapsed [3, 4] patients. However, no studies have reported on second primary cancer in patients who developed eosinophilia or hyperinterleukinemia-6 during treatment with lenalidomide, and this is the first reported case. For clarifying the prognosis and causality in such cases, it is necessary to accumulate a greater number of cases of eosinophilia occurring during treatment with lenalidomide and to carefully examine the long-term incidence and prognosis of second primary cancer in such patients.

Conflict of interest The authors declare that they have no conflict of interest.

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