LETTER TO THE EDITOR

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Development of unexpected severe thrombocytopenia just after initiating lenalidomide: possible involvement of an immunologic mechanism

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Lenalidomide (Len) is one of the second-generation immunomodulatory drugs (IMiDs) for treatment of multiple myeloma. Len is also known to show an antitumor effect through a variety of mechanisms, including inhibition of cytokine signaling, angiogenesis, and induction of tumor cell apoptosis [1]. In addition, Len can induce immune dysregulations and cause autoimmunity. Adverse events of Len are, generally, leukopenia, thrombocytopenia, deep venous thrombosis, skin rash, opportunistic infections, and others. Myocarditis, Basedow disease, autoimmune hemolytic anemia, cold agglutinin disease, and acquired hemophilia have also occurred; those were thought to be autoimmune disorders. Similarly, immune thrombocytopenic purpura (ITP) is an autoimmune disease. Only a few cases were reported of ITP associated with Len. In this letter, we report the experience of a severe and transient reduction in platelets soon after administration of Len and the possible involvement of an immunological mechanism that prevented excluding ITP from the differential diagnosis.

A 74-year-old woman was diagnosed with monoclonal gammopathy undetermined significance (MGUS, Bence Jones-λ) in July 2005 and MGUS progressed to asymptomatic myeloma by November 2012. In December 2017, she was referred to our hospital for progression of anemia (Hemoglobin (Hb) 9.1 g/dl) and hypercalcemia (12.1 mg/dl). She was admitted to our hospital, and bone marrow examination showed the increase of plasma cells, which confirmed the progression to symptomatic multiple myeloma. She was treated with Len (15 mg/body) and dexamethasone (20 mg/body/weekly). On day 5 after the initiation of the treatment, she complained of skin rash and malaise. Cytopenia due to drug toxicity had not then severely developed. On day 14, thrombocytopenia suddenly progressed to 10,000/μl. Her Hb was 10.9 g/dl and leukocyte was 7,060/μl, and the percentage of immature platelet fraction (IPF) was comparatively increased to 14.3%. The number of platelets was too low to measure the mean platelet volume. Anti-platelet antibody and PA-IgG were not elevated. Anti-nuclear antibody and ds-DNA antibody were not elevated, and cytomegalovirus C7-HRP was negative (Table 1). A bone marrow biopsy proved normocellular with adequate megakaryocytes and there was no evidence of dysplasia or neoplasm. Plasma cells in the bone marrow had rather decreased comparably with the time of admission. And there were no signs of disseminated intravascular coagulation (DIC) or viral infection. On the other hand, she presented exacerbations of skin rash and temporarily increased proteinuria. For the decrease in platelet count, platelet transfusion was given. Platelet count did not respond at all. Anti-HLA antibody screening was performed but donor-specific antibodies were not detected. From these findings, we speculated that this severe thrombocytopenia could be caused by an immunological mechanism, such as ITP. Len was discontinued and the patient was treated with prednisolone (PSL) at the dose of 0.5 mg/kg. The platelet count promptly increased to 149,000/μl after 14 days of steroid therapy and steadily kept on tapering.

One case report [2] and summary of four cases summaries [3] were previously reported as Lenalidomide-associated ITP (Table 2). No previous cases including the present case had a history of autoimmune disorders. Our case occurred ITP in the first cycle but in previous cases, it occurred after 3 cycles. All patients had been treated with dexamethasone at the dosage of 20–40 mg/weekly for myeloma, and after diagnosis of ITP, they all were treated with PSL, and Len was discontinued. Some cases had relapsed after re-treatment with Len, and one

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Table 1. Laboratory data of the current case

WBC	7060	/μl	TP	6.3	g/dl	IgG	596 mg/dl
Band	9	%	ALB	60.9	%	IgA	38 mg/dl
Seg	63	%	α1	8.2	%	IgM	35 mg/dl
Eos	4	%	α2	12.6	%		
Baso	0	%	β1	5	%	Anti-platelet ab	Negative
Mo	13	%	β2	3.7	%	PAIgG	48 ng/10^7 cells
Ly	11	%	γ	9.6	%		
RBC	278	× 10^4/μl	Alb	4	g/dl	ANA	x40
Hgb	10.9	g/dl	T.Bil	1.5	mg/dl	Homogeneous	x40
Hct	24.2	%	D.Bil	0.5	mg/dl	Speckled	x40
MCV	87.1	fl	I.Bil	1.0	mg/dl	ds-DNA ab	<10 IU/ml
MCH	30.2	pg	AST	12	U/l		
MCHC	34.7	%	ALT	21	U/l	FLC κ	8.4 mg/d
RDW	15.4	%	LDH	212	U/l	FLC λ	349 mg/d
Plt	1.0	× 10^4/μl	ALP	304	U/l	FLC (κ/λ ratio)	0.02
Ret	0.89	%	ChE	130	IU/l		
IPF	14.3	%	γ-GTP	21	U/l	CMV pp65C7-HRP	Negative
			UA	4.6	mg/dl		
APTT	35	sec	BUN	22.9	mg/dl		
PT	1.09		Cre	0.79	mg/dl		
Fibg	307	mg/dl	Na	134	mEq/l		
D-dimer	1.3	μg/ml	K	4.44	mEq/l		
FDP	3.5	μg/ml	Ca	7.6	mg/dl		
AT-3	64	%	Mg	3.1	mg/dl		
			Cl	99	mEq/l		
			CRP	3.64	mg/dl		

Table 2. Previous reports of Len-associated ITP and the current case

	case 1[2)]	case 2[3)]	case 3[3)]	case 4[3)]	case 5[3)]	Current Case
Age (y)	66	27	66	76	78	74
Sex	Female	Male	Female	Female	Female	Female
MM type	NE	NE	IgG-κ	IgG-λ	Amyloidosis IgA-λ	BJ-λ
Dose of Len (mg/body)	25	25	15 - lower dose	15	15	15
Dose of Dex combinated with Len (mg/body)	20	0	20	NE (used)	20	20
Cycle at ITP	3rd cycle	NE (>4 cycle)	5–6th cycle	3rd cycle	6th cycle	1st cycle
Len retreatment after ITP	NA	NA	3 times	1 time	NA	1 time
Outcome/relapse	Recovered/–	Recovered/–	Recovered/3 times	Recovered/–	Steroid dependent	Recovered/–
BM findings	NE	Mgk normal	Absent of Plasma cell, MgK++	NE	Mgk++	Mgk; normal
Number of pre-treatment	2nd line	Maintenance therapy after ASCT	2nd line	2nd line	2nd line	NA
Platelet count at ITP (/μl)	4.4 × 10^4	0.1 × 10^4	1.7 × 10^4	0.5 × 10^4	1.8 × 10^4	1.0 × 10^4
ITP-asosiated symptom	NA	Petechiae	NA	NA	Diffuse pupura	NA
Other Aes	NE	Alopecia	Moderate hematologic toxicity	NE	Proteinuria	Skin rash, proteinuria, anorexia
Treatment for ITP	PSL 1 mg/kg	HD-DEX, IVIG	PSL 1 mg/kg, IVIG, Rituximab	PSL 1 mg/kg	PSL 1 mg/kg	PSL 0.5 mg/kg
Effect of Len	PR	CR	PR	VGPR	PR	PR

NE: Not evaluated, NA: No applicable, MM: Multiple myeloma, Len: Lenalidomide, ITP: immune thrombocytopenia purpura, BM: Bone marrow, Mgk: Megakaryocyte, AE: adverse event, HD-DEX: high dose dexamethasone, IVIG: intravenous immunoglobulin, PSL: prednisolone, CR: Complete remission, RP: partial response, VGPR: Very good partial response

case was refractory to PSL. The present case presented proteinuria and the exacerbation of skin rash caused by Len. These findings suggested immune dysregulation from Len. Similar findings, such as proteinuria and alopecia, were also observed in previous cases. Therefore, careful attention must be paid to serious thrombocytopenia when adverse events induced by Len are suddenly exacerbated in any cycle of treatment. Such immune dysregulation might induce the auto-reactive immunoglobulin. Our case did not have a high level of PA-IgG and we could not detect the immunoglobulin as the pathogen of ITP. PA-IgG is not the specific marker of ITP, and the relationship between the type of immunoglobulin and pathogenesis of ITP is the very difficult problem. In some reports, the warm-reacting platelet-associated IgM (PA-IgM) was presented in some patients with ITP [4], and others reported the waldenström macroglobulinemia patient of ITP who had the anti-platelet IgM [5]. PA-IgM has not been tested in the current case, but IgM has tended to recover from treatment. Perhaps, the platelet reduction might have arisen in the process of the treatment's being responded, and the rebuilding of the immunity.

Another mechanism, which induced ITP, was the association of monoclonal gammopathy. In this case, Len therapy was very effective, and 24-hours urine protein before treatment was 9.25 g/day, but it decreased to 0.85 g/day after 1 course of Len and dexamethasone therapy. This means plasma cells were successfully reduced and thereafter some pathogenic clone of plasma cells might be selected at the presentation of ITP. Actually, both MGUS [6] and MM-associated ITP [7] were reported previously. All previous cases were IgG, IgA or IgM-type, but there are no cases which present Bence-jones type. In this point of view, our case is the first report of Bence-jones type MM that developed ITP.

In summary, there are two possibilities for the mechanism of Len inducing severe thrombocytopenia from aberrant immunologic status. One is the immunoglobulin production from the myeloma cells, which were selected by the anti-tumor effect of Len. And another is the production from the normal plasma cells, which were activated by immune dysregulation effect of Len after Len killed myeloma cells.

Lenalidomide will be used more widely, because this drug has been found to be effective for many hematological disorders and situations, e.g. like some kinds of lymphoma, adult T-cell leukemia, and initial therapy of multiple myeloma. When unexpected severe thrombocytopenia is encountered during Len therapy, ITP is one of the important differential diagnoses, and it is preferable to discontinue Len, and commence treatment by intravenous immunoglobulin or steroid therapy.

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