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Suspected Immune Thrombocytopenic Purpura Induced by Lenalidomide for the Treatment of Myelodysplastic Syndrome with Deletion of Chromosome 5q: A Case Report

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Lenalidomide (LEN), one of the key drugs in the treatment of myelodysplastic syndromes (MDS) with 5q deletion, as well as multiple myeloma (MM), has various immunomodulatory effects and has been associated with autoimmune diseases, including immune thrombocytopenic purpura (ITP). A 78-year-old man presented with pancytopenia and was diagnosed with MDS with 5q deletion and other chromosomal abnormalities. Two cycles of LEN therapy (one cycle: 10 mg/day for 21 days) resulted in a transient improvement in anemia, followed by MDS progression with severe thrombocytopenia (4×10^9/L) refractory to platelet transfusions. As other non-immune and alloimmune causes of transfusion-refractory thrombocytopenia were excluded, and the level of platelet-associated immunoglobulin G was extremely high compared with the level before treatment with LEN, the diagnosis of ITP was highly suspected. Despite treatment with prednisolone (PSL), eltrombopag, and repeated platelet transfusions, his platelet count did not increase, and he died of a gastrointestinal hemorrhage. Several cases of ITP induced by LEN used to treat MM had been reported, but the platelet count recovered after administration of PSL in these previous cases. However, we should be mindful of using LEN for patients with MDS because its treatment may become extremely difficult if ITP develops.

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Introduction

Lenalidomide (LEN), an immunomodulatory drug (IMiDs) similar to thalidomide and pomalidomide, is widely used as a standard drug for multiple myeloma (MM) and is also effective for myelodysplastic syndromes (MDS) with deletion 5 (5q− syndrome) (List et al. 2006; Merz et al. 2020). IMiDs bind to human cereblon (CRBN), which is the substrate receptor of the CRL4 E3 ubiquitin ligase complex. The binding of CRBN to IMiDs leads to the degradation of Ikaros family zinc finger proteins 1 and 3 (IKZF1 and IKZF3), which are essential transcription factors in MM (Krönke et al. 2014; Liu et al. 2014; Asatsuma-Okumura et al. 2019). CRBN also degrades casein kinase 1 alpha (CK1α), a multifunctional protein that regulates cell cycle progression, apoptosis, autophagy, and immune responses (Krönke et al. 2015). In 5q− syndrome, a deletion in the long arm of chromosome 5, where the casein kinase 1 alpha 1 (CSNK1A1) gene encoding CK1α is located, results in CK1α haploinsufficiency. LEN exerts its effects by inducing CK1α degradation. The CK1α degradation activity of thalidomide and pomalidomide is much weaker than that of LEN (Krönke et al. 2015).

Owing to its various immunomodulatory effects,

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including the promotion of interleukin (IL)-2 and interferon (IFN)-γ secretion and reduction of regulatory T-cell suppressor function (Galustian et al. 2009; Gandhi et al. 2014; Balaian et al. 2016; Lindner and Krönke 2016; Neuber et al. 2017), LEN has been associated with autoimmune diseases, such as autoimmune thyroiditis and cold agglutinin disease (Darabi et al. 2006; Brauer et al. 2012; Montefusco et al. 2014). To date, there have been seven cases of immune thrombocytopenic purpura (ITP) (Herold et al. 2011; Pompa et al. 2016; Meguri et al. 2018; Forehand Iii et al. 2020) induced by LEN, in all of which LEN was administered for the treatment of MM. Here, we report a case of MDS that became extremely transfusion-refractory after treatment with LEN, for which ITP-like pathogenesis was highly suspected.

Case Presentation

A 78-year-old man, with a history of gastric ulcers at the age of 47 years and no medical history of autoimmune diseases, presented with numbness in both feet. The findings of a physical examination were negative, except for purpura in the lower extremities. He showed severe pancytopenia with a white blood cell (WBC) count of 2.7 × 10^9/L (reference range 4.0-8.0 × 10^9/L) with 53% neutrophils, a hemoglobin level of 3.4 g/dL (reference range 14.0-17.0 × 10^9/L), and a platelet count of 24 × 10^9/L (reference range 130-400 × 10^9/L). He was immediately hospitalized (day 1), and repeated transfusions of red blood cells and platelet concentrates were performed, maintaining hemoglobin levels ≥ 6 g/dL and platelet counts ≥ 10 × 10^9/L. The bone marrow aspirate demonstrated hyperplasia with 3% blast cells, an increase in megakaryocyte levels, and a decrease in erythroblast levels, with dysplastic cells mainly of the myeloid lineage, such as neutrophils with ringed nuclei, myeloperoxidase (MPO)-negative neutrophils, and other myelodysplastic cells characteristic of 5q− syndrome (Fig. 1a-c). Flow cytometry analysis revealed 4.8% abnormal cells: CD13+, CD33+, CD34+, and HLA-DR+. The karyotype was 43, X, −Y, del(5)(q?), −13, −18[14]/46, XY[6] (Fig. 2a). A fluorescence in situ hybridization (FISH) test showed 94% CSF1R-negative cells, supporting the characteristics of 5q− syndrome. Because the chromosome showed complex abnormalities in addition to 5q deletion, the patient was diagnosed with MDS with multilineage dysplasia and first treated with azacytidine (AZA 140 mg/day, 7 days); however, he showed no improvement. Subsequent treatment with LEN (one cycle: 10 mg/day for 21 days) resulted in an increase in red blood cell (RBC) count, and he became transfusion-independent. The patient was discharged on day 68, and LEN treatment was continued in the outpatient setting.

However, after the 2nd cycle of LEN, his pancytopenia exacerbated [WBC 0.9 × 10^9/L (blast 1%, stab 1%, segmented 48%, eosinophil 0%, basophil 0%, lymphoid 46%, monocyte 4%), Hb 5.1 g/dL, platelet count 4 × 10^9/L], and he was hospitalized again (day 102). The bone marrow aspirate demonstrated hypoplasia with 1.4% blast cells, with dysplastic cells mainly of the erythroid lineage, such as multinuclear erythroblasts, ringed sideroblasts, and periodic acid-Schiff (PAS)-positive erythroblasts (Fig. 1d-h). Flow cytometry analysis revealed 3.8% abnormal cells: CD13+, CD33+, and glycophorin-A+. Chromosome analysis showed very complex abnormalities, including tetrasomy 8, as shown in Fig. 2b. The FISH test using the probe

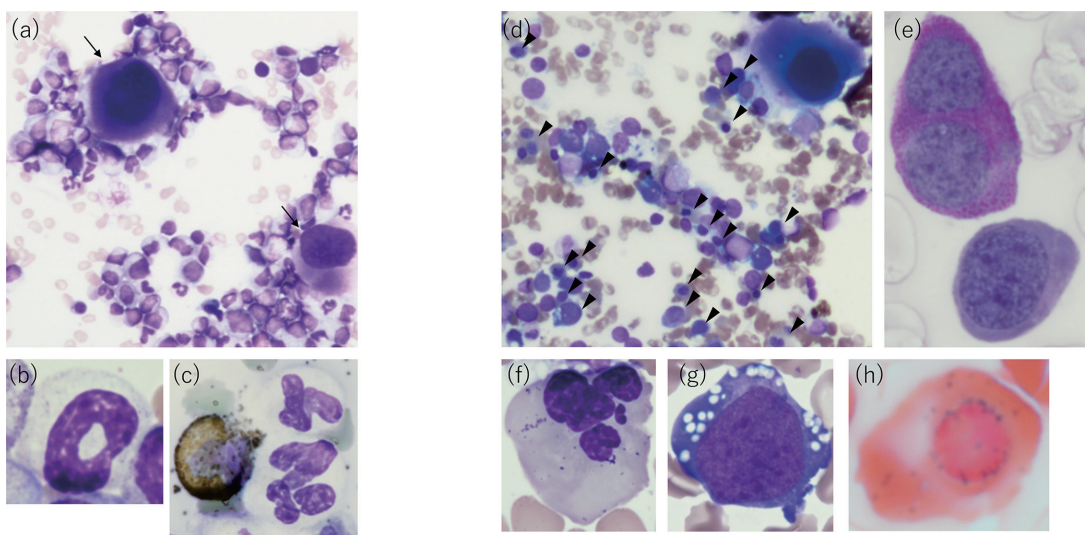

Fig. 1. Bone marrow images on days 1 (a-c) and 102 (d-h).
(a) Increase of megakaryocytes (indicated by arrows) (May-Giemsa staining, × 100). (b) Ringed-nuclear neutrophil (May-Giemsa staining, × 1,000). (c) Myeloperoxidase (MPO)-negative neutrophils (myeloperoxidase staining, × 1,000). (d) Increase of erythroblasts (indicated by arrowheads) (May-Giemsa staining, × 100). (e) Periodic acid-Schiff (PAS)-positive erythroblasts (PAS staining, × 1,000). (f) Multinucleated erythroblasts with megaloblastic changes (May-Giemsa staining, ×100). (g) Erythroblasts with cytoplasmic vacuolations (May-Giemsa staining, × 1,000), (h) Ringed erythroblasts (iron staining, × 1,000).

of the 8th chromosome revealed 72% of cells with four signals, supporting the karyotype of tetrasomy 8. Bone marrow biopsy showed mostly a hypoplastic marrow, with an increase in the population of blast cells with CD34+ and p53+ (Fig. 3). There were no signs of the hemophagocytic syndrome: no increase of macrophages, nor increase of serum ferritin levels (815 ng/mL at the first admission and 1,076 ng/mL at the second admission; reference range 39.9-

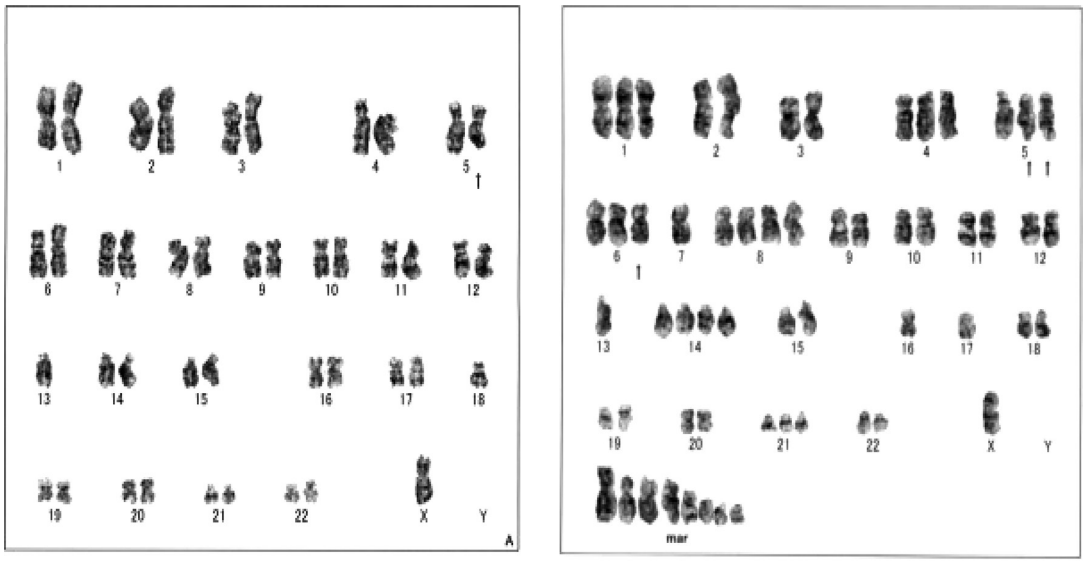

Fig. 2. Karyotypes on days 1 (a) and 102 (b).
(a) 43, X, −Y, del(5)(q?), −13, −18[14]/46, XY[6]. (b) 58<2n>, X, −Y, +1, +4, +5, del(5)(q?)x2, +del(6)(q?), −7, +8, +8, −13, +14, +14, −16, −17, +21, +8mar[1]. In the karyotype analysis on day 102, chromosomes were obtained from 5 cells, each of which showed different complex abnormalities (chromosomes per cell were 58, 61, 62, 63, and 126), and the representative was presented.

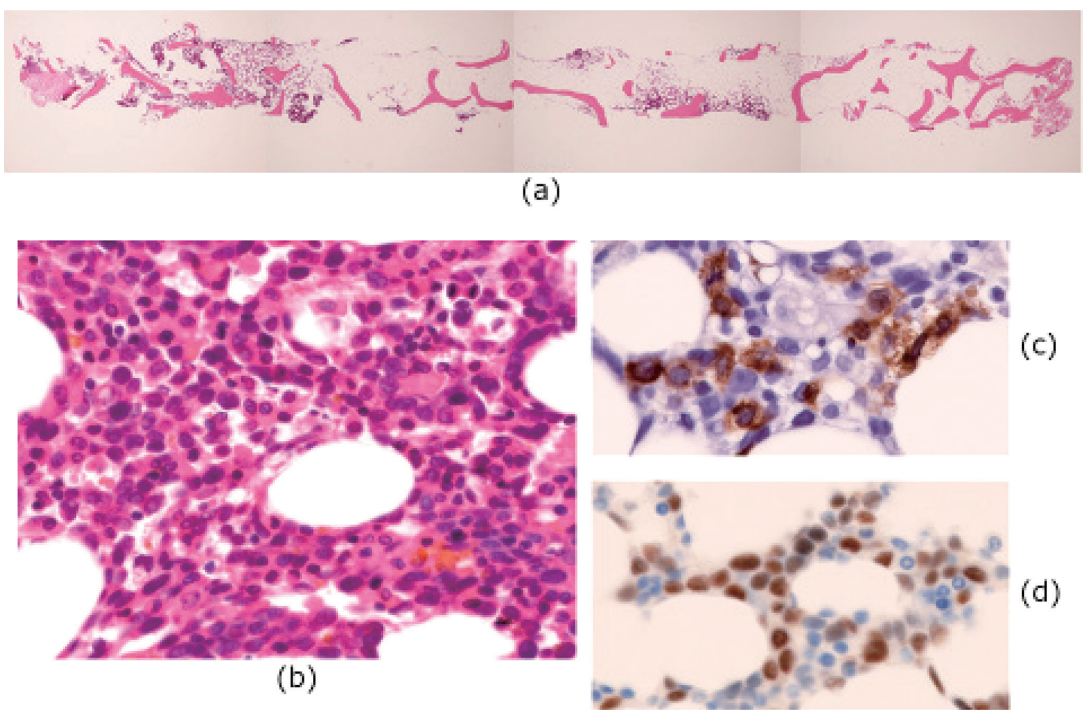

Fig. 3. A bone marrow biopsy on day 102.
Hematoxylin and eosin staining revealed (a) hypocellular marrow (the cell density was about 10%) (× 40), with (b) patchy cellular areas. Immunohistochemical analysis of the bone marrow biopsy revealed that the tumor cells were positive for (c) CD34 and (d) p53.

465.0 ng/mL). Notably, the percentage of paroxysmal nocturnal hemoglobinuria (PNH) RBCs, which was negative (0.000%) at the first admission, became positive (0.020%), indicating that PNH clones developed during LEN treatment. The diagnosis of MDS progression was confirmed, and with the cessation of LEN, transfusion therapy was first attempted to improve the patient's condition.

However, the patient's thrombocytopenia was unresponsive to transfusions (Fig. 4), despite the lack of fever, massive hemorrhage, splenomegaly, and any signs of disseminated intravascular coagulation (DIC). Refractoriness to platelet transfusion was confirmed by a CCI-1 (corrected platelet count increment at one-hour post-transfusion) of 4.8 $\times 10^3/\mu L$. Because his human leukocyte antigen (HLA) antibody and human platelet antigen (HPA) antibody tests were negative, and the level of platelet-associated immunoglobulin G (PAIgG) was high at 447 ng/10^7 cells (normal range 0-47; it was 93 ng/10^7 cells at first admission), the diagnosis of ITP was suspected. The number of megakaryocytes in the bone marrow neither increased nor markedly reduced, as depicted in the Fig. 1d, which we presume was not incompatible with ITP. Treatment with prednisolone (PSL 30 mg/day) was initiated on day 109, with no improvement. Although treatment with eltrombopag (25 mg/day) was added on day 116 and increased to 75 mg/day on day 121, the platelet count did not increase, and he died of a gastrointestinal hemorrhage on day 124.

This case report has been approved by the ethics committee of Tohoku Medical and Pharmaceutical University (2021-4-066).

Discussion

We herein report a rare case of MDS that became extremely transfusion-refractory after treatment with LEN, for which ITP-like pathogenesis was highly suspected. ITP is a diagnosis of exclusion, and the most (and only) reliable criterion is the response to treatment such as corticosteroids (Miltiadous et al. 2020). Thus, the diagnosis of ITP in a patient with MDS, who naturally does not respond to corticosteroids or other treatments for ITP, is quite difficult. We suspected ITP for the following reasons. First, unlike the condition before treatment with LEN, thrombocytopenia was transfusion-refractory, as demonstrated by the low CCI-1 level (Slichter et al. 2005). Second, the non-immune causes of transfusion-refractory thrombocytopenia, such as fever, DIC, splenomegaly, and hemorrhage, were excluded (Balduini et al. 2001). Third, HLA and HPA antibody tests were negative, indicating that alloimmune thrombocytopenia was unlikely. Fourth, the level of PAIgG was extremely high compared to that before treatment with LEN. Although the specificity of PAIgG for ITP is thought to be low (Kelton et al. 1989; Gilli et al. 2012), a recent study showed that PAIgG was significantly higher among non-responders to corticosteroids than among responders, indicating that high levels of PAIgG may have clinical significance in ITP (Saburi et al. 2021). Fifth, LEN has been known to induce ITP, as described previously (Herold et al. 2011; Pompa et al. 2016; Meguri et al. 2018; Forehand Iii et al. 2020). The lack of increase in megakaryocyte populations, as well as the lack of responsiveness to PSL or eltrombopag, could be explained by the concurrent exis-

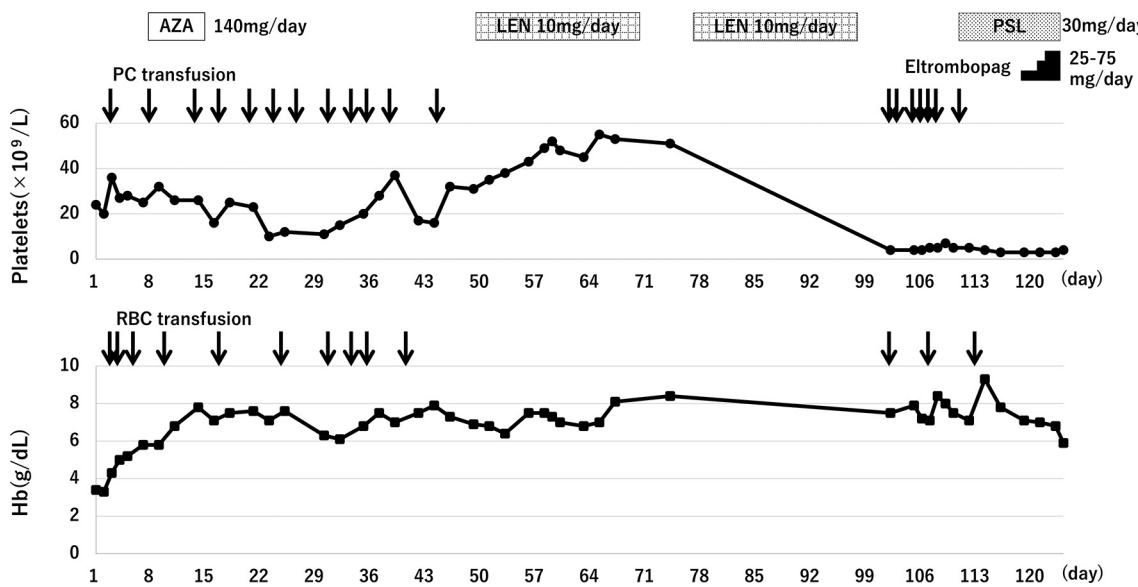

Fig. 4. Clinical course of the patient.
He was initially transfusion-dependent (platelet transfusion-responsive). One cycle of LEN (10 mg/day) resulted in an increase in hemoglobin levels and platelet counts, and he became transfusion-independent. After the second cycle of LEN, the hemoglobin levels and platelet counts decreased, and he became platelet transfusion-refractory. Eltrombopag (25 mg/day) was added on day 116 and increased to 75 mg/day on day 121. AZA, azacytidine; LEN, lenalidomide; PSL, prednisolone; PC, platelet concentrate; Hb, hemoglobin.

tence of MDS and the short follow-up period before death.

To date, seven cases of ITP induced by LEN, all in cases of MM, have been reported (Herold et al. 2011; Pompa et al. 2016; Meguri et al. 2018; Forehand Iii et al. 2020) (Table 1). Two patients were men and five were women aged 59 years or older, except for Case 1 (27 years old). ITP occurred mainly after more than two cycles of LEN treatment; the median time from the initiation of LEN to the development of ITP was 2.5 months, ranging from 14 days to a year. Platelet counts were $< 20 \times 10^9$/L in all but one patient (Case 2). Bone marrow findings were consistent with ITP; chromosome analyses were available for only one case (Case 1: normal karyotype). In all the previous cases, despite the lack of autoantibodies, the diagnosis of ITP rather than the direct suppression of thrombopoiesis by LEN was highly likely, because thrombocytopenia persisted after the discontinuation of LEN. In addition, the platelet counts recovered after the standard treatment for primary ITP, which included corticosteroids, high-dose immunoglobulin, rituximab, or splenectomy. In one case, ITP recurred after the patient resumed LEN (Case 2). The immunomodulatory effects of LEN, such as promoting IL-2 and IFN-γ secretion and reducing regulatory T-cell suppressor function (Galustian et al. 2009; Gandhi et al. 2014; Balaian et al. 2016; Lindner and Krönke 2016; Neuber et al. 2017), are thought to be the cause of ITP in these cases. Similar mechanisms may have occurred in the present case.

The development of PNH clones after the treatment with LEN was intriguing. Although the presence of PNH clones in MDS, as well as aplastic anemia (AA), is well known, the expansion of PNH clone size has been observed in more AA cases than in MDS cases (Fattizzo et al. 2021). AA-like pathogenesis may have occurred in the current case. Bone marrow aspiration and biopsy after LEN treatment showed a hypocellular marrow, and a T1-weighted sagittal magnetic resonance (MR) image of the lumbar spine showed multiple foci of dark signals on a bright background (data not shown). Interestingly, Dasanu and Alexandrescu (2009) reported a case of LEN-induced AA. In this report, a 64-year-old man, after treatment with LEN 10 mg/day for 3 weeks, developed severe pancytopenia (neutrophil 210/μL, Hb 8.9 g/dL, platelet 7×10^9/L) and a severe hypocellular marrow, which spontaneously improved within 15 weeks of LEN discontinuation. Flow cytometric IFN-γ expression was shown to be significantly increased, which is known to be induced by LEN as described above (Lindner and Krönke 2016) and has long been considered one of the pathogeneses in the development of AA (Smith et al. 2016).

In addition to the development of ITP, MDS progression was also observed in our case after LEN treatment, which may be related to TP53 mutations (Giagounidis et al 2005; Ximeri et al. 2010). TP53 mutations occasionally occur in patients with 5q− syndrome, and among patients with 5q−, those harboring a TP53 mutation had significantly worse outcomes than those without mutation (median

Table1. Reported cases of immune thrombocytopenic purpura (ITP) induced by lenalidomide (LEN).

Case No.	Age(y)/Sex	Diagnosis	Doses of LEN (mg)	LEN Cycles	Time from the start of LEN to ITP	Platelet counts (10^9/L) when ITP developed	Treatments for ITP	Outcomes	References
1	27/M	MM	25	4	11 months	1	High dose DEX, IVIG	Recovered	Herold et al. (2011)
2	66/F	MM	25	5	6 months	44	PSL 1 mg/kg	Recovered	Pompa et al. (2016)
3	76/F	MM	15	3	2 months	5	PSL 1 mg/kg	Recovered	Pompa et al. (2016)
4	78/F	MM	15	6	5.5 months	18	PSL 1 mg/kg	Dependent on PSL	Pompa et al. (2016)
5	66/F	MM	15	5	3 months	17	PSL 1 mg/kg, IVIG, RTX	Recovered	Pompa et al. (2016)
6	74/F	MM	15	1	14 days	10	PSL 0.5 mg/kg	Recovered	Meguri et al. (2018)
7	59/M	MM	10	1	28 days	9	PSL 1 mg/kg, IVIG, RTX, splenectomy	Recovered	Forehand Iii et al. (2020)

ITP, immune thrombocytopenic purpura; LEN, lenalidomide; MM, muleiple myeloma; PSL, prednisolone; DEX, dexamethasone; IVIG, high dose intravenous immunoglobulin therapy; RTX, rituximab.

overall survival 23 vs. 66 months) (Kulasekararaj et al. 2013). Jädersten et al. (2011) demonstrated, using sensitive deep-sequencing technology, that TP53 mutated populations may occur at an early disease stage in almost one-fifth of patients with MDS with 5q− syndrome; mutations were present years before disease progression and were associated with an increased risk of leukemic evolution. In the current case, TP53 mutation clones were clearly demonstrated to be present in the bone marrow after the three-month treatment with LEN; a small fraction of such clones likely existed at the time of initial diagnosis. Thus, our current case indicates that the presence of TP53 mutation should always be examined by immunohistochemistry before LEN administration in patients with 5q− syndrome with or without other chromosomal abnormalities, as recommended previously (Saft et al. 2014).

The management of severe thrombocytopenia caused by simultaneous occurrence of ITP and bone marrow failure (BMF) syndromes is challenging. Although ITP and AA are both caused by immunological mechanisms, their simultaneous occurrence is quite rare. Jachiet et al. (2021) compared the clinical outcome of patients with chronic myelomonocytic leukemia (MDS/CMML)-associated ITP (n = 41) and primary ITP (n = 75). Patients with MDS/CMLL-associated ITP had a higher incidence of severe bleeding (26% vs. 4%, p = 0.0009) involving the central nervous system or gastrointestinal tract. As suggested in this paper, the best choice for this situation would be thrombopoietin receptor agonists, such as eltrombopag, which might work for both ITP and BMF syndromes. Another choice may be high-dose intravenous immunoglobulin therapy, although its effect is transient and limited to ITP-like pathogenesis. Here, we administered eltrombopag to our patient, but he died before it might have taken effect.

In conclusion, we report a patient with MDS harboring 5q− who underwent extremely complicated changes, which might be induced by the various immunomodulatory effects of LEN. The complicated changes may include a decreased production of platelets, either due to the progression of MDS, or the development of aplastic anemia-like pathogenesis, or LEN-induced marrow suppression, or the combinations of these. However, a decreased production of platelets can usually be managed by platelet transfusions. The striking feature of this case was an abrupt development of platelet transfusion-refractoriness, which we fully discussed was possibly due to ITP-like pathogenesis caused by LEN. Because LEN is effective in a wide variety of hematological diseases, including chronic lymphocytic leukemia and diffuse large B-cell lymphoma (Strati et al. 2019; Ioannou et al. 2021; Li et al. 2021), awareness of the various effects of LEN is needed. In particular, we should be mindful of using LEN for patients with MDS, because treatment of MDS may become extremely difficult if ITP develops.

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Conflict of Interest

The authors declare no conflict of interest.

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