



## Case reports

## Secondary pure red cell aplasia in multiple myeloma treated with lenalidomide



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## ABSTRACT

Pure red cell aplasia (PRCA) is a rare disorder characterized by marked erythroid hypoplasia with maturation arrest in the bone marrow. Secondary acquired PRCA may be associated with hematologic disorders. A few case reports have described PRCA associated with multiple myeloma (MM). However, the clinical course and mechanism of PRCA associated with MM remain unknown. We herein report two cases of PRCA associated with MM in patients undergoing treatment with lenalidomide.

### 1. Introduction

Pure red cell aplasia (PRCA) is a rare disorder characterized by marked erythroid hypoplasia with maturation arrest in the bone marrow. This disorder may be congenital or develop as an acute or chronic acquired syndrome. Acquired PRCA may be either a primary disorder or secondary to another disorder or agent. Primary acquired PRCA is an autoimmune disorder that is frequently antibody-mediated. Secondary acquired PRCA may be associated with collagen vascular/autoimmune disorders such as systemic lupus erythematosus; lymphoproliferative disorders such as chronic lymphocytic leukemia or large granular lymphocyte leukemia; infections, particularly B19 parvovirus; thymoma and other solid tumors; or a variety of other disorders, drugs, or toxic agents [1].

Acquired PRCA may present as a primary hematological disorder in the absence of any other disease. A few case reports have described PRCA associated with multiple myeloma (MM) [2–5]. However, the clinical course and mechanism of PRCA associated with MM remain unknown. We herein report two cases of PRCA associated with MM in patients undergoing treatment with lenalidomide.

### 2. Case 1

A 77-year-old woman was diagnosed with symptomatic MM (IgG  $\lambda$  type), Durie Salmon stage III A, ISS II. Laboratory examination at the diagnosis showed a white blood cell count of  $3.7 \times 10^9/L$ , hemoglobin of 9.5 g/L, platelet count of  $129 \times 10^9/L$ , lactate dehydrogenase 121 U/

L, calcium 8.8 mg/dL, creatine 0.46 mg/dl, estimated glomerular filtration rate 96 mL/min/1.73 m<sup>2</sup>, and IgG 7229 mg/dL. Bone marrow examination showed a total nucleated cell count of 27,000/ $\mu$ L with plasma cell concentration of 9.4%. She did not have any bone disease on X-ray. She underwent two cycles of an Ld regimen (lenalidomide and dexamethasone). She subsequently developed severe anemia. Laboratory examination showed a white blood cell  $2.4 \times 10^9/L$ , hemoglobin 6.8 g/L, platelet  $107 \times 10^9/L$ , reticulocyte  $3.98 \times 10^3/\mu$ L, lactate dehydrogenase 1337 U/L, and total bilirubin 1.9 mg/dL. Increase of lactate dehydrogenase and bilirubin were suspected hemolytic anemia, however, coombs test was negative and reticulocyte count was low, which was compatible with ineffective erythropoiesis due to sudden erythroid maturation arrest. Bone marrow examination showed a total nucleated cell count of 14,000/ $\mu$ L with a myeloid cell concentration of 41.2%, erythroid cell concentration of 0.4%, lymphoid cell concentration of 38.4%, monocyte concentration of 12.0%, and plasma cell concentration of 4.2%. The serum vitamin B12 and folic acid concentrations were normal. Expression of CD55 and CD59 on granulocytes was within the reference range. We diagnosed the patient with PRCA and began treatment with cyclosporine at 140 mg/day. Hemoglobin concentration improved from 6.8 g/L to 10.2 g/L within one month. Lenalidomide was suspected to be the cause of the PRCA; therefore, the lenalidomide was stopped and only dexamethasone was given intermittently for treatment of the MM. Although the patient maintained a partial response for 5 years, the MM subsequently relapsed. She began treatment with a VCD regimen (bortezomib, cyclophosphamide, and dexamethasone), which was not sufficiently

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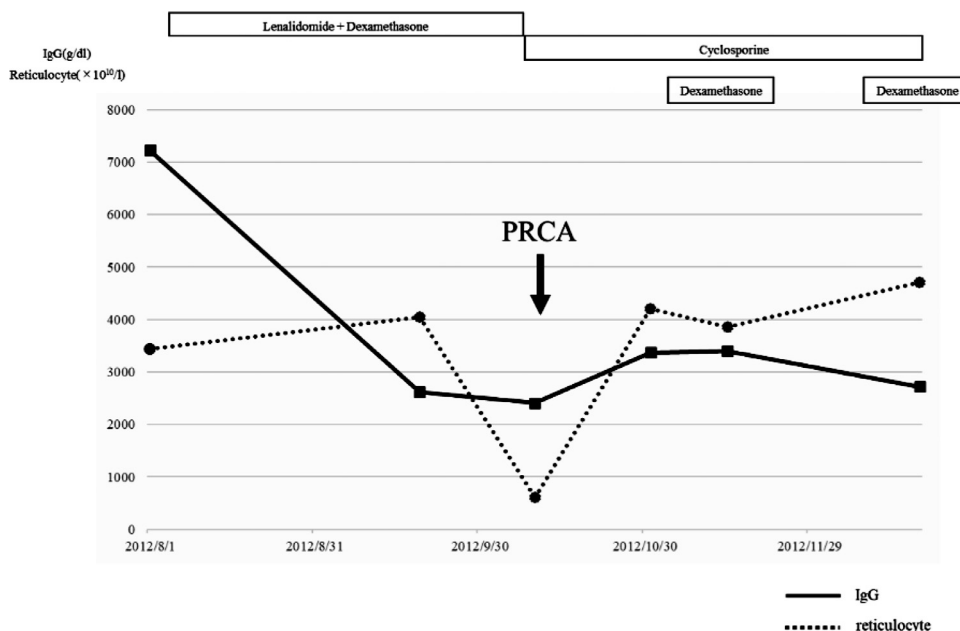
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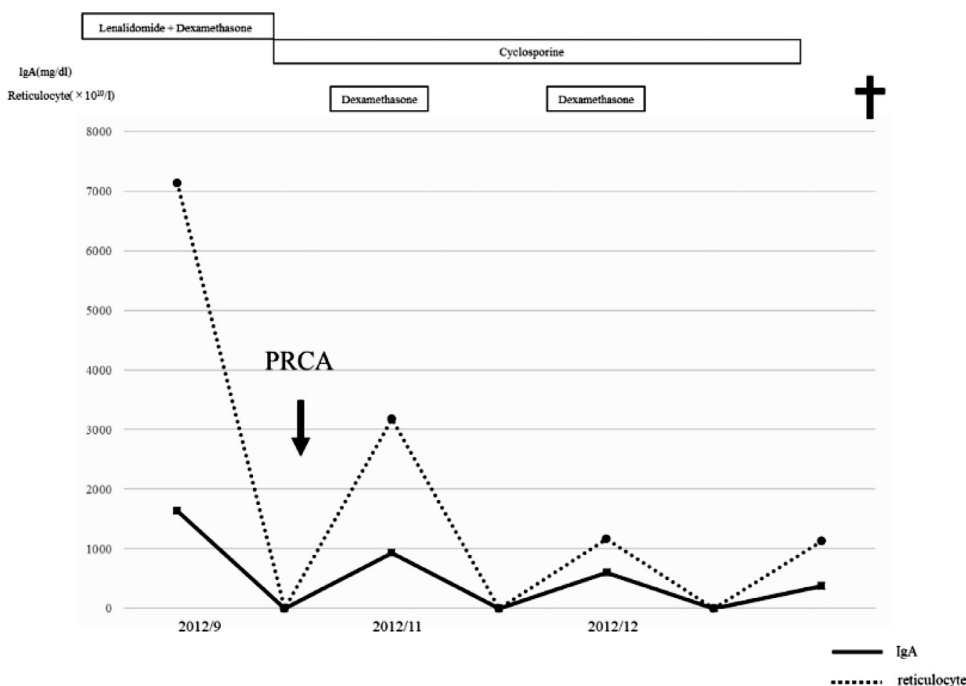
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**Fig. 1.** Case 1: A 77-year-old woman diagnosed with MM (IgG λ type). She underwent treatment with two cycles of an Ld regimen (lenalidomide and dexamethasone). She subsequently developed severe anemia. Cyclosporine was begun at 140 mg/day, and the anemia improved within 1 month.



**Fig. 2.** Case 2: A 73-year-old man diagnosed with MM (IgA λ type). He underwent treatment with a BD regimen (bortezomib and dexamethasone). After nine cycles of the BD regimen, he was switched to the Ld regimen (lenalidomide at 5 mg/day and dexamethasone at 20 mg/day). After 11 cycles of Ld, he suddenly developed anemia. He began treatment with cyclosporine at 200 mg/day. The anemia slowly improved. However, the MM gradually progressed and he died 6 months after the development of PRCA.

effective, and was finally switched to pomalidomide. The PRCA did not worsen during treatment with pomalidomide. At the time of this writing, she had stopped all treatment for MM and PRCA because of the development of lung cancer.

**3. Case 2**

A 73-year-old man undergoing dialysis for diabetic renal dysfunction was diagnosed with symptomatic MM (IgA λ type), Durie Salmon stage III B, ISS III. Laboratory examination at the diagnosis showed a white blood cell count of  $4.2 \times 10^9/L$ , hemoglobin of 7.1 g/L, platelet count of  $232 \times 10^9/L$ , lactate dehydrogenase 191 U/L, calcium 9.0 mg/dL, creatine 3.54 mg/dl, estimated glomerular filtration rate 14 mL/

min/1.73 m<sup>2</sup>, and IgA 1821 mg/dL. Bone marrow examination showed a total nucleated cell count of  $7/\mu L$  with plasma cell concentration of 27.0%. He had old lumbar compression fracture on X-ray. He began treatment with a BD regimen (bortezomib and dexamethasone) as an induction regimen. After nine cycles of the BD regimen, the MM became resistant. The treatment was switched to an Ld regimen (lenalidomide at 5 mg/day and dexamethasone at 20 mg/day). After 11 cycles of Ld, he suddenly developed anemia. Laboratory examination showed a white blood cell count of  $12.3 \times 10^9/L$ , hemoglobin 7.9 g/L, platelet  $153 \times 10^9/L$ , reticulocyte count  $22.5 \times 10^3/\mu L$ , lactate dehydrogenase 298 U/L, total bilirubin 0.5 mg/dL. Bone marrow examination showed a total nucleated cell count of 13,200/ $\mu L$  with a myeloid cell concentration of 47.8%, erythroid cell concentration of 3.1%, lymphoid

cell concentration of 21.3%, monocyte concentration of 7.1%, and plasma cell concentration of 20.8%. The serum vitamin B12 and folic acid concentrations were normal. Expression of CD55 and CD59 on granulocytes was within the reference range. We diagnosed the patient with PRCA and began treatment with cyclosporine at 200 mg/day. The anemia slowly improved, hemoglobin concentration from 7.9 g/L to 9.9 g/L, and the patient maintained a partial response. Lenalidomide was suspected to be the cause of the PRCA; therefore, the lenalidomide was stopped and the patient was given only dexamethasone for treatment of the MM. However, the MM gradually progressed and the patient died 6 months after the development of PRCA.

#### 4. Discussion

PRCA is an acquired anemia that may be idiopathic or secondary to a variety of neoplastic, autoimmune, or infectious diseases or to drug exposure. Most cases of PRCA are considered to be autoimmune-mediated. MM is a plasma cell disorder characterized by osteolytic bone lesions, hypercalcemia, renal failure, and anemia. Although anemia is a common end-organ feature of MM, PRCA with erythroid maturation arrest is not a typical finding in patients with MM. Korde et al. recently performed a systematic assessment of monoclonal gammopathy-associated PRCA [6]. They found that among 51 patients with PRCA, 24% had a monoclonal gammopathy disorder. Three patients who were treated with anti-MM drugs exhibited reticulocyte recovery. Therefore, the authors speculated that a functional relationship exists between plasma cell and erythroid precursors in patients with monoclonal gammopathy-associated PRCA. A few case reports have described that patients developed PRCA undergoing treatment with anti-MM drugs [5,6]. Among them, two patients were using bortezomib. It is difficult to determine whether PRCA is induced by MM itself or induced by drugs. Reports of drug-induced PRCA have mostly involved erythropoietin, phenytoin, isoniazid, azathioprine, and zidovudine [7]. A few reports of lenalidomide-induced PRCA have been described in patients with myelodysplastic syndrome [8,9], but not in patients with MM. Figs. 1 and 2

Both patients in the present report developed PRCA after treatment with lenalidomide; thus, we considered drug-induced PRCA to be likely, and the lenalidomide was stopped in both patients. However, as Korde et al. described [6], if PRCA is associated with the activity of MM, we should not have stopped the lenalidomide. Although the optimal course of action is very difficult to judge, we suggest that another anti-MM treatment should be continued in patients with poor control of MM.

We consider that MM itself might be associated with PRCA and that

anti-MM treatment agents might trigger the development of PRCA. Further investigation is warranted to elucidate the pathogenetic mechanism between MM and PRCA.

#### Conflict of interest

The authors declare no competing financial interest in relation to the work.

#### Authors' contributions

(1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data: A.N., S.F., A.S., T.N., Y.T., Y.A., A.K., M.H., H.Y., K.I., T.I. (2) drafting the article or revising it critically for important intellectual content; A.N., T.I., S.N. (3) final approval of the version to be submitted.: A.N., T.I.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.06.005.

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