Good’s Syndrome-Associated Pure Red Cell Aplasia with Myelodysplastic Syndrome

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Abstract

We report a case of Good’s syndrome-associated pure red cell aplasia (PRCA) with myelodysplastic syndrome (MDS). In this case, effector memory T (T_em) cells were expanded in the bone marrow. It remains uncertain whether the development of MDS was caused by the basic marrow defects or radiation therapy. However, since CD8⁺ perforin⁺ T_em cells expanded in the bone marrow, as was previously described for 3 of our patients with thymoma-associated PRCA, it is highly possible that the pathogenic mechanism of PRCA that is accompanied by thymoma is related to the expanded CD8⁺ perforin⁺ T_em cells in this MDS-complicated case.

Key words: pure red cell aplasia, thymoma, Good’s syndrome, myelodysplastic syndrome


Introduction

Good’s syndrome is a rare syndrome associated with thymoma and immunodeficiency, which was first described in 1954. In thymoma-associated PRCA, a few studies have demonstrated the presence of clonal or oligoclonal T-cell expansion (1, 2). Here, we report for the first time a case of MDS and PRCA development after thymectomy and irradiation in Good’s syndrome.

Case Report

In August 2005, chest X-ray examination of a 69-year-old man revealed an abnormal shadow. Chest CT scan revealed that he had an anterior mediastinal tumor suspected to be thymoma. He underwent surgery and the tumor was removed. Pathological diagnosis was invasive thymoma, with type AB, Masaoka stage III (3). Subsequently, he was treated with radiation to the mediastinum (total 54 Gy). In December 2009, the laboratory findings showed white blood cell count (WBC) 5.1×10⁹/L, hemoglobin (Hb) 9.7 g/dL (reticulocyte 2.9%), platelet count (Plt) 279×10⁹/L, and he was pointed out to have moderate normochronic normocytic anemia. Bone marrow examination revealed over 10% atypism in all series (Fig. 1) (blast: 1.2%, erythroblast: 17.6%). On the basis of morphological findings, he was diagnosed with MDS. In June 2010, he was referred to our hospital owing to advanced anemia. The laboratory findings showed WBC 4.3×10⁹/L, Hb 6.0 g/dL (reticulocyte 0.10%), Plt 212×10⁹/L. Bone marrow examination revealed no erythroblasts (blast: 0.5%). The large granular lymphocytes were not increased. Serum parvovirus B19 DNA was negative. We diagnosed thymoma-associated PRCA with MDS. Additionally, the B-cell population was highly reduced and CD4/8 ratio in the T-cell population was inverted (0.40) as determined by flow cytometric analysis of bone marrow mononuclear cells (BM-MNCs); IgG and IgM were also severely reduced (IgG 371 mg/dL, IgM 12 mg/dL) in blood serology (B-cell population in the bone marrow and serum immunoglobulin were not investigated on August 2005 and June 2010). Therefore, we diagnosed Good’s syndrome-associated PRCA with MDS.

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Although karyotypic analysis of the bone marrow revealed 46, XY, by G-banding, deletion Y and trisomy 15 were detected by spectral karyotyping method. In early July he was admitted to our hospital owing to septic shock, with *Escherichia coli* and *Staphylococcus aureus*, and was successfully treated with antibiotics and intravenous gammaglobulin. We then started to treat the Good’s syndrome-associated PRCA with MDS using cyclosporine at 300 mg/day. On the 13th day, reticulocytosis (6.42%) occurred, but the hemoglobin level was elevated only slightly (from 6.0 mg/dL to 7.9 mg/dL) owing to ineffective hematopoiesis of MDS. In addition, his renal dysfunction worsened and he developed severe general edema. We discontinued cyclosporine therapy and started dose reduction cyclosporine at 50 mg/day again.

**Discussion**

Intriguingly, in the present case, the CD8⁺/perforin⁺ T-cell population was significantly increased in the bone marrow (64.8%) (Fig. 2). This T-cell subpopulation expressing CD8⁺ perforin⁺ CCR7⁺⁺ CD62L⁺⁺ CD27⁺ CD28⁺⁺ CD45RO⁻ CD45RA⁻ (55.8%) is consistent with the CD8⁺/ perforin⁺ effector memory T (T_{EM})-cell subset (4). The T-cell receptor beta (TCR-β) gene of BM-MNCs was clonal rearranged by polymerase chain reaction (PCR) method. Bone marrow biopsy confirmed the expansion of the CD8⁺ granzyme B⁺ T-cell subpopulation, together with the absence of a CD20⁺ B-cell subpopulation (Fig. 3). Patients with thymoma have been reported to also exhibit PRCA and hypogammaglobulinemia in 5% and 6-11% of cases, respectively (5, 6). In a recent systematic review, 34.8% of patients with Good’s syndrome were found to also exhibit PRCA (7). This is about seven-fold higher than for patients with thymoma alone. This may be related to the fact that patients with Good’s syndrome have activated memory T cells. The principal immunological characteristics of Good’s syndrome are hypogammaglobulinemia, few or absent B cells, inverted CD4/CD8 ratio, CD4 T-cell lymphopenia, and impaired T-cell mitogenic response. However, the association of impaired maturation of myeloid precursors, neutropenia and eosinopenia is also observed in many cases, suggesting that the basic defect may be in the bone marrow (7).

In this case, we suspected that the cause of severe septic shock due to two species of bacteria was related to hypogammaglobulinemia, reduced CD4 T-cell number, and impaired T-cell function. The characteristics of Good’s syndrome suggest association of thymoma with B lymphopenia. The explanation for this is that cytokines, possibly secreted by bone marrow stromal cells, may influence the growth and differentiation of both thymic and B-cell precursors (8). Indirect evidence for this explanation comes from murine studies, showing that limitin, an interferon-like cytokine pro-
Figure 2. Immunophenotypic analysis of proliferative T cells in the bone marrow mononuclear cells (BM-MNCs) from patients with thymoma-associated PRCA with hypogammaglobulinemia and MDS. The number of CD8+/perforin+ T cells in BM-MNCs was significantly increased compared with that in the controls (Control 1-3). The size of the T-cell subpopulation expressing CD8+/perforin+ CCR7low CD62Llow CD27+ CD28low CD45RO± CD45RA+, which was consistent with the CD8+/perforin+ TEM-cell subset, was increased in the bone marrow (Case 1: 55.8% vs. Control 1: 23.8%).

Figure 3. Immunohistochemistry of the bone marrow biopsy tissue. In Hematoxylin and Eosin staining (HE) (×40 and ×600), there were no erythroblasts in the bone marrow. Expanding lymphocytes in the bone marrow were weakly positive for CD4 and strongly positive for CD8 and Granzyme B. CD20-positive B cells in the bone marrow were not observed.

duced by a bone marrow stromal cell line, preferentially inhibits precursor B cell growth and differentiation (9).

MDS with erythroid hypoplasia is a rare form of MDS that has been proposed by some to represent a novel and distinct entity. In a series of 360 cases of MDS diagnosed in a single institution over a 10-year period, 1.7% were found to have MDS with erythroid hypoplasia (10). In the present case of Good’s syndrome, MDS and PRCA
also developed. It remains uncertain whether the development of MDS was caused by the basic marrow defects or as a side effect of radiation therapy. However, since CD8\(^+\) perforin\(^+\) TEM cells expanded in the bone marrow, as previously described for 3 of our patients with thymoma-associated PRCA and thymoma-derived lymphocytes can survive for a long time in the peripheral tissue (11), it is highly possible that the pathogenic mechanism of PRCA that is accompanied by thymoma is related to the expanded CD8\(^+\) perforin\(^+\) TEM cells in this MDS-complicated case.

The authors state that they have no Conflict of Interest (COI).

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