Myelodysplastic Syndrome Accompanied by Addison’s Disease and Multiple Autoimmune Phenomena: Steroid Therapy Resolved Cytopenias and All Immune Disorders

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Abstract

We report here a patient with myelodysplastic syndromes (MDS), which was complicated with several autoimmune disorders and asymptomatic immunologic abnormalities. An 82-year-old woman with refractory anemia (RA) rapidly developed thrombocytopenia with the appearance of symptoms such as purpura, fatigue, anorexia, and weight loss. Furthermore, clinical examinations revealed that she also had Addison’s disease, rheumatoid arthritis, and autoimmune hematological diseases such as thrombocytopenia and hemolytic anemia. However, the cytopenia and all autoimmune disorders were remarkably improved after she received steroid therapy.

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Key words: autoimmune disease, rheumatoid arthritis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by hypercellular bone marrow with multi-lineage dysplasia, and peripheral cytopenia as a result of ineffective hematopoiesis. Complications of immunologic abnormalities, especially autoimmune disorders, have been reported to be rather frequent in patients with MDS (1).

Addison’s disease is also occasionally observed in patients with various autoimmune disorders. For example, the combined occurrence of Addison’s disease with either type I diabetes mellitus or Hashimoto’s thyroiditis is well known as a polygranular syndrome type II, also known as Schmidt syndrome (2). However, the hematological disorders (except for pernicious anemia) are rarely observed in patients with Addison’s disease.

Case Report

In April 1997, an 82-year-old woman with a 2-year history of thrombocytopenia (37×10^9//) was referred to our hospital. She had been treated for hypertension, but had no other medical history or blood transfusions. Her bone marrow (BM) findings showed hypercellularity with low blast cell counts and the trilineage dysplasia of hematopoietic cells. A cytogenetic analysis of BM cells revealed a normal karyotype. At this time, we had diagnosed the patient as having refractory anemia (RA) based on the diagnostic criteria of the French-American-British classification of MDS (3). In addition, she was classified into a low risk group of MDS according to the international prognostic scoring system (IPSS) (4).

Twenty-two months later, she was hospitalized because of the progression of thrombocytopenia (5×10^9//) and increasing sense of fatigue, anorexia, and weight loss (−7 kg for 24 months). On admission, she showed pale conjunctiva, pigmentation of the systemic skin and oral cavity (Fig. 1), and petechiae on her foot. Her MP and PIP joints were slightly swollen and deformed. Low blood pressure (96/48 Torr) was also observed. There was no hepatosplenomegaly.

A complete blood count showed a hemoglobin level of 10.2 g/dl, a platelet count of 3×10^9//, and white blood cell count of 3.5×10^9// with 51% neutrophils, 9% eosinophils, 29% lymphocytes, and 11% monocytes. A BM aspirate on admission revealed a hypercellular marrow with megakaryocytic hyperplasia (Fig. 2). The percentage of blasts in the BM was 3.6%. A chromosomal analysis showed a normal karyotype. These he-
matological findings were consistent with RA in MDS. She was still scored as a low risk group according to IPSS (4). Since the platelet-associated IgG (PAIgG) was extremely elevated at 11,466.7 ng/10^7 cells, the megakaryocytic hyperplasia was also suggestive of autoimmune thrombocytopenia. In addition, laboratory findings such as a positive result for Coombs’ test, an increased indirect bilirubin level (0.88 g/dl), low level of serum haptoglobin (<10 mg/dl), an elevated reticulocyte count (1.7%) and erythroid hyperplasia in BM (L/E=1.47) all suggested that she also had autoimmune hemolytic anemia.

Endocrine investigations showed a lack of serum cortisol (<1.0 μg/dl) and a highly elevated ACTH concentration (1,100 pg/ml). Her serum aldosterone concentration was decreased to 37 pg/ml, the lower limit of the normal range (normal <36 to 240). The plasma renin level was 0.7 ng/ml/h (normal <0.3 to 2.9). These results confirmed the coexistence of primary adrenocortical insufficiency with MDS. A thin-slice scanning of abdominal computed tomography (CT) showed no abnormal morphological changes in the bilateral adrenal glands. In addition to these CT findings, no past history of tuberculosis, and no calcification of the adrenal gland indicated that tuberculosis was not thought to be the cause of adrenal insufficiency. Her physical findings, such as systemic pigmentation and low blood pressure, were also consistent with the symptoms of Addison’s disease. Furthermore, rheumatoid factor (RF) was
positive at a titer of 1: 32 and RAPA was 1: 64. Serum C-reactive protein was 1.3 mg/dl and the erythrocyte sedimentation rate was 30 mm/h. The swelling of the joint joints, morning stiffness and the radiographic findings of these joints all supported the diagnosis of rheumatoid arthritis with a low activity. Her serum total protein measuring 6.8 g/dl was within the normal range. However, she showed a polyclonal gammopathy which was 27.2% of γ-globulin fraction in whole serum. Decreased complement components were also detectable. Diabet es mellitus, and thyroid or parathyroid dysfunction were not seen. A prolongation of APTT due to circulating anticoagul ants was also observed.

Thereafter, the patient was orally treated with 25 mg/day (0.6 mg/kg) of prednisone. After the initiation of steroid therapy, her anemia improved rapidly in accordance with increased haptoglobin and decreased b2-microglobulin levels. Thrombocytopenia was also improved with disappearance of PAIgG. In addition, autoimmune manifestations such as hyperpigmentation, anorexia, and weight loss were clearly improved, and the ACTH level was dramatically normalized. After reducing the steroids to 5 mg/day, the complete resolution of all clinical manifestations, including cytopenia has been maintained over one year to date.

**Discussion**

In MDS patients, various immunological abnormalities have been reported relatively frequently. Ten to twenty percent of MDS patients have been reported to have accompanying autoimmune disorders (2, 5, 6). This high incidence implies a non-fortuitous association between MDS and autoimmune disorders. Yet, the pathophysiologic basis of MDS for autoimmunity is still unknown. Conversely, it is also well known that Addison’s disease is frequently found in association with other autoimmune disorders (7).

In MDS, skin rashes of an autoimmune etiology are particularly common among the complications reported (1). In addition, autoimmune complications such as rheumatoid arthritis, autoimmune hemolytic anemia, and a wide variety of vasculitic conditions represented by cutaneous vasculitis, Sweet syndrome, pyoderma gangrenosum and Behçet syndrome (8) were also reported in cases of MDS, which are likely to be a consequence of immunological derangement of MDS which is possible derived from the MDS clone (1). Determining the origin of MDS clone, since most transformation of MDS into acute leukemia is myeloid, it is suggested that the MDS clone is a myeloid progenitor cell (9). On the contrary, there are several reports of acute lymphoblastic leukemia (ALL) transformation of MDS of all subtypes (10). Thus, it is still not clear whether these immunologic abnormalities are caused by abnormal lymphocytes derived from the MDS clone or by the indirect effects of abnormal cytokine-production and antigen-presentation by the disordered monocytes (1). In addition, asymptomatic immunologic abnormalities are also frequent in patients with MDS. In the present case as well, a gammopathy, the presence of ANA, and a positive result for direct Coombs’ test are reported as the most common features (5). However, as far as we know, Addison’s disease has not been reported as a complication of MDS.

It has been reported that autoimmune disorders may be the primary cause of death in some MDS patients. Nevertheless, how the association with autoimmune disorders influences the prognosis for MDS patients is still unclear. It has been reported that the median survival duration of all MDS patients was 25 months, whereas it was 9 months for the MDS patients accompanied by autoimmune manifestations, suggesting a poor prognosis (11). In contrast, another report demonstrated that complicated autoimmune manifestations did not influence the prognosis for MDS (6). However, it is noteworthy that all these immunologic disorders have been reported to show a good response to immunosuppressive therapy (2, 5). According to IPSS, the present case was categorized into a low risk group, and indeed, after receiving immunosuppressive therapy with prednisolone, not only the autoimmune manifestations but also the cytopenia have dramatically improved. Furthermore, hematological remission has been maintained for over a year after reduction of the steroids. Her BM still showed some morphological abnormalities such as hypogranularity of granulocytes, or slightly irregular nuclei of megakaryocytes. Chromosomal analysis of her BM remained normal. Both improvement of MDS and reduction of hemolysis and immunologic thrombocytopenia may have contributed to the hematological remission in this case.

This is one of the rare cases of MDS showing a variety of autoimmune disorders and asymptomatic serological abnormalities. However, the good response of all her clinical manifestations, including cytopenia, to the steroid therapy strongly suggests a common abnormal immunologic background which may be caused by a clonal stem cell disorder, in this case. Moreover, it is hypothesized that certain cases of MDS have an immunologic pathogenic basis. Accumulation of further careful observations of patients with both MDS and autoimmune disorders may clarify the immunopathogenesis and also create a new category of these syndromes.

**References**

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