Bacterial Pneumonia-induced Persistent Remission of Severe Immune Thrombocytopenia after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

A 53-year-old woman with chronic myeloid leukemia received allogeneic hematopoietic stem cell transplantation. After neutrophil engraftment, her platelet count exceeded 100,000/μL at day 64. While she was receiving corticosteroid treatment for chronic graft versus host disease (GVHD), her platelets suddenly dropped to 6,000/μL at day 210 and she was diagnosed with immune thrombocytopenia (ITP). Corticosteroids, intravenous high-dose gamma globulin (IVIg) and a splenectomy failed to increase her platelet count. She developed bacterial pneumonia at day 599 and antibiotic therapy was initiated. Soon after, her platelet count continuously increased. Her GVHD and ITP are now in remission without any ongoing treatment.

Key words: CML, allogeneic stem cell transplantation, ITP, GVHD, infection

(Intern Med 55: 179-183, 2016)
(DOI: 10.2169/internalmedicine.55.4724)

Introduction

Immune thrombocytopenia (ITP) is mediated by platelet autoantibodies that accelerate platelet destruction and inhibit platelet production. If the clinical presentation is not that of life-threatening bleeding, corticosteroids are considered the standard initial treatment. Approximately two thirds of patients achieve a complete or partial response with corticosteroids at standard doses (1). However, only 10-15% of all adult patients with ITP who receive corticosteroid therapy have a long-lasting remission (1). Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms in which both impaired platelet production and T cell-mediated effects play a role (2-6). Previous reports have demonstrated the partial correction of ITP during viral, bacterial and Mycoplasma infection (Table) (7-11). Despite these clinical observations, the pathogenesis of ITP remains unknown.

Generally, ITP after stem cell transplantation is seen in relation to infection, graft versus host disease (GVHD) and rarely, as an autoimmune phenomenon due to immune dysregulation. A low platelet count in chronic GVHD patients is among the most consistent and robust negative survival predictors across chronic GVHD studies in allogeneic stem cell transplantation (12-14). We report a case of severe ITP following allogeneic stem cell transplantation for chronic myeloid leukemia (CML), with the complete remission of ITP after bacterial infection.

Case Report

A 53-year-old woman with CML and an intolerance for Imatinib underwent bone marrow transplantation from an unrelated HLA-matched male donor. She received a conditioning regimen of fludarabine (25 mg/m²) for 5 days combined with melphalan (70 mg/m²) for 2 days. Acute GVHD prophylaxis was administered, consisting of tacrolimus and a short course of methotrexate. Neutrophil engraftment was achieved on day 16 and her platelet count exceeded 100,000/μL at day 64. The patient’s acute GVHD peaked at

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Received for publication December 15, 2014; Accepted for publication April 29, 2015
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We diagnosed the patient with ITP and started the administration of prednisolone (1 mg/kg) with tacrolimus. Despite the increased dose of immunosuppressants, the platelet transfusions did not increase the patient’s platelet counts. Her \(^3^\)C urea breath test for assessment of Helicobacter pylori (H. pylori) infection was negative. She underwent a splenectomy at day 370 following the intravenous administration of high-dose gamma globulin (IVIg; 0.4 g/kg for 5 days), but her platelet count immediately dropped to 3,000/μL. At day 541, the patient lost consciousness and was admitted to the emergency department of our hospital. Computed tomography (CT) of the head showed an acute subdural hemorrhage (ASDH). Her symptoms of chronic limited type GVHD remained unchanged, with no evidence of the development of new chronic GVHD lesions. A second infusion of IVIg failed to increase her platelet count. She was discharged from the hospital without platelet recovery; however, her central nervous system symptoms disappeared completely.

She developed a high fever and productive cough on day 599. A chest X-ray examination performed at that time was normal (the laboratory test results are shown in Table). The patient was administered moxifloxacin hydrochloride, after her C-reactive protein level increased to 12.2 mg/dL. At the time, her \(\beta\)-D glucan level was 4.4 pg/mL and she was negative for galactomannan, while her chronic GVHD symptoms remained only cutaneous. Her symptoms of infection continued despite the administration of antibiotics and she was administered linezolid twelve days after starting antibiotics treatment. Chest CT showed nodular inflammatory lesions in both of the lungs, consistent with pneumonia (Fig. 2). We could not detect the pathogens of her pneumonia from sputum or blood culture examinations. While the infection developed, the patient’s platelet counts increased consistently. Soon after starting linezolid she recovered, and

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### Table. Laboratory Data.

| Variable                        | Reference Range* | Day 210 (onset ITP) | Day 541 (onset ASDH) | Day 599 (onset infection) |
|---------------------------------|------------------|---------------------|----------------------|--------------------------|
| White-cell count (μL)           |                  |                     |                      |                          |
| Neutrophils                     | 4,000 - 8,000    |                     |                      |                          |
| Band forms                      |                  |                     |                      |                          |
| Lymphocytes                     |                  |                     |                      |                          |
| Monocytes                       |                  |                     |                      |                          |
| Eosinophils                     |                  |                     |                      |                          |
| Red-cell count (μL)             | 380 - 480 ×10\(^6\) | 377×10\(^6\) | 389×10\(^6\) | 358×10\(^6\) |
| Hemoglobin (g/dL)               | 11.5 - 15.5      | 11.4                | 12.1                | 10.6                     |
| Platelet count (μL)             | 140,000 - 400,000| 6,000               | 3,000               | 13,000                   |
| Prothrombin time (sec)          | 9.3 - 13.8       | 10.1                |                      |                          |
| Activated partial thromboplastin time (sec) | 25 - 36 | 25 |                      |                          |
| Fibrinogen (mg/dL)              | 200 - 399        | 258                 |                      |                          |
| Fibrin/fibrinogen degradation products (μg/mL) | < 5.0 | 2.9 |                      |                          |
| Total protein (g/dL)            | 6.7 - 8.3        | 7.3                 | 4.1                 | 4.3                      |
| Albumine (g/dL)                 | 3.9 - 4.8        | 3.9                 | 11                  | 14                       |
| Alanine aminotransferase (U/L)  | < 30             | 16                  | 27                  | 19                       |
| Asparate aminotransferase (U/L) | < 35             | 11                  | 46                  | 14                       |
| \(\gamma\)-glutamyl transpeptidase(U/L) | < 35  | 35  | 210                | 200                      |
| Alkaline phosphatase (U/L)      | 100 - 310        | 305                 | 373                 | 286                      |
| Total Bilirubin (mg/dL)         | 0.2 - 1.1        | 0.6                 | 0.9                 | 0.6                      |
| C-reactive protein (mg/dL)      | < 3              | <0.09               | 0.73                | 7.07                     |

*The reference ranges use at Tokai University Hospital.

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Figure 1. Bone marrow aspirate on day 210 showed normal cellularity with a slight increase in the number of megakaryocytes without obvious dysplasia (May-Giemsa staining).
her platelet counts continued to increase. The maximum platelet count was 612,000/μL, and to date the level has consistently remained between 350,000 and 450,000/μL (Fig. 3).

**Discussion**

Previous reports have shown transient remission of ITP after viral or bacterial infection (7-10). However, all cases showed the recurrence of thrombocytopenia after the infection was controlled. This case is the first report of the complete remission of ITP after infection. In previous reports, all patients had chronic ITP and the pathogens of infection were not specific (the same as this case). When the patient developed pneumonia, her blood pressure was in the normal range, and the results of coagulation studies were also normal, except for the elevation of her fibrinogen level. These findings and the effectiveness of linezolid treatment suggested that the pathogen causing the pneumonia in this patient was gram-positive bacteria. The bone marrow aspiration examination revealed that there were a considerable number of megakaryocytes in the bone marrow. Therefore,
the thrombocytopenia in this patient is suggested to be a case of true ITP following hematopoietic stem cell transplantation. Such cases, which are occasionally reported, have previously been treated with increased doses of immunosuppressive drugs, splenectomy, androgens and anti-D immunoglobulin (15, 16).

Following the patient's splenectomy and the first IVIg treatment, the platelet response time was only a few weeks. Moreover, the second IVIg treatment for intracranial bleeding showed no platelet response. Although prednisone and IVIg are recommended for the emergency treatment of patients with uncontrolled bleeding, in this case, the IVIg twice failed to increase the platelet count (2). Splenectomy is a widely accepted second-line treatment for ITP, although approximately 14% of patients who undergo splenectomy do not respond and 20% of responders relapse weeks, months, or years later (17). In a previous report, there was a trend towards a positive outcome with a young age (defined as ≤37 years) at splenectomy (p=0.07) (17). However, the report concluded that there were no predictive factors for failure to respond to splenectomy.

In this case, the cause of developing ITP was unremarkable. Generally, patients who undergo allogeneic stem cell transplantation are treated with a range drugs at high doses. Thus, drug-induced thrombocytopenia was a candidate cause of the development of ITP. Drug-induced platelet destruction is usually caused by drug-induced antibodies, but this can be difficult to prove (18). It should be noted, however, that the patient had not used any of the commonly implicated drugs (18), in the three months before she developed ITP. H. pylori eradication therapy, which shifts the monocyte Fcγ receptor balance towards the inhibitory FcγRIIB in ITP patients (19), is becoming very popular in Japan for the treatment of ITP in adults. Although the patient was negative for H. pylori, the development of bacterial pneumonia might alter the FcγR balance of monocytes/macrophages, and the patient’s asplenic condition might have had an additional effect. However, there is no evidence to confirm the mechanisms of this phenomenon.

Although chronic GVHD-associated ITP has a poor prognosis (13), this patient was able to discontinue the immunosuppressant therapy four weeks after developing the infection without the progression of GVHD. This patient has achieved disease remission in both ITP and chronic GVHD. To the best of our knowledge, this is the first report of the complete remission of chronic GVHD after infection. ITP after allogeneic stem cell transplantation is considered to be unresponsive to treatment, relentless, and fatal (20). Physicians should therefore consider administering thrombopoietin receptor agonist for patients who are diagnosed with ITP after stem cell transplantation. However, the mechanism by which recovery from ITP after infection occurs is unknown and the reporting of these cases is important to assist in its elucidation.

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

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