Unrelated bone marrow transplantation improves Crohn's disease in a patient with myelodysplastic syndrome that developed from aplastic anemia: A case report

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Abstract. The present study describes the case of a 56-year-old male who was admitted to hospital due to pancytopenia. He was diagnosed as having acquired severe aplastic anemia (SAA). Immunosuppressive therapy with cyclosporine was transiently effective; however, the pancytopenia recurred. Bone marrow aspiration did not reveal an increased number of blasts, although it revealed trilineage dysplasia. Chromosomal analysis of the bone marrow demonstrated der(1;7) with abnormalities on chromosome 1. A diagnosis of a transformation from SAA to myelodysplastic syndrome (MDS) was made. High-grade fever and lower abdominal pain developed at approximately the same time. The patient was diagnosed as having Crohn's disease (CD). Treatment consisting of mesalazine and adalimumab was commenced. After two courses of azacitidine treatment, allogeneic bone marrow transplantation was performed, preceded by a reduced-intensity conditioning regimen, including fludarabine, cytarabine and cyclophosphamide. Tacrolimus and short-term methotrexate were used as prophylaxis against graft-versus-host disease. Chromosomal analysis of the bone marrow revealed a 100% donor-derived abnormal karyotype. The patient has since then remained in complete remission of both MDS and CD. On the whole, the present study demonstrates that allogeneic hematopoietic stem cell transplantation may be a promising treatment strategy for patients with combined MDS and CD. However, its use should be carefully considered.

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Introduction

Acquired severe aplastic anemia (SAA) is regarded as a result of the immune-mediated destruction of hematopoietic cells (1). Aplastic anemia (AA) may co-exist with or appear to evolve to myelodysplastic syndrome (MDS) (1). MDS is a clonal disorder characterized by cytopenia arising from ineffective hematopoiesis and is associated with an increased risk of developing acute myeloid leukemia (AML) (2). Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract. CD is characterized by the presence of transmural inflammation and endoscopic findings of longitudinal ulcers or skip lesions.

The concurrent presence of MDS and CD has been reported (3-6). However, reports of patients treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) for MDS in which CD improved are rare, particularly in Japan. The present study describes the case of a 56-year-old male with CD who achieved complete remission (CR) following allogeneic bone marrow transplantation (allo-BMT) for high-risk MDS.

Case report

A 56-year-old male was admitted to Gifu Municipal Hospital due to pancytopenia. Laboratory data upon admission were as follows: White blood cell count, $3.1x10^9$/l with 51.4% neutrophils, 40.6% lymphocytes, 3.0% eosinophils, 0.0% basophils and 5.0% monocytes; red blood cell count, $1,780x10^9$/l; hemoglobin levels, 6.7 g/dl; hematocrit, 19.7%; reticulocytes, 1.49%; and platelet count, $36.0x10^9$/l. Blood biochemistry revealed mildly increased lactate dehydrogenase levels (297 IU/l). Bone marrow biopsy and aspiration revealed a markedly hypocellular marrow without apparent dysplasia, with no increase the number of blasts in the bone marrow (Fig. 1A and B). A bone marrow smear was stained according to the May-Grünwald-Giemsa method. May-Grünwald-Giemsa staining was performed as briefly described below: The blood smear was prepared and air-dried. The smear was then fixed for 3 min with methanol at room temperature and then stained with May-Grünwald stain (cat. no. 5053; Muto Pure Chemicals Co., Ltd.) diluted with an

equal volume of distilled water for 5 min at room temperature. The smear was then placed without washing in a 1:3 solution of Giemsa stain (cat. no. 1500; Muto Pure Chemicals Co., Ltd.) diluted with distilled water for 10 min at room temperature. The smear was then washed in distilled water and allowed to dry. Chromosomal analysis of the bone marrow demonstrated a normal karyotype. For the detection of PNH-type granulocytes, phycoerythrin (PE)-labeled anti-CD11b monoclonal antibodies (cat. no. 347557; BD Biosciences), fluorescein-isothiocyanate (FITC)-labeled anti-CD55 (cat. no. 555693; BD Biosciences), and FITC-labeled anti-CD59 (cat. no. 550976; BD Biosciences) were used in combination with isotype-matched control mAbs as previously described (7). For the analysis of PNH-type RBCs, PE-labeled anti-glycophorin A mAb (cat. no. R707801-2; Dako; Agilent Technologies, Inc.) was used instead of anti-CD11b mAb. Fresh peripheral blood was diluted to 3% with phosphate-buffered saline, and 50 μl diluted blood was incubated with PE-labeled anti-glycophorin A mAb, FITC-labeled anti-CD55, and anti-CD59 mAb on ice for 25 min. At least 10^5 CD11b-positive granulocytes and glycophorin A-positive RBCs within each corresponding gate were analyzed using a FACScan flow cytometer (BD Biosciences). Flow cytometric analysis revealed that the red blood cells and granulocytes were 100% positive for CD55 and CD59; there were no paroxysmal nocturnal hemoglobinuria (PNH) clones. Magnetic resonance imaging (MRI) of the spine revealed severely fatty bone marrow. The patient was diagnosed with acquired SAA. Immunosuppressive therapy with cyclosporine (CsA, 4 mg/kg, 200 mg/day) was commenced. This was effective and improved his pancytopenia. However, 1 year and 6 months following the initiation of CsA treatment, his pancytopenia recurred. Bone marrow aspiration did not reveal an increased number of blasts; however, it revealed trilineage dysplasia (Fig. 1C and D). Azan staining was performed to confirm the fibrotic changes. Azan staining was performed as briefly described as follows: The smear was stained in Azocarmine G solution (cat. no. 40012; Muto Pure Chemicals Co., Ltd.) for 1 h at room temperature and then washed with running tap water. The smear was then fixed in 5% phosphomolybdic acid solution for 1 h at room temperature and washed with running tap water and rinsed using distilled water. The smear was then stained with aniline blue-orange G mixture (cat. no. 40051; Muto Pure Chemicals Co., Ltd.) for 30 min at room temperature and the slide was wiped with filter paper to drain off the solution. Chromosomal analysis of the bone marrow demonstrated der(1;7) with abnormalities on chromosome 1[46, XY 17/20: 46, XY, +1, der(1;7) 3/20]. A diagnosis of a transformation from AA to MDS with refractory cytopenia with multilineage dysplasia (RCMD) was made. High-grade fever and lower abdominal pain developed at approximately the same time. A colonoscopy revealed a longitudinal ulcer and bleeding from the colorectal mucosa in the terminal ileum (Fig. 2A and B). A biopsy of these lesions was reported as suggestive of CD. A pathological examination revealed that lymphocytes infiltrated with focal irregularity.

Since characteristic features of CD, such as longitudinal ulcer, fever, abdominal pain and pathological findings were present, a definitive diagnosis of CD was made. Treatment consisting of mesalazine (3,000 mg/day) and adalimumab (40 mg/day/every 2 weeks) was commenced. The Revised International Prognostic Score for MDS (IPSS-R) (8) was high; the IPSS score was intermediate-2 and the WHO classification-based prognostic scoring system (WPSS) (9) score was high. Thus, allo-HSCT was planned. Donor selection was performed with the aid of the Japanese Association for Marrow Donor Program. Two courses of azacitidine (AZA; 75 mg/m^2/day, days 1-7) were administered as an induction therapy assuming allo-HSCT. Following AZA treatment, his pancytopenia improved, and chromosomal analysis of the bone marrow revealed a normal karyotype. It was considered that the patient was able to tolerate the pre-transplant conditioning treatment, and it was decided that allo-BMT should be performed, that was preceded by a reduced-intensity conditioning regimen, including fludarabine (30 mg/m^2 daily, days-7 to -3), cytarabine (2 g/m^2 daily, days-5 to -3) and cyclophosphamide (50 mg/kg daily, day-2). A total of 2 Gy total body irradiation were administered on day-8. Tacrolimus (FK506) and short-term methotrexate were used for prophylaxis against graft-versus-host disease (GVHD) (10). allo-HSCT was performed with a HLA-matched sibling as the donor. This conditioning regimen was used as a prospective study for MDS in Gifu Municipal Hospital. The administration of adalimumab was continued until 2 months following engraftment. On day 20, the neutrophil count exceeded 0.5x10^9/l. FK506 treatment was continued until 4 months following engraftment. A chromosomal analysis of the bone marrow revealed 100% donor-derived abnormal karyotype. No severe diarrhea caused by GVHD was observed during the course of engraftment. Adalimumab treatment for CD was continued until 3 months following engraftment. The administration of mesalazine has been continued. At 1 year and 3 months following allo-BMT, although the amount of Wilms' tumor 1 mRNA in the peripheral blood was 1x10^2 copies/g RNA, complete chimerism was confirmed by a 100% donor-derived karyotype. The digestive symptoms caused by CD were resolved. A colonoscopy revealed almost normal mucosa in the terminal ileum (Fig. 2C and D). The patient has remained in CR for both MDS and CD.

Discussion

The present study describes the case of a patient with MDS that developed from AA. The results of bone marrow biopsy and aspiration revealed the diagnosis of SAA. However, the possibility of the accurate diagnosis of this patient being idiopathic cytopenia of uncertain significance (ICUS) should be considered. This case may have developed as ICUS; hence, CsA may have become refractory and the patient may have then developed MDS. Otherwise, the patient may have had MDS from the beginning.

Acquired AA is an immune-mediated disease. AA, MDS and PNH constitute the bone marrow failure syndrome. These diseases overlap with each other, and a differential diagnosis may occasionally be difficult, as these diseases share underlying mechanisms. Of note, the transformation from AA to MDS has sometimes been observed (11). Some cases of MDS are immune-mediated, and in particular, as in the case presented herein, underlying mechanisms may have included immune-mediated destruction. Thus, autoantibodies are easily produced in MDS. Indeed, Saif *et al* (12) reported

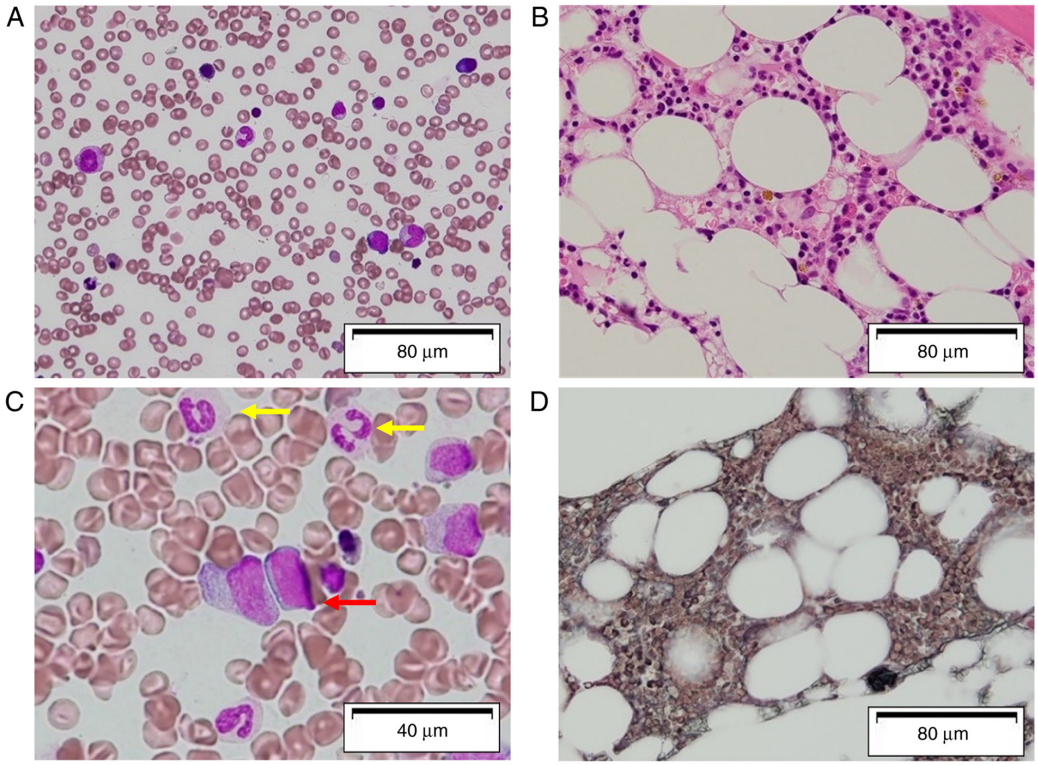

Figure 1. Bone marrow aspiration and biopsy. Hematopoietic elements in the bone marrow upon admission were markedly reduced. (A) May-Grunwald-Giemsa staining, bone marrow aspiration; original magnification, x400. (B) May-Grunwald-Giemsa staining, bone marrow biopsy; original magnification, x400. Bone marrow smear on the second admission indicated neutrophilic dysplasia (yellow arrows) and blasts (red arrows). (C) May-Grunwald-Giemsa staining, bone marrow aspiration; original magnification, x1,000). Bone marrow biopsy on the second admission did not indicate fibrotic changes. (D) Azan staining, bone marrow aspiration; original magnification, x400.

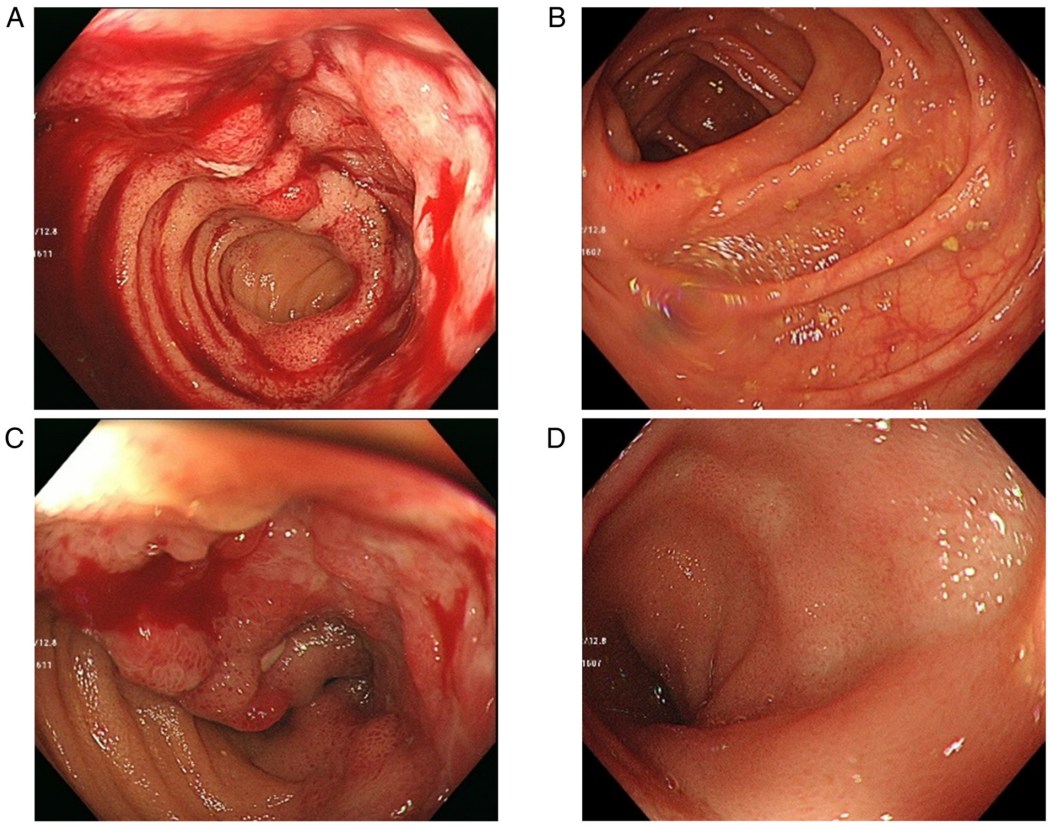

Figure 2. Colonoscopy evaluation. Colonoscopy findings (A and B) before and (C and D) after allogeneic hematopoietic stem cell transplantation. Colonoscopy before treatment revealed (A) bleeding and (B) a longitudinal ulcer from the colorectal mucosa in the terminal ileum. (C and D) Colonoscopy after allogeneic hematopoietic stem cell transplantation indicated the disappearance of bleeding and the longitudinal ulcer.

that autoantibodies were observed in 34% of patients with MDS. However, the mechanism of autoantibody production remains unclear in MDS. Autoantibody production may occur due to the impaired immune response with the overproduction of inflammatory cytokines (13,14). CD is a relapsing inflammatory disease, and it appears to result from the impaired interaction of the intestinal commensal microbiota.

Eng *et al* (4) first reported the concurrent development of MDS and CD in 1992. A potential role of immune dysfunction as a common pathogenic factor has also been suggested (15). MDS is a common disease affecting the elderly, and CD is a common disease affecting young individuals; thus, the concurrent development of MDS and CD is rare. However, some reports have described the concurrent development of MDS and CD (3-6,16). Previous studies have demonstrated that the incidence of MDS in patients with inflammatory bowel disease ranged from 170-550/10^5 individuals (17,18). This incidence appears to be higher than that in the general population. A pathophysiological link between MDS and CD has been suggested on the basis of a common immunologic impairment (3-6,16). CD is an autoimmune disease, and there is evidence to indicate that MDS is also known to be related to autoimmunity (19). Indeed, CD is treated with immunosuppressive therapy, and some patients with MDS respond well to immunosuppressive therapy with cyclosporine and/or antithymocyte globulin (20). The association between the development of CD and the treatment of AA is not clear. It is possible that there is an insult that triggers an autoimmune attack against both the marrow and bowel. The same immunological trigger may initiate simultaneous attacks on the bone marrow and bowel. However, it is difficult to identify the exact trigger. Regardless of the trigger, it may be more reasonable to assume that general autoimmunity is activated.

The patient in the present study received adalimumab and mesalazine simultaneously. These agents may have also affected the clinical course of this patient. Although the administration of adalimumab and mesalazine was continued, the digestive symptoms caused by CD remained until allo-HSCT, and these symptoms were resolved following allo-HSCT. This clinical course revealed that the clinical effects of adalimumab and mesalazine were limited. In addition, the benefits of FK506 and MTX as immunosuppressive therapy for allo-HSCT should be considered. It may be possible that these immunosuppressive therapies led to the remission of CD. However, the remission of CD was continued following the discontinuation of these immunosuppressive therapies; hence, it was considered that allo-HSCT led the remission of CD.

Hu *et al* (21) reported a case similar to the one in the present study. They reported the case of a patient with CD and MDS who was successfully treated with allo-HSCT. Hu *et al* (21) also hypothesized the mechanisms underlying the of curative effects on CD as follows: Autoimmune T-cell clonal proliferation and the excessive secretion of interleukin (IL)-1, IL-6 and tumor necrosis factor α by lymphocytes have been observed in patients with MDS. These cytokines may play an important role in the development of CD (21). Another hypothesis to explain the pathophysiological link between MDS and CD is based on chromosomal abnormalities. Eng *et al* (4) reported 3 cases of the concurrent development of MDS and CD with clonal abnormalities of chromosome 20. However, it remains unknow as to how these chromosomal abnormalities are related to CD. Such chromosomal abnormalities were not found in the case in the present study. The third hypothesis is that the phagocytosis and killing capacity of neutrophils are decreased in patients with MDS. Local infection of the mucosa may play an important role in the development of CD (21). Thus, CD may develop following a local infection in an immunocompromised host with MDS. The final hypothesis is that the association of MDS and CD may be coincidental; however, this last hypothesis appears unlikely. Case-control studies are thus required to rule out these possibilities.

A thorough review of the recent literature revealed that reports of MDS combined with CD treated with HSCT were extremely rare (21). Generally, allo-HSCT is increasingly used as a curative treatment option for hematological malignancies (22). The IPSS-R is an age-adjusted risk score based on the percentage of marrow blasts, modified cytogenetic risk groups and the severity of cytopenia (8). In the case presented herein, the patient was classified as high-risk. Thus, allo-HSCT was selected. When allo-HSCT is performed, the immune system of the patient is transiently destroyed by the conditioning regimen, and a new immune system derived from the donor is reconstructed. The new reconstructed immune system may restore the autoimmunity of CD (23). Ditschkowski *et al* (24) reported that 10 out of 11 patients remained free of inflammatory bowel disease following allo-HSCT for hematological malignancies. These results demonstrate that allo-HSCT may be a promising treatment strategy for patients with combined MDS and CD. However, CD is listed in the hematopoietic stem cell transplantation specific comorbidity index (25). Chronic inflammation of the gastrointestinal mucosa by CD may destroy the defensive function of the mucosa. The infection risk of the gastrointestinal tract may be increased due to chronic inflammation. In addition, this chronic inflammation may increase the risk of aggravation of CD. The indications for allo-HSCT for patients with combined MDS and CD should thus be carefully considered.

In conclusion, allo-HSCT may be a promising treatment strategy for patients with combined MDS and CD. However, its use should be carefully considered.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HG, TH, KF, TT and HT prepared the manuscript. HG, KF, TT, TH and HT performed the literature search. HG, HT, YK, KY, YS and SK conceived and designed the study. HG and TH drafted the manuscript for important intellectual content.

HG KF and TT prepared the figures. All authors gave final approval of the version to be published. HG and HT confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The patient provided written informed consent for his participation in this case report.

Patient consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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