

Case Report

Epstein-Barr virus-related post-transplant lymphoproliferative disorder occurring after bone marrow transplantation for aplastic anemia in Down's syndrome

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Abstract: It is well established that Down's syndrome exhibits a predisposition to development of leukemia, however, association between aplastic anemia and Down's syndrome is exceptional. Herein, we describe a case of aplastic anemia occurring in Down's syndrome following post-transplant lymphoproliferative disorder (PTLD) after bone marrow transplantation (BMT). A 27-year-old Japanese male with Down's syndrome presented with a headache. Laboratory tests revealed severe pancytopenia, and bone marrow biopsy demonstrated hypocellular bone marrow with decrease of trilineage cells, which led to a diagnosis of aplastic anemia. One year after diagnosis, he was incidentally found to have an anterior mediastinal tumor, which was histopathologically diagnosed as seminoma. Subsequently, he received BMT from a female donor, and engraftment was observed. Three months after transplantation, he experienced cough and high fever. Biopsy specimen from the lung revealed diffuse proliferation of large-sized lymphoid cells expressing CD20 and EBER. These lymphoid cells had XY chromosomes. Thus, a diagnosis of EBV-associated PTLD was made. This is the seventh documented case of aplastic anemia occurring in Down's syndrome. Association between aplastic anemia and Down's syndrome has not been established, therefore, additional clinicopathological studies are needed. Moreover, this is the first case to undergo BMT for aplastic anemia in Down's syndrome. Although engraftment was observed, he developed EBV-positive PTLD. The neoplastic cells of the present case were considered to be of recipient origin, although the majority of PTLD cases with BMT are of donor origin.

Keywords: Aplastic anemia, Down's syndrome, bone marrow transplantation, Epstein-Barr virus, post-transplant lymphoproliferative disorder

Introduction

It is well established that Down's syndrome exhibits a predisposition to the development of hematological disorders, and the risk of leukemia, especially acute megakaryoblastic leukemia (M7), in Down's syndrome is higher than in the general population [1]. However, association between aplastic anemia and Down's syndrome is exceptional. Only 6 cases of aplastic anemia in Down's syndrome have been documented in the English literature [2-7].

Post-transplant lymphoproliferative disorder (PTLD) is a lymphoid or plasmacytic prolifera-

tion that develops as a consequence of immunosuppression in a recipient of a solid organ, bone marrow or stem cell allografts [8]. The majority of PTLD cases are associated with Epstein-Barr virus (EBV). In this report, we describe a case of EBV-associated PTLD occurring after bone marrow transplant (BMT) for aplastic anemia in Down's syndrome.

Case report

A 27-year-old Japanese male with Down's syndrome presented with a headache. Laboratory tests revealed pancytopenia (red blood cell count $2.24 \times 10^{12}/L$ (range 4.10-5.30), hemo-

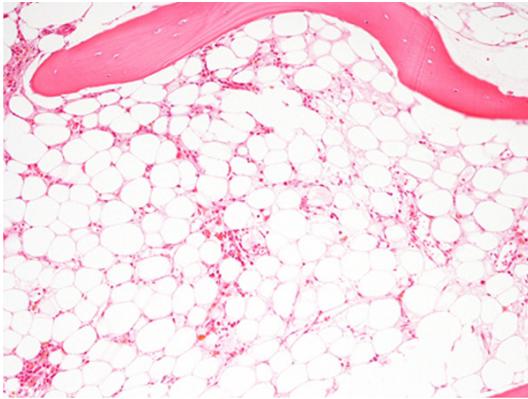


Figure 1. Histopathological features of the bone marrow. Hypocellular marrow with decrease of trilineage hematopoietic cells, HE, $\times 100$.

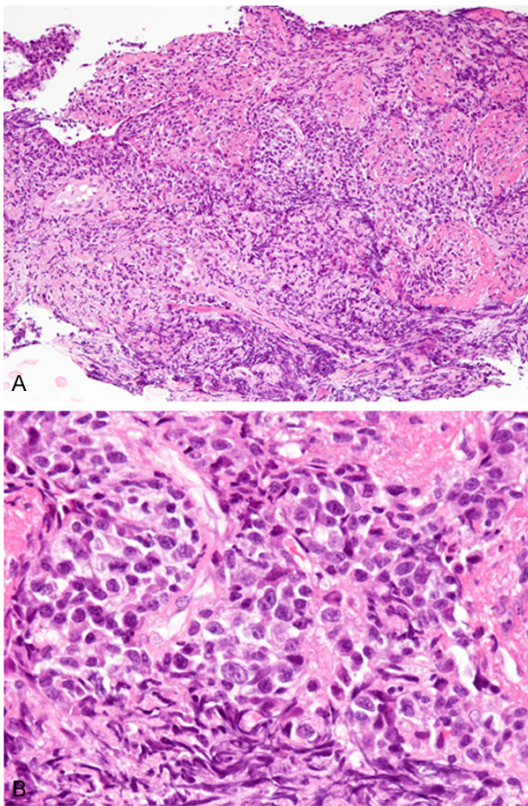


Figure 2. Histopathological features of the lung biopsy. A: Diffuse proliferation of large-sized lymphoid cells, HE, $\times 100$. B: Lymphoid cells have large nuclei with small nucleoli, HE, $\times 400$.

globin 7.2 g/dL (range 12.4-17.0), white blood cell count $1.0 \times 10^9/L$ (range 3.0-8.0), and platelet count $11 \times 10^9/L$ (range 150-400). Bone marrow biopsy demonstrated hypocellular marrow with decrease of trilineage hemato-

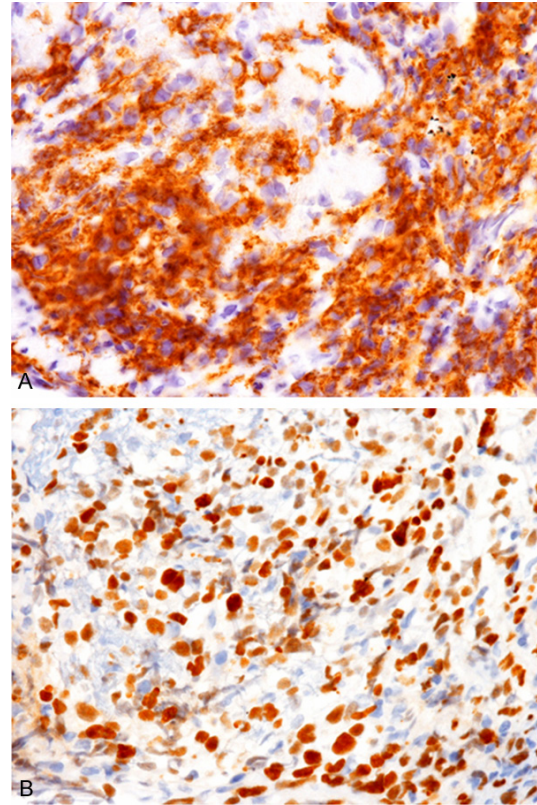


Figure 3. Immunohistochemical and *in situ* hybridization findings of the lung biopsy. Lymphoid cells are positive for CD20 (A) and EBER (B), $\times 400$.

poietic cells (**Figure 1**), which led to a diagnosis of aplastic anemia. One year after the diagnosis, the pancytopenia had worsened (red blood cell count $2.09 \times 10^{12}/L$, hemoglobin 6.1 g/dL, white blood cell count $0.5 \times 10^9/L$, platelet count $5 \times 10^9/L$), and he was hospitalized for BMT to treat the aplastic anemia. A chest computed tomography for surveillance incidentally showed a relatively well-circumscribed tumor, measuring 5 $\times$ 5 cm, with a cystic component in the anterior mediastinum. Under a clinical diagnosis of thymoma, total resection of the anterior mediastinal tumor was performed. Postoperative histopathological diagnosis was mediastinal seminoma. The histopathological and clinical characteristics of mediastinal seminoma of this patient were previously reported [9].

The postoperative course was uneventful; however, the supraclavicular lymph nodes were enlarged 9 months after the surgery. Subsequently, radiation therapy was performed (total 40 Gy), which led to the disappearance of lymph node swelling.

Table 1. Clinicopathological features of aplastic anemia in Down's syndrome

Case No.	Age	Gender	Bone marrow	Outcome	Reference
1	17 years	Male	Hypocellular	Improved by steroid therapy	[2]
2	12 years	Male	Hypocellular	Died of cerebellar hemorrhage	[3]
3	27 months	Female	Hypocellular	Improved by steroid therapy	[4]
4	1 year	Male	Hypocellular	Died of bone marrow failure	[5]
5	2 years	Female	Hypocellular	Improved by steroid therapy	[6]
6	11 years	Female	Hypocellular	Transient, improved by transfusion and thyroxine	[7]
Present Case	27 years	Male	Hypocellular	Bone marrow transplant was successful, however, the patient died of PTLD.	

PTLD, Post-transplant lymphoproliferative disorder.

Pancytopenia did not improve by frequent transfusions (red blood cell count $2.32 \times 10^{12}/L$, hemoglobin 6.8 g/dL, white blood cell count $0.2 \times 10^9/L$, platelet count $5 \times 10^9/L$), thus, he received BMT from a female donor 25 months after the surgery. The post-transplant course was uneventful, and myeloid recovery was observed 20 days after the transplantation. However, he experienced cough and high fever 3 months after the transplantation. Computed tomography revealed pneumonia of the bilateral lungs. Antibiotics were not effective; therefore, transbronchial biopsy was performed. His serum EBV level was 51×10^4 copies/mL (range <100). He succumbed to multiple organ failure 1 week after the last episode.

Histopathological study of the biopsy specimen of the lung showed diffuse proliferation of large-sized lymphoid cells (**Figure 2A**). These lymphoid cells had large nuclei with small nucleoli (**Figure 2B**).

Immunohistochemical and *in situ* hybridization studies were performed using an autostainer (Ventana) by the same method as previously reported [10-14]. CD20 and MUM1 were expressed in these large lymphoid cells (**Figure 3A**), but CD3, CD5, CD10, CD138, bcl-2, bcl-6, and cyclin D1 were not expressed. EBER was also expressed in these large lymphoid cells (**Figure 3B**).

Southern blotting analysis revealed that these lymphoid cells showed EBV clonality. Moreover, fluorescence *in situ* hybridization analysis demonstrated that these lymphoid cells had XY chromosomes; therefore, these lymphoid cells were considered to be of recipient origin.

Accordingly, an ultimate diagnosis of EBV-associated PTLD occurring after BMT for aplastic anemia was made.

Discussion

In this report, we describe the seventh documented case of aplastic anemia in Down's syndrome. **Table 1** summarizes the clinicopathological features of the previously reported 6 cases of aplastic anemia in Down's syndrome as well as the present one. The median age of the patients was 10.3 years (range from 1 to 27 years), and the male to female ratio was nearly equal (males: females 4:3). In four of 7 cases, pancytopenia improved by steroid therapy or transfusion. Moreover, two of these cases showed transient bone marrow suppression [2, 7], and the case reported by Gathwala *et al.*, who had hypothyroidism and pancytopenia, improved by transfusion and thyroxine treatment. In the remaining three cases, the patients died of cerebellar hemorrhage, bone marrow failure, and PTLD [3, 5]. Association between Down's syndrome and aplastic anemia has not been established, therefore, additional clinicopathological studies are needed to clarify it.

The peculiar clinical features of the present case were the occurrence of mediastinal seminoma and PTLD after BMT. This is the first documented case of mediastinal seminoma occurring in Down's syndrome [9] although it is well known that the incidence of testicular tumor in Down's syndrome is increased as compared to the general population [15], and moreover, only a few cases of germ cell tumors at extragonadal sites have been reported in Down's syndrome [16, 17]. Further, this case was the first to undergo BMT for aplastic anemia in Down's syndrome. Myeloid recovery was observed 20

days after the transplantation, however, the patient developed EBV-associated PTLD.

PTLD is classified as early lesions (plasmacytic hyperplasia and infectious mononucleosis-like PTLD), polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma type PTLD according to the recent WHO Classification [8]. The present case was classified as monomorphic B-cell PTLD because the lung biopsy revealed diffuse proliferation of large-sized lymphoid cells expressing CD20, which resembled diffuse large B-cell lymphoma. It is well known that most monomorphic B-cell PTLD are of non-germinal center type based on immunohistochemical analysis, and EBV-associated cases generally have a late germinal center/post germinal center phenotype (CD10⁺, bcl-6⁺, MUM1⁺) [18]. The immunophenotype of the present case corresponded to the post germinal center phenotype (CD10⁺, bcl-6⁺, MUM1⁺).

In addition, it has been reported that the majority of PTLD cases with BMT are of donor origin because successful engraftment results in the nearly complete replacement of the recipient's immune system by the donor cells [19]. However, the neoplastic cells of the present case were considered to be of recipient origin because fluorescence *in situ* hybridization analysis clearly demonstrated that these lymphoid cells had XY chromosomes. This may be due to the presence of residual recipient EBV-infected B-cells in the recipient body although successful engraftment was observed after BMT.

Disclosure of conflict of interest

None.

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EBV-PTLD occurring in Down's syndrome

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