

## Case Report

# Occurrence of Epstein-Barr virus-associated plasmacytic lymphoproliferative disorder after antithymocyte globulin therapy for aplastic anemia: a case report with review of the literature

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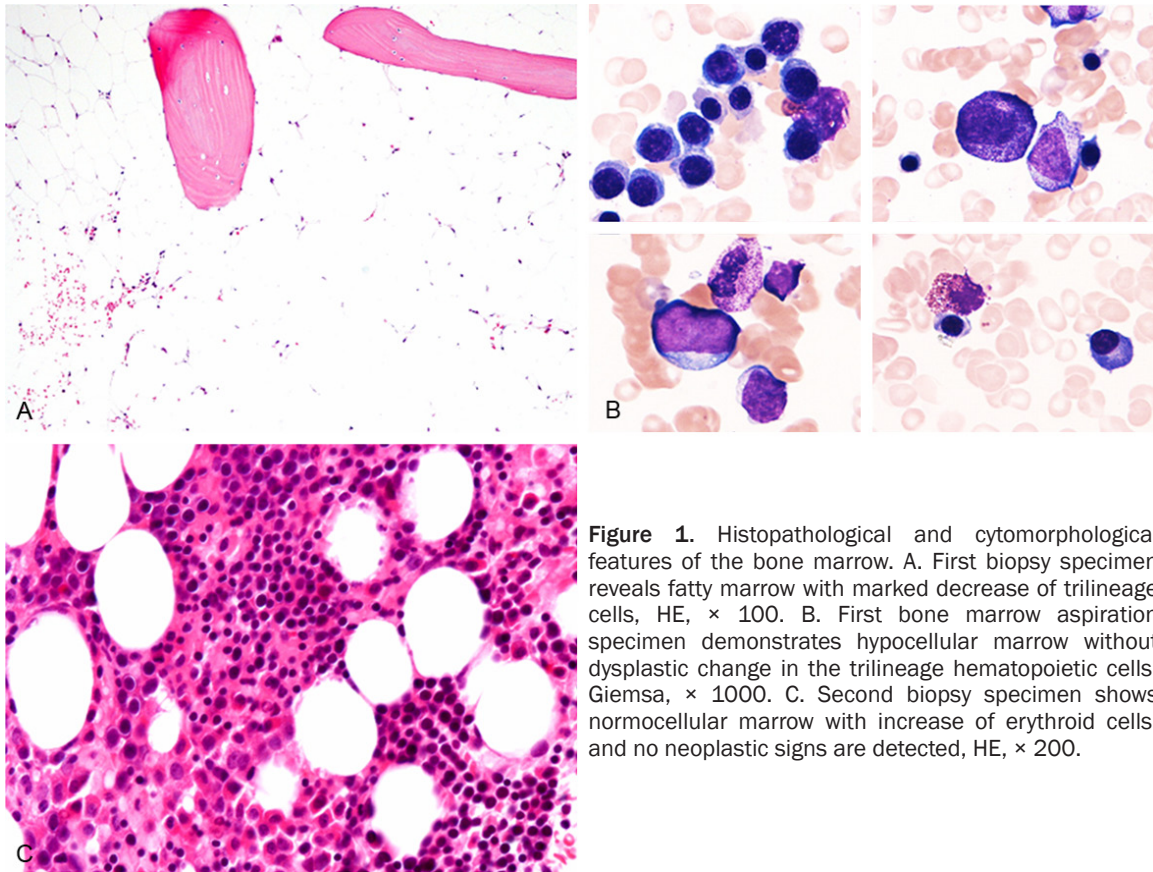
**Abstract:** It is well established that patients with immunosuppression have a higher risk of development of lymphoproliferative disorders (LPDs), and Epstein-Barr virus (EBV) is associated with development of LPDs. Aplastic anemia (AA) is an immune-mediated hematological disorder, and immunosuppression therapy (IST), such as antithymocyte globulin (ATG), is widely used for treatment of AA. However, occurrence of LPD without bone marrow transplantation has been extremely rarely documented in patients with IST for AA. Herein, we report the 6<sup>th</sup> documented case of EBV-associated LPD after IST for AA and review the clinicopathological features of this extremely rare complication. A 46-year-old Japanese female was admitted for evaluation of progressive pancytopenia. Bone marrow biopsy revealed fatty marrow with marked decrease of trilineage cells, and bone marrow aspiration demonstrated no dysplastic changes. IST with rabbit ATG was administered, after which, she developed high fever. Bone marrow aspiration showed increase of atypical plasma cells with mildly enlarged nuclei and irregular nuclear contour. These atypical plasma cells were EBER-positive. Accordingly, a diagnosis of EBV-positive plasmacytic LPD was made. Most cases of LPDs are B-cell origin, and plasmacytic LPD is a rare subtype. The current report is the second case of plasmacytic LPD in patients with IST for AA. Therefore, detailed histopathological and immunohistochemical analyses are needed for correct diagnosis and treatment, and additional studies are needed to clarify the clinicopathological features of EBV-LPD after IST for AA.

**Keywords:** Epstein-Barr virus-associated lymphoproliferative disorder, antithymocyte globulin therapy, aplastic anemia

## Introduction

It is well established that patients with immunosuppression have a higher risk of development of lymphoproliferative disorders (LPDs), and immunodeficiency-associated LPDs are classified into four categories according to the recent World Health Organization Classification: lymphoproliferative diseases associated with primary immune disorders, lymphomas associated with HIV infection, post-transplant LPDs, and other iatrogenic immunodeficiency-associated LPDs [1]. Epstein-Barr virus (EBV) is known to be associated with development of LPDs, which is referred to as EBV-associated LPDs [1].

Aplastic anemia is an immune-mediated hematological disorder characterized by pancytopenia in the peripheral blood and hypocellularity of trilineage cells in the bone marrow [2]. Antithymocyte globulin (ATG) is widely used for treatment of AA, and the majority of patients show hematological improvement after T-cell depletion by ATG [2, 3]. Cyclosporine A (CsA) is also an immunosuppressive drug used for AA [3]. Immunosuppressive therapy (IST) shows high efficacy for AA, however, it is associated with several complications, such as the occurrence of myelodysplastic syndrome and acute myelogenous leukemia [4, 5]. Further, albeit extremely rare, occurrence of LPDs after IST for



**Figure 1.** Histopathological and cytomorphological features of the bone marrow. A. First biopsy specimen reveals fatty marrow with marked decrease of trilineage cells, HE,  $\times 100$ . B. First bone marrow aspiration specimen demonstrates hypocellular marrow without dysplastic change in the trilineage hematopoietic cells, Giemsa,  $\times 1000$ . C. Second biopsy specimen shows normocellular marrow with increase of erythroid cells, and no neoplastic signs are detected, HE,  $\times 200$ .

AA without bone marrow transplantation has been documented [6-10]. Herein, we describe the 6<sup>th</sup> documented case of EBV-associated LPD after IST for AA and review the clinicopathological features of this extremely rare complication.

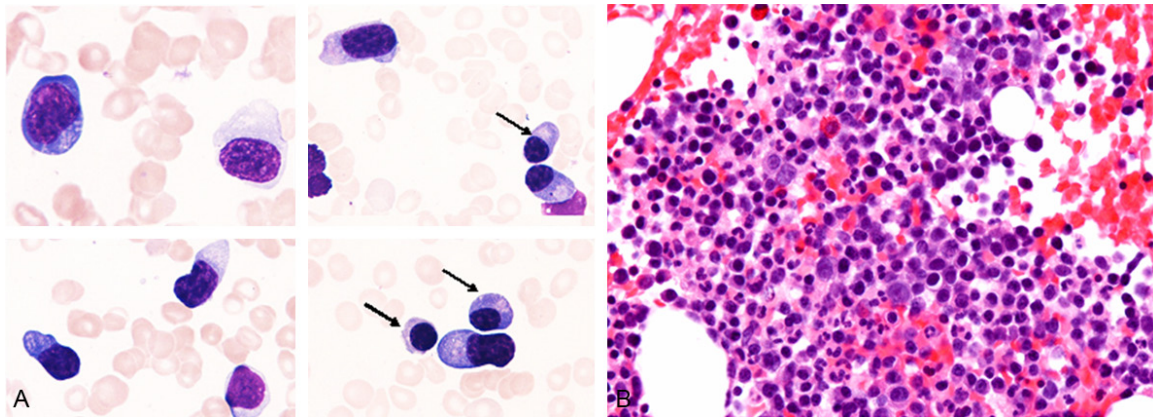
#### Case report

A 46-year-old Japanese female was admitted to our hospital for evaluation of progressive pancytopenia. She had been pointed out thrombocytopenia 6 years earlier, and progressive pancytopenia had developed 1 year earlier. Laboratory tests showed pancytopenia (red blood cells  $3.35 \times 10^{12}/L$  (range 3.8-4.8), white blood cells  $1.9 \times 10^9/L$  (3.0-8.0), and platelets  $26 \times 10^9/L$  (150-400)). Bone marrow biopsy revealed fatty marrow with marked decrease of trilineage cells (**Figure 1A**). Accordingly, a diagnosis of AA was made. Thus, steroid therapy was administered, however, pancytopenia did not improve. Laboratory investigations at the time of admission showed continuation of pancytopenia (hemoglobin 11.6 g/dL (range 11.3-

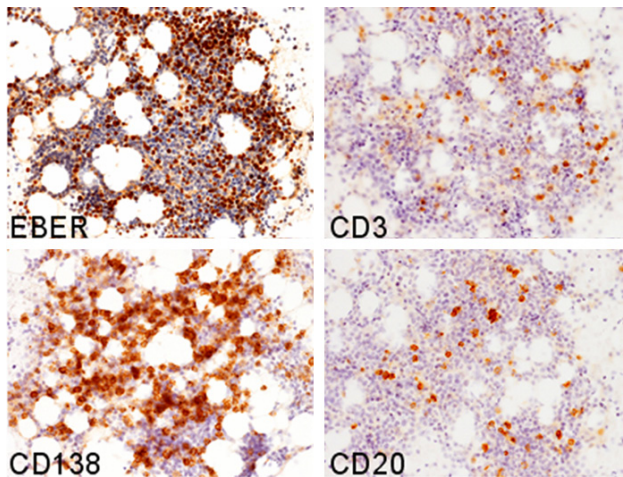
15.0), red blood cells  $3.57 \times 10^{12}/L$ , white blood cells  $2.0 \times 10^9/L$  (neutrophils 9.5% and lymphocytes 84.5%), platelets  $15 \times 10^9/L$ , and reticulocytes 15%). Liver and renal function tests were within normal ranges. Bone marrow aspiration revealed hypocellular bone marrow with decrease of megakaryocytes, however, no dysplastic signs were detected in the trilineage hematopoietic cells (**Figure 1B**). Bone marrow biopsy showed normocellular bone marrow with erythroid hyperplasia, and no neoplastic signs were detected (**Figure 1C**). Chromosomal analysis of the bone marrow demonstrated an abnormal karyotype with trisomy 8.

According to these findings, she was diagnosed with AA (very severe form according to the classification by Camitta *et al.* [11]), and was administered immunosuppressive therapy (IST) with rabbit ATG (3.75 mg/kg/day), CsA (drug blood level of 150-250 mg/kg), and prednisolone (1.2-2.5 mg/kg).

On the 26<sup>th</sup> day of IST, she developed high fever and exanthema. Serum levels of lactate dehy-



**Figure 2.** Cytomorphological and histopathological features of the bone marrow after immunosuppression therapy for aplastic anemia. A. The presence of atypical large-sized plasma cells with irregular cytoplasmic and nuclear contour (as compared to normal-appearing plasma cells (arrows)), Giemsa,  $\times 1000$ . B. Hypercellular bone marrow with increase of atypical plasma cells with mildly enlarged nuclei and irregular nuclear contour, HE,  $\times 400$ .



**Figure 3.** Immunohistochemical and *in situ* hybridization features of the bone marrow after immunosuppression therapy for aplastic anemia. Abundant EBER- and CD138-positive cells are observed, however, only a few CD3- and CD20-positive cells are present,  $\times 200$ .

drogenase, aspartate aminotransferase, and alanine aminotransferase had gradually increased. Bone marrow aspiration was performed again because atypical lymphocytes were detected in the peripheral blood (5% of leukocytes) on the 33<sup>rd</sup> day of IST.

The third bone marrow aspirate specimen demonstrated hypocellular marrow with decrease of megakaryocytes. Atypical large-sized plasma cells with irregular cytoplasmic and nuclear contours were detected (11.8% of all bone marrow cells) (**Figure 2A**). Bone marrow clot section showed hypercellular marrow with increase of

atypical plasma cells with mildly enlarged nuclei and irregular nuclear contour (**Figure 2B**).

Immunohistochemical and *in situ* hybridization studies were performed using an autostainer (Ventana) by the same method as previously reported [12-16]. Many CD138-positive plasma cells were present in the bone marrow, however, only a few CD3- and CD20-positive lymphocytes were observed (**Figure 3**). *In situ* hybridization analysis revealed many cells positive for EBV encoded small RNAs (EBER) in the bone marrow (**Figure 3**), which corresponded to the distribution of CD138-positive cells.

Polymerase chain reaction for EBV-DNA revealed  $7.9 \times 10^6$  copies/mL (range  $<100$ ) in the peripheral blood. Moreover, reactivation of varicella-zoster virus (VZV) was detected in the biopsy of the skin eruption and cytomegalovirus (CMV) reactivation was indicated by the biopsy of the gastric ulcer. Serum C7-HRP was positive (12/50,000 cells).

According to these results, an ultimate diagnosis of EBV-associated plasmacytic LPD with reactivation of VZV and CMV after rabbit ATG therapy for aplastic anemia was made.

After the diagnosis, IST was discontinued, and antivirus therapy for CMV was administrated. Subsequently, the EBV-DNA viral load decreased, and serum C7-HRP reduced to below the cutoff level. She underwent frequent blood



**Table 1.** Clinicopathological features of Epstein-Barr virus-associated lymphoproliferative disorder after antithymocyte globulin therapy for aplastic anemia

Case No.	Age/ Gender	Source of ATG	Immunosuppression drugs	Histopathology	EBV infected cells	Reactivated virus	Reference
1	36/Male	Horse	Cyclosporine A	EBV-LPD	Not available	Not available	[6]
2	38/Male	Horse	Cyclosporine A, prednisolone	Infectious mononucleosis	B-cell	None	[7]
3	42/Female	Rabbit	Cyclosporine A	DLBCL	B-cell	Not available	[8]
4	55/Male	Horse	None	EBV-LPD	Plasma cell	CMV	[9]
5	55/Male	Rabbit	Cyclosporine A	EBV-LPD	B-cell	None	[10]
Present Case	46/Female	Rabbit	Cyclosporine A, prednisolone	EBV-LPD	Plasma cell	CMV, VZV	

ATG, antithymocyte globulin; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; VZV, varicella-zoster virus.

transfusions without chemotherapy, and has been free from LPD recurrence for 30 months after the diagnosis.

## Discussion

LPDs are defined as lymphoid or plasmacytic proliferative lesions that develop as a consequence of immunosuppression, such as under conditions following organ or bone marrow transplantation [1]. Iatrogenic immunodeficiency-associated LPDs occur in a setting of IST with drugs including methotrexate and infliximab [1]. EBV is associated with development of LPDs, and approximately 30-50% of LPDs in RA patients treated with methotrexate are EBV-positive [17, 18]. Although the occurrence of myelodysplastic syndrome and acute myelogenous leukemia after IST for AA has been recognized [4, 5], development of LPD is extremely rare without bone marrow transplantation. Scheinberg *et al.* reported that none of the 78 patients in their study with severe AA who had received different IST developed EBV-LPD [19]. **Table 1** summarizes the clinicopathological features of the five previously reported cases of EBV-LPD after IST for AA as well as the present one [6-10]. This disorder predominantly affects middle-aged people (male/female 4/2), CsA is frequently used as an immunosuppressive drug, and the most common histopathology of the disorder is EBV-LPD (4 cases). The prognosis of EBV-LPD after IST for AA may be favorable because most cases, including the present one, had no recurrence of EBV-LPD after cessation of IST. Calistri *et al.* reported a case of infectious mononucleosis after ATG treatment for AA [7]. The patient complained of enlarged and painful cervical lymph nodes after the 20<sup>th</sup> day of ATG therapy. Although histopathological analysis of the lymph nodes was not performed,

the presence of atypical lymphocytes and high EBV DNA in the peripheral blood led to a diagnosis of infectious mononucleosis [7]. The most commonly affected organ of this disorder is the lymph node [7, 8, 10]. Sugimoto-Sekiguchi *et al.* reported a very interesting case who developed general malaise and appetite loss after IST (ATG and CsA) for AA. Because of a positive occult blood test of the stool, he underwent colonoscopy, which revealed multiple tumorous lesions in the colon. Biopsy from a colon tumor demonstrated EBV-LPD [10]. Although it has been well recognized that post-transplant EBV-LPDs frequently occur in extranodal sites [16], their case was the first one of EBV-LPD after IST for AA without bone marrow transplantation occurring in the extranodal site [10]. The current case is the first report of EBV-LPD affecting the bone marrow after IST for AA. Moreover, a few cases of non-EBV-associated LPD after IST for AA have also been documented [20, 21].

Rabbit ATG was used in three cases including the present one, and horse ATG was administered in the remaining cases. It has been estimated that rabbit ATG has a greater degree and duration of T-cell depletion, and shows more immunosuppressive efficacy than horse ATG [22]. Therefore, the risk of complication including the development of EBV-LPD may be increased in the cases who receive rabbit ATG than in those with horse ATG therapy.

Most cases of iatrogenic EBV-LPDs are of B-cell origin [1]. According to the analysis of 135 reported cases of MTX-related LPDs with detailed histopathological features, the most common subtype is diffuse large B-cell lymphoma (64/135 cases), followed by Hodgkin lymphoma and lymphoid proliferation of Hodgkin-

like features (33/135 cases) [1]. Albeit rare, plasmacytic LPD has been reported in patients following organ transplantation [23, 24]. This type of disorder is an unusual form of monomorphic post-transplant LPDs [1, 23, 24] that is histopathologically characterized by the proliferation of monomorphic plasma cells expressing CD138 and lacking CD20 expression, and resembles multiple myeloma [23]. Karuturi *et al.* analyzed the clinicopathological features of plasmacytic post-transplant LPD cases [23], and they found that among 7,428 cases who had received solid organ transplantation from 1988 to 2012, 210 patients (3%) developed LPDs, and 9 of them had plasmacytic LPD (4% of LPD cases) in their series [23]. All patients presented with extranodal lesion and often subcutaneous tumor as well, and seven of these 9 cases were EBV-positive [23]. Moreover, Trappe *et al.* reported 8 cases of plasmacytic LPD after solid organ transplantation [24], and while three of these 8 cases were EBV-positive, none of them had bone marrow involvement [24]. Plasmacytic LPD occurring in patients with iatrogenic immunodeficiency is extremely rare. A case of plasmacytic LPD after ATG therapy for AA has been reported [9], and the current report is the second documented case of plasmacytic LPD after IST for AA. The frequency of plasmacytic LPD in patients who receive ATG therapy for AA can be high (2/6 cases of EBV-LPD), therefore, additional clinicopathological study is needed.

In the present case, chromosomal analysis of the bone marrow specimen diagnosed as AA demonstrated trisomy 8. In the series of 600 adult AA cases reported by Kim *et al.*, 95.3% of cases showed a normal karyotype, and the most frequent abnormality was trisomy 8, followed by monosomy 7/deletion of 7q and deletion of 1q [25]. Although trisomy 8 is also observed in cases of hypoplastic myelodysplastic syndrome [26], no dysplastic change was observed in the trilineage hematopoietic cells of the bone marrow of this case, therefore, a diagnosis of AA was made.

In the present case, concurrent reactivation of CMV and VZV was observed in a setting of development of EBV-LPD. Albeit extremely rare, concurrent reactivation of multiple viruses with development of EBV-LPD without transplantation has been reported [27], and CMV reactivation in a patient with EBV-LPD after IST for AA

has also been documented (Table 1) [9]. Therefore, monitoring for virus reactivation other than EBV is also important in patients who receive IST, including ATG therapy.

In conclusion, we describe an extremely rare case of plasmacytic EBV-LPD after IST for AA. Albeit rare, plasmacytic LPD can occur in patients who receive IST without transplantation, and multiple virus reactivations can develop. Therefore, detailed histopathological and immunohistochemical analyses are needed for correct and rapid diagnosis and treatment, and additional studies are needed to clarify the clinicopathological features of EBV-LPD after IST for AA.

## Disclosure of conflict of interest

None.

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