T-cell lymphoma with a granulomatous lesion of the lungs after autologous hematopoietic stem cell transplantation against Epstein–Barr virus-positive diffuse large B-cell lymphoma: a case report

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Case Report

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Abstract

Background

Post-transplant lymphoproliferative disorders (PTLDs) are serious lymphoid and/or plasmacytic proliferations that occur after undergoing solid organ or hematopoietic stem cell transplantation (HSCT). In the context of HSCT, most reported PTLDs have occurred in patients who received allogenic HSCT (AlloHSCT), but only a few cases have been reported in autologous HSCT (AHSCT) recipients. Primary pulmonary T-cell lymphoma cases are also rare and have been reported mostly in case studies.

Case presentation:

A 53-year-old female patient initially presented with enlargement of the left cervical lymph nodes and was diagnosed as Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL). She was treated with R-CHOP, R-ACES, and autologous HSCT (AHSCT) and went into remission. Four years later, computed tomography results revealed multiple lung nodules, and abnormal infiltration and sustained and progressing hypogammaglobulinemia was observed. The pathological specimen of video-assisted thoracoscopic surgical lung biopsy demonstrated extensive invasion of lymphocytes with notable granuloma findings. Flow cytometric immunophenotyping analysis showed that lymphocytes were positive for CD3 and CD5; especially, CD3 was expressed in the cytoplasm. Southern blot analysis revealed rearrangements of the T-cell receptor Cβ1 gene. She was diagnosed with peripheral T-cell lymphoma, regarded as T-cell PTLD accompanied by granulomatous lesion.

Conclusion

Here, we report a rare case of T-cell lymphoma that mainly affected the lungs with the presentation of notable granulomatous findings following AHSCT against EBV-positive DLBCL. This uncommon presentation of rare lung lesions of granulomatous T-cell lymphoma could be related to the manifestation of a PTLD associated with sustained hypogammaglobulinemia.

Background

Post-transplant lymphoproliferative disorders (PTLDs) are rare lymphoid and/or plasmacytic proliferations that develop as a consequence of immunosuppression in recipients of solid organ or hematopoietic stem cell transplantation (HSCT) (1). The incidence of lymphoproliferative disorders in transplant recipients is 30–50 times higher than that in the general population and ranges from 2 to 10%, and the incidence of PTLDs after HSCT is less than 1% (2, 3).

Most PTLDs are of B-cell origin and are related to the Epstein–Barr virus (EBV). T-cell PTLDs, in contrast, constitute fewer than 15% of PTLDs in Western countries (4).
In the context of HSCT, most cases of PTLD are reported in patients who received allogenic HSCT (AlloHSCT). However, to the best of our knowledge, only 25 published cases of PTLD following autologous HSCT (AHSCT) have been reported as case reports (5–25).

Primary pulmonary lymphoma (PPL) is uncommon and accounts for only 0.5–1% of all primary pulmonary malignancies, less than 1% of all cases of non-Hodgkin's lymphoma (NHL) (26). Seventy to 80% of PPL cases are B cell origin (27). In contrast, primary pulmonary T-cell lymphoma cases are rare and have been reported mostly in case studies (28, 29).

Here, we report a rare case of T-cell lymphoma that mainly affected the lungs with the uncommon presentation of notable granulomatous findings following AHSCT against EBV-positive DLBCL.

**Case Report**

1. First lymphoid neoplasm

A 53-year-old woman initially presented with enlargement of the left cervical lymph nodes in 2013. Cervical node biopsy revealed atypical medium to large lymphocytes diffusely infiltrated (Fig. 1A, B). Laboratory studies showed low IgG and IgA levels (445 and 83 mg/dL, respectively) with normal IgM levels. Immunohistochemistry analysis showed that lymphocytes were positive for CD20 (Fig. 1C) and negative for CD3 and CD10 (data not shown). Furthermore, in situ hybridization (ISH) revealed that lymphocytes were positive for EBV-encoded small RNA (EBER) (Fig. 1D). She was diagnosed with EBV-positive DLBCL.

She received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in 2013 and was treated with R-ACES (rituximab, high-dose Ara C, carboplatin, etoposide, and steroids) chemotherapy followed by AHSCT in 2014. She then achieved complete remission.

2. Second lymphoid neoplasm

She was temporarily affected by pneumonia in 2017 and paranasal sinusitis in 2018. Subsequently, she presented with wheezing, and chest X-ray and computed tomography (CT) revealed multiple lung nodules and consolidations (Fig. 2A-C) in 2018. Positron emission tomography showed an abnormal accumulation of 18F-fluorodeoxyglucose (FDG) in bilateral lungs (Fig. 2D). In addition, an abnormal uptake of FDG was observed in the supraclavicular, mediastinal, hilar, paraaortic, and mesenteric lymph nodes (Fig. 2D).

Laboratory tests showed a gradual progression of hypogammaglobulinemia with low IgG, IgA, and IgM levels (367, 25, and 33 mg/dL, respectively). Polymerase chain reaction (PCR) was conducted on the whole-blood EBV DNA level, and the DNA levels were found to have increased up to $1.0 \times 10^3$ copies/mL from $2.0 \times 10^2$ copies/mL. Video-assisted thoracoscopic surgery (VATS) was performed for a biopsy of the left upper lobe of the lung. The macroscopic examination of the lung revealed multiple nodules, while
the microscopic examination demonstrated diffuse infiltration of lymphocytes with multiple granulomas and fibrotic change (Fig. 3A-C). The lymphocytes were mainly small to medium-sized and contained slight nuclear irregularities (Fig. 3D). Immunohistochemical staining revealed that lymphocytes were positive for CD3 and focally positive for CD20 (Fig. 3E, F). The lymphocytes destructively infiltrated the alveolar epithelium by immunostaining for AE1/AE3 (Fig. 3G). The lymphocytes were mainly positive for CD4 and focally positive for CD8 and TIA1 (data not shown). In the granulomas, epitheioi cells were positive for CD68 KP1 (Fig. 3H). ISH results revealed that some lymphocytes were positive for EBER (Fig. 3I). Grocott staining, Wade-Fite staining, and Giemsa staining were negative. The blood test and lung pathological findings did not show any evidence of infection and other granulomatous lesions such as granulomatous angiitis and sarcoidosis.

Flow cytometric immunophenotyping analysis of the specimen revealed that the proportion of surface CD3 was 29.9% and that of cytoplasmic CD3 was 74.4% (Fig. 4A, B). The proportions of CD2+, CD4+, CD5+, CD7+, and CD8+ cells were 92.5%, 73.6%, 84.7%, 71.0%, and 16.0%, respectively. In contrast, the proportions of CD10, CD19, CD20, CD25, surface Ig, and TdT were all <10% (data not shown). Southern blot analysis of the specimen indicated rearrangements of the T-cell receptor Cβ1 gene (Fig. 4C). She was subsequently diagnosed with peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), regarded as T-cell PTLD accompanied by notable granulomatous lesion.

The patient was treated by prednisolone and received alloHSCT, which was followed by tacrolimus and methotrexate. However, she did not achieve neutrophil engraftment and developed pneumonia. Finally, she died of septic shock on day 20 post-AlloHSCT about 8 months after the diagnosis of T-cell lymphoma.

Discussion

We describe a rare case of lymphoma as T-cell PTLD after chemotherapy and AHSCT for EBV-positive DLBCL. Our patient was diagnosed with EBV-positive DLBCL of the cervical LN at the age of 53 years, and multiple lung lesions of PTCL-NOS and granulomas, with sustained hypogammaglobulinemia, were observed four years after the achievement of complete remission following chemotherapy and AHSCT for DLBCL.

PTLDs are lymphoid and/or plasmacytic proliferations that develop as a consequence of immunosuppression after solid organ transplant and HSCT. PTLDs are classified into four categories: non-destructive PTLDs (9%), polymorphic PTLDs (6%), monomorphic PTLDs (82%), and classic Hodgkin lymphoma (3%) (1, 30). They are mostly associated with EBV infections but can also present in EBV-negative individuals. PTLDs encompass morphologically heterogeneous entities with variable clinical behavior (1, 30). Majority PTLDs are of B-cell origin, whereas T-cell PTLDs represent 2–15% of all PTLD cases. In T-cell PTLDs, the most common types are PTCL-NOS (19–36%) and hepatosplenic T-cell lymphoma (12–14%) (3, 4).
T-cell PTLDs exhibit a substantially shorter survival than B-cell PTLDs. Montanari et al. demonstrated that the median survival of T-cell PTLDs is 102 days, whereas the median survival of B-cell PTLD is 1.5 years (31). In a study of T-cell PTLDs, Herreman et al. reported that approximately 78% (21 cases of 27) of PTCL-NOS patients died, 90% of which died within one year after diagnosis (3). These reports indicated that beyond the immunological factors that give rise to PTLDs in general, these diseases may share similar biological features to their non-PTLD counterparts (31). Our patient died about eight months after the onset of PTLD with poor response to treatment, including AlloHSCT. Thus, the prognosis of our case is also inferior, which is consistent with the results of previously reported T-cell PTLD cases.

The incidence of PTLDs ranges from 2 to 10% in all transplant recipients, and the incidence of PTLDs after HSCT is less than 1% (2, 3). Fewer reports, mostly case studies, have shown the development of PTLDs following AHSCT in comparison with AlloHSCT (5–25). In addition, the cases of T-cell origin are even fewer. To the best of our knowledge, only six cases out of 25 PTLDs following AHSCT have been reported to be of T-cell origin. Thus, our case is a very rare case of PTLD, which occurred after AHSCT and is of T-cell origin (5–25).

Our patient showed sustained and progressive hypogammaglobulinemia with recurrent respiratory infections after R-CHOP for DLBCL. Because hypogammaglobulinemia has been recognized before AHSCT for DLBCL treatment, this condition could not be related to transplantation. A subset of patients has been reported to develop persistent hypogammaglobulinemia after rituximab treatment (32–39). Thus, hypogammaglobulinemia and respiratory infections, which were the cause and background of our case, led us to consider the possibility of the side effects of rituximab or primary immunodeficiency (PID), such as common variable immunodeficiency (CVID), which is a heterogeneous entity characterized by varying degrees of hypogammaglobulinemia and recurrent bacterial infections (40). In our case, unfortunately, the value of serum immunoglobulin was not measured before R-CHOP treatment against DLBCL. However, the patient's history did not indicate recurrent respiratory infections prior to chemotherapy for DLBCL. Considering the history and age, our case seems unlikely to match typical PID such as CVID.

Most reported cases of PTLDs developing after AHSCT are associated with EBV infections (5–25). Consistent with this phenomenon, in our patient, the EBV DNA level in the blood increased at the onset of T-cell PTLD, and the pathological specimen also showed focal EBER-positive findings. Previous reports of T-cell PTLD suggest that EBV may infect T-cells and cause PTLD or EBV may infect B-cells and indirectly contribute to T-cell PTLD; however, a detailed role for EBV has not been confirmed in T-cell PTLD (17, 41, 42). Because we detected only a small number of EBER-positive lymphocytes in the lung specimen in our case, it is impossible to clearly distinguish whether these positive cells were B-cells or T-cells. However, whether the EBV infected cell type is B-cell or T-cell, EBV infection is thought of as one of the causes of T-cell PTLD.

In a case of DLBCL treated with rituximab, the consecutive development of hypogammaglobulinemia and PTCL-NOS has been reported (36). Hypogammaglobulinemia was accompanied by repeated respiratory
infections like CVID (36). We referred to this case because our patient presented persistent hypogammaglobulinemia with gradual aggravation. Thus, PTLD in our case might have been correlated to the advancement of hypogammaglobulinemia in addition to EBV infection.

In our case, the VATS specimen showed notable lymphocyte infiltration and multiple granulomas with fibrotic change. No clinicopathological cause of the granuloma was found such as tuberculosis, fungal infection, sarcoidosis, or granulomatous angiitis. As a differential diagnosis, the granulomatous findings can be cited as being related to Lennert’s lymphoma (LeL), a rare variant of PTCL-NOS characterized by prominent small clusters of epithelioid histiocytes (43, 44). However, LeL was reported to constitute only 0.71% of PTCL and relatively rarely invade the extranodal foci; therefore, this pulmonary lesion is considered to not be a typical LeL-related finding (45, 46). In contrast, considering our case background of hypogammaglobulinemia, this lung granulomatous lesion can also be interpreted as being a lesion associated with the granulomatous lymphocytic interstitial lung disease (GLILD) in addition to a PTCL-NOS lesion. GLILD is defined as distinct interstitial lung disease occurring in patients with persistent hypogammaglobulinemia such as CVID. This is associated with a lymphocytic infiltrate and/or granuloma in the lung that is unexplained by other conditions (47). However, despite the association of this granulomatous lesion to LeL or GLILD-like changes, the occurrence of this lung lesion is very rare and is an interesting finding in addition to the PTCL-NOS lung lesion. The rare pulmonary lesions of T-cell lymphoma with notable granulomatous changes in our case may be relevant to the background PTLD in our case, following treatment including rituximab with the persistent hypogammaglobulinemia.

In conclusion, we report a rare case of T-cell lymphoma mainly affecting the lungs with notable granulomatous findings that developed post-AHSCT against EBV-positive DLBCL. This uncommon presentation of rare lung lesions of granulomatous T-cell lymphoma could be related to the manifestation of a PTLD associated with sustained hypogammaglobulinemia.

Abbreviations

CT: Computed tomography; CVID: Common variable immune deficiency; DLBCL: Diffuse large B-cell lymphoma; EBER: EBV-encoded small RNA; EBV: Epstein–Barr virus; GLILD: Granulomatous lymphocytic interstitial lung disease; HSCT: Hematopoietic stem cell transplantation; ILD: Interstitial lung disease; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; PTLD: Post-transplant lymphoproliferative disorder; VATS: Video-assisted thoracoscopic surgery

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki and was approved by the Human and Animal Ethics Review Committees of Nippon Medical School, Japan (30-07-964).

Consent for publication
Written informed consent was obtained from the patient for publication of this report and accompanying images.

**Availability of data and materials**

The data and materials are available upon request from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

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No funding has been gained by the authors for this research.

**Authors' contributions**

YK and YT were responsible for histological diagnosis and collecting the data and wrote the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Diffuse large B-cell lymphoma in the cervical lymph node. (A) The node architecture was effaced by diffuse infiltration lymphocytes. (B) Higher magnification of the boxed area in (A) reveals diffuse infiltration of the medium and large lymphocytes. (C) Immunostaining revealed that the lymphocytes were positive for CD20. (D) In situ hybridization showed that these cells were positive for EBV-encoded small RNA (EBER). (B-D) Serial sections. Scale bar: 2 mm (A), 60 μm (B-D).
Figure 2

Radiographic features of T-cell PTLD. (A-C) Chest X-ray and computed tomography scan showed multifocal pulmonary consolidations and nodules. (D) 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed an accumulation of FDG in the bilateral lung nodules and the lymph nodes.
Figure 3

Pathologic findings of the VATS specimen. (A) In the lung tissue, multiple nodules were observed. (B, C) High power views showed notable infiltration of lymphocytes with multiple granulomas (*) and fibrotic change. (D) The lymphocytes were small to medium-sized with slight nuclear irregularities. (B-D) Higher magnification of the boxed area in (A), (B), and (C), respectively. (E, F) The lymphocytes were positive for CD3 (E) and focally positive for surface CD20 (F). (G) The lymphocytes destructively infiltrated the alveolar epithelium (AE1/AE3). (H) Epithelioid cells of the granulomas were positive for CD68 KP1. (I) Some of the lymphocytes were positive for EBER. (C, E-I) Serial sections. Scale bar: 7 mm (A), 1 mm (B), 150 μm (C, E-I), 60 μm (D).
A

Surface membrane

Gate A 73.1% (7312 cells)

B

Cytoplasm

Gate A 88.4% (8840 cells)

C

Control

Patient

Ba: BamH I
Ec: EcoR I
Hi: Hind III

M: Protein Molecular Weight Markers
(λ DNA/Hind III)

M  Ba  Ec  Hi
23.1  9.42  6.56  4.36
2.32
2.03

Ba: BamH I
Ec: EcoR I
Hi: Hind III

M: Protein Molecular Weight Markers
(λ DNA/Hind III)
Figure 4

Flow cytometric analysis and Southern blot analysis of TCR β gene rearrangements of the VATS specimen. (A, B) CD3 was focally expressed on the surface membrane (A) and expressed in the cytoplasm (B). (C) DNA from the lung tissue involved in lymphocyte infiltration after AHSCT was digested with selected restriction enzymes (BamHI (Ba), EcoRI (Ec), and HindIII (Hi) for TCR β gene). Control DNA was obtained from donated cord blood. DNA was probed with a Cβ1 probe. TCR β gene rearrangements were detected on Ba, Ec, and Hi digest.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklistEnglish20133.pdf