Case Report

Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders, Diffuse Large B-Cell Lymphoma Type, in a Patient with Behçet’s Disease Treated with Cyclosporine A

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Abstract
A 40-year-old man had been treated for Behçet’s disease (BD) with cyclosporine A (CsA) for 14 years. He presented multiple lymphadenopathies with fever. Histological examination of surgical biopsy showed other iatrogenic immunodeficiency-associated lymphoproliferative disorders, diffuse large B-cell lymphoma type with positivity for Epstein-Barr virus encoding RNA-1 (EBER-1). BCL2-IgH, BCL6-IgH, and MYC-IgH translocations were not detected. CsA was stopped, and R-CHOP therapy was initiated. However, his lymphoma was chemotherapy resistant and rapidly progressed. To the best of our knowledge, this is the first case of diffuse large B-cell lymphoma that occurred in a BD patient treated with CsA reported in English. Both BD and CsA are associated with the pathogenesis of lymphoma. We also describe extremely rare cases in the form of a literature review.

Introduction
Behçet’s disease (BD) is a systemic disorder that is characteristic of oral and genital ulcers, skin lesions, and uveitis. BD is sometimes accompanied by hematological malignancies [1–3]. Of those, lymphoma is relatively rare [1–3]. We experienced diffuse large B-cell
lymphoma (DLBCL) arising in a 40-year-old patient with BD treated with cyclosporine A (CsA) for 14 years. CsA is a calcineurin inhibitor (CI) and is known to be associated with tumorigenesis [4]. CI suppress tumor-specific immune responses by inhibiting helper T-cell functions as well as cytotoxic T-cell responses [5]. We herein report a rare case associated with CsA-related other iatrogenic immunodeficiency-associated lymphoproliferative disorders (Oii-LPDs), DLBCL type (Oii-DLBCL), in BD.

**Case Presentation**

**Clinical Presentation**

A 40-year-old man was admitted to our hospital with fever lasting for 10 days. He had suffered from BD and was treated with prednisolone, colchicine, and CsA for 14 years. His symptoms of BD presented as almost all skin lesions with repeated skin abscesses. He had a high fever of 39°C and bilateral cervical lymphadenopathies that were soft and painful. He showed leukocytosis (19,470/μL), neutrophilia (16,000/μL), and moderate normochromic anemia (hemoglobin 10.4 g/dL). The serum levels of C-reactive protein and soluble interleukin-2 receptor were 11.03 mg/dL and 5,261 U/mL, respectively. Epstein-Barr virus (EBV) DNA in peripheral blood was 7,000 copies/mL. Systemic computed tomography revealed swelling of the bilateral cervical, axillary, and mediastinal lymph nodes, and positron emission tomography showed that the maximum standardized uptake value was 20. Malignant lymphoma or tuberculous lymphadenitis was suspected, and cervical lymph node biopsy was performed. He was ultimately diagnosed with Oii-DLBCL according to the WHO classification revised fourth edition [6] because he had been treated with immunosuppressant therapy.

He received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy. Although withdrawal of CsA was required, the dose of CsA was tapered gradually due to his active skin lesions. After 5 cycles of R-CHOP, his axillary lymph nodes were still swelling, although his cervical lymph nodes had shrunk. EBV DNA in peripheral blood was 3,000 copies/mL. Therefore, needle biopsy of the axillary lymph node was performed. The histological findings were Oii-DLBCL, the same as the findings from the prior biopsy. Since the treatment effect of R-CHOP chemotherapy was shown as stable disease and CD20 expression turned out to be negative, he was treated with gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy. After one cycle of GDP, EBV DNA in peripheral blood was 5,000 copies/mL. After two cycles of GDP, EBV DNA in peripheral blood decreased to less than the standard value. Then, he was treated by etoposide, cytarabine, cisplatin, and methylprednisolone (ESHAP) chemotherapy as second salvage therapy.

**Pathological Presentation**

Resected lymph nodes before chemotherapy were 37 and 15 mm in diameter. Histological examination showed diffuse proliferation of mostly medium to large lymphoid cells (Fig. 1A). Immunohistochemically, tumor cells were CD79a (+), PAX5 (+), CD20 (60%), CD30 (5%), cMYC (10%), CD5 (0%), CD10 (0%), CD23 (0%), MUM1 (0%), BCL2 (0%), BCL6 (0%), GCET1 (0%), and FOXP1 (0%) (Fig. 1B–D). The Ki-67 labeling index was 60% (Fig. 1E). EBV encoding RNA-1 (EBER-1) positivity was detected by in situ hybridization (ISH) (Fig. 1F). Small T cells were intermingled with tumor cells. Gene rearrangement of the immunoglobulin heavy chain was detected by polymerase chain reaction. BCL2-IgH, BCL6-IgH and MYC-IgH translocations were not detected by fluorescence in situ hybridization (FISH). The patient was diagnosed with Oii-LPDs, DLBCL-type, according to WHO classification revised fourth edition [6] since he had been treated with immunosuppressant therapy.
Fig. 1. Cervical lymph nodes biopsy before chemotherapy. Mostly large lymphoid cells were diffusely proliferating and intermingled with small T cells (A). Large lymphoid cells are CD79a positive (B), CD20 positive (C), CD30 partially positive (5%) (D), Ki-67 labeling index 60% (E), and Epstein-Barr virus encoding region in situ hybridization positive (F).

Fig. 2. Axillary lymph node biopsy after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy. Large lymphocytes similar to the former biopsy were proliferating and intermingled with small T cells (A). They were CD79a positive (B), CD20 negative (C), CD30 few positive (<1%) (D), BCL2 positive (80%) (E), Ki-67 labeling index 40% (F).
The biopsy after R-CHOP showed diffuse growth of large atypical lymphocytes (Fig. 2A), which were similar to former findings from cervical lymph node specimens. On immunohistochemistry, large cells are CD79a (+), BCL2 (80%), MUM1 (70%), cMYC (10%), CD20 (0%), CD30 (<1%), CD5 (very focally), CD10 (0%), CD23 (0%), BCL6 (10%), GCET1 (0%), and FOXP1 (0%) (Fig. 2B–E). Ki-67 labeling index was 40% (Fig. 2F). EBER-1 positivity was detected by ISH. Small T cells were intermingled with tumor cells.

**Discussion**

BD is sometimes accompanied by hematological malignancies [1–3]. Among hematological malignancies with BD, myelodysplastic syndrome (MDS) is most common (22–48%) [2,3]. Conversely, lymphoma is a relatively rare complication (0.02–3.1%) [2,3]. We searched “Behçets disease” and “lymphoma” in PubMed, and there were 7 available studies published in English from 2000 to 2020 (Table 1) [1,7–12]. All cases had been treated with immunosuppressants such as colchicine, steroids, azathioprine, and dexamethasone.

**Table 1. Lymphoma cases associated with Behçet’s disease**

| First author, year | Age/Male | Medication for Behçet's disease | Duration, years | Lymphoma | Time from Behçet's disease to lymphoma (year) | Site | EBV infection | Treatment | Outcome |
|--------------------|-----------|---------------------------------|----------------|----------|-----------------------------------------------|------|--------------|-----------|---------|
| Cengiz M, 2001     | 47/M      | Cyclophosphamide, NSAIDs       | N/A            | Hodgkin lymphoma, nodular sclerosis     | 7     | N/A          | N/A       | ABVD, RT | N/A     |
| Cengiz M, 2001     | 42/M      | Colchicine, NSAIDs             | N/A            | Non-Hodgkin lymphoma, diffuse mixed cell | 8     | N/A          | N/A       | Mitoxantrone, etoposide, ifosfamide | N/A     |
| Kastura Y, 2003    | 49/M      | Steroid, Colchicine            | 0.6            | Cytotoxic T-cell lymphoma                | 0.6   | Perirenal space, orbit | CHOP     | Death (OS 41 days) |
| Oyo Y, 2005        | 75/F      | Steroid, Colchicine            | 17             | Diffuse large B-cell lymphoma            | 17    | Cerebrum     | -         | RT      | PD (ileum involvement) |
| Cheley I, 2008     | 40/M      | Steroid, Azathioprine          | 2              | Cutaneous gamma-delta T-cell lymphoma   | 2     | Skin         | N/A       | Chemotherapy (detail was unknown) | CR      |
| Souabni L, 2008    | 32/M      | Steroid, Diamodiphenyl sulfone | 10             | Diffuse large B-cell lymphoma            | 14    | Tonsil       | +         | CHOP, RT | CR      |
| Meydan AD, 2011    | 53/M      | Cyclophosphamide, Prednisolone | 3              | Nodular lymphocyte-predominant Hodgkin lymphoma | 27    | LN         | N/A       | VEEP, ABVD, RT | CR but recurrence after 7 years After second therapy, CR |
| Meydan AD, 2011    | 67/M      | Colchicine                     | 23             | Diffuse large B-cell lymphoma            | 23    | Tonsil       | LN         | CHOP, RT | CR      |
| Yamazaki K, 2013   | 71/F      | Cyclophosphamide               | ≤20            | HHV-8-unrelated PEL-like lymphoma        | 31    | Pleural effusion, ascites | R-CHOP   | Death (OS 9 months) |
| Present case       | 40/M      | Cyclophosphamide               | 14             | Diffuse large B-cell lymphoma            | 14    | LN         | +         | R-CHOP, GDP, ESHAP | SD      |

M, male; F, female; PEL, primary effusion lymphoma; NSAIDs, non-steroidal anti-inflammatory drugs; N/A, not available; LN, lymph node; EBV, Epstein-Barr virus; V, vincristine, etoposide, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ESHAP, etoposide, cytarabine, cisplatin and methylprednisolone; OS, overall survival; CR, complete remission; PD, progressive disease; SD, stable disease.
lymphocyte activation or inflammatory cytokine storms in BD are considered to be associated with lymphoma [3, 7]. Three patients were EBV-positive. Our patient had been treated with steroid and CsA for a long time and had an active EBV status. In Table 1, DLBCL cases with BD are shown in only 3 studies that were published in English. Their treatment outcomes varied. Two patients showed complete remission (CR), but 1 patient experienced recurrence.

BCL2-IgH, BCL6-IgH, and MYC-IgH translocations were associated with worse prognosis in DLBCL [8, 9]. While previous reports did not mention BCL2-IgH, BCL6-IgH, and MYC-IgH translocations, they were not detected in our first biopsy specimen before initiating chemotherapy.

Lymphoma that arises in patients who have been treated with immunosuppressants is now classified as Oii-LPDs [6], and the DLBCL type is the most common type. In particular, Oii-DLBCL associated with rheumatoid arthritis is most common [10], but other autoimmune diseases including ulcerative colitis [11], are also associated with Oii-DLBCL. Among Oii-LPDs, CI-associated Oii-LPD cases are uncommon, and their profiles or prognosis are not fully under-

### Table 2. Lymphoma cases after calcineurin inhibitor (CI)

| First author, year | Age/Sex | Primary disease | CI Type | Dose | Duration, years | Histological type | Time from CI to lymphoma, years | EBV infection | Site | Treatment | Outcome |
|--------------------|---------|-----------------|---------|------|----------------|------------------|-------------------------------|----------------|------|-----------|---------|
| Corazza M, 2003    | 61/F    | Psoriasis       | CsA     | 3 mg/kg/day | 8              | Primary cutaneous 8 CD30+ large T-cell lymphoma | N/A             | Skin | Withdrawal of CsA MACOP-B | Death (OS 4 years) |
| Ogata M, 2004      | 70/M    | Refractory anemia | CsA     | 3.3 mg/kg/day | 1              | Diffuse large B-cell 1 lymphoma | –              | Stomach | Withdrawal of CsA, resection | CR |
| Shibahara T, 2004  | 33/M    | Ulcerative colitis | CsA     | 200 mg/4 day | N/A           | Diffuse large B-cell 4 lymphoma | N/A             | Rectum | Withdrawal of CsA, CHOP | CR |
| Mougel F, 2006     | 37/M    | Atopic dermatitis | CsA     | 2.5–4 mg/kg/day | 1              | Cutaneous T-cell lymphoma, transformed into CD30+ large cell lymphoma | N/A             | Skin | Withdrawal of CsA, CHOP, hematopoietic stem cell transplantation | CR |
| Vakeva, L, 2008    | N/A     | Palmoplantar psoriasis | CsA     | <2 mg/kg/day | 1              | MALT lymphoma | N/A | N/A | N/A | N/A |
| Gattu S, 2010      | 55/F    | Psoriasis       | CsA     | 2–5 mg/2 kg/day | 0.3           | Diffuse large B-cell 2 lymphoma | –              | Ileum | Withdrawal of CsA, resection | CR |
| Quéreux G, 2010    | 36/M    | Psoriasis       | CsA     | 3 mg/kg/day | 0.1           | Primary cutaneous 0.5 CD4+ pleomorphic T-cell lymphoma | –              | Skin | Pegylated liposomal doxorubicin | Death (OS 6 months) MTX 3 months Etanercept 3 months |
| Sekiguchi Y, 2012  | 69/F    | MCTD            | TAC     | 3 mg/day | 1              | Diffuse large B-cell 1 lymphoma | –              | LN | Withdrawal TAC, R-CHOP, intrathecal anticancer drug injection | PD |
| Yamazaki K, 2012   | 71/F    | Behçet's disease | CsA     | 100 mg/220 day | ≥20            | HHV-8-unrelated PEL-like lymphoma | ≥20            | Pleural effusion, ascites | R-CHOP | Death (OS 9 months) |
| Ohara M, 2018      | 55/M    | Myasthenia gravis | TAC     | N/A | 16             | Peripheral T-cell lymphoma, not otherwise specified | –              | LN, spleen | Withdrawal TAC, CHOP PR | PSL 16 years |
| Present case       | 40/M    | Behçet's disease | CsA     | 50–150 mg/day | 14             | Diffuse large B-cell 14 lymphoma, NOS | +              | LN | R-CHOP, GDP, ESHAP, SD | PSL 14 years |

MCTD, mixed connective tissue disease; CI, calcineurin inhibitor; CsA, cyclosporine A; TAC, tacrolimus; PEL, peripheral effusion lymphoma; EBV, Epstein-Barr virus; LN, lymph node; MACOP-B, methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisolone, and bleomycin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; GDP, gemcitabine, dexamethasone, and cisplatin; ESHAP, etoposide, cytarabine, cisplatin and methylprednisolone; OS, overall survival; CR, complete remission; PD, progressive disease; SD, stable disease; MTX, methotrexate; PSL, prednisolone; N/A, not available.
stood. When CsA was used for skin disease, lymphoma occurred in 0.3% of these patients [4]. We searched “cyclosporin” and “lymphoma” or “tacrolimus” and “lymphoma” in PubMed, and 8 lymphoma cases associated with CsA [4, 12–16] and 2 lymphoma cases associated with tacrolimus [5, 17] have been reported in English in the available literature from 2000 to 2020 (Table 2). EBV is also linked to Oii-LPDs. However, EBV was detected in only 1 case. Nine of 10 cases did not use or stopped using CI after being diagnosed with lymphoma. Two patients achieved CR only by the withdrawal of the CI and 4 patients achieved CR with chemotherapy. However, 3 patients died, and 1 patient had progressive disease. Most patients with CI-associated lymphoma showed a better prognosis, but some patients, especially whose lymphoma types are histologically aggressive, had more severe disease course. DLBCL associated with a CI occurred in the gastrointestinal tract or lymph nodes. Three patients with DLBCL arising in the gastrointestinal tract showed better prognosis than the patient with nodal DLBCL. One patient with nodal DLBCL was negative for the BCL2-IgH translocation in FISH, but neither the BCL6-IgH nor MYC-IgH translocation status was available. Gene translocation were not studied in the 3 other patients with DLBCL. Our patient was resistant to chemotherapy, and his prognosis was worse than that of other CI-associated Oii-LPDs. This may be because our patient could not stop cyclosporine immediately after diagnosis since his BD was still active. Additionally, his EBV viral load was high after initiating chemotherapy. The viral load of EBV is suspected to be associated with Oii-LPDs activity [18]. In addition, CD20 expression had converted and was negative in the second biopsy specimen after R-CHOP chemotherapy, and resistance to rituximab therapy was suspected [19]. Although BCL2 expression had converted and was positive in the second biopsy specimen, the expression of BCL6 and cMYC was still negative, and the patient did not have double- or triple-expressing lymphoma. It was not clear whether the conversion of the BCL2 expression was associated with the outcome.

In conclusion, we report a case of Oii-DLBCL that occurred during CsA treatment for BD. To the best of our knowledge, this was the first case of DLBCL in a BD patient treated by CsA published in English. Furthermore, we first studied all of the BCL2-IGH, BCL6-IgH, and MYC-IgH translocation statuses in patients with BD-associated lymphoma or CI-associated Oii-LPDs. Since there are only a few DLBCL cases with BD or CI-associated Oii-LPD, we need to evaluate more patients to understand their immunophenotype, genetics, and prognosis to reveal their prognostic factors.

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Statement of Ethics

Because the patient had been transferred to another hospital, we could not obtain the written informed consent to publish this case from him. This study was approved by the Research Ethics Committee of Yamagata University Faculty of Medicine (2019-S-92) and was performed in accordance with the Declaration of Helsinki. Research Ethics Committee decided that this report did not need the written informed consent because the information regarding individual features from which others can identify the patient were excluded.
Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Author Contributions

Data presentation, U.Y., O.R., Y.A., K.T., S.K., K.T., T.N., A.N.Y., U.A., T.T., and I.K.; writing, U.Y., O.R.; final review and editing, O.R.; all authors approved the manuscript.

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