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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Keywords

Behçet's disease · Cyclosporine A · Lymph node · Diffuse large B-cell lymphoma · Epstein-Barr virus

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.

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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

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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/ μ L), neutrophilia (16,000/ μ L), 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).

Table 1. Lymphoma cases associated with Behçet's disease

First author, year	Age/ Sex	Medication for Behçet's disease		Lymphoma					Outcome
		Drug	Duration, years	Histological type	Time from Behçet's disease to lymphoma (year)	Site	EBV infection	Treatment	
Cengiz M, 2001	47/M	Cyclophosphamide NSAIDs	N/A N/A	Hodgkin lymphoma, nodular sclerosis	7	N/A	N/A	ABVD, RT	N/A
Cengiz M, 2001	42/M	Colchicine NSAIDs	N/A 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 0.6	Cytotoxic T-cell lymphoma	0.6	Perirenal space, + orbit		CHOP	Death (OS 41 days)
Ono Y, 2005	75/F	Steroid Colchicine	17 4	Diffuse large B-cell lymphoma	17	Cerebrum	-	RT	PD (ileum involvement)
Chelly I, 2008	40/M	Steroid Azathioprine	2 2	Cutaneous gamma-delta T-cell lymphoma	2	Skin	N/A	Chemotherapy (detail was unknown)	CR
Souabni L, 2008	32/M	Colchicine Steroid Diaminodiphenyl sulfone	10 10 8	Diffuse large B-cell lymphoma	14	Tonsil	+	CHOP, RT	CR
Meydan AD, 2011	53/M	Cyclophosphamide Prednisolone	3 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	N/A	CHOP, RT	CR
Yamazaki K, 2013	71/F	Cyclosporine	≥20	HHV-8-unrelated PEL-like lymphoma	31	Pleural effusion, + ascites		R-CHOP	Death (OS 9 months)
Present case	40/M	Steroid Cyclosporine	14 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; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; RT, radiation therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; VEEP, vincristine, epirubicin, etoposide, 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.

The biopsy after R-CHOP showed diffuse growth of large atypical lymphocytes (Fig. 2A), which were resemble to former findings from cervical lymph node specimen. 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 “Behçet's 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 diaminodiphenyl sulfone. Chronic

Table 2. Lymphoma cases after calcineurin inhibitor (CI)

First author, year	Age/ Sex	Primary disease	CI			Lymphoma					Outcome	Other immuno-suppressants
			Type	Dose	Duration, years	Histological type	Time from CI to lymphoma, years	EBV infection	Site	Treatment		
Corazza M, 2003	61/F	Psoriasis	CsA	3 mg/kg/day	8	Primary cutaneous CD30 ⁺ large T-cell lymphoma	8	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 lymphoma	1	–	Stomach	Withdrawal of CsA, resection	CR	
Shibahara T, 2006	33/M	Ulcerative colitis	CsA	200 mg/day	4	Diffuse large B-cell lymphoma	4	N/A	Rectum	Withdrawal of CsA, CHOP	CR	PSL 4 years
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	1	N/A	Skin	Withdrawal of CsA, CHOP, hematopoietic stem cell transplantation	CR	Topical treatment of TAC
Vakeva, L, 2008	N/A	Palmoplantar pustulosis	CsA	<2 mg/kg/day	1	MALT lymphoma	N/A	N/A	N/A	N/A	N/A	
Gattu S, 2010	55/F	Psoriasis	CsA	2–5 mg/kg/day	2	Diffuse large B-cell lymphoma	2	–	Ileum	Withdrawal of CsA, resection	CR	MTX 3 years
Quéreux G, 2010	36/M	Psoriasis	CsA	3 mg/kg/day	0.3	Primary cutaneous CD4 ⁺ pleomorphic T-cell lymphoma	0.5	–	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 lymphoma	1	–	LN	Withdrawal TAC, R-CHOP, intrathecal anticancer drug injection	PD	PSL 26 years
Yamazaki K, 2013	71/F	Behçet's disease	CsA	100 mg/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	16	–	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 lymphoma, NOS	14	+	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.

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-

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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