

Case Study

# Unilateral conjunctival infiltration of Adult T-cell leukemia/lymphoma. Case report and literature review

Joji Shimono,<sup>1,4)</sup> Shigeki Kaino,<sup>2)</sup> Kohei Okada,<sup>1,4)</sup> Kazuo Oshimi,<sup>1)</sup> Yusuke Ishida,<sup>3)</sup>  
Tatsuro Takahashi,<sup>3)</sup> Takuto Miyagishima,<sup>1)</sup> Takanori Teshima<sup>4)</sup>

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell lymphoma caused by human T-cell leukemia virus type 1 infection. Although conjunctival lymphoma is commonly reported with B-cell lymphoma, it rarely occurs in cases of ATLL. A 73-year-old Japanese female patient was admitted to our institution with evidence of abnormal lymphocytes, lymphadenopathy, and lung nodular lesions. Acute type ATLL was diagnosed, and therapy following the mLSG15 protocol was initiated. At the end of the second course, new bone lesions were detected. A modified treatment regimen was scheduled, but was postponed due to the appearance of gastrointestinal symptoms. Close observation resulted in a diagnosis of cytomegalovirus enteritis. One month after the diagnosis, the patient developed pain and discomfort in her left eye, which was determined to be due to a bulbar conjunctival tumor. Pathological findings revealed conjunctival infiltration of ATLL. Mogamulizumab treatment was initiated and was successful in eradicating the conjunctival lesions after the first course. However, at the end of the third course of therapy, pancytopenia was noted. Therefore, mogamulizumab therapy was discontinued, and the patient was on follow-up observation. Although there was no relapse of the conjunctival lesions, the patient died 1 year after the initial diagnosis, following therapy resistance.

**Keywords:** Adult T-cell leukemia/lymphoma, Conjunctival lymphoma, Ocular adnexal lymphoma

## INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell lymphoma caused by human T-cell leukemia virus type 1 (HTLV-1) infection, and is classified as smoldering type, chronic type, acute type, or lymphoma type, according to the diagnostic criteria by Shimoyama.<sup>1</sup> mLSG15 is one of the efficient chemotherapy regimens for ATLL, but the outcomes of patients treated by chemotherapy are still unsatisfactory.<sup>2</sup> Recently, mogamulizumab, an antibody drug targeting CC chemokine receptor 4 (CCR4), has been reported to be efficacious for ATLL, and is widely used for ATLL treatment.<sup>3</sup>

Conjunctival lymphoma is one type of ocular adnexal lymphoma.<sup>4</sup> Other ocular adnexal lymphomas exhibit infiltrating lymphoma cells into the eyelid and orbit.<sup>4</sup> Only 1-2% of all non-Hodgkin lymphoma cases are ocular adnexal lymphomas.<sup>5</sup> In a previous study involving 108 cases of ocular adnexal lymphoma, infiltration into the orbit was observed in 64%, into the conjunctiva in 28%, and into the eyelid in 8%.<sup>6</sup> The main histological subtypes of ocular adnexal lymphoma are extranodal marginal zone lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, and

follicular lymphoma.<sup>7</sup> The percentage of T-cell ocular adnexal lymphoma is less than 1%.<sup>7</sup>

Invasion of ATLL into extranodal organs, such as the skin, central nervous system, gastrointestinal tract, liver, and spleen, has been reported,<sup>1</sup> but ocular invasion is rarely reported.<sup>8-14</sup> We describe here a case of bulbar conjunctival infiltration during the course of acute type ATLL.

## CLINICAL COURSE

A 73-year-old Japanese female patient was admitted to our hospital with a complaint of difficulty in swallowing, which was attributed to sore throat. Computed tomography revealed a swollen right cervical lymph node, and numerous nodular lesions in the lung, pharynx, larynx, and both sides of the palatine tonsils. Hematological examination demonstrated a white blood cell count of 10010 cells/ $\mu$ L, a total lymphocyte count of 3503 cell/ $\mu$ L (lymphocytes, 10%; atypical lymphocytes, 25%), and a lactate dehydrogenase level of 353 IU/L (normal range: 124-222 IU/l). Serological examination for HTLV-1 antibody was positive, and biopsy of the tonsils led to a diagnosis of acute ATLL according to

Received: June 15, 2017. Revised: October 24, 2017. Accepted: October 24, 2017.

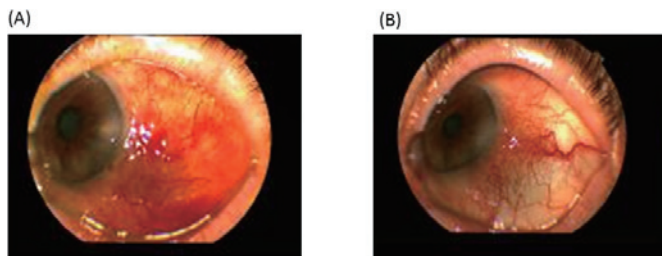
<sup>1)</sup>Department of Hematology, Kushiro Rosai Hospital, Kushiro, Japan, <sup>2)</sup>Department of Ophthalmology, Kushiro Rosai Hospital, Kushiro, Japan, <sup>3)</sup>Department of Pathology, Kushiro Rosai Hospital, Kushiro, Japan, <sup>4)</sup>Department of Hematology, Hokkaido University Faculty of Medicine, Sapporo, Japan

**Corresponding author:** Joji Shimono, Department of Hematology, Kushiro Rosai Hospital, 13-23 Nakazono-chou, Kushiro, Hokkaido 085-8533, Japan.

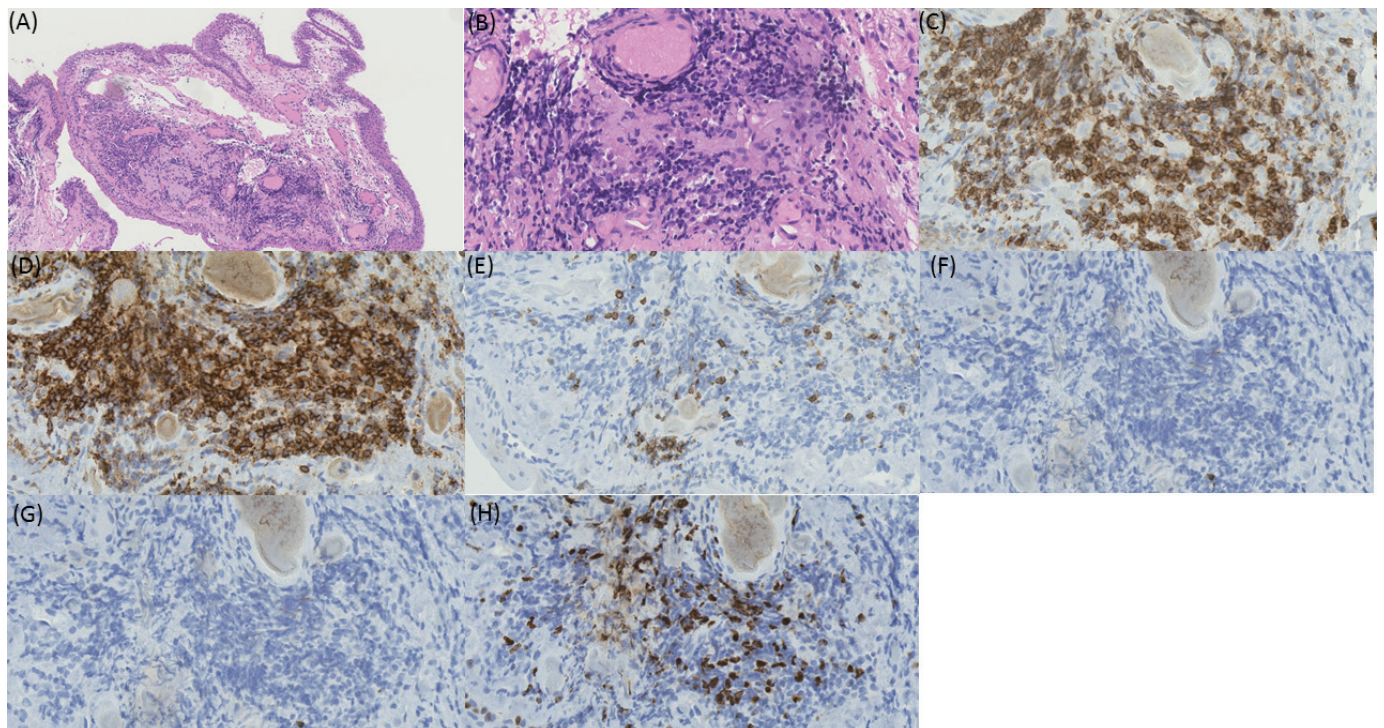
E-mail: fveritable6@yahoo.co.jp

Shimoyama's classification. The patient was placed on the mLSG15 chemotherapy regimen. However, after the second therapy course, she complained of shoulder and back pain, and the therapy was terminated. Osteolytic lesions at the pain site were found on MRI. Fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed enhanced uptake in the left scapula, spine, pelvis, and in the humerus and femur of both limbs. A modified treatment regimen was scheduled, but was postponed due to the appearance of diarrhea, vomiting, and anorexia. Upper gastrointestinal endoscopy was performed, and a diagnosis of cytomegalovirus enteritis was made, for which valganciclovir treatment was initiated. One month after the diagnosis of cytomegalovirus enteritis, symptoms of pain and discomfort of the left eye appeared. No swollen superficial lymph nodes or other skin abnormalities were found on physical examination. Salmon

patch-like appearance with vascularity on the ear side of the left bulbar conjunctiva (Fig. 1-A) was noted, but no lesions were present in the right eye. Other ocular parameters (Vd 0.7 (0.8), Vs 0.2 (0.6), and Td 10 mmHg, Ts 10 mmHg) were normal. Fundus examination revealed no abnormal findings other than mild cataract. No invasion into any other site was observed on orbital MRI. Figure 2 shows the biopsy of the left bulbar conjunctival lesions. Infiltration of medium-sized atypical lymphocytes into the conjunctival submucosa was found on histology. In immunohistochemistry analysis, atypical lymphocytes were positive for CD3 and CD4, and negative for CD8, CD20, and TIA-1. The Ki-67 labeling index was approximately 30-40%. Moreover, head MRI and cerebrospinal fluid examination did not demonstrate any invasion of the neoplastic cells into the central nervous system. Treatment of mogamulizumab at a dose of 1 mg/kg every 8 weeks was started, and the bulbar conjunctival lesions disappeared at the end of the first course of treatment (Fig. 1-B). However, pancytopenia was observed at the end of the third course. Although the reason for pancytopenia after mogamulizumab is unknown, we stopped mogamulizumab therapy as it was a suspected cause. The patient was placed on follow-up observation. After discontinuation of therapy, she presented with recurrence of left cervical lymphadenopathy. There was no relapse of the bulbar conjunctival lesions, but the patient died after initial diagnosis, following therapy resistance.



**Fig. 1.** Left bulbar conjunctival lesions. (A) Salmon patch-like appearance observed in left conjunctiva. (B) Conjunctival lesions disappeared at the end of the first course of mogamulizumab.



**Fig. 2.** Histology of left conjunctival lesions. (A, B) Atypical lymphocytes were infiltrating into the substantial propria of the conjunctiva (HE staining, x100, x400). (C) Tumor cells were positive for CD3 (x400). (D) Tumor cells were positive for CD4 (x400). (E) Tumor cells were negative for CD8 (x400). (F) Tumor cells were negative for CD20 (x400). (G) Tumor cells were negative for TIA1 (x400). (H) The Ki-67 labeling index was approximately 30-40% (x400).

**DISCUSSION**

Ophthalmological diseases caused by HTLV-1 infection encompass direct invasion of ATLL,<sup>8-18</sup> HTLV-1-related uveitis,<sup>19</sup> and cytomegalovirus retinitis,<sup>13</sup> as per the reports available to date. Conditions of ATLL infiltration into the eye are classified as ocular adnexal lymphoma and intraocular lymphoma. Previous reports suggested that in cases of intraocular lymphoma, ATLL infiltration into the central nervous system is higher than in cases of ocular adnexal lymphoma.<sup>8-18</sup> In the present patient, mLSG15 therapy was not efficacious, and bulbar conjunctival lesions were observed during treatment for cytomegalovirus enteritis. Conjunctival biopsy revealed infiltration of atypical lymphocytes, although there was no evidence of cytomegalovirus infection. No central nervous infiltration was observed during the clinical course in this patient.

Ocular adnexal lymphoma associated with ATLL is rare, and only 7 cases have been reported.<sup>8-14</sup> This may be due to the publication bias because ATLL is well-known to infiltrate extranodal organs. Table 1 shows the clinical manifestations in previous reports and our report. The specific infiltration sites of ocular lesions were the orbit,<sup>8</sup> eyelid and conjunctiva,<sup>9</sup> eyelid, iris and orbit,<sup>10</sup> orbit and choroidal folds,<sup>11</sup> conjunctiva,<sup>12</sup> eyelid<sup>13</sup> and conjunctiva.<sup>14</sup> Four cases were bilateral infiltration<sup>8,10,13,14</sup> and three cases were unilateral infiltration.<sup>9,11,12</sup> In the previously reported cases, three were classified as acute type, one as chronic type, and one as lymphoma type, according to the Shimoyama classification. Infiltration of atypical lymphocytes (flower cells) in peripheral blood was found in 5 cases (83.3%, 5/6). There is only one reported case of primary ocular lymphoma.<sup>11</sup>

The pathogenic mechanism of ocular infiltration of ATLL is not clear. It has been reported that the expression of CXC chemokine receptor 4 (CXCR4)/C-X-C motif chemokine 12 (CXCL12),  $\alpha 4$  integrin, and Sphingosine-1-phosphate receptor 3 (S1PR3) is higher in ocular adnexal lymphoma in B-cell lymphoma than lymph node infiltration in B-cell lymphoma cases.<sup>20</sup> In ocular adnexal lymphoma of ATLL cases, there is a possibility that these molecules are involved in cell trafficking for ocular infiltration.

Salmon patch-like appearance is a characteristic macroscopic finding of conjunctival B-cell lymphoma.<sup>21</sup> This was a characteristic macroscopic finding in all cases of conjunctival ATLL, including in our patient and three previously reported cases.<sup>9,11,14</sup> This was considered to be caused by lymphocyte infiltration into the substantial propria of the conjunctiva.<sup>22</sup> In our patient, this appearance suggested the infiltration of ATLL cells into the substantial propria of the conjunctiva. Therefore, irrespective of histological lymphoma subtype, salmon patch-like appearance is indicative of conjunctival lymphoma.

In summary, we here described a patient with acute type ATLL complicated by bulbar conjunctival infiltration. The conjunctival lesions were rapidly and successfully treated with mogamulizumab therapy. Salmon patch-like appearance of the affected area of the conjunctiva may indicate ATLL infiltration into the conjunctiva.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest in this study.

**Table 1.** Clinical manifestations of ocular adnexal lymphoma in ATLL

Case	Age (y)	Sex	Symptoms	ATLL subtype	PB infiltration	Location	Localized or Systemic	Unilateral or Bilateral	Therapy	Therapy effect	Outcome
1	41	M	Pain behind the eye	Acute	+	Orbit	Systemic	Unilateral	Radiation	NA	Dead/disease progression
2	77	F	NA	NA	+	Eyelid, Conjunctiva	Systemic	Bilateral	NA	NA	NA
3	43	F	Blurred vision	Acute	+	Eyelid, Iris, Orbit	Systemic	Bilateral	VP16, VDS and CBDCA	+	NA
4	64	M	Swelling	Lymphoma	-	Orbit, Choroidal folds	Localized	Unilateral	CHOP	+	Alive 1 years
5	29	M	Blurred vision	NA	+	Conjunctiva	Systemic	Bilateral	NA	NA	NA
6	53	M	NA	NA	NA	Eyelid	NA	Unilateral	NA	NA	NA
7	36	F	Conjunctival hyperemia	Chronic	+	Conjunctiva	Systemic	Bilateral	VP16	+	Dead/disease progression
Our case	73	F	Pain	Acute	+	Conjunctiva	Systemic	Unilateral	Mogamulizumab	+	Dead/disease progression

M, Male. F, Female. NA, Not available.

Case1 (Ref 8), Case2 (Ref 9), Case3 (Ref 10), Case4 (Ref 11), Case5 (Ref 12), Case6 (Ref 13), Case7 (Ref 14).

## REFERENCES

- 1 Shimoyama M: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. A report from the Lymphoma Study Group (1984-87). *Br J Haematol* 79 : 428-437, 1991
- 2 Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, *et al.*: VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. *J Clin Oncol* 25 : 5458-5464, 2005
- 3 Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, *et al.*: Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 30 : 837-842, 2012
- 4 Moslehi R, Schymura MJ, Nayak S, Coles FB: Ocular adnexal non-Hodgkin's lymphoma: a review of epidemiology and risk factors. *Expert Rev Ophthalmol* 6 : 181-193, 2011
- 5 Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphoma. *Cancer* 29 : 252-260, 1972
- 6 Knowles DM, Jakobiec FA, McNally L, Burke JS: Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. *Hum Pathol* 21 : 959-973, 1990
- 7 Ferry JA, Fung CY, Zukerberg L, Lucarelli MJ, Hasserjian RP, *et al.*: Lymphoma of the ocular adnexa: A study of 353 cases. *Am J Surg Pathol* 31 : 170-184, 2007
- 8 Lauer SA, Fischer J, Jones J, Gartner S, Dutcher J, *et al.*: Orbital T-cell lymphoma in human T-cell leukemia virus-1 infection. *Ophthalmol* 95 : 110-115, 1988
- 9 Takahashi K, Sakuma T, Onoe S, Akasaka T, Tazawa Y: Adult T-cell leukemia with leukemic cell infiltration in the conjunctiva. A case report. *Doc Ophthalmol* 83 : 255-260, 1993
- 10 Kohno T, Uchida H, Inomata H, Fukushima S, Takeshita M, *et al.*: Ocular manifestations of adult T-cell leukemia/lymphoma. A clinicopathological study. *Ophthalmol* 100 : 1794-1799, 1993
- 11 Yoshikawa T, Ogata N, Takahashi K, Mori S, Uemura Y, *et al.*: Bilateral orbital tumor as initial presenting sign in human T-cell leukemia virus-1 associated adult T-cell leukemia/lymphoma. *Am J Ophthalmol* 140 : 327-329, 2005
- 12 Buggage RR, Smith JA, Shen D, Chan CC: Conjunctival T-cell lymphoma caused by human T-cell lymphotropic virus infection. *Am J Ophthalmol* 131 : 381-383, 2011
- 13 Ohba N, Matsumoto M, Sameshima M, Kabayama Y, Nakano K, *et al.*: Ocular manifestations in patients infected with human T-lymphotropic virus type 1. *Jpn J Ophthalmol* 33 : 1-12, 1989
- 14 Kamoi K, Nagata Y, Mochizuki M, Kobayashi D, Ohno N, *et al.*: Formation of Segmental Rounded Nodules During Infiltration of Adult T-Cell Leukemia Cells Into the Ocular Mucous Membrane. *Cornea* 35 : 137-139, 2016
- 15 Kumar SR, Gill PS, Wagner DG, Dugel PU, Moudgil T, *et al.*: Human T-cell lymphotropic virus type 1-associated retinal lymphoma. A clinicopathologic report. *Arch Ophthalmol* 112 : 954-959, 1994
- 16 Mori A, Deguchi HE, Mishima K, Kitaoka T, Amemiya T: A case of uveal, palpebral, and orbital invasions in adult T-cell leukemia. *Jpn J Ophthalmol* 47 : 599-602, 2003
- 17 Shibata K, Shimamoto Y, Nishimura T, Okinami S, Yamada H, *et al.*: Ocular manifestations in adult T-cell leukemia/lymphoma. *Ann Hematol* 74 : 163-168, 1997
- 18 Levy-Clarke GA, Buggage RR, Shen D, Vaughn LO, Chen CC, *et al.*: Human T-cell lymphotropic virus type-1-associated t-cell leukemia/lymphoma masquerading as necrotizing retinal vasculitis. *Ophthalmol* 109 : 1717-1722, 2002
- 19 Mochizuki M, Tajima K, Watanabe T, Yamaguchi K : Human T lymphotropic virus type 1 uveitis. *Br J Ophthalmol* 78 : 149-154, 1994
- 20 Middle S, Coupland SE, Taktak A, Kidgell V, Slupsky JR, *et al.*: Immunohistochemical analysis indicates that the anatomical location of B-cell non-Hodgkin lymphoma is determined by differentially expressed chemokine receptors, sphingosine-1-phosphate receptors and integrins. *Exp Hematol Oncol* 4 : 10, 2015
- 21 Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, *et al.*: Conjunctival Tumors: Review of Clinical Features, Risks, Biomarkers, and Outcomes—The 2017 J. Donald M. Gass Lecture. *Asia Pac J Ophthalmol (Phila)* 6 : 109-120, 2017
- 22 Jakobiec FA.: Ocular adnexal lymphoid tumors: progress in need of clarification. *Am J Ophthalmol* 145 : 941-950, 2008