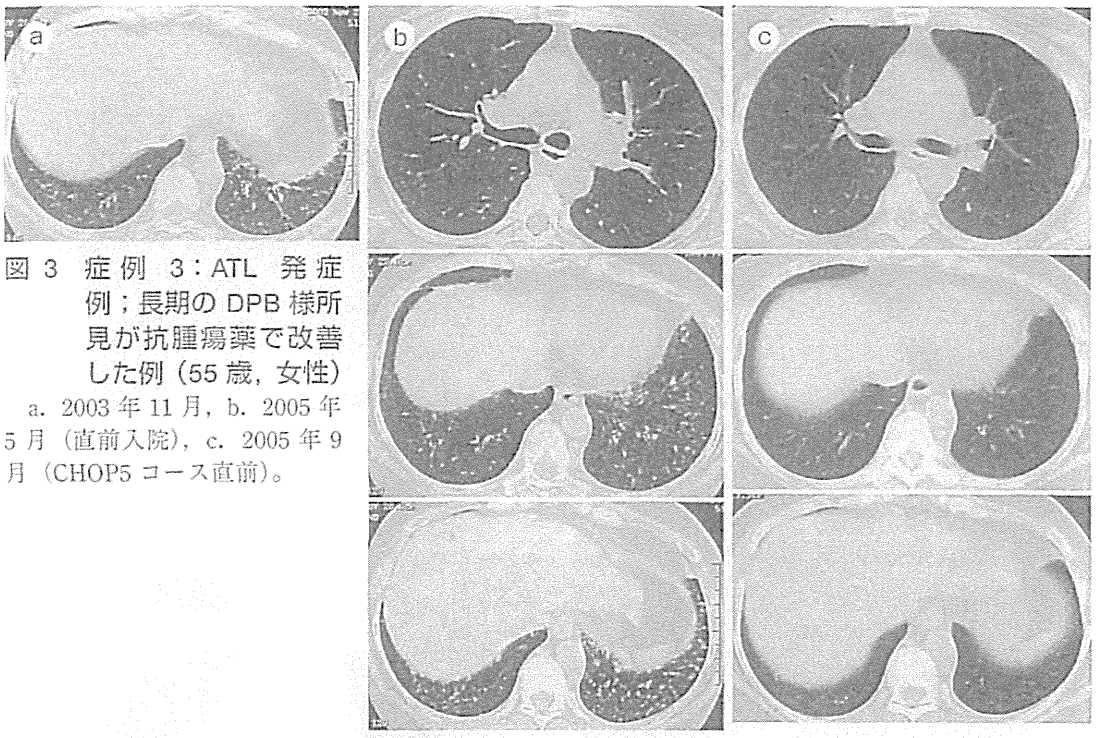

図 3　症例 3：ATL 発症例；長期の DPB 様所見が抗腫瘍薬で改善した例（55 歳，女性）
a. 2003 年 11 月，b. 2005 年 5 月（直前入院），c. 2005 年 9 月（CHOP5 コース直前）。

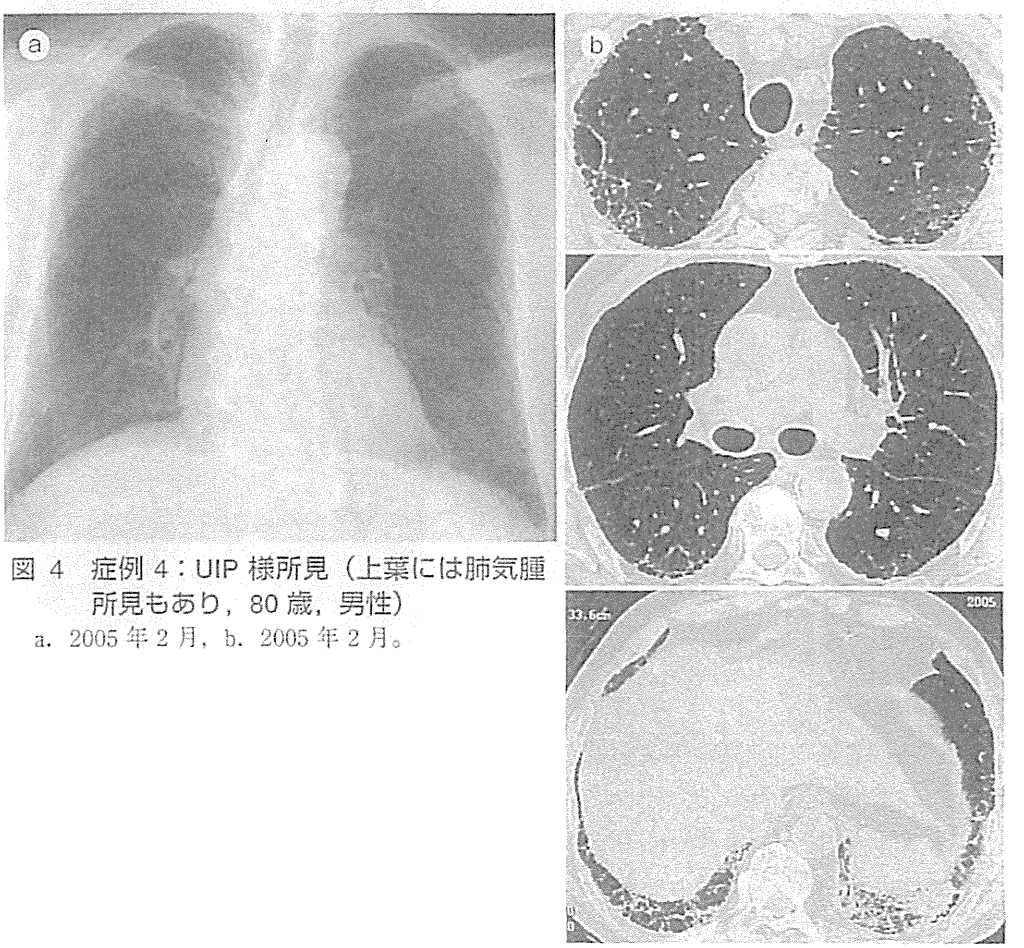

図 4　症例 4：UIP 様所見（上葉には肺気腫所見もあり，80 歳，男性）
a. 2005 年 2 月，b. 2005 年 2 月。

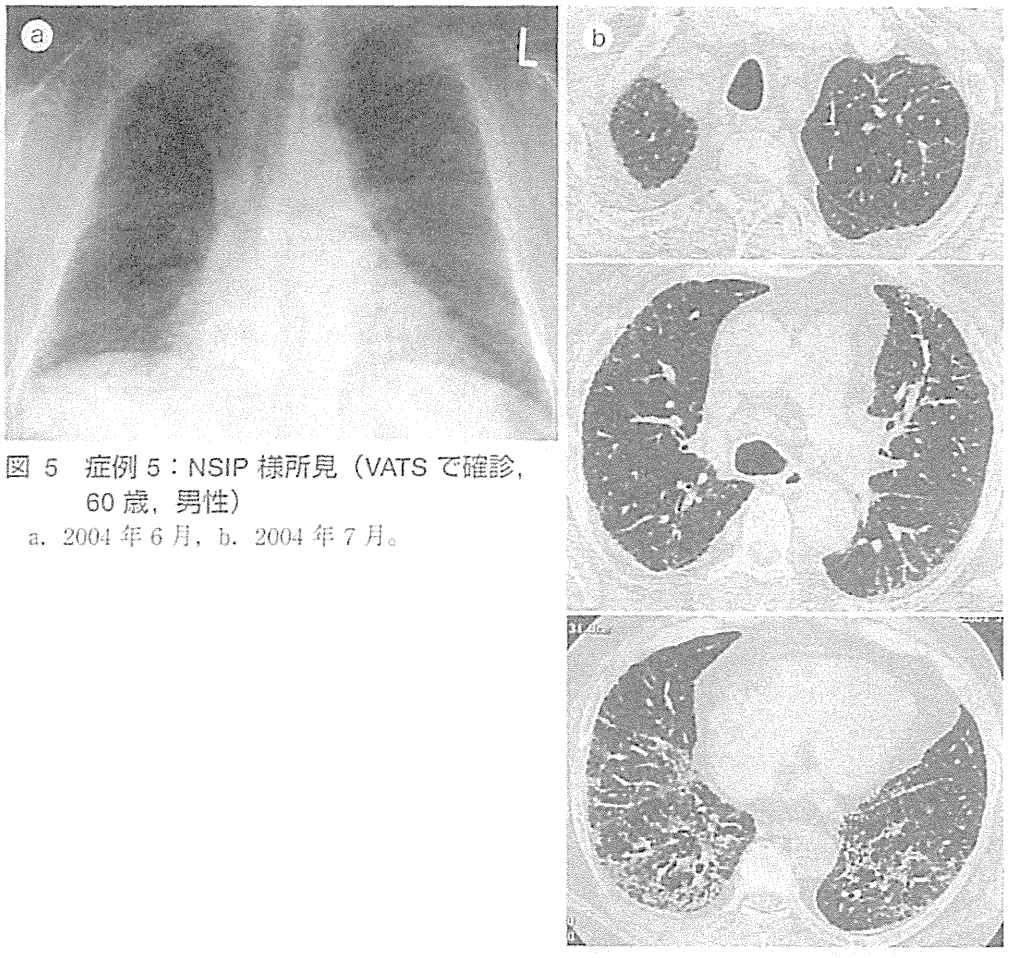

図 5　症例 5：NSIP 様所見（VATS で確診，60 歳，男性）
a. 2004 年 6 月，b. 2004 年 7 月。

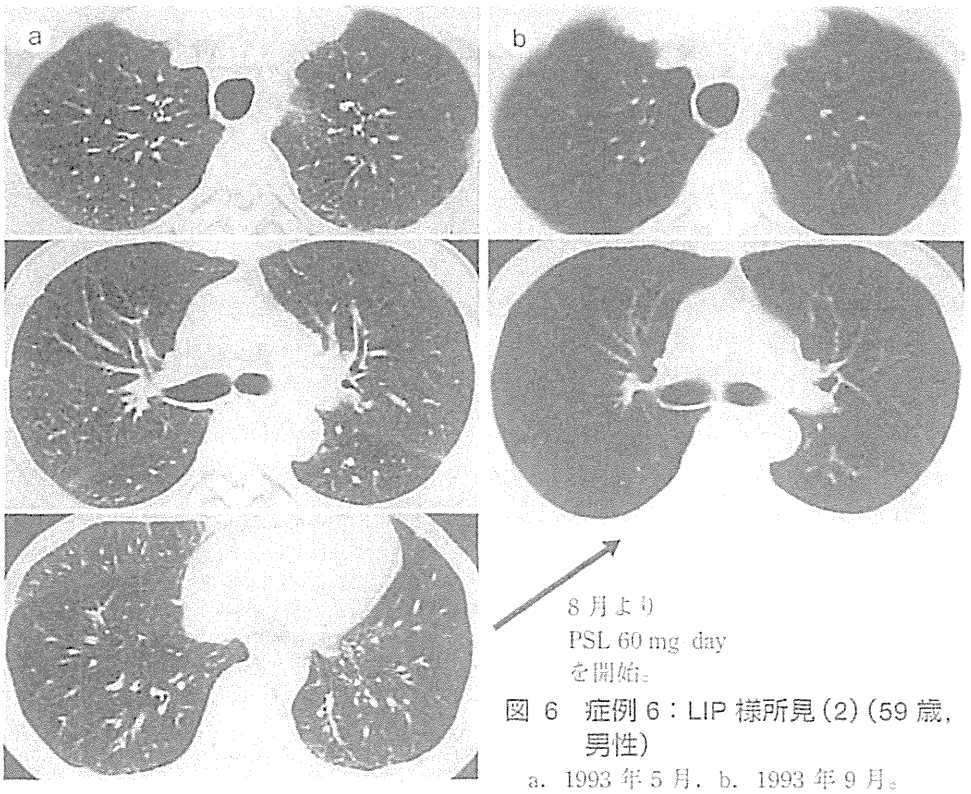

図 6　症例 6：LIP 様所見 (2) (59 歳，男性)
a. 1993 年 5 月，b. 1993 年 9 月。

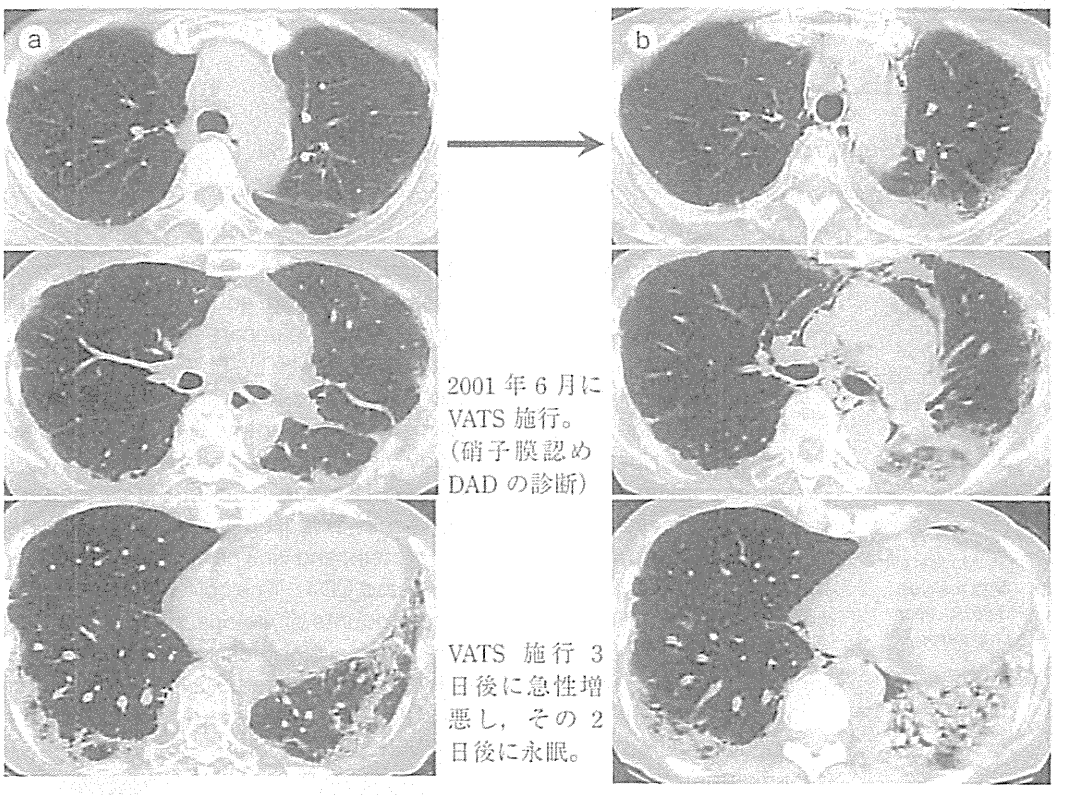

図 7　症例 7：AIP 所見（63 歳，女性）
a. 2001 年 6 月，b. a. の 15 日後。

disorder). 日胸疾患会誌 1992；30：787-95.
4) Sugimoto M, Kitaichi M, Ikeda A, et al. Chronic bronchioalveolitis associated with human T-cell lymphotropic virus type I infection. Curr Opin Pulm Med 1998；4：283-93.
5) Kadota J, Mukae H, Fujii T, et al. Clinical similarities and differences between human T-Cell lymphotropic virus type 1-associated bronchiolitis and diffuse panbronchiolitis. Chest 2004；125：1239-47.
6) Yamamoto M, Matsuyama W, Oonakahara K, et al. Infuruence of human T lymhotropic virus type I on diffuse pan-bronchiolitis. Clin Exp Immunol 2004；136：513-20.
7) 迎　　寛，東山康仁，森川　透，ほか．びまん性汎細気管支炎における HTLV-Ⅰ感染の関与．日胸疾患会誌 1994；32：17-24.
8) 兼島　洋，大城　元，宮国孝彦，ほか．慢性気道疾患での抗 HTLV-Ⅰ抗体陽性者と陰性者の臨床的比較検討．日胸 1995；54：386-93.
9) 緒方彩子，濱田直樹，前山隆茂，ほか．診断に BAL が有用と考えられたくすぶり型成人 T 細胞白血病合併間質性肺炎の 1 例．日呼吸会誌 2010；48：293-7.
10) Liu M, Yang L, Zhang L, et al. Human T-cell leukemia virus type 1 infection leads to arrest in the G1 phase of the cell cycle. J Virol 2008；82：8442-55.
11) Teruya H, Tomita M, Senba M, et al. Human T-cell leukemia virus type I infects human lung epithelial cells and induces gene expression of cytokines, chemokines and cell adhesion molecules. Retrovirology 2008；5：86.
12) Boxus M, Willems L. Mechanisms of HTLV-1 persistence and transformation. Br J Cancer 2009；101：1497-501.
13) Yamazato Y, Miyazato A, Kawakami K, et al. High expression of p40tax and pro-inflammatory cytokines and chemokines in the lungs of human T-lymphotropic virus type 1-related bronchopulmonary disorders. Chest 2003；124：2283-92.

frontiers in
MICROBIOLOGY

MINI REVIEW ARTICLE
published: 24 July 2012
doi: 10.3389/fmicb.2012.00270

HTLV-1 uveitis

Koju Kamoi and Manabu Mochizuki*

Department of Ophthalmology and Visual Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Edited by:
Toshiki Watanabe, The University of Tokyo, Japan

Reviewed by:
Hidekatsu Iha, Oita University, Japan
Xin Geng, University of California, USA

****Correspondence:***
Manabu Mochizuki, Department of Ophthalmology and Visual Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
e-mail: m.manabu.oph@tmd.ac.jp

Human T cell lymphotropic virus type 1 (HTLV-1) is the first retrovirus described as a causative agent of human disease. Following adult T cell leukemia/lymphoma and HLTV-1-associated myelopathy/tropical spastic paraparesis, HTLV-1 uveitis (HU) has been established as a distinct clinical entity caused by HTLV-1 based on seroepidemiological, clinical, and virological studies. HU is one of the most common causes of uveitis in endemic areas of Japan and can be a problematic clinical entity all over the world. HU occurs with a sudden onset of floaters and foggy vision, and is classified as an intermediate uveitis. Analysis of infiltrating cells in eyes with HU revealed that the majority of infiltrating cells were $CD3^+$ T cells, but not malignant cells or leukemic cells based on their T cell receptor usage. HTLV-1 proviral DNA, HTLV-1 protein, and viral particles were detected from infiltrating cells in eyes with HU. HTLV-1-infected $CD4^+$ T cell clones established from infiltrating cells in eyes with HU produced large amounts of various inflammatory cytokines, such as IL-1, IL-6, IL-8, TNF-α, and interferon-γ. Taken together, HU is considered to be caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in eyes; therefore, topical and/or oral corticosteroid treatment is effective to treat intraocular inflammation in patients with HU. Further investigation is needed to establish a specific treatment for HU.

Keywords: HTLV-1, uveitis, ocular inflammation, $CD4^+$ T cell, T cell clone

INTRODUCTION

Retrovirus was first described in the 1970s (Temin and Baltimore, 1972), but its causal relationship with human diseases was not identified until the early 1980s when human T cell lymphotropic virus type 1 (HTLV-1) was identified as an etiologic agent of adult T cell leukemia/lymphoma (ATL; Poiesz et al., 1980; Hinuma et al., 1981; Yoshida et al., 1984). After the discovery of the link between HTLV-1 and ATL, HLTV-1 was also found to be a causal agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP; Gessain et al., 1985; Osame et al., 1986) and HTLV-1 uveitis (HU; Mochizuki et al., 1992a,b,c).

HTLV-1 uveitis, the third clinical entity of HTLV-1 infection, was established by a series of studies in the highly endemic area of southern Kyushu, Japan. Clinical case reports from this area suggested possible associations of HTLV-1 carriers with various ocular manifestations (Ohba et al., 1989). In the 1990s, the first set of evidence that indicated the causative implication of HTLV-1 in uveitis was reported by Mochizuki and colleagues. They showed clinical and laboratory data consisting of seroepidemiology, clinical features, detection of proviral DNA and mRNA of HTLV-1 from ocular tissues, and detection of viral particles from T cell clones (TCC) derived from the aqueous humor of the patient (Mochizuki et al., 1992a,b). Since then, it has been well established that uveitis is significantly related to HTLV-1. Here, we review historical findings that contributed to the establishment of the HU entity and recent advancements that deepen our understanding of HU.

SEROEPIDEMIOLOGY

HTLV-1 infection is known to have unique geographic distribution and is prevalent in Japan, Melanesia, the Caribbean Islands, Central America, South America, and Central Africa. It is estimated that 20 million people carry the virus worldwide (Watanabe, 2011). This virus is etiologically linked with HU, which is one of the most common causes of uveitis in the endemic area of Japan and can be a problematic clinical entity all over the world (Yoshimura et al., 1993; Takahashi et al., 2000; Merle et al., 2002; Pinheiro et al., 2006; Miyanaga et al., 2009). Uveitis is a sight-threatening inflammatory disorder affecting the intraocular tissues (Forrester, 1991) and is the third leading cause of blindness in developed countries. The etiology of uveitis is categorized as infectious or non-infectious and varies depending on the genetic background of the population and the prevalence of the pathogenic agent in the area. Clinically, the etiology of approximately 30% of cases could not be defined even when careful examinations were performed. A survey comparing the etiologies of uveitis in different areas of Japan demonstrated that the proportion of undefined etiologies was particularly high in southern Kyushu as compared to those in northern Kyushu and Tokyo. Seroepidemiological comparison studies (Mochizuki et al., 1992a,b; Shirao et al., 1993) in these highly endemic and non-endemic areas revealed that the HTLV-1 seroprevalence in patients with idiopathic uveitis was significantly higher than that in the following two control groups: patients with etiology-defined uveitis and patients with non-uveitic ocular diseases (**Figure 1**). This was the first clue suggesting that HTLV-1 infection is significantly related to uveitis. Uveitis is now recognized as a distinct clinical entity related to HTLV-1 and is designated as HU. The seroprevalence of HTLV-1 in the general Japanese population is known to have decreased after serological screening tests of HTLV-1 in blood donors started

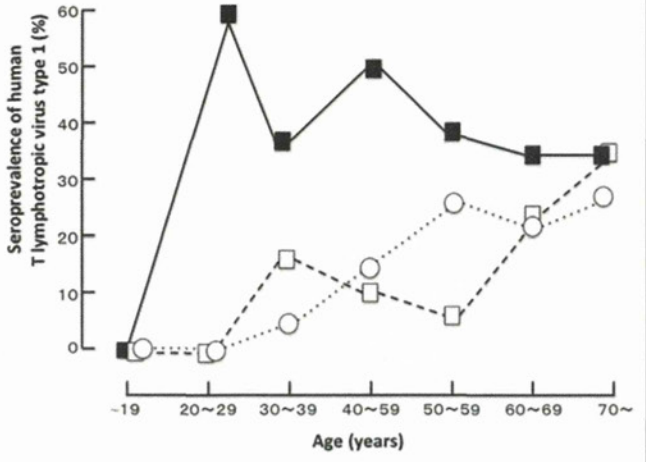

FIGURE 1 | The age distribution of the seroprevalence of human T cell lymphotropic virus type 1 in a highly endemic area (Miyakonojo, southern Kyushu, Japan; Shirao et al., 1993 with permission). ■, patients with idiopathic uveitis; □, patients with uveitis from a defined cause; ○, patients with non-uveitic ocular diseases.

in 1987, as blood transfusion and breastfeeding from mother to child are major routes of viral transmission (Iwanaga et al., 2009). A recent survey (Miyanaga et al., 2009) in the HTLV-1 endemic region revealed that the most common clinical entity was still HU, followed by Vogt–Koyanagi–Harada disease, sarcoidosis, and others. However, new cases of HU clearly decreased with time, while the prevalence of Vogt–Koyanagi–Harada disease and sarcoidosis has not changed much in the last two decades. The age distribution of HTLV-1 seroprevalence of all patients with uveitis including HU and of patients with uveitis excluding HU showed that the HTLV-1 seroprevalence increased with age in patients of both groups (Yoshimura et al., 1993; Takahashi et al., 2000; Miyanaga et al., 2009). As for the sex, higher prevalence rates were found in women, especially after 40 years of age. HTLV-1 is known to be transmitted by infected lymphocytes in sperm and this may contribute to the higher prevalence of the disease in women than in men (Yoshimura et al., 1993; Takahashi et al., 2000; Miyanaga et al., 2009). As for the prevalence of HU in different parts of the world, the prevalences of HU in Martinique (Merle et al., 2002) and Brazil (Rathsam-Pinheiro et al., 2009) are lower than that in Japan (Yamamoto et al., 1999; Pinheiro et al., 2006). In general, as migration to metropolitan areas is on the rise, the number of HTLV-1 carriers in metropolitan areas (for example, Tokyo) is significantly increasing (Uchimaru et al., 2008), although the number of carriers is still the highest in the endemic areas. In consideration of this evidence, it is estimated that the number of patients with HU is prospectively increasing in metropolitan areas. Therefore, careful examination concerning HU is needed for the diagnosis of uveitis.

CLINICAL MANIFESTATIONS

A recent report indicated that ocular disturbances may be the first manifestations of HTLV-1 infection to come to clinical attention, in addition to neurologic and rheumatologic signs and symptoms (Poetker et al., 2011). Therefore, all patients presenting for an initial diagnosis should be strictly screened for ocular symptoms. The major symptoms of HU at initial presentation are sudden onset of floaters, foggy vision, and blurred vision. Other symptoms are pain/burning, itching, and foreign body sensation. These symptoms appear in all geographic regions according to studies in Japan, Brazil, and Martinique (Yoshimura et al., 1993; Merle et al., 2002; Pinheiro et al., 2006). Regarding the anatomic diagnosis of uveitis according to the criteria of the International Uveitis Study Group, most patients had an intermediate degree of uveitis with moderate or heavy vitreous opacities (fine cells and lacework-like membranous opacities). The vitreous opacities were the most impressive findings and were accompanied by mild iritis and mild retinal vasculitis, but no uveoretinal lesions (Yoshimura et al., 1993). The ocular inflammation of HU was unilateral or bilateral (Yoshimura et al., 1993; Merle et al., 2002; Pinheiro et al., 2006). An association between HU and Graves' disease has been reported; HU occurs after the onset of Graves' disease in all cases (Yamaguchi et al., 1994). The most recent study (Miyanaga et al., 2009) reported a similar incidence of HU after Graves's disease as that reported by Yamaguchi et al. (1994). Only a few cases of HU develop into HAM/TSP, but no literature has reported that ATL develops in patients with HU during their clinical course. Further patient-tracking research is ongoing to determine whether HU is a risk factor for the development of ATL or HAM/TSP.

DIAGNOSIS

Considering seroepidemiological and clinical studies, the diagnosis of HU should be based on seropositivity for HTLV-1 with no systemic evidence of HTLV-1-related diseases (such as ATL or HAM/TSP) and exclusion of other uveitis entities with defined causes. Therefore, all clinical entities of uveitis with defined causes should be excluded by careful ophthalmic and systemic examinations. Patients with HU should not have ophthalmic and systemic symptoms that are compatible with other types of uveitis such as Behçet's disease, Vogt–Koyanagi–Harada syndrome, and sarcoidosis.

PATHOGENESIS

Eye research has progressed significantly in accordance with the development of modern molecular biological technology, such as the polymerase chain reaction and flow cytometry. Many fundamental findings have been obtained in the study of HU pathogenesis. The cells floating in the anterior chamber of the eye with HU consisted of lymphocytes with a small proportion of macrophages. No malignant cells or leukemic cells were detected in the aqueous humor of the patients with HU (Masuoka et al., 1995). The majority of infiltrating cells in the aqueous humor of patients with HU were $CD3^+$ T cells (Ono et al., 1997). Analysis by polymerase chain reaction of ocular-infiltrating cells revealed that HTLV-1 proviral DNA was detected in almost all patients with HU. However, proviral DNA was not detected in patients with uveitis of other defined etiology who were seropositive for HTLV-1. These data suggest that HTLV-1-infected cells are present at the local site of HU (Ono et al., 1997). Furthermore, expression of viral mRNA was detected by

reverse transcriptase-polymerase chain reaction from the inflammatory cells in the aqueous humor. More direct evidence of HTLV-1 in the pathogenesis of HU has been provided by using TCC derived from intraocular tissues of eyes with HU. Proviral DNA of HTLV-1 was identified in TCC from the ocular fluid (Sagawa et al., 1995). Immunohistochemical staining showed that HTLV-1 env and gag proteins were detectable in HTLV-1 provirus-positive TCC. Furthermore, electron microscopic observation of the TCC identified HTLV-1 virus particles, the mean diameter of which was 102 nm (Sagawa et al., 1995). Most HTLV-1-infected TCC had a $CD3^+CD4^+CD8^-$ phenotype and had polyclonal TCRα usage (Sagawa et al., 1995). The HTLV-1-infected TCC produced significant amounts of IL-1α, IL-2, IL-3, IL-6, IL-8, IL-10, TNF-α, IFN-γ, and GM-CSF, which are potent cytokines capable of inducing immune reactions and inflammation at the intraocular tissue level (Sagawa et al., 1995). These data suggest that cytokine production by HTLV-1-infected T cells in intraocular tissues is responsible for intraocular inflammation, i.e., uveitis (**Figure 2**). In addition to this molecular biological/immunological evidence, virological research supported the pathogenicity of HTLV-1 in the eye by the following three pieces of evidence: (1) the HTLV-1 provirus load in patients with HU is significantly higher than that in asymptomatic carriers without uveitis (Ono et al., 1995); (2) the proviral load in peripheral blood mononuclear cells correlates with the intensity of intraocular inflammation (Ono et al., 1998); and (3) the proviral load in the eyes of patients with HU is significantly higher than that present in peripheral blood mononuclear cells (Ono et al., 1997). Serologic data showed that the antibody level against HTLV-1 in patients with HU was similar to that in asymptomatic carriers of HTLV-1, but was lower than that in patients with HTLV-1-associated myelopathy (Mochizuki et al., 1992b). Antibody to the virus in the aqueous humor was also detected in all tested samples from patients with HU. Flow cytometry analysis indicated that the CD4 fraction was elevated and the CD8 fraction was decreased in peripheral lymphocytes from patients with HU, thereby elevating the CD4/8 ratio in the HU group as compared with the seronegative group. Furthermore, the CD25 fraction of T lymphocytes with expression of interleukin 2 receptors was significantly elevated in patients with HU. The serum levels of soluble interleukin 2 receptors (sIL2R or sCD25) were also significantly higher in patients with HU than in seronegative healthy controls (Yoshimura et al., 1993). Taken together, these laboratory data suggest that the immune-mediated mechanism, particularly involving $CD4^+$ T cells, plays a critical role in the pathogenesis of HU.

THERAPY

Immunopathogenesis studies of HU showed that the majority of ocular-infiltrating cells are inflammatory cells, but not malignant cells. Also, a series of studies showed that HU is caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in the eyes of the patients. Furthermore, the addition of corticosteroids in the culture medium suppressed the cytokine production (Sagawa et al., 1995). Therefore, corticosteroid treatment is effective for treating the intraocular inflammation of patients with HU by suppressing the cytokine production of HTLV-1-infected $CD4^+$ T cells. Clinical management should be performed according to the degree of ocular inflammation. HU with a mild degree of ocular inflammation can be managed by topical non-corticosteroidal or corticosteroidal anti-inflammatory drugs. A sub-Tenon's injection of corticosteroids may be used when the patients have moderate inflammatory activity in the vitreous cavity. If the vitreous inflammatory activity and the retinal vasculitis are severe, oral corticosteroids should be given, but the long-term administration of a systemic corticosteroid should be avoided. In most cases, intraocular inflammation is markedly improved with these therapies and complete remission is achieved. The visual prognosis for cases of HU is generally good with these corticosteroid treatments, although approximately 60% of patients experience recurrences of uveitis (Yoshimura et al., 1993).

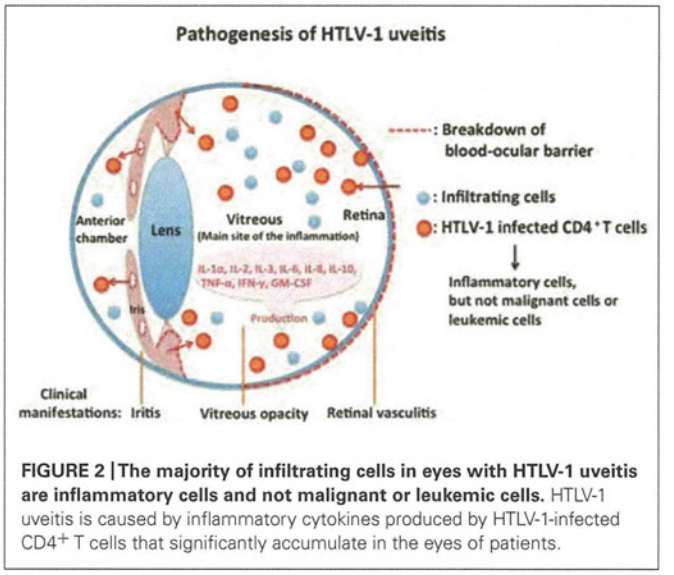

FIGURE 2 | The majority of infiltrating cells in eyes with HTLV-1 uveitis are inflammatory cells and not malignant or leukemic cells. HTLV-1 uveitis is caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in the eyes of patients.

CONCLUSION

We reviewed the seroepidemiological, clinical, molecular biological, and virological studies that established the HU entity and clarified the immunopathogenesis and the clinical management of HU. Corticosteroid is the only effective treatment for HU to suppress the cytokines produced by infiltrating HTLV-1-infected cells; however, it is unknown whether long-term corticosteroid treatment adversely affects patients with HU. Many mechanisms in HU remain unclear, such as how HTLV-1-infected $CD4^+$ cells break down the ocular blood barrier and why the vitreous humor is the major site of inflammation (**Figure 2**). We may be able to find more effective treatments if we can understand the mechanism of HU in more detail. Recent studies have shown new insights into HTLV-1 infection and pathogenesis by pursuing the molecular functions of HTLV-1 basic leucine zipper factor and Tax (Yasunaga and Matsuoka, 2011). However, few studies have been conducted to apply these new findings to HU research. Further investigation is needed to establish a specific treatment for HU. HU results from HTLV-1 infection; therefore, the most important means of preventing this disease is by spreading the knowledge about HTLV-1.

REFERENCES

Forrester, J. V. (1991). Uveitis: pathogenesis. *Lancet* 338, 1498–1501.

Gessain, A., Barin, F., Vernant, J. C., Gout, O., Maurs, L., Calender, A., and de Thé, G. (1985). Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* 8452, 407–410.

Hinuma, Y., Nagata, K., Hanaoka, M., Nakai, M., Matsumoto, T., Kinoshita, K. I., Shirakawa, S., and Miyoshi, I. (1981). Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc. Natl. Acad. Sci. U.S.A.* 78, 6476–6480.

Iwanaga, M., Chiyoda, S., Kusaba, E., and Kamihira, S. (2009). Trends in the seroprevalence of HTLV-1 in Japanese blood donors in Nagasaki Prefecture, 2000–2006. *Int. J. Hematol.* 90, 186–190.

Masuoka, K., Sagawa, K., Mochizuki, M., Oizumi, K., and Itoh, K. (1995). Polyclonal use of T-cell receptor alpha for human T-cell lymphotropic virus type 1-infected T cells. *Invest. Ophthalmol. Vis. Sci.* 36, 254–258.

Merle, H., Cabre, P., Olindo, S., Merle, S., and Smadja, D. (2002). Ocular lesions in 200 patients infected by the human T-cell lymphotropic virus type 1 in Martinique (French West Indies). *Am. J. Ophthalmol.* 134, 190–195.

Miyanaga, M., Shimizu, K., Kawaguchi, T., Miyata, K., and Mochizuki, M. (2009). A clinical survey of uveitis in HTLV-1 endemic region. *Ocul. Immunol. Inflamm.* 17, 335–341.

Mochizuki, M., Watanabe, T., Yamaguchi, K., Tajima, K., Yoshimura, K., Nakashima, S., Araki, S., Miyata, N., Mori, S., and Takatsuki, K. (1992a). Uveitis associated with human T-lymphotropic virus type-1 (HTLV-1): seroepidemiologic, clinical, and virological studies. *J. Infect. Dis.* 166, 943–944.

Mochizuki, M., Watanabe, T., Yamaguchi, K., Yoshimura, K., Nakashima, S., Shirao, M., Araki, K., Takatsuki, K., Mori, S., and Miyata, N. (1992b). Uveitis associated with human T cell-lymphotropic virus type 1. *Am. J. Ophthalmol.* 114, 123–129.

Mochizuki, M., Yamaguchi, K., Takatsuki, K., Watanabe, T., Mori, S., and Tajima, K. (1992c). HTLV-1 and uveitis. *Lancet* 399, 1110.

Ohba, N., Matsumoto, M., Sameshima, M., Kabayama, Y., Nakao, K., Unoki, K., Uehara, F., Kawano, K., Maruyama, I., and Osame, M. (1989). Ocular manifestations in patients infected with human T-lymphotropic virus type I. *Jpn. J. Ophthalmol.* 33, 1–12.

Ono, A., Ikeda, E., Mochizuki, M., Matsuoka, M., Yamaguchi, K., Sawada, T., Yamane, S., Tokudome, S., and Watanabe, T. (1998). Provirus load in patients with human T-cell leukemia virus type 1 uveitis correlates with precedent Graves' disease and disease activities. *Jpn. J. Cancer Res.* 89, 608–614.

Ono, A., Mochizuki, M., Yamaguchi, K., Miyata, N., and Watanabe, T. (1995). Increased number of circulating HTLV-1 infected cells in peripheral blood mononuclear cells of HTLV-1 uveitis patients: a quantitative polymerase chain reaction study. *Br. J. Ophthalmol.* 79, 270–276.

Ono, A., Mochizuki, M., Yamaguchi, K., Miyata, N., and Watanabe, T. (1997). Immunologic and virologic characterization of the primary infiltrating cells in the aqueous humor of human T-cell leukemia virus type-1 uveitis. Accumulation of the human T-cell leukemia virus type-1-infected cells and constitutive expression of viral and interleukin-6 messenger ribonucleic acids. *Invest. Ophthalmol. Vis. Sci.* 38, 676–689.

Osame, M., Usuku, K., Izumo, S., Ijichi, N., Amitani, H., Igata, A., Matsumoto, M., and Tara, M. (1986). HTLV-I associated myelopathy: a new clinical entity. *Lancet* 8488, 1031–1032.

Pinheiro, S. R., Martins-Filho, O. A., Ribas, J. G., Catalan-Soares, B. C., Proietti, F. A., Namen-Lopes, S., Brito-Melo, G. E., Carneiro-Proietti, A. B., and Interdisciplinary HTLV-I/II Research Group (GIPH). (2006). Immunologic markers, uveitis, and keratoconjunctivitis sicca associated with human T-cell lymphotropic virus type 1. *Am. J. Ophthalmol.* 20, 1–5.

Poetker, S. K., Porto, A. F., Giozza, S. P., Muniz, A. L., Caskey, M. F., Carvalho, E. M., and Glesby, M. J. (2011). Clinical manifestations in individuals with recent diagnosis of HTLV type I infection. *J. Clin. Virol.* 51, 54–58.

Poiesz, B. J., Ruscetti, F. W., Gazdar, A. F., Bunn, P. A., Minna, J. D., and Gallo, R. C. (1980). Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc. Natl. Acad. Sci. U.S.A.* 77, 7415–7419.

Rathsam-Pinheiro, R. H., Boa-Sorte, N., Castro-Lima-Vargens, C., Pinheiro, C. A., Castro-Lima, H., and Galvão-Castro, B. (2009). Ocular lesions in HTLV-1 infected patients from Salvador, State of Bahia: the city with the highest prevalence of this infection in Brazil. *Rev. Soc. Bras. Med. Trop.* 42, 633–637.

Sagawa, K., Mochizuki, M., Masuoka, K., Katagiri, K., Katayama, T., Maeda, T., Tanimoto, A., Sugita, S., Watanabe, T., and Itoh, K. (1995). Immunopathological mechanisms of human T cell lymphotropic virus type 1 (HTLV-I) uveitis. Detection of HTLV-I-infected T cells in the eye and their constitutive cytokine production. *J. Clin. Invest.* 95, 852–858.

Shirao, M., Yoshimura, K., Mochizuki, M., Araki, S., Miyata, N., Yamaguchi, K., Takatsuki, K., Watanabe, T., Mori, S., and Tajima, K. (1993). Uveitis in human T-lymphotropic virus type I (HTLV-I) carriers-1. A seroepidemiological study. *Nippon Ganka Gakkai Zasshi* 97, 726–732.

Takahashi, T., Takase, H., Urano, T., Sugita, S., Miyata, K., Miyata, N., and Mochizuki, M. (2000). Clinical features of human T-lymphotropic virus type 1 uveitis: a long-term follow-up. *Ocul. Immunol. Inflamm.* 8, 235–241.

Temin, H. M., and Baltimore, D. (1972). RNA-directed DNA synthesis and RNA tumor viruses. *Adv. Virus Res.* 17, 129–186.

Uchimaru, K., Nakamura, Y., Tojo, A., Watanabe, T., and Yamaguchi, K. (2008). Factors predisposing to HTLV-1 infection in residents of the greater Tokyo area. *Int. J. Hematol.* 88, 565–570.

Watanabe, T. (2011). Current status of HTLV-1 infection. *Int. J. Hematol.* 94, 430–434.

Yamaguchi, K., Mochizuki, M., Watanabe, T., Yoshimura, K., Shirao, M., Araki, S., Miyata, N., Mori, S., Kiyokawa, T., and Takatsuki, K. (1994). Human T lymphotropic virus type 1 uveitis after Graves' disease. *Br. J. Ophthalmol.* 78, 163–166.

Yamamoto, J. H., Segurado, A. A., Hirata, C. E., Sampaio, M. W., Souza, E. C., Ukui, Y., Cliquet, M., Saéz-Alquézar, A., Olivalves, E., and Mochizuki, M. (1999). Human T-lymphotropic virus type 1 infection and ocular manifestations in São Paulo, Brazil. *Arch. Ophthalmol.* 117, 513–517.

Yasunaga, J., and Matsuoka, M. (2011). Molecular mechanisms of HTLV-1 infection and pathogenesis. *Int. J. Hematol.* 94, 435–442.

Yoshida, M., Seiki, M., Yamaguchi, K., and Takatsuki, K. (1984). Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia virus in the disease. *Proc. Natl. Acad. Sci. U.S.A.* 81, 2534–2537.

Yoshimura, K., Mochizuki, M., Araki, S., Miyata, N., Yamaguchi, K., Tajima, K., and Watanabe, T. (1993). Clinical and immunologic features of human T-cell lymphotropic virus type I uveitis. *Am. J. Ophthalmol.* 116, 156–163.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 May 2012; paper pending published: 22 May 2012; accepted: 10 July 2012; published online: 24 July 2012.

Citation: Kamoi K and Mochizuki M (2012) HTLV-1 uveitis. Front. Microbio. 3:270. doi: 10.3389/fmicb.2012.00270

This article was submitted to Frontiers in Virology, a specialty of Frontiers in Microbiology.

REVIEW

HTLV infection and the eye

Koju Kamoi and Manabu Mochizuki

Purpose of review
Human T-cell lymphotropic virus (HTLV) is the first discovered retrovirus causing malignancy in human. HTLV infection affects host's ocular tolerance and causes various diseases in the eye. Here we discuss the manifestations, mechanisms, treatments, and future directions of HTLV-related ocular diseases.

Recent finings
Recent serological researches showed that the number of HTLV-1 carriers in metropolitan area was increasing, although seroprevalence of HTLV-1 in general population was decreased after screening serological tests in blood donors started. The most common clinical entity of uveitis was still HTLV-1 uveitis in HTLV-1 highly endemic area, but prevalence of HTLV-1 uveitis varies in different parts of the world. As for treatment of inflammation, tacrolimus and 5-azacytidine were reported to be effective for autoimmune manifestations in HTLV-1-related overlap syndrome (deratomyositis/Sjogren's syndrome) and HTLV-1-related myelodysplastic syndrome. Interleukin-2 receptor targeted therapies improved scleritis in patients with adult T-cell leukemia/lymphoma caused by HTLV-1. Basic researches identified that HTLV-1 tax and HTLV-1 basic leucine zipper factor play critical roles in the HTLV-1-related disease and are now being investigated as targeted therapies.

Summary
Development of modern molecular biology makes it possible to reveal deep insights of HTLV-1-related ocular diseases. Although effective therapies based on basic researches have been reported, further endeavor is necessary to establish much more specific treatments of the ocular diseases.

Keywords
adult T-cell leukemia/lymphoma, Keratoconjunctivitis sicca, HTLV-1 basic leucine zipper factor, HTLV-1 tax, HTLV-1 uveitis

INTRODUCTIONS

Retrovirus is a RNA virus encoding for a reverse transcriptase, which translate the viral RNA into a DNA provirus, which in turn is rapidly incorporated into the host's genome [1]. Retroviruses are currently classified into oncoviruses and lentiviruses. Oncoviruses are associated with haematological proliferations and tumours of connective tissues in animal species. Human T-cell lymphotropic viruses (HTLVs) are the representative viruses and HTLV-1 was the first retrovirus described as a causative agent of human disease [2,3]. Lentivirus induces chronic and progressive pulmonary and/or neurological diseases in animal species. The representative virus in human is HIV, which was previously named HTLV-3 and now reclassified into HIV and is a causative agent of AIDS [1].

Human retrovirus (HTLV/HIV) infection affects on host's ocular tolerance, which results in various diseases, particularly uveitis [4–6]. Although HIV-related ocular manifestations are well known among ophthalmologists, their knowledge of HTLV-related ocular manifestation seems to be insufficient. The information of HTLV infection is now important because a recent survey indicates that HTLV-1 carriers are estimated to spread from local endemic areas to nonendemic metropolitan areas [7]. Therefore, we believe that this review of HTLV might be enough for ophthalmic practice and hope that this might highlight scientific attention to HTLV-1 infection among ophthalmologists.

Department of Ophthalmology & Visual Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Tokyo, Japan

Correspondence to Professor Manabu Mochizuki, Department of Ophthalmology & Visual Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan. Tel: +81 3 5803 5296; e-mail: m.manabu.oph@tmd.ac.jp

Curr Opin Ophthalmol 2012, 23:557–561
DOI:10.1097/ICU.0b013e328358b9ec

KEY POINTS

- HTLV-1 carriers are estimated to spread from local endemic areas to nonendemic metropolitan areas.
- HTLV-1 ocular manifestations can be mainly classified into three groups, uveitis, opportunistic infection/malignant infiltration of the eye in ATL patients and keratoconjunctivitis sicca.
- The most frequent ocular manifestation of HTLV-1 infection that ophthalmologists should keep in mind is HTLV-1 uveitis.
- HTLV-1 tax and HTLV-1 basic leucine zipper factor (HBZ) are thought to be responsible for immune dysregulation and may contribute to ocular manifestations.

HUMAN T-CELL LYMPHOTROPIC VIRUS INFECTION AND SEROLOGY

Retrovirus was first described in 1970s [8], but the causal relationship with human diseases was identified in the early 1980s when HTLV-1 was identified as a causative agent of adult T-cell leukemia/lymphoma (ATL) [2,3]. After the discovery of HTLV-1, related viruses have been isolated and HTLV is now composed of four related HTLVs, that is HTLV-1 to HTLV-4 [9]. However, only HTLV-1 has been obviously linked to human diseases at present.

HTLV-1 infection is known to have unique geographic distribution, and is prevalent in southern part of Japan, Melanesia, the Caribbean Islands, Central and South America, as well as central Africa. It is estimated that 20 million people carry the virus worldwide [10]. The current survey indicated that the seroprevalence of HTLV-1 in general population (in Japan) is known to be decreased after screening serological tests of HTLV-1 in blood donors started in 1987 because blood transfusion and breastfeeding from mother to child are major routes of the viral transmission [11]. However, another survey indicated that the number of HTLV-1 carriers in the metropolitan area is significantly increasing because of migration from the endemic areas to the metropolitan areas [7]. Therefore, ophthalmologists, especially in the metropolitan area, are required to know HTLV-related ocular manifestation to avoid misdiagnosis.

OCULAR MANIFESTATIONS IN HUMAN T-CELL LYMPHOTROPIC VIRUS-1 INFECTION

A recent report indicated that ocular complains were the first manifestation of HTLV-1 infection to come to clinical attention, in addition to neurologic and rheumatologic complains [12]. The most frequent ocular manifestation of HTLV-1 infection that ophthalmologists should keep in mind is HTLV-1 uveitis [13]. HTLV-1 uveitis is now recognized as the third clinical entity of HTLV-1 infection following ATL and HTLV-1-associated myelopathy/tropical spastic paraparesis [14–16]. Clinical entity of HTLV-1 uveitis was established by a series of research conducted by Mochizuki *et al.* in 1990s. They showed clinical and laboratory data consisting of seroepidemiology, clinical features, detection of proviral DNA and mRNA of HTLV-1 from ocular tissues, and detection of viral particles from T-cell clones (TCCs) derived from the aqueous humor of the patient [4,5]. Since then, it has been well established that uveitis is significantly related to HTLV-1. In addition to HTLV-1 uveitis, many other ocular manifestations, which are proved linkage to HTLV-1 infection, have been reported all over the world. Taken together, HTLV-1 ocular manifestations can be mainly classified into three groups, uveitis, opportunistic infection/malignant infiltration of the eye in ATL patients and keratoconjunctivitis sicca (KCS).

HUMAN T-CELL LYMPHOTROPIC VIRUS-1 UVEITIS

Seroepidemiological comparison study [4,5,17] in endemic/nonendemic area revealed that the HTLV-1 seroprevalence in patients with idiopathic uveitis was significantly higher than that in following two control groups: patients with cause defined as uveitis and patients with nonuveitic ocular diseases. This was the first clue suggesting that HTLV-1 infection is significantly related to uveitis. The uveitis is now recognized as a distinct clinical entity related to HTLV-1 and designated as HTLV-1 uveitis.

Recent survey [18] in the endemic area revealed that the most common clinical entity of uveitis was still HTLV-1 uveitis, followed by Vogt–Koyanagi–Harada (VKH) disease, sarcoidosis and others. However, the new patients of HTLV-1 uveitis clearly decreased with time, although VKH disease, sarcoidosis and others do not have changed much in the last two decade. As for the prevalence of HTLV-1 uveitis in different parts of the world, the prevalence of HTLV-1 uveitis in Martinique [19], and that of HTLV-1 uveitis in Brazil are lower than that reported in Japan [20,21]. HTLV-1 uveitis's major symptoms at initial presentation were sudden onset of floater, foggy vision and blurred vision. Other complains are pain/burning, itching and foreign body sensation. Most patients had an intermediate uveitis with moderate or heavy vitreous opacities (fine cells and lacework-like membranous opacities). The vitreous opacities were the most impressive findings and were accompanied by mild iritis and mild

retinal vasculitis but no uveoretinal lesions [22]. The ocular inflammation of HTLV-1 uveitis was unilateral or bilateral [19,20,22]. Interesting observation was reported in HTLV-1 uveitis patients that was an association with Graves' disease. HTLV-1 uveitis occurred after the onset of Graves' disease in all cases [23]. The incidence of HTLV-1 uveitis after Graves' disease in the first report was very similar to that of the latest [18].

As for the mechanism of HTLV-1 uveitis, analysis of infiltrating cells in the eye with HTLV-1 uveitis revealed that the majority of infiltrating cells were $CD3^+$ T cells, but not malignant cells or leukemic cells based on their T-cell receptor usage [24]. HTLV-1 proviral DNA, HTLV-1 protein and viral particle were detected from ocular infiltrating cells in the eye of HTLV-1 uveitis patients [4,5]. A series of researches showed that HTLV-1 uveitis was caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that are significantly accumulated in the eye of the patients. HTLV-1-infected $CD4^+$ TCCs established from infiltrating cells in eyes of HTLV-1 uveitis patients produced a large amount of various inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF-α) and interferon (IFN)-γ [25]. Furthermore, addition of corticosteroids in the culture medium suppressed the cytokine production [26].

ADULT T-CELL LEUKEMIA/LYMPHOMA-RELATED OCULAR SYMPTOM

Opportunistic infection and malignant infiltration of the eye are main ophthalmic features of ATL patients. The representative opportunistic infection in the eye is cytomegalovirus retinitis [27]. Cytomegalic cell infiltration and accompanied retinal necrosis can be seen. This ocular manifestation is similar to that of patients with AIDS, and is also associated with poor prognosis. Many case reports indicate that HTLV-1-infected leukocytes can infiltrate into the almost all tissue in the eye, which cause various ocular manifestations in such areas as orbita, cornea, iris, lens, vitreous, uvea, retina, sclera, optic nerve [28]. In addition to these regions, choroidal manifestation was newly reported and identified as a distinct ocular manifestation of ATL patient [28].

Investigation of the eye in HTLV-1-infected patients has progressed significantly in accordance with development of modern molecular biology technology such as microdissection, PCR, cytokine detection system and Flow cytometry. ATL cells are characterized by the expression of IL-2 receptor alpha (IL-2Rα) (CD25), which is not expressed in normal resting T cells. The recent technology showed that elevated levels of soluble IL-2Rα may suggest direct ocular infiltration of ATL cells, as ATL cells secrete soluble forms of IL-2Rα into the vitreous [28]. Detection of soluble IL-2Rα in vitreous may be a cue of ocular infiltration and prognosis [29].

KERATOCONJUNCTIVITIS SICCA

KCS is usually a part of Sjögren's syndrome. HTLV-1-associated tear film changes were first reported when investigating mice expressing the *Tax* gene and developing a Sjögren's syndrome -like clinical symptom [30]. The association between Sjögren's syndrome and HTL V-1 in humans was found in an endemic zone higher prevalence of this virus among the carriers of the syndrome than in the seronegative control group [31]. Development of clinical Sjögren's syndrome manifestations in HTL V-1 carriers have been explained by the activated autoreactive T cells, which break immunological tolerance and result in Sjögren's syndrome. However, KCS associated with HTLV-1 infection might differ from ocular manifestation in primary or secondary Sjögren's syndrome because it does not reveal immunological alteration related to a rheumatologic disease [19,32–34]. Therefore, the mechanism of HTLV-1-associated Sjögren's syndrome is still controversial. However, some patients have more than one of these HTLV-1-associated inflammatory conditions, that is overlap syndrome. HTLV-1 infection can change immunological status by T cell activation and various cytokines, which may contribute to the development of overlap syndrome. Infected activated T cells are thought to proliferate and infiltrate into not only the eye [26] but also other organs and secrete a variety of cytokines, including IL-1, IL-2, IL-3, IL-6, TNF-α and IFN-γ [35]. For example, a report presented that a HTLV-1 carrier had clinical and pathological features of overlap syndrome, which consisted of Sjögren's syndrome and dermatomyositis.

TREATMENT OF HUMAN T-CELL LYMPHOTROPIC VIRUS-1-RELATED OCULAR MANIFESTATION

HTLV-1 uveitis is considered to have caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells, which significantly accumulated in the eye of the patients, and, therefore, topical and/or oral corticosteroid treatment is effective to treat HTLV-1 uveitis patients by suppressing cytokine production of HTLV-1-infected $CD4^+$ T cells for their intraocular inflammation [4,5,13]. Clinical management should be performed according to their degree of ocular inflammation. HTLV-1