Panuveitis induced by donor-derived CD8⁺ T cells after allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia

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ABSTRACT

Purpose: This article presents a case of panuveitis that occurred after unrelated allogeneic hematopoietic stem cell transplantation (allo-HSCT) in a patient with lymphoma-type human T-cell leukemia virus type-1 (HTLV-1)-associated adult T-cell leukemia (ATL). Observations: A 45-year-old man developed unilateral panuveitis 18 months after undergoing allo-HSCT. He underwent vitrectomy, and depositions of grey-white granules localized on the retinal artery were observed in the eye. Cytological examination of the vitreous aspirates showed that the atypical lymphoid cells stained positive for CD3 and CD8, but negative for CD4, B-cell markers, and cytomegalovirus antigen. Interphase fluorescence in situ hybridization using X- and Y-chromosome probes revealed complete donor chimerism in CD8⁺ T cells in the vitreous aspirates. Conclusions and importance: Donor-derived CD8⁺ T lymphocytes can induce panuveitis like HTLV-1-associated uveitis after allo-HSCT in patients with ATL. Pathological diagnosis of vitreous infiltration by vitrectomy is helpful in patients with ATL. Donor-derived CD8⁺ T lymphocytes-induced panuveitis is recurrent but susceptible to regional corticosteroid treatment.

1. Introduction

Adult T-cell leukemia (ATL) is a rare lymphoproliferative malignancy caused by chronic infection of the human T-cell leukemia virus type-1 (HTLV-1).¹ The annual rate of ATL is estimated to be between 7.7 and 8.7 per 10,000 in HTLV-1 carriers.² The 4-year overall survival is 24.8% with the mean survival time of 11.7 months in patients with ATL in a recent nationwide hospital-based study in Japan.³ ATL is divided into four clinical subtypes, including acute, lymphoma, chronic, and smoldering. Among them, acute, lymphoma, and chronic types with unfavorable prognostic factors types are categorized as aggressive ATL and were associated with a poor prognosis; the median survival time was 8–10 months.⁴ Thus, because of the rarity and poor prognosis of ATL, there have been limitations to note ocular manifestations in ATL. Recently, a survey of cases of ocular manifestation of ATL have revealed that intraocular infiltration of ATL is the most prevalent in Japan, followed by opportunistic infections, such as those of cytomegalovirus (CMV), herpesvirus, and Toxoplasma gondii.⁵ Inflammatory cell infiltration, the clinical features of which resemble HTLV-1-associated uveitis (HAU), was also described as a consequence of ATL invasion.⁶,⁷ Therefore, it is necessary to determine the phenotypes of cells infiltrating the eye of ATL patients because treatment plans differ for ATL cell invasion, opportunistic infections, and inflammatory cell infiltrates such as HAU.

HTLV-1 virus remain latent for a long time by maintaining a low rate of replication, which can induce inflammation in the central nervous system (CNS) and eye, cause genetic changes, or augment cell growth.⁸ HAU and HTLV-1-associated myelopathy/tropical spastic paraparesis
2. Case report

A 45-year-old man with adult T-cell leukemia (HAM/TSP) were chronic inflammatory disorders caused by HTLV-1 infection in the CNS and eye. Although HTLV-1 infection causes ATL, HAU, and HAM/TSP, the strength of HTLV-1-specific cytotoxic T-cell (CTL) responses, which serve as anti-tumor or anti-virus immunity, is different among ATL, HAU and HAM/TSP patients. HTLV-1-specific CD8+ CTLs are reportedly active for long-term in patients with HAM/TSP, suggesting that HAU is evoked by a HTLV-1-specific monoclonal population of cells. On the other hand, although ATL has a poor prognosis since early after its onset, ATL progresses slowly as it takes decades for HTLV-1-infected T cells to transform into ATL cells via genetic changes and deficiency or anergy of HTLV-1-specific CTL responses. Allogeneic HSCT restores HTLV-1-specific CTL responses in patients with ATL who have survived without any relapse in a long time after HSCT.

To our knowledge, this is a primary report of panuveitis in a patient who had infiltration of donor-derived CD8-positive cells after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for aggressive ATL, although the principal phenotype of ATL or inflammatory cells in HAU is CD4+ cells.

2. Discussion

It is crucial to determine ATL cell invasion of the CNS, including the eye, because CNS progression has been observed in 10–20% of patients with aggressive ATL with fatal outcomes in a short period. In the present case, analysis of vitreous samples revealed that the infiltrated vitreous cells obtained were donor-derived CD3+, CD4+, and CD8+ T lymphocytes but not CD4- T lymphocytes. Although HTLV-1 virus can
infect various types of cells including CD4 T and CD8 T lymphocytes and monocyte/macrophages, the principal target of HTLV-1 virus infection is CD4 T cells. Therefore, the phenotype of clonal expansion of ATL cells is generally identified as CD3, CD4, and CD8 in majority cases, whereas it is either CD3, CD4, and CD8, CD3, CD4, and CD8, or CD3, CD4, and CD8 in some cases. Clonal expansion of HTLV-1-infected CD8 T lymphocytes, but not CD8 lymphocytes, leads to a malignant phenotype and subsequent tumorigenesis. Approxi-

mately 5% of HTLV-1-infected individuals develop ATL 30–50 years after the initial infection. ATL recurs owing to the growth of recipient-derived ATL cells after allo-HSCT. Thus, these results suggest that donor-derived HTLV-1-infected CD8 T lymphocytes were not cancerous in this case because of the short period of transformation to ATL cells, although HTLV-1 transmission can occur from recipient cells to donor cells.

Inflammatory cell infiltration accompanied by ATL cells, which is known as ATL-cell induced uveitis (AIU), was a dominant candidate in this case because ATL had recurred in the skin 6 months prior. Moreover, the incidence of intraocular tumor cell invasion is prevalent in patients with ATL in Japan. Allogeneic HSCT induces a graft-versus-ATL effect, which is a HTLV-1-specific CTL response to combat ATL cells after HSCT, causing improvement in the clinical course of ATL. In this case, the patient achieved CR after HSCT and survived longer than the mean survival time, indicating that allogeneic HSCT successfully induced HTLV-1-specific CTL responses. These results suggest that infiltration of donor-derived CD8 T lymphocytes was associated with AIU. However, in this case, cytological analysis did not show any signs of ATL cell invasion, indicating that recipient-derived ATL cells had invaded at the onset but were killed by donor-derived CD8 T cells before vitrectomy.

In patients with HAU, HTLV-1 is potent in infecting intraocular cells, including retinal pigment epithelial (RPE) cells. HTLV-1-infected RPE cells impair retinal homeostasis and promote the expression of intercellular adhesion molecule-1 on RPEs to attract HTLV-1. In an analysis of a murine HTLV-1 model, cross-reactivity of HTLV-1 antigen with retinal antigens induced proinflammatory responses in the retina. Therefore, these results suggest that donor-derived CD8 T lymphocytes accumulate and elicit inflammatory responses similar to those in HAU to elicit HTLV-1-infected intraocular cells, such as RPE cells, and/or to react retinal antigens in the eye of the recipient, although there is no evidence of persistent HTLV-1 infection in intraocular cells, including RPE cells, in this case. Further studies are necessary to determine whether persistent HTLV-1 infection exists in intraocular cells in patients with ATL.

4. Conclusions

To our knowledge, this is a primary case of panuveitis induced by donor-derived CD8 T lymphocytes in a patient with aggressive ATL after allo-HSCT. The number of cases with donor-derived inflammatory cell infiltration may increase because allo-HSCT can elicit strong HTLV-1-specific CTL responses, thereby improving the prognosis in some cases of ATL. Vitrectomy is useful for the differential diagnosis of ATL cell invasion, opportunistic infections, and inflammatory cell infiltrates such as HAU. Detection of donor-derived CD8 T cell infiltration in the eye may be a sign of inflammatory cell responses, including ATL-cell-induced uveitis. Furthermore, donor-derived CD8 T lymphocytes-induced uveitis is recurrent but well-controlled because of its susceptibility to regional corticosteroid treatment in patients with ATL after allo-HSCT.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Authorship

All authors declare that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

Atsunobu Takeda received grants from Alcon, AMO Japan, Novartis, and Santen Pharmaceutical; and lecture fees from Novartis, AMO Japan, and NIDEK CO., Ltd. Koh-Hei Sonoda received grants from Alcon, Novartis, and AMO Japan; and lecture fees from Santen Pharmaceutical, Alcon, AMO Japan, Bayer, Novartis, Kowa Pharmaceutical, Senju Pharmaceutical, Otsuka Pharmaceutical, and RE Medical; consulting
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