Cytomegalovirus Pneumonia after Anti-CC-chemokine Receptor 4 Monoclonal Antibody (Mogamulizumab) Therapy in an Angioimmunoblastic T-cell Lymphoma Patient

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive T-cell lymphoma. A 63-year-old man was diagnosed with AITL. He received 6 cycles of CHOP therapy, but showed progressive disease. Subsequently, he received ESHAP chemotherapy; however, it was not effective. He received mogamulizumab (an anti-CCR4 monoclonal antibody). After 4 cycles, his respiratory condition worsened and he was diagnosed with cytomegalovirus (CMV) pneumonia. Despite antiviral and antibiotic therapy, he died. We speculate that the combination of progressive lymphoma with mogamulizumab and chemotherapy likely caused CMV pneumonia. Because mogamulizumab therapy causes immunosuppression, if CMV pneumonia is suspected, then rapid treatment should be initiated.

Key words: lymphoma, mogamulizumab, cytomegalovirus pneumonia

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Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive T-cell lymphoma, classified as a peripheral T-cell lymphoma (PTCL) according to the World Health Organization classification criteria (1). The prognosis for AITL is poor (2); cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy is often used as the first-line therapy for patients with AITL; however, the treatment outcomes have been reported to be limited (3).

Mogamulizumab is a defucosylated anti-CC-chemokine receptor 4 (CCR4) monoclonal antibody used for the treatment of adult T-cell leukemia/lymphoma, that has recently shown improved treatment outcomes (4). Of note, CCR4, which is expressed by most adult T-cell leukemia/lymphoma cells, including PTCLs, and is known to be a marker for type 2 helper or regulatory T (Treg) cells, is associated with a particularly poor prognosis (5, 6). Recently, Ogura et al. reported the effectiveness of mogamulizumab for patients with relapsed PTCL and cutaneous T-cell lymphoma with an acceptable toxicity (7). In a previous study, the overall response rate to mogamulizumab was 50% for patients with AITL, with the most common adverse events being infusion reaction and skin rash (4). Mogamulizumab is a new monoclonal antibody, and thus, adverse events regarding infection remain largely unknown. We herein experienced an AITL patient suffering from cytomegalovirus (CMV) pneumonia after mogamulizumab therapy.

Case Report

A 63-year-old man was diagnosed with clinical stage IVB AITL with pulmonary involvement, pleural and pericardial effusion, and supradiaphragmatic lymph node involvement 5 months previously. At diagnosis, no bone marrow involvement was detected. A serology test for CMV antibody IgG was performed, which showed positive results. The patient received 6 cycles of CHOP therapy. After the therapy, he complained of a fever, bone pain in the...
CMV infection typically occurs in immunocompromised hosts such as patients with acquired immunodeficiency syndrome, undergoing organ or stem cell transplantation, or with hematological malignancies.

Recently, several monoclonal antibodies, such as alemtuzumab (anti-CD52) and rituximab (anti-CD20), have been associated with the development of CMV infection (8, 9). Rituximab increases the number of normal CD20-positive cells (9), while alemtuzumab causes lymphocytotoxic immunosuppression through the suppression of T-cell function and decrease in the number of CD4 cells (10). Ohyama et al. described that 2 of 4 patients with ATLL who underwent mogamulizumab therapy developed CMV infection (11). Two patients with CMV infection achieved molecular CR. One patient died because of CMV encephalitis. Furthermore, Ishida et al. reported that 4 patients (14%) who received mLSG15 combined with mogamulizumab developed CMV infection, which was not observed in the patients who received mLSG15 therapy alone (12). This report suggested that the addition of mogamulizumab to systemic therapy might further increase the incidence of CMV infection. CCR4 is not only expressed on tumor cells, but also on Treg cells (11); hence, the decrease in the number of Treg cells is expected to be involved in the development of immune disorders. Chemaly et al. reported that, out of 3091 patients with lymphoma, 31 patients experienced CMV pneumonia (13), whereas in the report by Tay et al., of 534 patients with lymphoma, 48 patients experienced CMV infection, and 4 patients were diagnosed with CMV pneumonia (14). CMV infection is believed to develop as a result of intensive immunochemotherapy and monoclonal antibody treatment in patients with lymphoma.

CMV pneumonia is defined by the detection of CMV in the bronchoalveolar lavage fluid or lung tissue samples, combined with the clinical symptoms. However, as our patient’s general condition was very poor, bronchoscopy could not be performed. Furthermore, in the sputum specimen, only normal flora was detected, and β-D-glucan and Aspergillus antigenemia were negative. CMV pneumonia typically presents as general findings, such as ground-glass opacities and patchy consolidation on CT. Therefore, CMV pneumonia is typically diagnosed according to CMV antigenemia, a CT scan and other examinations, such as those mentioned above. However, Chemaly et al. described that 53% of lymphoma patients with CMV pneumonia had co-infections (13). Our patient was a severely immunocompromised host, thus he may have had undetermined co-infections. Chang et al. suggested that CMV antigenemia was not sensitive for patients with CMV pneumonia (15). Indeed, if possible, bronchoscopy should be performed when CMV pneumonia is suspected.

Lastly, Tay et al. reported that out of a total 534 lymphoma patients, all 12 patients with CMV infection or end-organ disease who died had progressive disease (14). Similarly, in our case, it is possible that CMV pneumonia may also be associated with refractory lymphoma.

In conclusion, the present case demonstrated that the combination of the progressive status of lymphoma with the use of mogamulizumab and intensive chemotherapy likely resulted in CMV pneumonia. Mogamulizumab is known to cause immunosuppression, and thus, if CMV pneumonia is suspected, then rapid treatment with antibiotic therapy
should be initiated. Furthermore, careful monitoring for CMV infection is recommended for patients receiving mogamulizumab combined with intensive chemotherapy.

The authors state that they have no Conflict of Interest (COI).

References

1. Swerdlow SH, Campo E, Harris NL. World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues. IARC Press, Lyon, France, 2008.
2. Mourad N, Mounier N, Brière J, et al; Groupe d’Etude des Lymphomes de l’Adulte. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d’Etude des Lymphomes de l’Adulte (GELA) trials. Blood 111: 4463-4470, 2008.
3. Zhao S, Zhang L, Zhang M, et al. Angioimmunoblastic T-cell lymphoma: the effect of initial treatment and microvascular density in 31 patients. Med Oncol 29: 2311-2316, 2012.
4. Ishida T, Joh T, Uike N, 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.
5. Ishida T, Inagaki H, Utsunomiya A, et al. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res 10: 5494-5500, 2004.
6. Ohshima K, Karube K, Kawano R, et al. Classification of distinct subtypes of peripheral T-cell lymphoma unspecified, identified by chemokine and chemokine receptor expression: analysis of prognosis. Int J Oncol 25: 605-613, 2004.
7. Ogura M, Ishida T, Hatake K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol 32: 1157-1163, 2014.
8. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 101: 4267-4272, 2003.
9. Aksoy S, Harputluoglu H, Kilickap S, et al. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 48: 1307-1312, 2007.
10. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 110: 2316-2323, 2007.
11. Ohyama Y, Kumode T, Eguchi G, Yamaguchi T, Maeda Y. Induction of molecular remission by using anti-CC-chemokine receptor 4 (anti-CCR4) antibodies for adult T cell leukemia: a risk of opportunistic infection after treatment with anti-CCR4 antibodies. Ann Hematol 93: 169-171, 2014.
12. Ishida T, Jo T, Takemoto S, et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol 169: 672-682, 2015.
13. Chemaly RF, Torres HA, Hachem RY, et al. Cytomegalovirus pneumonia in patients with lymphoma. Cancer 104: 1213-1220, 2005.
14. Tay MR, Lim ST, Tao M, Quck RH, Tay K, Tan TT. Cytomegalovirus infection and end-organ disease in Asian patients with lymphoma receiving chemotherapy. Leuk Lymphoma 55: 182-187, 2014.
15. Chang H, Tang TC, Hung YS, Lin TL, Kuo MC, Wang PN. Cytomegalovirus infection in non-transplant patients with hematologic neoplasms: a case series. Chang Gung Med J 34: 65-74, 2011.

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