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Case Report

Reduced CC Chemokine Receptor 4 Expression in Tumor Cells after Lenalidomide Treatment for Adult T-Cell Leukemia/Lymphoma: A Case Report

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Keywords

Adult T-cell leukemia/lymphoma · CC chemokine receptor 4 · Immunomodulatory drug · Lenalidomide

Abstract

Introduction: CC chemokine receptor 4 (CCR4), which is involved in leukocyte migration, is expressed in most tumor cells in patients with adult T-cell leukemia/lymphoma (ATLL). ***Case Presentation:*** Here we report the case of a 78-year-old man diagnosed with lymphoma-type ATLL expressing CCR4. The patient was administered two cycles of lenalidomide but died because of sepsis 5 months after the initial diagnosis. Autopsy revealed ATLL cells at several sites. Immunohistochemical analysis revealed that these ATLL cells had reduced CCR4 expression. ***Conclusion:*** The present case suggests that treatment should be carefully determined in ATLL with reference to a history of lenalidomide use and CCR4 expression.

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is an aggressive T-cell malignancy that typically emerges after decades of asymptomatic infection with chronic human T-lymphotropic virus type 1 infection [1]. ATLL cells often express CC chemokine receptor 4 (CCR4) [2], an adhesion

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molecule expressed in a subset of CD4-positive T cells and certain T-cell lymphoma subtypes, and CCR4 expression in ATLL cells is highly associated with skin involvement and poor prognosis [3].

Chemotherapy or allogeneic stem cell transplantation is administered to prolong survival in patients with ATLL subtypes associated with poor prognosis, such as the lymphoma-type ATLL [4]. In Japan, immunomodulatory drugs (IMiDs), such as lenalidomide, are increasingly used as new therapeutic options in patients with ATLL. IMiDs exert direct antitumor and immunostimulatory effects by promoting the degradation of the transcription factors Ikaros and Aiolos and suppressing the activation of the nuclear factor kB pathway, which is important for the proliferation of tumor cells including ATLL cells [5, 6]. Furthermore, IMiDs enhance the transcriptional activity of activating protein-1 (AP-1) and promote interleukin 2 production, which enhances T-cell activation [7, 8]. Here, we report the case of a patient with ATLL, in whom CCR4 expression in ATLL cells was decreased after lenalidomide treatment.

Case Presentation

The patient was a 78-year-old man undergoing regular evaluation in our hospital after surgery for colon cancer. Computer tomography obtained 2 years after surgery revealed multiple enlarged lymph nodes and splenomegaly, and ^{18}F-fluorodeoxyglucose accumulation was observed at both sites by positron emission tomography/computed tomography images (Fig. 1). Serologic tests revealed positivity for human T-lymphotropic virus type 1 antibodies. Biochemical tests showed elevated levels of aspartate aminotransferase (87 U/L; reference, 13–30 U/L), alanine aminotransferase (70 U/L; reference, 10–42 U/L), and soluble interleukin 2 receptor (66,696 U/mL; reference, 121–613 U/mL). Morphological analysis of blood cells revealed 0.5% abnormal lymphocytes. Biopsy samples were collected from the lymph nodes in the left neck 2 months after the initial evaluation, and immunohistochemical examination revealed diffuse infiltration of abnormal T cells characterized by irregular nuclear contours and variably prominent nucleoli. These cells were positive for CD3, CD4, CD5, and CCR4 (Fig. 2).

The patient was diagnosed with lymphoma-type ATLL and determined to be at high risk for disease progression according to the simplified ATLL prognostic index. Oral lenalidomide was initiated based on the patient's intention and general condition, and he received two cycles at a dose of 25 mg/body on days 1–21 of each 28-day cycle. Computed tomography revealed reduced size of mediastinal lymph nodes (Fig. 3).

Four months after treatment initiation, he was admitted to our hospital with general malaise. On admission, body temperature was 38.3°C and blood pressure was 90/52 mm Hg. Physical examination revealed bilateral diminished breath sounds and bilateral leg edema. Complete blood count revealed the following: white blood cell count, 1.94 × 10^9/L with 0.5% abnormal lymphocytes; neutrophil count, 0.99 × 10^9/L; lymphocyte count, 0.51 × 10^9/L; red blood cell count, 134 × 10^{10}/L; hemoglobin, 56 g/L; and platelet count, 0.6 × 109/L. Coagulation tests revealed increased prothrombin time-international normalized ratio (2.74; reference, 0.87–1.03), prolonged activated partial thromboplastin time (45.7 s; reference, 28.0–36.0 s), and elevated concentration of fibrin/fibrinogen degradation products (19.8 μL/mL; reference, <5.0 μL/mL). Serum albumin was decreased (2.1 g/dL; reference, 3.9–4.9 g/dL), and C-reactive protein was elevated (7.6 mg/dL; reference, <0.3 mg/dL). Computed tomography revealed infiltrative shadows in the left lung and reduction in the size and number of enlarged mediastinal lymph nodes. He was diagnosed with pneumonia and disseminated intravascular coagulation and

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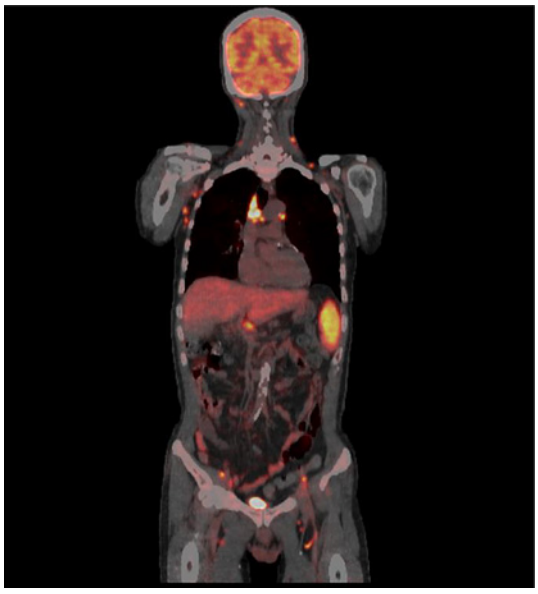

Fig. 1. Pretreatment positron emission tomography/computed tomography showing increased accumulation of ^{18}F-fluorodeoxyglucose in multiple lymph nodes and spleen.

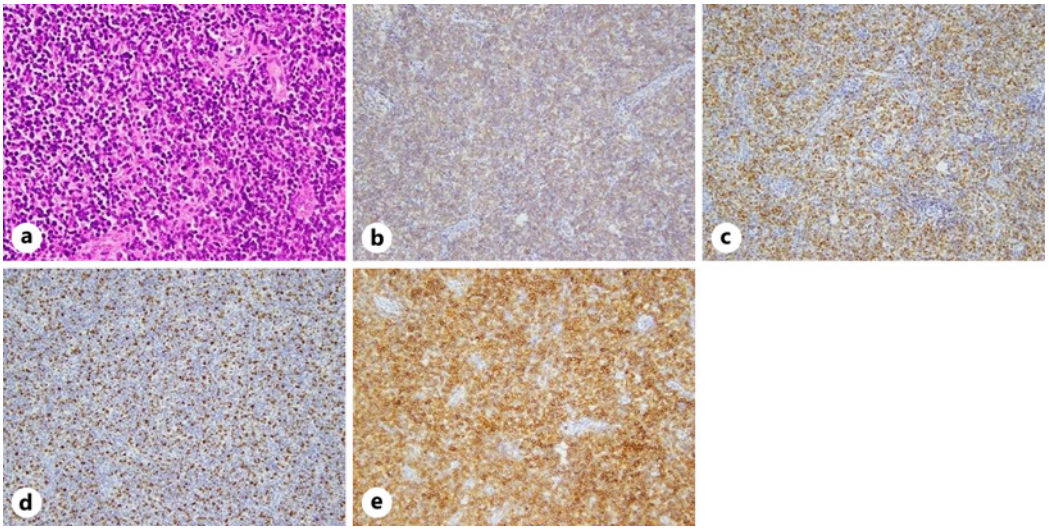

Fig. 2. Histopathologic examination of lymph node biopsy specimens from the left neck. Numerous large lymphocytes with nuclear atypia are observed. The specimen is positive for CCR4. **a** Hematoxylin and eosin staining; magnification, ×100. **b–e** Immunohistochemical staining for CD3 (**b**), CD4 (**c**), CD5 (**d**), and CCR4 (**e**); magnification, ×100.

treated with cefozopran, doripenem, and blood transfusion; however, he died 14 days after the admission.

Autopsy revealed sepsis due to *Candida albicans* as the cause of death. Further examination revealed the presence of ATLL cells at several sites, including the mediastinal lymph nodes and spleen. Immunohistochemical analysis of the samples collected from these two sites revealed that ATLL cells were positive for CD3, CD4, and CD5; however, ATLL cells in the mediastinal lymph nodes exhibited reduced CCR4 expression and ATLL cells in the spleen were negative for CCR4 (Figs. 4, 5).

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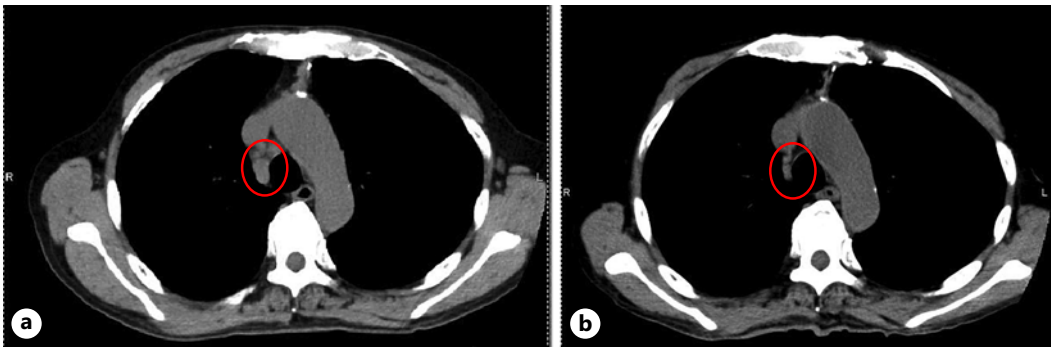

Fig. 3. Comparison of computed tomographic images obtained before (**a**) and after (**b**) treatment showing a reduction in the size of mediastinal lymph nodes (red circles).

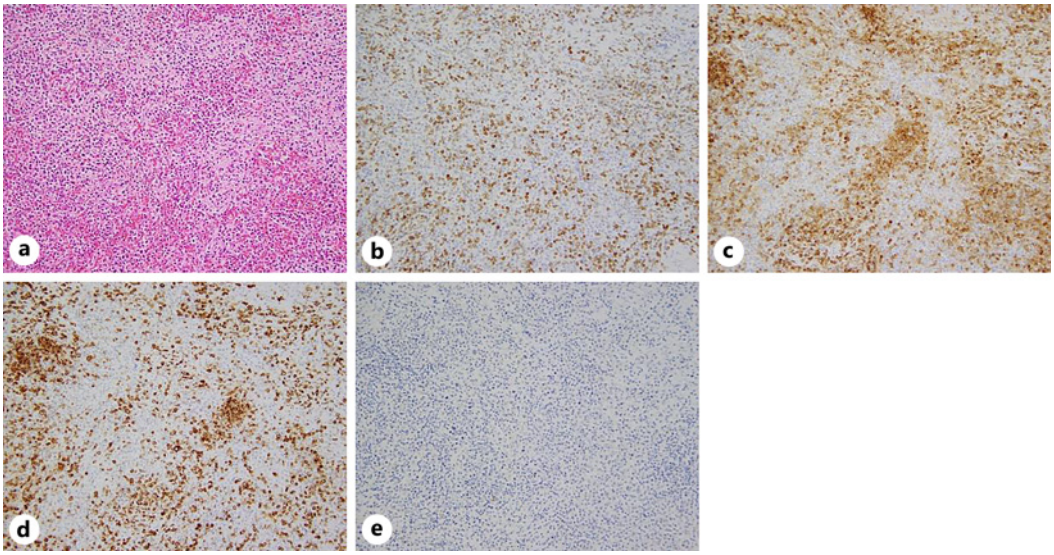

Fig. 4. Histopathologic examination of spleen specimen showing ATLL cells, which are negative for CCR4. **a** Hematoxylin and eosin staining, ×100. **b–e** Immunohistochemical staining for CD3 (**b**), CD4 (**c**), CD5 (**d**), and CCR4 (**e**); magnification, ×100.

Discussion

In the present case, the reduction in CCR4 expression observed in ATLL cells after lenalidomide therapy might be due to the impact of lenalidomide on the transcriptional activity of AP-1, leading to the suppression of transactivation by FOS-related antigen-2 (Fra-2), although additional studies are warranted to obtain direct evidence.

AP-1 binding sites in the proximal region of the CCR4 promoter are major regulatory elements responsible for CCR4 expression in ATLL cells [9]. The AP-1 family of transcription factors regulates many biological processes, such as proliferation, differentiation, survival, and apoptosis [10]. AP-1, whose expression is involved in the regulation of oncogenes in various lymphomas including ATLL [11], is a dimeric complex, including the FOS, JUN, ATF, and MAF protein families [12]. Fra-2 and JunD, which belong to the FOS and JUN protein families, respectively, are highly expressed in ATLL cells and induce CCR4 expression [11].

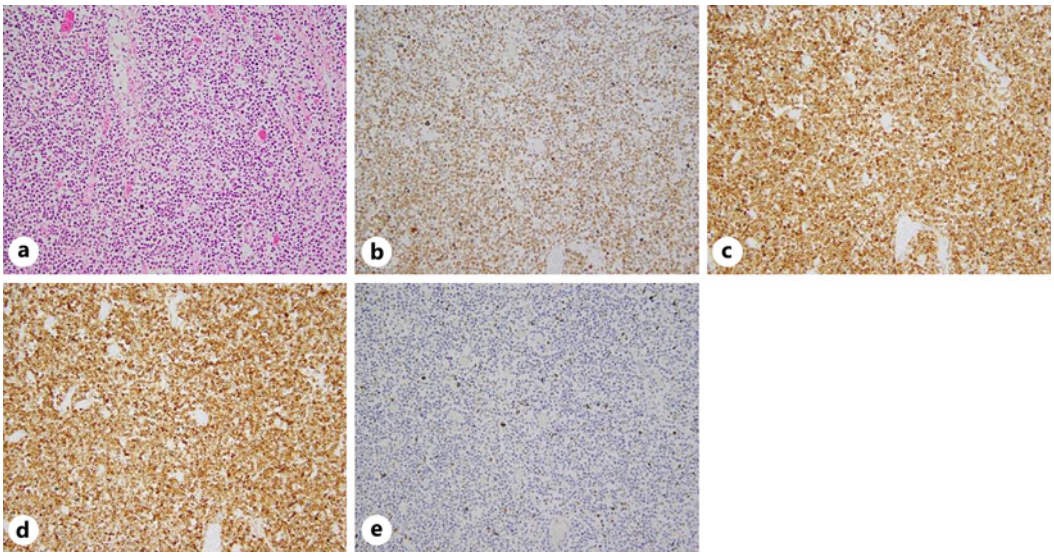

Fig. 5. Histopathologic examination of mediastinal lymph node specimen showing ATLL cells with reduced CCR4 expression. **a** Hematoxylin and eosin staining, ×100. **b–e** Immunohistochemical staining for CD3 (**b**), CD4 (**c**), CD5 (**d**), and CCR4 (**e**); magnification, ×100.

Additionally, Fra-2 can exert a suppressive or stimulatory effect on transactivation depending on the stimulus [13].

Lenalidomide has diverse effects in different cell types [8], and enhancement of AP-1 activity mediated by lenalidomide can lead to the suppression of Fra-2 transactivation in ATLL cells in some patients. Suppressed transactivation in ATLL cells might have led to a reduction in CCR4 expression in these cells.

In recent years, mogamulizumab, a monoclonal anti-CCR4 antibody, has been introduced as a new therapeutic option for ATLL. In patients with relapsed/refractory ATLL, mogamulizumab often results in complete remission [14]. When lenalidomide does not provide sufficient treatment outcome, mogamulizumab may be an alternative.

In summary, CCR4 expression should be carefully examined in patients with ATLL treated with lenalidomide, which might reduce CCR4 expression in ATLL cells. The effect of lenalidomide on CCR4 expression requires further case studies to evaluate its potential impact on clinical decision making in patients with ATLL. The CARE Checklist has been completed by the authors for this case report and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539122).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethics approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Masatomo Shimizu participated in the patient's care, wrote the manuscript and provided manuscript edits. Jun Hatooka and Yuuki Kinoshita participated in the patient's care and provided manuscript edits. Emi Yasuda obtained essential images. Taiji Yokote and Akihisa Imagawa provided their expertise.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author Masatomo Shimizu upon reasonable request.

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