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INTERNAL MEDICINE

□ CASE REPORT □

Recurrence of Psoriasis Vulgaris Accompanied by Treatment with C-C Chemokine Receptor Type 4 (CCR4) Antibody (Mogamulizumab) Therapies in a Patient with Adult T cell Leukemia/ Lymphoma: Insight into Autoinflammatory Diseases

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Abstract

Adult T cell leukemia / lymphoma (ATL) is one of the most aggressive hematological malignancies caused by human T-lymphotropic virus type-I (HTLV-1). Mogamulizumab is a new defucosylated humanized monoclonal antibody agent which targets C-C chemokine receptor type 4 (CCR4) expressed occasionally on the surface of ATL cells. However, adverse events such as drug eruptions have also been highlighted, at least in part, via the dysfunction of regulatory T cells (Tregs). We herein report a pronounced recurrence of systemic psoriasis vulgaris accompanied by the treatment of mogamulizumab in a patient with ATL. Pathological examinations may suggest a mechanistic link between the recurrence of autoinflammatory diseases and anti-CCR4 antibody therapies.

Key words: adult T cell leukemia / lymphoma (ATL), C-C chemokine receptor type 4 (CCR4), regulatory T cell (Treg), psoriasis vulgaris, autoinflammatory disease

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Introduction

Among a variety of hematological malignancies, the prognosis is extremely poor in patients with adult T cell leukemia/ lymphoma (ATL) (1, 2). Some previous reports have suggested that the origin of ATL may be regulatory T cells (Tregs) (3). Recently, a new antibody agent, mogamulizumab, which binds specifically to chemokine receptor type 4 (CCR4), was launched for the treatment of intractable ATL (4). The drug exerts outstanding anti-ATL effects through the regulation of antibody-dependent cellular cytotoxicity (ADCC) activities (5). However, adverse events such as drug eruptions and Stevens-Johnson syndrome have also been reported, presumably via the profound reduction of Tregs (6). In this context, we herein report a rare case of drastic recurrence of systemic psoriasis vulgaris via the administration of mogamulizumab in a patient with ATL (unfavorable chronic subtype).

Autoinflammatory diseases are non-autoimmune disorders of inappropriate inflammation provoked by autostimulatory mechanisms through a variety of extracellular or intrinsic signaling molecules (7). In particular, psoriasis vulgaris is caused, at least in part, by the autostimulation of mast

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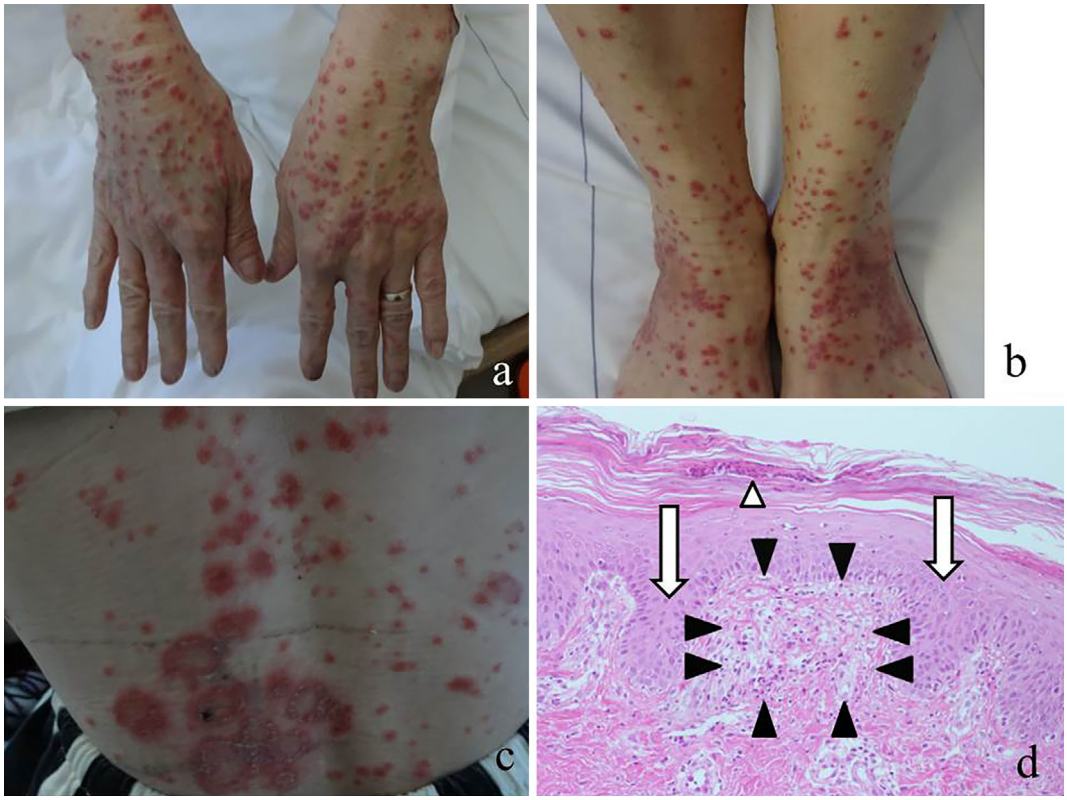

Figure 1. **Macroscopic and microscopic findings in the skin of the patient. a-c) Newly occurring nodular erythemas (15-60 mm in diameter) after mogamulizumab administration. The plaques were erythematous with sharply-defined margins and hyperkeratosis. d) The pathological examination of the nodular erythemas (Hematoxylin and Eosin staining 200×) revealed Munro's microabscess (empty arrow-head), infiltration of lymphocytes into the superficial dermis (circled by black arrow-heads), and elongation of rete ridges (empty arrows), hyperkeratosis, all of which were compatible with the findings of psoriasis vulgaris.**

cells (8), in which a lower activity of Tregs is considerably involved in its pathophysiology. Indeed, the present case demonstrated a substantial reduction of functional Tregs in the skin during a recurrence of psoriasis vulgaris after mogamulizumab administration. Therefore, the present case led us to hypothesize that a mogamulizumab-induced excessive reduction of functional Tregs may aggravate a variety of autoinflammatory diseases.

Case Report

A 46-year-old female visited our hospital complaining of systemic lymphadenopathy and general malaise. She had been a healthy carrier of human T-lymphotropic virus-I (HTLV-1). In the peripheral blood, the white blood cell count was 85,000/μL (neutrophils 6%, lymphocytes 32%, monocytes 2%, and abnormal lymphocytes 60%), hemoglobin was 8.2 g/dL and platelet count was 32.8×10^4/μL. By flow cytometry analyses of the peripheral blood, we detected ATL cells with $CD4^+$, $CD8^-$, $CD25^+$, thereby diagnosing her with ATL (unfavorable chronic type with elevated lactate dehydrogenase). Unfortunately, standard chemotherapy did not improve her lymphadenopathy. Despite subsequent salvage chemotherapy, ATL cells in the peripheral blood remained. Because a CCR4 test (9) was positive, we administered 5 courses of mogamulizumab therapy (4).

Surprisingly, systemic nodular erythemas emerged at the end of the fifth course of mogamulizumab therapy. Initially, we considered such erythemas to be mogamulizumab-induced dermatitis, thus we discontinued mogamulizumab administration. A dermatological inspection revealed that the erythemas were characterized by a distinct border from adjacent normal skin, accompanied by apparent hyperkeratosis (Fig. 1a-c). A pathological examination demonstrated parakeratosis in the surface epidermis, Munro's abscess and the infiltration of inflammatory cells (Fig. 1d). These findings were consistent with those of psoriasis vulgaris. The entire clinical course of her psoriasis vulgaris was approximately 20 years, with several cycles of remission and aggravation. In sharp contrast to the present systemic erythema, extension of the skin lesion in a previous episode of psoriasis vulgaris was localized only in the occipital area. Eventually, the current recurrence of psoriasis vulgaris was improved by beclomethasone ointment and phototherapy within 2 weeks.

Both functional Tregs and ATL cells are known to be positive for CD4, CCR4 and FoxP3 (4, 9-13). Therefore, we distinguished functional Tregs from ATL cells by the presence of atypical nuclei. In immunohistochemical analyses

performed during recurrence of psoriasis vulgaris, the number of FoxP3-positive lymphocytes without atypical nuclei, which corresponded to normal Tregs, was 13 lymphocytes per 10 high power fields (HPF) (1.3 cell counts / HPF +-1.4). In contrast, these lymphocytes were substantially increased to 39 lymphocytes per 7 HPF (5.6 cell counts / HPF +-6.5) when psoriasis vulgaris was much improved (Fig. 2a-1, a-2 and c-1). Similarly, the number of CCR4-positive lymphocytes without atypical nuclei was 12 lymphocytes per 10 HPF (1.2 cell counts / HPF +-1.1). These lymphocytes also increased to 26 lymphocytes per 7 HPF (3.7 cell counts / HPF +-5.0) (Fig. 2b-1, b-2 and c-1). These findings may indicate that a reduction of normal Tregs was involved in the recurrence of psoriasis vulgaris. On the other hand, in the skin lesions from psoriasis vulgaris, FoxP3-positive as well as CCR4-positive lymphocytes with atypical nuclei, which corresponded to residual ATL cells, were substantially reduced to 13 lymphocytes per 7 HPF (1.9 cell counts / HPF +-2.9) from 79 lymphocytes per 10 HPF (7.9 cell counts / HPF +-4.1), and 9 lymphocytes per 7 HPF (1.3 cell counts / HPF +-1.5) from 110 lymphocytes per 10 HPF (11.0 cell counts / HPF +-6.3), respectively (Fig. 2c-2). CD4-positive lymphocytes also decreased (Fig. 2d-1 and d-2). These results indicated that mogamulizumab robustly suppressed the progression of ATL. After mogamulizumab therapy, the patient received hematopoietic stem cell transplantation from a human leukocyte antigen (HLA)-identical sibling donor, which thus resulted in complete remission. The status of psoriasis vulgaris remained in complete remission even after the hematopoietic stem cell transplantation.

Methods for immunofluorescent analyses of CCR4- and FoxP3-positive lymphocytes in skin lesions

Biopsied samples from the skin lesion were subjected to hematoxylin-eosin staining and immunofluorescent analyses for CCR4 (POTELIGEO® test IHC, Kyowa Medex, Japan) (11) and FoxP3 (Perm Buffer Set. Cat No. 421403). We counted the number of CCR4-positive, and FoxP3-positive lymphocytes per 400× power fields in consecutive sections.

Discussion

During the treatment of ATL, the case exemplified an expeditious emergence of systemic psoriasis vulgaris (Fig. 1). At the time point of recurrence, the functional Tregs were markedly diminished as evidenced by FoxP3 and CCR4 immunohistochemistry analyses, raising the possibility that mogamulizumab administration may have a considerable impact on the pathophysiology of systemic psoriasis vulgaris. In the present case, erythematous skin lesions were consistent with psoriasis vulgaris in both the macroscopic and microscopic findings, where the dermatological involvement of ATL cells was subtle (Fig. 2a-1 and b-1). Additionally, in the dermatological inspection, the phenotype of the erythemas largely differed from that in drug eruption. Although it is occasionally hard to discriminate psoriasis vulgaris from drug eruption during the pathological examination, eosinophil-poor drug eruptions observed in this case appeared to be unusual. This notion is reinforced by the fact that such erythemas completely disappeared during the treatment for psoriasis vulgaris. After five courses of mogamulizumab, the circulating level of mogamulizumab was presumed to be saturated, as assessed by the biological half-life of mogamulizumab (5). The time point was synchronized when the skin lesions of psoriasis vulgaris were extended systemically. In sharp contrast to the present erythema, the extension of the skin lesion in a previous episode of psoriasis vulgaris was localized only in the occipital area. All these findings strongly suggest the causal relationship between the emergence of systemic psoriasis vulgaris and the administration of mogamulizumab.

Psoriasis vulgaris is one of representative autoinflammatory diseases with an incidence of approximately 2% worldwide (14). In its pathogenesis, plasmacytoid dendritic cells (pDCs) are deeply involved, which play a critical role in responding to bacterial or viral DNA through Toll-like receptors, thereby producing interferon α, interferon β and interleukin-6 (IL-6) (15). In patients with psoriasis vulgaris, an antimicrobial peptide, LL37, is expressed in the infection sites and released from injured dermis or keratinocytes. Recent data suggest that LL37 activates pDCs and provokes autoinflammation (16). IL-6 induces Th0 cell differentiation into Th17 cells, which may also exacerbate psoriasis vulgaris (17). On the other hand, Tregs are known to eliminate pathogenic T cells such as Th17 cells (18). Furthermore, a recent work suggests that the depletion of functional Tregs might aggravate psoriasis vulgaris (19). Taken together, it is reasonable to speculate that mogamulizumab may have contributed to the recurrence of psoriasis vulgaris in this case.

It should be noted that CCR4 is expressed not only on the surface of ATL cells, but also on normal lymphocytes including Tregs, monocytes and platelets (4). On the other hand, FoxP3 is a master regulatory gene in the development and function of Tregs (10). Importantly, the reduction of FoxP3-positive lymphocytes is linked to the dysfunction of Tregs (11, 12). Following mogamulizumab treatment, FoxP 3-positive lymphocytes without atypical nuclei, which corresponded to normal Tregs in the skin lesions, were substantially decreased (Fig. 2a-1, a-2 and c-1), with a concomitant marked reduction of CCR4-positive lymphocytes without atypical nuclei (Fig. 2b-1, b-2 and c-1). These findings indicate that skin erythemas were caused by an autoinflammatory mechanism via the dysfunction of Tregs, rather than skin invasion of residual ATL cells. In addition, this result does not contradict the notion that Tregs are the origin of ATL cells (3). In fact, previous studies (5, 13) have demonstrated the substantial reduction of functional Tregs by the treatment of mogamulizumab. Furthermore, it is widely accepted that the balance between Tregs and Th17 cells is important for immunological homeostasis (20).

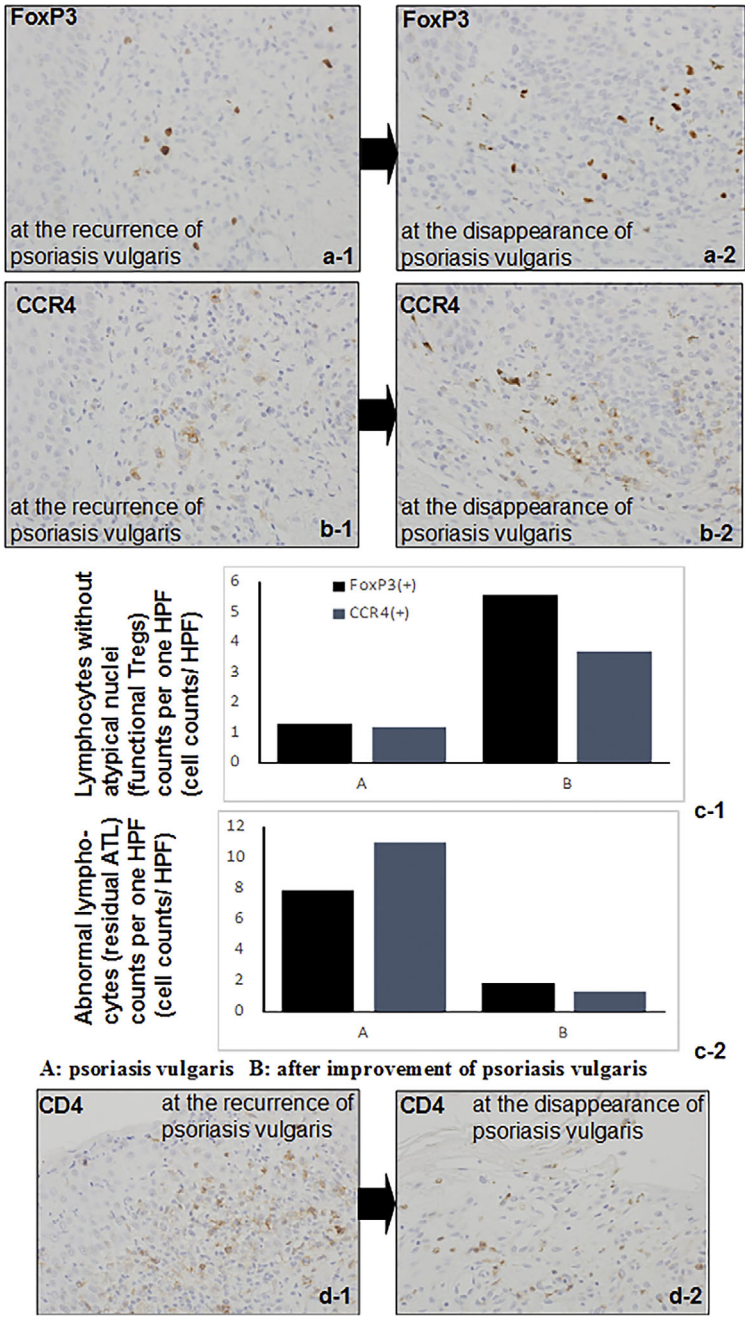

Figure 2. **Immunofluorescence analyses in the skin of the patient (400×). FoxP3 is a master regulatory gene for the function of Tregs. a-1, b-1) Both FoxP3-positive and CCR4-positive lymphocytes were substantially decreased when psoriasis vulgaris emerged, 13 lymphocytes per 10 HPF and 12 lymphocytes per 10 HPF, respectively. a-2, b-2) In contrast, after psoriasis vulgaris improvement, both FoxP3-positive and CCR4-positive lymphocytes without atypical nuclei were markedly increased (39 lymphocytes per 7 HPF and 26 lymphocytes per 7 HPF, respectively). Moreover, the immunoreactive intensity of CCR4-positive lymphocytes in b-2 was stronger than those in b-1. c-1) A graphic demonstration of the cell counts per one HPF resulting from the immunofluorescence analyses. After the skin lesions of psoriasis vulgaris improved, FoxP3-positive lymphocytes without atypical nuclei increased approximately 4-fold and CCR4-positive lymphocytes without atypical nuclei also increased approximately 3-fold. Consequently, normal Tregs showed a marked trend to decrease. c-2) A graphic demonstration of the cell counts per one HPF as evidenced by the immunofluorescence analyses. FoxP3-positive lymphocytes with atypical nuclei were substantially reduced approximately 1/4-fold and CCR4-positive lymphocytes with atypical nuclei, which corresponded to residual ATL cells, were also substantially reduced approximately 1/9-fold. d-1, d-2) CD4-positive lymphocytes also decreased. These findings indicate that her skin erythemas were caused by the dysfunction of normal Tregs, rather than skin invasion of residual ATL cells.**

Collectively, the present case may provide insight into the mechanistic link between the dysfunction of Tregs and pathophysiology of recurrence of autoinflammatory diseases.

Written informed consent was obtained from the patient for publication of this case report.

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

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