The Journal of dermatology (2017.6) 44(6):e117-e118..

Cutaneous adverse reaction of mogamulizumab, an anti-CC chemokine receptor 4 monoclonal antibody: Shared histopathological features with thymoma-associated multi-organ autoimmunity.

Kyoko Kanno, Masaru Honma, Akemi Ishida－Yamamoto

Cutaneous adverse reaction of mogamulizumab, an anti-CC chemokine receptor 4 monoclonal antibody: shared histopathological features with thymoma-associated multiorgan autoimmunity

Kyoko Kanno, Masaru Honma, Akemi Ishida-Yamamoto

Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan

Corresponding author: Kyoko Kanno, MD

Department of Dermatology, Asahikawa Medical University

Midorigaoka Higashi 2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan.

Email: k-kanno@asahikawa-med.ac.jp

Phone: +81-166-68-2523

Fax: +81-166-68-2529

Word counts: 498 words

Dear Editor,

Adult T cell leukemia-lymphoma (ATL) is an aggressive hematological neoplasm caused by human T cell leukemia virus infection. Mogamulizumab, a monoclonal antibody against CC chemokine receptor 4 (CCR4), exhibits a prominent inhibitory effect on ATL cells via antibody-dependent cytotoxicity [1]. Here, we report a case of papulosquamous eruption during mogamulizumab therapy, and the lesional T cell subset was also analyzed.

A 72-year-old Japanese man presented with up to ϕ 2cm, coalescent scaly light red plaques on the almost entire body without any exanthema. He had two-year history of ATL and had been treated by mogamulizumab. While ATL cells in the peripheral blood were disappeared, the skin rash classified into the grade 2 AR (Common Terminology Criteria for Adverse Events v4.0) was emerged following the eighth mogamulizumab infusion (Fig a). The histopathology showed moderate acanthosis, and vacuolar degeneration of basal epidermal keratinocytes with exocytosis as well as perivascular and interstitial lymphocytic infiltration. Necrotic keratinocytes scattered from subcorneal to basal layers of epidermis (Fig b). The most of infiltrating lymphocytes were CD8-positive but only few lymphocytes were positive for FoxP3 (3%) or IL-17 (7%) (Fig c). These clinical and histopathological findings led to the

diagnosis of anti-CCR4 antibody-related cutaneous AR.

CCR share partly redundant or overlapping roles in the recruitment of leucocytes to the skin. Mogamulizumab, the first therapeutic agent targeting CCR4 closely associated with skin-homing regulatory T-cells (T_{reg}) and type 2 helper T-cells (Th_2), shows highly therapeutic effect against ATL, but frequently induces cutaneous AR in up to 50% of patients. While the cutaneous AR can be a reason for discontinuation of mogamulizumab, the skin rash possibly reflects favorable prognosis because of strongly suppressed CCR4-expressing T cell subset [2]. Interestingly, the histopathology and the subset of infiltrating lymphocytes in the present case lesion greatly simulate those of thymoma-associated multiorgan autoimmunity (TAMA).

TAMA is a rare autoimmune disorder, accompanied by autoimmune colitis, hepatitis and graft-versus-host disease (GVHD)-like skin damage, in which liquefaction degeneration of the basal epidermis with exocytosis and dyskeratotic keratinocytes, and presence of superficial perivascular lymphocytes are observed, suggesting similar mechanism with AR of mogamulizumab . Although the precise mechanism remains unknown, the lack of autoimmune regulator and minimal expression of FoxP3 in intralesional T-cells due to functional loss of thymus are suggested in enterocolonopathy of TAMA [3]. Similarly to our case, the ratio of FoxP3-positive T_{reg} against CD4 or

CD8-positive T-cells is decreased in cutaneous lesion of TAMA, suggesting activation of self-reacting cytotoxic T-cells due to insufficient T_{reg} function [4], and this phenomenon is also seen in SJS/TEN lesions. IL17-producind T cells playing a crucial role in the pathomechanism of GVHD [5], are inversely increased in the cutaneous lesion [4], but not in our case. The difference of Th17 cell counts might reflect the distinct mechanism of these disorders or altered phases of the disease.

The clinical and histopathological characteristics of the papulosquamous eruption observed in our case might be associated with negatively regulated Th_2/T_{reg} cells during mogamulizumab therapy, partly sharing a similar pathomechanism with TAMA.

References

1 Ishida T, Ito A, Sato F *et al.* Stevens-Johnson syndrome associated with mogamulizumab treatment of adult Tcell leukemia/lymphoma. *Cancer Sci* 2013; 104: 647-50

2 Yonekura K, Tokunaga M, Kawakami N et al. Cutaneous Adverse Reaction to Mogamulizumab May Indicate FavourablePrognosis in Adult T-cell Leukaemia-lymphoma. *Acta Derm Venereol* 2016 in press

3 Hanafusa T, Azukizawa H, Kitaba S et al. Diminished regulatory T cells in cutaneous legions of thymomma-associated multi-organ autoimmunity: a newly described paraneoplastic autoimmune disorder with fatal clinical course. *Clin Exp Immunol* 2011; 164: 164-170.

4 Kurose K, Ohue Y, Wada H et al. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. *Clin Cancer Res.* 2015 ;21: 4327-4336.

5 Henden AS, Hill GR. Cytokines in Graft-versus-Host Disease. *J Immunol.* 2015; 194: 4604-4612.

Figure legends

Figure: The clinical and histopathological characteristics of the case

a) The clinical manifestation of the case. Coalescent scaly light red plaques distributes on the almost entire body.

b) The histopathology of the lesion. Moderate acanthosis and vacuolar degeneration of basal keratinocytes with exocytosis are observed. Necrotic keratinocytes also scatter from upper to basal layers of epidermis. Scale bars: 100 μm

c) The immunohistochemistry for CD4, CD8, FoxP3 and IL-17. Scale bars: 100 μm