

SHORT COMMUNICATION

Stevens-Johnson Syndrome Associated with Mogamulizumab-induced Deficiency of Regulatory T cells in an Adult T-cell Leukaemia Patient

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Stevens-Johnson syndrome (SJS) is a rare but extremely severe drug-induced eruption characterised by widespread necrosis or apoptosis of the epidermis (1). The main causal factor for SJS is an aberrant activation of CD8 T cells. Although the dysfunction of the regulatory T cells (Treg) is considered a possible cause of excess CD8 T cells activation (2), the actual significance of Tregs *in vivo* remains unknown.

CASE REPORTS

A 54-year-old man with relapsed adult T-cell leukaemia-lymphoma (ATL) (stage IVB) was referred to our clinic with multiple erythema and small red papules on his lower legs (Fig. 1a). Eight days earlier (day 0) he had started weekly treatment with mogamulizumab, a humanised anti-CC chemokine receptor 4 (CCR4) monoclonal antibody that depletes CCR4⁺ tumour cells in ATL patients. Histological examination of the papules exhibited inflammatory cell infiltration in the perivascular and interface between the dermis and the epidermis (Fig. 2a). CD8⁺ cells were mainly located in the perivascular region, and forkhead box P3 (FOXP3)⁺ Tregs existed in the interface (Fig. 2b,

c). Necrosis of epidermal cells was not detected. We diagnosed the skin rash as a drug-induced eruption by mogamulizumab. As topical difluprednate treatment did not control the skin rash, we discontinued the third course of mogamulizumab treatment, and started 30 mg of oral prednisolone treatment on day 12.

Although the erythema and papules temporarily improved after the systemic steroid therapy, the clinical manifestations spread over his trunk and extremities (Fig. 1b) on day 28 accompanied by severe conjunctivitis, erosion and swelling of oral mucosa (Fig. 1c), and high fever. Histological examination on day 28 revealed severe epidermal cell necrosis and vacuolar changes with significant numbers of CD8⁺ cells in the interface in accord with the absence of Tregs (Fig. 2d–f). Flow cytometry analysis revealed that Tregs in blood had disappeared by day 17 (Fig. 3a, b). We diagnosed the patient as SJS induced by mogamulizumab. We initiated pulse therapy with methylprednisolone (500 mg/day × 3 days) plus tacrolimus (1.5 g/day × 2 days), followed by methylprednisolone treatment (70 mg/day). After these treatments, the skin rash gradually improved. We carefully tapered the dose of methylprednisolone to 30 mg/day. Even after the discontinuation of mogamulizumab

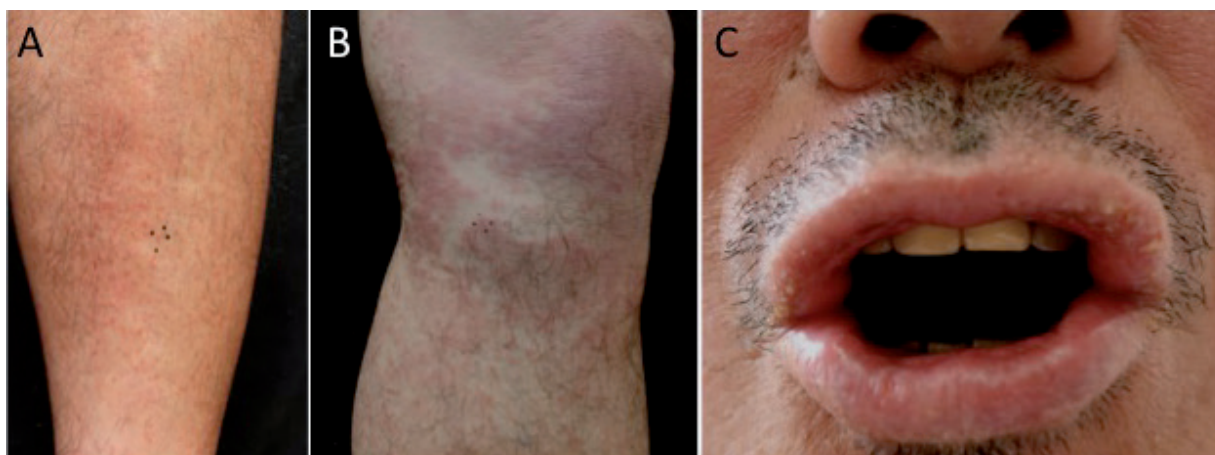


Fig. 1. Multiple erythema and small papules on day 8 (A). Erythema multiforme-like erythema on extremities (B), and erosion and swelling of oral mucosa on day 28 (C).

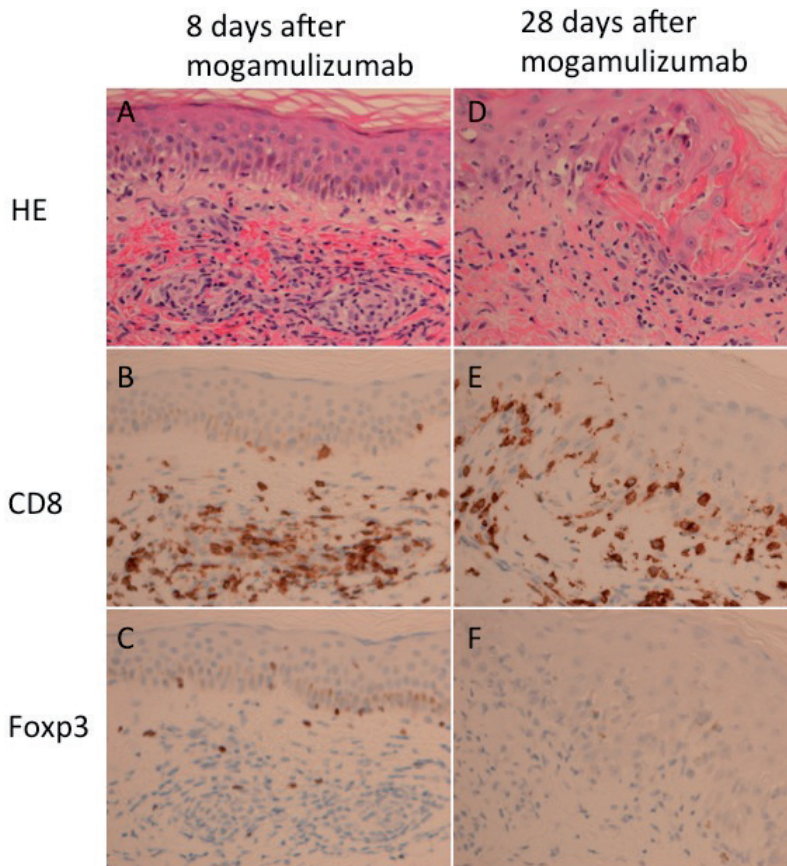


Fig. 2. Histological and immunohistochemical (IHC) findings 8 (A–C) and 28 days (D–F) after mogamulizumab treatment. (A, D) Haematoxylin and eosin staining. IHC for CD8 (B, E) and FOXP3 (C, F). Original magnification: $\times 40$.

therapy, the patient achieved a complete remission in ATL. He was discharged on day 81.

DISCUSSION

Mogamulizumab was approved in Japan in March 2012 as a novel therapy for relapsed or refractory ATL,

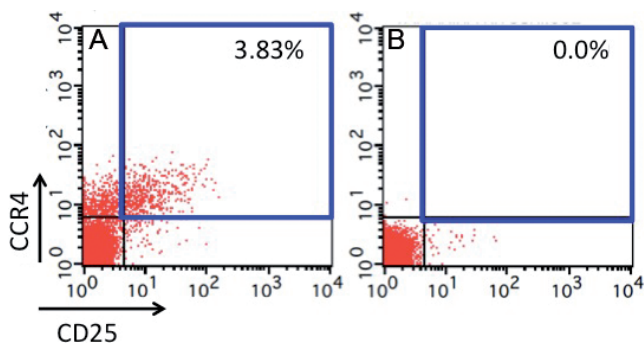


Fig. 3. Flow cytometry analysis for CCR4⁺CD25⁺CD4⁺CD3⁺ non-tumour cells in peripheral blood before (A) and 17 days (B) after the mogamulizumab therapy. Data are gated on CD4⁺CD3⁺ cells.

because tumour T cells of ATL patients are CCR4⁺ in nearly 90% of cases (3). Although it significantly improves the clinical symptoms in ATL patients, it sometimes induces severe adverse effects of the skin, such as SJS and toxic epidermal necrolysis (4). In the current case, the development of SJS was inversely correlated to the presence of Tregs in the skin. Tregs were probably depleted by mogamulizumab, because CCR4 is highly expressed on Tregs as well as on ATL tumour cells (4, 5). Although more cases are to be analysed, our case may provide *in vivo* evidence that absence of Treg functions in skin is the primary cause of SJS, at least during the treatment with mogamulizumab.

It has been reported that the skin lesion by mogamulizumab usually developed after the fourth or subsequent infusion (4, 6), while the skin lesion in our case developed just after the second infusion. Thus far, it remains unknown what kind of factors determine the onset or severity of adverse skin reaction by mogamulizumab (6). Further research is required to reveal the mechanism.

The authors declare no conflict of interest.

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