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SHORT COMMUNICATION

CD30-positive Cutaneous Pseudolymphoma Caused by Tocilizumab in a Patient with Rheumatoid Arthritis: Case Report and Literature Review

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Tocilizumab is a biological disease-modifying anti-rheumatic drug (DMARD) that targets interleukin 6 (IL-6) receptor, blocking IL-6 signalling (1). Tocilizumab has shown efficacy in the treatment of rheumatoid arthritis (2); however, it sometimes induces cutaneous adverse reactions. We report here a case of pseudolymphoma caused by tocilizumab, manifesting as an unusual cutaneous eruption. We also review the literature concerning drug eruption caused by tocilizumab, and pseudolymphoma caused by biologics in general.

CASE REPORT

A 68-year-old woman was referred to our department for evaluation of an eruption on her face and trunk. She had developed palpable papules and erythema 7 days after the fifth administration of tocilizumab for her rheumatoid arthritis. Physical examination revealed erythematous solid papules on her face (Fig. 1A) and trunk. Biochemical profiling revealed an elevated γ-GTP level (41 U/l; normal <32 U/l). At the first visit, a skin biopsy from a papular lesion revealed a massive infiltration of lymphocytes, some of which had large nuclei with prominent nucleoli in the upper and middle dermis (Fig. 1B). The infiltrates were intermingled with eosinophils. Immunohistochemical study of infiltrating cells showed that $CD4^+$ cells were dominant and, notably, large atypical cells expressed CD30 (Fig. 1C). However, Southern blot analysis demonstrated no clonal T-cell receptor (*TCR*)-*Cβ1* gene rearrangement in a skin sample. The eruption was diagnosed as $CD30^+$ pseudolymphoma, possibly due to tocilizumab. To clarify the causative drug, a lymphocyte stimulation test (LST) with tocilizumab was performed, as described previously (3). ^{3}H-thymidine incorporation was significantly increased by the addition of 8.7×10^{-7} M tocilizumab (corresponding to Cmax) to the peripheral lymphocyte culture, with a stimulation index of 2.1 (Fig. 1D). Based on the clinical course and laboratory examination, the rash was diagnosed as $CD30^+$ pseudolymphoma due to tocilizumab. The patient was treated with topical betamethasone butyrate propionate ointment and tocilizumab was discontinued. Her eruption gradually improved over a period of 2 months.

DISCUSSION

Several cases of drug eruptions due to tocilizumab have been reported previously. We reviewed the literature in English and in Japanese and found 7 case reports describing drug eruptions due to tocilizumab (4–10). Seven out of 8 patients were female. The mean interval between the last drug intake and the appearance of drug eruption is relatively short (3.6 days). Interestingly, 2 cases developed after the first administration of tocilizumab. Clinical manifestations were as follows; maculopapular (2 cases), skin ulcer (1 case), psoriasiform eruption (1 case), pustules (1 case), toxicoderma (1 case), and pseudolymphoma (our patient). Furthermore, to our knowledge, this is the first report of pseu-

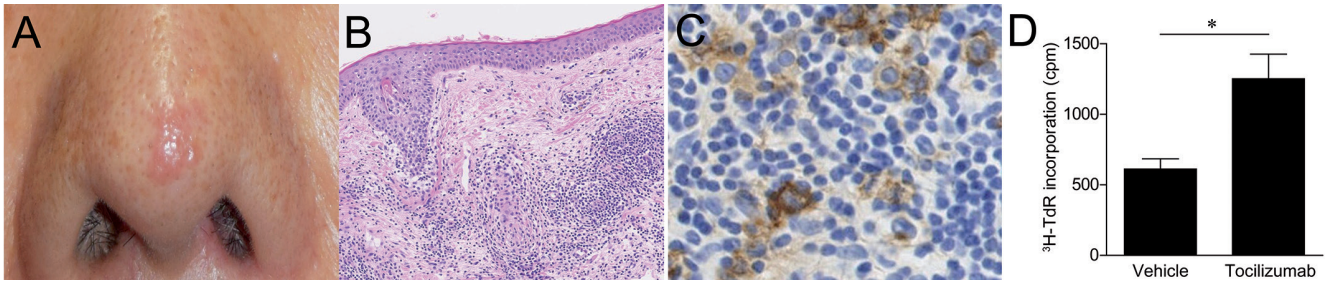

Fig. 1. Representative clinical appearance, histology, and lymphocyte stimulation test (LST) to tocilizumab. (A) Clinical appearance, showing erythematous solid papules on the patient's nose. (B) Massive lymphocytes infiltration into the dermis. Some of these cells have large nuclei with prominent nucleoli (haematoxylin and eosin; original magnification ×100). (C) The infiltrate consists of $CD30^+$ cells by immunohistochemistry (original magnification ×400). (D) LST showing elevated ^{3}H-thymidine (TdR) incorporation in response to tocilizumab added to a 72-h culture of patient's peripheral blood mononuclear cells (PBMC). *$p<0.05$, compared with the control without addition of tocilizumab.

dolymphoma caused by tocilizumab. Pseudolymphoma can be caused by a variety of medicines. Although the detailed mechanism of pseudolymphoma remains unclear, disturbance of cytokine balance might contribute to the pathogenesis of pseudolymphomatous drug eruption. Indeed, other types of biologics, anti-tumour necrosis factor (TNF)-α drugs, have been reported to cause pseudolymphoma (11–13); there have been 4 reported cases including our case. The mean interval between first administration of TNF-α and appearance of pseudolymphoma is longer (mean 218.8 days) than that of non-biologic drugs (14).

In conclusion, it should be kept in mind that pseudolymphoma can occur after treatment with tocilizumab. Further investigation is necessary to clarify the exact pathogenesis of drug-induced pseudolymphoma.

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