

Development of Nodular Lesions after Dupilumab Therapy in Erythrodermic Mycosis Fungoides with Interleukin-13 Receptor $\alpha 2$ Expression

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Accepted Aug 11, 2022; Epub ahead of print Aug 11, 2022

Acta Derm Venereol 2022; 102: adv00766. DOI: 10.2340/actadv.v102.2234

Dupilumab, an interleukin (IL)-4 receptor α (IL-4RA) monoclonal antibody, is a novel therapeutic agent for moderate-to-severe atopic dermatitis (AD), which suppresses IL-4/IL-13-mediated Th2 responses. Advanced mycosis fungoides (MF) and Sézary syndrome (SS) have a Th2-dominant microenvironment, similar to AD, which is thought to be beneficial for the development of MF/SS (1). However, there have been several reports of MF/SS cases that have progressed after dupilumab therapy for the misdiagnosis of AD (2). We report here a case of erythrodermic MF diagnosed based on the development of new nodules after dupilumab therapy. We also examine the expression of IL-13 receptor $\alpha 2$ (IL-13RA2) in the lesional skin to elucidate the mechanism behind the exacerbation.

CASE REPORT

A 47-year-old woman with generalized erythroderma and flat nodules on the cheeks was referred to our department. Scattered erythema had developed on her body and extremities 5 years previously. The lesions expanded gradually and became pruritic erythroderma 2 years previously. Based on a clinical diagnosis of severe AD, dupilumab was administered in the local clinic 1 month before her first visit. At that time, she was not being treated with any systemic medicine other than dupilumab. After the single dupilumab injection, flat nodules developed on her cheeks. She had no medical history of immunosuppressive therapies. On admission,

clinical examination revealed erythroderma with flat nodules on the cheeks (Fig. 1a, b) and generalized peripheral lymphadenopathy. The skin biopsy specimens from the erythrodermic lesion showed superficial dermal band-like infiltration of medium- to large-sized atypical lymphoid cells without epidermotropism (Fig. 1c, d). These cells were positive for CD3 and CD4, and negative for CD7 and CD8 (Fig. 1e, f, and data not shown). CD30 was partially positive (Fig. 1g). Nodular infiltration of similar cells was found in the superficial to deep dermis in the flat nodule (Fig. 1h). Moreover, mild folliculotropism was found. Laboratory studies revealed increased levels of lactate dehydrogenase (465 U/l; reference range 122–222 U/l) and soluble IL-2 receptor (6,296 U/ml; reference range 122–496 U/ml). The white blood cell count was within normal (6,400/ μ l; reference range 3,100–8,400/ μ l) and the lymphocyte count was 1,280/ μ l. The manual blood count failed to find abnormal lymphocytes. Flow cytometric analysis of the peripheral blood revealed that CD4⁺ T cell count was 5,786/ μ l and that the CD4/CD8 ratio was 16.45. Polymerase chain reaction detected the same monoclonal rearrangement of the T-cell receptor γ -chain in the skin and the blood. Human T-cell leukaemia virus type 1 antibody was negative. Positron emission computed tomography detected generalized peripheral lymphadenopathy with the uptake, but not extracutaneous organ involvement. Based on these findings, the patient was diagnosed with erythrodermic MF with suspected blood involvement. A combination treatment of narrow-band ultraviolet B (UVB) irradiation and oral bexarotene was started. Two weeks after starting therapy, the manual blood count revealed circulating abnormal lymphocytes with irregular nuclei (338/ μ l), whereas the white blood cell count was still within normal. Her skin symptoms were now in partial remission and the circulating abnormal lymphocytes decreased to 77/ μ l after 4 months of follow-up.

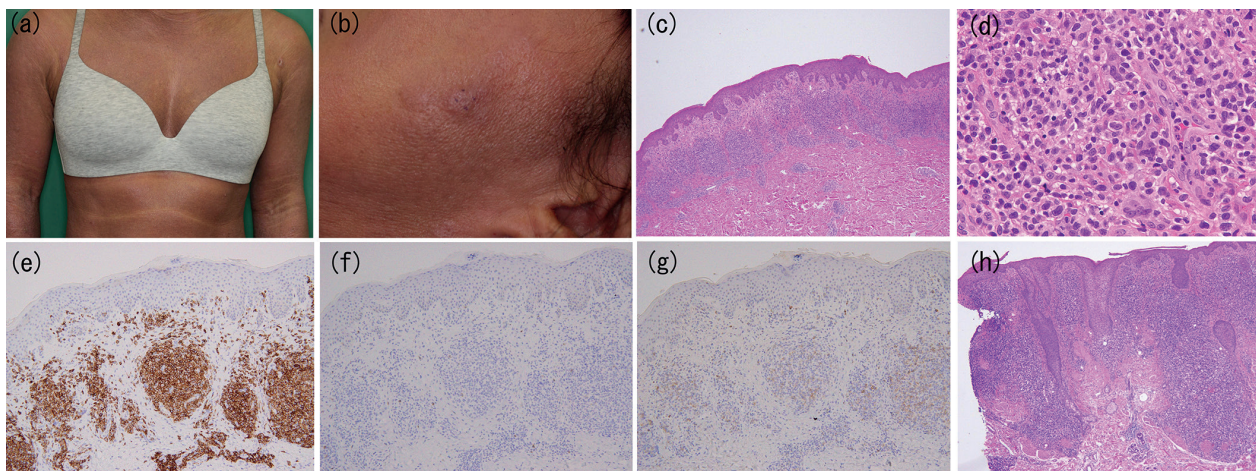


Fig. 1. (a, b) Clinical presentation at first visit. (a) Generalized erythroderma and (b) flat nodules on the cheek. (c, d) Histopathological findings of erythrodermic lesion showing superficial dermal band-like infiltration of medium- to large-sized atypical lymphoid cells without epidermotropism (haematoxylin-eosin (H&E), (c) $\times 40$, (d) $\times 400$). (e–g) Immunostaining for (e) CD4, (f) CD8 and (g) CD30 ($\times 100$). (h) Histopathological findings of the flat nodule showing nodular infiltration of atypical lymphoid cells in the superficial to deep dermis (H&E $\times 40$).

DISCUSSION

The mechanism of MF/SS progression after dupilumab is unknown. One hypothesis is that IL-13 may mediate proliferative signals in MF/SS tumour cells (2, 3). IL-13 is associated with proliferation, survival, adhesion, and metastasis, and thought to be a therapeutic target in various malignancies (4). In cutaneous T-cell lymphoma, IL-13 is overexpressed in tumour cells and considered as an autocrine proliferative factor (5). IL-13 usually mediates its signal through IL-4RA and IL-13RA1 heterodimer, which can be blocked by dupilumab. In contrast, IL-13 also binds with higher affinity to IL-13RA2 than to IL-13RA1. IL-13RA2 serves as a decoy receptor in normal tissues, whereas it mediates IL-13-originated proliferative signals in some malignancies, such as pancreatic cancer, ovarian cancer, and glioblastoma (6–8). Although it is unclear whether the IL-13–IL-13RA2 interaction mediates the signals in cutaneous T-cell lymphoma, the increase in IL-13 binding to IL-13RA2, which cannot be blocked by dupilumab, may be associated with the exacerbation of MF/SS after dupilumab.

IL-13RA2 expression was examined in the current case and 4 other MF cases (2 plaque MF and 2 tumour MF) by immunohistochemistry using a rabbit anti-IL-13RA2 monoclonal antibody (clone E7U7B, Cell Signaling, Danvers, MA, USA). It was found that large-sized mononuclear cells in this erythrodermic MF case and 1 other plaque MF case were positive for IL-13RA2 (**Fig. 2a**). In contrast, 3 out of 4 MF cases showed completely negative staining for IL-13RA2 (**Fig. 2b**). Thus, IL-13RA2 expression may be different, depending on cases. IL-13

activates an AP-1 variant containing c-Jun (9), and AP-1 is a critical transcription factor that regulates cyclin D1 expression and controls cell life and death (10). We next investigated IL-13 using rabbit anti-IL-13 polyclonal antibody (LifeSpan Biosciences, Seattle, WA, USA) and cyclin D1 expression in the current case. Many infiltrating mononuclear cells were positive for IL-13 (**Fig. 2c, d**), which were consistent with a previous report (5). Cyclin D1 expression was higher in the flat nodule compared with the erythrodermic lesion (**Fig. 2e, f**), suggesting that IL-13–IL-13RA2 interaction may be involved in the development of flat nodules in the current case.

A few MF/SS cases have been reported to be improved by dupilumab treatment (11–13). Lazaridou et al. (11) reported 2 cases of MF/SS treated with dupilumab for refractory pruritus. Dupilumab was not effective in 1 case, which was finally diagnosed as SS. Another case was diagnosed as MF, accompanied by AD, and dupilumab was administered, resulting in an improvement in the pruritus and partial remission of MF after 4 months of follow-up. Mollanazar et al. reported 1 case of SS accompanied by AD treated with comprehensive multimodality therapy including bexarotene, interferon- γ , interferon- α , narrow-band UVB irradiation, and extracorporeal photopheresis (ECP) (12). As only partial remission was achieved under treatment for 6 months, dupilumab was added, and a dramatic improvement in skin lesions was achieved. Dupilumab had been continued for 6 months without deterioration. Steck et al. (13) reported 1 case of SS whose skin symptoms and pruritus were markedly improved by the addition of dupilumab to ECP. Dupilumab

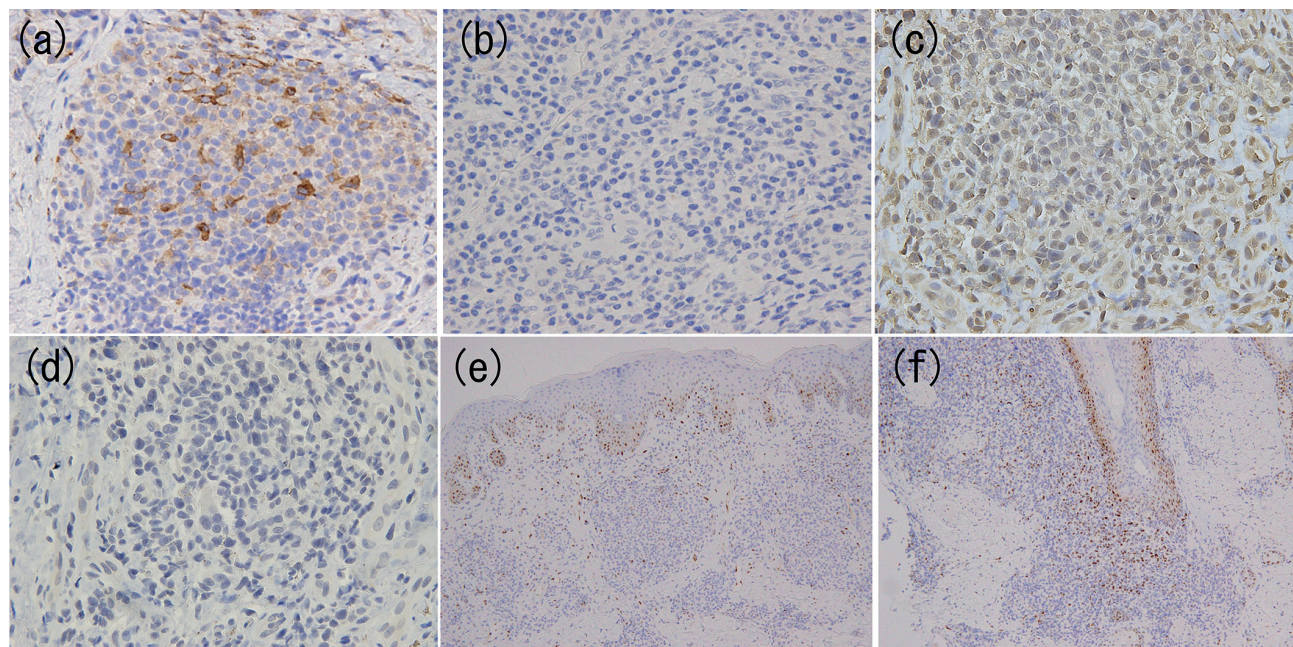


Fig. 2. (a, b) Immunostaining for interleukin (IL)-13 receptor $\alpha 2$ (IL-13RA2) of (a) this erythrodermic mycosis fungoides (MF) case and (b) the representative MF case negative for IL-13RA2 (original magnifications $\times 400$). (c, d) Immunostaining for (c) IL-13 and (d) isotype control of this erythrodermic MF case (original magnifications $\times 400$). (e, f) Immunostaining for cyclin D1 of (e) erythrodermic lesion and (f) the flat nodule of this erythrodermic MF case (original magnification $\times 100$).

had been continued, and the efficacy had been maintained for 44 weeks. Collectively, dupilumab may be beneficial in some cases of MF/SS, although long-term follow-up data are still lacking. The relief of pruritus, resistant to several current therapies, may also be expected.

Currently, dupilumab cannot be used generally for the treatment of MF/SS because it is unclear which cases may benefit from the drug without worsening. IL-13RA2 expression in tumour cells might be associated with progression of MF/SS and absence of IL-13RA2 might be a possible marker for using dupilumab in MF/SS. However, this report examined only 1 case, and larger studies with more cases are necessary.

ACKNOWLEDGEMENT

The authors thank Mayumi Tamaki for technical assistance.

This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology in Japan (20K08683).

The authors have no conflicts of interest to declare.

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