Development of a Prominent Granulomatous Eruption after Interferon-γ Therapy in a Patient with Mycosis Fungoides

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Sir,

Granulomatous inflammation is a fairly unusual phenomenon in skin lesions of cutaneous T-cell lymphomas and a rare phenomenon in cutaneous B-cell lymphomas (1, 2). Histologically, non-necrotizing epithelioid (sarcoid-like) granuloma is the most frequent type (2). The origin, pathogenesis, and biological significance of granulomatous reactions in cutaneous lymphomas remain unclear. We report here a case of mycosis fungoides (MF) in a woman who developed prominent granulomatous lesions on her face after treatment with interferon (IFN)-γ.

CASE REPORT

A 64-year-old Japanese woman presented with a 2-year history of generalized erythematous pruritic eruption, which gradually evolved into multiple nodules. She had had hyperthyroidism for 14 years. Initial examination revealed slightly scaly erythematous patches on her face, trunk and extremities, and several nodules on her back and right forearm (Fig. 1a, b). She was otherwise healthy, with no lymphadenopathy or hepatosplenomegaly. A peripheral blood examination revealed normal counts of leukocytes (4200/μl) with 1% atypical lymphocytes. Soluble interlekin-2 receptor was normal, and anti-human T-lymphotropic virus-1 antibody was negative. A biopsy specimen from a nodule on the right forearm showed a large number of atypical lymphocytes with hyperchromatic, convoluted nuclei infiltrated in the dermis into subcutaneous fat, and invading the epidermis in a single cell fashion (Fig. 1c). Immunohistochemically, the tumour cells were positive for CD3 and CD4, but negative for CD7, CD8, CD30 and CD56. A Southern blot analysis of the tumour cells exhibited monoclonal rearrangement of T-cell receptor (TCR) β gene (Cβ1). Computed tomography showed no abnormality in the internal organs. Based on these findings, we diagnosed the skin lesions as MF, stage IIB ($T_3N_0M_0B_0$), according to the staging and classification of MF.

We treated the patient with systemic IFN-γ injections: 5×10^5 international unit (IU) daily, 5 times per week for 2 weeks; and 7.5×10^5 IU daily, 5 times per week for the following week. She also received narrowband ultraviolet B (nUVB) irradiation (total dose 6000 mJ/cm^2). The skin lesions were markedly improved with these treatments. However, indurated erythematous lesions appeared on her face 4 weeks after the cessation of IFN-γ therapy (Fig. 2a). A histological study of a biopsy specimen from a facial lesion revealed prominent collections of histiocytes without central necrosis throughout the dermis (Fig. 2b, c). Periodic acid-Schiff, Grocott and Ziehl-Neelsen stains were all negative. A Southern blot analysis showed no monoclonal rearrangement of TCR Cβ1 gene. The serum level of angiotension-converting enzyme was within the normal range, and a chest X-ray was normal. We tentatively diagnosed her as having an IFN-γ-induced granulomatous reaction, following IFN-γ therapy. After the combination therapy of systemic IFN-γ and nUVB irradiation, we continued nUVB phototherapy for MF. Since tranilast (Rizaben®) is widely used for the treatment of cutaneous granulomatous reactions, such as sarcoidosis, in Japan (3), we started tranilast treatment

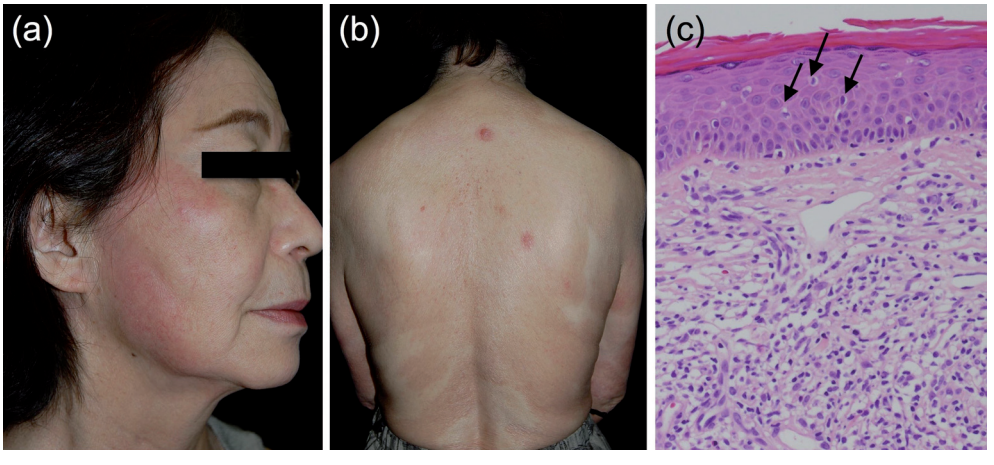

Fig. 1. Initial presentation; (a, b) erythematous patches, (c) histological picture of the right arm, with invasion of atypical lymphocytes in epidermis (*arrows*) (haematoxylin & eosin ×200).

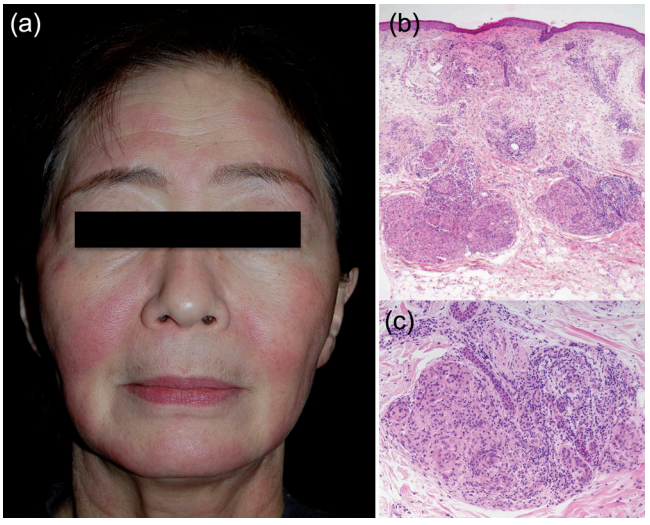

Fig. 2. (a) Facial erythema appearing after IFN-γ treatment. (b) Low-power and (c) high-power views of the histology of facial erythema showing granulomas (haematoxylin & eosin ×40 and ×100, respectively).

of her granulomatous eruption, resulting in a remarkable improvement after 3 months. Inhibition of collagen synthesis in cutaneous fibroblasts by tranilast has been proposed as the underlying mechanism (4).

DISCUSSION

A granulomatous tissue reaction induced by IFN-γ treatment has been documented previously in a case of localized cutaneous leishmaniasis, who developed epithelioid cell granuloma during IFN-γ therapy with a high number of lesional HLA-DR$^+$ macrophages (5). The essential role of IFN-γ in the granuloma formation has also been proved in a murine system (6). The possible causal relationship of systemic IFN-γ treatment with the development of cutaneous sarcoidosis has been reported (7). Our previous study showed that combination therapy of IFN-γ and nUVB irradiation resulted in marked elevation of T-helper (Th)1 chemokines in patients with MF (8).

Our patient also provided an important notion that granulomatous lesions occurred preferentially in the pre-existing skin lesions of MF. Epidermal keratinocytes at the early stage of MF can produce Th1 chemokines (9), and Th1 chemokine receptor CXCR3 is expressed in the tumour cells of granulomatous MF (10). These findings suggest that the skin lesions of MF provide the conditions under which granuloma develops upon IFN-γ administration. Therefore, a possible explanation for the formation of granuloma may be the effects of IFN-γ as part of the therapeutic regimen used for MF.

The authors declare no conflict of interest.

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