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CASE STUDY

A case of psoriasiform drug eruption caused by temozolomide

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Abstract

Psoriasiform drug eruption is defined as condition similar to psoriasis triggered by drug administration, including *de novo* development of psoriasis or exacerbation of pre-existing psoriasis. Herein, we describe a 52-year-old Japanese woman, who developed disseminated psoriasiform lesions following administration of temozolomide, a remedy for glioblastoma, although cutaneous adverse events by this drug was very rare. In addition, we assume that altered inflammatory signals associated with psoriasis, such as activation of signal transducer and activator of transcription 3 (STAT3), might be involved in the underlying pathomechanism of drug eruption caused by temozolomide.

KEYWORDS
drug induced psoriasis, psoriasiform drug eruption, signal transducer and activator of transcription 3 (STAT3), temozolomide, Th17

1 | INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by epidermal hyperproliferation and immunocyte infiltration with unknown etiology. However, it is well known that drug use can develop of de novo psoriasis or exacerbation of pre-existing psoriasis.[1] Certain drugs including β-blockers, Ca antagonists, lithium, chloroquine, and interferons could be culprits of psoriasis.[1,2] Some drugs may have pharmacological mechanisms to trigger psoriatic condition in those who are genetically predisposed rather than simple allergic mechanisms. For example, β-blockers, known as common triggers of psoriasiform drug eruption, cause a decrease in cAMP and intracellular Ca levels in epidermal keratinocytes, resulting in dysregulation of differentiation and promoting keratinocyte proliferation, thereby inducing keratinization similar to psoriasis.[3] Therefore, allergy tests for identifying responsible drugs such as patch testing or drug-induced lymphocyte stimulation test (DLST) are not always relevant. In addition, the duration of drug administration until the onset of skin lesion varies from 1 month to several years.[2] Therefore, it is difficult to diagnose of psoriasiform drug eruption. In this report, we describe a case of psoriasiform drug eruption due to temozolomide (TMZ), a standard remedy for glioblastoma. To our knowledge, this is the first report of TMZ-induced psoriasiform eruption, which allowed us to discuss the possible pathomechanism.

2 | CASE REPORT

A 52-year-old Japanese woman, who was suffering from glioblastoma, was given a regimen of TMZ 240 mg/day for 5 days every 4 weeks. She had taken no medication before that and no past or family history of psoriasis. After 6 cycles of TMZ therapy, a number of erythematosquamous small macules appeared on her lower trunk and extremities, but no joint pain was present (Figure 1A,B). Histological examination of the lesion in the leg revealed manifestations similar to psoriasis including hyperkeratosis, parakeratosis,

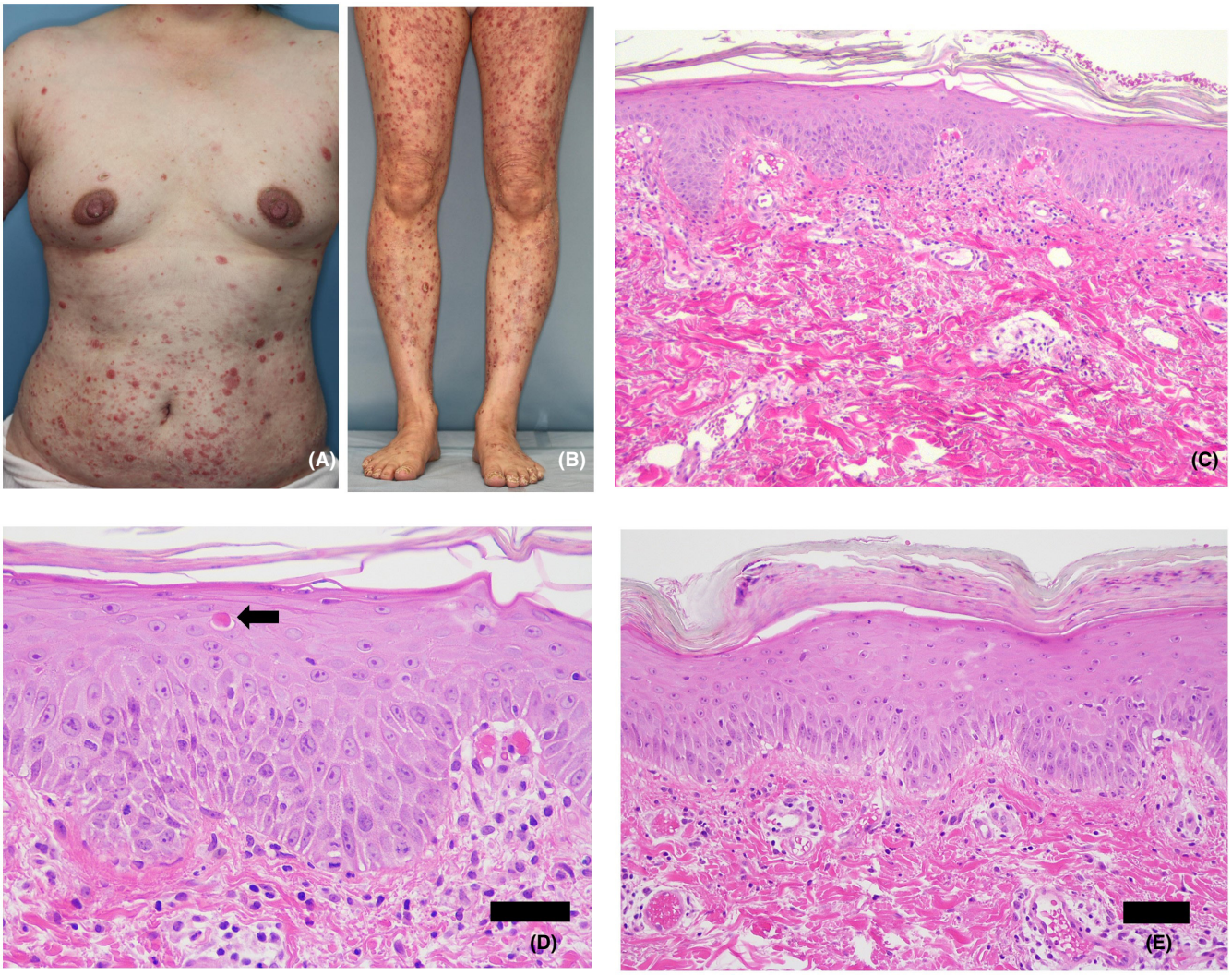

FIGURE 1 (A, B) A number of psoriasis-like, scaly erythematous lesions developed in the trunk and extremities at the initial visit. (C) Histological features of skin biopsy from the lower leg reveals a slight epidermal thickening, vacuolar changes of the basal epidermis (Hematoxylin and eosin staining; H&E, ×100 magnification). (D) Arrow indicates a dyskeratotic cell in the epidermis (H&E, ×400). (E) There are subcorneal neutrophilic infiltrates, loss of granular layer in the epidermis, vacuolar changes of the basal epidermis, and perivascular mononuclear cell infiltrates in the upper dermis (H&E, ×200)

subcorneal neutrophilic infiltrates, loss of granular layer, epidermal thickening and perivascular lymphocytic infiltrates in the upper dermis (Figure 1C). Also, there were features supporting drug eruption such as dyskeratotic cells (arrow, Figure 1D) and vacuolar changes of the basal epidermis (Figure 1E). Although DLST with TMZ was negative, a diagnosis of psoriasiform drug eruption due to TMZ was suspected according to the clinical course after starting TMZ and the histological findings as described above. The patient discontinued TMZ, and treatment with apremilast at a dose of 60 mg/day, narrow-banded ultraviolet B (NB-UVB) phototherapy and topical ointment of combinational vitamin D3 and corticosteroid (maxacalcitol and betamethasone butyrate propionate) were started. Six months later, all the psoriasis-like lesions subsided. Then she resumed TMZ at a reduced dose at 40 mg/day for 5 days, thereafter its dose was gradually increased every month. When the fifth cycle of the regimen of TMZ (160 mg/day) was introduced, psoriasis-like skin rash flared up. The skin rash appeared within a few days after administration of TMZ (Figure 2A,C), but it was relieved by topical application.

After the skin lesions disappeared, we performed scratch patch testing with TMZ, which however turned out to be negative. Next, we administered TMZ at a dose of 40 mg to the patient. After 6 h, she exhibited mixed non-keratotic and keratotic erythema appeared on her abdomen (Figure 2D,E). Histological examination of the skin biopsy of the non-keratotic erythema revealed vacuolar changes and mild perivascular lymphocytic infiltrated in the upper dermis (Figure 2F). On the other hand, in the keratotic, scaly erythema, there were hyperkeratosis, parakeratosis, subcorneal neutrophilic aggregation, vacuolar changes, and mixed inflammatory cell infiltrates of eosinophils, neutrophils and mononuclear cells around dermal vessels (Figure 2G). Finally, a diagnosis of psoriasiform drug eruption due to TMZ was made. Immunostaining of the psoriasiform lesion with anti-phosphorylated Tyr 705 STAT3

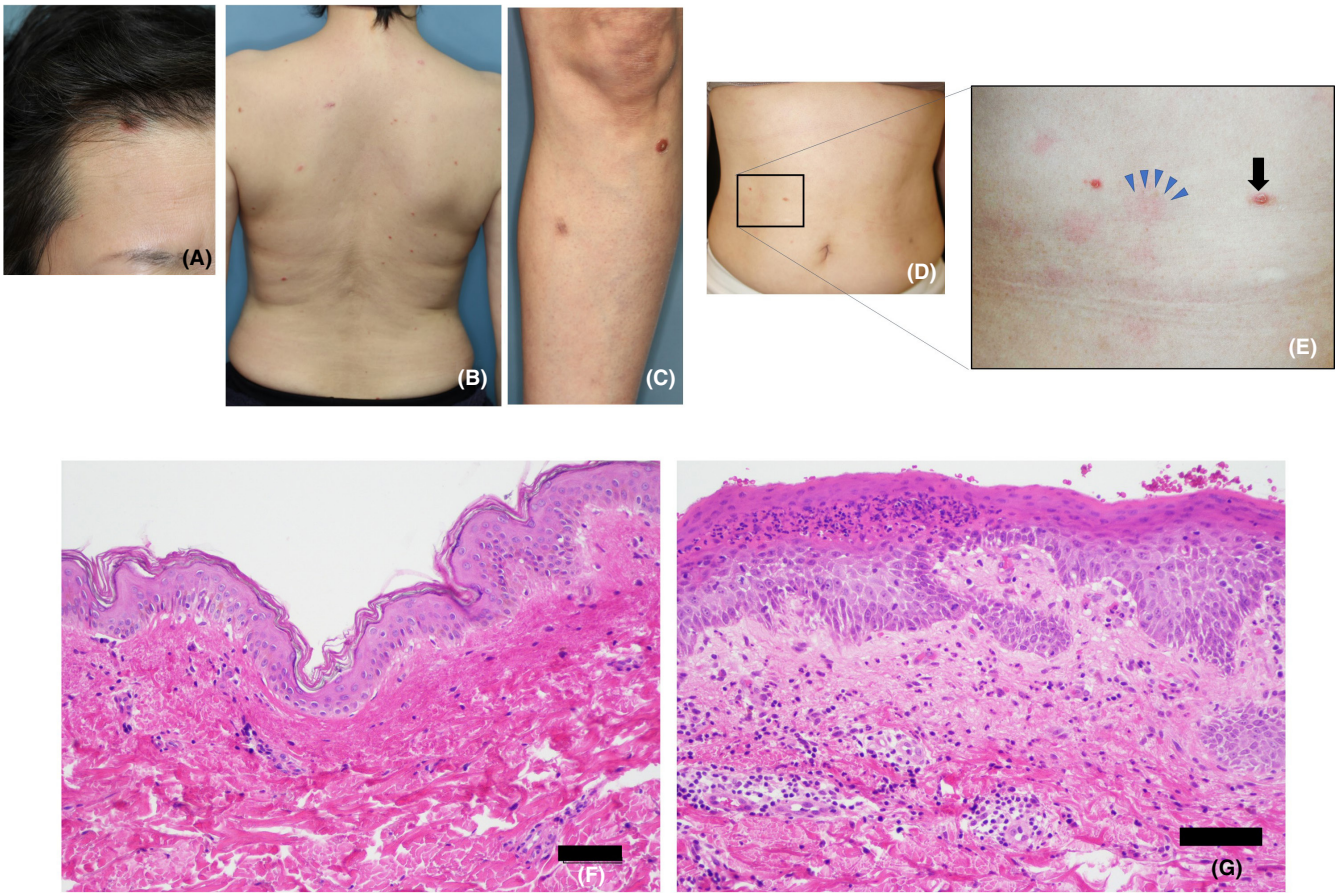

FIGURE 2 (A–C) A few days after the administration of TMZ (160 mg), psoriasis-like skin rashes appeared scattered all over the body. (D) Mixed non-keratotic and keratotic erythema appeared on her abdomen 6 h after administration of TMZ. (E) The arrow head indicates non-keratotic irregular erythema and arrow indicates keratotic drop-like erythema. (F) Histology of the non-keratotic lesion reveals vacuolar changes and mild perivascular mononuclear cell infiltrates in the upper dermis (H&E, ×200). (G) Histology of the keratotic erythema shows hyperkeratosis, parakeratosis, subcorneal neutrophilic aggregation, vacuolar changes of the basal epidermis, and perivascular cell infiltrates with eosinophils and neutrophils mixed with mononuclear cells in the upper dermis (H&E, ×200)

(PY-STAT3) revealed the intra-nuclear STAT3 activation in the keratinocytes of the suprabasal layer of epidermis (Figure 3B), while PY-STAT3 was marginally observed, if any, in the basal layer of normal epidermis (Figure 3A), supporting that TMZ-induced lesion recapitulated the psoriatic epidermal change based on the STAT3 status.[4]

3 | DISCUSSION

Psoriasiform drug eruption, also called drug-induced psoriasis, refers to induction of psoriasis de novo or exacerbation of pre-existing psoriasis triggered by drug administration.[1,2] It is often difficult to diagnose psoriasiform drug eruption because of following reasons. First, the duration of the onset of skin lesion after medication was variable, ranging from a few weeks to several years.[1,2] Second, some cases of psoriasiform drug eruption persisted after the suspected drug were discontinued. Third, the clinical features of psoriasiform drug eruption were diverse types of psoriasis including plaque type, guttate type, pustular type, erythroderma type and others.[2]

Histological features are one of clues that distinguish psoriasiform drug eruption from conventional psoriasis. In general, psoriasiform drug eruptions are characterized by mixed histological findings of both psoriasis and drug eruption; the former composed of hyperkeratosis with parakeratosis, loss of the granular layer, Munro's microabscess, and the latter composed of interface dermatitis with vacuolar changes, dyskeratotic cells, lichenoid reaction, or eosinophil infiltration in the upper dermis.[2] Accordingly, our patient showed the mixed histological manifestations in both the primary drug eruption and provoked lesions by challenging of TMZ. Therefore, we diagnosed as psoriasiform drug eruption due to TMZ. We previously reported a case of psoriasiform drug eruption caused by pravastatin, leading to consequent establishment of de novo psoriasis independent of use of pravastatin.[5]

TMZ is a second-generation alkylating agent that is recommended as the standard remedy for glioblastoma.[6] The general dosing schedule for patients with recurrent disease is 150–200 mg/m^2 once daily for 5 days per 28-day cycle. The most common side effects are nausea, myelosuppression, interstitial pneumonia, and cerebral hemorrhage.[6] There have been only a few reports of drug

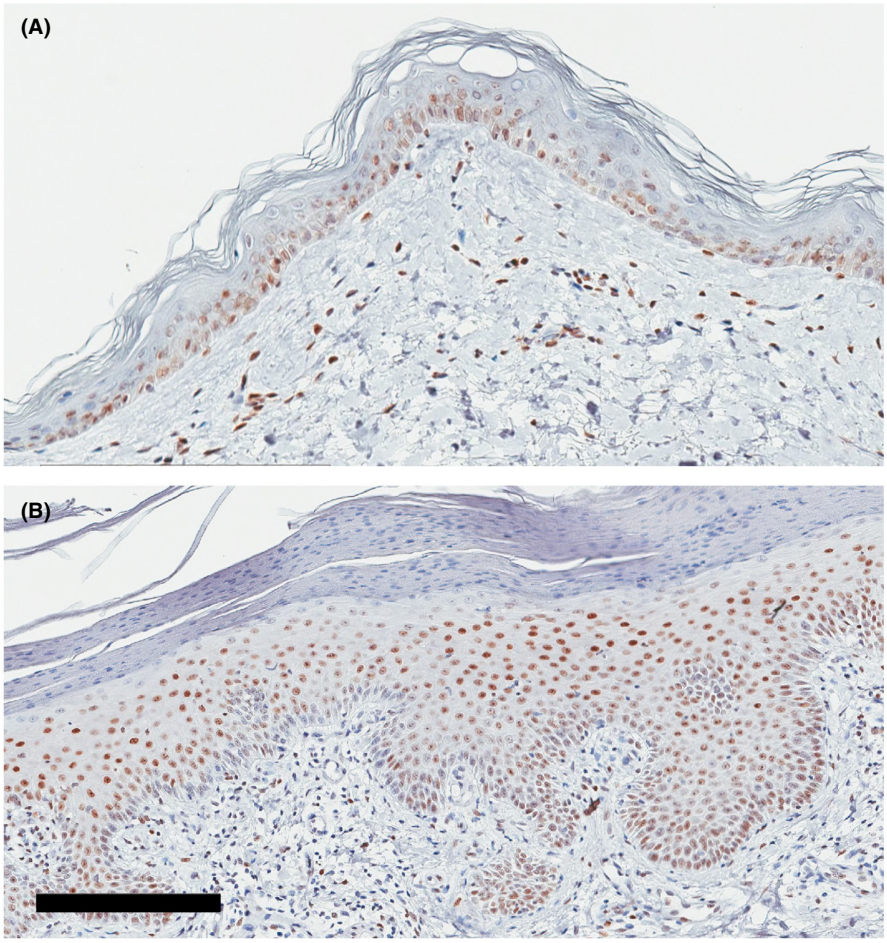

FIGURE 3 Immunohistochemistry with phosphorylated Tyr 705 STAT3 (PY-STAT3). (A) In normal skin, some, if any, of keratinocytes in the basal epidermis are positive for PY-STAT3 (PY-STAT3 staining, ×20). (B) In the TMZ-induced psoriasform lesions, PY-STAT3 is uniformly positive in the subra-basal layer of epidermis (PY-STAT3 staining, ×10)

eruptions caused by TMZ, including erythematous papules and Stevens-Johnson syndrome, but psoriasiform drug eruption have never been reported as far as we investigated.[7] Although the mechanism of pathogenesis underlying psoriasiform drug eruption caused by TMZ is unclear, we hypothesized an involvement of signal transducer and activator of transcription 3 (STAT3).

The interaction between epidermal keratinocytes and T cells is essential for the pathogenesis of psoriasis, and the activation of STAT3 is a prerequisite for its development.[8] Following the breakdown of the epidermal barrier, innate immune activation induces the differentiation, maturation and activation of Th17 cells through the production of TNF and IL-23 by dendritic cells and others. Consequently, IL-17 and IL-22 produced by Th17 cells induce epidermal inflammation, leading to production of chemokine production in turn induce Th17 cells and neutrophils to migrate toward the skin. In the pathogenesis of psoriasis, the activation of STAT3 in epidermal keratinocytes is not only located at the very upstream in the inflammatory circuit but also a consequence of stimulation with IL-20 family cytokines including IL-22.[8]

In recent years, TMZ resistance in patients has been discussed in the treatment of glioma. TMZ methylates guanine in the DNA of tumor cells, inducing apoptosis and exerting an antitumor effect, but in resistant tumor tissues, the repair enzyme O^6-methilguanine-DNA methyltransferase (MGMT) may block to methylating guanin, results in resistance to TMZ.[9] Although there are several provided mechanisms for resistance to anti-cancer drugs, STAT3 activation has been suggested to be keypoint.

STAT3 is also known that exerts an anti-apoptotic effect of tumor cells in various malignancies including skin cancer, and glioma is no exception. It has been reported that STAT3 activation increases the expression of IL-10, TGF-β, and FOXP3 in suppressor T cells, thereby inhibiting tumor cell apoptosis by acting on CD8+ T cells and dendritic cells, as well as inducing the expression of Bcl-2, Bcl-xL, cyclinD1, etc., to promote the growth of vascular epithelium around the tumor.[10] In fact, it has been reported that STAT3 expression correlates with glioblastoma grade and shortened life expectancy.[11] According to Kohsaka et al., STAT3 was also involved in the regulation of MGMT expression, and there was a correlation between the expression level of MGMT and that of STAT3.[12] In other words, TMZ administration may increase the expression of STAT3 and MGMT as a negative feedback pathway, leading to resistance to TMZ.

In our study, we hypothesized that Th17-assciated cytokines and signaling pathway, mainly STAT3, activated by TMZ administration, not only had an anti-apoptotic effect on tumor cells but also induced keratinization in epidermal keratinocytes, resulting in psoriasis-like phenotype. Interestingly, PY-STAT3 was uniformly stained in the supra-basal layer of epidermis, recapitulating the distribution of PY-STAT3 in the psoriatic epidermis.[4] However, it remained elusive

whether TMZ affected T cells as well, since STAT3 activation is required for the Th17 differentiation.[13] Further studies would be warranted.

DECLARATION SECTION

Approval of the research protocol: No human participant was involved in this study.

Informed consent: N/A

Registry and the Registration No. of the study/trial: N/A

Animal Studies: N/A

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR BIOGRAPHY

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