SHORT COMMUNICATION

Papuloerythroderma of Ofuji Associated with Elevated Varicella-zoster Virus Complement-fixing Antibody Titers Following BNT162b2 mRNA COVID-19 Vaccination

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Papuloerythroderma of Ofuji (PEO) is a rare chronic skin disease first described by Ofuji et al. (1). Torchia et al. established diagnostic criteria for PEO consisting of 5 necessary and 5 minor criteria (2). The 5 necessary criteria are as follows: erythroderma-like eruptions formed by the coalescence of flat-topped, red-to-brown papules with a cobblestone-like appearance; sparing of skin folds and creases (deck-chair sign); itching; histopathological exclusion of cutaneous T-cell lymphoma (CTCL) (and other skin diseases); and absence of causative factors. The 5 minor criteria are as follows: age > 55 years, male sex, peripheral and/or tissue eosinophilia, increased serum immunoglobulin (Ig)E levels, and peripheral lymphopenia.

Messenger RNA-based BNT162b2 vaccine from Pfizer-BioNTech was developed to prevent coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3). Diverse cutaneous adverse reactions associated with the BNT162b2 vaccine have been reported (4–9), most of which develop within 3 weeks after the first primary vaccination; however, the long-term cutaneous effects of the BNT162b2 vaccine are unknown. We recently reported 15 cases of BNT162b2 vaccine-triggered late-onset maculopapular eruptions, which developed in older adults several months after the first primary dose. They were associated with mildly elevated varicella-zoster virus (VZV) complement-fixing antibody (VZV-CF Ab) titres (see below) without clinical signs of herpes zoster (HZ) (10). After booster vaccinations of the BNT162b2 vaccine were started, 3 patients with PEO presented to us in 12 months. These patients received the last booster dose of BNT162b2 vaccination several months before the appearance of PEO eruptions. All 3 patients exhibited mildly elevated VZV-CF Ab titres without clinical symptoms of HZ.

Here, we describe the 3 cases of PEO and discuss the relationship among BNT162b2 vaccination, PEO eruptions, and mild elevation in VZV-CF Ab titres, with reference to previously reported BNT162b2 vaccine-triggered maculopapular eruptions associated with a mild elevation of VZV-CF Ab titres.

CASE REPORT

The patients were 3 Japanese older men aged 76, 74, and 76 years, designated patients 1, 2, and 3, respectively. A summary of the 3 patients is presented in **Table I**. The patients developed generalized pruritic skin lesions approximately 6, 7, and 3.5 months after the last booster dose of the BNT162b2 vaccine. The 3 patients had been treated at dermatology clinics with various medicines for 3, 2, and 2.5 months, respectively, without improvement and were then referred to us. Dermatological examination revealed that

Table I. Summary of the 3 patients with papuloerythroderma of Ofuji

Factor	Patient 1	Patient 2	Patient 3
Age (years), sex	76, M	74, M	76, M
Last BNT162b2 vaccination	First booster dose: July 2022	Second booster dose: June 2022	Second booster dose: August 2023
Time of onset of PEO eruptions	January 2023	January 2023	November 2023
Interval between the last BNT162b2 vaccination and the onset of PEO eruptions	Approximately 6 months	Approximately 7 months	Approximately 3.5 months
Time of the first dermatological examination	March 2023	March 2023	February 2024
Percentage of peripheral eosinophils (reference, < 8.5%) (account of peripheral eosinophils)	17.5% (2,023/mm^3)	23.2% (1,918/mm^3)	19.8% (1,443/mm^3)
Percentage of peripheral lymphocytes (reference, 16.5–49.5%)	11.3%	15.4%	16%
Serum IgE (reference, < 173 IU/ml)	32.1 IU/mL	ND*	96.0 IU/mL
VZV-CF Ab titre (positive at ×4 or higher)	×8	×8	×4
History of herpes zoster	–	–	–
Internal solid malignancy**	–	Information was not obtained	–
Treatment and its outcome	Oral betamethasone/*d*-chlorpheniramine maleate → Improvement within 2.5 months	Oral betamethasone/*d*-chlorpheniramine maleate and topical clobetasol propionate → No improvement in 5 days. The treatment was further continued for 5 days but the outcome is unknown because the patient is lost to follow-up	Oral rupatadine fumarate and bilastine and topical difluprednate sulfate → Almost improvement within 8 months
Comorbidity	IgG4-related disease	Cerebral infarction, mitral regurgitation, and paroxysmal atrial fibrillation	Hypertension
Others	The patient developed similar eruptions 3 months after the second booster dose of BNT162b2 vaccination, which was successfully treated with oral betamethasone/*d*-chlorpheniramine maleate within 2 months	The patient committed suicide suffering from severe itching	

M: male; VZV-CF Ab: varicella-zoster virus (VZV) complement-fixing antibody; PEO: papuloerythroderma of Ofuji; Ig: immunoglobulin.
*Not determined. **Screening for internal solid malignancy includes plain chest and abdomen X-ray, abdominal echo, upper gastrointestinal endoscopy, thyroid ultrasound, 2x faecal occult blood, and prostate-specific antigen.

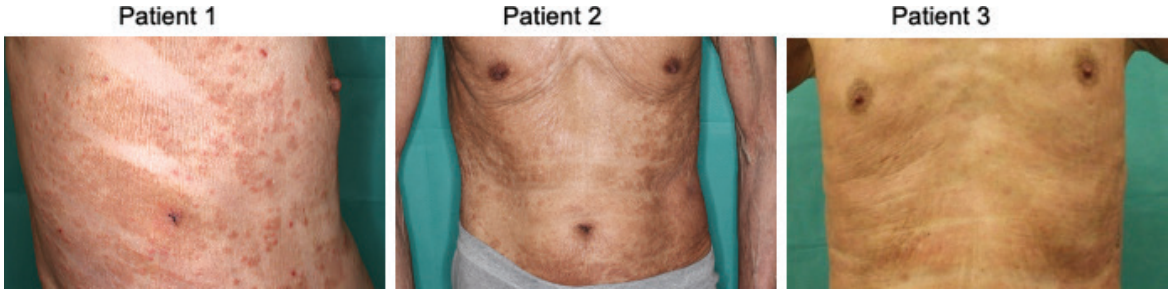

Fig. 1. Clinical findings of the skin lesions of the trunk of patients 1, 2, and 3. Widespread erythematous macules containing multiple flat papules. The erythematous macules spared transverse skin folds with a fairly clear border, which produced the characteristic "deck-chair" sign.

the 3 patients commonly had indurated erythematous macules containing flat papules on the trunk and extremities, producing an erythrodermatous appearance (**Fig. 1**). There was a typical "deck-chair" sign in the abdominal or side skin folds. Laboratory investigations revealed an increase and decrease in the eosinophil and lymphocyte percentages, respectively. The VZV-CF Ab titres in the 3 patients were commonly positive either at ×4 or ×8 (negative at lower than ×4). Histological examination revealed an inflammatory infiltrate comprising lymphocytes and eosinophils around the vessels and between the collagen bundles in the upper dermis of all 3 patients (**Fig. 2**). Based on clinical, laboratory, and histological findings, 3 patients were diagnosed with PEO.

DISCUSSION

All 3 patients developed PEO eruptions 3.5–7 months after the last booster dose of BNT162b2 vaccine with mildly elevated VZV-CF titres. In our experience, VZV-CF Ab titres, which are generally negative in adult individuals, become positive after the onset of HZ, showing levels of ×4–32 in the acute phase. They then reach levels of ×128–1024 during the acme phase and subsequently decline gradually over 1,000 days (11). Although VZV-CF titers in the 3 patients were mildly elevated (we define "mild elevation of VZV-CF Ab titres" as VZV-CF Ab titres at ×4–32 in the previous [10] and present studies), none of them had experienced HZ in the past. Therefore, the elevated VZV-CF Ab titres observed in these 3 patients could not be attributed to recent HZ. Based on our previous proposal that mild elevation of VZV-CF Ab titres without clinical signs of HZ is indicative of recent subclinical reactivation of VZV (10), we consider that the mild elevation of VZV-CF Ab titres in these 3 patients with PEO also indicates recent subclinical VZV reactivation.

We compared several aspects between the present 3 PEO cases and 15 cases of BNT162b2-triggered maculopapular eruptions we have recently reported (10) (**Table II**). Both PEO eruptions and maculopapular eruptions developed in older adults several months after the last BNT162b2 vaccination. The morphological appearance of papules in PEO eruptions is similar to that in maculopapular eruptions. Both eruptions are associated with mildly elevated VZV-CF Ab titres. These facts suggest that PEO eruptions in the 3 patients are also BNT162b2 vaccine-triggered late-onset cutaneous adverse reactions. If this is the case, 1 possible mechanism underlying BNT162b2 vaccine-triggered PEO eruptions is that these eruptions are delayed-type hypersensitivity reactions to the spike proteins translated by the BNT162b2 vaccine. BNT162b2 vaccine-triggered maculopapular eruptions have been attributed to this mechanism (10). Regarding the mechanism of BNT162b2 vaccine-triggered elevation of VZV-CF Ab titres, we speculate that the BNT162b2 vaccine causes immune dysregulation, including decreased cellular immunity against latent VZV by impairing VZV-specific CD8+ T cells, resulting in an elevation of VZV-CF Ab titres through reactivation of latent VZV. Although these hypothetical mechanisms underlying BNT162b2 vaccine-triggered PEO eruptions associated with elevation of VZV-CF Ab titres are valid, it is difficult to explain the aetiological involvement of the elevation of VZV-CF Ab titres in PEO eruptions. VZV is unlikely to be a direct causative virus of PEO eruptions as BNT162b2 vaccine-triggered eruptions in these patients were not HZ but PEO eruptions. In contrast, even if the PEO eruptions in the 3 patients developed independently of BNT162b2 vaccina-

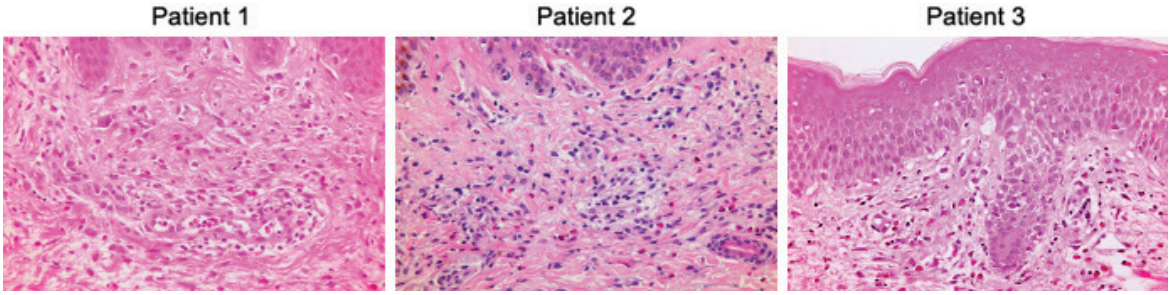

Fig. 2. Histopathological findings of the skin lesions of patients 1, 2, and 3. Perivascular and interstitial infiltrate comprising lymphocytes and eosinophils in the upper dermis (haematoxylin and eosin, original magnification ×200).

Table II. Comparison of 3 cases of papuloerythroderma of Ofuji and 15 cases of BNT162b2-triggered maculopapular eruptions

Factor	Three cases of papuloerythroderma of Ofuji	Fifteen cases of BNT162b2-triggered maculopapular eruptions
Patients' age	Range: 74–76 years Mean: 75.3 years	Range: 57–90 years Mean: 73.7 years
History of BNT162b2 vaccination before onset of skin eruptions	First and second primary vaccination and first and secondary booster vaccination in 2 patients; first and second primary vaccination and first booster vaccination in 1 patient	First and second primary vaccination in all 15 patients
Interval between the last BNT162b2 vaccination and the onset of PEO eruptions	Range: approximately 3.5–7 months Mean: approximately 5.5 months	Range: approximately 0.5–8 months Mean: approximately 2.5 months
Characteristics of skin eruptions	Indurated erythematous macules containing a number of flat papules on the trunk and extremities, producing an erythrodermatous appearance associated with deck-chair sign in the abdominal or side skin folds	Maculopapular eruptions on the trunk and extremities associated with diffuse erythematous macules
Histological findings	Inflammatory infiltrate comprising lymphocytes and eosinophils around the vessels and between the collagen bundles in the upper dermis of all 3 patients Epidermal spongiosis accompanied by exocytosis of eosinophils and lymphocytes in 1 patient	Mild perivascular lymphocyte infiltration in the upper dermis in all 6 specimens obtained
Itching in the skin eruptions	Present in all 3 patients	Present in 12 patients and absent in 3 patients
VZV-CF Ab titre	×8: 2 patients ×4: 1 patient	×32: 1 patient×16: 6 patients; ×8: 8 patients

tion, it is obvious that PEO is associated with subclinical VZV reactivation in some patients. Thus far, VZV reactivation has not been investigated in non-vaccine-related PEO patients. Further examination of VZV-CF Ab titres in PEO patients who did not receive COVID-19 vaccination will reveal whether PEO eruptions are generally associated with mild elevation of VZV-CF Ab titres. It is also important to examine whether COVID-19 vaccines other than BNT162b2 trigger PEO.

Many studies have reported clinical VZV reactivation due to SARS-CoV-2 infection either during disease progression or after recovery (12, 13). In addition, previous studies have demonstrated that COVID-19 vaccines, including BNT162b2, can trigger the clinical reactivation of latent VZV (12, 14, 15). The present study and these studies suggest that SARS-CoV-2 infection and COVID-19 vaccines cause the reactivation of latent VZV, although the reactivation levels of VZV are variable.

Although the underlying aetiology of PEO has not been clarified, a causative link between PEO and several diseases, including internal solid malignancies, such as stomach cancer and colon cancer, haematological neoplasms, such as non-Hodgkin's lymphoma and Hodgkin's lymphoma, and infections, such as hepatitis C and sepsis, has been considered (2). Although we consider that PEO in the present 3 patients was triggered by previous BNT162b2 vaccination, we cannot exclude the possibility that PEO was associated with the diseases described above. We are planning to carefully follow-up patients 1 and 3 (patient 2 committed suicide) for the future development of internal solid malignancy and haematological neoplasms. It is also important to continue to focus on changes in cutaneous lesions because it has been reported that some patients with PEO later developed a CTCL (2).

The author has no conflict of interest to declare.

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