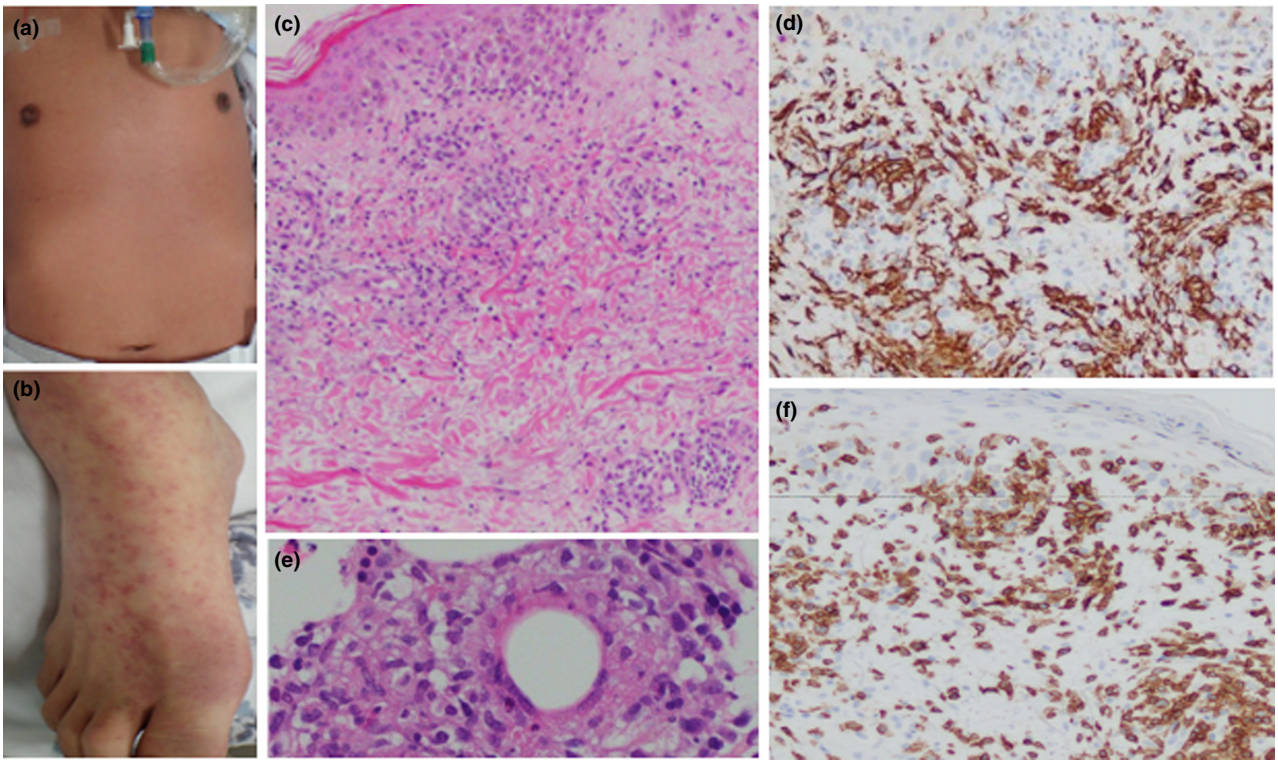

Figure 2 Clinical manifestations and histopathology of a skin biopsy from violaceous erythema. (a) Diffuse erythema without erosion involving the trunk. (b) Violaceus plaques were diffusely distributed on feet. (c) Histopathology of a skin biopsy. Hematoxylin and eosin staining. ×100. (d) Immunohistochemical staining for CD163. ×200. (e) Histopathology of bone marrow biopsy. Hematoxylin and eosin staining. ×400. (f) Immunohistochemical staining for CD3. ×200.

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Haemorrhagic bullous pyoderma gangrenosum following COVID-19 vaccination

Dear Editor,

Pyoderma gangrenosum (PG) is a destructive, inflammatory, neutrophilic dermatosis and often associated with an underlying systemic disease. PG is characterized by a rapidly progressive ulcer with a purulent, necrotic base and a raised, violaceous, undermined border developing from the breakdown of painful nodules or pustules.[1,2] Clinical variants of PG include ulcerative, bullous, pustular, vegetative and peristomal.[1,2] There have been various cutaneous reactions reported after COVID-19 vaccination. However, to our knowledge, there has been no COVID-19 vaccination-associated PG reported.

A 46-year-old otherwise healthy male presented with fever (38.4°C) and painful blisters on the extremities for 5 days. He had received the first-dose ChAdOx1 nCov-19 (Oxford-AstraZeneca) vaccination 2 weeks before presentation. Dermatologic examination revealed numerous haemorrhagic blisters on his hands, elbows, knees, legs and feet and scattered necrotic ulcers

with granulomatous bases and undermined edges developing after blisters ruptured (Fig. 1a, b, and c). Histopathological examination obtained from the ulcer edge on the left leg showed neutrophilic and lympho-histiocytic infiltrates in the undermining oedematous ulcer edge and underlying dermis (Fig. 1d). A direct immunofluorescence study and blood and tissue cultures for bacteria, fungus, mycobacteria, and herpes virus were all negative. Laboratory testing revealed normal liver and renal function, complete blood count, prothrombin time, and activated partial thromboplastin time, except for mild elevated C-reactive protein, D-dimer (873 ng/mL FEU; reference range, ≤ 550 ng/mL) and fibrinogen (483 mg/dL; reference range, 190–380 mg/dL) levels. Anti-nuclear antibody and anti-basement membrane zone antibody were unremarkable. The workup of vasculitis showed normal anti-neutrophil cytoplasmic antibody, protein-C, protein-S, anti-phospholipid antibodies and cryoglobulin levels. Negative anti-platelet-factor 4 testing further excluded the possibility of vaccine-induced thrombotic thrombocytopenia. Haemorrhagic bullous PG was diagnosed on clinical and histopathologic grounds. The patient did not have any underlying diseases, such as haematological malignancy, inflammatory bowel disease (IBD) and autoimmune disease. Naranjo causality assessment showed an association between vaccination and PG. The patient was treated with intravenous methylprednisolone (1 mg/kg/day) and cyclosporin (150 mg/day) for 1 month during admission. Repeated wound cultures did not identify microorganisms. The ulcerated lesions gradually healed without developing new blisters (Fig. 1e); oral methylprednisolone and cyclosporin were tapered to 8 mg/day and 100 mg/day, respectively, during his last follow-up, 1 month after discharge.

Bullous PG manifesting with a growing central necrotic and haemorrhagic blister has rarely been reported.[3] PG is a diagnosis of exclusion, which is made primarily based on clinical features. A skin biopsy taken from an active ulcer border with tissue cultures to exclude other aetiologies of ulcerations and infections is recommended. Systemic corticosteroids are first-line therapies with cyclosporine as a second-line treatment.[1,2] PG often has an associated systemic disease, such as IBD, monoclonal gammopathy, hematologic malignancy, arthritis, infection and collagen-vascular disease, while bullous PG is significantly associated with haematological malignancies.[1,2] The results of autoimmune and tumour markers, protein electrophoresis, peripheral blood smear, colonoscopy and whole body computed tomography in this patient were unremarkable. PG following SARS-CoV-2 infection and other neutrophilic dermatoses after COVID-19 vaccination have been documented.[4–6] COVID-19 vaccines can induce intensive T- and B-cell responses against SARS-CoV-2 and unwanted off-target immune-stimulatory effects, subsequently eliciting cutaneous T-cell-dependent disorders.[4] T-cell expansion and inflammatory cytokines play a role in PG.[2] Systemic corticosteroids are first-line therapies, either as an intravenous high dose (0.5–1 mg/kg/day) or pulse corticosteroid (1000 mg/day).[1,2] Cyclosporine (2.5–5 mg/kg/day) is used as a second-line treatment, and other immunosuppressive agents, including azathioprine, methotrexate and mycophenolate mofetil, have been used.[1,2] Biologics, including anti-tumour necrosis

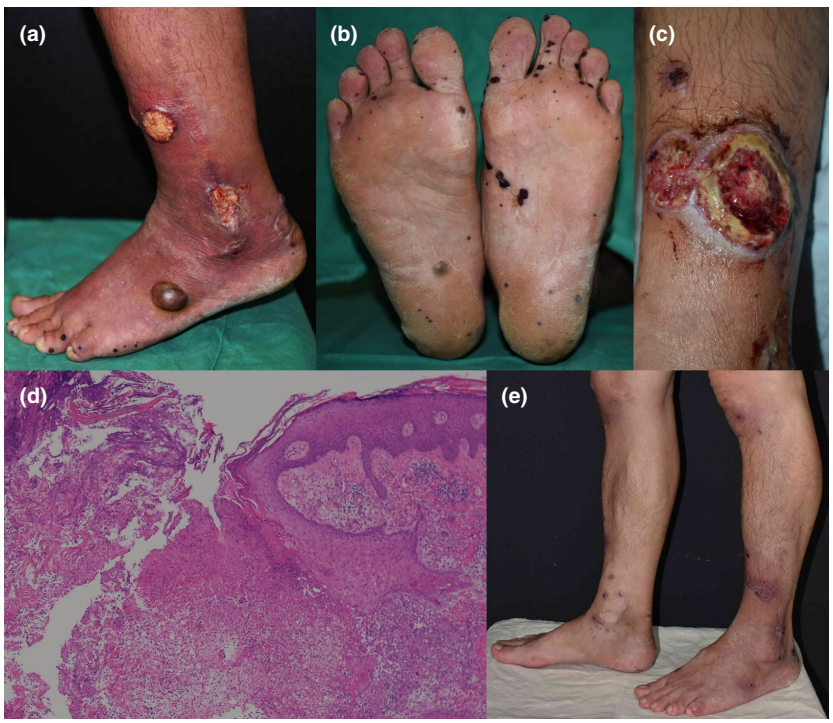

Figure 1 COVID-19 vaccination-associated haemorrhagic bullous pyoderma gangrenosum. (a–c) Numerous haemorrhagic blisters and scattered necrotic ulcers with granulomatous bases and undermined edges on the lower legs and feet. (d) Histopathology showing an undermining ulcer edge with subepidermal oedema, haemorrhage and dermal inflammatory infiltrates including numerous neutrophils (haematoxylin–eosin, original magnification ×200). (e) Healed ulcerated lesions without new blisters after 1 month of treatment.

factors (anti-TNFs) and interleukin-1 receptor antagonists (IL-1RAs), have been used to treat refractory PG effectively.[1,2] Considering the response to COVID-19 vaccination may be reduced while receiving systemic immunomodulatory therapies, systemic corticosteroids at a prednisone-equivalent dose of ≥20 mg/day, methotrexate and mycophenolate mofetil are recommended to be hold for 1–2 weeks in patients undergoing COVID-19 vaccination, while anti-TNFs or IL-1RAs may be alternative options with less interfering the antibody titers.[7]

We reported a case of PG following COVID-19 vaccination, which posed a diagnostic challenge. The present case highlights the characteristic manifestations of haemorrhagic bullous PG, which is both an uncommon clinical variant of PG and a rare cutaneous reaction to COVID-19 vaccine. Early recognition and adequate immunomodulants treatment often yield a favourable prognosis.

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Conflict of interest

None declared.

Data availability statement

Data available on request from the authors.

Y.-T. Hung,[1,2] W.-H. Chung,[1,2,3] T.-F. Tsai,[1,2] C.-B. Chen[1,2,3,*]

[1]Department of Dermatology, Chang Gung Memorial Hospital, Linkou, Taipei, and Keelung branches, Taoyuan, Taiwan, [2]Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Linkou branch, Taoyuan, Taiwan, [3]College of Medicine, Chang Gung University, Taoyuan, Taiwan

*Correspondence: C.-B. Chen. E-mail: chunbing.chen@gmail.com

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Two cases of axillary lymphadenopathy diagnosed as diffuse large B-cell lymphoma developed shortly after BNT162b2 COVID-19 vaccination

Dear Editor,

We describe two patients with diffuse large B-cell lymphoma (DLBCL), which developed as axillary lymphadenopathy after BNT162b2 COVID-19 vaccination.

Case 1 was a 67-year-old Japanese man who visited Tokyo-kita Medical Center complaining of a 6.0-cm subcutaneous mass in the left axilla 2 weeks after the second BNT162b2 vaccination. Tenderness and a palpable lymph node (LN) in the left axilla were noted 1 day after the first BNT162b2 vaccination. Computed tomography revealed an enlarged LN in the left axilla (Fig. 1a), and it was suspected as a reactive lymphadenopathy. However, the nodule became bigger and was accompanied with redness of the surrounding skin. Hence, biopsy specimens were taken from the swollen LN and erythematous skin (Fig. 1b). Histopathological examination revealed a diffuse infiltration of large, atypical lymphocytes with centroblast and immunoblast in the LN (Fig. 1c) and the skin. The large, atypical lymphocytes were stained strongly with CD20, BCL2 and MUM-1/IRF4 (Fig. 1d–f) and were negative for CD3. The Ki-67 positivity was over 80%. He was diagnosed with DLBCL, and R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) regimen was initiated, resulting in the shrinkage of the LN.

Case 2 was an 80-year-old Japanese woman who visited the University of Yamanashi Hospital due to an enlarging nodule in her left axilla 1 day after the second BNT162b2 vaccination. The nodule appeared 2 days after the first vaccination. Ultrasonography detected a 4.1-cm round mass with blood flow (Fig. 2a), which was suggestive of lymphadenopathy. Two months after the first consultation, the nodule gradually enlarged, and computed tomography revealed a 6.0-cm mass in the left axilla (Fig. 2b) and another 2.8-cm mass in the left mesentery. A biopsy of the nodule in the left axilla (Fig. 2c) demonstrated a sheet-like diffuse infiltration of atypical lymphocytes (Fig. 2d). The atypical cells were positive for CD20 (Fig. 2e), BCL6 and BCL2 and negative for CD3 and MUM-1/IRF4. The Ki-67 positivity was over 90%. A diagnosis of germinal centre B-cell

