

Pyoderma Gangrenosum Triggered by COVID-19 Vaccination in a Patient with Ulcerative Colitis: A Case Report

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Abstract

Pyoderma gangrenosum (PG) is a rare inflammatory skin disease that is difficult to diagnose. PG may be an extra-intestinal manifestation of ulcerative colitis (UC). In recent times, coronavirus disease (COVID-19) vaccines have caused various adverse cutaneous reactions. However, to the best of our knowledge, combinations thereof have not been reported. We encountered a case of PG triggered by COVID-19 vaccination in a patient with UC. A 40-year-old woman developed severe pain and an abscess in the dorsum of the left foot after receiving the first dose of the messenger RNA (mRNA)-based Pfizer/BioNTech BNT162b2 COVID-19 vaccine. Severe painful ulcers with purulent necrosis and gaseous gangrene progressed rapidly along the extensor tendons and muscles to the toes and ankle. Although surgical debridement can worsen PG by triggering pathergy, we nonetheless performed wide debridement including partial extensor tenotomy with abscess drainage to prevent progression to pyogenic ankle arthritis and to rescue the toes. Antibiotics, corticosteroids, and anti-coagulants were prescribed during surgical wound management via negative pressure therapy. After the lesion improved, the skin and soft tissue defect were covered using a superficial circumflex iliac artery perforator free flap and a split-thickness skin graft. The patient was satisfied with the foot salvage, and could walk unaided (without a brace or cane) from 8 weeks after the final surgery. PG may be rare even in UC patients, but mRNA-based COVID-19 vaccines may find an immunosuppressive niche. A high level of caution and suspicion of skin manifestations after vaccination is essential.

Keywords

foot, pyoderma gangrenosum, ulcerative colitis, Pfizer/BioNTech BNT162b2 COVID-19 vaccine

Introduction

Pyoderma gangrenosum (PG), a neutrophilic auto-inflammatory dermatosis, is a rare skin disease. Although the etiology or pathogenesis is unknown, PG is thought to be an immune reaction induced by inappropriate neutrophil activity that triggers neutrophilic dermatosis followed by rapid development of painful, cutaneous necrotic ulcerations.¹ PG is characterized by painful pustules or nodules that become ulcerated. PG may be an extra-intestinal manifestation of ulcerative colitis (UC).² The incidence varies from 0.4 to 2.6% in patients with inflammatory bowel disease.³ PG may be combined with rheumatological or autoimmune diseases, or hematological malignancies. PG commonly affects the lower extremities and trunk, but can involve any part of the body including the perineal region, peristomal sites, and previous surgical incisions.

Since December 2019, when a novel coronavirus disease (COVID-19) was first reported in Wuhan, Hubei Province, China,^{4,5} the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has spread across the globe.

The rapid development of various COVID-19 vaccines has helped to drastically decrease the devastating burden of the pandemic. Like other vaccines, COVID-19 vaccines can cause a variety of adverse events, including injection site pain, erythema, induration or edema, fatigue, headache, fever, chills, myalgia, arthralgia, lymphadenopathy, and hypersensitivity reactions.^{6–8} Several cutaneous manifestations after

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messenger RNA (mRNA)-based COVID-19 vaccination have been reported, including urticaria, eczematous dermatitis, and granulomatous inflammation.^{9,10} Herein, we report a 40-year-old woman with UC who presented with a rapidly progressing PG lesion of one foot dorsum after the first dose of the Pfizer/BioNTech BNT162b2 COVID-19 vaccine. Informed consent was obtained from the patient for publication of this report and the accompanying images.

Case Report

A 40-year-old woman visited our emergency department with left foot pain and purulent discharge from a dorsal foot wound. She had no fever and her vital signs were stable. Laboratory findings revealed a hemoglobin level of 8.6 g/dL; slight thrombocytosis ($557 \times 10^9/L$; normal 150–450 $10^9/L$); a normal white blood cell count; an elevated C-reactive protein level (11.70 mg/dL; normal 0–0.3 mg/dL); a positive anti-PR3 antibody reaction (73.8 IU/mL; normal <20 IU/mL); a slightly elevated fibrinogen level (413.9 mg/dL; normal 160–410 mg/dL); and an elevated D-dimer level (1.64 mg/L FEU; normal 0–0.55 mg/L FEU). Antinuclear and antineutrophil cytoplasmic antibody status, and the prothrombin and activated partial thromboplastin times, were normal. On physical

examination, the wound was 7 × 7-cm in dimension with a central skin defect and internal pus. The margin was violaceous with palpating gas crepitus, and the soft tissue was very friable. The lesion was extremely painful and progressed rapidly (Figure 1). She had been diagnosed with UC at our hospital 2 years prior. However, she ceased follow-up on her own initiative 19 months prior when her gastrointestinal symptoms became tolerable on medications. Even after arbitrary cessation of medication including mesalazine and methylprednisolone, she had only intermittent bloody stools for the recent 2 months. She had received the first dose of the messenger RNA-based Pfizer/BioNTech BNT162b2 COVID-19 vaccine 2 weeks prior. The left foot pain and swelling commenced 1 week later. She visited a local clinic and received a steroid injection into the painful left foot dorsum. However, the swelling worsened. Ulcerative vesicles and pustules appeared 2 days prior to the emergency department visit. Radiography revealed air (gas) in the dorsal soft tissue and magnetic resonance imaging showed a mixture of infectious soft tissue and abscesses.

We performed an emergency operation for exploration, debridement, and abscess drainage. The operative findings included skin and subcutaneous necrosis, and a peritendinous infection along the extensor tendons. All five metatarsophalangeal joints were involved; a diffuse progressive infection was evident. All infected extensor tendon sheaths were excised and debrided; we performed second and third extensor digitorum tenotomy and dorsalis pedis arterial ligation. An infectious, medial dorsal cutaneous branch of superficial peroneal nerve underwent neurectomy; and an infectious, intermediate dorsal cutaneous branch of superficial peroneal nerve was subjected to neurolysis. All obvious abscesses were maximally drained with contiguous debridement and irrigation, followed by negative pressure wound therapy (NPWT)



Figure 1. The left foot. A 7 × 7-cm ulcerative lesion with a purulent discharge, a violaceous margin, and gaseous crepitus.



Figure 2. Negative pressure wound therapy was performed after consecutive necrotic tissue debridement with abscess drainage and irrigation.

using a vacuum-assisted closure system (V.A.C.[™], KCI®, San Antonio, Texas, USA) for 14 days. After confirming that the infection was grossly controlled (Figure 2) and that the laboratory inflammatory findings had normalized, we referred the patient to our plastic surgery team. A superficial circumflex iliac artery perforator free flap combined with a split-thickness skin graft was performed (Figure 3). Biopsies were performed at the ulcer edge consistent with diagnostic criteria according to the referenced Delphi consensus.¹¹ The biopsy of the ulcer revealed erosion, hemorrhagic necrosis, and abscess formation of/in the epidermis, as well as neutrophilic aggregations with necrosis in the upper dermis and subcutis, consistent with acute suppurative inflammation including PG (Figure 4). Four tissue cultures were performed from different sites of initial purulent wound prior to debridement

surgery, and the blood culture was also performed. All microbiological studies, including aerobic and anaerobic microbes in blood and tissues, were negative. Interferon-gamma release assay was negative and skin biopsies showed no tuberculoid granulomas or other characteristic histopathologic features of tuberculosis. Sigmoidoscopy to follow-up the untreated UC revealed complete loss of the vascular pattern, diffuse nodular mucosal swelling, and erosion, but fortunately nothing worse than had been observed at the last follow-up 2 years prior.

During the above treatment, the patient received methylprednisolone 40 mg/day intravenously for 5 days and was then changed to oral prednisolone that was progressively tapered every 3 days. The initial intravenous antibiotics were ceftriaxone 4 g/day and clindamycin 1800 mg/day, with a change to cefobactam 6 g/day after 2 weeks. Since



Figure 3. A superficial circumflex iliac artery perforator free flap and a split-thickness skin graft were placed.

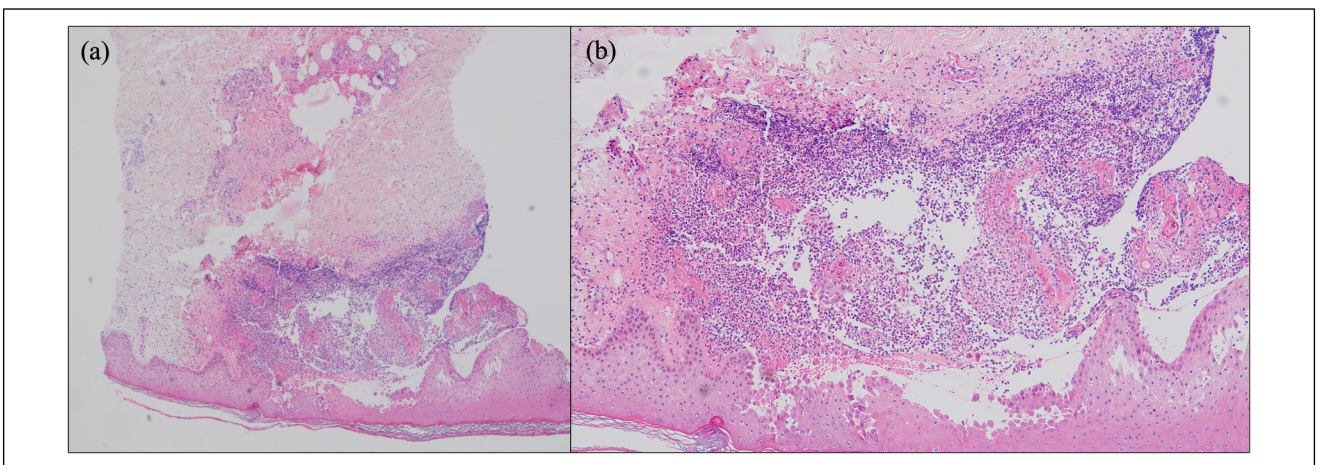


Figure 4. Histopathology revealed erosion and hemorrhagic necrosis of the epidermis, and neutrophil infiltration into the dermis and subcutis [hematoxylin-eosin, original magnifications $\times 40$ for (a) and $\times 100$ for (b)].

she received high-dose glucocorticoid therapy, prophylactic antibiotic treatment was maintained to prevent secondary infection. Rivaroxaban 20 mg was administered throughout the entire hospital stay until the laboratory hypercoagulation profile normalized. After confirming that the wound had healed and that the flap was stable (about 2 weeks after surgery), the patient commenced active ankle range-of-motion exercises and was allowed to walk with crutches (without weight-bearing) for 4–6 weeks in a boot. After 8 weeks, she could walk with full weight-bearing, without crutches or a cane. Twelve weeks after flap surgery, she could walk on her own in wide-toe boxed shoes. She was satisfied with the foot salvage despite sequelae of toe stiffness and sensory loss of the foot dorsum.

Discussion

PG is an uncommon, ulcerative auto-inflammatory dermatosis. The initial clinical signs include painful skin nodules, which usually occur new or after minor trauma, then rapidly progress to large ulcers with eroded margins and sloughy necrotic bases.^{12,13} Local treatments include limb elevation, dressings, wet compresses, and topical steroids. Systemic treatments include corticosteroids, thiopurines, cyclosporine, infliximab, and intravenous antibiotics.^{2,14–16} Although PG is not associated with UC disease activity, PG can be an extra-intestinal manifestation in patients with acute severe UC.² The previously diagnosed UC of our patient had not recently been treated, but the sigmoidoscopic findings had not worsened. We suggest that the PG ulcer was not associated with UC activity, being rather immunologically triggered by the COVID-19 vaccine. Although rapid vaccine development has saved many lives, the vaccines cause several side-effects, including skin manifestations. Several studies over the past 2 years have reported skin side-effects after COVID-19 vaccination, including PG.^{17–21} To the best of our knowledge, a PG ulcer triggered by COVID-19 vaccination in a patient with UC has not been reported.

During the treatment of our patients, the following diagnoses should be differentiated: Infectious diseases such as tuberculosis, rheumatic diseases (eg, sarcoidosis, vasculitis etc), and other immune dysregulation diseases. We excluded bacterial or tuberculosis infection by repeated bacterial cultures, interferon-gamma release assays, and tissue biopsies. Autoinflammatory phospholipase C γ 2 (PLC γ 2)-associated antibody deficiency and immune dysregulation (APLAID) should also be differentiated when the patients have atypical skin lesions with gaseous gangrene. APLAID is an autosomal dominant chromosomal disease characterized by recurrent blistering skin lesions and inflammatory cell infiltration into the joints, eyes, and gastrointestinal tract.^{22–24} If the patient has recurrent respiratory tract infections, skin disorders, inflammatory symptoms such as arthritis, abdominal pain, low serum immunoglobulin (Ig)G, IgA, and IgM levels,

ALPAID should be considered as a differential diagnosis. However, clinically and serologically, the possibility of these disease was low, so they were excluded.

The literature states that PG wound debridement is usually contraindicated because this can exacerbate the PG ulcers. However, in real clinical situations, it is not uncommon for patients with PG to undergo surgical debridement after visiting the emergency department rather than visiting a dermatologist due to a rapidly progressing disease.^{1,25,26} Our patient had received a steroid injection into the foot before visiting our emergency department. We hypothesize that the injection served as the initial minor trauma, which induced the PG ulcer that could be exacerbated via surgical debridement. Jin et al²⁷ reported that a combination of intravenous immunoglobulin and intermittent NPWT completely healed a refractory PG ulcer. Our patient was referred to an internal medicine expert and a plastic surgeon of our hospital, and received systemic treatments (corticosteroids with antibiotics) combined with local wound management. The PG lesion healed completely.

We report this case for two reasons. First, PG may be a rare adverse event even in patients with UC, but COVID-19 vaccination may find an immunosuppressive niche that clinicians should consider, especially in the current unprecedented pandemic situation. Second, caution should be exercised when determining injection therapy for musculoskeletal pain in patients with underlying autoimmune diseases or immunosuppressive conditions.

Declaration of Conflicting Interests

No author has any potential conflict of interest in terms of the research, authorship, and/or publication of this article.

Ethical approval

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References

1. Maverakis E, Marzano AV, Le ST, et al. Pyoderma gangrenosum. *Nat Rev Dis Primers*. 2020;6(1):81. doi: 10.1038/s41572-020-0213-x
2. Jena A, Sachan A, Singh AK, Sharma V. Multifocal pyoderma Gangrenosum at presentation in a patient with acute severe ulcerative colitis. *Inflamm Bowel Dis*. 2022;28(6):e84–e85. doi: 10.1093/ibd/izab309
3. States V, O'Brien S, Rai JP, et al. Pyoderma Gangrenosum in inflammatory bowel disease: A systematic review and meta-

- analysis. *Dig Dis Sci.* 2020;65(9):2675-2685. doi: 10.1007/s10620-019-05999-4
4. Hui DS, Azhar EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis.* 2020;91:264-266. doi: 10.1016/j.ijid.2020.01.009
 5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. The lancet.* 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5
 6. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med.* 2021;384(7):643-649. doi: 10.1056/NEJMra2035343
 7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med.* 2020;383(27):2603-2615. doi: 10.1056/NEJMoa2034577
 8. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* 2021;384(5):403-416. doi: 10.1056/NEJMoa2035389
 9. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol.* 2021;85(1):46-55. doi: 10.1016/j.jaad.2021.03.092
 10. Magro C, Crowson AN, Franks L, et al. The histologic and molecular correlates of COVID-19 vaccine-induced changes in the skin. *Clin Dermatol.* 2021;39(6):966-984. doi: 10.1016/j.clindermatol.2021.07.011
 11. Maverakis E, Ma C, Shinkai K, et al. Diagnostic criteria of ulcerative pyoderma Gangrenosum: A Delphi consensus of international experts. *JAMA Dermatol.* 2018;154(4):461-466. doi: 10.1001/jamadermatol.2017.5980
 12. Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: An updated review. *J Eur Acad Dermatol Venereol.* 2009;23(9):1008-1017.
 13. Weizman AV, Huang B, Targan S, et al. Pyoderma gangrenosum among patients with inflammatory bowel disease: A descriptive cohort study. *J Cutan Med Surg.* 2014;18(5):361. doi:10.2310/7750.2013.13103
 14. Argüelles-Arias F, Castro-Laria L, Lobatón T, et al. Characteristics and treatment of pyoderma gangrenosum in inflammatory bowel disease. *Dig Dis Sci.* 2013;58:2949-2954.
 15. Chatzinasiou F, Polymeros D, Panagiotou M, Theodoropoulos K, Rigopoulos D. Generalized pyoderma Gangrenosum associated with ulcerative colitis: Successful treatment with infliximab and azathioprine. *Acta Dermatovenereol Croat.* 2016;24(1):83-85.
 16. Mikail M, Wilson A. Infliximab treatment for large, multifocal, abdominal pyoderma gangrenosum associated with ulcerative colitis: A case report. *SAGE Open Med Case Rep.* 2020;8:2050313-20964113. doi: 10.1177/2050313X20964113
 17. Mohd AB, Mohd OB, Ghannam RA, Al-Thnaibat MH. COVID-19 Vaccine: A possible trigger for pyoderma Gangrenosum. *Cureus.* 2022;14(5):e25295. doi: 10.7759/cureus.25295
 18. Barry M, AlRajhi A, Aljerian K. Pyoderma Gangrenosum induced by BNT162b2 COVID-19 vaccine in a healthy adult. *Vaccines (Basel).* 2022;10(1):87.
 19. Toyama Y, Kamiya K, Maekawa T, Komine M, Ohtsuki M. Pyoderma gangrenosum following vaccination against coronavirus disease-2019: A case report. *Int J Dermatol.* 2022;61(7):905-906. doi: 10.1111/jid.16255
 20. Hung YT, Chung WH, Tsai TF, Chen CB. Haemorrhagic bullous pyoderma gangrenosum following COVID-19 vaccination. *J Eur Acad Dermatol Venereol.* 2022;36(8):e611-e613. doi: 10.1111/jdv.18132
 21. Franceschi J, Darrigade AS, Sanchez-Pena P, Legrain-Lifermann V, Milpied B. Pyoderma gangrenosum after mRNA-based SARS-CoV-2 vaccine. *J Eur Acad Dermatol Venereol.* 2022;36(12):e969-e970. doi: 10.1111/jdv.18389 Online ahead of print.
 22. Ombrello MJ, Remmers EF, Sun G, et al. Cold urticarial, immunodeficiency and autoimmunity related to PLCG2 deletions. *N Engl J Med.* 2012;366:330-338.
 23. Zhou Q, Lee GS, Brady J, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase C gamma2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. *Am J Hum Genet.* 2012;91(4):713-720.
 24. Neves JF, Doffinger R, Barcena-Morales G, et al. Novel PLCG2 mutation in patient with APLAID and cutis laxa. *Front Immunol.* 2018;9:2863. doi: 10.3389/fimmu.2018.02863
 25. Long CC, Jessop J, Young M, Holt PJ. Minimizing the risk of post-operative pyoderma gangrenosum. *Br J Dermatol.* 1992;127(1):45-48. doi:10.1111/j.1365-2133.1992.tb14826.x
 26. Zuo KJ, Fung E, Tredget EE, Lin AN. A systematic review of post-surgical pyoderma gangrenosum: Identification of risk factors and proposed management strategy. *J Plast Reconstr Aesthet Surg.* 2015;68(3):295-303. doi:10.1016/j.bjps.2014.12.036
 27. Jin SY, Chen M, Wang FY, Wang F. Applying intravenous immunoglobulin and negative-pressure wound therapy to treat refractory pyoderma Gangrenosum: A case report. *Int J Low Extrem Wounds.* 2021;20(2):158-161. doi:10.1177/1534734620940459