Pyoderma Gangrenosum and COVID-19: A Series of Three Cases Involving Female Breast

Dear Editor,

Pyoderma gangrenosum (PG), a rapidly progressing, non-infectious, neutrophilic disorder is associated in about 70% of cases with conditions such as inflammatory bowel disease (64%), rheumatoid and inflammatory arthritides (16%), hematological/visceral malignancies (11%), and intake of drugs. Diagnosis is clinical; dense neutrophilic dermal infiltrate histopathologically may exclude differentials and be corroborative.

COVID-19 infection can develop cutaneous manifestations such as pseudochilblains, vesicular, urticarial, maculopapular exanthemata, livedo reticularis, and necrosis. Covishield[R] vaccination (ChAdOx1 nCoV-19, recombinant, replication-deficient chimpanzee adenovirus vector vaccine encoding SARS-CoV-2 Spike (S) glycoprotein manufactured by Serum Institute of India) entails two 0.5 ml intramuscular injections, 14-16 weeks apart, each containing 5×10^{10} virus particles.[1] It is followed often by a delayed large local reaction and sometimes by injection site reactions, urticarial/morbilliform eruptions, chilblains, erythromelalgia, pityriasis rosea-like reactions, herpes zoster, flares of herpes simplex, erythema multiforme, etc.[2]

Case summaries [Table 1], clinical [Figure 1], and histopathological [Figure 2] photographs illustrative of the three patients of PG involving the female breast are presented. We discuss the overlapping inflammatory cytokine profile linking the COVID-19 infection/its vaccination with PG and also the salient features of the cases of PG involving breast reported hitherto.

Increased pro-inflammatory cytokines such as TNF-α, IL-1, IL-8, IL-12, IL-17, IL-23, and IL-6 are central to the pathogenesis of PG. COVID virus, too, causes cytokine storms releasing IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-gamma. COVID vaccination triggers autoimmunity through molecular mimicry and hyperinflammation induced by adjuvants. Thus, the inflammatory cytokine profile of PG and COVID-19 disease/vaccination can be similar or may even overlap.[3] In pemphigus vulgaris, autoreactive T cells induce/maintain antidesmoglein-1 and antidesmoglein-3

Table 1: Case summaries

	Case 1 [Figure 1: a-b]	Case 2 [Figure 1: c-d]	Case 3 [Figure 1: e-f]
Age	42 years	37 years	40 years
Comorbidities	_	Pemphigus vulgaris since 8 Y (Body mass index—31.8 kg/m^2)	Systemic lupus erythematosus since 5 months
Vaccination	Unvaccinated	Two doses	One dose
RT-PCR for COVID-19	Positive	_	_
Presentation	Incision and drainage of "abscess" soon followed by rapidly enlarging, painful granulating ulcer of the left breast.	One painful ulcer over right breast, each a week after Covishield[R] injection	Painful ulcer right breast, a fortnight after single injection of Covishield[R]
Laboratory			
TLC/Neutrophils%	3900/mm^3/51%	13200/mm^3/74%	11900/mm^3/91%
ESR	72 mm	53 mm	87 mm
CRP	35 mg/dL	15.5 mg/dL	86 mg/dL
Urine protein	Trace	Nil	Trace
D-dimer	4800 mg/L FEU	Normal	Normal
Dsg 3	-	108.1 RU/ml	-
ANA	-	-	1:100
dsDNA, U1-SnRNP, Ro 52/60	-	-	+
Treatment	Parenteral>oral steroids×10 weeks Intra-lesional triamcinolone acetonide 10 mg/ml on ulcer edge Cyclosporine 200 mg OD×4 weeks.	Prednisolone 30 mg/day×5 weeks Oral dapsone 100 mg BD	IV methylprednisolone 250 mg OD×3 days IV cyclophosphamide 1/2 g fortnightly; six cycles Hydroxychloroquine 200 mg OD
Prognosis	Death following sepsis	Improved	Improved

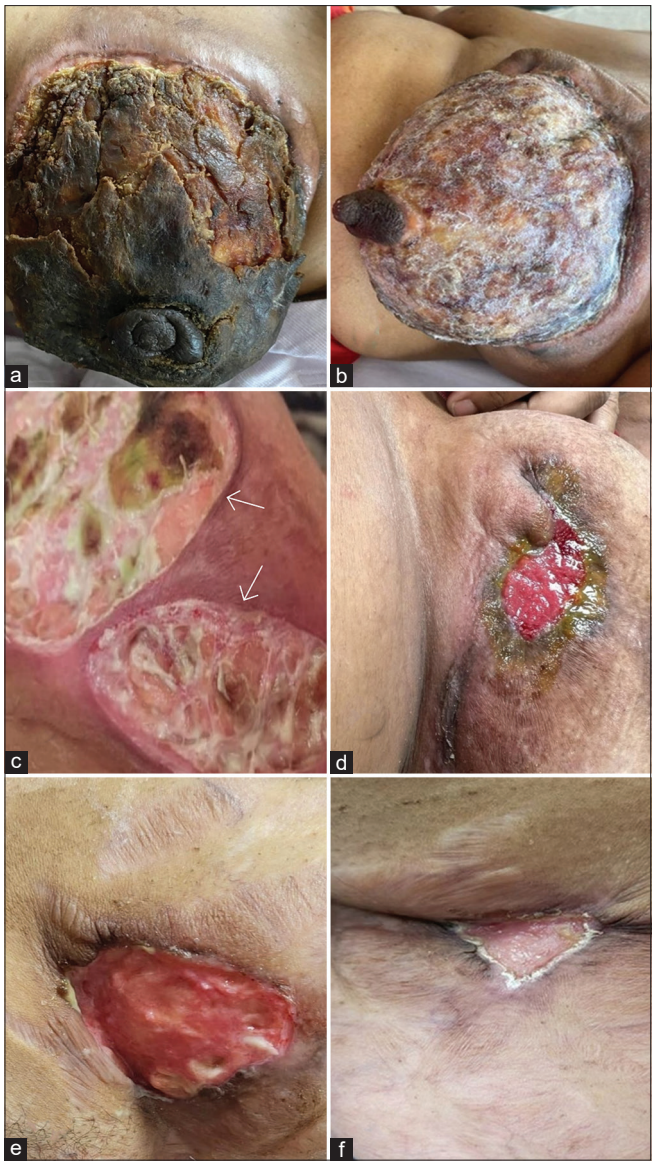

Figure 1: Case 1 (a) on presentation and (b), on day 75; Case 2 (c) on presentation, white arrow indicate first and second ulcer and (d) after 35 days, Case 3 (e) on day 1, and (f) on day 60

autoantibodies. Serum levels of IFN-gamma are reduced and of IL-8, elevated, latter seen also in PG.[4] In systemic lupus erythematosus, genetic mutations, environmental factors, and gender predisposition generate proinflammatory milieu producing IFN-α, IL-6, and IL-10 causing activation of inflammasome and abnormal neutrophils.[5]

A review of English literature hitherto showed 150 reported cases of PG involving breast none in association with COVID-19 infection/vaccination. Preceding surgical intervention was reported in 70%, such pathergy followed incision and drainage of the probable breast abscess of our first case. Just one among the eight cases of PG reported after COVID-19 disease, and none of the 6 following its vaccination involved the breast. Systemic Lupus Erythematosus was reported in 23 cases and pemphigus

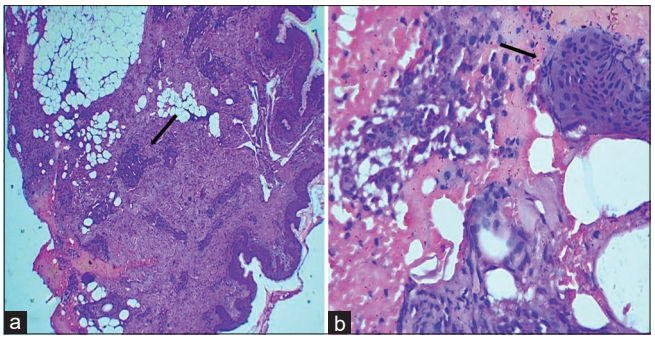

Figure 2: (a) Fibro-collagenous dermal stroma with adnexal structures and dense inflammatory infiltrate (Black arrow) (H & E stain, 10x); (b) Neutrophilic abscess and fibrin deposition (H and E Stain, 40x). Arrows indicate, a) dense inflammatory infiltrate and b) neutrophilic absces

vulgaris, in a single case. However, PG may have been independently associated with COVID-19 disease/vaccine and could have occurred probably, not conclusively, as a result of altered course of pre-existing autoimmune conditions. Still, cases vaccinated for COVID-19 as well as those with dysregulated immune status should have extended follow-up as a measure of abundant caution. Also, the occurrence of PG, even for sites other than those of vaccinations, should be monitored as induction of PG can augment potentially life-threatening COVID-19 disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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