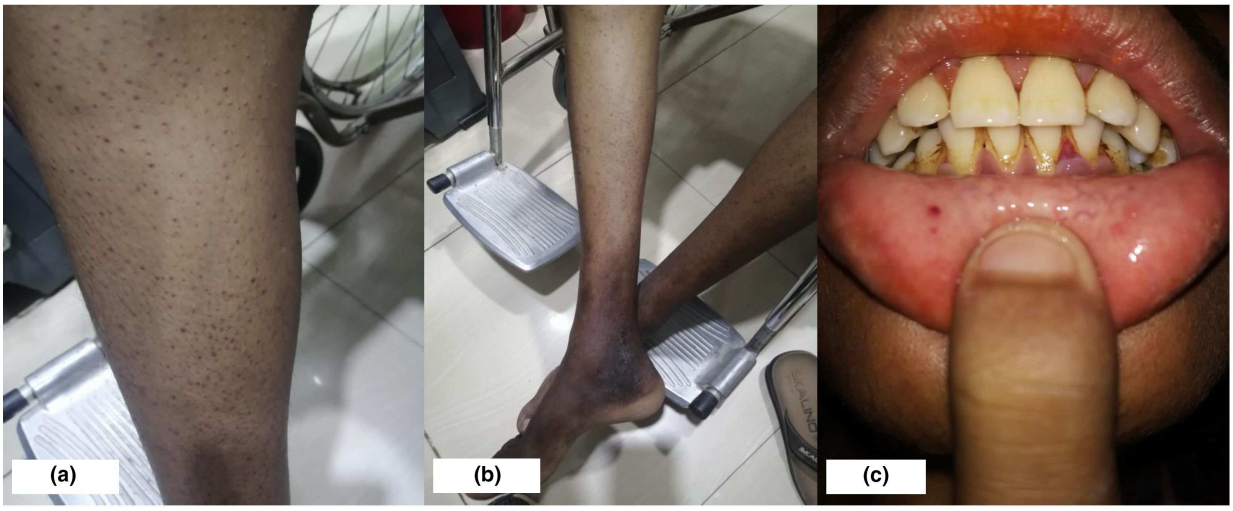

Figure 1 (a) Scattered perifollicular haemorrhagic and hyperkeratotic papules over left leg; (b) purpuric rash coalescing together to form large confluent ecchymoses on both lower legs; and (c) punctate haemorrhages on the oral mucosa with gingivitis.

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Phenotypic spectrum of serious cutaneous-only adverse event following immunization with COVID-19 vaccines: a multicentre case series and literature review

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Dear Editor,

A phenotypic range of exclusively cutaneous adverse events following immunization (AEFI) with COVID-19 vaccines has been reported. Currently, there is no formal consensus on advice given to affected individuals pertaining to their subsequent COVID-19 vaccines, which is increasingly pertinent as countries such as the UK launch a further booster phase of the COVID-19 mass vaccination programme, owing to concerns over waning immunity from initial vaccinations. We describe the phenotypic spectrum of rare but serious cutaneous AEFI and explore the evidence underlying AEFI, based on the literature and our multicentre case series. We used the World Health Organization (WHO) definition for serious adverse event as 'any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity'.[1]

This multicentre case series (Table S1[2–14]) comprised 21 patients (10 men, 11 women; aged 21–83 years) with ethnicities reported as White British (n = 16), South Asian (n = 3), Black (n = 1) and Chinese (n = 1), who presented with serious cutaneous-only AEFI during the period February–August 2021.

The phenotypic spectrum of these AEFI is described in Table S2 together with supportive literature and relevant case histories. Table S1 describes the affected patients' decisions (where known) on whether to receive further doses of COVID-19 vaccine and their outcome. Table S3 summarizes the literature on the estimated prevalence of cutaneous AEFI from COVID-19 vaccination (of all severities) and the outcomes when subsequent COVID-19 vaccination has been accepted.

A key attributing factor to the lack of global consensus regarding clinical guidance on subsequent dose of COVID-19 vaccine following serious cutaneous AEFI from COVID-19 vaccination is the difficulty in distinguishing between causation and coincidental presentation of an

adverse event and the temporal relation to any vaccines received. Potential pathomechanisms leading to AEFI with COVID-19 vaccinations are described in Table S4.

Serious cutaneous AEFI remain exceedingly rare as demonstrated from supporting literature. However, we could not identify high-level scientific evidence (i.e. Level 1–3) to guide clinicians and patients on how to make informed decisions on whether to accept their subsequent dose (if eligible as part of a local immunization programme). We recommend that clinicians should carry out a personalized risk–benefit analysis, taking into consideration factors such as the risk of potential harm from contracting COVID-19 infection (risks increase with age and certain types of comorbidities), efficacy and risk profile of locally available COVID-19 vaccines (risk profile may differ between vaccines and patient groups), local availability of risk mitigation systems (described in Table S5), availability of antibody titre level testing services to determine adequacy of past immunizations, causality assessment of the previous AEFI (using the WHO–Uppsala Monitoring System)[1] and patient preference. Table S5 outlines our pragmatic but cautious consensus approach to considering potential management options for clinicians to use when counselling patients about future COVID-19 vaccines following a serious cutaneous AEFI. This should be in conjunction with a holistic approach with individualized risk–benefit analysis for each patient. Our recommendations will evolve as new evidence emerges over time.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Multicentre case series (n = 21).
Table S2. Phenotypic spectra of serious cutaneous-only adverse events following immunization with COVID-19 vaccines.
Table S3. Summary of the literature on the prevalence of cutaneous adverse events following immunization with COVID-19 vaccination, and the outcome of those who accepted a subsequent dose of the vaccine.
Table S4. Possible pathomechanisms underlying cutaneous adverse events following immunization with COVID-19 vaccination.
Table S5. The range of options we consider as potentially appropriate for discussion with patients about whether to accept a further booster dose in the future.

Risankizumab-induced paradoxical pustular psoriasis

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Dear Editor,

Pustular psoriasis (PP) represents a rare and severe form of psoriasis that typically requires treatment with systemic immunosuppression. Paradoxically, PP may be induced by systemic agents including inhibitors of anti-tumour necrosis factor (TNF)-α or interleukin (IL)-12/23 (e.g. ustekinumab).[1] Risankizumab is a humanized IgG monoclonal antibody inhibitor of the p19 subunit of IL-23 and is licensed for treatment of moderate to severe plaque psoriasis.[2] To date, there have been no cases of risankizumab-induced PP described in the literature. We report the case of a woman who presented with PP following treatment with risankizumab.

A 45-year-old white woman presented with a 3-week history of progressive worsening of her plaque psoriasis with associated pustulation. Her medical history included obesity, insulin-independent Type 2 diabetes mellitus and a 22-year history of chronic plaque psoriasis. There was no reported history of PP. There was no history of medication changes, infection or recent systemic corticosteroid therapy, but there was a long history of multiple life stressors, with a recent (1 month before presentation) stressor preceding worsening of her psoriasis. The patient had previously been treated with the systemic immunosuppressants methotrexate and ciclosporin, and had developed secondary failure to adalimumab, secukinumab, ixekizumab, guselkumab and etanercept. She had been started on risankizumab 5 months before presentation.

At presentation, the patient was systemically well with stable vital signs, but she had an increased C-reactive protein level of 33 mg/L (normal < 7 mg/L). Her mobility was impaired secondary to skin pain.

On examination, inflamed plaques of psoriasis were noted diffusely on the limbs (Fig. 1) and trunk (Fig. 2) with interspersed studded pustules. Coalescing lakes of pus were observed on the trunk and limbs, with 50% of her body surface area affected.

Risankizumab was stopped and ciclosporin 1.5 mg/kg twice daily was started, which improved the psoriasis and the pustules resolved. She has now been on ciclosporin for several months, with a view to changing to infliximab.

In Phase lll trials, adverse events following risankizumab have been found to be comparable with those of placebo.[2] Paradoxical reaction (the appearance or exacerbation of a pathological condition that does usually respond to that drug class[3]) were initially described in patients undergoing treatment with anti-TNF drugs, and include psoriatic eruptions, PP, eczematous eruptions and lupus-like reactions.[2] However, reports of cutaneous paradoxical reactions also exist for other biologic agents, including anti-IL-17/17R, anti-IL-12/23 and anti-IL4Rα drugs.[3] There have been reports of paradoxical rheumatological reactions to the anti-IL-23 p19 drug guselkumab,[4] with PP specifically having been reported as a paradoxical reaction to this drug.[4]

Although it can often be difficult to differentiate paradoxical PP from an exacerbation of the underlying

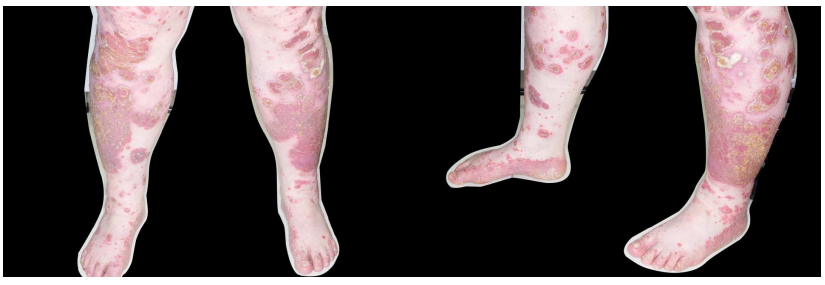

Figure 1 Psoriasis with pustulation of the legs.

