Pityriasis following COVID-19 vaccinations: a systematic review

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Abstract

In the wake of a global COVID-19 pandemic, where innovations in vaccination technology and the speed of development and distribution have been unprecedented, a wide variety of post-vaccination cutaneous reactions have surfaced. However, there has not been a systematic review that investigates pityriasis eruptions and the associated variants following COVID-19 inoculations. A PubMed search using *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* was performed to find case reports from the earliest record through November 2022. Data including types of vaccination and pityriasis were extracted and a quality review was performed; 47 reports with 94 patients were found: 64.9% had pityriasis rosea (PR), 3.2% PR-like eruptions, 16.0% pityriasis rubra pilaris, 7.4% pityriasis lichenoides et varioliformis acuta, 3.2% pityriasis lichenoides chronica, and 5.3% had reactions described as *atypical*. The top three COVID-19 vaccinations reported were Pfizer-BioNTech (47.9%), Oxford-AstraZeneca (11.7%), and Moderna (8.5%). Pityriasis reactivity was reported most frequently after the Pfizer-BioNTech vaccination, with pityriasis rosea being the most common variant. A large difference was additionally found between the ratio of post-vaccination pityriasis reactions following Pfizer and Moderna vaccinations (5.63), and the ratio of Pfizer's usage in the United States as of December 28, 2022 relative to that of Moderna (1.59). Further studies with adequate follow-up periods and diagnostic testing will thus need to be performed to elucidate the root of this discrepancy and better characterize the association between different pityriasis reactions and COVID-19 vaccinations.

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Introduction

The introduction of vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a critical factor in halting the progression of COVID-19. With the induction of novel vaccines, the interest is shifting toward understanding possible adverse reactions. Currently, many vaccine formulations dominate the global market; Moderna's (Spikevax™), Pfizer-BioNtech's (Comirnaty®) mRNA vaccines, and Johnson & Johnson's viral vector vaccine are some, among others.[1] Each has had various reactions reported, including various cutaneous eruptions that have been investigated and described to varying degrees.[2]

Due to a large vaccination effort, dermatological manifestations are thus likely to appear.[3] Among them, pityriasis and its variants. Pityriasis rosea (PR) is a self-limiting papulosquamous disease affecting adolescents and young adults with an unclear etiology.[4] Although there are variants in presentation, classic PR will present with a sudden onset of a solitary patch, referred to as the herald patch, typically found on the trunk. Subsequently, a secondary eruption of round to oval macules will appear along the cleavage lines, referred to as a Christmas tree distribution.[4] Pityriasis rubra pilaris (PRP) is another papulosquamous disease with an unknown etiology affecting children and adults. There are five subtypes of PRP, with the most classic findings including red-orange papules and plaques, perifollicular keratosis, and waxy keratoderma.[5] Pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) are on two ends of the clinical spectrum. Overall, pityriasis lichenoides presents with recurrent erythematous to pruritic papules that can spontaneously regress.[6] PLEVA has an acute course, with lesions described as crusted and vesiculopapular. PLC has a chronic relapsing course; its lesions are scaly instead of crusted.[6]

While there are systematic reviews exploring the cutaneous sequela of COVID-19 vaccination in general, there are yet to be any focusing specifically on the incidence and manifestations of different pityriasis conditions in this setting. This systematic review aims to quantify and qualify occurrences of pityriasis conditions following COVID-19 vaccination in an effort to elucidate any correlations or patterns that could provide clinical insight.

Methods

This systematic review was conducted in accordance with PRISMA guidelines. Articles were retrieved from the PubMed database using the search formula: "((COVID-19) OR (COVID) OR (SARS-Cov-2)) AND (pityriasis)." No restrictions were applied to the year of publication and all articles from the earliest record to November 2022 were included.

Inclusion and exclusion criteria

During the initial screening, two independent reviewers assessed each article's title and abstract to exclude articles that were reviews, meta-analyses or published abstracts, not in English, not published in a peer-reviewed journal, did not use human subjects, and did not address the development of pityriasis or pityriasis-like manifestations following vaccinations against COVID-19. Subsequently, two independent reviewers screened the remaining articles by evaluating them in their entirety. The following inclusion criteria were followed: the case report is in English and describes the development of pityriasis or pityriasis-like manifestations in patients who received a COVID-19 vaccination of any type. In the event that there was a disagreement, a third reviewer made the decision to include or exclude a publication. The process of study selection is summarized in Figure 1.

Quality assessment

Using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports, two independent reviewers (GM and VT) assessed the quality of each publication. In the event that there was a disagreement, a third reviewer decided the final score for that publication.

A total of eight criteria were used to assess the quality of the publication, including clearly described demographics, patient history with timeline, patient's current clinical condition at the beginning of the case study, diagnostic tests, treatment, patient outcome, appropriate follow-up period, and takeaway lessons. An adequate follow-up period was considered as 9 months or more since the resolution of symptoms. As recurrence of pityriasis rosea and PRP is very rare, and only reported in 1-3% of cases of the former, the time period to relapse in PLEVA was used.[7-9] Furthermore, a set follow-up period of 9 months was additionally chosen to better monitor the instances of recurrence of pityriasis following resolution of symptoms, regardless of the type. Each publication was assigned a score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) for each criterion. Scores from each criterion were then added to generate an overall score for each publication, with the maximum score that a publication could obtain being a score of 16.

Results

Study design and patient demographics

Our case study selection criteria are detailed in Figure 1. 47 case reports and series describing pityriasis reactions in 94 patients were identified. These cases, detailed in *Supplementary Table 1*, consisted of 42 females and 52 males aged 15-85 years old with an average age of 44.53 and a standard deviation of 16.66. All studies included patients who had received a dose of vaccination within two weeks of presenting to the office with a form of pityriasis. None of the patients had concurrent dermatological conditions and only one had an active COVID-19 infection.[10] Previous medical histories were reported in twenty of the cases and included the following: hypertension,[11-15] type 2 diabetes,[12,16,17] psoriasis,[12,18,19] mild hidradenitis suppurativa,[20,21] alopecia areata,[22] chronic pancreatitis and arrhythmia,[11] 1-year history of glioblastoma,[23] transverse myelitis,[19] moderate hepatic steatosis and familial hypercholesterolemia,[24] metabolic syndrome, hypothyroidism, and chronic kidney disease,[12] as well as chronic lymphocytic leukemia and chronic obstructive pulmonary disease,[12] fever with myalgia two days prior,[25] arthrosis,[13] vitiligo,[17] fatty liver,[16] arthrosis,[14] acute lymphocytic leukemia in remission,[12] urticaria several months prior,[26] Hashiomoto's,[27] transient ischaemic attack, coronary artery disease, and dyslipidemia.[28]

Summary of COVID-19 vaccinations, doses, and reactions

The vaccination types which preceded the pityriasis reactions were described as follows, listed from greatest to least incidence: 45 were Pfizer-BioNTech (47.9%),[11,12,14,18-20,22,28-42] 11 were Oxford-AstraZeneca (11.7%),[13,15,23-25,27,43-45] 8 were Moderna (8.5%)[10,12,21,26,46,47], 22 were Coronavac (23.4%),[16,17,41,48,49] 2 were Sinopharm (2.1%),[50] 2 were "COVID-19 vaccine by Beijing institute of biological products company" (2.1%),[51] 1 Johnson & Johnson (1.1%),[52] 1 was Covaxin (1.1%),[53] and two were listed as "unspecified mRNA" (2.1%).[54,55]

While there are several types of pityriasis, 61 (64.9%) of the reactions were diagnosed as PR,[20,21,23,25-28,30-32,38,39,41,42,44,47-56] and 3 (3.2%) as PR-like.[22,33] 15 (16.0%) reactions resulted in PRP,[10-13,15-18,24,36,45,46] and 7 (7.4%) were diagnosed as PLEVA,[12,14,19,37,40,43,50] and 3 (3.2%) were diagnosed as PLC.[29,34,35] 5 (5.3%) were described as "atypical".[41] 51 of the 97 cases reported the existence of herald patches in a variety of locations including the arm, wrist, breast, axilla, back, abdomen, and thigh.[20,22,27,28,30-33,38,39,41,42,47-49,52-56] Only one case reported a herald patch occurring at the inoculation site.[22] Four cases reported additional symptoms including fatigue,[35,40] pruritus,[50] and onycholysis with orange border on both great toenails.[24] These pityriasis reactions were observed an average of 9.77 days after the first dose in 49 (52.1%) cases,[12-15,20,21,23-26,28,29,31,33,39-41,43-45,49-53,56] after the second dose in 32 (34.0%) cases,[12,13,17,22,27,28,32,37-39,41,42,47,51,54,55] after both doses in 9 (9.6%) cases,[16,18,19,22,34,35,38,46,48] and after a booster shot in 4 (4.3%) cases.[10,11,36,50]

Clinical testing performed

Of the 94 patients, 51 were not biopsied, 2 refused biopsy,[44,55] and 41 had a biopsy performed to confirm the diagnosis.[10-20,22-26,29,34-38,40,41,43,45-48,50,52-54]

Histories of previous reactions were gathered and testing for viral infections was performed by many of the studies. Only one patient had a concurrent COVID-19 infection,[10] while one patient had their first reaction during a COVID-19 infection,[37] and another one had a previous reaction to a vaccination, which was a statin-induced myopathy.[24] Testing for other viral infections in a variety of combinations was reported in 18 patients with the following results, all negative: general reports of a negative viral result,[27,32,33,36,37,40] HIV,[14-17,34,35,45,46] hepatitis B and C virus,[14,34] anti-neutrophilic cytoplasmic antibody,[34] herpes simplex virus 1/2, Epstein-Barr virus, and varicella zoster virus,[56] negative for human herpesvirus 6/7,[23,35] hepatitis B and C,[15,16,35,45] and toxoplasma,[35] syphilis,[15,23] treponema pallidum.[14] There were also two patients who refused blood testing.[26,55]

Treatments reported for pityriasis reactions

Treatments of PR and PR-like reactions were a combination of the following: topical and oral corticosteroid(s) including prednisolone, mometasone, betamethasone,[21,22,26,28,33,38,41,44,50,52] standard triamcinolone 0.1% ointment,[20,23,31,42,55] doxycycline,[22,29,34] oral acyclovir,[30] ganciclovir,[51] valaciclovir,[51] antihistamines,[21,28,33,41] emollients,[53] and L-lysine.[27] Pityriasis rosea was reported to have resolved on its own in two cases.[28,56]

For the treatment of PRP and PLEVA, many combinations were tried with varying levels of success. As far as PRP is concerned, Hlaca *et al*. reported that acitretin and topical mometasone 0.1% resulted in complete resolution of symptoms 4 months after treatment, a combination that was also implemented by Hunjan *et al*.[11,18] Additional successful treatments included the use of methotrexate,[12] oral and topical corticosteroids such as prednisone,[12,15,17,45] emollients,[15] isotretinoin,[13] and ixekizumab,[16] while ustekizumab showed partial improvement in one case and none in another.[36] Two PRP cases in this systematic review did not report the patient's final outcome after initiation of treatment,[24,46] while in another case, the patient was lost to follow-up.[10]

For the treatment of PLEVA, Sechi *et al*. were able to achieve remission after 10 weeks of topical 2% fusidic acid and 0.1% betamethasone cream use.[12] Additional treatments that were reported in PLEVA patients that achieved remission of symptoms included oral corticosteroids,[14,37,40,43] doxycycline,[19] narrowband Ultraviolet B therapy,[37] emollients and mometasone furoate creams.[43] A course of doxycycline was attempted in the case of the patient with a PLC eruption by Al Muqrin *et al.*, however the final outcome of the treatment was not reported.[29] In the other two PLC patients reported in this systematic review, symptoms resolved either through the use of doxycycline or on their own, leaving hyperpigmented macules.[34,35]

Quality and risk of bias

The quality assessment outlined in *Supplementary Table 2* produced scores ranging from 9 to 16. Only one publication received a perfect score.[16] The majority of publications failed to report an appropriate follow-up period. Only 13 cases reported an inappropriate follow-up period.[12,14,15,18-20,26,28,34,40,43,48,52] For this review, an appropriate follow-up period was defined as a follow-

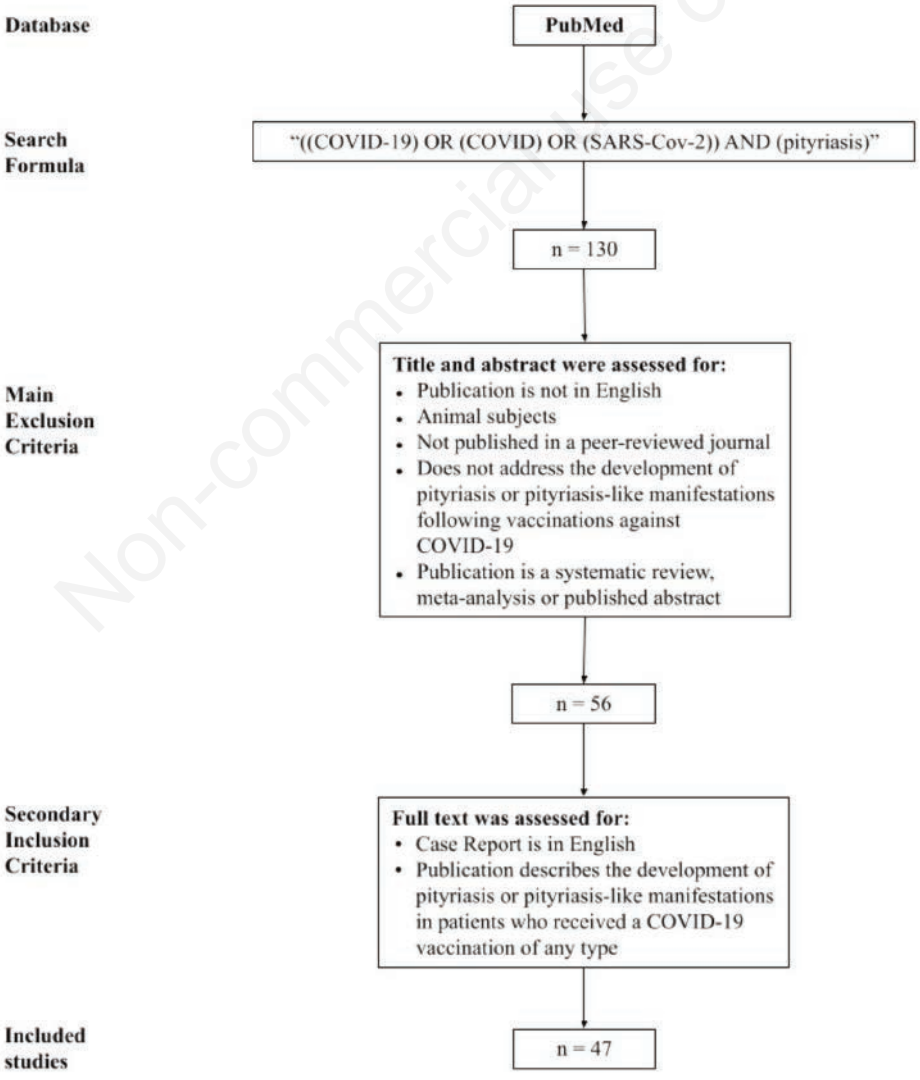

Figure 1. Flowchart depicting selection process of publications for this systematic review, number of publications (n).

up appointment after at least 9 months since resolution of symptoms, with a period of less than 9 months was reported as an inadequate follow-up period.

Additionally, 11 publications did not describe the patient's outcome,[10,24,25,29,31,32,37,42,44,47,50] and 2 publications were assessed to have inadequately described the patient's outcome.[45,56] A publication was considered inadequate reporting of the patient outcome if it did not further describe the resolution of symptoms with a timeline of when it was resolved. Furthermore, 6 publications,[25,32,35,39,47,56] failed to report if there was any treatment provided. Lastly, only one publication did not mention or expand on takeaway lessons from the case study.[33] All publications reported demographics, patient history, clinical condition upon presentation, and method of clinical assessment.

Discussion

COVID-19 vaccine-related reported cutaneous reactions

An array of cutaneous reactions following COVID-19 vaccinations have been documented, with the most common being local injection site reactions and delayed large local reactions.[57] Other reported cutaneous reactions following COVID-19 vaccinations range from urticaria to erythema multiforme, herpes simplex reactivation and pityriasis-like lesions.[3,58] It is noted that in general most cutaneous COVID-19 vaccine reactions occur after the first dose.[57,59] Moreover, these reactions occur at lower frequency, tend to be self-limiting and are not currently a contraindication to vaccination.[58] It is also important to note that the reactions listed are not specific to just COVID-19 vaccines. It is hypothesized that because there are common cutaneous reactions between a vaccine and the infection caused by the virus that it targets, the source may not be damage done by the virus and may instead be the process of immune activation against the virus.[60]

Proposed etiologies of pityriasis and history of vaccine reactions

Several types of pityriasis have been linked to vaccinations, including COVID-19, in many case reports over the past few years. In general, the pathophysiology of pityriasis can be described as an immune disorder with aggravation of the immune system response due to an antigenic trigger.[12,18,61,62] However, an exploration into vaccination reactivity can help elucidate the disease mechanism, as it is still under debate and investigation.

Pityriasis rosea and its less common variants, such as inverse pityriasis, are self-limited and usually resolve within 6-8 weeks. This was true for all of our PR case reports. PR's exact pathogenesis is unknown, but is theorized to be related to viral infections, with the strongest evidence for HHV-6 and HHV-7.[4,63-65] While not all case reports included viral testing, the patients that were tested for viruses in this systematic review, including COVID-19, were all negative. Cases of PR and PR-like reactions concurrent with COVID-19 have been described as well in the literature.[32,66,67] There have also been reports of PR or PR-like reactions after vaccination for human papillomavirus,[68] bacillus Calmette-Guérin,[69] smallpox,[70] hepatitis B,[71] pneumococcus,[72] yellow fever,[73] and influenza.[74,75]

PRP also has an unclear disease mechanism outside of the inherited subtype related to a CARD14 gene mutation.[5] Non-genetic cases of PRP have been linked to physical trauma, multiple autoimmune conditions, HIV infections, and malignancies.[5] Additional cases of PRP have been reported after vaccination with diphtheria-pertussis-tetanus and oral poliovirus.[76]

PLEVA and PLC are the same disease on two ends of the clinical spectrum. While PLEVA and PLC pathogenesis clearly falls under the category of a T-cell lymphoproliferative disorder, the etiology of this T-cell activity is less clear. Connections to specific infections such as HPV,[77] measles, mumps and rubella (MMR),[78-81] anti-tetanus and diphtheria,[82] parvovirus B19 and HIV, medications such as estrogen-progesterone and TNF-α, and even graft-versus-host disease, have all been suggested as potential causes of

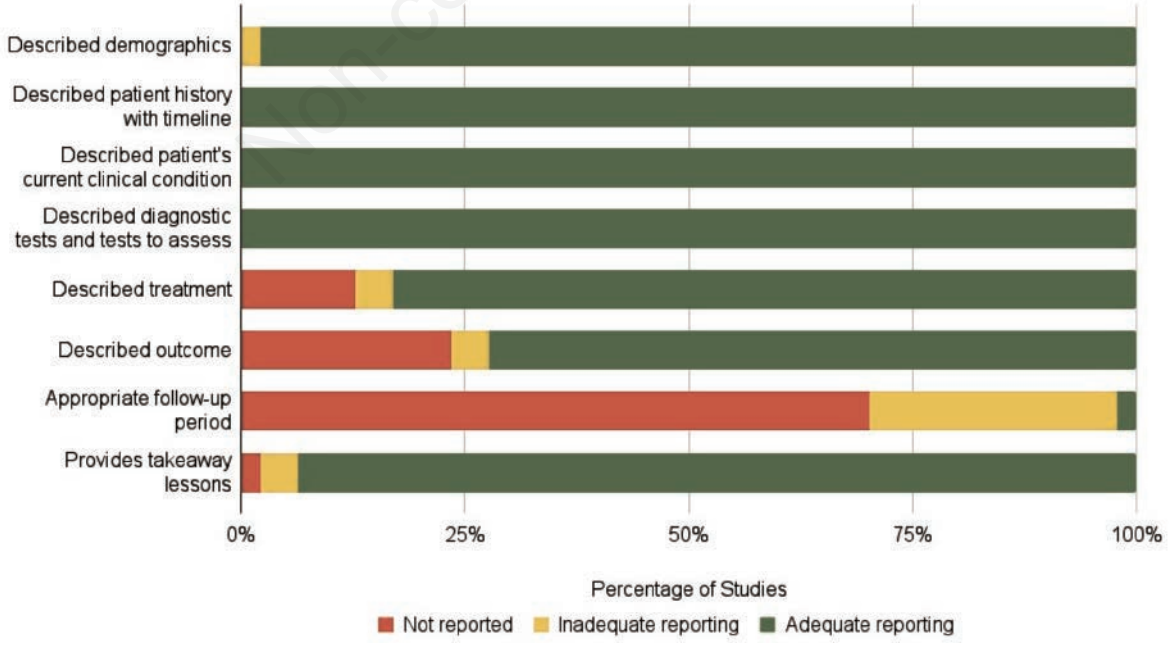

Figure 2. Scores for each criteria of quality presented as percentages across all included studies.

cases of PLEVA and PLC.[6] Pityriasis lichenoides following COVID-19 vaccinations may be due to a delayed hypersensitivity response against vaccine excipients, the spike protein, or due to molecular mimicry resulting in a T-cell-mediated hypersensitivity skin reaction.[83] This is highlighted by the case of Makila *et al.*, in which the patient developed PLEVA during a COVID-19 infection, and had recurrence of symptoms one month after their second vaccine dose.[37] Previous incidences of PLEVA reaction after vaccination have been reported for MMR,[78-81] anti-tetanus-diphtheria,[82] and influenza vaccinations.[61]

Data trends in vaccination types

Though the case studies examined in this paper are unlikely to be exhaustive of all pityriasis reactions that have occurred and have not been reported in literature, we found far more of the reactions described were after Pfizer-BioNTech vaccinations (47.9%) than after vaccination with the Moderna vaccine (8.5%), resulting in a ratio of 5.63. When comparing this to the total vaccination rates in the United States as of December 28, 2022 (59.63% of which were Pfizer and 37.49% were Moderna), we calculated a far lower ratio of 1.59, indicating a higher difference in the level of reactivity risk between the two, though they are both novel mRNA vaccines using similar technology.[84] We believe that more investigation into the cause of this difference is warranted. Though the cases we investigated included reactions worldwide, we were unable to ascertain complete worldwide data on the use of both vaccines. The Moderna vaccine is administered at higher rates in the United States than in most other countries, so the actual ratio difference may be greater at the global level.[84]

Quality of current case literature

Most of the studies included in this systematic review lacked sufficient follow-up, despite their overall quality being satisfactory, as illustrated in \ 2. As mentioned previously, an appropriate follow-up period was reported in 1 publication,[16] and was inadequately reported in 13 cases.[12,14,15,18-20,26,28,34,40,43,48,52] The rest of the cases did not describe any follow-up period after resolution of symptoms; therefore, it is hard to assess any possibility of recurrence of the pityriasis conditions described in this review. Aside from pityriasis, it has been reported that vaccinations may cause the recurrence of pre-existing dermatologic conditions.[85] This further drives the importance of adequate follow-up periods, and further studies should ensure proper follow-up, as this information may help clinicians better understand any long-term risks of flare-ups or recurrence of PR, PRP, PLEVA, PLC, and possibly other dermatological conditions. Although all case studies mentioned in this review described the method of diagnosis, diagnostic tests such as biopsy diagnosis were not performed in all cases. Due to the vaccine's novelty, information from a histopathological examination may aid in the future diagnosis of cutaneous reactions against the COVID-19 vaccine.

Conclusions

Pityriasis conditions (PR, PRP, PLEVA, and PLC) have been reported as cutaneous manifestations of COVID-19 vaccinations. This review found a greater incidence of pityriasis reactions associated with the Pfizer-BioNTech vaccine, with the most diagnosed pityriasis type being PR. A significant absence of follow-up periods was found throughout the case studies, preventing thus monitoring of disease progression and recurrence. Future reports should focus on possible differences in Pfizer-BioNTech and Moderna vaccines to help explain the greater prevalence of pityriasis reactions with the former, as well as they should incorporate adequate diagnostic testing and follow-up periods to better characterize the association between the different types of pityriasis reactions and COVID-19 vaccinations.

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Online supplementary material:

Supplementary Table 1. Summary of patient demographics, vaccine types and doses prior to onset of reaction, developed pityriasis subtype, time to onset of symptoms and duration of reaction following COVID-19 vaccination.
Supplementary Table 2. Quality Assessment of publications. The maximum score a case study could achieve was a score of 16.