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REVIEW ARTICLE

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Pityriasis rosea-like cutaneous eruption as a possible dermatological manifestation after Oxford-AstraZeneca vaccine: Case report and brief literature review

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Abstract

Pityriasis rosea (PR) has been manifested in patients suffering from COVID-19 as well as after vaccine protocols against SARS-CoV-2. It has a possible association with the HHV-6B virus (*roseola infantum*) and can be controlled by antivirals such as acyclovir as well as by the amino acid L-Lysine that showed a positive result in reducing the number of lesions and healing time. The aim of this study was to report a case of PR after a second dose of Oxford-AstraZeneca, the adopted therapy and a brief literature review. A 53-year-old woman, phototype II, presented an erythematous lesion in the posterior right thigh 15 days after the second dose of Oxford-AstraZeneca vaccine. Eight days after the initial injury, new injuries appeared in the calf, buttocks and thighs. The diagnosis was PR with a 5-week eruption cycle. The treatment consisted of the use of L-Lysine, 3 grams loading dose and 500 mg for 30 days and moisturizing/healing lotion, starting 14 days after the herald patch. After the 5th week of the disease cycle, there were no new eruptions and the repair cycle continued for up to 8 weeks leaving some residual skin spots. It is concluded that the patient may be a carrier a latent virus, HHV-6, and the vaccine administration with immune system stimulation, would have activated the possible virus causing PR. L-Lysine helped to control the manifestation by limiting the number of lesions and their location, which were restricted to the legs, thighs and buttocks.

KEYWORDS
amino acid, AstraZeneca, human herpesvirus 6-7, L-Lysine, pityriasis rosea, vaccine

1 | INTRODUCTION

With the emergence of the current devastating pandemic, efforts joined in the search for vaccines that could reduce panic, socioeconomic consequences and especially the circulation of the virus being the immunizing agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the most important countermeasure to fight the pandemic, the coronavirus disease-19 (COVID-19).

Since December 2020, several effective vaccines against COVID-19 have been developed and approved in record time,[1–6] and numerous new vaccines are in the final stages of clinical trials.[7]

Several vaccines have been approved based on randomized, controlled, and blinded clinical trials. Among them are two messenger RNA-based vaccines: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Modern) that encode the SRA-CoV-2 spike protein antigen encapsulated in lipid nanoparticles; the ChAdOx1nCov-19 (AstraZeneca) developed with a recombinant adenoviral vector from chimpanzee encoding the SRA-CoV-2 spike glycoprotein, the Ad26.COV2.S (Johnson & Johnson/Janssen) with a type 26 recombinant adenovirus encoding the spike glycoprotein of SARS-CoV-2 and, for emergency use in 22 countries, the inactivated vaccine against SRA-CoV-2 (CoronaVac).[8]

The ChAdOx1nCoV-19 (AZD1222) vaccine was developed at Oxford University, consists of a replication-deficient chimpanzee adenoviral gene (ChAdOx1) and contains the antigen gene, a SARS-CoV-2 structural surface glycoprotein (spike protein nCoV-19). In adults over 18 years of age, it was found to be effective against COVID-19 with a good safety profile in interim analyzes of ongoing clinical trials.[3] This non-replicating viral vector, the modified adenovirus, makes the immune system identify the spike protein, promoting a protective response against infection in case of exposure to SARS-CoV-2.[9]

What has been observed is that these vaccines have shown adverse effects in some people and among them are pain at the injection site, fever, headache, nausea and vomiting.[1,2] In some individuals there were skin reactions and among them there were reports of pityriasis rosea, 52 cases between January and June 2021.[10]

Pityriasis rosea (PR) is a benign skin disease, erythematous-squamous papules distributed on the trunk and extremities that starts, in most cases, with a single, oval, pink lesion called "mother patch" or "herald patch" showing a centrifugal growth measuring 2–10 cm in diameter. This lesion can remain isolated and single for 1 or 2 weeks when new secondary lesions of 0.5 to 1.5 cm appear in the thorax, abdomen, back and proximal extremities of the limbs. The initial phase is characterized by salmon-colored plaques, in the clinical phase a scaling begins and finally, the healing process is characterized by the lightening of the spots.[11–14] The evolution can vary from 6 to 8 weeks and can last from 3 to 6 months. Regression is spontaneous, leaving changes in skin color that disappear over the months. However, despite self-resolution, some dermatologists prescribe drugs such as antihistamines and corticosteroids, as well as sunbathing, which help when itching and with residual skin spots.[11,14]

Regarding etiology, fungi, bacteria and viruses were suggested, and the possibility of the involvement of autoimmune processes and pharmacological idiosyncrasies was also pointed out, however, some characteristics suggest that it is an infectious process which more recent trends attribute to a virus.[11,12,14–16]

Studies have shown a strong association of PR with human herpesviruses (HHV-6 and HHV-7) as an etiological factor[12,14–16] and with the suspicion of this viral involvement, therapy with antivirals such as acyclovir was indicated[15,17,18] as well as alternative therapy with L-Lysine amino acid[14,19] that showed positive results in reducing healing time as limiting the number of lesions when started at the beginning of the dermal manifestation, as soon as possible, still the first 2 weeks, in the viral multiplication phase.[14,19,20]

It is noteworthy that L-Lysine may also be associated with an increases excretion of an essential amino acid for some viruses initial replication, the L-Arginine.[21,22] Therefore, the use of L-Lysine together with a reduction in the intake of L-Arginine, present in supplements and foods such as chocolate, peanuts, nuts, gelatin, cashew nuts, corn, coconut, oats, coffee and raisins, can make difficult for the virus to enter in the cell remaining it in virion form limiting the evolution of the disease.[14,20]

Currently, PR has been associated as a dermal manifestation of SARS-COV-2 (COVID-19).[16,23,24] Although the diagnosis of PR has become more common during the COVID-19 pandemic, it is still unclear whether this cutaneous manifestation is secondary to the direct invasion of SARS-CoV-2, because in PR lesions the virus protein was found, whether it is due to reactivation of latent viruses such as HHV-6/7 and HHV-4 or EBV (Epstein–Barr virus) by the immunomodulatory capacity of COVID-19 to reactivates them or whether due to other factors.[16] Among the other factors is PR as a secondary reaction after vaccine protocols[25–31] being an important alert to dermatologists and other professionals in the area to assist in diagnosis.

In the midst of COVID-19 pandemic with several vaccine protocols being applied, the aim of this study was to report a case of RP after a second dose of Oxford-AstraZeneca, the adopted therapy and a brief literature review on the subject.

2 | CASE REPORT

A written consent form was obtained from the patient, aiming at reporting the case with unidentified photos.

Female, 53 years old, 61 kg, phototype II, with autoimmune disease diagnosed as Hashimoto's Thyroiditis using 125 mg levothyroxine sodium and without epidemiology for COVID-19, received the first and second dose of the Oxford-AstraZeneca vaccine in February 2021 and April 2021 respectively.

Eight hours after the first dose, she developed a 39-degree fever, joint pain, chills and headache, the latter remaining mild for 15 days. Fifteen days after the second dose of the vaccine, a reddish, erythematous lesion with mild itching was noticed on the posterior right thigh, above the knee joint (Figure 1). The patient thought it was a fungal lesion and self-medicating with a cream made up of ketoconazole (20 mg/g) + betamethasone dipropionate (0.64 mg/g), without noticing any improvement.

After 8 days the lesion was larger, measuring approximately 2 cm, with a scaly appearance and arising new smaller lesions in the calf, buttocks and thigh (Figures 2 and 3). An appointment with the dermatologist was scheduled 6 days after the secondary lesions, that is, 14 days after the initial lesion. The diagnosis was PR with suspension of the antifungal cream and prescription of a moisturizing, antiseptic and healing gel of 1.5 mg/g bismuth subgallate and 45.0 mg/g zinc oxide. An infectious disease specialist was also consulted confirming the diagnosis of PR as a reaction post-vaccination based on clinical characteristics and recent immunization history.

L-Lysine capsules were prescribed, a loading dose of 3 grams as a single dose, followed by 500 mg/day for 30 days starting 14TH days after the herald patch appeared. Restriction of foods and supplements containing the amino acid L-Arginine was also indicated. A few other lesions appeared in the following weeks, all limited to the lower limbs and buttocks, the last ones appearing in the 5th week on the left thigh (Figure 4A,B,C,D) and posterior left knee joint (Figure 5). At the end of 8 weeks, all lesions, only 12, were already in the repair phase, most of them with residual spots, as shown in Figures 1 and 2.

The patient had an undetected (negative) RT-PCR SARS-Cov-2 test, a total antibody the SARS-CoV-2 spike protein test—

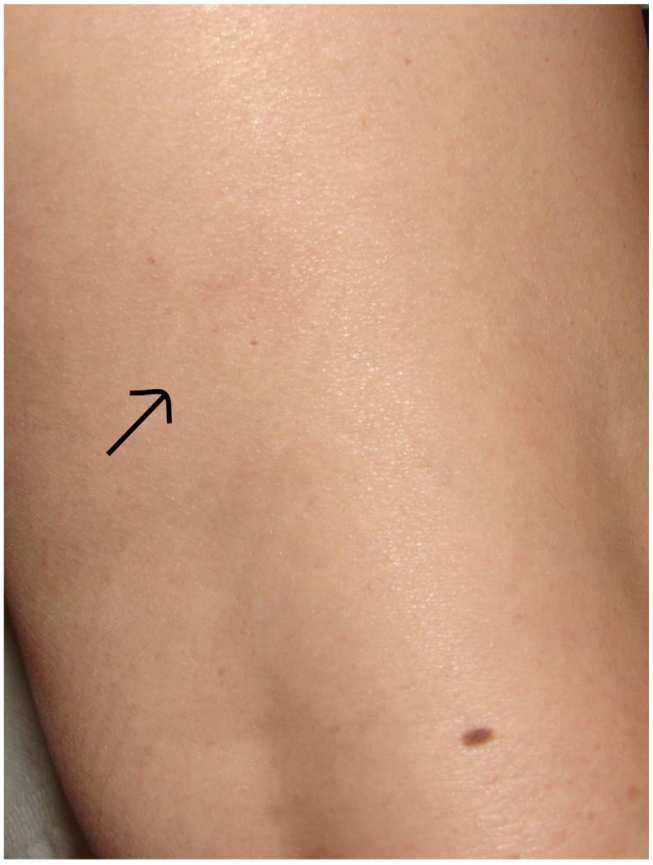

FIGURE 1 Herald Patch—7 weeks—right thigh—posterior knee

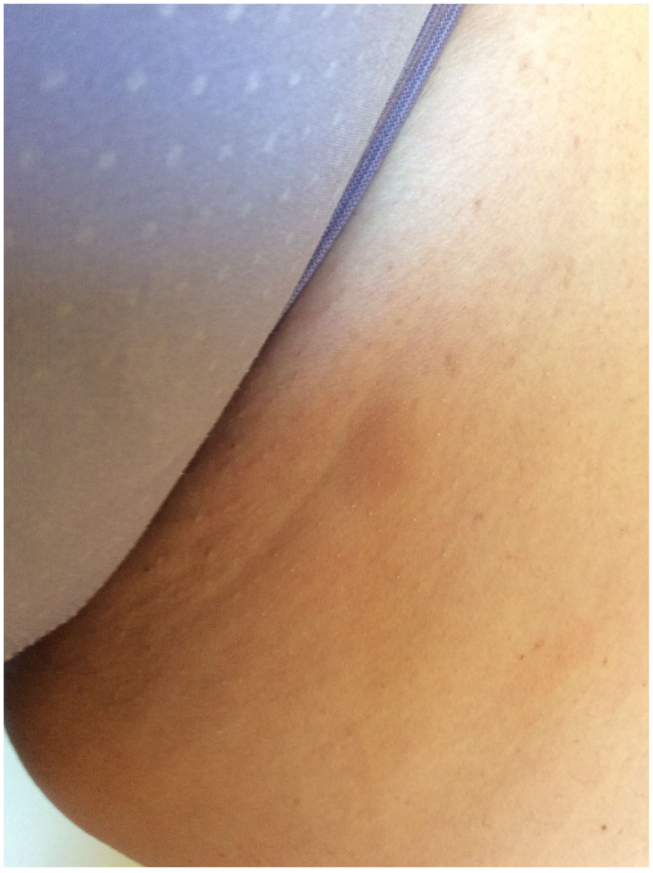

FIGURE 2 Lesion on the left thigh at 6 weeks

electrochemiluminescence method (positive)—67% (rv > 35%) and reported taking care of her daughter with roseola in 2008 and 2017 when the child developed the PR manifestation.

3 | DISCUSSION

The clinical case reported shows a skin reaction after a vaccine against the COVID-19 virus, diagnosed as PR despite the atypical condition, located only in the lower region of the trunk and lower limbs.

Dermoscopy has become an essential diagnostic tool in many diagnostic conditions in dermatology, such as melanocytic nevus lesions[32] however, in relation to dermoscopy in inflammatory skin lesions, knowledge is limited and there are few studies on the diagnostic technique of PR. Some authors investigated the dermoscopic features in PR lesions and the most common finding was collarette scale, which is also clearly visible to the naked eye. It was reported that many features that were not previously described for RP could be seen with the dermoscope, including irregular linear vessels, blood spots, brown blood cells and no brown structure, concluding that this exam can provide important clues to the diagnosis, especially in the atypical presentation of the entity.[33]

A punch biopsy could also be useful to check whether typical histological features of PR were present but both, dermoscopy or biopsy,

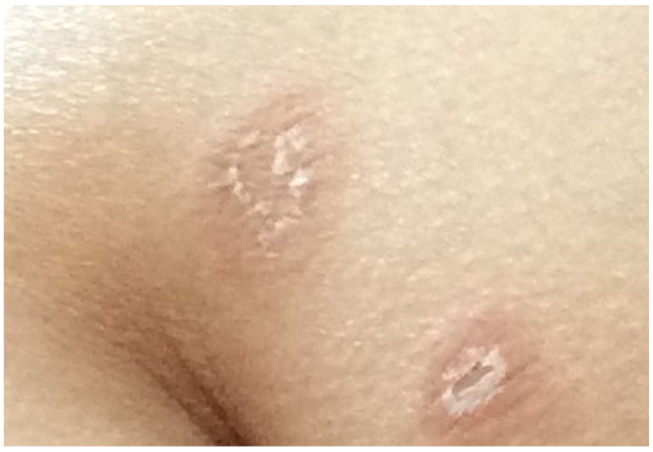

FIGURE 3 Lesion in buttocks at 2 weeks

were not indicated by the dermatologist or infectologist. They were categorical in the diagnosis of PR after collecting the clinical history and observing the injuries evolution.

Diagnosis of typical PR, with Christmas tree-shaped truncal involvement, is not difficult for doctors like dermatologists or general pediatrician however, its atypical presentations can be challenging even for these professionals.[13] In the typical form diagnostic doubts hardly arise but, as 20% of the cases present atypically, this can favor

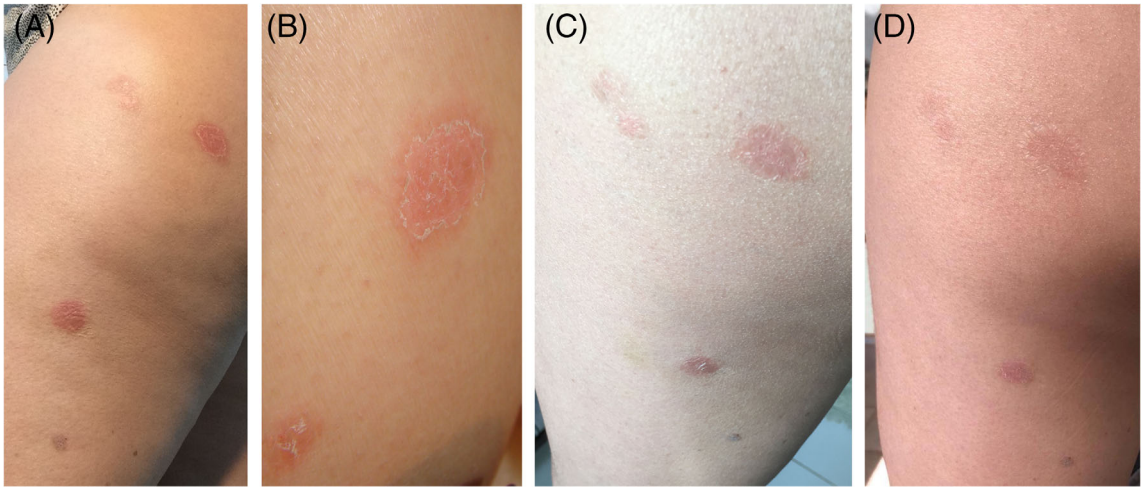

FIGURE 4 (A) Left thigh lesions at 10 days. (B) Larger lesion at 10 days. (C) Lesions at 14 days. (D) Lesions at 24 days

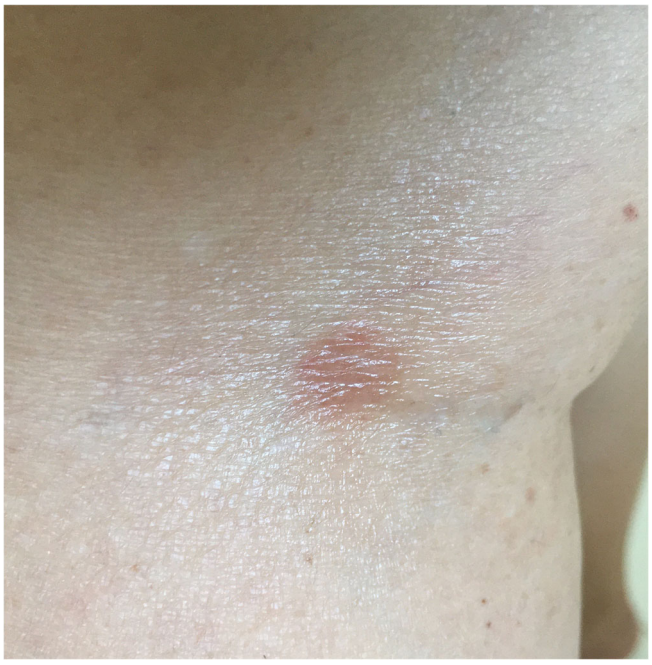

FIGURE 5 Lesion on the posterior left knee—10 days

unnecessary procedures and drug prescriptions.[34] Although it usually demonstrates a truncal predilection, this presentation may be absent in some patients who instead exhibit atypical features and distributions such as only lesions located in the extremities,[12] as seen in this case report. The fact that PR is also confused with other pathologies such as psoriasis, syphilis, allergic dermatoses and fungi[35] would justify the use of cream with ketoconazole and associations by the patient when the herald patch appeared.

Regarding the fact that the "mother patch" appeared soon after one of the doses of Oxford-AstraZeneca, there are other reports described of PR after other vaccine schedules, for example, against smallpox, tuberculosis, influenza, papillomavirus, poliomyelitis, tetanus, pneumococcus, triple viral (diphtheria-pertussis-tetanus), hepatitis B and yellow fever.[11] A report issued by the UK in June 2021 reports 52 cases of PR after Oxford-AstraZeneca vaccination in the first half of the year but does not give details of whether the reactions were after the first or second dose of the vaccine.[10] Other anti-SARS-CoV-2 vaccines also had PR as an adverse reaction[28–31] with the manifestation occurring after the first dose,[28] or after the second dose[28,30,31] and in some patients, the medallion (herald patch) and some lesions, occur after the first dose with exacerbation after the second dose.[29,31]

An international registry of cutaneous manifestations of SARS-CoV-2, established in March 2020, as collaboration between the American Academy of Dermatology and the International League of Dermatological Societies, was expanded on December 24, 2020, to collect information on reactions cutaneous with the use of vaccines against COVID-19. From December 2020 to February 2021, 414 skin reactions to the COVID-19 mRNA vaccines, Moderna (83%) and Pfizer (17%), were recorded. Delayed local reactions were the most common, followed by urticarial eruptions and morbiliform eruptions. Forty-three percent of patients with reactions to the first dose experienced recurrence after the second dose. Other less common reactions included the manifestations of herpes zoster, herpes simplex and PR-like reactions (PR-LE), these were present in 1 report after the first dose of Moderna, 2 reports after the first dose of Pfizer and 1 report after the second dose of Pfizer.[28]

Some authors differentiated between PR and PR-LE (like eruption or like reaction or post-drug/vaccine eruption) and inferred that there is a relevant importance in this distinction in order to assess the possibility of interrupting a medication or not. For them, typical PR can develop during but independently of therapy. If the manifestation occurs after the therapy start and in an atypical form (PR-LE), it is uncommon for the condition to resolve without interruption of treatment and it is suggested that the medication be discontinued if it is not extremely necessary, so that it is also avoid more dangerous skin reactions. According to the authors, the reactional PR-LE after the drug or vaccine would have a limited course, would disappear 14 days

after the drug was discontinued, and the mother patch would be absent, in addition to other characteristics. However, there are medications that act on the immune system, are indispensable and may favor the systemic reactivation of the latent human herpesvirus HHV-6/7 family virus.[36] Although the PR in this clinical case appeared after the vaccination schedule, it cannot be affirmed that it was a post-drug reaction exclusively (PR-LE) but rather a manifestation of viral activation, probably HHV-6, since the patient had contact with this virus in 2008 and 2017 while taking care of her daughter. The mother patch was present, and the cycle was 5 weeks of eruptions, characteristic of typical pityriasis rosea rather than pityriasis rosea-like eruptions according to the criteria defined by Drago et al.[36]

What can explain the emergence of PR in this clinical case is that an immune dysregulation induced by the specific infectious particles of the vaccine would have occurred, which would lead to the reactivation of the latent viruses.[37] This immune dysregulation mechanism is similar to what is observed in patients infected with COVID-19, also leading to other viral reactivations.[30] There is also the hypothesis of a less specific secondary reaction to the immune response as seen with other unrelated vaccines.[11,30] In a state of altered immunity, HHV-6/7 reactivation may result from a T cell-mediated skin-oriented reaction in an atypical presentation of self-limited PR.[27]

HHV-6 has two distinct variants with different immunological, biological and genetic properties. HHV-6A is considered more cytolytic with a higher level of virulence, HHV-6B would cause sudden exanthema (*Roseola infantum*).[14,38]

What would explain a possible cause of PR in this case report is the epidemiological factor. The daughter had roseola in 2008, becoming a latent carrier of HHV-6B and in 2017 she reactivated the virus with the PR condition. As the mother, patient in this case report, was exposed to the virus on these two occasions, it could have been transmitted while remaining latent and after the second dose of the AstraZeneca vaccine it was activated causing the PR manifestation.

The literature has shown several reports of cutaneous symptoms related both to the vaccination schedule against COVID-19 and related to the COVID-19 infection itself however, it is not yet known whether the SARS-CoV-2 virus or particles present in vaccines perform a role in the etiopathogenesis of dermatological diseases. A total of 0.8% of patients seen at a dermatology outpatient clinic between April 1 and May 15, 2019 presented PR cases, however, between April 1 and May 15–2020, 3.9% were cases of PR. After the pandemic, the number of patients with PR increased significantly, which may be related to HHV-6 reactivation.[39]

Cutaneous manifestations such as urticaria, chickenpox and acute edema have been reported in 0.2% of patients infected with COVID-19 in China and in 20% of patients in Italy. In Iran, a case of PR in a 27-year-old male has been associated with COVID-19 infection. Medical history reported fatigue, low-grade fever, anorexia, and gastroenteritis. After 3 days, an erythematous, scaly plaque appeared on the left forearm and other papular lesions appeared along the trunk and upper extremities on subsequent days. The parents were infected with SARS-CoV-2 and chest CT showed irregular ground-glass infiltration in the periphery and base of both lungs, consistent with COVID-19 infection.[23] and this year another study from February 16 to May 15, 2021, showed 405 reactions after vaccination with the BNT162b2 (Pfizer-BioNTech, 40.2%), mRNA-1273 (Modern, 36.3%) and AZD1222 (AstraZeneca, 23, 5%) of which 4.9% were from pityriasis rosea-like reactions[40] however, there are no reports in the literature until now about PR after the inactivated COVID-19 BIBP vaccine, developed by the China National Biotec Group (CNBG), Sinopharm.

The CoronaVac, another vaccine candidate against COVID-19 containing inactivated SARS-CoV-2, is a Chinese vaccine developed by Sinovac Life Sciences (Beijing, China). Randomized, double-blind, placebo-controlled clinical trials demonstrated the safety, tolerability and immunogenicity of this vaccine in healthy adults 18 years of age and older however, a case of pityriasis rosea in a patient following CoronaVac vaccination was reported. A 45-year-old female was received at the dermatology office with skin rashes which developed 4 days after the first dose of CoronaVac vaccine and it had been present for 1 week. The patient denied any history of allergies, recent infections, drug exposure or contact with anyone with COVID-19 infection. SARS-CoV-2 PCR tests performed from both the nasopharyngeal swab sample and the skin lesion biopsy were negative. The lesions faded within 3 weeks and 28 days after the first dose, she received the second dose and 4 days after, skin rashes were similarly reactivated at the previous lesion sites and faded within a week. The analyzes showed findings were consistent with typical pityriasis rosea rather than pityriasis rosea-like eruptions.[41]

In the last years, several treatment options have been proposed to combat the clinical manifestations of PR. In addition to topical antihistamines and corticosteroids,[11,14] antivirals such as acyclovir can also be indicated to control dermal symptoms, pruritus and to aid in the remission of PR by acting in the suppression of viral replication[17,18] however, for this to happen, it needs to be started in the first few days.[15] Another alternative treatment for PR would be the use of L-Lysine 3 grams for up to 3 days, loading dose, followed by 500 mg/day for 30 days[14,19] also starting in the first days of the manifestation of PR.[14] The antiviral potential of L-Lysine may be associated with the fact that this amino acid increases the excretion of L-Arginine by the kidney and intestine, decreasing its concentration and consequently its action on protein synthesis by the virus, preventing replication,[14,21] and that the lesions do not progress to the active clinical phase, disappearing in the prodromal phase.[14,20]

To avoid the reactivation of latent viruses of the herpesvirus family is important the lysine/arginine balance in the diet. To control the multiplication of the virus, when active, an increase in the supply of L-Lysine and a reduction in the intake of L-Arginine are indicated.[14,20] The fact that the patient in this report started L-Lysine with reduced L-Arginine intake, 14 days after the medallion appeared, may have contributed to the reduced number of lesions limited to the thighs (5), calf (1), posterior knee (1), and buttocks (5).

It has been suggested that during the COVID-19 pandemic, large-scale epidemiological studies should be conducted to elucidate whether there is in fact a relationship between vaccination regimens and the reactivation of latent viruses.[37] This mass investigation would be important to see whether this reactivation could be a coincidence

or a consequence, either in relation to reactivation by COVID-19 infection or by the anti-SARS-CoV-2 vaccines.

Overall, the data support that skin reactions post-immunizing agents anti-COVID-19 are generally non-hazardous and self-limiting and should not discourage vaccination. So far, there are no reports of patients who have experienced anaphylaxis or other serious adverse events.[28] Health professionals should be aware of these adverse reactions to the vaccine, carry out the appropriate management.[29] and reinforce with patients about the potential benefits of receiving immunizations, even if small reactions occur.[28]

4 | CONCLUSION

It is concluded that even if there are dermal reactions after vaccination against COVID-19, as they are not dangerous, patients should be advised to receive necessary doses, regardless of the immunizing agent.

PR is a benign, self-limiting disease, with spontaneous resolution and without a definitive treatment protocol, but with the supposed viral association, antivirals can be indicated and among them there is the proposal to use the amino acid L-Lysine with positive results.

Health professionals should be aware of the possibility of PR as a symptom of COVID-19 as well as a reaction to vaccines and provide the necessary counseling.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Maria Cristina Pedrazini: researcher responsible for monitoring the clinical case, data collection, bibliographic review and writing of the article. **Mariliza Henrique da Silva**: researcher responsible for diagnostic confirmation, technical information, bibliography reviews and support in writing; final article review. All authors read and approved the final draft.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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