

Clinical variants of Pityriasis Rosea and PR-like rashes produced by drugs or after COVID-19 infection/vaccination

ABSTRACT

Pityriasis rosea (PR) is a common erythematous-squamous dermatosis which almost always, is easily diagnosed. Mostly the disease presents in its classical form. However, clinical dermatology is all about variations and PR is not an exception. Variants of the disease in some cases may be troublesome to diagnose and confuse clinicians. Prompt diagnosis of the condition becomes essential to avoid unnecessary investigations. We hereby review and illustrate the typical and atypical presentations of the disease, including diverse forms of location and morphology of the lesions, the course of the eruption, and its main differential diagnoses. Although histologic features are not specific, they strongly correlate with dermoscopic findings, a new helpful diagnostic tool. Comparisons among the classical form with other variable findings in pediatric age, dark-skinned people, or its presentation during pregnancy are also analysed, so as the multiple causes of PR-like rashes produced by drugs or vaccinations. During the recent COVID-19 pandemic, PR and PR-like eruptions presented either during COVID-19 infection or after COVID-19 vaccinations, with many polymorphic manifestations. Recent findings that suggest a viral reactivation of human herpesvirus 6 and 7 in the origin of PR and its therapeutic alternatives are commented.

Keywords: *Pityriasis; pityriasis rosea; pityriasis rosea of Gibert; herald patch; papulo-squamous dermatosis; pityriasis rosea-like eruptions; pityriasis rosea and COVID-19 infection; pityriasis rosea and COVID-19 vaccination; pityriasis rosea and pregnancy; human herpesvirus 6 and 7*

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1. INTRODUCTION

Pityriasis rosea (PR) is a relatively common, self-limited papulo-squamous dermatosis of viral origin as accumulated evidence suggests. Its name simply means 'pink scaly rash'. It mainly appears in adolescents and young adults (10-35 years), and slightly more commonly in females according to some studies. It has a sudden onset, and in its typical presentation the eruption is preceded by a solitary patch termed 'herald patch', usually located on the trunk. Few days later, a secondary eruption appears, with little pink, oval macules, with a grayish peripheral scaling collarette around them, and with the free edges of the scales directed to the center of the lesions. The secondary rash adopts a characteristic distribution along the cleavage lines of the trunk, with a 'Christmas tree' configuration. In most cases, the eruption lasts for 6 to 8 weeks, although it may improve sooner or even take a few months. Its prevalence has been estimated to be 0.68% of dermatologic patients [1], varying from 0.39% [2] to 4.8% [3]. The overall prevalence of PR in the United States was 0.21 in a recent database analysis [4]; it was higher in the 18-25 age group (0.77%), and showed a female predominance of 3:1; its prevalence in racial groups was 0.24 in dark-skinned people, 0.21 in Hispanic, 0.20 in white races, and 0.17 in Asian [4].

Not so rarely (20%) [5,6], an atypical eruption may develop, concerning several aspects about the morphology or distribution of the lesions, their symptomatology and evolution. The purpose of this chapter is to update and illustrate the diverse clinical presentations of PR (Table 1), which may vary in morphology, symmetry, duration, size and distribution of lesions, oral involvement and symptomatology. In recent years, PR and PR-like eruptions have been reported during COVID-19 infection and after COVID-19 vaccinations, which added new features for its diagnosis. Most findings suggest a viral reactivation of human herpesvirus 6 and 7 (HHV-6/7) for the origin of the disease.

Table 1. Classification of pityriasis rosea (PR) and its clinical variants.

Classical PR
Pediatric PR
PR in dark-skinned people
PR during pregnancy
PR in the elderly

Clinical variants

Based on herald patch

No herald patch
Only herald patch (absence of secondary lesions)
Multiple herald patches
Herald patch in atypical location

Based on location of lesions

Limited to scalp
Limited to trunk
Limited to limbs-girdle (pityriasis *circinata et marginata* of Vidal)
Limited to flexures (inverse)
Limited to the extremities
Localized
Acral type
Along the lines of Blaschko
Unilateral
Oral

Based on morphology of lesions

Purpuric or hemorrhagic
Urticarial
Erythema multiforme-like
Papular
Follicular
Vesicular
Giant
Hypopigmented
Irritated
Psoriasiform

Based on course of the disease

Relapsing
Recurrent
Persisting
Relapsing and persisting

PR-like rashes (drug-induced)

PR during COVID-19 infection

PR and PR-like rashes after COVID-19 vaccination

Classical PR

A classical PR is preceded by the herald patch, an erythematous round or oval lesion with slightly elevated scaly borders and a paler center (Figure 1). Its name implies a plaque that is heralding a coming eruption. It gradually enlarges in a few days, usually reaching 2-5 cm in diameter despite a wide variation from 1 to 10 cm [7]. It is usually located on the trunk, although variants about its form and location have been reported, and is not always present or noticed by patients. In the compilation of five series done by Burch & Rowell in 1970, the sum of all made a total of 1,218 cases, in which the anatomical site of the primary lesion was -in descending order- trunk 662 cases (54.35%), arm 246 cases (20.19%), leg 165 cases (13.54%), head and neck 145 cases (11.90%) [8].

Prodromal symptoms, consisting of headache, abdominal or joint pain, mild fever, loss of appetite, general malaise, or flu-like symptoms are occasionally encountered. They may precede or accompany the eruption. Few days later (5-15 days), a secondary rash appears, consisting of similar, but smaller round to oval pink lesions, mainly located on the trunk with a 'Christmas tree' configuration (Figure 2a and b). By unknown

reasons they follow the skin tension lines, adopting an V-shaped distribution on the upper chest and upper back, and transverse on the lower trunk [9]. It usually starts in the chest, spreading successively in crops to the abdomen, back, arms and thighs ('from neck to knees'). Pruritus is usually mild or absent, but may be present in about 30% to 50% of cases, varying considerably in intensity. The eruption lasts for 6-8 weeks and fades, leaving no sequelae, although pigmentary changes may be seen, especially in dark-skinned people (hyperpigmentation in 7% in one series [10]. Older lesions improve gradually first and the newer lately. Generally, it only appears once throughout life.



Figure 1. Herald patch. Solitary erythematous-squamous lesion, sharply defined, round or oval and with a paler center, mainly located on the trunk (top right).

In 75% of patients the eruption appears between the ages of 10 to 35 years [11]. The youngest case reported was 3-month-old [12] and the oldest 82-years-old [13]. It has been reported in all climates and the supposed seasonal variation is contradictory according to various studies [14], a fruitless discussion already present since 1940 [15]. Higher incidences have been reported to prevail during colder months, rainy season, or even with a bimodal distribution based on data from different cities or countries [16]. The frequency of new cases by month and by year also shows wide fluctuations [8], and thus, it probably appears evenly throughout the year.



Figure 2a. Classical pityriasis rosea. Erythematous-squamous lesions of secondary eruption with a double herald patch.



Figure 2b. 'Christmas tree' configuration.

Pediatric PR

More rarely PR may affect children, with a frequency between 8% [17] to 12% [11] below 10 years, and 4% below 4 years of age in Caucasians [11], whereas in dark-skinned children it increases to 26% [18]. Younger case reports during infancy were 3,4 and 6-month-old children [12,19,20]. The frequency of PR under two years of age has been estimated between 0.1% to 0.3% [21]. Papular lesions prevail in pediatric PR, interspersed among round to oval lesions [22], with a short period between the herald patch and the general eruption (4 days vs 14 days in adults), and a shorter duration of the exanthema (16 days vs 45 days). The majority of cases have been described in children aged 3 to 9 years, contrasting with the illustrated case of 8-months of age (Figure 3), showing a classical variant. A Mexican series of 30 cases represented an incidence of 3.6 cases/each 1,000 dermatologic patients examined during a period of 10 years in a pediatric institute [23]; 56% presented with atypical forms, mainly with lesions located on the extremities (14 cases) or in axillae/groins exclusively (3 cases). In another series of 50 pediatric cases, atypical eruptions were found in 12 cases (24%) [24], with papular (8%), follicular (6%), urticarial (6%) or lichenoid lesions (4%).



Figure 3. Pediatric pityriasis rosea. Typical lesions of PR involving the back in an 8-month-old boy.

About one third [25,26] to a half of the cases in children show prodromal symptoms [17], and a history of a preceding upper respiratory tract infection is common, but very variable, ranging from 6.6% or 12% [23, 27], to 34% [24] or even 83.5% [28]. Inverse distribution of lesions (axillae and groins) shows a significant longer duration of the disease: median 17 [26] or 18 weeks [25]. A high prevalence of pruritus in children has also been noted, ranging from 62% [24] or 69% [25] to 72.6% [28] or 74% [26], although in other series it was lower or unremarkable [17,23]. Fever and myalgia were reported in 22 cases (44%) of a series of 50 cases [24]. Symptomless oropharyngeal lesions seem to be more common in childhood -estimated in 35% [29]- than in adult PR, mainly consisting of vesicles, papules, petechiae and strawberry tongue. Interestingly, oral involvement decreased with advancing age in a pediatric series, from 40% in age below 5 years, to 19% in age group 6 to 10 years, and 12% in age group 11 to 15 years [28].

PR in dark skinned people

Some atypical features of PR have been reported in dark-skinned people, especially concerning the unusual involvement of the face and scalp, the more frequent finding of papular lesions, and more secondary sequelae of pigmentation. Its denomination as 'rosea' has even been questioned, since that the erythematous hue is not seen in black or brown skins [30]. In a study of 50 children from Michigan (USA), more facial (30%) or scalp (8%) involvement was observed than in white populations: one third presented with papular lesions, 48% resolved with hyperpigmentation and 29% with hypopigmented lesions [31]. In South Africa PR tends to be more severe in Bantu people than in Europeans [32], a feature also found in Nigerians, with more extensive lesions and face involvement in 29% of cases [33]. In African series of PR, pediatric affection in children below 10 years of age showed higher frequencies than in other races, ranging from 21% in urban Bantu [34], 23.4% in Sudan [30] to nearly 25% in Uganda [35] or 26% in a series from Nigeria [33], although in others it was 8.9% [10], 15.7% [36] and 21.8% [3] in this country. In India, frequencies of 8.82% [37], 14% [38], 15% [39] and 22% [40] were found below the age of 10 years. A unique case in an Indian boy presented with initial lesions on the scalp mimicking pityriasis amiantacea, soon followed by a more typical eruption on the trunk [41].

PR during pregnancy

Due to an apparent prevalence of PR among females, something similar could be expected to occur during pregnancy, in which it has been estimated to appear with a frequency of 18% versus 6% in the general population [42]; however, there are no recent studies that confirm those old comparative percentages dating back to 1950, repeatedly cited in the relevant literature. Although PR has been always considered as a benign disease without associated complications, some studies have shown an apparent relation with abnormal pregnancy outcomes. An analysis of 38 pregnant women with PR showed that 9 of them had a premature delivery and 5 aborted; in 6 cases newborn children presented hypotonia, weak motility and hyporeactivity; in the group with abortion, 62% of mothers had developed PR within 15 weeks of gestation [43]. In a further study embracing 61 women with gestational PR, the total abortion rate was 13%, being noted that it presented in women in whom lesions were diffuse, with a long duration and accompanied by constitutional symptoms, such as fatigue, headache, insomnia or loss of appetite [43,44]. An alarming associated fact was that the mean viral load of HHV-6 was higher in pregnant women with complications than in those without [45].

On the contrary, in other studies of pregnant women with PR compared with matched controls, it was concluded that abortion rates were similar in both groups (13%) [46], so as there were the rates of birth complications compared with the general population [47]. However, a further case series analysis concluded that early onset, extensive and long rash duration and the presence of constitutional symptoms were directly associated with an unfavourable outcome [48], being suggested that a close follow-up should be done in pregnant women with PR onset before 15 weeks of gestation, with a wide rash distribution over 50% of the body area and associated enanthem, as well as the presence of constitutional symptoms [49,50]. All those data and -when possible- plasma analysis of viral loads of HHV-6/7 DNA by nested PCR should be evaluated in order to decide treatment alternatives [51, 52].

Individual case reports of PR developing during pregnancy have shown normal deliveries [53,54], including a case with associated local HHV-2 reactivation [55]. The description of craniosynostosis in the newborn of a woman who presented PR at the tenth week of gestation -which spontaneously resolved in the next 8 months post delivery- may be purely coincidental [56].

Anesthetic considerations have also been raised in pregnant women with PR, especially for neuraxial anesthesia when PR lesions affect the lumbar zone [57]. Concerns have arisen for possible hematogenous seeding to the central nervous system through puncturing that area, with risks of encephalitis or meningitis, although perhaps lower than for active HHV-2 infection. Thus, when general anesthesia carries contraindications in these patients, it has been suggested that an epidural anesthesia should be preferred when there are active PR lesions in that zone [57].

PR in the elderly

Although PR is uncommon in elderly people, a series of 7 cases was described in patients 65 to 75-years-old with a slight predominance of females [58]. Striking features were widespread distribution of lesions not limited to the trunk, more larger inflammatory and erythematous lesions, complete absence of pruritus and thus no need for treatment. Herald patch was found in most cases and the eruption followed a mild course.

2. CLINICAL VARIANTS OF PR

Atypical presentations of PR include several variations in the size, morphology, distribution and location of lesions, associated symptomatology and evolution of the disease. Some infrequent cases may present the classical eruption distributed on the trunk, accompanied by the unusual affection of other sites, such as palmar and plantar areas, finger or toe tips [59], eyelids, penis [60], or even the face [61]. As curiosities - with descriptions that have not been reported again-, at least three old publications have commented on characteristic rashes of PR exclusively located on the areas covered by bathing trunks, sparing tanned areas of the skin, with an abrupt cessation of the eruption at their borders [62-64]. This fact would suggest an ameliorating effect of sunlight in the disease, especially when the eruption develops when the skin its being exposed to the sun [65]. Similarly, a single case was reported in a woman treated with Roentgen rays, in whom a later eruption of PR spared the previously irradiated areas [62]. In other single case, anetodermic lesions appeared 6 weeks after in the same areas previously affected with PR and impetigo, with a 'Christmas tree' arrangement [66].

In a series of 27 cases of atypical PR collected during a period of 8 years, the most common atypical variants were papular (5 cases), purpuric (4 cases), vesicular (3 cases), and follicular (2 cases), although the total number of PR cases seen in that period was not mentioned [67]; atypical eruptions were more frequent in adults and in males, and 16 cases presented with localized forms, two of them with a zosteriform configuration [67]. Atypical cases were found in 27.6% of a series of 60 patients [68], 30% in another of 56 patients [10], 38% in 50 patients [40] and 38.5% in 88 patients [69]. In another cross-sectional study of 50 patients [70], 40% (20 cases) presented an atypical clinical presentation: the most common was inverse PR (6 cases), followed by papular PR (5 cases), and targetoid lesions (3 cases).

Atypical herald patch

The herald patch is a very valuable sign for clinicians in the diagnosis of PR, sometimes retrospectively obtained from anamnestic data or mostly by clinical observation when detectable. On some occasions patients have not realized they have it, for example when it is located on the back or buttocks. The frequency of its presentation has ever shown wide variations, ranging from 12% to 94% [15]. Its diverse, anomalous variants may rely on its number, size and location. Multiple herald patches have been rarely reported [71,72], but found in 5.5% of an old series [15]. Double herald patches (Figure 2a) have been also rarely found [10,39,73], although observed in 3 cases of a series of 27 atypical presentations of PR, with only 1 case of giant herald patch [67]. The latter was also described in a 18-month-old girl with a huge lesion almost encircling her lower back and pubis [74]. A unique case of a target-shape herald patch on the back with hypopigmented periphery and pigmented center was reported in a 9-year-old boy [75]. Herald patch has been described practically in all areas of the body [15], perhaps with the exception of the scrotum.



Figure 4a. Herald patch in atypical location. Herald patch on the left sole.



Figure 4b. Secondary eruption affecting proximal thighs in the same patient.

We had the opportunity to come across a patient who presented with a herald patch on a sole, and a secondary classical eruption on the trunk and proximal aspect of the extremities (Figure 4a and b). Only two cases with similar findings have been described [76,77], and in another single case it was reported on

a finger [78]. Only on two occasions it was described on the palms [79,80]. Only in one case it was reported to occur on the scalp [32], and in rare instances on the face or penis [15,81]. Its presentation in sites of vaccination, wounds, insect bites, friction with clothes or cutaneous infections is certainly fortuitous.

Finally, it should be noted that the herald patch has been reported to appear up to two months before the development of the secondary generalized eruption on the trunk [60], and in a single case -being situated on the face- it was followed within three hours by the typical secondary rash [82].

PR *circinata* and *marginata* of Vidal

Seen mainly in adults with few and large lesions only located on limbs-girdle, hips, shoulders, axillae or inguinal regions [33,60,83]. In some opportunities, groins, penis, scrotum and pubic mound appeared affected [84,85]. The lesions show a slow evolution, sometimes lasting months. They begin as small scaly macules that, by confluence and growth, acquire arcuate borders and a circinate configuration (Figure 5). The recent description of two pediatric cases -with lesions affecting pubis, vulva and perineum-, raises the need for retaining this possible diagnosis, especially when fungal infections and other diaper conditions are more commonly found at these ages [86]. Exceptionally, a 4-year-old girl presented three recurrent episodes in one year, within six months after the initial eruption: the lesions appeared on axillae and groins without affecting the trunk, as no herald patch in the recurrences [87]. Perhaps more appropriately, it should have been reported as relapsing PR (see below).



Figure 5. Pityriasis *circinata* and *marginata*. By confluence of lesions the eruption acquires a circinate configuration.

Inversus PR

The lesions are located on flexural areas, such as axillae, groins, flexor surface of the arm [88], face, neck (Figure 6a and b), and acral areas (palms and soles), without affecting the trunk [89]. It may be seen in children [90] and it has also been reported after COVID-19 vaccination [91]. Its frequency in a series of 214 PR cases was 2.3% [92], 5.22% in a series of 115 cases [93], and 18% in another that included 56 cases [10].



Figure 6a and b. Inversus PR. Lesions distributed on face and neck in two patients. The trunk is not affected.

PR of extremities

In this variant, the lesions are confined to the extremities, with typical squamous patches [94] (**Figure 7a and b**). The trunk supposedly does not appear affected [95]. In one case the lesions were mainly localized on the upper extremities, with a few lesions on the abdomen; erythematous scaly patches were found on arms, forearms, palms, web spaces and proximal nail folds [96]. Similarly, in other three of six reported atypical cases the eruption prevailed on the back of the hands, feet and lower legs; on the back of the feet, axillae and palms; and in left thigh, neck and lower legs, with few or absent lesions in the trunk [97]. In another series of 368 patients from Singapore, 22 cases (6%) presented with lesions mainly involving the extremities [13].



Figure 7a and b. PR of the extremities. Lesions affecting only the extremities in two different cases, without trunk involvement. **a:** Arms and forearms affection. **b:** Rounded scaly lesions on feet and legs.

Localized PR

Localized eruptions of PR had already been noted at the beginning of the past century, with lesions confined to the thighs, neck, or axillae and neck [60]. It has been suggested that such localized forms would essentially represent an abortive form of the disease [98]. A case was reported in a woman with PR typical lesions but only distributed on her left breast; the eruption did not extend over the next four weeks [99]. In a series of 115 cases, only two patients presented with localized lesions, one in the face, and the other in the side of the neck and upper trunk [93], while in another series it appeared in 6 of 56 cases (9%) [10].

Acral PR

The lesions are exclusively located on the back of the hands [100], palms, soles, wrists or lateral aspects of the soles [101,102] (Figure 8), without involvement of the flexures (axillae, groins and face), opposite to inversus PR. However, some cases have been included in this category, although presenting with lesions beyond palms and soles [59,103,104]. In a series, it was not clearly stated if their unique patient with palmar and plantar involvement had lesions exclusively in those areas, or just fortuitously accompanied a typical PR [70].



Figure 8. Acral pityriasis rosea. Desquamation affecting the palms.

PR along the lines of Blaschko

During an eight-year period, out of 507 patients with PR, only 3 cases (0.6%) presented with a Blaschkoid distribution of lesions [105]. A symmetrical and bilateral rash on the trunk following the lines of Blaschko was described in a boy after a sore throat [106]. In a young man, the lesions were distributed along the right thigh, which had also appeared after a sore throat [107]; in a woman after pharyngitis, a linear eruption was seen affecting the left shin and left arm [108]. More recently, a case of Blaschkoid PR after COVID-19 vaccination was reported in a woman with a herald patch located in the right side of the abdomen, followed two days later by secondary lesions -all of them with peripheral collarette scaling- linearly distributed towards the flank, back and medial aspect of the right thigh [109].

Unilateral PR

In a few cases PR has been reported with an unilateral distribution, presenting with a variable number of lesions but always parallel to the lines of skin cleavage. In most of them the clinical diagnosis was confirmed with skin biopsy. In a young woman the eruption was preceded by malaise and corizal symptoms, followed by hundreds of oval-shaped erythematous scaly lesions only over the right side of the trunk [110] (Figure 9a and b). Another case with large lesions on abdomen and lower back for 4 months was reported in a 18-

year-old man [111]. In another cases the lesions were distributed along the left [112] or right thigh [113], right side of the chest, back and axilla [114], lower back [115], left side of the trunk [116], left side of the trunk and abdomen [117], left side of the back [118], upper trunk and upper arm [119,120], right forearm [118] and neck at left [113]. Only in one case reported in a child, the lesions were located solely in one side of the body, starting from the right waist and shortly after affecting antero-lateral right thigh, right lower back, gluteal area, right arm and forearm [121]. It has been proposed that perhaps many forms of the so called 'unilateral laterothoracic exanthem' are actually forms of unilateral PR [122].

A unique case was reported with segmental PR lesions following a dermatome: after an episode of coryza and malaise, a 34-year-old woman presented with oval scaly plaques unilaterally distributed following the right T4 dermatome and not crossing the midline; a segmental, dermatomal or zosteriform PR variant was proposed [123].



Figure 9a and b. Unilateral pityriasis rosea. a: Lesions affecting only on the right aspect of the trunk. **b:** Oval-shaped erythematous scaly lesions (Courtesy of Dr. Nadia Ghariani).

Oral involvement in PR

Although PR is a well known condition since 1860, it was not until 1938 when oral involvement was firstly described [124], being suggested that its clinical picture could have changed over time [125]. Oral lesions in PR are more common in dark skinned people [126]. Their frequency is highly variable, sometimes with no affected patients in some series [10]. A search for oral lesions in one hundred cases of PR disclosed only one patient with a single ulcer in the buccal mucosa [127], while in other series, a 9% of oral lesions was found in Nigerians [33] and 16% in caucasians [128]. Similarly, a regular search for oral lesions in PR concluded with only one case after more than 300 examinations [129]. In another large series of 527 cases, 149 (28%) showed painless oropharyngeal lesions while the remaining 378 cases (72%) did not; oral affection was more frequent in children (41%) than in adults (27%) in the same study [130]. The lesions are sometimes difficult to differentiate from aphthous ulcers [88]. Its appearance should coincide with a generalized eruption that meets the characteristics of PR [6]. The lesions can be punctate, erosive, bullous or hemorrhagic, perhaps reflecting different stages in the evolution of the disease [131]; they have been categorized as punctate hemorrhages, erosions or ulcerations, erythematous macules (Figure 10), erythematous annular lesions, and erythematous plaques [131]. Eroded match head to pin sized lesions have been reported affecting the tongue, floor of the mouth, buccal mucosae and palate [132]. A case with geographic tongue-like lesions was described in an atopic child [133], and strawberry tongue has also been reported [17]. The lesions may not be present throughout the whole period of the cutaneous eruption, and may vary from solitary hemorrhagic macules to numerous variously sized lesions [125], mostly symptomless

and thus commonly overlooked. They are apparently seen more frequently during the height of the disease and disappear concomitantly as the skin eruption fades [125,129,134].



Figure 10. Oral involvement in pityriasis rosea. Diffuse erythema of the soft palate (Courtesy of Dr. Giulia Ciccarese).

Purpuric or hemorrhagic PR

Initially reported in 1944 [135], macular purpuric lesions and petechiae may appear over different locations (Figure 11) including the palate [136]. Purpuric lesions have been described bilaterally on the legs in a man with a typical rash on the trunk, affecting the lines of cleavage and with collarette scaling [6], and also in the upper limbs in a woman during the course of a typical PR rash [137]. However, herald patch and peripheral scaling may be absent [138].



Figure 11. Purpuric pityriasis rosea. Round and oval purpuric lesions affecting the neck of a young woman.

In a single case report, persistent and generalized purpuric lesions of PR were associated with positive IgM antibodies to Herpes simplex virus type 1 [139]. In other case affecting mainly the shins of a 7-year-old girl the lesions were purpuric and vesicular, consisting of purpuric polycyclic plaques -some of them with a central hemorrhagic bulla- while others presented as rosettes of vesicles and bullae on a purpuric base [140]. Annular lesions with rust colored centers have also been described [141]. Another case presented asymptomatic purpuric macules and papules affecting the trunk and arms [142]. The hemorrhagic nature in this variant of PR must be differentiated from purpura pigmentosa chronica, especially with the eczematoid form of Doucas & Kapetanakis [143], vasculitis and hematologic disease [144]. In few occasions, purpuric PR was associated with acute myeloid leukemia [145,146].

Urticarial PR

Palpable itchy wheals-like lesions with peripheral collarette scaling (Figure 12) following the lines of skin cleavage [6,60].



Figure 12. Urticarial pityriasis rosea. Palpable edematous, erythematous lesions with collarette scaling.

Erythema multiforme-like PR

In some cases, classical lesions of PR may be accompanied by targetoid lesions resembling erythema multiforme (EM) (Figure 13). It presents with papulo-squamous lesions, admixed with few targetoid lesions distributed on the trunk, face, neck, arms, forearms or legs [147-150]. There is no history of Herpes simplex infection. In two cases the eruption of EM-like plaques coexisted with papular lesions [148,151], even affecting penis and scrotum [152]. In a series of 5 cases the age range of presentation was 15 to 22 years, with a male:female ratio of 3:2 [148]. In two studies from India, 6% [70] and 10% [153] of cases presented with EM-like lesions.



Figure 13. Erythema multiforme-like pityriasis rosea. Papular and annular targetoid lesions resembling erythema multiforme.

Papular PR

Multiple small papular lesions, 1-3 mm in diameter with peripheral collarette, located on the trunk and proximal extremities, along the skin cleavage lines (Figure 14a and b). The papules may be follicular or millitary [60]. It appears predominantly in young patients [6], pregnant women and Afro-Caribbeans [154].



Figure 14a and b. Papular pityriasis rosea. a: Papular lesions with peripheral collarette (Courtesy of Priyanka Misra, Junior Resident, Dermatology, Burdwan Medical College, West Bengal, India). b: Herald patch on the neck and disseminated discrete papular eruption in a girl.

Follicular PR

It has been described in a 9-year-old boy with predominantly follicular scaly lesions, arranged in annular configuration [155]. The initial lesions consisted of pruritic plaques mainly located on the abdomen, thighs and groins; five days later, a striking follicular eruption - with central clearing and a peripheral collarette-developed on the posterior trunk. Prodromal symptoms included sore throat, malaise and low grade fever (Figure 15).



Figure 15. Follicular pityriasis rosea. Follicular lesions with scaling (Courtesy of Shankila Mittal, Junior Resident, Dermatology, Maulana Azad Medical College, New Delhi, India).

Vesicular PR

A generalized itchy eruption of vesicles of 2-6 mm in diameter with a rosette scaling has been described in young adults and children [140,150,156-159] (Figure 16). Vesicles can be detected in addition to erythematous papulo-squamous lesions or interspersed between crusted hemorrhagic papules [159]. The erythematous macules may also appear surrounded by vesicles in a rosette pattern [160]. When located on the face the lesions can mimic varicella, and dyshidrosis when affecting palms or soles [159].



Figure 16. Vesicular pityriasis rosea. Vesicular lesions surrounding round to oval plaques (Courtesy of Dibyendu Basu, Junior Resident, Dermatology, Medical College and Hospital, Kolkata, West Bengal, India).

In two young adult male patients a vesicular eruption of the soles and lateral aspects of the feet preceded or heralded in a week a typical eruption of PR, with scaly oval lesions distributed on the trunk, arms and complete lower extremities [157]. The initial vesicular eruption consisted of tense, slightly itchy, 1-9 mm vesicles, which progressed up to the ankles and soon followed by PR lesions which lasted 6 and 8 weeks each. There were negative findings for fungal and bacterial cultures and standard patch tests gave negative results.

On the other hand, vesicular lesions limited to palms and soles were observed during a typical rash of PR affecting the trunk and extremities [78,161].

In an old PR series, only 2 cases of vesicular PR were found out of a total of 380 cases [162].

Gigantea of Darier

The dimensions of lesions are greater than usual, ranging from 5 to 6.3 cm [60], or even more (Figure 17) and following the natural course of the disease. In one case the first lesion was described as a patch with the size and shape of a pear [163], and in another, with a huge plaque almost encompassing the lower back and the pubic region [74]. Gigantic PR lesions affecting the trunk have also been reported [164,165], in one case after influenza vaccination with almost erythrodermic giant lesions [165].



Figure 17. Giant pityriasis rosea. Large herald patch (Courtesy of Soumya Jagadeesan, Assistant Professor, Dermatology, Amrita Institute of Medical Sciences, Kochi, Kerala, India).

Hypopigmented PR

It is essentially similar to the classic PR, with a preceding herald patch and a secondary eruption, but with hypopigmented lesions from the beginning, mainly on the trunk ([Figure 18](#)). It is more frequent in dark-skinned individuals. It should not be confused with secondary hypopigmentation after a common PR. A unique case was reported in a 9-year-old boy with disseminated and hypopigmented scaly lesions mainly on the trunk, with a larger target-shape patch on his back, with hypopigmented periphery and a pigmented center [[75](#)].



Figure 18. Hypopigmented pityriasis rosea. Round to oval hypopigmented lesions during the whole course of the eruption.

Irritated PR

A PR with severe itch, pain and burning sensation on contact with sweat or clothes [5,166] (Figure 19). Occasionally the lesions may appear with secondary impetigo making diagnosis difficult or retarded [167]. In one case report, the changes in the lesions over time created confusion with guttate psoriasis, but leading finally to the diagnosis of PR *irritata* [166].

A rare exacerbation of PR after treatment with ampicillin has been reported in some patients from Nigeria [3]; when the medication was taken during the early PR eruption the lesions become worse and pruritus was more frequent, the rash appeared more extensive and urticated, and it took longer than usual to improve. This circumstance arose in 29 of 352 cases (8.23%) and was analogized to the ampicillin rash of infectious mononucleosis [3]. In other study from Nigeria, a few patients were affected in this same way [10], a fact that has not been reported in series from other countries.



Figure 19. Irritated pityriasis rosea. Symptomatic eczematous lesions (Courtesy of Dipti Das, Consultant Dermatologist, Dr Marwah's Skin Clinic, Mumbai, Maharashtra, India).

Psoriasiform

It has been rarely reported, representing 2.5% of cases in a series from Central India (1/40 cases) [153] and 3.3% (2/60) in another series from North Kerala [168]. It was nicely illustrated in a 17-year-old boy with erythematous scaly lesions on the back present for 2 months, which by coalescence evolved to form a large psoriasiform plaque; histopathological study was compatible with PR and the lesions disappeared spontaneously in one month [169].

Relapsing PR

It occurs within one year of the first episode, being reported among 2.8% [81] to 3.7% of patients [170]. Relapses usually show absence of herald patch, and the size and number of secondary lesions are smaller. The duration of this episode is shorter and with less severe constitutional symptoms [170]. Multiple relapses -though rare- have been described: 4 patients had two relapses and 2 patients had three relapses in a series of 21 cases of relapsing PR [170]. A single case report with frequent relapses during a period of 7 years was described in a 11-year-old girl, sometimes with several relapses within one year, with few lesions and changing locations [171]; human herpesvirus-7 DNA was detected in blood in the first episode and sometimes in saliva specimens during some of the relapses, which appeared during stressful events and preceded by itching.

Persistent PR

By definition it lasts more than 3 months. Its frequency in a series was 2% [1], and 13% in another [10]. Most patients (75%) show a herald patch [1] and complain of systemic symptoms (most commonly fatigue, headache, insomnia, or irritability). The eruption persists for 12-24 weeks. Oral lesions are common (75%), principally strawberry tongue, erythematous macules, vesicular lesions and petechiae. In one reported case the lesions progressed gradually for more than 5 months until the diagnosis was reached after performing a skin biopsy [172].

Recurrent PR

Rarely, there can be multiple episodes of PR in a life-time [87,173,174], suggesting that there is long-lasting immunity after a first episode. Recurrences may be single or occur two or three times, with variable intervals from months to thirty years [81]. The occurrence of five episodes is extremely unusual, with only two cases reported [173,174]. Its frequency has been estimated between 1-3% [175], 1.8% [11], 2.8% [81], 4.3% [176], and more recently 25.9% [177], suggesting that it may be underestimated due to reluctance of patients for consulting again for a banal eruption they already knew, or by the lack of follow-up studies [173]. The mean duration of recurrent episodes is shorter, constitutional symptoms are less severe, as so the cutaneous eruption [176]. The herald patch recurrence may appear in the same location [174], in another site, or even not be seen. Anecdotally, a woman presented a recurrence in the same month in two consecutive pregnancies [81]. Antecedent of atopy may be found up to 19% of cases [176]. In a single case report, recurrent episodes of PR were observed in a young male after injection of influenza A vaccine, and also 14 months later after receiving hepatitis-B vaccine, with larger lesions than those commonly observed [178]; the authors proposed possible associations with vaccine-induced stimulation with a stronger immune reaction, or to a rare vaccine component; however, most recurrences have no explanation. Only three cases have been reported in pediatric age, the first one as PR *circinata* and *marginata* (described above), the second in an 11-year-old boy with three episodes in six years (at 5, 9 and 11 years), all of them almost similar in duration and severity, with the herald patch at the same location in the two last episodes [175]; finally, the third one, in an 8-year-old girl that presented four successive episodes with annual periodicity, all of them with a different location of the herald patch (anterior thorax, left shoulder, back and neck) without secondary lesions during the fourth episode [179].

Relapsing and persisting PR

It has been described in a young man with three episodes of PR within one year-fulfilling the criteria for relapsing PR, and the last episode during 7 months consistent with persistent PR. Noteworthy, the patient presented with multiple oral ulcers [180]. The herald patch was noted on each successive episode, with different locations.

PR-like rashes

They consist of exanthematous rashes -not related with HHV-6/7 reactivation- which appear following the intake of several drugs: ACE inhibitors [181-183], allopurinol [184], asenapine [185], atenolol [186], benfluorex [187], bismuth [188], bupropion [189], clozapine [190], domperidone [191], ergotamine [192], gold [193-196], ibuprofen [197], interferon alpha 2a and b [198-200], isotretinoin [201,202], ketotifen [203], lamotrigine [204], lisinopril [205], lithium [206], loperamide [207], metronidazole [208], mustard oil application [209], nimesulide [210], non-steroidal anti-inflammatory agents [211,212], nortriptyline [213], omeprazole [214], ondasetron [215], terbinafine [216,217], pristinamycine [218], and topiramate [219].

More recently, PR-like eruptions have been reported after the use of biologics: Adalimumab [220], Dupilumab [221,222], Etanercept [223], Ibrutinib [224], Imatinib [225-231], Infliximab [232], Omalizumab [233] and Rituximab [234].

Many of them resemble PR vaguely (Figure 20a and b), so it can be considered as a separate condition. There is no previous herald patch and the eruption is more itchy, with poor response to antihistamines. The lesions are monomorphous, dusky or violet red [7], more diffuse, confluent [235], and persistent, without a 'Christmas-tree' distribution. It has also been stated that there are no prodromal symptoms and that mucous membranes could be involved; blood eosinophilia may be found, and histopathological features consist of

an interface dermatitis with eosinophils, sometimes including necrotic keratinocytes [236]. In a small case series report, two cases presented with a localized eruption restricted to radiotherapy fields for pelvic malignancies; no preceding herald patch was detected [237]. During a 3-year period of a program conducted in a drug-surveillance center in Italy, 8 cases out of 380 (2%) mimicking PR were detected [238]; the mean age was 68.6 years with a male prevalence of 6:8; itching was unresponsive to antihistamines and a sudden withdrawal was obtained after cessation of the corresponding drugs (mainly ACE inhibitors, or hydrochlorothiazide, allopurinol, nimesulide, and acetylsalicylic acid) in all of them.



Figure 20a and b. Pityriasis rosea-like rash. **a:** The eruption in this case was probably related to the ingestion of levothyroxine in a 33-year-old man, extensively affecting the trunk. **b:** The lesions are small and monomorphic (Courtesy of Dr. Elizabeth Rendic).

PR-like eruptions have been reported following vaccinations as well: Bacillus Calmette-Guerin as vaccine or immunotherapy [239-241], influenza [242,243], diphtheria, smallpox [244], hepatitis B [245], human papilloma virus [246], yellow fever [247], anti-rabies vaccine [248], and pneumococcus [249]. More recently, it was reported after monkeypox vaccination [250].

On other grounds, atypical eruptions have been reported in association with systemic symptoms and lymphadenopathies in two patients subsequently diagnosed with Hodgkin's disease [251,252]. Exceptionally, 4 cases of PR-like rashes have been reported after bone marrow transplantation for chronic myeloid leukemia, all of them with clinical and histopathological features of PR, but with coexisting histologic features of graft-versus-host reaction in three of them [253]. In only one case a herald patch was detected.

PR during COVID infection

During the recent COVID-19 pandemic, one of its main manifestations was the appearance of skin lesions, of which maculo-papular eruptions stood out with a frequency of 47% [254], among which PR type were not rare. Their main characteristics are summarized in [Table 2](#). It is observed that all cases of PR were typical, with pruritus or not, and showing varied symptoms. The majority of cases were confirmed with PCR for COVID-19. Though specific virologic investigations for HHV-6/7 reactivation were very rarely investigated in these cases [267], at least the clinical presentation was that of classical PR.

In a study of 347 Latin American patients from 25 countries analyzing the dermatological manifestations of COVID-19 infection, a predominance of women with 51.6% of cases and an average age of presentation of 40.87 years was found. It was observed that 13 (4%) of the 347 patients had PR-type lesions [268].

The cases of PR during the COVID-19 pandemic increased five-fold, from 0.8% before the pandemic to 3.9% during the pandemic [269,270]. COVID-19 infection may have played a role in reactivating herpesvirus 6 and 7 (HHV-6/7) and producing PR [271]. In addition, the presence of the spike protein of the SARS-CoV-2 virus (COVID-19) was demonstrated in the endothelial cells and perivascular lymphocytes in a patient with PR, who two weeks before presented with cough, general malaise, dysgeusia, myalgia, arthralgia and headache; nasopharyngeal swab for SARS-CoV-2 was negative, but the IgM and IgG antibodies were positive for SARS-CoV-2, three weeks after the start of PR. This demonstrated that SARS-CoV-2 infection of endothelial cells and lymphocytes may be the cause of PR [266].

Table 2. Clinical findings of PR cases reported during COVID-19 infection.

1 st Author Ref N ^o	Age	Sex	Clinical features T= typical	Relation PR/COVID	Studies
Birlutiu 255	54	F	T, pruritus	Respiratory symptoms, 1 week before rash	PCR (+) nasopharynx
Busto-Leis 256	26	F	T, pruritus	Symptoms suggestive of Covid-19, one month before rash.	IgG (+).
	48	F	T	Toes with perniois after contact with a case of Covid-19 in previous weeks	Serology (-). Presumptive diagnosis based on clinical findings and contact with a case with COVID-19.
Drago 257	16	M	T, without pruritus	Fever, cephalaea, fatigue, arthralgias, myalgias, anorexia, dizziness. Coincident with rash.	PCR (+) for COVID-19. Positive serology (+) for HHV 6,7 and Epstein-Barr. Parents COVID-19, 3 weeks before
Ehsani 258	27	M	T, pruritus	Fever, fatigue, acute gastroenteritis, anorexia, 3 days before rash	Axial tomography of thorax compatible with Covid-19. Parents with Covid-19, 40 and 50 days before.
Johansen 259	39	F	T, without pruritus	Asymptomatic	PCR (+) COVID-19
	23	F	T, pruritus	Asymptomatic	PCR (+) COVID-19
Khalili 260	7	F	T, pruritus	Cough, odynophagia, rhinorrhea, diarrhea, weeks before rash	PCR (+). Family same symptoms and PCR (+)
Mehry 261	26	F	T, without pruritus	Fever, cough, myalgia, 48 hours before rash	PCR (+) COVID-19
Mohammad 262	13	F	T, second case severe pruritus	NR	Second case Biopsy: PR
	58	F			
Ng 263	12	M	T, without pruritus	Fever, odinophagia, abdominal pain, diarrhea	PCR (+) nasopharynx
Öncü 264	10	M	T, without pruritus	Covid-19 one week before. Symptoms not reported	COVID-19 confirmed, no method mentioned
Veraldi 265	26	M	T, pruritus	Cephalea, weakness, arthralgia.	PCR (+) nose
	21	M	T, pruritus	Anorexia, abdominal pain, diarrhea and weakness	PCR (+) nose
Welsh 266	49	M	T, pruritus	Cough, general discomfort, dysgeusia, myalgias, arthralgias and cephalaea, 2 weeks before rash	Immunohistochemistry (+) for SARS-CoV-2 for spike protein in endothelial cells and lymphocytes.

NR=not reported. F=female. M=male.

Since SARS-CoV-2 can play a role as an activating agent, triggering the reactivation of HHV-6/7 and thus causing PR, some authors recommend, as far as possible, order tests for HHV-6/7 in patients with PR in the context of the COVID-19 pandemic [272,273]. Reactivation of latent HHV-6 and Epstein-Barr virus (EBV) infections has been demonstrated in a 16-year-old patient with PR and COVID-19 infection. The authors suggested that SARS-CoV-2 may play a role in the reactivation of HHV-6/7 and EBV and thus cause the manifestations of PR [257]. Other authors, in response to the previous case and their own experience in two patients, proposed that lymphopenia (which was seen in all of these patients) may play a role in viral reactivation [274]. It is interesting to note that in a study from 1962, in an analysis of 826 cases of PR seen over a period of 10 years in Sweden, no lymphopenia was detected in patients with classic PR [81].

PR and PR-like eruptions after COVID-19 vaccination

PR cases with typical or atypical clinical manifestations have been also reported after COVID-19 vaccination, including all vaccine types. Most authors did not differentiate between PR and PR-like rashes, and no specific investigations -such as detection of HHV-6/7 DNA in plasma or IgM antibodies in serum against HHV-6/7- were ever done in those reports [275]. A PR-like eruption is not related to HHV-6/7 reactivation, but rather a rash that resembles a true PR [276]. PR-like eruptions presented with more itchy and diffuse lesions, with a lack of herald patch and showing a prolonged course. The reported cases are summarized in Table 3, being noted that not all of them were verified with biopsy.

The COVID-19 vaccines may have produced an immune dysregulation which could have reactivated HHV-6/7, causing PR. An alternative option is that the vaccines may produce a delayed hypersensitivity reaction, similar to hypersensitivity reactions, such as rashes induced by medications; that fact can cause a PR type rash [271]. In a study of skin reactions following mRNA vaccination, PR-type rash was seen in 1-2% of cases [277], while in other it was 3.7% after Covaxin and Covishield vaccines [278]. A systematic review done in 2021 gave a frequency of 3% for PR after vaccinations [279].

Regarding the Oxford-AstraZeneca vaccine, a case of a typical PR was described one month after receiving

the first dose of the vaccine. It is striking in this case that the patient did not present recurrence of skin manifestations after the second dose of the vaccine [280].

Two other PR cases were reported after injection of the inactivated vaccine from the Beijing Institute of Biological Products Company; the first case was a 19-year-old young man presenting a classic PR two days after receiving the first dose of the vaccine; the second case was a 51-year-old man with a classic PR after the second dose of the vaccine; however the patient mentioned having similar lesions after the first dose [281]. In two cases from another publication, one of them presented with PR outbreaks after the first and second doses, the first with a heraldic plaque and the second with a more intense rash [282].

During the COVID-19 pandemic, a patient was described with erythema pernio and PR lesions at the same time [283]. In another study carried out in Iran in patients with skin manifestations within a month after vaccination for COVID-19, of 25 patients, only one (4%) presented a rash compatible with PR, two weeks after vaccination with Synopharm [284].

In a study of 414 cases of skin reactions attributed to Moderna and Pfizer vaccines, the presence of PR was seen in 1/267 patients after the first dose of Moderna and in 2/34 patients after the first dose of Pfizer and in 1/40 patients after the second dose of Pfizer [285]. More recently, a case review post COVID-19 vaccination grouped 29 publications with 113 reports, in which the most frequent involved vaccine was Pfizer BNT162b2 with 52 cases (46.9%); in most of them the average time for the eruption was 9 +/- 6.3 days after vaccination [286].

Table 3. Characteristics of PR rashes after diverse COVID-19 vaccinations.

1 st Author Ref n°	Age	Sex M/F	Clinic T/A	Vaccine N° of days before the rash=d 1 st or 2 nd dose	Studies Bp: PR= biopsy compatible with PR ND=not done. NR=not reported
Abdullah 287	40	M	T	7 d, 2 nd mRNA Covid-19	ND
Adya 288	21	M	A	4 d, Covishield ChAdOx1 nCov-19	Bp: PR
Akdas 289	45	F	T	4 d, 1 st and 2 nd Coronovac	PCR (-) for SARS-CoV-2 in nasopharynx and skin biopsy
Al Hatmi 290	19 30 70	M F M	T T T	7d, 1 st Pfizer 14d, 1 st Pfizer 21d, 2 nd AstraZeneca	Bp: PR ND Bp: PR
Arora 291	42	F	A	6d, 1 st , 4d 2 nd Covishield	BP: PR
Bin Rubaian 292	15	F	T	2 d, 2 nd Pfizer	Clinical diagnosis
Bostan 293	34	F	A	15 d, 2 nd mRNA for COVID-19	No evidence for COVID-19
Buckley 294	23	F	T	7d, 1 st Pfizer	ND
Burlando 295	31	M	T	30 d, 2 nd Pfizer	ND
Busto-Leis 256	26 29	M M	T T	7 d, 2 nd Pfizer 1 d, 2 nd Pfizer	Bp: PR, IgG(+) SARS-Cov-2. Bp: ND, IgG(+) SARS-Cov-2
Cafrune 280	44	M	T	30 d, 1 st AstraZeneca	Bp: PR
Carballido 296	35	M	T	NR, 1 st Pfizer	ND
Catalá 297	20 cases m:15.3	15 F 5 M	All T	11 cases Pfizer 5 cases Moderna 4 cases AstraZeneca	NR
Cohen 298	66	M	T	7 d, 1 st Pfizer	Bp: PR
Cyrenne 299	20 40	F M	T T	2 d, 1 st Pfizer 2 d, 1 st Pfizer	Bp: PR ND
Das 300	3 cases Age NR	NR	NR	Covishield	NR
Diab 301	7 cases m=39 (r 26-61)	6 F 1 M	NR	7,20,21 d, 1 st Sinopharm 7,10 d, 2 nd Sinopharm 21 d, 1 st and 2 nd AstraZeneca	ND
Dormann 302	19	NR	T	4 d, 1 st AstraZeneca	ND

Farinazzo 303	42 64	F M	T T	4 d, 2 nd Pfizer 5 d, 1 st Pfizer	ND ND
Fenner 304	56	F	A	7 d, Johnson & Johnson	Bp: PR
Freeman 305	31 cases Age NR	NR	NR	10 cases 1 st Moderna 6 cases 2 nd Moderna 3 cases 1 st Pfizer 5 cases 2 nd Pfizer 2 cases 1 st Aztraseneca 1 case Johnson & Johnson 1 case 1 st Coronavac 1 case 2 nd Coronavac 2 cases 1 st Unknown vacc	NR
Gökçek 306	68	M	T	1 st Coronavac	ND
Huang 281	19 51	M M	T T	2 d 1 st Covid-19 vaccine Beijing Institute of Biological Products C ^o . 7 d, 2 nd same C ^o .	Clinical diagnosis. 3 PCR (-) for COVID-19 Without studies but with systemic symptoms of COVID-19
Khattab 307	49 53	F M	T T	8 d, 1 st BNT162b2 7 d, 2 nd BNT162b2	Clinical diagnosis
Larson 308	29	F	T	7 d, 1 st Moderna	Bp: PR
Leerunyakul 277	52	F	A	14 d, ChAdOx1 nCov-19 Oxford/AstraZeneca	PR without herald patch and no desquamation. Bp: PR
McMahon 309	8 cases Age NR	NR	T	3 cases Moderna 4 cases Pfizer 1 case AstraZeneca	Bp: PR
Marcantonio-Santa Cruz 282	22 54	F F	A T	7 d, 2 nd Pfizer. 7 d, 1 st Pfizer	Bp: PR ND
Marghalani 310	37	F	T	2d, 1 st AstraZeneca	BP: PR
Martora 311	46 49 24	F M F	All T	6 d, 1 st Moderna mRNA-1273 7 d, Moderna 11 d, Moderna	Clinical diagnosis. All of them received the 2 nd dose because the rash did not contraindicate it
Mehta 312	24	M	T	1 d, 1 st Covishield	ND
Mohammad 262	46	F	T	30 d, Razi-COV PARS	Bp:PR
Niebel 313	40 63	F M	T T	8 d, 2 nd Pfizer 22 d, 1 st AstraZeneca	ND BP: PR
Pedrazini 314	53	F	T	15 d, 2 nd Oxford-Astrazeneca	Clinical diagnosis
Ramot 315	6 cases m=34.8 (r 23-66)	4 M 2 F	All T	3 d, 1 st Pfizer and 2 nd Pfizer 2 d, 1 st Pfizer and 2 nd Pfizer 10 d, 1 st Pfizer and 5 d, 2 nd Pfizer	Clinical diagnosis
Saraswat 278	11 cases NR	NR	NR	5 cases 1 st Covishield 3 cases 2 nd Covishield 3 cases 2 nd Covaxin	NR
Shakoei 284	56	M	T	14 d, 1st Sinopharm	ND
Shin 316	29	M	T	2 hours 2 nd mRNA-1273 for Covid-19	Bp: PR
Singh 317	24	M	T	5 d, 1 st Covid-19 Covaxin (BBV152)	Bp: PR
Temiz 318	31 cases m=44.9 (r 26-61)	18 F 13M	26 T 5 A	17 cases Coronavac 9,10,12,14,14,16,17,18,23 d, 1 st 3,8,8,9,9,10,16,21 d 2 nd Coronavac 14 cases Pfizer 5,7,9,11,12,16,18,19,21,21 d, 1 st 4,5,13,15 d, 2 nd Pfizer	5 cases Bp: PR 26 ND
Tihy 319	36	F	A	15 d, 2 nd Pfizer	Bp: drug reaction-like
Valk 320	30	F	T	3 d, 2 nd Pfizer	ND

Veraldi 321	5 cases m=41.8 (r 22-56)	3 M 2 F	All T	7,14,21 d, 1 st BNT162b2 14 d, 1 st mRNA-1273 21 d, 2 nd mRNS-1273	Bp: PR in 3 cases, not specified
Wang 322	40	M	T	7 d, 1 st mRNA-1273	Bp: PR
Yu 323	24	F	A	3 d, AstraZeneca	ND
Total 45 publications	169 cases	66 F 49 M NR 54	T 104 A 13 NR 52		ND 42, NR 65 Bp: PR in 27

Sex: M=male, F=female. Clinic: T=typical, A=atypical. m=median age. r= age range.

Summarizing the data included in the Table 3, forty-five publications were collected by us making a total of 169 cases. Of these, 66 were female and 49 male, with sex not being reported in 54 cases. Most of the eruptions were typical (104 cases) while 13 were not, and in 52 cases the features of the eruption were not described. The diagnosis of PR was done mainly on clinical grounds, and in only 27 cases a biopsy was done. Of all the vaccines mentioned, the majority of PR rashes occurred after administration of the Pfizer vaccine, followed by Moderna, Coronavac and AstraZeneca vaccines; there are very few publications about other vaccines. The highest number of PR cases occurred after the first vaccination (77 cases) and somewhat less after the second (53 cases), and in 36 cases this fact was not mentioned. There were only three cases in which PR occurred with both the first and second vaccination. This low figure is striking, perhaps due to the fact that the patients developed sufficient immunity to block a new reactivation of HHV-6/7 for a new PR or they just didn't report it. Having had a PR after the first vaccination was not a contraindication to receiving a second dose. Regarding the time elapsed from vaccination to the appearance of the rash, it showed very variable periods, from just 2 hours after the vaccine to 30 days after receiving it. The most frequent interval was 7 days, followed by 14 and 21 days.

In a systematic review of PR and PR-like eruptions after COVID-19 vaccinations done in 2023 [\[324\]](#), 111 cases were compiled from 31 publications: 36 cases (55.38%) were women and 29 were men (44.62%), but the gender of 46 of the 111 patients was not specified. The average age was 44.92 years, and as in the case of gender, the age of 32 patients was not recorded. In the 101 cases in which the vaccination number was specified before PR, 63 (62.37%) were after the first dose and 38 (37.62%) after the second dose. In most cases it was after mRNA vaccines such as Pfizer 38 cases (35.51%), or Moderna in 27 patients (25.23%). Other types of vaccine manufacturing were also implicated, such as Sinovac in 23 patients (21.49%), Astrazeneca in 11 patients (10.28%) and other vaccines in lower percentages. PR and PR-like rashes in 92 described cases appeared in an average of 8.58 days and recovery in 42 patients was 6.44 weeks. Clinical characteristics were not reported in 39 patients. Six patients (8.33%) of the remaining 72 patients presented an atypical PR, with vesicular lesions in 5 cases. In 34 (37.22%) of 72 patients there was a typical herald patch, in 36 cases (50%) they presented the typical appearance like a 'Christmas tree' and in 8 (10.53%) there was collarette-type peeling. The rash was on the trunk in 28 (87.5%) of the 32 cases in which this information was recorded and progressed to the lower extremities in 13 (40.62%), back in 5 (31.25%) and 7 to the abdomen (21.87%). Regarding symptoms, there was pruritus in 5 cases (31.25%), fever, myalgia, asthenia and headache, in one case (6.25%), and in 12 of 16 patients (75%) there were no symptoms. In addition to the cases of atypical PR (vesicular and purpuric), some patients also had fewer and larger lesions located in atypical areas such as the axillae, groins, and extremities [\[324\]](#).

In another study done in South Korea, 11 patients with PR before the COVID-19 pandemic versus 11 patients during the COVID-19 pandemic were compared. In the former there was a male predominance of 63.64% versus a 54.55% female predominance in the PR group during the pandemic. Another difference was pruritus: in the first group it was mild to moderate in 36.36% and absent in 63.64% of cases, while in the second group during the pandemic, pruritus was present in 81.82% of cases and in 72.73% it was mild to moderate. The classic PR pattern was seen in 81.8% of cases in patients with PR before the pandemic and in 63.6% of those with PR during the pandemic, giving a percentage of 18.2 % of atypical PR in the first group and 36.4% in the second; atypical PR consisted of erythema multiforme type eruption, Darier's giant PR and atypical distribution of lesions, which varied from 18.2% to 45.5% in the second group, affecting the submammary regions and intertriginous areas such as the groins and axillae, also called 'pityriasis *marginata* et *circinata* of Vidal' [\[325\]](#).

The histopathological pattern of PR consists in mild to moderate acanthosis, with focal and occasionally confluent parakeratosis and a perivascular lymphocytic dermal infiltrate with few eosinophils. The infiltrate may be dense, with serum crusts, spongiosis, Langerhans cell abscesses, papillary edema, and numerous

eosinophils. There is a second pattern with scarce dermal lymphocytic infiltration and finally a third psoriasiform pattern with irregular acanthosis and mounds of parakeratosis. The proportion of different histopathological patterns was different in PR cases before and during the COVID-19 pandemic. The percentages were as follows: dense pattern (63.6%), mild pattern (27.3%) and psoriasiform pattern (9.1%) in PR cases before the pandemic. During the pandemic their distribution was: dense pattern (9.1%), mild (36.4%) and psoriasiform (54.6%). In summary, in PR during the pandemic there was a higher prevalence of pruritus, a greater proportion of atypical PR and a predominance of a psoriasiform or mild histopathological pattern [325].

3. ETIOPATHOGENESIS

PR is a self-limited, acute inflammatory dermatosis, which occasionally could be persistent or recurrent. There are indications of its existence since 1798, when Wilan named it *roseola annulata*, or also Rayer (1828) as *erythema annulatum* and Wilson (1857) as lichen *annulatus serpiginosus* [326], but it was not until 1860 when Gibert described it in detail, calling it pityriasis rosea (PR), by which we know it to this day [327].

Concerning its etiology, a viral origin has been suspected for many decades, mainly based in prodromal symptoms in some cases, an apparent higher incidence during cold months, its appearance in clusters [328-330], or in members of the same family, simultaneously in couples, in a mother and daughter, or in sisters, although very rarely [331-334]. According to this, four decades ago, virus-like spherical particles were detected in herald patches of PR affecting epidermal intercellular spaces and cytoplasm of Langerhans cells, with cytolytic degeneration of adjacent keratinocytes [335]. Later, in another study also carried out using electron microscopy, mature enveloped virions were detected as typical HHV in 71% of skin samples from lesions of PR [336]. In addition, diminished levels of natural killer cells and B-cell activity in the lesions of PR have been observed, thus suggesting the role of a T-cell mediated immunity [337]. Besides, increased amounts of helper-inducer T cells and Langerhans cells have been found in the dermis [338], which possibly points towards viral antigen processing and presentation. Other inflammatory mediators are increased in PR, including interleukine-17, interferon gamma, vascular endothelial growth factor and chemokine CXCL10 [339]; however, in other study, interferon gamma was found to be decreased [340]. Serum interleukine-36 has been recently proposed as a biomarker for PR severity [341], so as interleukine-22, which showed increasing values according to disease severity, extent and duration [342]. An elevated expression of Toll-like receptors 3,7,8, and 9 was demonstrated by real-time PCR in skin biopsies of patients with active lesions of PR [343].

The increasing findings suggest a role of human herpesvirus (HHV) in the etiopathogenesis of PR. Additional evidences indicate that PR is associated with a reactivation of HHV-6/7 [344]. Their seroprevalence in adult people is very high (80-90%), coming from an infection acquired in childhood that presented at that time as exanthema *subitum*; both virus persist latent in salivary glands and other cells or tissues throughout life, and can reactivate under circumstances of immunosuppression, pregnancy, viral disease, or other undetermined causes. The lesions of PR then, would not be originated by direct viral infection of the skin, but rather as an exanthem produced by viral reactivation alone or through interaction with other viruses; HHV-7 may trigger HHV-6 reactivation, but the reverse has not been reported [345]. HHV-7 may help HHV-6 activation in latently infected cells, replicate its genome due to their similarity, or cause induction of cytokines that stimulate HHV-6 replication [346].

By means of immunohistochemical assays, moderate and intense staining for HHV-6 was significantly higher in PR patients than in the control group [347]. In another study, IgM antibodies against HHV-7 were negative in all 36 patients with PR, investigated by indirect immunofluorescent assay [348]. Similarly, IgG antibodies against HHV-6/7 in 35 patients with PR were not higher than those of 30 healthy controls [349], so as in another study with 14 PR cases and 15 controls [350].

By means of nested PCR, HHV-6/7 DNA has been detected in skin and other tissues in patients with PR [345]; similarly, a significant presence for HHV-6 was detected in lesional skin of PR in comparison to controls, but not for HHV-7 [351], which was also not detected in peripheral blood in 4 patients with PR and in 3 healthy controls [352]; a low detection of HHV-7 argues against its role in PR [353-355]. On the contrary, in another study by means of PCR, HHV-7 DNA was detected in cocultured peripheral blood mononuclear cells, lesional skin and plasma in all studied patients with acute PR, being the last finding indicative of active viral replication and a causal relationship [356,357]. Regrettably, there has been no concordance in diverse studies performed with PCR for HHV-6/7 in lesional skin or peripheral mononuclear

blood cells in PR patients. Significant differences were found by nested PCR detection of HHV-7 in lesional skin and serum of 22 PR cases with respect to controls, but not of HHV-6 [358], while no significant differences were found in lesional skin PCR for HHV-7 in 21 PR cases [359], in skin and serum PCR for HHV-6/7 [360], in peripheral blood mononuclear cells and plasma for HHV-6/7 DNA [361,362], so as no definite increase in antibody titres against HHV-6/7 [363], as well as negative IgM titres and no significant increase or decrease in IgG antibody titres against HHV-7 [348]. In another study of 25 PR cases, different determinations were analysed: HHV-6 IgM was negative in all patients and HHV-7 IgM was positive in only two cases [364]; in tissue samples HHV-6 DNA was detected in 7 cases and HHV-7 DNA in 12 cases in a first evaluation, with negative results in the control group; in blood, HHV-7 DNA was positive in 11 cases in a second evaluation, statistically significant with respect to controls; of 12 cases with positive HHV-7 DNA in tissue samples, only 4 were positive for blood DNA samples, and only one was positive for HHV-7 IgM as well as for both previous parameters [364]; the authors conclude that HHV-6/7 may act as triggers in some PR cases, but that other factors could participate. Viral culture for HHV from skin biopsies of 24 PR patients was negative in other study, as well as PCR DNA detection for HHV-6/7 [365].

The finding of viral HHV-7 DNA in blood cells or tissues does not implicate a causative role, but rather a latent infection since it may be detectable in most healthy people; its simultaneous detection both in plasma and skin would aim better in that sense [360]. The transitory nature of viremia for antibody measurement and the variable timing of skin biopsies for viral PCR study may have influenced the disparity detected in the different studies [363]. The rise/decrease of antibody titres for HHV-6/7 that would confirm a recent active infection has shown inconstant findings [363], which in part may depend on the natural variable timing from onset and duration of PR rash, widely variable from case to case. The high seroprevalence of HHV-6/7 in the general population and the antigenic cross-reactivity between both virus complicate the matter even more [349]. In order to avoid discrepancies in further studies about the role of HHV-6/7 in PR, it has been suggested that both plasma and tissue samples should be tested for detecting IgG and IgM antibody responses and viral load respectively, the latter preferably using calibrated quantitative real-time polymerase chain reaction (CQ RT-PCR) [366].

Viral reactivations in PR have been demonstrated for HHV-6/7 and Epstein-Barr virus during COVID-19 infection in one patient [257]. On the other hand, worsening of hepatitis C disease was observed during development of PR [367], being noted that HHV-6 may increase the severity of hepatitis-C infection [368]. In another case, persistence of pruritus -despite treatment- in a patient with PR, revealed a hepatitis B infection [369]. Similarly, in a pilot study, occult hepatitis-B virus infection -sometimes associated with HHV-7 co-infection- has been detected in a series of PR patients from India [370]. HHV-6/7 reactivation also seemed to be the etiologic factor for the consecutive development of PR and Bell's palsy in a girl, with complete improvement of both conditions after treatment with oral prednisone and acyclovir [371].

4. DIAGNOSIS

The diagnosis of PR is essentially clinical as summarized in Table 4 [372], and in rare circumstances a biopsy may be required. Histological features are not specific, mainly showing an eczematous pattern [373,374]. Its most common features include spongiosis, papillomatosis with papillary dermal edema, mild perivascular lymphohistiocytic infiltrate, exocytosis and extravasated erythrocytes in the papillary dermis and partly in the epidermis. Other findings include dermal melanophages, absence or decrease of the granular cell layer, homogenization of papillary collagen, and less constantly focal parakeratosis. The finding of dyskeratotic cells was initially reported as an incidental feature in one case [375], but later confirmed in three series of 29, 52 and 34 cases, appearing in 55% and 57.3% and 70.58% respectively [37,376,377]. No histopathological or immunohistochemical differences have been detected between the heraldic plaque and the lesions of the secondary eruption [378]. A valuable histopathological sign is the 'salute sign' or 'take-off sign', in which there is a detachment and elevation of the parakeratotic stratum corneum above the spongiotic epidermal focus, corresponding to the scales at the edges of PR patches [379,380]. The main difference among new and old lesions is the finding of eosinophils in the inflammatory infiltrate in the later [374], which can also be seen in PR-like drug eruptions [381]. On the other side, early and guttate psoriasis can overlap significantly with PR, both on clinical and histopathological grounds. Recently, interleukin-36 immunostaining has proved to be useful in differentiating both conditions: all psoriasis variants strongly express IL-36 while PR do not, as so pityriasis lichenoides [381].

Table 4. Diagnostic criteria of pityriasis rosea [372,382].

Mandatory clinical features

- Discrete circular or oval lesions
- Scaling within most lesions
- Peripheral collarette scaling and central clearance on at least two lesions

Optional clinical features

- Trunk and proximal limb distribution (less than 10% acral lesions)
 - Distribution mostly along cutaneous cleavage lines
 - Previous herald patch (from history or clinical observation)
-

Dermoscopy is another useful tool for diagnosis, being more useful in plaque lesions than in papules, where scaling is minimal or absent [383]. The collarette of the edge of the lesions appears as fine peripheral peeling, like hanging curtains [384]. A yellowish background color is also characteristic [385]. In one study, a yellowish-orange color in the background, irregular dotted vessels, and a yellowish-white color of the scales along with their irregular peripheral distribution were detected; this work included 8 patients with phototype III, 9 with phototype IV and 3 with phototype V [386]. Thus, there could be differences depending on the tone of the skin: in dark races the background color is opaque red and blood vessels are not observed, while in light skin the background color is yellowish and the vessels can be observed up to 100% of cases [387]. In a study of 20 Mediterranean light-skinned patients with PR, punctate vessels were detected in 100% of cases, a yellowish background color in 65%, and peripheral peeling in 70% [388]. In a recent report of 162 lesions of 54 patients from Uganda, the authors describe a violaceous background in 89.51%, white scales in 99.38%, diffuse scaling in 35.19%, perifollicular scaling in 37.65% and pigmentary changes as brown dots in 40.74% [389]. Dermoscopic findings of the most comprehensive dermoscopic study of 100 lesions from 64 patients with PR are summarized in [Table 5](#) [390].

Table 5. Dermoscopic features of 100 PR lesions [modified from Elmas et al, 390].

	Dermoscopic features	Frequency %
Scale	Peripheral collarette	84
	Irregular scales	23
Background	Central yellow, peripheral reddish	40
	Central reddish, peripheral yellow	11
	Diffuse yellow	14
	Diffuse reddish	31
	Central skin-colored, peripheral reddish	4
Vascular features	Peripheral dotted vessels with patchy distribution	35
	Scattered dotted vessels	30
	Scattered irregular lineal vessels	13
	Irregular lineal vessels with patchy distribution	7
Other	Red globules	20
	Brown globules	7
	Brown structureless	5
	Blood spots	10

Dermoscopic features of PR strongly correlate with histopathologic findings of the disease [391], both summarized in [Table 6](#). An early lesion shows a diffuse red background with a central collarette and peripheral dotted vessels; as it evolves, the collarette moves to the periphery and the reddish background decreases, leading successively to central yellow and peripheral red, diffuse yellow, scale decreasing, and finally brown structureless areas and globules [391].

Table 6. Correlation of histopathologic and dermoscopic findings in PR [391].

Histopathology	Dermoscopy
Vascular dilatation	Diffuse red background
Salute sign	Collarette scaling
Focal parakeratosis	Patchy scaling
Capillary dilatation in dermal papillae	Peripheral dotted vessels
Basal layer melanization and dermal melanophages	Brown structureless areas
Erythrocyte extravasation	Red globules
Hemosiderin deposits	Brown spots

The use of a dermatoscope with a triple light source with non-polarized light (NPL), polarized light (PL) and ultraviolet light (UVL) has the advantage of demonstrating the classic hanging curtain sign, that represents the collarette peeling. With the isolated use of NPL the sign is seen only in 60% of cases. This could be especially useful in atypical PR cases [392].

The main differential diagnoses that dermoscopy can arise are psoriasis and nummular dermatitis, in which the peeling occurs throughout the lesions. The other differential diagnosis is tinea corporis, but in this case the scaling is thicker, and towards the center of the lesion the skin is less inflamed compared to PR lesions [384]. Dermoscopy has also been used to help differentiate PR from guttate psoriasis, which can occasionally be really difficult. In PR there is a nonspecific distribution of red dots and the peeling is irregular, while in guttate psoriasis the red dots have a uniform distribution and the peeling is whitish and diffuse. In both conditions there is a red background. In PR, in addition to the white scales, brown scales can be observed with a central or peripheral distribution depending on the state of the disease; in early lesions the peeling is central, and in the later stages the peeling becomes peripheral [393].

Mainly for research reasons than for practical use, biophysical and ultrasonographic studies have been recently used to evaluate the skin in PR: stratum corneum hydration and dermal echodensity in PR were significantly lower than in normal skin, whereas erythema, pH and transepidermal water loss were higher in PR lesions, correlating with histopathological findings [394]. Similarly, line-field confocal optical coherence tomography has proved to be effective as a helpful aid in the diagnosis of PR [395].

5. DIFFERENTIAL DIAGNOSIS [396]

Classical PR should not lead to doubts in its diagnosis. However, in some situations, the symptoms or rather the clinical presentation may be troublesome. PR-like eruptions secondary to drugs should be discarded from the beginning with a directed and exhaustive anamnesis, as well as the following conditions:

Secondary syphilis: Meticulous history taking, previous history of chancre, lymphadenopathy, positive VDRL test, and histology showing plasma cells are suggestive. Lesions of secondary syphilis are monomorphous and always asymptomatic; they almost always affect palms and soles. Patchy alopecia with 'moth eaten' lesions on the scalp or beard may be found [397]. In a 16-year retrospective study, only 2 cases of syphilis were detected out of a total of 142 patients with a PR-type rash, via rapid plasma reagin test (RPR). In a proposed algorithm for syphilis screening in PR, the authors suggested that in the event of a suspected rash with the characteristics of PR but in the absence of a heraldic plaque, involvement of the oral mucosa, and finding of palmo-plantar lesions or lymphadenopathy, then a social and sexual history should be performed considering various parameters: male sex 20-29 years old, men who have sex with men, HIV(+), history of incarceration, sex work, multiple sexual partners or unsafe sexual practices, among others. If one or more risk factors are detected, a VDRL or RPR test should be requested [398]. Likewise, recurrent PR should always be tested for syphilis due to its similarity to the rash of secondary syphilis [175].

Dermatophytosis: It may be troublesome to differentiate when the only lesion of PR is the herald patch. However, a mycotic lesion expands progressively and very slowly, showing a clear center, whereas herald patch grows rapidly in a few days and then remains inalterable. Positive KOH mount is the pointer.

Guttate psoriasis: History of sore throat, presence of rain-drop pattern and histology are important clues. Scales are thicker and silvery-white, without 'Christmas tree' appearance and absence of herald patch. The Auspitz sign (superficial bleeding points after scraping of the lesions) is absent in PR. Changes of the lesions during the course of PR can make reaching a diagnosis truly difficult [166].

Erythema annulare centrifugum: One or more erythematous, annular or polycyclic lesions that enlarge centrifugally and clear towards the center, showing a fine scale a few millimeters behind the advancing elevated edge. It commonly appears on the trunk, buttocks or thighs, it is usually asymptomatic and fades in weeks to months, although it may show recurrences.

Subacute cutaneous lupus erythematosus: Photo-sensitivity is the rule, with photo-distributed lesions. Besides, histopathology shows epidermal atrophy and basal layer degeneration.

Rarely, primary HIV infection, seborrheic dermatitis, drug rash, erythema multiforme and cutaneous T cell lymphoma may also be confused with PR. Hypopigmented variant of PR may be confused with pityriasis alba (lesions are mainly located on the face or arms and it is usually associated with atopic dermatitis), hypopigmented mycosis fungoides (lesions are large, persistent, and mainly distributed on buttocks and lower trunk), and progressive macular hypomelanosis of the trunk (lesions are slowly progressive, tend to coalesce, and do not show desquamation). Very infrequently, PR can mimic cutaneous mastocytosis [399].

In pregnant women, differential diagnosis can be extended to 'pruritic urticarial papules and plaques of pregnancy' (PUPPP), also known as polymorphic eruption of pregnancy. The eruption arises symmetrically on the abdomen -in and around striae- and later spreads to upper arms, back, breasts and thighs. It generally appears in the first pregnancy, usually during the third trimester.

6. THERAPEUTIC OPTIONS

Many cases require no treatment at all, only reassurance directed to the patients and their parents, underlying the benign nature and self-limited duration of the disease, which do not leave sequelae and that other members of their family or friends almost always will be not affected. As stated, just reassurance and little else [400]. Nevertheless, some patients may become anxious or concern because of their physical aspect and uncertainties about the disease, with risk of depression [401]. At this respect, a study of quality of life in children with PR showed that major concerns came from their parents more than themselves, specially about its unknown etiology, infectivity or routes of transmission, and possible complications or relapses of the disease [402]; it was concluded that spending more time in initial counseling of children and parents is preferable than repeated follow-up, or patients asking of a second or even third opinion from other clinicians: 'it is likely that you are going to get worse rather than better, but the rash will then slowly begin to resolve' [402].

Therapeutic options when needed (in the case of many or symptomatic lesions) include the use of emollients or low potency topical corticosteroids, and antihistamines when itching. The use of oral macrolides (erythromycin, clarithromycin and azithromycin) has shown controversial results [403-407], or proved not to be effective [408]. Initially, these were found to be beneficial, but recent studies show that macrolides are ineffective in the management of PR, or at least more studies are needed [409].

Since the current concepts of etiopathogenesis imply the role of HHV-6/7 in the causation of PR, antivirals like acyclovir [410-413] and valacyclovir have been found to be useful [414]. They may improve PR eruption by reducing erythema and formation of new lesions. Their doses are still to be determined: acyclovir 400 mg 3 times daily is as effective as 800 mg 3 times daily for a week [411]; valacyclovir was effective in a dosis of 1 gr 3 times daily for a week in two series of 3 [414] and 9 cases [415]; however, many of them were also treated in conjunction with a topical triamcinolone 0.1% cream, and the time elapsed until complete clearance of lesions was almost similar to that of usual resolution of the disease in many of the patients. Similarly, in another study comparing high doses of acyclovir (4 gr/day for 10 days) with erythromycin (400 mg QID for 10 days), the acyclovir group showed better results, with complete response in most of them, but 8 weeks after treatment [416]. In other comparative study between acyclovir and erythromycin, both were effective but acyclovir showed better results in the first weeks [417]. On the contrary, in other study, acyclovir in dosis of 800 mg five times daily for a week was not superior to placebo [418]. An early prescription could be important, and eligible patients seem to be those with large eruptions or with worsening symptoms. In a meta-analysis, it was concluded that acyclovir was superior to placebo when used during the first week, but not superior to symptomatic treatment when used at week four [419]. On the other hand, other studies have concluded that the response to acyclovir was irrespective of the duration of PR, without significant differences if prescribed within the first week or later [412]; acyclovir 800 mg 5 times/day was prescribed, with complete response at 7 days in 53.3% of cases, and 86.6% at 14 days (compared with 10% and 33.3%

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in placebo group) [412]. More or less similar findings were noted in a previous study, with 46.4% and 78.5% of erythema reduction at 7 and 14 days respectively [411]. In other series acyclovir (400 mg five times a day) was given within 7 days or less after the onset of disease in all cases, of which 30% showed a complete response by the end of the second week of therapy and 65% by the end of fourth week [351]. In other meta-analysis it was concluded that high doses of oral acyclovir was effective for regression of PR on the 14th day [420]. It should be kept in mind that PR is not a viral infection *per se*, but rather an inflammatory response which possibly follows a viral reactivation [421], and also that acyclovir lacks significant antiviral effect against HHV-6/7 due to the lack of the enzyme thymidine kinase in them, necessary for the drug anti-viral action [421]. One publication even mentions a patient who presented a classic PR while receiving acyclovir at a dose of 400 mg twice a day for the past 5 months as suppressive therapy for genital herpes [422].

A statement about the management of PR has been raised [423]. Main conclusions include an adequate diagnosis, impact of the eruption in the quality of life since many patients do not necessitate any treatment, and use of oral acyclovir 400 mg three times daily for seven days, when not contraindicated or possible adverse effects are suspected. An update of a Cochrane review from 2007 was done in 2019 evaluating interventions for PR: the main conclusions were that acyclovir probably improves the eruption of PR better than placebo but its optimal dose remains unknown; none macrolides antibiotics (azithromycin, clarithromycin or erythromycin) have proved to be effective on the rash; new trials are necessary evaluating other antivirals and their doses, as well as ultraviolet B phototherapy and common dermatologic symptomatic treatments [424]. A similar analysis was done later in 2023, concluding again that macrolides are not recommended and that there is moderate quality evidence to support acyclovir monotherapy -but with not clear dosages- which may be indicated in recalcitrant or severe cases [425].

Today there is no standardized therapy for PR. The evaluation of the effectiveness of the different alternatives can lead to erroneous or dubious conclusions due to the moment when consulting and the highly variable duration and symptomatology -case by case- of a self-limiting disease [426]. Routinary use of systemic corticosteroids is not recommended and their use should be restricted to serious cases with extensive or hard to manage eruptions [409]. In a double-blind randomized placebo-controlled trial to evaluate the efficacy of oral prednisolone in PR, improvement of the rash and pruritus was better in the prednisolone-treated group, but relapses were higher after complete clearance [421]. In another study, a series of patients showed exacerbation of the disease when treated with oral corticosteroids (triamcinolone acetonide or dexamethasone), with increase of itching, in the number of lesions, greater involvement of acral areas and longer duration of the eruption, which improved after discontinuing therapy [427].

In one case of persistent PR unresponsive to conventional therapies, off-label Abrocitinib was prescribed in an oral dosage of 100 mg/day, showing complete regression of lesions in a pair of weeks [428]; however, this therapy raised concern in other authors about using an immunosuppressive drug in a viral reactivation such as PR, suggesting caution on its prescription [429].

Phototherapy has shown conflicting results, with improvement or worsening of clinical parameters, reducing pruritus or not, and not even changing the course of the disease. Thus, its effectiveness is debated and further studies need to be conducted [430-433]. However, ultraviolet B (UVB) decreased pruritus and extent of disease in a half of one series of 20 cases [434] and narrow band UVB proved to be effective in reducing pruritus, erythema and scaling in another study [435]. Its association with an oral compound of indigo naturalis showed better results than using it alone in a Chinese meta-analysis [436].

A recent and innovative proposal has been formulated regarding the use of oral L-lysine in the treatment of PR. L-lysine is an essential amino acid that competes with L-arginine, another amino acid that is necessary for herpesvirus replication: lack of L-arginine prevents viral replication. L-lysine and L-arginine are antagonistic by using the same cellular transporters, and L-lysine also promotes renal and intestinal L-arginine catabolism [437]. Variations in the intake of both amino acids have been used successfully in the treatment of Herpes simplex infections, in which the administration of L-lysine would have a similar effect to that of acyclovir [438]. L-lysine is commercially available in the form of a dietary supplement in capsules, and its intake must be associated with a decrease in the concomitant consumption of L-arginine. Given the relationship of HHV-6/7 with PR, Roxo et al from Brazil in 2018 [439] were the first to test L-lysine orally in two patients with PR, with significant reduction in lesions after administration of 500 mg of L-lysine twice a day for 15 days. In another later case, also from Brazil, an 11-year-old boy with PR was treated with 250 mg L-lysine on an empty stomach and with restriction of dietary L-arginine: on the fourth day the lesions stopped appearing, the initial lesions regressed and a complete resolution was obtained after 2 weeks of oral L-lysine

therapy [438]. L-lysine is a safe nutritional supplement, but controlled studies are necessary to determine its usefulness in PR, even as monotherapy [440] and establish its optimal doses, as well as determining -in a self-limited process such as PR- when its indication would be beneficial, or not.

7. CONCLUSIONS

The diagnosis of typical PR should not be difficult for any clinician, and can almost always be done based on clinical findings and anamnestic data. Nevertheless, its atypical presentations -as defined here- can be a challenge and should be kept on mind, especially when other initial diagnoses have been raised. The main relevant and guiding features -that must be searched directly- include the history of prodromes and the herald patch; the development of a secondary rash mainly located on the trunk and following the cleavage lines; the presence of rounded lesions with collarette scaling at the periphery, with the free edges of the scales directed towards the center. Despite their high variability and non-specificity, oral lesions should be routinely investigated.

Drug-intake must be always diligently investigated. VDRL should be done in case of palmar/plantar lesions or when a social and sexual history reveals risk factors for sexually transmitted diseases. The need of a biopsy is exceptional, but sometimes required. Dermoscopy is a useful tool that can help establish the diagnosis.

In most cases, especially when mild or asymptomatic, treatment is not necessary, apart from reassurance: 'it may worsen but will finally improve in a few weeks'. Antihistamines, emollients or low potency topical corticosteroids could be prescribed when necessary, considering they will not alter the natural self-limited course of the disease and that they will merely act improving the symptoms. Macrolides are not useful.

The prescription of antivirals such as acyclovir or valacyclovir may be promising, but their doses, time of prescription and eligible patients are still to be determined.

Until recently PR was considered a harmless disease during pregnancy, but today this fact has been questioned and its real risk has not been clearly determined. Until then and in doubt, a logical premise would be to keep under strict surveillance women who contract PR during the first weeks of pregnancy, as well as those who present a disseminated rash accompanied by florid symptoms. The use of systemic antivirals in these cases should be evaluated jointly between the obstetrician and the dermatologist, considering both risks and benefits.

Given the short and variable duration of a predictable disease, as well as the time elapsed when consulting -highly inconstant patient to patient-, make it really complex to plan therapeutic trials and demonstrate their true effectiveness. Future studies with any medication should be carefully planned to achieve valid conclusions and clearly determine from/when they can be indicated, to whom, and the definitive doses.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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