

# Clinical manifestations and treatment outcomes in prurigo pigmentosa (Nagashima disease): A systematic review of the literature



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**Background:** Prurigo pigmentosa (PP) is a rare inflammatory dermatosis characterized by pruritic erythematous papules that coalesce to form a reticulate pattern. PP is often misdiagnosed, and patients are treated with ineffective therapies. Although the majority of reports about PP are from East Asia, patients of all backgrounds can be affected.

**Objectives:** To perform a systematic review of reported PP cases with the purpose of summarizing the clinical presentation and treatment of PP.

**Methods:** MEDLINE and Embase were searched for original articles describing PP. We identified 115 studies from 24 countries representing 369 patients to include in the analysis.

**Results:** Of the 369 patients included in the analysis, the mean age was 25.6 years (range: 13-72 years) with 72.1% (266 of 369) female. Risk factors or aggravating factors were described in 52.3% (193 of 369) of patients and included dietary changes (25.5%, 94 of 369), friction (8.4%, 31 of 369), sweat (7.6%, 28 of 369), and ketonuria (5.1%, 19 of 369). Of those patients who experienced PP following dietary changes, 40.4% (38 of 94) started a ketogenic diet. Minocycline monotherapy was the most frequently prescribed treatment for PP (20.9%, 77 of 369), achieving complete resolution in 48.1% (37 of 77) of patients.

**Conclusions:** PP is sometimes associated with ketogenic diets and can be effectively managed with oral tetracyclines. (JAAD Int 2021;3:79-87.)

**Key words:** inflammatory skin disease; ketogenic diet; ketosis; Nagashima; Nagashima's disease; prurigo pigmentosa; systematic review.

## INTRODUCTION

Prurigo pigmentosa (PP), also known as Nagashima disease, is a rare inflammatory skin condition characterized by a recurrent pruritic rash that resolves with net-like hyperpigmentation. It is most frequently reported in young women, typically of East Asian descent. Although PP is morphologically diverse, it often presents as erythematous papules or plaques that combine to form a reticulate

pattern, most commonly on the back, chest, and neck. Histopathological examination can differentiate between early or late PP lesions. Early lesions present with superficial perivascular neutrophilic infiltrates, whereas later lesions contain lymphocytic infiltrates and melanophages.<sup>1</sup>

Although the pathophysiology of PP is not well understood, it has been associated with dieting, nutritional deficiency, and adult-onset Still disease

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(AOSD). First-line treatment includes antibiotics such as minocycline, doxycycline, and dapsone.<sup>2-4</sup> In patients presenting with ketosis or nutritional deficiencies, resuming a balanced diet can be effective.<sup>5</sup> Importantly, topical corticosteroids are ineffective in patients with PP.<sup>6</sup>

Although PP is most frequently reported in East Asia, it has been described in patients of varying ethnicities, suggesting that PP is underdiagnosed in other countries because of a lack of awareness.<sup>7</sup> Some patients endure years of misdiagnoses, ineffective treatments, and multiple recurrences before PP is correctly identified.<sup>8</sup> Thus, it is important for health care workers to recognize PP and its risk factors in order to provide appropriate treatment. The goal of this systematic review was to identify and summarize reported cases of PP.

## METHODS

### Search strategy

The MEDLINE (1946-2020), and Embase (1980-2020) databases were searched using the OVID interface on October 17, 2020, in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.<sup>9</sup> No language restrictions and no publication period restrictions were applied. The following keywords were used for the search: “Prurigo Pigmentosa” or “Nagashima” (Supplemental Table 1).

### Study eligibility criteria

Original articles that described PP were included if they met the following criteria: (1) included patients with a diagnosis of PP and (2) were observational (i.e., case reports, case series, or cross-sectional or cohort studies). The following studies were excluded: (1) animal and in vitro studies, (2) systematic reviews or review articles, and (3) commentaries.

### Study selection

The literature search was done by 2 independent reviewers (S.M. and M.S.) who reviewed the list of titles, abstracts, and full texts to identify eligible studies. Discrepancies between the 2 reviewers were discussed, and in the case of a disagreement, a third reviewer (A.M.) was consulted before a final decision was made. Reference lists from the included articles

were reviewed to identify additional studies that were not found in the initial search.

### Data collection

Data collection was independently conducted by 2 reviewers (A.A. and S.A.), who reviewed and extracted the data from the included studies.

Discrepancies between the 2 reviewers were discussed, and in the case of a disagreement, a third reviewer (A.M.) was consulted before a final decision was made. The outcome measures were defined as follows:

1. “Race” was categorized based on the National Institutes of Health’s Racial Categories and Definitions.<sup>10</sup>
2. “Duration with PP” was defined as the length of time from when the pa-

tient first experienced symptoms of PP.

3. “Biopsy confirmation” was noted as “yes” if the diagnosis of PP was confirmed by biopsy.
4. “Treatment(s) for PP” was defined as any therapy the patient received for their PP lesions. Dose, frequency, and duration were included in brackets if available.
5. “Resolution” was noted as “complete (CoR)” if there was excellent resolution of lesions with or without hyperpigmentation, “partial (PR)” if there were residual lesions, “no resolution (NoR)” if there was no improvement, and “worsened (W)” if the lesions increased in size or severity after treatment. If the lesions resolved, but the degree of improvement was not specified, resolution was reported as PR.
6. “Resolution period” was defined as the period of time between treatment of PP and improvement of lesions.
7. “Recurrence of PP lesions despite treatment” was noted as “yes” if new lesions appeared or existing ones progressed after treatment and “no” if resolution was stable.

### Level of evidence

The levels of evidence for all included articles were assessed by S.M., S.A., and A.A. according to the Oxford Centre for Evidence-Based Medicine. Case reports and case series received scores of 5 and 4, respectively.<sup>11</sup>

## CAPSULE SUMMARY

- This is the most extensive systematic review of prurigo pigmentosa to date. We critically assessed all reported cases of prurigo pigmentosa in order to characterize its clinical presentation and treatment.
- By highlighting the clinical presentation of prurigo pigmentosa, this article aims to reduce misdiagnoses, unnecessary treatments, and recurrences.

*Abbreviations used:*

AOSD:	adult-onset Still disease
CARP:	confluent and reticulated papillomatosis
IL-6:	interleukin 6
PP:	prurigo pigmentosa

## RESULTS

### Study demographics and patient characteristics

Following screening of the titles and abstracts of 403 articles, the full texts of 183 studies were reviewed. In total, 115 studies met the inclusion criteria and were used for data collection and analysis (Fig 1, Table I). Overall, 69.6% (80 of 115) of the studies were case reports with a level of evidence of 5, and 30.4% (35 of 115) were case series with a level of evidence of 4. Of the 369 patients that were included in the analysis, the mean age was 25.6 years (range: 13-72 years) with 72.1% (266 of 369) females and 27.9% (103 of 369) males.

Overall, studies from 24 countries were included in our analysis. The geographic breakdown of the literature was 38.2% (44 of 115) East Asia, 36.5% (42 of 115) Europe, 14.8% (17 of 115) Americas, 6.1% (7 of 115) Middle East, 2.6% (3 of 115) Oceania, and 1.7% (2 of 115) South Asia. Race was reported for 74.5% (275 of 369) of the patients and consisted of 76.0% (209 of 275) Asian, 22.2% (61 of 275) White, 1.1% (3 of 275) Hispanic, and 0.73% (2 of 275) Black. Previous reports noted that PP was described most frequently in East Asia. This is in line with our data, in which 66.4% (245 of 369) of the patients were from studies conducted in East Asia. It was suggested that PP is rarely diagnosed outside of East Asia because of a lack of awareness among clinicians and histopathologists rather than a predisposition to PP in patients of East Asian descent.<sup>7</sup> Among reports from East Asia in which race was reported, all patients with PP were of Asian descent (100%, 174 of 174). In reports from the Middle East, Australia, Europe, and North America, the racial breakdown of patients with PP was 60.4% (61 of 101) White, 34.7% (35 of 101) Asian, 3.0% (3 of 101) Hispanic, and 2.0% (2 of 101) Black. These findings suggest that PP occurs in patients of various racial backgrounds and is likely underdiagnosed outside of East Asia.

Comorbidities were reported in 12.7% (47 of 369) of patients and of these, 29.8% (14 of 47) presented with diabetes mellitus, 29.8% with atopic disease (14 of 47), and 6.4% (3 of 47) with AOSD.

### Clinical characteristics

On average, patients presented with an 18.3-month (range: 0.07-160 months) history of undiagnosed PP. No patient reported a family history of PP, although 1 study described monozygotic twins who presented with PP within months of each other.<sup>12</sup> Local pruritus was noted in 80.2% (296 of 369) of patients. Risk factors or aggravating factors were identified in 52.3% (193 of 369) of patients and included dietary changes (25.5%, 94 of 369), friction (8.4%, 31 of 369), sweat (7.6%, 28 of 369), ketonuria (5.1%, 19 of 369), and hormonal changes (2.4%, 9 of 369). Within the subset of patients who changed their diet shortly before the onset of PP, 40.4% (38 of 94) started a ketogenic diet.

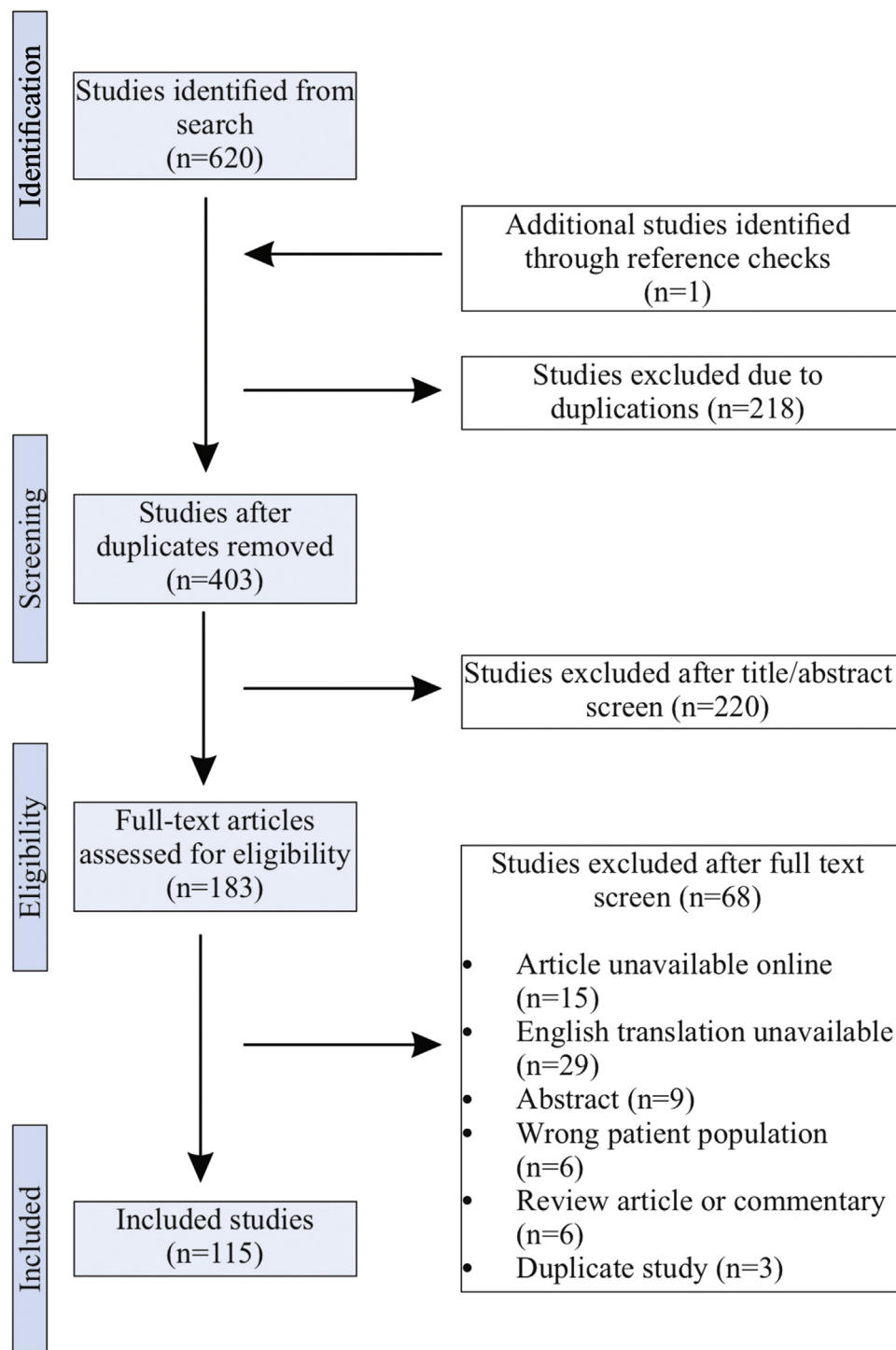
Lesions were commonly described as erythematous papules (44.2%, 163 of 369), macules (9.2%, 34 of 369), and excoriations (5.1%, 19 of 369) and typically appeared in a reticulated pattern (47.4%, 175 of 369). Hyperpigmentation was present in 24.9% (92 of 369) of patients. Lesions appeared most frequently on the back (66.4%, 245 of 369), chest (53.4%, 197 of 369), and neck (36.9%, 136 of 369).

PP was confirmed by biopsy in 83.2% (307 of 369) of patients. Histopathological findings included perivascular infiltration of leukocytes (61.8%, 228 of 369), spongiosis (32.0%, 118 of 369), melanophages (21.1%, 78 of 369), epidermal hyperplasia (10.6%, 39 of 369), and necrotic keratinocytes (6.0%, 22 of 369). The most prominent cell types were neutrophils (41.2%, 152 of 369) and eosinophils (31.2%, 115 of 369).

### Treatment

Approximately 20.9% (77 of 369) of the patients with PP had previously received treatment for their lesions. Of these, 32.5% (25 of 77) tried 1 drug, 27.3% (21 of 77) tried 2 drugs, and 40.3% (31 of 77) tried 3 or more drugs. The most common pharmacological agents that were previously prescribed to patients were topical corticosteroids (76.6%, 59 of 77), systemic corticosteroids (42.9%, 33 of 77), and antihistamines (46.8%, 36 of 77).

Treatment regimens were described in 93.0% (343 of 369) of patients. The most common treatment class used was tetracyclines. Overall, minocycline monotherapy was the most common treatment prescribed for PP (22.4%, 77 of 343), achieving complete resolution in 45.5% (35 of 77) and partial resolution in 9.1% (7 of 77) of patients. The mean (SD) resolution period was 34.5 days ( $\pm$ 36.8 days), and recurrence was noted in 9.1% (7 of 77) of patients after stopping treatment. Recurrence occurred on average 19.8 months (range: 3-48 months) after stopping minocycline. In 5 of these patients, second-line



**Fig 1.** Prurigo pigmentosa. Literature screening flow diagram using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (Figure adapted from <http://prisma-statement.org>.)

treatments were reported: 4 patients received minocycline with complete resolution and 1 patient received dapson with partial resolution. Minocycline combined with dietary changes was reported in 1.8% (6 of 343) of patients with 66.7% (4

of 6) achieving complete resolution and 33.3% (2 of 6) achieving partial resolution. Minocycline was also used in combination with topical corticosteroids in 7.0% (24 of 343) of patients, resulting in complete resolution in 12.5% (3 of 24) and partial resolution in

**Table I.** Outcomes of first-line treatments used for prurigo pigmentosa

Treatment class	Treatment	No. of times reported	Resolution NR (No. of times)	No resolution (No. of times)	Partial resolution (No. of times)	Complete resolution (No. of times)	Average resolution period (days)*	Recurrence NR (No. of times)	No recurrence (No. of times)	Recurrence occurred (No. of times)
Tetracycline monotherapy	Minocycline	77	33	2	7	35	34.5	47	23	7
	Doxycycline	56	1	1	25	29	23.4	6	44	6
	Tetracycline <sup>†</sup>	6	-	-	6	-	-	-	5	1
	<b>Total</b>	<b>139</b>	<b>34</b>	<b>3</b>	<b>38</b>	<b>64</b>		<b>53</b>	<b>72</b>	<b>14</b>
Tetracyclines and dietary changes	Minocycline and diet	6	0	-	2	4	26.0	3	3	-
	Doxycycline and diet	5	-	-	-	5	48.5	-	4	1
	<b>Total</b>	<b>11</b>	<b>0</b>	<b>-</b>	<b>2</b>	<b>9</b>		<b>3</b>	<b>7</b>	<b>1</b>
Tetracycline combination therapies	Minocycline and TCS	24	15	-	6	3	33.3	17	7	-
	Minocycline and antihistamines	3	3	-	-	-	-	3	-	-
	Minocycline and antihistamines and TCS	2	-	-	2	-	10.5	-	2	-
	Doxycycline and antihistamine and SCS	3	3	-	-	-	-	3	-	-
	Doxycycline and dapsone	2	-	-	2	-	14.0	1	1	-
	Doxycycline followed by minocycline	2	-	-	2	-	-	-	2	-
	<b>Total</b>	<b>36</b>	<b>21</b>	<b>-</b>	<b>12</b>	<b>3</b>		<b>24</b>	<b>12</b>	<b>-</b>
Topical corticosteroids	TCS monotherapy	4	1	1	2	-	127.0	1	1	2
	TCS and antihistamines	4	3	-	1	-	180	3	1	-
	SCS	4	-	-	2	2	19.5	3	1	-
	<b>Total</b>	<b>12</b>	<b>4</b>	<b>1</b>	<b>5</b>	<b>2</b>		<b>7</b>	<b>3</b>	<b>2</b>
Dapsone	Dapsone monotherapy	20	12	-	1	7	14.4	17	1	2
	<b>Total</b>	<b>20</b>	<b>12</b>	<b>-</b>	<b>1</b>	<b>7</b>		<b>17</b>	<b>1</b>	<b>2</b>
Antibiotics monotherapy	Roxithromycin	2	-	-	-	2	7.5	-	2	-
	Sulfisomezole	2	-	-	-	2	10.5	-	-	2
	Clarithromycin	2	-	-	-	2	7.0	-	2	-
	<b>Total</b>	<b>6</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>6</b>		<b>-</b>	<b>4</b>	<b>2</b>
Retinoid monotherapy	Oral isotretinoin	2	-	-	-	2	90.0	-	1	1
	<b>Total</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>2</b>		<b>-</b>	<b>1</b>	<b>1</b>
Conservative or no treatment	Changing diet	12	-	-	7	5	30.0	7	5	-
	Insulin (patients with DM)	6	-	-	1	5	16.5	4	2	-
	Self-resolving	6	-	-	1	5	71.0	2	4	-
	<b>Total</b>	<b>24</b>	<b>-</b>	<b>-</b>	<b>9</b>	<b>15</b>		<b>13</b>	<b>11</b>	<b>-</b>

- (hyphen), 0; *DM*, diabetes mellitus; *No.*, number; *NR*, not reported; *SCS*, systemic corticosteroids; *TCS*, topical corticosteroids.

\*Average time in days to reach partial or complete resolution after starting treatment.

<sup>†</sup>Specifics not reported.

25.0% (6 of 24). The other commonly used tetracycline was doxycycline. Doxycycline monotherapy was prescribed in 16.3% (56 of 343) of cases, with 51.8% (29 of 56) of patients reporting complete resolution and 44.6% (25 of 56) reporting partial resolution. The mean (SD) resolution period was 23.4 days ( $\pm$ 18.8 days), and recurrence occurred in 10.7% (6 of 56) of patients after stopping doxycycline. The mean time to recurrence after completing doxycycline treatment was not reported.

Other antibiotics, such as dapsone, were also effective in treating PP. Dapsone monotherapy was prescribed in 5.8% (20 of 343) of cases and resulted in complete resolution in 35.0% (7 of 20) and partial resolution in 5.0% (1 of 20) of patients. The mean (SD) resolution period was 14.4 days ( $\pm$ 9.4 days) and recurrence occurred in 10.0% (2 of 20) of patients after stopping therapy.

In some patients, dietary changes (3.5%, 12 of 343) alone were sufficient to treat PP. Of these patients, 41.7% (5 of 12) achieved complete resolution and 58.3% (7 of 12) achieved partial resolution. Overall, the mean (SD) resolution period was 30.0 days ( $\pm$ 10.0 days). Specific dietary modifications for treatment were described in 4 patients.<sup>5,13,14</sup> All 4 patients had started a ketogenic diet prior to developing PP: 3 for weight loss and 1 for management of intractable seizures. In all cases, increasing carbohydrate intake resulted in complete resolution of lesions. In 1 study, specific dietary changes were not described; however, urinary ketones were detected in 80% (8 of 10) of patients, suggesting low carbohydrate intake. Treatment of PP by resuming a balanced diet cleared the lesions and reduced the urinary ketone levels.<sup>15</sup>

Pregnancy was identified as an exacerbating factor in 5 patients, of whom 3 suffered from malnutrition: 2 patients were hospitalized because of severe hyperemesis gravidarum and 1 patient was following a strict diet to prevent nausea and vomiting.<sup>16-18</sup> All 3 patients had elevated urinary ketones and presented early in their pregnancy at an average of 12 weeks. Fluid and nutritional restoration resulted in complete resolution in 1 patient; the resolution coincided with loss of ketonuria.

## DISCUSSION

Although the etiology of PP is unknown, it has been associated with metabolic disorders. PP occurred with ketoacidosis as a complication of poorly controlled diabetes as well as ketosis following adherence to a calorie-restrictive or low-carbohydrate diet, fasting, anorexia nervosa, or

bariatric surgery. In these metabolic states, low serum glucose or insulin levels stimulate ketone synthesis in the liver, resulting in elevated levels of ketone bodies, which can be detected in the blood or urine.<sup>19</sup> Ketone bodies may accumulate around blood vessels, resulting in perivascular inflammation and neutrophilic infiltration. Accordingly, treatment with tetracyclines and other antibiotics may be effective partly because they inhibit neutrophil chemotaxis.<sup>20,21</sup> Resuming a balanced diet or initiating insulin therapy reduced ketone levels and resolved lesions, whereas an increase in ketone levels was associated with PP recurrence.<sup>15,17</sup> These findings suggested that ketone bodies may play a role in the pathogenesis of PP.

PP was also diagnosed in patients with AOSD.<sup>22-24</sup> The underlying mechanism is not well understood, but previous work showed increased interleukin 6 (IL-6) expression in lesions from PP patients when compared with that in eczema controls.<sup>25</sup> IL-6 has previously been implicated in AOSD pathogenesis, and targeted IL-6 antibodies showed clinical efficacy in AOSD.<sup>26,27</sup> Thus, increased IL-6 levels from AOSD may trigger PP. In some patients, PP flares were associated with hormonal changes, such as during pregnancy, menstruation, and polycystic ovary syndrome.<sup>16-18,28-33</sup> Worsening of PP during menstruation and pregnancy suggests a possible role for hormones in the disease pathogenesis; however, there is no evidence to suggest oral contraceptives or hormone replacement therapy alter the disease course. Thus, it is unclear if estrogen directly plays a role in PP pathogenesis. PP may also be associated with bacterial infections. One study reported on a patient presenting with PP and gastritis caused by *Helicobacter pylori* infection. Treatment of the gastritis with antibiotics and proton pump inhibitors resolved the PP lesions with no recurrence.<sup>34</sup> In addition to endogenous risk factors, PP also was found to be triggered by exogenous factors, such as sweating, friction, and contact allergens.

Among our included studies, no family history of PP was reported. However, 1 study reported on monozygotic twins who were both diagnosed with PP within months of each other. Both twins experienced symptoms for years with 1 twin reporting a 10-year history of chronic relapsing pruritic dermatosis and the other twin reporting a 4-year history of a similar eruption. They did not report a family history of PP, and no risk factors were identified.<sup>12</sup> This study suggested that there may be a genetic predisposition for the development of PP, which was further supported by reports of PP occurring in a segmental distribution, indicative of genetic mosaicism.<sup>35,36</sup>



PP is often misdiagnosed, delaying treatment by months or years. Lesions may be mistaken for eczema or contact dermatitis.<sup>29,37</sup> However, eczema commonly responds well to topical or oral corticosteroids, whereas PP does not. If contact dermatitis is suspected, patch testing can be done to determine if the patient is experiencing an allergic response. PP may also be confused with confluent and reticulated papillomatosis (CARP). CARP generally presents with hyperkeratinized papillomatous lesions, which are not present in PP.<sup>37</sup> Moreover, neutrophilic exocytosis, interface dermatitis, spongiosis with vesiculation, and dyskeratosis are histopathological features of PP that are typically not observed in CARP.<sup>33,38</sup> PP is also significantly more pruritic, and hyperpigmentation from PP lesions takes much longer to resolve compared with CARP lesions.<sup>38</sup>

This systematic review had several limitations. First, most articles were case reports or case series, with an overall mean evidence level of 4.7. Second, histopathological confirmation of PP was not noted in 16.8% (62 of 369) of patients, making it difficult to confirm the clinical diagnosis. Third, PP is characterized by its recurrent nature, but 26.0% (96 of 369) of cases did not report on recurrence after therapy. Thus, although treatment may have initially been effective, we were unable to capture its long-term efficacy in some patients. Fourth, adverse drug events were not reported in 97.0% (358 of 369) of patients, making it difficult to assess potential side effects. Finally, many studies were excluded because they were either unavailable online or no English translation was available.

Despite these limitations, our study provides important information about the clinical presentation and management of PP. Results from future studies will be important to confirm the risk factors associated with PP and to evaluate potential treatments. Increasing awareness about PP will reduce misdiagnoses, unnecessary treatments, and recurrences.

#### Conflicts of interest

Dr Jensen Yeung has been a speaker, consultant, and investigator for AbbVie, Allergan, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, GSK, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, and Xenon. Dr Mufti, Dr Mirali, author Abduekmula, Dr McDonald, Dr Alabdulrazzaq, and author Sachdeva have no conflicts of interest to declare.

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**Supplemental Table I.** Search strategy

#	Searches	Results
1	Prurigo Pigmentosa.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, tn, dm, mf, dv, kw, dq]	332
2	Nagashima.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, tn, dm, mf, dv, kw, dq]	304
3	1 or 2	620
4	remove duplicates from 3	412

Database(s): Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946-Present, Embase Classic+Embase 1947 to 2020 October 17.