Venous Insufficiency is a Clear Provoker of Pigmented Purpuric Dermatosis

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Received April 1, 2021
Revised July 30, 2021
Accepted September 8, 2021

Background: Pigmented purpuric dermatosis (PPD) is a chronic disorder characterized by distinct petechial hemorrhage and brownish pigmentation. The cause of PPD is unclear, but several underlying conditions are associated with it. Previous reports suggest that venous insufficiency (VI) might be related to PPD; however, a clear correlation remains unelucidated.

Objective: To elucidate the causal relationship between PPD and VI.

Methods: A total 118 patients diagnosed with PPD in the Department of Dermatology, Pusan National University Hospital from November 2006 to July 2019 were retrospectively reviewed. Doppler ultrasonography of the lower extremities was performed in 56 PPD patients, who were then divided into two groups: PPD with and without VI. We compared the clinical features between the two groups. In the PPD with VI group, we assessed the correspondence ratios between PPD and VI lateralities, and between the PPD distribution and the veins involved.

Results: VI was detected in 35 of the 56 patients (62.5%). The PPD with VI group was significantly associated with wider distribution, darker coloration and longer disease duration. There was a positive correlation of laterality between PPD and VI, and between PPD distribution and the vein involved.

Conclusion: This findings suggest that VI is a clear provoker of PPD.

Keywords: Doppler ultrasonography, Pigmentation disorders, Venous insufficiency

INTRODUCTION

Pigmented purpuric dermatosis (PPD) is a cutaneous disorder characterized by non-palpable petechiae and purpuric patches on a brownish background. Commonly observed on the lower extremities, PPD is divided into several subtypes: (1) Schamberg disease, (2) Majocchi’s purpura annularis telangiectodes, (3) pigmented purpuric lichenoid dermatosis of Gougerot and Blum, (4) eczematid-like purpura of Doucas and Kapetanakis, and (5) Lichen aureus. Although PPD is generally benign, it may be chronic, progressive and resistant to most treatments¹.

While the cause of PPD remains unclear, several co-factors, such as diabetes mellitus, dyslipidemia, hepatitis B and C infections, allergic reactions, trauma and chronic venous insufficiency (VI) of the lower extremities, have been suggested to be associated with PPD²⁻⁴. Among these, the relationship between PPD and VI is not fully established. VI is a chronic condition in which blood pools in the veins, straining their walls due to venous reflux. This condition usually affects the lower legs and has various manifestations, such as edema, skin pigmentation, and ulceration⁵⁻⁷. Only one study has evaluated the venous function in the lower extremities of PPD patients using Doppler ultrasonography². However, it could not clearly elucidate the correlation between PPD and VI due to a small sample size and the absence of a control group. Although VI has been suggested as a potential contributor of PPD, the exact relationship is uncertain. Thus, in this study, we investigated this correlation to aid clinical management and help adjust the
treatment plan for PPD.

MATERIALS AND METHODS

Study population and design
The study protocol was approved by the Pusan National University Yangsan Hospital Institutional Review Board, Busan, Korea (IRB No. 05-2019-057). Subjects were recruited from outpatients who had lesions diagnosed as PPD. PPD diagnosis was made by its typical clinical and histopathological features. We excluded patients with the typical clinical manifestation of stasis dermatitis (severe hyperpigmentation, swelling, irritation and ulceration). A total 118 patients diagnosed with PPD in the Department of Dermatology, Pusan National University Hospitals from November 2006 to July 2019 were retrospectively reviewed. We received the patient’s consent form about publishing all photographic materials.

Among these, 56 patients agreed to undergo a Doppler ultrasonography of the lower extremities, which was done by the radiologists in our hospital. The presence of VI, along with the veins involved, especially the great saphenous vein (GSV) or the short saphenous vein (SSV), was mainly assessed, and diagnosis of VI was confirmed by the presence of venous reflux in Doppler ultrasonography, showing retrograde or reversed flow with a duration over 500 ms for superficial veins. Based on the Doppler ultrasonographic findings, the patients were divided into two groups: PPD with or without VI.

Between the two groups, we compared the age, sex, co-morbid conditions, area involved, color of the lesion, disease duration, and the treatment outcomes. The treatment outcomes were assessed through clinical photos at the 3 months of treatment in only 15 patients in each group who treated only with mid-potency topical steroids, and the treatment outcomes were classified into the following four categories: (1) completely resolved, (2) substantially improved, (3) partially improved, and (4) unimproved or aggravated.

In the PPD with VI group, we assessed the correspondence ratios between PPD and VI lateralities, and between PPD distribution and the vein involved (GSV vs. SSV).

Statistical analysis
All statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). We used the chi-square test (or Fisher’s exact test) to compare the above mentioned parameters between the PPD with or without VI groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

All 56 patients who consented to Doppler ultrasonography had Schamberg disease, of which 35 were male (62.5%) and 21 were female (36.5%). The male to female ratio was 1.67. The overall mean age at diagnosis was 52.7 years, ranging from 24 to 94 years. VI was detected in 35 of the 56 patients (62.5%), with bilateral VI in 14 patients (40.0%), right only VI in 14 patients (40.0%), and left only VI in 7 patients (20.0%). The GSV was the most commonly involved vein (57.1%), followed by the SSV (31.4%), and combined (11.5%).

Table 1. Comparison of demographics and clinical features between PPD with VI and PPD without VI

| Variable | PPD with VI (n=35) | PPD without VI (n=21) | p-value |
|----------|-------------------|-----------------------|---------|
| Mean age of onset (yr) | 53.5 | 52.1 | 0.204 |
| Sex ratio (male:female) | 1.74 | 1.63 | 0.140 |
| Underlying conditions | | | |
| Dyslipidemia | 11 (31.4) | 7 (33.3) | |
| Diabetes mellitus | 7 (20.0) | 7 (33.3) | |
| Hypertension | 7 (20.0) | 5 (23.8) | |
| Angina | 4 (11.4) | 4 (19.0) | |
| Malignancy | 2 (5.7) | 3 (14.3) | |
| Thyroid dysfunction | 2 (5.7) | 1 (4.8) | |
| Involved area (BSA, %)* | 3.5 | 2.3 | <0.05 |
| Color of lesions | | | <0.05 |
| Black | 4 (11.4) | 1 (4.8) | |
| Dark brown | 7 (20.0) | 1 (4.8) | |
| Light brown | 15 (42.9) | 13 (61.9) | |
| Red | 9 (25.7) | 6 (28.6) | |
| Disease duration (mo) | 12.1 | 6.9 | <0.05 |
| Treatment outcome (1~4)† | 3.2 | 1.7 | <0.05 |

Values are presented as mean or number (%). PPD: pigmented purpuric dermatosis, VI: venous insufficiency, BSA: body surface area, -: not not available. *BSA was estimated with assumption of palm surface area as 1% of the total body surface area. †Treatment outcome was scored as (1) completely resolved, (2) substantially improved, (3) partially improved, and (4) unimproved or aggravated.
Comparison between the PPD with and without VI groups

The comparison of demographics and comorbidities between the PPD with and without VI groups is presented in Table 1. The mean age of onset was 53.5 years in the PPD with VI group, and 52.1 years in the PPD without VI group. The sex ratio was similar in both groups (1.74 in PPD with VI, 1.63 in PPD without VI). The most common concomitant underlying conditions were dyslipidemia (31.4% and 33.3% in the PPD with and without VI group, respectively), followed by diabetes mellitus (20.0% and 33.3%, respectively), and hypertension (20.0% and 23.8%, respectively) in both groups.

The intergroup comparison of the clinical features of PPD is presented in Table 1. PPD with VI presented a significantly wider involved area than PPD without VI (3.5% and 2.3%, respectively; p<0.05). In both groups, the most common color of the PPD lesion was light brown (42.9%), followed by red (25.7%), dark brown (20.0%), and black (11.4%). Although light brown and red were the predominant colors in both groups, the proportion of black/dark brown color was significantly higher in the PPD with VI group than in the other (31.4% and 9.5%, respectively; p<0.05). PPD with VI showed a significantly longer duration of the disease than the other group (12.09 months and 6.86 months, respectively; p<0.05). Most patients (80.4%) showed a substantial or partial improvement. The treatment outcomes were as follows: completely resolved (7.1%), substantially improved (37.5%), partially improved (42.9%), and unimproved or aggravated (12.5%). There was a significant difference in treatment responses between the two groups (p<0.05).

Comparison between PPD and VI in the group of PPD with VI

We assessed the correspondence ratios between PPD and VI lateralties, and between PPD distribution and the involved vein (Table 2, 3). We found a positive correlation of laterality between VI and PPD (p<0.05). When VI occurred bilaterally, PPD lesions were more likely to be bilateral (92.8% in bilateral

Table 2. Correspondence ratios between PPD and VI literalities

| Variable          | VI laterality | Correlation between VI and PPD |
|-------------------|---------------|--------------------------------|
|                   | Both side     | Right side only | Left side only | Group with positive correlation | Group without positive correlation | p-value |
| PPD laterality    |               |                 |               |                                |                                |         |
| Both side         | 13 (92.8)     | 4 (26.7)        | 2 (33.3)      |                                |                                |         |
| Right side only   | 1 (7.2)       | 11 (73.3)       | 0             |                                |                                |         |
| Left side only    | 0             | 0               | 4 (66.7)      |                                |                                |         |
| VI laterality     |               |                 |               | 28 (80.0)                       | 7 (20.0)                        | <0.05   |

Values are presented as number (%). PPD: pigmented purpuric dermatosis, VI: venous insufficiency.

Table 3. Correspondence ratios between PPD distribution and the vein involved (only in the PPD with VI group; n=35)

| Variable       | Type of involved vein | Correlation between involved vein and distribution of PPD |
|----------------|-----------------------|----------------------------------------------------------|
|                | GSV                   | SSV            | Combined      | Group with positive correlation | Group without positive correlation | p-value |
| Distribution of PPD |                     |                |               |                                |                                |         |
| Anterior       | 18 (45.0)             | 6 (16.7)       | 5 (31.3)      | 60 (65.2)                       | 32 (34.8)                       | <0.05   |
| Medial         | 16 (40.0)             | 4 (11.1)       | 4 (25.0)      |                                |                                |         |
| Posterior      | 2 (5.0)               | 10 (27.8)      | 2 (12.5)      |                                |                                |         |
| Lateral        | 4 (10.0)              | 16 (44.4)      | 5 (31.3)      |                                |                                |         |

Values are presented as number (%). PPD: pigmented purpuric dermatosis, VI: venous insufficiency, GSV: great saphenous vein, SSV: short saphenous vein.
Moreover, PPD lesions tended to show the same laterality if VI occurred unilaterally (73.3% in right only VI, 66.7% in left only VI). Furthermore, there was a positive correlation between the type of vein involved and the PPD lesion distribution \((p<0.05)\). In case of VI in GSV, PPD lesions were more likely to be distributed on the medial (40.0%) and anterior (45.0%) parts, consistent with the ascending route of GSV. In case of VI in SSV, PPD lesions were more likely to be distributed on the lateral (44.4%) and posterior (27.8%) parts, consistent with the ascending route of SSV (Fig. 1).

**DISCUSSION**

PPD is a group of cutaneous disorders with non-palpable petechiae and purpuric patches on a brownish background, resulting from the deposition of hemosiderin, which is a consequence of the extravasation of erythrocytes in the papillary dermis. The etiology of PPD remains obscure. Various cofactors like venous hypertension, gravitational dependency, strenuous exercise, orthostatic pressure, capillary fragility, focal infections, drug and chemical ingestion, and contact allergens have been suggested as potential triggers of PPD\(^1,2\). Additionally, while associations between PPD and multiple systemic diseases such as dyslipidemia, viral hepatitis, and some bleeding disorders have been proposed, these associations are not yet completely understood.

VI is a chronic condition caused by the functional impairment of venous drainage in the lower extremities. Chronic VI could present various clinical symptoms ranging from varicose veins, edema, skin discoloration to ulceration in advanced cases\(^6,7\). The venous system of the lower extremities is classified according to its location and relationship with the muscle fascia. It includes the superficial, deep, and perforating veins\(^8,9\). Since the rupture and dilation of the end capillaries in the papillary dermis is the main pathological mechanism of PPD, we postulated that a dysfunction of the superficial venous system might be the main cause of skin changes. Therefore, this superficial venous system, which is composed of GSVs, SSVs, and their tributaries, was mainly examined in this study.

The clinical association between superficial venous system dysfunction and skin ulcer or stasis dermatitis has been reported\(^10,11\). However, there is no study clearly demonstrating the relationship between PPD and VI. Gönül et al.\(^5\) reported the first study where PPD patients underwent a Doppler ultrasonography for the investigation of VI incidence. They reported that 75% of the PPD patients had VI and suggested a possible link between the two. However, they could not elucidate a clear correlation due to a small sample size and the absence of a control group. The present study noted VI in 62.5% of the PPD patients. Results from both studies indicate that VI is closely related to PPD.

Comparison between the PPD with or without VI groups did not reveal any significant differences in the age of onset and the sex ratio. The incidence of concomitant underlying diseases was also similar in both the groups. The most common of these conditions was dyslipidemia (31.4% and 33.3% in the PPD with and without VI group, respectively) followed by diabetes mellitus (20.0% and 33.3%, respectively), hyper-
tension (20.0% and 23.8%, respectively). In the analysis of the clinical characteristics of PPD (Table 1), the PPD with VI group showed a wider distribution and darker coloration of the lesions, a greater extended disease duration, and a poorer treatment response than the PPD without VI group. These findings underscore the significance of VI in the pathogenesis of PPD.

In the PPD with VI group, we found a clear causal relationship between PPD and VI. We assessed the correspondence ratios between PPD and VI lateralities, and between PPD distribution and the vein involved. We found a positive correlation of laterality between PPD and VI. When VI occurred on only one side of the lower extremity, PPD lesions were more likely to be distributed on the same side. Furthermore, there was a positive correlation between the type of veins involved, i.e., GSV or SSV and the distribution of PPD lesions.

Considering the ascending route of GSV and SSV (Fig. 1), we speculated that GSV-related PPD can predominate on the anterior and medial sides, and SSV-related PPD can predominate on the posterior and lateral sides of the lower leg. In case of GSV insufficiency, PPD lesions were more likely to be distributed on the medial and anterior parts, consistent with ascending route of GSV (Fig. 2). While medially and anteriorly located PPD lesions were more associated with GSV (64.1%) than SSV (18.9%), laterally and posteriorly distributed PPD lesions were more associated with SSV (66.7%) than GSV (15.4%), respectively.

The limitations of this study are as follows: Doppler ultrasonography was performed only in consenting patients, all of which had Schamberg disease, and also the perforated and deep veins were not evaluated. Due to small number of patients included, we could not perform multivariate analysis adjusting other possible risk factors of PPD. And so, there can be a selection bias. Despite these limitations, our study’s findings might form meaningful result that VI plays an important role in the development of PPD.

Furthermore, we can observe the improvement of PPD in few patients who had a surgical treatment of VI (Fig. 3). We believe that this is another critical evidence that VI is a clear contributor of PPD.

Considering the results of this study, there could be clear causal relationship between PPD and VI. Doppler ultrasonography of the lower extremity should be considered if the PPD shows a wider distribution, darker coloration, a greater extended disease duration, and poorer treatment outcomes than the usual typical PPD. This is the largest study to investigate the relationship between PPD and VI, and suggests that VI may be an important risk factor of PPD.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.
FUNDING SOURCE

None.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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