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CASE REPORT

# The vanishing port-wine stain birthmark—consideration for a rare type of congenital vascular anomaly

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## Abstract

Capillary malformations (MCs), also referred to as port-wine stains (PWSs), or port-wine birthmarks (PWBs) represent one of the most common congenital vascular birthmarks. They consist of ectatic postcapillary venules within the papillary and superficial reticular dermis. The pathogenesis is due to a somatic activating mutation in guanine nucleotide–binding protein G(q) subunit alpha which mosaically occurs in endothelial cells (ECs) during embryogenesis. As a true congenital vascular malformation, PWSs are always present at birth, appearing as a flat pink to red macula mostly arising in the head and neck unilaterally. Although lightening during the first few months of life is possible, these lesions generally stay stable or thicken and darken over time. Consequent functional impairment, tissue thickening, development of blebs, and psychological burden may be relevant, so early laser therapy should often be considered to deter progression. What we present here is a unique cohort of 10 children presented to the Vascular Birthmarks Foundation (VBF) in Latham, NY, between 2016 and 2021, who were followed over time for cutaneous vascular anomalies present at birth. The clinical features were strongly suggestive of PWSs. However, all 10 of these children showed a significant spontaneous regression of the lesions during the observational period. In four cases, there was complete resolution. According to the international literature, capillary malformations persist throughout life and typically grow and darken if early laser treatment is not initiated. Such spontaneous improvement is extremely rare after the first 6 months of life. In the present case series, we photographically documented this previously unreported circumstance.
Level of evidence: Level V, risk/prognostic study.

**Keywords** Capillary malformation · Port-wine stain · Differential diagnosis · Spontaneous regression · Natural improvement

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## Introduction

The latest 2018 update of the International Society for the Study of Vascular Anomalies (ISSVA) classification for vascular anomalies has finally clarified the last three decades confusion generated by the incorrect and fragmented use of terminology relating to vascular lesions (Tables 1 and 2) [1–3].

According to this current classification, vascular lesions are divided into two main groups: vascular tumors, such as infantile hemangioma (IH), which are characterized by hyperplasia; and vascular malformations, which are characterized by hypertrophy [4].

Capillary malformations (CMs), commonly known as *naevus flammeus* or port-wine stains (PWSs) due to the characteristic pink or purplish appearance of the involved

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area, are the most frequent vascular malformations of the skin. Although rare acquired forms are reported in the literature [5, 6], they normally consist of benign congenital malformations of the superficial dermal venulo-capillary plexus, and are thus typically present at birth.

The incidence ranges from 0.3 to 0.5 per 100 of newborns in the USA while a rate of 0.1–2% is registered worldwide, without gender distribution differences [7–11]. While most PWSs show a sporadic inheritance pattern, there is a number of associated congenital syndromes in which they manifest greater diffusion in addition to bone hypertrophy such as in Klippel-Trenaunay syndrome (KTS) or neurological involvement, as seen in the Sturge-Weber Syndrome (SWS) [12].

As with other vascular anomalies, PWSs may appear anywhere in the body but the face is vastly more affected (90%), followed by the neck, trunk, legs, and arms [4, 13–16].

Facial CMs generally show a dermatomal distribution involving the cutaneous territory pertaining to the trigeminal sensory nerve, with a likely predilection for its maxillary (V2) division. These lesions are usually lateralized respecting the midline, but in some cases they can grow widely, extending to neighboring anatomical areas [9, 10, 17]. In addition to the skin, oral and nasal cavities, mucosa, tongue, gingiva, and pharynx can also be affected, leading sometimes to significant complications such as dysphagia, dysphonia, dyspnea, vision impairment, or spontaneous bleeding [13, 18].

Etiopathogenetically, the primum movens of CMs development is recognizable in a missense activating somatic mutation in guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) or, less frequently, in guanine nucleotide-binding protein 11 (GNA 11). These G proteins are involved in the MAP/MEK cell proliferation pathway mediating signals between G-protein-coupled receptors and downstream effectors [7, 12, 13].

As is typical with mosaic genetic alterations, they only occur in the endothelial cells of the vascular lesion leading

**Table 2** ISSVA classification for capillary malformations[2]

| Capillary malformations (CMs) |
|---|
| Nevus simplex/salmon patch, "Angel kiss", "Stork bite" |
| Cutaneous and/or mucosal CM (also known as "port-wine" stain) |
| Nonsyndromic CM |
| CM with CNS (central nervous system) and/or ocular anomalies (Sturge-Weber syndrome) |
| CM with bone and/or soft tissues overgrowth |
| Diffuse CM with overgrowth (DCMO) |
| Reticulate CM |
| CM of MIC-CAP (microcephaly-capillary malformation) |
| CM of MCAP (megalencephaly-capillary malformation-polymicrogyria) |
| CM of CM-AVM |
| Cutis marmorata teleangiectatica congenita (CMTC) |
| Others |
| Teleangiectasia |
| Hereditary hemorrhagic teleangiectasia (HHT) |
| Others |

**Table 1** ISSVA classification for vascular anomalies [2]

| Vascular Anomalies | | | | |
|---|---|---|---|---|
| Vascular Tumors | Vascular Malformations | | | |
| | Simple | Combined* | Of major named vessels | Associated with other anomalies |
| Benign<br>Locally aggressive or borderline<br>Malignant | Capillary malformations (CM)<br>Lymphatic malformations (LM)<br>Venous malformations (VM)<br>Arteriovenous malformations (AVM)<br>Arteriovenous fistula (AVF) | CVM, CLM<br>LVM, CLVM<br>CAVM<br>CLAVM<br>Others | Affect:<br>Lymphatics<br>Veins<br>Arteries<br>Anomalies of:<br>Origin<br>Course<br>Number<br>Length<br>Diameter (aplasia, hypoplasia, stenosis, ectasia/aneurysm)<br>Valves<br>Communication (AVF)<br>Persistence (of embryonal vessel) | Klippel-Trenaunay syndrome<br>Parkes-Weber syndrome<br>Servelle-Martorell syndrome<br>Sturge-Weber syndrome<br>Limb CM + congenital non-progressive limb overgrowth<br>Maffucci syndrome<br>Macrocephaly—CM<br>Microcephaly—CM<br>CLOVES syndrome<br>Proteus syndrome<br>Bannayan-Riley-Ruvalcaba syndrome<br>CLAPO syndrome |

*Abbreviations: *CVM*, capillary-venous malformation; *CLM*, capillary lymphatic malformation; *LVM*, lymphatic venous malformation; *CLVM*, capillary lymphatic venous malformation; *CAVM*, capillary arteriovenous malformation; *CLAVM*, capillary lymphatic arteriovenous malformation

to a vessel morphogenesis disruption which results in multiple dilatated, thin-walled capillaries and venules within the papillary and superficial reticular dermis, with no evidence of cellular proliferation [9, 12, 19–21].

Initially, PWSs clinically appear as flat pink or bright red hued patches. Although they may lighten during the first few months of life, probably due to the physiological anemia of infancy, this phenomenon is not predictive of a spontaneous regression of the vascular stain [13, 22].

In contrast to other birthmarks such as hemangioma or the so-called salmon patches, capillary malformations normally persist throughout life and have no tendency toward involution.

Unlike these nosological entities, PWSs persist, untreated, into adulthood becoming thicker and raised, as well as of a darker violaceous color as a result of progressive vascular ectasia [12, 23]. This is thought to be a consequence of a neural vascular tone modulation lack resulting from both sympathetic and sensory perivascular innervation flaw, as immunohistochemically documented by Smoller [24] and Rydh [25].

Approximately two-thirds of patients with PWSs may develop more severe morphological changes like isolated or multiple aggregated nodules (cobblestone pattern) and progressive soft tissue and/or bone hypertrophy [26, 27]. This risk is particularly true in Sturge-Weber and Klippel-Trenaunay syndromes [28].

These modifications are conspicuous by the age of 50 but often begin early with overgrowth of soft and bone tissues appearing at an average age of nine and fifteen years, respectively, and during the third decade of life (20 s) for nodules raising [12, 13].

Based on clinical and histological evidences, Finley and colleagues [29] differentiated between thickening and nodules occurring in PWSs. Thickening was defined as an exaggeration of the ectasia process whereas nodules were polypoid tumors consisting of thick- and thin-walled vessels of varying caliber and surrounding stroma proliferation, which they categorized as arteriovenous malformations (AVMs) [27].

Chen et al. [30], in a clinicopathological study on 31 patients with nodules arising within a facial PWS, determined that in addition to AVMs, pyogenic granulomas (PGs), consisting of a mass of capillaries and venules containing numerous inflammatory cells, probably is an important contributory factor to the PWS nodularity. The author observed a particular propensity of these nodules to involve the second branch of the trigeminal nerve, possibly due to the extended vascularity of this facial area or as an effect of sun exposure. These results confirm what was previously described by Klapman et al. [27].

Location, size, and the progression of a PWS are the factors that mainly influence both the functional and the psychological aspects of these patients.

Difficulty in speaking and eating, as well as visual acuity impairment and dyspnea may significantly compromise the activities of daily living [18].

Facial disfigurement, especially in large, thicker, and more nodular textured lesions, can often lead to social stigmatization resulting in lowered levels of self-esteem and isolation [12, 14, 31].

Despite several therapies proposed over time, the flashlamp-pumped pulsed dye laser (PDL) currently remains the gold standard treatment for port-wine stains [23, 28, 32, 33]. Based on the key principle of selective photothermolysis, which involves selective destruction of abnormal vessels due to the transfer of thermal energy to oxyhemoglobin, it is established as the most effective management modality for PWS, safely performable as early as 6 weeks of age [17, 34, 35].

However, the laser energy does not effectively penetrate beyond 100–300 micron explaining why a consistent number of PWSs responds only partially to the treatment and only 10% of patients show complete resolution [23, 36, 37].

This partial benefit of laser therapy is particularly evident when applied to those progressive and thicker PWSs with nodularity and hypertrophy, which are usually both persistent and resistant [38]. In order to obtain better outcomes and avoid the need for the possible disfiguring surgery [39], many authors recommend early PDL treatment, possibly within the first year of age [40–42].

## Cases report

A total of 10 children aged between 1 to 6 days (mean 3.0; median 3) presented to the Vascular Birthmarks Foundation (Latham, New York), complaining of a macular vascular skin lesion and were followed up over a 5-year time period (from 2016 to 2021). There were 7 males (70.00%) and 3 females (30.00%). Six patients were Caucasian (60.00%), 2 patients were Asian American (20.00%), 1 African American (10.00%), and 1 child was of Indo-American ethnicity (10.00%). All patients were born at full term following a normal uncomplicated pregnancy. The mothers of the patients denied any medications during pregnancy, except for vitamin supplements in 2 cases. Referring to the Fitzpatrick skin types classification, 2 patients had type III (20.00%), 4 patients type II (40.00%), 2 children type I (20.00%), and 2 patients showed IV skin type (20.00%). According to their parents, vascular patches were fully present and evident at birth, in all cases. Furthermore, all 10 children were in excellent health, with no co-pathologies or therapies administered during the observational period. All parents were

told that their baby had a PWS. The clinical features of the skin lesions we considered were site, color, thickness, borders, and evolution. These are summarized in Table 3. In all cases, the diagnosis was based on clinical examination and no instrumental investigation was considered necessary for its confirmation. The head and neck region was affected in all cases, while only 1 (10.00%) child showed upper chest and shoulder involvement. Regarding the topographic distribution of facial lesions, the second trigeminal nerve branch area was the most involved (70.00%), followed by the V1/ophthalmic territory (60.00%). Only 1 patient showed limited involvement of the mandibular district (10.00%), while in 1 case the involvement of an entire half-face was documented (10.00%).

In most cases, the color of the skin lesions ranged from pink to light red (60.00%), followed by the darker or more purplish shade (40.00%) which in 3 cases (30.00%) was quite dark. All children showed unraised vascular patches with well-demarcated margins, which appeared nuanced and less defined in 4 cases (40.00%). No bruits were auscultated and no thrills were detected in all children examined. After diagnosis within the first days of life, subsequent evaluations were carried out at variable time intervals (mean 12.38 months, median 10.5 months). In all the cases presented, a noticeable improvement in terms of lightening of the skin lesions could be confirmed, while in 4 (40.00%) cases their complete regression was observed. No treatments, of any kind, were performed in all cases.

### Patient 1

Patient 1 was a 9-month-old Asian American male born with a pink-red vascular stain that involved the glabella, nose, left cheek, periorbital, and temporal regions. According to his parents, the patch was present at birth (Fig. 1a) as a flat lesion showing irregular but well-demarcated borders. The patient's birth was uncomplicated and subsequent to a normal pregnancy. The child was in excellent health and neither instrumental investigations nor treatments were performed. At 9 months of age, we documented an almost complete disappearance of the lesion (Fig. 1e).

### Patient 2

This patient was a Caucasian male born with a reddish flat macula on the right cheek partially extended to the ipsilateral chin. The parents did not report perinatal complications or other concomitant diseases. The vascular lesion presented at birth as a flat, dark red-purplish patch with well-defined margins (Fig. 2a). During the first months of life, a progressive lightening of the lesion was noted, which became more consistent around 12 months as is possible to observe in Fig. 3d. Even in this case, given the typical clinical presentation of the lesion, no diagnostic investigations were necessary, and no treatment was carried out.

### Patient 3

The third patient was a 6-month-old Caucasian male born with a flat, bright red vascular stain in the right periorbital and frontal region, cheek, and upper lip (Fig. 3a). The lesion was partially blanchable and presented geographic morphology with well-demarcated borders. As reported by the parents, the stain initially remained stable growing proportionally with the child and then clearly lightened towards the age of 6 months (Fig. 3b). The child was in full health, with normal ophthalmologic and neurologic findings.

### Patient 4

Patient 4 was a Caucasian girl reported to our Clinic by her parents on the first day of life complaining of a vascular birthmark involving the right V2 area (Fig. 4a). The vascular stain was flat, homogeneous pink in color and extended to the whole cheek, and superiorly to the frontotemporal region. The margins were clearly identifiable but continued in a more nuanced manner with the surrounding skin. Partial fading of the lesion was observed during the first month (Fig. 4b and c) and continued steadily until its complete spontaneous resolution, as found on clinical examination 18 months later (Fig. 4f).

### Patient 5

Patient 5 was a 3-week-old African American male with a dark skin phototype (Fitzpatrick skin-type IV). At the end of a normal gestation, he was born with a large telangiectatic, flat, bright red macula distributed with a segmental pattern over the left latero-cervical, upper chest, and shoulder regions. From the first week of age, the stain appeared lightened compared to birth and its improvement continued until the evaluation at 25 days of life, although it persisted. After that time, the patient did not return for follow-up (Fig. 5).

### Patient 6

Patient 6 was a 4-year-old Indo-American boy with no past medical history. At birth, he presented a very extensive dark and flat, homogeneous red-purplish vascular lesion involving the entire left half-face and partly extended controlaterally to the upper lip, cheek, and fronto-temporo-parietal region, as shown in Fig. 6a. After about 4 years, the parents sent us a photograph in which it is clear that the birthmark has largely resolved spontaneously, except for a small right malar area. According to the parents, the patient did not undergo any treatment during that time period.

**Table 3** Summary of epidemiological and clinical data from the children included in this case series

| Patient no | Sex | Etnicity | Gestation and birth | Present at birth | Age at diagnosis | Age at last evaluation | Health state, copatologies | Skin type (Fitzpatrick classification) | Site | Clinical presentation | Investigations | Treatments | Clinical course |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | Asian American | At term, uncomplicated | Yes | 4 days | 9 months | Excellent, none | III | Glabella, nose, left cheek and temporal region | Pink-red<br>Flat<br>Well-demarcated irregular borders | None | None | Complete involution |
| 2 | M | Caucasian | At term, uncomplicated | Yes | 3 days | 12 months | Excellent, none | II | Right cheek | Dark purplish<br>Flat<br>Well-defined borders | None | None | Improved |
| 3 | M | Caucasian | At term, uncomplicated | Yes | 5 days | 6 months | Excellent, none | I | Right upper lip, cheek and frontal region | Bright red<br>Flat<br>Geographic well-defined borders | None | None | Improved |
| 4 | F | Caucasian | At term, uncomplicated | Yes | 1 day | 18 months | Excellent, none | II | Right cheek, periocular and frontotemporal regions | Pink<br>Flat<br>Nuanced borders | None | None | Complete involution |
| 5 | M | African American | At term, uncomplicated | Yes | 2 days | 25 days | Excellent, none | IV | Left latero-cervical, upper chest and shoulder regions | Bright red<br>Flat<br>Telangiectatic<br>Well-defined borders | None | None | Improved |
| 6 | M | Indo-American | At term, uncomplicated | Yes | 3 days | 4 years | Excellent, none | IV | Left half-face and right cheek | Dark red-purplish<br>Flat<br>Well-defined borders | None | None | Improved |
| 7 | F | Caucasian | At term, uncomplicated | Yes | 6 days | 14 months | Excellent, none | I | Left periocular, cheek and frontotempo-roparietal regions | Dark red-purplish<br>Flat<br>Geographic well-defined borders | None | None | Complete involution |

**Table 3** (continued)

| Patient no | Sex | Etnicity | Gestation and birth | Present at birth | Age at diagnosis | Age at last evaluation | Health state, copatologies | Skin type (Fitzpatrick classification) | Site | Clinical presentation | Investigations | Treatments | Clinical course |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | M | Caucasian | At term, uncomplicated | Yes | 2 days | 2 months | Excellent, none | II | Right cheek, eyelid and fronto-temporal regions | Pale pink Flat Geographic nuanced borders | None | None | Complete involution |
| 9 | F | Caucasian | At term, uncomplicated | Yes | 1 day | 13 months | Excellent, none | II | Right half-face | Reddish Flat Nuanced borders | None | None | Improved |
| 10 | M | Asian American | At term, uncomplicated | Yes | 3 days | 1 month | Excellent, none | III | Right upper lip, cheek, medial canthal regions and median forehead | Pale purplish Flat Nuanced borders | None | None | Improved |


**Fig. 1** Patient 1 at age of 4 days (**a**), 7 days (**b** and **d**), 5 months (**c**), and 9 months (**e**). The complete regression of the PWS is evident (**e**)


**Fig. 2** Red-purplish flat macula involving the right cheek of patient 2 at the age of 3 days (**a** and **c**), 7 months (**b**), and 1 year (**d**)

## Patient 7

Patient 7 was a light-skinned Caucasian girl born with a macular vascular lesion in the left periocular region, forehead, and cheek. The left parietal and temporal scalp were also widely involved. The patch was flat, deep purplish-red, and partially blanchable. The child was in excellent health, with no visual or neurological deficits. The lesion

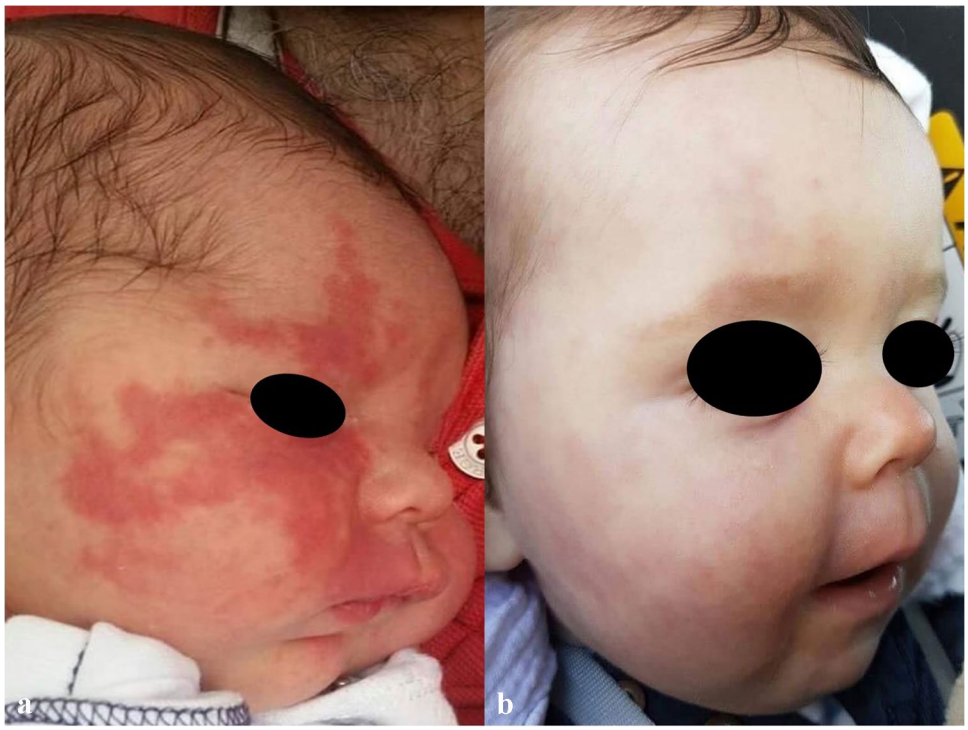


**Fig. 3** Bright red geographic port-wine stain on right front, cheek, periorbital, and upper lip of patient 4 at the age of 5 days (**a**) and 6 months (**b**)

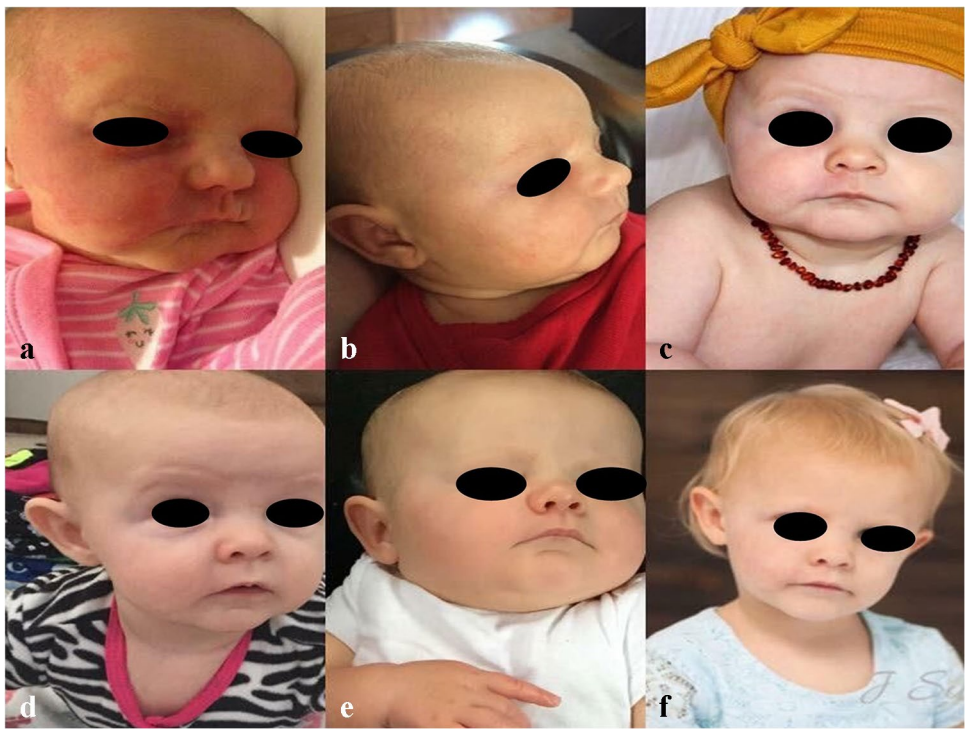


**Fig. 4** Patient 4 at the age of 1 day (**a**), 1 month (**b**), 3 months (**c**), 5 months (**d** and **e**), and 18 months (**f**)

was clinically diagnosed as a PWS. The parents preferred to wait before considering any treatment. At the clinical examination at age of 14 months, there was no longer any sign of the vascular stain (Fig. 7).

## Patient 8

Patient 8 was a Caucasian male born from eutocic full-term birth with a flat, pale pink stain with geographic borders over

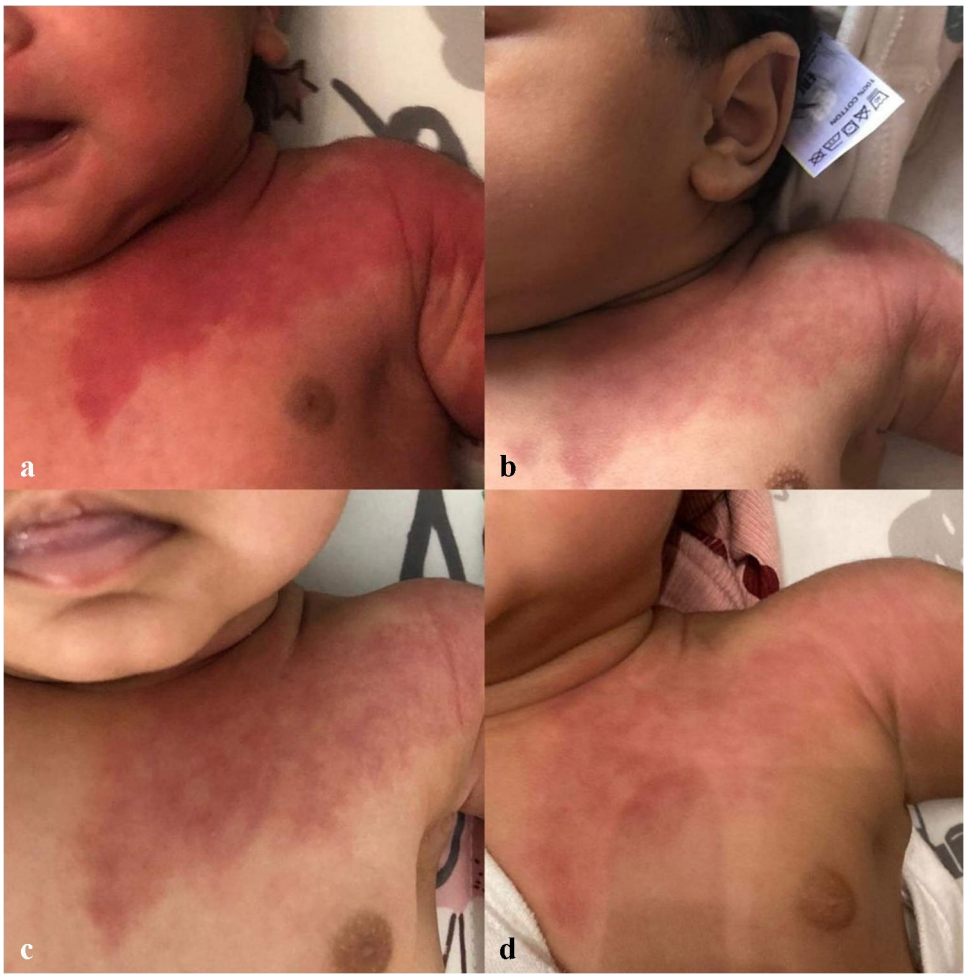


**Fig. 5** Patient 5 at the age of 2 days (**a**), 7 days (**b**), 14 days (**c**), and 25 days (**d**)

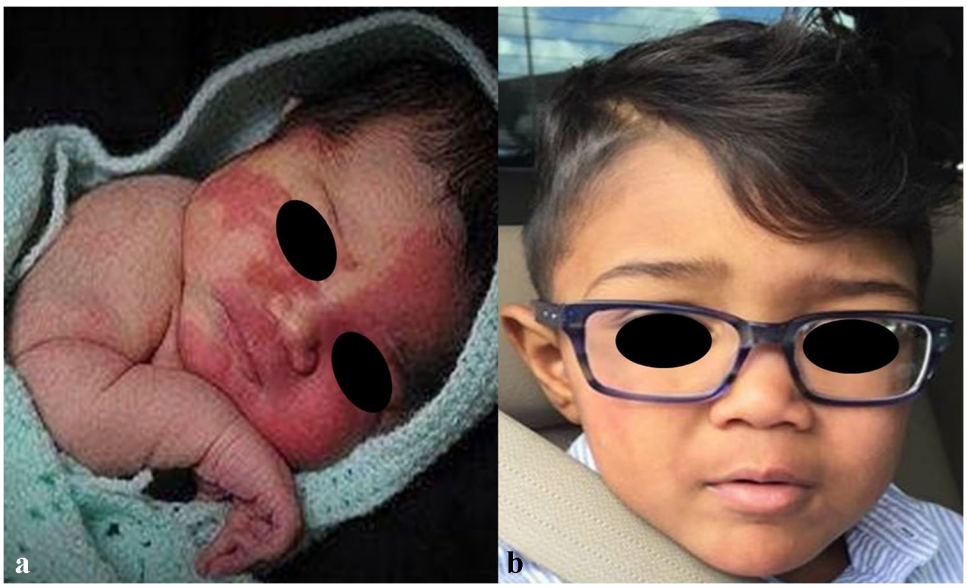


**Fig. 6** Patient 6 at the age of 3 days (**a**) and 4 years (**b**). A minimal remnant of the vascular lesion is visible on the right cheek (**b**)

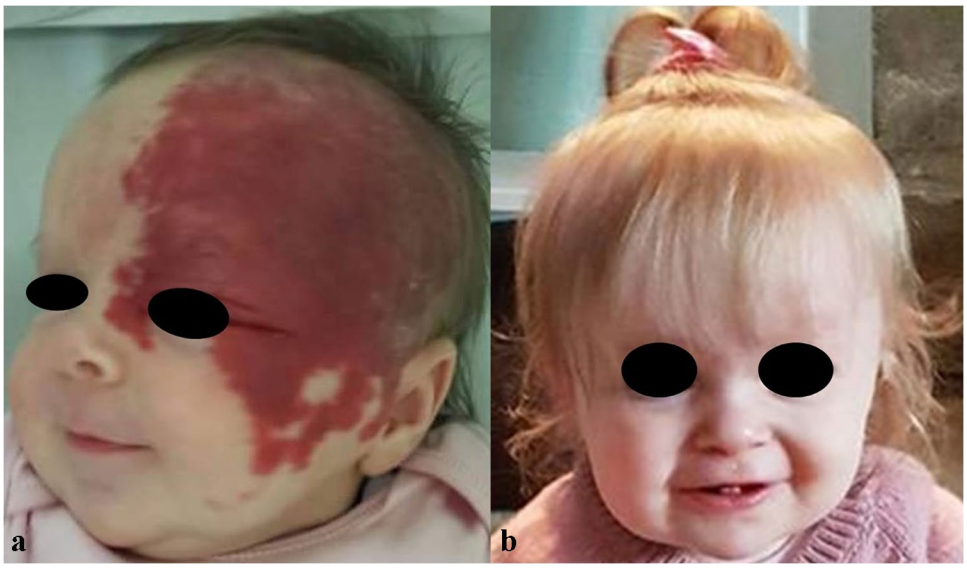


**Fig. 7** Complete resolution of the extensive left V1–V2 port-wine stain of patient 7. Clinical evaluation at the age of 6 days (**a**) and 14 months (**b**)

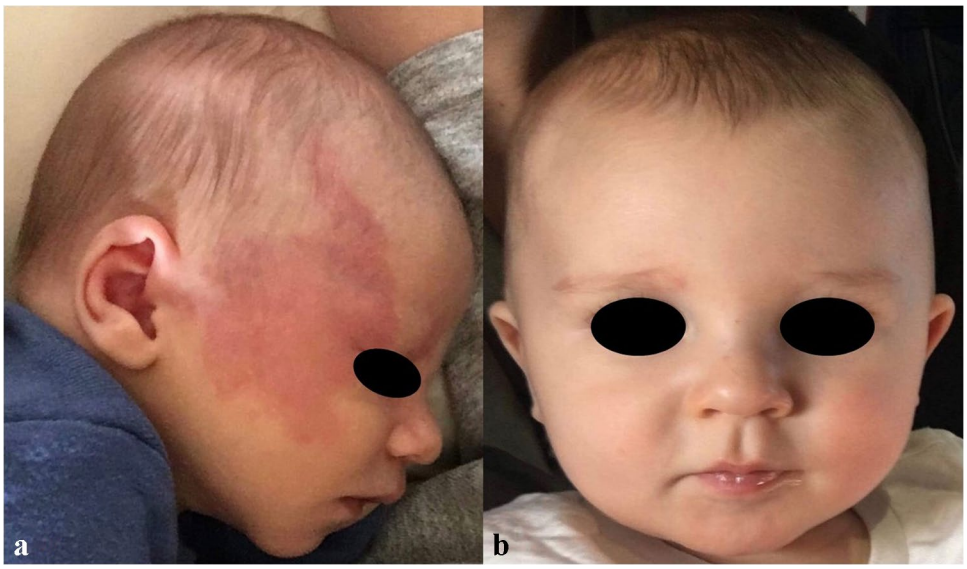


**Fig. 8** Patient 8 at the age of 2 days (**a**) and 2 months (**b**)

the right cheek, eyelid, and frontotemporal region. About 2 months after delivery, the lesion had completely disappeared without any treatment being done (Fig. 8).

## Patient 9

The ninth patient was a Caucasian girl who we were able to evaluate at birth and about 1 year later. She presented a reddish vascular stain involving most of her right face, flat and blanchable, more pronounced on the cheek. In that short period of time up to 13 months of age, the lesion markedly improved in color until it was no longer visible in different areas of its original extension (Fig. 9).

## Patient 10

Patient 10 was an Asian American male born with a flat, purplish vascular birthmark of the right upper lip, cheek, and medial canthal region, as well as nose and median forehead. The lesion was clinically consistent for a PWS. At about 1 month of age, the skin discoloration appeared much improved, especially in the middle third of the affected side of the face (Fig. 10).


**Fig. 9** Patient 9 at the age of 1 day (**a**) and 13 months (**b**)

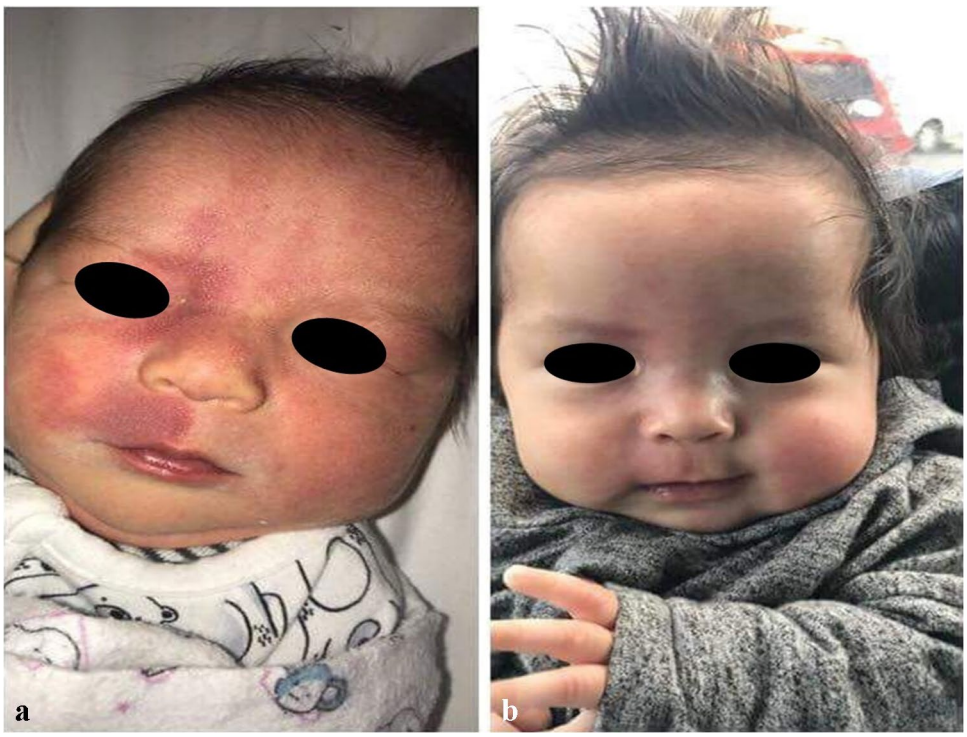


**Fig. 10** Patient 10 at the age of 3 days (**a**) and 1 month (**b**)

## Discussion

PWS is one of the most common vascular birthmarks. As a congenital condition resulting from a sporadic genetic alteration, it is always present at birth. Histologically, it consists of dilated ectatic postcapillary venules in the superficial (papillary and upper reticular) dermis with no vessel proliferation.

An equal gender distribution of PWSs is reported in the international epidemiological data, with a higher incidence in whites [7, 10, 43]. In our cases, there were more males ($n=7$; 70.00%) than females ($n=3$; 30.00%) with a prevalence of Caucasian ethnicity ($n=6$; 60.00%) compared to Asian ($n=2$; 20.00%), African ($n=1$; 10.00%), and Indian ($n=1$; 10.00%). Therefore, a light skin type (Fitzpatrick skin-type I or II) was the most common in our patients ($n=6$; 60.00%).

The diagnosis of PWS is habitually clinical due to the easily detectable features of the lesion.

Capillary malformation typically presents as a solid macula or patch of varying size and shape, pink or red in color with various possible shades up to purple. At an early stage, the stain is quite chromatically homogeneous and flat, with well-defined geographic borders that separate it from the surrounding normal skin. Characteristically, PWS does not fade when pressure is applied to it but partial blanching is possible, and are usually firm [44]. The lesions can be single or multiple and localized or widespread. They are not warm [45] and painful to palpation and usually do not bleed spontaneously, although they are more prone to do so if traumatized or scratched. Facial PWSs generally show a segmental distribution conforming to the trigeminal nerve, with a predilection for the middle third of the face and so are often lateralized [43, 45, 46].

The common vascular lesions that can mimic a port-wine stain and that need to be distinguished in the differential diagnosis are mainly the hemangioma and the nevus simplex (Table 4).

According to the ISSVA classification system, hemangiomas are divided into infantile (IH) and congenital (CH) types. Infantile hemangioma is a benign vascular neoplasm resulting from endothelial cells proliferation. Affecting approximately 4–12% of neonates, it represents the most common tumor of infancy and 70% of all hemangiomas. It almost always appears within the first 6 weeks of life, and usually between 2 and 5 weeks, with a variable aspect from erythematous plaques with a lobulated surface (superficial IH) to soft dermal or subcutaneous blue-purple nodules (deep IH) depending on the lesion growth depth. IH follows a triphasic model of evolution. After a first proliferative phase that culminates in a maximum size at the age of 3–5 months, IH peculiarly exhibit a plateau stage followed by an involutionary trend beginning within the first year of life and ordinarily ending with resolution of the lesion by the age of nine. During this phase, the lesion shows a change in color which becomes grayish-purple extending centrifugally from the center to the periphery. Although the vascular stain involutes in most cases, fibrofatty residuum may sometimes persist [17, 22, 28, 36]. Since the vascular stains were already present in all 10 patients we observed at the time of birth, in addition to the different clinical and developmental characteristics, we excluded the infantile form of hemangioma as a possible diagnostic hypothesis.

On the other hand, congenital hemangioma is less common representing 30% of all hemangiomas. As well as the infantile variety, CH is a vascular tumor but, as it develops its proliferative phase during intrauterine life, it is characteristically present at birth as a mature lesion. It can be classified into three subtypes based on the natural history. Rapidly involuting congenital hemangioma (RICH) is fully grown at birth and usually involutes within 12–18 months of age, sometimes leaving an excess of atrophic skin as a result. RICHs clinically manifest as raised plaques or properly exophytic masses, oval-shaped and bluish-gray-colored, sometimes surrounded by a pale halo. Telangiectasia may be present on the surface of the lesion and a central depression, possibly occupied by ulceration or scar, is often observed.

Likewise RICH, non-involuting congenital hemangioma (NICH) typically present as solitary lesion frequently involving the head and neck or the extremities but differs from it due to its tendency to persist after birth, growing proportionally with the affected child. On physical examination, it usually appears as a pink to purple protruding lesion, commonly superimposed by a prominent telangiectasia and often showing a peripheral blanching and/or a blue pallor centrally.

Both RICH and NICH are generally warmer to touch compared with the perilesional normal skin [36, 47, 48].

Rapidly involuting congenital hemangioma, as it is present at birth and tends to improve rapidly during the first few months thereafter, could sometimes generate diagnostic doubts in those cases in which it occurs in the form of thin plaque. Even in this case, however, the different modality of clinical presentation allowed us to exclude this vascular tumor from differential diagnosis certainty. All the vascular lesions documented in the present case series, in fact, were flat, different in color from the classic congenital hemangioma and lacking the typical peripheral halo.

Another vascular birthmark that can be confused with the typical port-wine stain, as noted above, is the nevus simplex. Nevus simplex, also known as salmon patch, is certainly the most commonly observed vascular stain at birth, with a prevalence ranging from 40–50% to nearly 82% of newborns. As the PWS, it consists of dilated superficial blood vessels which are mainly capillaries in the papillary dermis, presumably representing in this case the persistence of fetal

**Table 4** Clinical features of port-wine stains and similar facial vascular lesions

| Vascular malformation | Synonyms | Presence at birth | Location and distribution* | Color | Borders | Type of lesion and thickness | Other clinical features | Blanching with pressure | Overlying skin temperature (compared to the surrounding skin) | Clinical course |
|---|---|---|---|---|---|---|---|---|---|---|
| Port-wine stain | Nevus flammeus | Yes | Lateralized locations (unilateral or bilateral), respecting the midline (not solely midline position without lateral involvement)<br>Dermatomal distribution, mainly involving the V2 trigeminal area | Pink to dark red–purple | Well-defined and geographic | Solid macula or patch, initially flat, firm | | Partially | No difference | Persistent and progressive, with thickening and darkening<br>Possible lightening during the first few months of life<br>Possible developing of nodularity and hypertrophy of the soft and bony tissues |
| Nevus Simplex | Salmon patch<br>Angel's kiss<br>Stork-bite<br>Nevus roseus | Yes | Midline, with no dermatomal distribution | Pink to bright red | Indistinct | Macula, Flat | More evident during Valsalva maneuver<br>Often V-shaped in the glabellar and forehead region | Partially | No difference | Fading (except for those on the nape or occipital region) |
| Infantile hemangioma (IH) | | No<br>Possible presence of "nascent" or "premonitory" lesion" (vasoconstricted or bruised area) | Indifferent | Bright red/erythematous (superficial IH)<br>Blue-purple (deep IH)<br>Grayish (involuting IH) | Well-defined | Placque or nodule, raised, compressible | Possible ulceration<br>Possible atrophic scar, hypopigmentation and/or fibrofatty tissue (involuted IH) | Yes | Warmer | Triphasic evolution (proliferation—plateau—involution) |
| RICH | | Yes, fully grown | Indifferent | Grayish-blue | Well-defined | Raised placque or exophytic mass, compressible | Prominent teleangiectasia on the surface<br>Possible central depression | Yes | Warmer | Rapid involution |
| NICH | | Yes, mature | Indifferent | Pink-purple | Well-defined | Raised placque or exophytic mass, compressible | Peripheral pale blanching or blue halo | Yes | Warmer | Persistent |

*Referred to head and neck vascular lesions

circulating pattern of the skin [49]. These vascular lesions tend to be located at midline positions, such as the forehead and the glabellar region ("angel's kiss"), the nape of the neck and the occipital area ("stork-bite"), the nose, the philtrum, and the lumbosacral region. In addition to their characteristic topographical location, the pink or brighter red color and the indistinct margins of these macules are also helpful clues in clinical identification. Furthermore, these stains are partially blanchable with pressure and may become more evident during physical exertion, crying, or in relation to ambient temperature changes. In contrast to PWSs, facial nevus simplex regularly fades significantly or even disappears entirely over time, except for nuchal forms which usually persist, and is rarely detected after the age of 6 [9, 22, 46, 49].

Considering the pale pink color and the more nuanced borders, patient 8 presented a lesion similar to the salmon patch but incompatible for the lateral location. Referring to the site, patient 10 showed a fairly median lesion but frankly purplish in color.

Based on the clinical features observed in the cases here presented, we considered the lesions found to be typical PWSs with a certain diagnostic confidence.

No further investigations, such as doppler ultrasound (DUS) or magnetic resonance imaging (MRI) were performed during the follow-up of our patients.

Ultrasound and doppler sonography are exceptional tools in documenting vascular chambers and phleboliths in venous malformations as well as the typical high-flow of AVMs. However, they do not provide additional information to the clinical assessment of PWSs and are therefore not routinely performed. Rather than in diagnosis, these imaging techniques may be more useful in fast and non-invasively quantifying the response of the lesion to laser treatment [50].

MRI should be carried out whenever the diagnosis is uncertain and if a syndromic form of PWS, such as Sturge-Weber syndrome, is suspected.

Sturge-Weber syndrome is a neurocutaneous disorder characterized by the association of a facial PWS with ipsilateral leptomeningeal and ocular choroidal vascular malformations (capillary-venous malformations) [9]. Several authors demonstrated a direct correlation between the anatomic distribution and extent of facial PWSs with the risk of SWS developing. The involvement of the ophthalmic trigeminal area is strongly predictive for underlying central nervous and/or ocular impairment, mainly in extensive and bilateral PWSs or those affecting the upper eyelid [46, 51, 52]. Waelchili and colleagues recognized forehead lesions lengthening from the midline to the temporal region and including the upper eyelid as the most predictive of SWS association [53]. Glaucoma is the most frequent ophthalmological complication in SWS patients and generally the onset is early in the first year of life. However, as late manifestation remains possible, specialist evaluations must continue regularly over time. Seizures, headache, mental retardation, behavioral, and emotional problems, as well as hemiparesis are common neurological symptoms in affected individuals [51].

Among our cases, five children had PWSs with risky topographical distribution for Sturge-Weber Syndrome. Especially in patient 7, the lesion fully satisfied Waechici's criteria, involving entirely the forehead and upper eyelid stretching to the ipsilateral temporo-parietal region and maxillary dermatome. Interestingly, this was also a case of complete disappearance of the port-wine stain we observed.

The correct timing for MRI neurologic screening in asymptomatic patients with suspected syndromic facial PWS is still debated [46, 51]. Sudarsanam et al. argue that in addition to ophthalmological follow-up, obviously indicated in all cases of facial PWS with V1 distribution, MRI should be performed when the lesion affects the eyelid region or reaches the maxillary/mandibular areas [51]. Rozas-Munoz and colleagues consider 6 months to 2 years of age as a reasonable interval for performing MRI [46]. Considering that the MRI is insensitive in newborns and all the children at risk for SWS we evaluated had a normal neurological and ophthalmological developing on clinical examination, this diagnostic investigation was not performed at the time of this study but will be considered in the near future.

It is well established that PWSs do not regress on their own, but rather persist throughout life [3, 23]. Progressive thickening and darkening over time are the typical natural history of these vascular malformations [12].

In 1980, Barsky et al. histologically demonstrated the direct correlation between age and the increased percentage of dermis occupied by malformed vessels, justifying the raising of the initially flat lesions over time [54].

Across time, PWSs may develop nodularity leading to soft and bony tissues hypertrophy in adulthood [12, 13, 27], with subsequent esthetic and functional complications.

It should be noted that some PWS lightening may occur in the first weeks or months of life, probably due to a temporary drop in the circulating hemoglobin concentration in the blood [22]. This physiological phenomenon could have partially contributed to the improvement we observed in our cases. However, the significant degree of blanching we reported is unlikely to be entirely explained by the anemia of infancy, at least in the four cases of complete resolution of the PWSs.

To the best of our knowledge, those we reported in the present study are the first documented cases of significant to complete spontaneous resolution of port-wine stains in English literature.

Searching for the keywords "capillary malformation" or "port-wine stain" and "spontaneous regression" or "spontaneous improvement" on PubMed, Scopus, and Google Scholar, only two papers were found.

Wilson et al. described a case of a 3-year-old Caucasian child with an extensive red–purple macula involving his right posterior parietal and temporal regions, the right cheek and the ipsilateral mandibular area, neck, chest, and the right arm [55]. The vascular stain was present at birth and clinically diagnosed to be a PWS. After treatment of a total area of about 1.1% (7.76 $cm^2$) of the entire lesion (650 $cm^2$) with the flashlamp-pumped pulsed dye laser performed within the age of 20 months, a significant vanishing extended to the whole stain was noted. The authors argue that the laser therapy they performed, due to the narrowness of the treated areas, was unlikely to have played a role in the phenomenon they observed. In our case series, no treatment has ever been carried out so this possible confounding factor can certainly be excluded.

Barlow and colleagues described a singular case of spontaneous regression of small arteriovenous malformations of the limb in a 19-year-old with Parkes-Weber Syndrome [56]. This is a clinical condition defined as the association of capillary, venous, and lymphatic malformations with an AVM. Although it was documented at the first MRA performed, no evidence of abnormal arteriovenous connection was then detected at angiography repeated 2 months later. Thrombosis secondary to contrast and traumas are hypothesized as possible causes of lesions regression.

An objective of the present study was to identify a possible correlation between the spontaneous improvement of PWSs and the individual clinical-epidemiological variables of the patients included in this case series. Male sex (70.00%), Caucasian ethnicity (60.00%), skin-type II (40.00%), right side (60.00%), V1–V2 anatomical distribution (80.00%), and pink to red color (50.00%) were the most frequent parameters registered. Nevertheless, we do not consider a predictive pattern of spontaneous PWS improvement recognizable.

The flashlamp-pulsed dye laser at 595-nm wavelength currently remains the mainstay and first-line therapy for esthetically sensitive PWSs [9, 13, 23]. Several experts have demonstrated that initiating early treatment may result in better outcomes and greater patient satisfaction [15, 23, 35].

The smaller size and thickness of the vascular stain, together with the reduced skin content of melanin and collagen justify the greater effectiveness of laser therapy in infancy [35].

Furthermore, early laser treatment is known to reduce the risk of later development of nodularity and hypertrophy, which clearly complicate therapy by making the lesion resistant [23, 26]. Preventing the child from developing a traumatic memory of the procedure is another advantage to consider.

Since there are no predictive factors on port-wine stains evolution, and their spontaneous improvement remains exceptional, even if possible, we think that laser treatment should not be delayed.

Clearly, a first limitation of this case series is the small number of patients which does not allow for meaningful statistical inferences. This is due to the rarity of the phenomenon presented.

Another major limitation is the lack of specimens to histologically document quantitative and/or structural changes of dermal abnormal vessels.

## Conclusions

Port-wine stains do not normally improve over time. Spontaneous regression is quite exceptional. We consider this photographic documentation an interesting contribution to the knowledge of capillary malformations. This could also be useful for discussing the parents' expectations about the evolution of the lesions.

However, the difficult identification of predictive factors for a spontaneous improvement of port-wine stains confirms the need for laser treatment as early as possible.

In addition, with a modest estimate of 0.03% of the population, worldwide, affected by a PWS, and according to theworldcounts.com, 140 million babies are born each year, resulting in a little over potentially, 4,000,000 babies born each with a PWS, this number is an extremely low occurrence to warrant any statistically significant inferences. At the very least, it is an interesting phenomenon.

**Author contribution** Conceptualization: A.P.; writing—original draft: A.P.; visualization: A.P., S.N., M.D.B., A.A.; resources: L.R-S.; data Curation: L.R-S.; writing—review and editing: S.N.; validation: A.A., L.C., G.C.; investigation: R.F., I.M.; supervision: L.C., G.C.

## Declarations

**Ethics approval** All procedures performed involving the human participant were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of this study, it was granted an exemption by the Institutional Review Board of the University Hospital of Modena, Italy.

**Consent to publish** The authors affirm that parents or legal guardians consented to publication of this report and clinical photographs.

**Conflict of interest** Arrigo Pellacani, Linda Rozell-Shannon, Sara Negrello, Mattia Di Bartolomeo, Alexandre Anesi, Raimondo Feminò, Ilaria Mariotti, Luigi Chiarini, and Giacomo Colletti declare no conflict of interest.

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