Characterization of vascular stains associated with high flow

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Background: High-flow vascular stains (HFVS) are lesions that have the appearance of capillary malformations/port wine stains but are associated with increased arterial flow.

Objective: To identify features of HFVS that differentiate them from typical "slow-flow" port wine stains.

Methods: Retrospective multicenter cohort study of HFVS evaluated across 7 centers was conducted. HFVS were characterized by clinical features (warmth, thrill, rapid capillary refill), radiologic findings (fast flow), or mutations associated with capillary malformation-arteriovenous malformation syndrome. Investigators reviewed photographs.

Results: The study reviewed 70 patients with HFVS (47 multifocal and 23 solitary). Most were flat (77%), warm to the touch (60%), and red or pink-red in color (35%), with heterogeneous color saturation (73%) and well-defined borders (71%). Regional soft tissue swelling/overgrowth was common (47%). Head and neck location was most common (38%). Among 34 HFVS with photographic review over time, all demonstrated changes in appearance.

Limitations: Retrospective design, recall bias, lack of standardized time points or visual analog scale, and image variability.

Conclusion: Heterogeneity of stain color saturation, warmth to touch, peripheral pallor, and overgrowth/soft tissue swelling help distinguish HFVS from port wine stains. Darkening of color and increased border demarcation may develop over time. These findings raise suspicion for HFVS and provide an indication to assess for extracutaneous involvement. (J Am Acad Dermatol 2021;84:654-60.)

Key words: arteriovenous malformation; AVM; capillary malformation; CM; CM-AVM; dermatology; pediatric dermatology; port-wine stain; PWS; vascular anomaly; vascular birthmark; vascular malformation; vascular stain.

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Capillary malformation (CM) is an umbrella term used to describe vascular malformations composed of the smallest vessels. The term "vascular stain" is also often used synonymously with CM. That CMs are heterogeneous has been recognized. Port-wine stains (PWS), termed "typical" PWS or "slow-flow" PWS, are a relatively common form of CM, occurring in approximately 0.5% of the population.[1] They are typically uniform, pink, red, or purple macules and patches distributed anywhere on the body.[2]

High-flow vascular stains (HFVS) can be defined as vascular stains that have the appearance of CMs but are associated with increased arterial flow. These stains are less common than PWS and differ in clinically important ways, including a higher risk of associated morbidities, such as local progression, ulceration, and risk of intracranial or other internal organ disease. Upon initial presentation, distinguishing HFVS from typical PWS may be difficult.

CAPSULE SUMMARY

- High-flow vascular stains mimic "slow-flow" port-wine stains, but their prognosis and associated anomalies differ.
- Increased awareness of clinical characteristics, including stain color heterogeneity, warmth, soft tissue swelling, sharp demarcation, and color darkening over time may trigger suspicion of a diagnosis of high-flow vascular stains mimic and direct clinical management.

The concepts that vascular stains differ and that their clinical features predict underlying associations are not new.[3] Investigators have attempted to differentiate CMs, including PWS, from the stains of CM-arteriovenous malformation (AVM) syndrome on the basis of clinical features.[4] Identification of the genetic causes of disorders associated with vascular stains has also allowed for a more nuanced appreciation of morphologic differences. Vascular stains with sharply defined "geographic" borders are often associated with *PIK3CA* mutations and blotchy faint stains with *GNA11* mutations.[5,6]

Importantly, HFVS may represent early-stage or quiescent AVMs, which confer a higher risk of regional complications, including pain, ulceration, overgrowth, and venous varicosities due to arteriovenous shunting.[2,7] In addition, HFVS associated with CM-AVM syndrome may signify the presence of central nervous system AVMs, particularly in the setting of a positive family history or in the presence of multifocal stains, a feature that may take months or years to develop. The identification of the genetic etiology of CM-AVM syndrome—mutations in *RASA1* and *EPHB4*—has facilitated their identification and enabled more precise diagnosis and targeted screening for extracutaneous associations. In this study we focus on further defining the clinical characteristics of HFVS, both in patients with proven CM-AVMs and those with sporadic HFVS.

MATERIALS AND METHODS

A retrospective multicenter cohort study of HFVS evaluated at pediatric dermatology and vascular anomalies centers between January 1, 2007, and July 31, 2017, was performed at Columbia University, University of California, San Francisco, Hospital de la Santa Creu i Sant Pau, Centre Hospitalier Universitaire Sainte-Justine, Hospital for Sick Children, Mayo Clinic, and Sydney Children's Hospital. Confirmatory findings of HFVS included the presence of warmth, a thrill, or rapid capillary refill on examination, radiologic features of high flow on ultrasound (US) or magnetic resonance imaging (MRI), or a documented mutation in genes causing CM-AVM syndrome. Vascular stains also met 1 of 2 possible size criteria: solitary lesions $\geq$2 cm in the widest diameter or multifocal lesions, including those $<$2 cm in diameter associated with CM-AVM. Data, including patient demographics, diagnostic evaluation, and clinical characteristics of HFVS, were entered into a Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN) database and analyzed. Clinical photographs were reviewed by principal investigators at Columbia University, University of California, San Francisco, and the Hospital de la Santa Creu i Sant Pau through the use of Health Insurance Portability and Accountability Act-compliant videoconferencing software (SecureVideo, Alameda, CA). Conferences focused on defining clinical features of HFVS at different time points. In the case of multifocal stains, features of the largest, most prominent stain were characterized.

RESULTS

A total of 70 HFVS were reviewed. Radiologic imaging, including US with Doppler and MRI/magnetic resonance angiography (MRA), supported the diagnosis in 54 patients (77%). Ten patients (14%) were diagnosed based on genetic testing. Five patients (7%) were diagnosed on clinical examination findings alone (warmth to palpation, rapid capillary refill, or both); 1 patient (1%) was

Abbreviations used:

AVM: arteriovenous malformation
CM: capillary malformation
HFVS: high-flow vascular stain
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
PDL: pulsed-dye laser
PWS: port-wine stain
US: ultrasound

diagnosed clinically in the setting of a positive family history. Forty-seven HFVS were multifocal (67%), and 23 were solitary (33%). Of the 70 HFVS, 58 (83%) measured >2 cm in the widest diameter. Among solitary lesions, 35% were estimated to measure between 10 and 20 cm in the widest diameter, and 22% ranged between 5 and 10 cm.

Eleven patients were previously reported in the medical literature.[8-10] Patient characteristics are summarized in Table I. All but 1 patient was younger than 18 years at the first evaluation by a dermatologist, with 81% noted within the first month of life, and 66% were first evaluated before age 5 years. Typical PWS was the preliminary diagnosis in 33% of patients, and HFVS was initially suspected in 47%. Progression of the lesion, as defined by a change in associated symptoms, behavior, or appearance (including but not limited to ulceration, pain, functional impairment and development of a thrill), was noted in 29% of patients before age 5 years.

The clinical features of the HFVS at initial presentation are summarized in Table II. Most were flat (77%), warm to the touch (60%), and red or pink-red in color (35%). Heterogeneity of stain color saturation, as defined by the investigators as variation in the intensity of the color within the stain, was present in 73% of stains. Most stains displayed sharp borders (71%), 49% had a pale rim, and 29% had "archipelago-like" borders with craggy inlets and outlets (Fig 1). A smaller subset demonstrated borders that evolved from blotchy to sharply demarcated or archipelago-like in quality. Six (9%) were characterized by macules or papules residing within or around the primary stain (Fig 2). Warmth or a thrill to palpation was reported more commonly in solitary stains compared with multifocal stains (78% and 52% compared with 51% and 9%, respectively). Regional overgrowth, soft tissue swelling, or both, was seen more frequently in solitary stains (65% vs 38%; Fig 3). Heterogeneity of stain color saturation was more common in solitary than in multifocal stains, although the difference was less pronounced (83% vs 68%). Rapid capillary refill was observed in 25 of the 30 total cases (83%) where this characteristic was evaluated.

Table I. Patient characteristics and high-flow vascular stain distribution

Variable	Patients (N = 70), No.	Percentage
Sex		
Female	43	61
Male	27	39
Race		
White	58	83
Asian	2	3
Native Hawaiian	2	3
Black	1	1
Race unknown/otherwise specified	7	10
Full-term	33	47
Preterm	6	9
CM-AVM syndrome	41	59
Parkes Weber syndrome*	9	13
Central nervous system abnormalities	3	4
Cardiovascular system abnormalities	10	14
Family history of vascular anomalies	31	44
Positive *RASA1* (all multifocal)	20	29
Positive *EPHB4* (all multifocal)	7	10
Predominance on		
Head and neck†	28	40
Cheek	17	24
Neck	10	14
Ear	7	10
Lower extremities	24	34
Trunk	17	24
Upper extremities	15	21
Perineum/buttock	7	10

CM-AVM, Capillary malformation-arteriovenous malformation; *No.*, number.
*Rare syndrome involving capillary malformations and arteriovenous fistulas associated with limb hypertrophy and high-output heart failure.
†Several stains extended beyond a single anatomic region.

Follow-up photographs and clinical information were available for 34 patients (14 solitary and 20 multifocal). All demonstrated changes in appearance over time, the most common being a change in color (62%), increased border demarcation (47%), expansion in size (26%), increased pale halo prominence (24%), and increased venous prominence (21%). The acquisition of a brown hue was the most common color change noted over time (57%). Symptoms developed in 13 patients (19%)

Table II. Characteristics of high-flow vascular stain at first presentation

Variable	Patients (N = 70), No.	Percentage
Size		
≥2 cm	58	83
<2 cm	12	17
Macular	54	77
Papular	13	19
Pale rim	34	49
Heterogeneity of stain color saturation	51	73
Venous prominence	25	36
Overgrowth and/or soft tissue swelling	33	47
Warmth	42	60
Rapid capillary refill	25	36
Thrill	16	23
Sharp or well-demarcated borders	50	71
Archipelago or coast of Maine borders	20	29
Smudgy or poorly demarcated borders	22	31

No., Number.

during their course: 7% experienced bleeding, 6% disfigurement, 4% pain, 4% functional impairment, 4% skin breakdown, 3% infection, and 1% cardiac failure or decompensation.

Results from genetic testing of blood samples were available for 57% of patients. Of the patients with genetic testing, 50% had *RASA1* mutations, and 18% had *EPHB4* mutations (all multifocal lesions). Excision or embolization was performed in 8 patients (11%), a "watchful waiting" approach to management was assumed in 56%, and 20% were treated with pulsed-dye laser (PDL).

DISCUSSION

Vascular stains, often referred to as CMs, represent a heterogenous group of vascular malformations. This case series defines the clinical characteristics of HFVS, a group of vascular stains that are often erroneously diagnosed as typical PWS. This is an important distinction, because the management of these entities varies in important ways: whereas typical PWS may lighten with PDL therapy, HFVS are typically less responsive to laser treatment, and some authors believe that there is a risk of progression of underlying AVMs in the setting of trauma.[11-13] A diagnosis of HFVS also necessitates closer follow-up for risk of progression compared with a typical PWS.

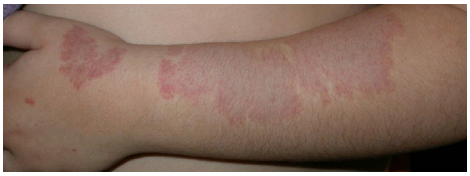

Fig 1. High-flow vascular stain: pale purple patch with heterogeneity of stain saturation, archipelago-like borders, and a pale peripheral rim.

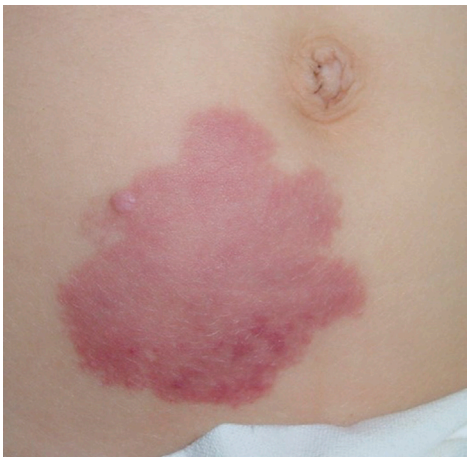

Fig 2. High-flow vascular stain: a pink patch shows heterogeneous color saturation and a thin papular component.

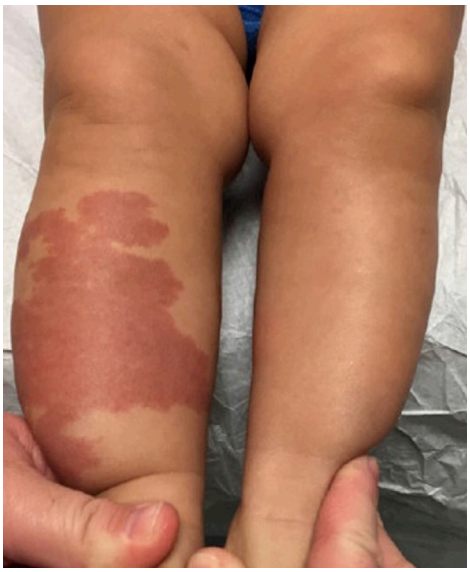

Fig 3. High-flow vascular stain: well-defined patch on the lower extremities with archipelago-like borders and regional soft tissue swelling.

Advances in the understanding of the genetic causes of vascular anomalies have allowed for more precise genotype-phenotype correlations. Next-generation sequencing has permitted the detection

of mutations within lesional tissue at relatively low variant allele frequency, making it possible to further correlate the phenotypes of vascular stains with specific genotypes. Most typical PWS are now known to be caused by somatic activating mutations in *GNAQ*, *GNA11*, or occasionally *PIK3CA*.[2,5,7] Moreover, a spectrum of somatic mutations, including *PIK3CA*, *GNAQ* and *GNA11*, *MAP2K* and *KRAS*, are found in patients with overgrowth syndromes, many of whom have associated vascular stains.[5,14,15] Somatic activating mutations in *MAP2K1* have been associated with isolated extracranial AVMs, many of which had overlying vascular stains and germline mutations in *RASA1* and *EPHB4*.[16]

Precision genomics will play an increasingly important role in characterizing vascular stains, but testing is not widely available. Therefore, the ability to detect phenotypic differences between vascular stain types becomes important for guiding clinical care, particularly in evaluating potential comorbidities and predicting outcomes.

In our cohort, the diagnosis of a HFVS was suspected in nearly half of patients upon first presentation to dermatologists with expertise in vascular anomalies. Features that are clues to HFVS are summarized in Table II and include heterogeneity of stain color saturation, pale rims, the presence of sharp borders—some with archipelago-like edges—and change in stain appearance over time. Associated features include warmth to touch, overgrowth or localized soft tissue swelling, and venous prominence. Heterogeneity of stain color saturation and the presence of pale rims may reflect a steal phenomenon, relative differences in capillary refill, or both. These features can be subtle in younger patients and missed at first evaluation. Some features, including the presence of a peripheral halo, venous prominence, or both, are sometimes better appreciated in photographs than during the clinical examination, further emphasizing the importance of keeping a photographic record over time.

Consistent with previous reports, the head and neck were the most commonly involved sites. Localization of lesions to the cheek and ear supports previous observations by Enjolras and others that these are sites for which AVMs have a strong predilection.[7] The correlation between these sites and "choke" regions linking angiosomes (discrete zones of skin, subcutaneous tissue, and bone supplied by a single artery) may offer insight into this pattern.[17,18] That these and other cephalic structures are disproportionately enlarged during the phase of embryogenesis when malformations are thought to occur may also be relevant.[19]

Whether all HFVS are early stage AVMs is unclear. This remains an area of controversy, both for the stains of CM-AVM and for those with solitary stains without CM-AVM.[20] Among the HFVS in the cohort, 61 (86%) were warm, pulsatile, or both, in keeping with Schobinger stage I or II AVMs.[19] Pain, bleeding, or skin breakdown was demonstrated in 13%, meriting a stage III classification, and 1 patient (1%) with congestive heart failure met criteria for stage IV.

Among the patients with photographs over time, changes in appearance were demonstrated in all HFVS, most commonly in the color (increasingly brown) and stain color saturation. Other changes commonly seen included the development or increased prominence of peripheral pallor believed to represent a steal phenomenon associated with local ischemia, increased border demarcation, and increased nodularity. Pyogenic granuloma lesions have also been reported to arise within AVMs.[21,22] The histopathologic features of the papules observed in our cohort were unknown.

The dermoscopic pattern of *RASA1*-associated HFVS has been described and features a biphasic pattern of branched linear vessels overlying a brown reticular pigmentary network that disappears with compression,[23] resembling that of the café au lait macules observed in neurofibromatosis type I (another *RASA1*-associated disorder). Although dermoscopic data for our cohort were not available, it could be speculated that the increase in brown coloration noted in our patients over time resulted from a darkening of the underlying pigmentary network. Associated venous changes, including venous hypertension and venous stasis, could also contribute to this change.

There are no consensus-derived guidelines for the evaluation of HFVS. Within our cohort, we found that the workup was relatively uniform across institutions: 40 patients (57%) underwent genetic testing of peripheral blood samples (mostly *RASA1*), and 55 patients (79%) underwent some form of imaging (80% MRI/MRA, 75% Doppler US, and 4% computed tomography angiography). Genetic testing supported a diagnosis of HFVS in 68% of patients; however, most of the patients in our cohort were seen before mutations in *MAP2K* and *EPHB4* were reported in the literature as a cause of AVM and CM-AVM, respectively.[15,16] US and MRI/MRA supported a diagnosis of HFVS in 80% of patients. These findings underscore the importance of imaging (US, magnetic resonance, or both) and referral for genetic testing in the evaluation of patients with suspected HFVS.

The findings from this study have important implications for the evaluation and treatment of HFVS compared with typical PWS. Most PWS are diagnosed clinically, with rare indications for US or biopsy. PDL therapy is the intervention of choice. By

contrast, HFVS merit evaluation with Doppler US at a minimum, followed by additional imaging as indicated by the clinical findings. For example, imaging of the central nervous system would be indicated in the setting of multifocal lesions or positive genetic testing for CM-AVM syndromes.

Trauma in the form of biopsy may carry a risk of bleeding or inciting disease progression if the HFVS is indeed an AVM. PDL treatment of known HFVS has been discouraged by some authors for similar reasons and may not be effective; however, a recently published article suggests that an effective response to PDL is possible for some patients.[10,11,13] Early identification of HFVS can help guide appropriate evaluations, limit unnecessary interventions, and provide patients the opportunity to seek the appropriate multidisciplinary care.

Limitations of this study include its retrospective and unblinded design, relatively small sample size, and potential recall bias in identifying cases. Review over time was not possible for all patients nor was information (eg, swelling) uniformly recorded. The photographs used to characterize features of HFVS varied in quality.

CONCLUSIONS

Clinical features common to HFVS, including variation in stain color, heterogeneity of stain color saturation, archipelago-like borders, warmth to touch, overgrowth/soft tissue swelling, and venous prominence, may help physicians distinguish early-stage HFVS from PWS. The evolution in the appearance of these lesions must be emphasized. Regular surveillance over time is likely to reveal additional telltale features of HFVS, including acquisition of a brown hue, increased border demarcation, and resistance to laser therapy. US and MRI/MRA frequently assist in supporting the diagnosis. Genetic testing, which is now available for CM-AVM syndromes, is another tool that can help direct management in those with multifocal stains. Given the degree of nuance involved in making an early diagnosis of HFVS and the tendency for HFVS to develop more characteristic changes over time, clinicians should recommend follow-up visits for patients with vascular stains that show these features and consider imaging if the evolution raises concerns.

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