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Types of phacomatosis pigmentovascularis associated with nevus cesius

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Abstract

Phacomatosis pigmentovascularis (PPV) is a term encompassing a group of disorders characterized by the coexistence of segmental pigmented nevi of melanocytic origin and segmental capillary nevi. Several variants are characterized by a hallmark nevus cesius. Systematic reviews on the topic are lacking. An extensive review and critical reassessment of worldwide literature was carried out. A total of 435, 17, 19, and 17 cases of phacomatosis cesioflammea, phacomatosis cesiomarmorata, phacomatosis cesioflammeomarmorata, and phacomatosis melanocesioflammea, respectively, were identified. Specific clinical manifestations emerged for each variant. Postzygotic mosaic mutations affecting the *GNAQ* or *GNA11* genes have been identified for all these entities. Four cases of nevus cesius associated with nevus anemicus (NA) were also retrieved. Phacomatosis cesioflammea is confirmed to be the most common PPV type by far. Its extracutaneous manifestations mostly consist of Sturge–Weber–Klippel–Trénaunay syndrome–like abnormalities, and ocular melanoma is a rare but relevant occurrence. The clinical associations of phacomatosis cesioflammeomarmorata mostly seem to result from the presence of cutis marmorata telangiectatica congenita. Phacomatosis cesioflammeomarmorata seems to resemble phacomatosis cesioflammea in several respects. A high frequency of NA and the Klippel–Trénaunay phenotype (or leg-length discrepancy) was observed in phacomatosis melanocesioflammea. The existence of "pseudodidymosis cesioanemica" is also corroborated.

Keywords: phacomatosis pigmentovascularis, phacomatosis cesioflammea, *GNA11*, *GNAQ*, nevus anemicus

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Introduction

Phacomatosis pigmentovascularis (PPV) is a term encompassing a group of disorders characterized by the coexistence of a segmental pigmented nevus of melanocytic origin and segmental capillary nevus. Two main classifications have been followed to date, one initiated by Ota et al. in 1947 (1) and updated until 2003 to include five types (2), and one by Happle in 2005 (3) progressively updated until 2020 to include six variants (4–6). The Happle classification is now firmly established as the more appropriate one. Phacomatosis cesioflammea (PCF)—or nevus cesius (NC) associated with nevus flammeus (NF)—is by far the most commonly observed type, with hundreds of cases reported to date. Phacomatosis cesiomarmorata (PCM)—or NC associated with cutis marmorata telangiectatica congenita (CMTC)—amounts to a few dozen published cases as identified in reviews that considered PubMed® only (7, 8).

A similar number of instances of the two PPV types characterized by nevus roseus (NR), associated with either a macular nevus spilus (MNS), (phacomatosis spilorosea, PSR) or a flag-like hypermelanotic nevus (FHN), (phacomatosis melanorosea, PMR) were thoroughly searched for and assessed per recent critical reappraisals of the literature (9, 10). The variants phacomatosis cesioflammeomarmorata (PCFM: the co-occurrence of NC, NF, and CMTC) and phacomatosis melanocesioflammea (PMCF: the co-occurrence of NC, NF, and FHN) were framed last, considering a handful of previously reported instances (5, 6). It was suggested that patients not fitting the definitions above be provisionally placed in the "wastebasket" term of "unclassifiable PPV," of which only a few cases are currently known to still stand as such (9). To the author's knowledge, there is no comprehensive review of NC-associated PPV types.

Methods

An extensive review of worldwide literature up to April 2025 was carried out, using PubMed®, Google Scholar, Global Index Medicus, ResearchGate (researchgate.net), WorldCat® (worldcat.org), CNKI (https://oversea.cnki.net/index/), China/Asia On Demand (https://caod.oriprobe.com/), and J-STAGE (https://www.jstage.jst.go.jp/) as primary tools. The reference lists of every article retrieved were consulted. Google Translate (https://translate.google.com) and Yandex Translate (https://translate.yandex.com/) were used to translate unknown languages.

A case-by-case critical reassessment was carried out. The following inclusion criteria were considered: 1) presence of any combination of the hallmark PPV nevi as defined above, and 2) presence of written or iconographic data considered sufficient to achieve a diagnosis. Exclusion criteria included 1) redundant publications, 2) diagnosis judged to be wrong, 3) data considered insufficient for a diagnosis, 4) citations of PPV in articles or books not reporting original findings, and 5) incomplete bibliographic citations. Diagnostic and therapeutic procedures, which varied widely across the decades and geographic provenience of reports, were not recorded nor analyzed.

Results

A full list of references that the results below are based on is available in Supplementary File 1. Older articles, mostly belonging to the Japanese literature, mention dozens of published PPV cases but could not be retrieved for this study, some not even as a complete citation, including the seminal paper by Ota et al. (1).

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Phacomatosis cesioflammea

This review of the literature retrieved 435 cases that fit the diagnosis of PCF, of which 320 were described in full-text articles describing single or multiple individual cases, 45 in abstracts, and 70 in large case series with available iconography or a sufficiently detailed description. Another 230 patients, too concisely described or only mentioned in large case series, were excluded because it was challenging to confirm the diagnosis of PCF and in order to avoid potential redundancies with other publications.

The average age at presentation was 12.7 years (range 0–83), but the cutaneous manifestations were already noticed at birth or early in life. The female-to-male ratio was 1.3:1. The plurality of patients were of East Asian descent (at least 135 cases), but white, Indian, Hispanic, middle Eastern, and black groups were also well represented (at least 62, 61, 46, 26, and 17 instances, respectively).

The hallmark NC consisted of an Ota nevus (possibly involving the eye and oral cavity) or a large dermal melanocytosis, or a combination of the two (Figs. 1A–E). The lesions followed a type 4 pattern of cutaneous mosaicism ("patchy without midline separation") or, less frequently, a type 2 pattern ("checkerboard"; Fig. 1F), the latter being detectable in 26 out of the 169 cases (15.4%) in which the anatomical distribution and iconography allowed an evaluation. The Bork–Baykal phenomenon (i.e., sparing of the areola or nipple by a nevus) was present in all 27 instances in which the anterior chest was clearly visualized (Fig. 1A). The NC was evenly distributed bilaterally in 65.8% of cases, was predominantly right sided in 17.1%, and was left sided in 15.6%. The head and neck were the prominent localization of the NC (70.2%), with the upper part of the trunk (57.7%), lower part of the trunk (54.0%), leg (39.4%), and arm (30.3%) less frequently affected.

The NF was always characterized by various hues of reddish purple, likely dependent, at least in part, on age and anatomical localization, and it followed a flag-like pattern (Figs. 1A–E). In at least 14 cases, the nevus was not homogeneous, but instead showed a regular, finely reticulated texture in all or part of its area (Fig. 1G), but without attaining the visual impression typical of CMTC. The NF was evenly distributed bilaterally in 41.6% of cases, was right sided in 31.9% of cases, and was left sided in 26.6% of cases. The head and neck were the prominent localization of the NF (73.2%), with the upper part of the trunk (69.6%), arm (57.3%), lower part of the trunk (51.1%), and leg (46.6%) being less frequently affected. On 13 occasions, the NC and NF were contralateral with respect to each other.

Additional cutaneous manifestations are reported in Table 1. By far the most frequent extracutaneous association of PCF was the Sturge–Weber (SW) and/or Klippel–Trénaunay (KT) phenotype with eye (mostly glaucoma), central nervous system (CNS; mostly leptomeningeal angiomatosis with cortical atrophy), or soft tissue involvement (mostly hypertrophy, 54.6% of cases; Table 2). In 21 cases (4.8%), extracutaneous abnormalities did not include SWKT-like manifestations (Table 3). Other than extracutaneous abnormalities, cardiovascular anomalies were the most frequently encountered ones. Extracutaneous manifestations



Figure 1 | A) 3-month-old female with extensive dermal melanocytosis involving the chest, upper abdomen and arm together with intensely red, flag-like nevus flammeus of the face, chest and left arm. Sparing of the areola by the nevus cesius (Bork-Baykal phenomenon) can be glimpsed on the right side (modified and reprinted under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike License (CC BY-NC-SA) from Dutta et al. Indian J Dermatol. 2019;64:217-23). B) Large dermal melanocytosis of the upper back and arms with checkerboard nevus flammeus of the back in a 4-year-old female (reprinted and modified with no prior permission required [copyright of the Indian Journal of Dermatology, Venereology and Leprology] from Goyal et al. Indian J Dermatol Venereol Leprol. 2010;76:307). C) 66-year-old female displaying a predominantly left-sided nevus cesius of the back juxtaposed to a right sided, dark purple nevus flammeus (reprinted and modified from [Wang et al. J Dtsch Dermatol Ges. 2019;17:1179-82] with permission from Wiley). D) 7-month-old infant presenting with right sided nevus flammeus (intermingling with a nevus anemicus on the forehead) and bilateral melanosis bulbi; bilateral buphthalmos, as the expression of glaucoma, is also visible (modified and reprinted under the terms of the Creative Commons Attribution License (CC BY) from Atalay et al. Glokom-Katarakt. 2017;12:151-4). E) "Oral" phacomatosis cesioflammea: left sided nevus flammeus involving the vermilion and palate, partially overlapping with patchy, bilateral nevus cesius of the hard palate (modified and reprinted under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License from Fathima Hazna et al. J Skin Sexually Transmitted Dis. 2024;6:188-91). F) Flag-like nevus cesius of the right side of the back associated with right-sided nevus flammeus of the neck, upper back and arm (reprinted and modified from [Namiki T et al. J Dermatol. 2017;44:e32-3.] with permission from Wiley). G) Generalized patchy distribution of large blue spots associated with nevus flammeus which shows a reticular pattern on the back (modified and reprinted, as allowed for academic re-use, from Mecarini et al. J Pediatr Neonat Individualized Med. 2022;11:e110203.).

were not detected in 40.6% of cases. Notably, 15 cases of choroidal melanomas have been reported in PCF patients: nine females, six males, average age 56.7 years (range 17–83), all white patients but one (11), two metastatic (12, 13).

Skin biopsies for histological examination were seldom performed, and they revealed typical features of NC or NF. Genetic analysis was carried out on 23 individuals, revealing postzygotic mosaic mutations in either the *GNAQ* or *GNA11* gene (12 and nine cases, respectively). When mentioned, the specific mutations were *GNAQ* (pR183Q) in nine cases (14–17), *GNAQ* (pA183G) in three cases (7, 18), *GNA11*(pR183C) in six cases (17, 19), *GNA11*(pA183C) in two cases (20, 21) and *GNA11*(pR183S) in one case (14).

Table 1 | **Additional cutaneous manifestations of phacomatosis cesioflammea.**

Manifestation	Occurrences
Nevus anemicus	83
Congenital triangular alopecia	15
Café-au-lait spots*	9
Nevus spilus*	3
Toenail hypoplasia	2
Hypochromic nevus, epidermal nevus, Becker nevus (with ipsilateral breast hypoplasia), segmentally arranged senile freckles, aberrant dermatoglyphs	1 each
Neoplasms	
Lobular capillary hyperplasia	2
Mastocytosis	2
Skin tag	2
Lipoma, basal cell carcinomas, hemangioma of infancy, malignant melanoma, milium, angiokeratoma	1 each
Autoimmune conditions: linear morphea, discoid lupus erythematosus, vitiligo	1 each

*These lesions were small and not anatomically related to the hallmark cutaneous nevi, hence they were judged to be a random finding.

Phacomatosis cesiomarmorata

Seventeen cases of PCM were identified (see Tables 4 and 5 for epidemiological and some clinical findings). In five cases, CMTC

Table 2 | **Main extracutaneous manifestations of phacomatosis cesioflammea.**

Manifestation	Occurrences
Sturge–Weber–Klippel–Trénaunay phenotype	
Glaucoma	74 (unilateral), 34 (bilateral)
Central nervous system involvement*	105
Soft tissue hypertrophy	166
Other neural abnormalities	
Bilateral sensorineural hypoacousis	4
Developmental delay	2
Attention deficit hyperactivity disorder	2
Unilateral anosmia	1
Unilateral hemifacial spasms	1
Other ocular abnormalities	
Iris mammillations	8
Cataract	7
Megalocornea	2
Retinal atrophy	2
Myopia, strabismus, iris atrophy, retinal vascular abnormalities, heterochromia iridis	1 each

*Reported manifestations varied from description of symptoms (seizures, developmental delay, etc.) to laboratory changes (electroencephalographic changes, cortical atrophy, etc.), the latter depending at least in part on technological advances available at the time of publication and study site.

Table 3 |Other extracutaneous manifestations of phacomatosis cesioflammea.

Manifestation	Occurrences
Cardiovascular abnormalities	
Veins: Aplasia/hypoplasia/dysplasia	16
Ectasia/varicosity	9
Chronic venous ulceration	7
Arteries: Stenosis	4
Arteriovenous malformation	2
Lymphatics: Chylous ascites, chylothorax	1 each
Heart: Ventricular septal defects	4
Atrial septal defects	2
Patent ductus arteriosus	2
Valvular abnormalities	1
Skeletal abnormalities	
Digit malformations	7
Limb length discrepancy	3
High arched palate, spina bifida occulta, lipohypoplasia, pectus excavatum	1 each
Ear, nose, throat	
Subglottic stenosis	3
Lingual malformations	3
Laryngeal hypoplasia, preauricular fistula, dental anomalies	1 each
Genitourinary abnormalities	
Renal agenesis/hypoplasia	4
Testicular hydrocele	3
Renal cysts	2
Hypospadia	1
Neoplasms	
Choroidal melanoma	15
Conjunctival melanoma in situ, optic disc melanocytoma, intramedullary and retroperitoneal melanocytoma, cystic hygroma of jaw, renal angiomas, perirenal lipomatosis, splenic lymphangioma, polycythemia vera	1 each
Genetic conditions	
Down syndrome	2
Neurofibromatosis type 1	2
Selective immunoglobulin A deficiency, Loeys–Dietz syndrome, Wolf–Hirschhorn syndrome, Williams syndrome	1 each
Miscellaneous	
Raynaud phenomenon	2
Hepatosplenomegaly	2
Umbilical hernia	1

Note. Common acquired chronic conditions (e.g., diabetes mellitus) were very seldom mentioned and are not reported here for the sake of simplicity.

displayed the typical violaceous, coarse, and irregularly shaped net-like pattern and was arranged in a flag-like distribution (Fig. 2A). In all other instances, CMTC appeared as a finer, more regular reticulum, often with less discernible lateralization (Fig. 2B). In cases characterized by the former presentation, no ocular manifestations were observed. The most frequent extracutaneous manifestation was soft tissue atrophy of the limb affected by CMTC. Extracutaneous abnormalities were absent in 47.0% of cases. In the only case tested, a mosaic *GNA11* mutation (pR183C) was detected (22). An additional 11 PCM cases are mentioned in several large case series, one also revealing a mosaic *GNA11* mutation (pA183C) (14).



Figure 2 | A) Phacomatosis cesiomarmorata. Large blue spot on the lower back and glutei associated with right-sided, flag-like, classically appearing cutis marmorata telangiectatica congenita (reused under the terms of the CC BY-NC-ND license from [Du et al. JAAD Case Rep. 2016;2:28-30]). B) Phacomatosis cesiomarmorata. Extensive blue spots with superimposed, systematized, finely reticulated cutis marmorata telangiectatica congenita (reprinted and modified with no prior permission required [copyright of the Indian Journal of Dermatology, Venereology and Leprology] from [Nanda et al. Indian J Dermatol Venereol Leprol. 2016;82:298-303.]). C) Phacomatosis cesioflammeomarmorata. 5-month-old Japanese female featuring a dark pink nevus flammeus intermingled with nevus anemicus on the right side of the face, large dermal melanocytosis of the right side of trunk and lower limb (D), where cutis marmorata telangiectatica congenita can be observed (E) (reprinted and modified from [Shimizu et al. J Dermatol. 2015;42:1006-7] with permission from Wiley). F) Phacomatosis melanocesioflammea. Segmental hyperpigmented patch (flag-like hypermelanotic nevus) on the left side of abdomen and upper thigh with large blue spots (asterisks) overlapping with left-sided nevus flammeus (arrows) (G), which can also be observed on the sole (H) of a 2-year-old female (modified and reprinted under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike License (CC BY-NC-SA) from Dutta et al. Indian J Dermatol. 2019;64:217-23).

Phacomatosis cesioflammeomarmorata

Nineteen instances, of which 12 were identified by this study, were consistent with PCFM (Tables 4 and 5, Figs, 2C–E). In two cases (10.5%), the NC was distributed in a flag-like pattern. A typical appearance of CMTC was present in seven cases (36.8%). A SWKT phenotype occurred in 57.9% of cases. Clinical manifestations were limited to the skin in 35.2% of cases. A mosaic GNA11 mutation (pA183C) was found in one instance (7).

Phacomatosis melanocesioflammea

This study adds 10 discovered cases of PMCF to the seven already retrieved (6), bringing the total to 17 (Tables 4 and 5, Figs. 2F–H). Both the FHN and NF followed a flag-like segmental pattern, whereas the NC was always patchy, involving the eyes in only four cases (23.6%). Whenever the written description or iconographic quality allowed for an evaluation, the capillary malformation had a pink hue (seven cases) or a purple one (five cases), in a fashion apparently independent of age and anatomical location. No extracutaneous abnormalities were reported in two cases (11.8%). Nevus anemicus (NA) was frequently present (47.0%), and a SWKT phenotype was present in 70.6% of cases. In one case, a mosaic *GNA11* mutation (pR183C) was detected in an unspecified "pigmentary lesion" (17).

Association of nevus cesius and nevus anemicus

Four cases of NC paired with NA were retrieved in worldwide literature (Table 6) (23–26).

Other mentions of "phacomatosis pigmentovascularis"

A unique association of NC, NF, and nevus vascularis mixtus, amounting to PCF and mixed vascular nevus syndrome, was reported by Hayashi et al. (27).

A list of references representing redundant publications and ones describing cases judged to not actually represent NC-associated PPV is reported in Supplementary File 1.

Retrieved cases fitting the diagnosis of PSR, PMR, and unclassifiable PPV, and diagnoses of nevus roseus–associated PPV judged to be wrong are listed elsewhere (9, 10). This study identified an additional two instances of PMR (28, 29). A cumulative 23 cases of either PSR or PMR, six of unclassifiable PPV, and eight of not-otherwise-specified PPV were mentioned across several case series.

Table 5 | **Additional manifestations of nevus cesius–associated phacomatosis pigmentovascularis other than phacomatosis cesioflammea.**

	Occurrences		
	PCM	PCFM	PMCF
Sturge–Weber–Klippel–Trénaunay phenotype			
Glaucoma	—	7	4
Central nervous system involvement*	—	2	3
Soft tissue hypertrophy	—	5	9
Other ocular abnormalities			
Glaucoma	1†	—	—
Microcornea	1	—	—
Buphthalmos, leukocoria	1	—	—
Retinal hypoperfusion	1	—	—
Myopia	—	1	—
Soft tissue and skeletal abnormalities			
Leg atrophy	3	—	—
Leg hypertrophy	1†	—	—
Leg length discrepancy	—	—	2
Tibial cyst	—	—	1
Central nervous system abnormalities*	4†	—	—
Peripheral nervous system abnormalities: facial neuropathy	—	1	—
Cardiovascular abnormalities			
Atrial septal defect	1	1	—
Venous anomalies	1	1	—
Ventricular septal defect	—	1	—
Genitourinary abnormalities: hypospadia	1	1	
Cutaneous abnormalities			
Nevus anemicus	—	4	8
Congenital triangular alopecia	—	1	—
Preauricular tragus	—	1	—
Freckles, nevus sebaceus, plexiform neurofibroma	—	—	1 each

*Reported manifestations varied from description of symptoms (seizures, developmental delay, etc.) to laboratory changes (electroencephalographic changes, cortical atrophy, etc.), the latter depending at least in part on technological advances available at the time of publication and study site.
†These manifestations cannot be considered part of a Sturge–Weber–Klippel–Trénaunay phenotype because of the lack of a nevus flammeus.
PCFM = phacomatosis cesioflammeomarmorata, PCM = phacomatosis cesioflammea, PMCF = phacomatosis melanocesioflammea.

Table 4 | **Some clinical characteristics of nevus cesius–associated phacomatosis pigmentovascularis other than phacomatosis cesioflammea.**

	Phacomatosis cesiomarmorata		Phacomatosis cesioflammeomarmorata			Phacomatosis melanocesioflammea		
Avg. age at diagnosis, years (range)	2.8 (0–21)		4.3 (0–28)			7.1 (1–19)		
Female-to-male ratio	2.4:1		0.9:1			0.7:1		
Ethnic distribution, %								
White	20.0		15.8			0.0		
East Asian	26.7		57.9			76.5		
Hispanic	13.3		15.8			5.9		
Indian	20.0		5.3			11.8		
Middle Eastern	13.3		5.3			5.9		
	NC	CMTC	NC	NF	CMTC	FHN	NC	NF
Side of nevus, %								
Bilateral	75.0	64.3	78.9	47.4	68.4	56.2	68.7	37.5
Right	12.5	7.1	15.8	31.6	21.1	25.0	31.3	43.7
Left	12.5	28.6	5.3	21.1	10.5	18.8	0.0	18.8
Location of nevus, %								
Head/neck	52.6	50.0	36.8	78.9	15.8	37.5	56.2	68.7
Upper trunk	72.2	78.6	68.4	52.6	68.4	62.5	62.5	56.2
Lower trunk	83.3	92.9	78.9	36.8	68.4	56.2	68.7	56.2
Arm	33.3	64.3	15.8	31.6	63.2	43.7	31.2	56.2
Leg	72.2	100.0	52.6	21.1	89.4	75.0	31.2	68.7

CMTC = cutis marmorata telangiectatic congenita, FHN =flag-like hypermelanotic nevus, NC = nevus cesius, NF = nevus flammeus.

Table 6 | **Reported cases of the association of nevus cesius and nevus anemicus.**

Ref.	Diagnosis age (yrs)	Sex	Ethnicity	Nevus cesius	Nevus anemicus	Additional manifestations
23	24	F	East Asian	Bilateral Ota and Ito nevus	Left sided on neck	
24	6	M	White	Left-sided melanosis bulbi	Left sided on face and neck	
25	1.5	M	Indian	Blue spot on left buttock	Left thigh	Smooth muscle hamartomas of forehead and scalp; café-au-lait spot on right side of chest
26	8	F	East Asian	Bilateral Ota nevus with melanosis bulbi	Bilateral on face	

F = female, M = male.

Discussion

This is an extensive review of PPV. For comparison, the previously largest review, published only a few years ago, comprised 176 cases of PPV of all types (7).

PCF is the most common PPV type by far, at 435 out of 537 cases (81.0%), and this figure is likely to be even higher when considering the several large case series mentioned above. Several indications, including hundreds of reported cases, the publication of single-center series comprising up to several dozen cases, and a great increase in reporting in recent years lead one to believe that PCF might not be an exceedingly rare condition. Indeed, the relative frequency of PPV was estimated at 5.8 per 100,000 pediatric patients at a center in Mexico (30). The prevalence of PCF in females is relevant, but whether this is the result of true pathomechanisms, or instead results from sociocultural factors leading to females more frequently receiving medical attention, remains to be determined. The greater number of cases from East Asia, particularly Japan, probably reflects earlier knowledge about the condition in that geographical area, but this seems to have faded in recent decades.

The hallmark NC presented in all its known manifestations (known as Ota nevus, Ito nevus, or large dermal melanocytosis), most commonly in a patchy pattern without midline separation. However, a small percentage of cases were characterized by a lateralized flag-like distribution. The significance of these different distributions, in both isolated and syndromic NC cases, has never been investigated or discussed in the literature to my knowledge. The Bork–Baykal phenomenon was inevitably present, confirming a finding that was first identified in 2017 for both isolated NC (31) and syndromic NC (32).

The clinical features of NF in PCF do not seem to differ from NF when observed either isolated or as part of other syndromes. In a minority of cases, the lesion displayed a finely reticulated, regular appearance, which should prompt careful differentiation from both CMTC and the admixing of NF with NA. In two instances, reticulated NF was associated with a mosaic *GNA11*(pA183C) mutation (20, 21), a finding corroborated by its observation in the context of SW syndrome as well (33).

NA is confirmed to be the main cutaneous association of PCF, being present in a relevant minority of instances; as a matter of fact, it was even considered a defining criterion of some PPV variants in earlier classifications. NA was invariably intermingled with NF, which is the result of allelic twin spotting clinically manifesting as vascular twin nevi (nevi vasculares gemini). The other, probably nonrandom, skin manifestation of PCF is congenital triangular alopecia (CTA). Also known as Brauer nevus, it is currently uncertain whether this condition is a manifestation of mosaicism (34). Despite a handful of cases detected in association with other congenital syndromes (mostly chromosomal abnormalities), CTA is otherwise a sporadic and isolated condition. Further clinical and genetic studies are warranted to better understand the association between PCF and CTA.

Extracutaneous manifestations occur in the majority of patients with PCF and seem to largely depend on the presence of NF. In fact, they mostly consist of Sturge–Weber and/or KT syndrome–like abnormalities ipsilateral to the nevus and affecting the soft tissue, eyes, or CNS. In the soft tissue and eyes they mostly cause signs and symptoms depending upon increased vascularization such as hypertrophy or glaucoma, respectively. Within the CNS, the occupation of space by ectatic vessels causes atrophy of the cerebral cortex, as widely documented in recent decades thanks to the availability of techniques such as computed tomography and magnetic resonance imaging. Occasional reports of malformations affecting peripheral deep veins, arteries, or lymphatic vessels also parallels what is sometimes observed in association with KT syndrome (35). However, in PCF vascular malformations often occur in the absence of SWKT-like signs and may be a disease-specific manifestation. The contribution of NC to extracutaneous anomalies seems to be limited to its role in the development of glaucoma through an Ota nevus, confirming the findings observed in the isolated nevus (36).

This review confirms that PCF, like all other PPV variants, does not confer an increased risk of developing malignancies. A possible exception is represented by case reports and small series describing the occurrence of ocular melanoma in PCF patients featuring an Ota nevus. Because the number of reported instances ($n = 17$) is very similar to that from a recent review of melanoma in the setting of isolated Ota nevus ($n = 16$) (37), it is conceivable that PCF confers a slightly increased risk of ocular melanoma, if only considering the relatively common occurrence of Ota nevus in the general population.

It is now firmly established that PCF is caused by postzygotic mosaic *GNAQ* or *GNA11* mutations. As mentioned above, it is possible that different gene mutations might translate into slightly different clinical manifestations.

First mentioned in 2000 (38), PCM was identified in 2003 (2), and only 17 cases appear to have been published. PCM features either of the known variants of CMTC; that is, the classic coarse net-like pattern and the regularly reticulated one (39). The extracutaneous manifestations mostly seem to result from the presence of CMTC. In fact, segmental asymmetry, mostly due to soft tissue atrophy or, less frequently, hypertrophy, is the best-known noncutaneous association of CMTC, and glaucoma and CNS defects, including cerebrovascular malformations and cortical atrophy, are sometimes reported as well (40).

PCFM was framed in 2019 based on a case report and a few instances taken from the literature (5). This study greatly increases the number of known instances. The co-occurrence of CMTC and NF is a well-known association; in PCFM, NF is often confined to the head and neck, with CMTC affecting the rest of the body. PCFM is characterized by the absence of the Sturge–Weber phenotype,

but otherwise it seems to resemble PCF in several other respects.

As demonstrated elsewhere (6), PMCF corresponds to what was originally labeled "PPV type IV" (41). This review unearthed many further cases in the literature. Together with PMR, this is the only PPV variant featuring an FHN; interestingly, in approximately half of the cases the NF looked lighter and pinker than seen, for instance, in PCF, hence somewhat resembling NR. In terms of clinical associations, a high frequency of NA and KT phenotype (or leg-length discrepancy) was observed. Causative mosaic mutations of PCM, PCFM, and PMCF might affect the *GNA11* gene as detected in one individual each (7, 17, 22).

In 2011, Hernández-Núñez et al. described a 6-year-old boy affected by a NA involving the left half of his face and associated with ipsilateral melanosis bulbi (24). This case was defined as "didymosis cesioanemica" by Happle (42). Three more instances of this association were retrieved in the literature (23, 25, 26), hence corroborating the existence of this truly exceptional entity. I suggest the term *pseudodidymosis cesioanemica* to define it, whereby the term *pseudodidymosis* replaces the no longer tenable concept of nonallelic didymosis and subtends binary genodermatoses composed of at least two nevi deriving from different cell lineages (43). Because the term *phacomatosis* historically implies the presence of internal anomalies (particularly ocular ones), it is best avoided in this case.

The other two known variants of PPV (PSR and PMR) feature a NR and have been extensively reviewed elsewhere, together with the few cases still considered "unclassifiable" (9, 10). Many of these occurrences are mentioned in several studies, but regrettably a critical reassessment was not possible due to a fundamental lack of details. It is therefore conceivable that additional PPV variants exist and will still be discovered (9). Supplementary File 2 contains a summary table of established PPV types and one for "unclassifiable" cases with relevant references.

As a final note, a review of the diagnosis and management of the various types of PPV fell outside of the scope of this study. Nonetheless, it is worth mentioning that 1) the diagnosis remains purely clinical, being based on the correct identification of the hallmark nevi, 2) the treatment of the cutaneous manifestations is advised mostly for cosmetic purposes, with a growing number of laser sources being reported as effective in case reports and series for both pigmented and capillary nevi, and 3) from a dermatological standpoint, it seems warranted to refer patients at least to pediatrics (or general medicine for adults), or to ophthalmology, neurology, or any other specialty based on individual symptoms and signs for identification and management of any extracutaneous manifestations.

Conclusions

To sum up, PPV can now be considered a somewhat outdated umbrella term and should no longer be used in clinical settings, with the possible exception of cases not fitting one of the recognized PPV variants. PCF is the most common and best-known PPV type. Further studies might help clarify whether some occasional but distinguishing features (e.g., checkerboard-arranged NC, reticulated NF, associations with vascular malformations, or presence of CTA) bear any clinical or genetic implications. Further case reports and genetic studies on PCM, PCFM, PMCF, and pseudodidymosis cesioanemica will contribute to better characterizing these exceedingly rare entities.

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