Phacomatosis spilosebacea: A new name for a distinctive binary genodermatosis

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Phacomatosis pigmentokeratotica (PPK) is defined by the association of papular nevus spilus arranged in a flag-like pattern and sebaceous nevus following Blaschko's lines. A systematic search of the worldwide literature retrieved 95 well-established PPK cases. An additional 30 cases were excluded for a number of reasons. Based on this study, we propose to rename PPK *phacomatosis spilosebacea* (*PSS*). Mosaic mutations of the *HRAS* gene are the only proven cause of PSS. The extracutaneous abnormalities of PSS result from various degrees of intermingling of Schimmelpenning syndrome and papular nevus spilus syndrome. PSS seems to be a condition at particularly high risk of developing basal cell carcinoma, urogenital malignancies, and vitamin D–resistant hypophosphatemic rickets. Extracutaneous abnormalities were detected in approximately 75% of PSS cases. (J Am Acad Dermatol 2023;89:764-73.)

Key words: basal cell carcinoma; cancer; genodermatosis; nevus sebaceus; nevus spilus; papular nevus spilus; phacomatosis pigmentokeratotica; phacomatosis spilosebacea; RASopathy; rickets; sebaceous nevus.

The association of papular nevus spilus (PNS) and linear epidermal nevus (EN) of the non-epidermolytic, organoid type was framed by Happle et al.[1] in 1996 and named *phacomatosis pigmentokeratotica* (*PPK*). The new term soon found consensus, and dozens of new cases have been published since, indicating that PPK is more common than initially thought. After having been shown to be caused by a postzygotic *HRAS* mutation,[2] PPK is now considered to be part of the spectrum of mosaic RASopathies, together with nevus sebaceus (or sebaceous nevus [SN]), Schimmelpenning syndrome,[3] isolated PNS,[4] and (in all likelihood, pending genetic confirmation) PNS syndrome.[5] Because the 2 nevi were found to originate from 1 single heterozygous *HRAS* mutation in a pluripotent progenitor cell, the hypothesis of twin spotting has been revoked by its author (RH).[6]

However, reports containing incorrect diagnoses or unrecognized cases of PPK, as well as non-comprehensive reviews of the literature, might have contributed to convey incomplete or even misleading data to the medical-scientific community. Furthermore, it seems clear that the very denomination of PPK can now be taken as fairly inaccurate. In fact, both the *pigmento-* and *-keratotica* parts are too generic a definition for what are a PNS and an SN, respectively. A quarter of a century after its original identification, we carried out a reappraisal of PPK based on the available evidence.

REVIEW OF THE LITERATURE

A systematic search of the worldwide literature up to May 2020 was carried out using PubMed, Embase, Scopus, Google Scholar, Global Index Medicus, and J-Global as primary tools. A critical reassessment of the retrieved material yielded a combination of *ante litteram*, unrecognized, and correctly diagnosed instances, amounting to 95 well-established PPK cases.[2,7-93] Published material containing convincing evidence (either written or iconographic) of the association of a PNS and an SN, which were large enough to follow one of the patterns of cutaneous mosaicism, was included. Insufficiently detailed or ambiguous descriptions,[94-106] inability to retrieve the material,[107-111] redundant publications,[112-123] and diagnoses judged incorrect[124-126] were reasons for exclusion; 2 other cases[127,128] were also excluded because of only partial information (Fig 1).

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The average age at presentation was 17.8 years (range, 0-67 years), but the cutaneous manifestations were already noticed early in life. The male-to-female ratio was 1.4. The vast majority of patients were White (71.4%) or east Asian (20.9%).

The PNS always followed the flag-like pattern of mosaicism and varied widely in terms of hue of the background pigmentation (from nearly invisible to very dark), as well as the density and appearance of superimposed papular and macular lesions (from sparsely scattered and monomorphic to intensely packed and variable in color and size) (Fig 2). The SN, always arranged along the lines of Blaschko, often appeared florid and yellow-orange on the scalp and thinner and brownish on the rest of the body (Fig 1). As already noticed before,[129] in a couple of cases, the EN consisted of the rare morphologic variant of nevus marginatus (characterized by a flat reddish area in the center surrounded by an elevated margin).[46,49]

CAPSULE SUMMARY

- This review provides an extensive and critical reassessment of so-called phacomatosis pigmentokeratotica, including previously undiagnosed cases and excluding incorrectly diagnosed ones.
- This study suggests a new, more appropriate name, *phacomatosis spilosebacea*, and details the features of this condition.

Both nevi were localized preferentially on the left side of the body (left-to-right ratio of 1.3 for both). The 2 lesions were fully or predominantly ipsilateral in 71.1% of cases. The upper part of the trunk was involved by the PNS in 73.6% of cases, followed by the head and neck region (63.7%), lower part of trunk (51.6%), arm (47.2%), and leg (20.9%). The head and neck were the prominent localizations of the SN (87.9%), with the upper part of the trunk (52.7%), arm (33.0%), lower part of trunk (27.5%), and leg (17.6%) being less frequently affected. The SN also featured oral or ocular involvement in 10 and 2 cases, respectively (Table I).

When performed, biopsies of the PNS always showed various patterns of melanocyte hyperplasia, with the maculopapular component of the nevus most commonly representing junctional or compound melanocytic nevi. Histology of the SN showed features of nevus sebaceus in 45 cases and of nonorganoid EN (ie, purely keratinocytic) in 12. With regard to the latter subgroup, only 3 patients were older than 13 years.[21,31,58] Among these, 1 patient had Turner syndrome.[31] In the other 2 instances, the biopsy might have been taken from lesions of the trunk or limbs.

Genetic analysis was performed in 13 patients and always showed a postzygotic *HRAS* mutation in both nevi (c.37G4C [p.Gly13Arg] in 9 patients,[2,71,76,84,85,90] c.182A4G [p.Gln61Arg] in 3 patients,[2,89] and c.181C4A [p.Gln61Lys] in 1 patient[91]).

Cutaneous lesions superimposed on the nevi, as well as additional mucocutaneous manifestations, are listed in Table I. Table II details the extracutaneous associations, which include skeletal, neural, cardiovascular, and ocular abnormalities in decreasing order of frequency (45.3%, 42.1%, 6.3%, and 6.3%, respectively). Rickets (not included in the skeletal manifestations mentioned) was diagnosed in 25 (26.3%) cases and internal malignancies in 10 (10.5%).[2,9,16,41,46,48,61,65,84,85] No extracutaneous anomalies were detected or mentioned in 23 (24.2%) cases (36 [37.9%] cases when including manifestations caused by soluble/hormonal factors, neoplasms, and unrelated conditions). A fatal outcome in patients with PPK was mentioned in 3 instances (metastatic squamous cell carcinoma,[9] metastatic rhabdomyosarcoma,[16] and cardiorespiratory arrest in the setting of extensive malformations[52]).

In addition to the aforementioned 95 PPK cases, a cluster of 12 patients emerged that featured an EN (often sebaceous) associated with segmental café-au-lait spots (more appropriately called *flag-like hypermelanotic nevus*[130]).[131-142] This group of patients (7 male and 5 female) was characterized by early age at presentation and prominent anomalies of central nervous system, heart, bones, and eyes (75.0%, 50.0%, 41.7%, and 33.3% of patients, respectively). A postzygotic *KRAS* mutation was detected in both nevi of a tested individual, who also happened to be affected by a urogenital malignancy.[141]

DISCUSSION

Nature of hallmark nevi of PPK

The hallmark nevi of PPK, PNS, and SN seem to distribute preferentially over the head and trunk and tend to be ipsilateral. These patterns are probably related to the nature and migration pathways of the causative, mutated cell lines early during embryogenesis.

Although little doubt arose when diagnosing the PNS on clinical and histologic grounds in most cases, biopsy failed to show features of an organoid nevus with sebaceous differentiation in a lesser proportion of cases. As highlighted before, in addition to failure

Abbreviations used:

BCC: basal cell carcinoma
EN: epidermal nevus
MM: malignant melanoma
PNS: papular nevus spilus
PPK: phacomatosis pigmentokeratotica
PSS: phacomatosis spilosebacea
SN: sebaceous nevus

to detect or report such findings, the minimal presence or even absence of sebaceous glands could be explained both by hormonal (underdevelopment before puberty) and anatomic factors (biopsy samples taken outside of the head and neck region). Thus, we emphasize the paradoxical fact that in a biopsy from SN lesions of Schimmelpenning syndrome outside the head and neck area, the histopathologic diagnosis may be keratinocytic nevus, although the comprehensive diagnosis is SN.[129] In this regard, it is worth mentioning the case of a 16-year-old girl with Turner syndrome (a condition featuring hypogonadism with delayed/absent puberty) in whom a biopsy of the EN taken from the scalp failed to highlight sebaceous differentiation.[31] Hence, it seems appropriate to reinforce the view that the hallmark EN of PPK is indeed an organoid nevus with sebaceous differentiation, either *in fieri* or fully developed.

A new name for PPK

Based on such considerations, we suggest renaming PPK as *phacomatosis spilosebacea* (*PSS*), where *spilo-* refers to the PNS and *-sebacea* to the SN as defined earlier. Also considering that we are not aware of any cases of a systematized PNS associated with any other EN type alone, the term *PSS* seems an appropriate approximation regardless of the histopathologic features of the SN.

Other cutaneous manifestations of PSS

Both the PNS and SN were reported to occasionally harbor other benign lesions and malignant transformation. The relationship between nevi spili and malignant melanoma (MM) remains debatable[143]; however, reports of only 2 MMs in PSS leads one to believe that the latter cannot be considered a particularly high-risk MM precursor. The most frequently occurring malignancy in PSS is basal cell carcinoma (BCC), diagnosed in 14 (14.6%) cases. In general, the incidence of BCC arising on an SN may be overestimated, because basaloid proliferation is a common finding and could represent a confounding factor for pathologists. Indeed, the true incidence of BCC on SNs might not exceed 1%.[144,145] Even taking into account a number of possible biases, the gross comparison between these figures suggests that PSS represents a condition featuring a relatively high BCC risk when compared to that of Schimmelpenning syndrome.

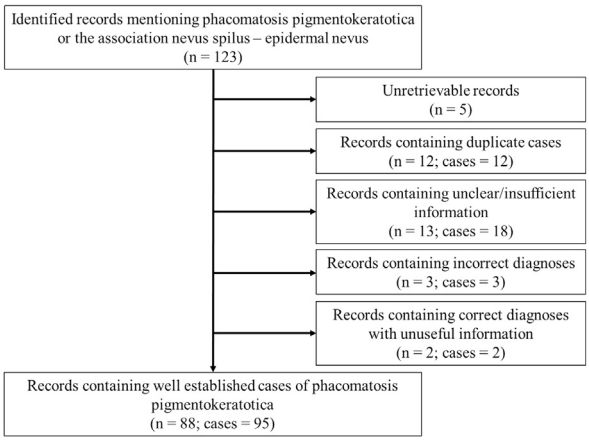

Fig 1. Flow chart of the literature analysis.

Extracutaneous manifestations of PSS

In general, PSS shows a wide range of severity of clinical manifestations. In fact, a fraction of patients displayed gross abnormalities and deficits, gravely impairing their functioning and quality of life. At the other end of the spectrum, in a quarter of cases, no extracutaneous abnormalities were present, thereby limiting the impact of PSS to cosmetic disfigurement and the need for long-term monitoring for malignant transformation. Indeed, the majority of patients with PSS displayed variable combinations of 1 or few malformations, mainly involving the skeletal, neural, and endocrine systems.

It seems clear that features such as hemihypertrophy and ocular abnormalities are more frequent in Schimmelpenning syndrome than in PSS. On the other hand, manifestations such as unilateral muscular atrophy and peripheral neurologic dysfunctions (e.g., hyperesthesia, hyperhidrosis) might be related to the contribution provided by the PNS, as seen in PNS syndrome.[4]

PSS and vitamin D–resistant hypophosphatemic rickets

The association between PSS and vitamin D–resistant hypophosphatemic rickets appears to be striking and represents a distinctive feature of PSS emerging from our review. The occurrence of vitamin D–resistant rickets in the setting of mosaic syndromes featuring ENs or melanocytic nevi is well known and is thought to be caused by the up-regulated production of soluble molecules (such as fibroblast growth factor 23) or interference with their

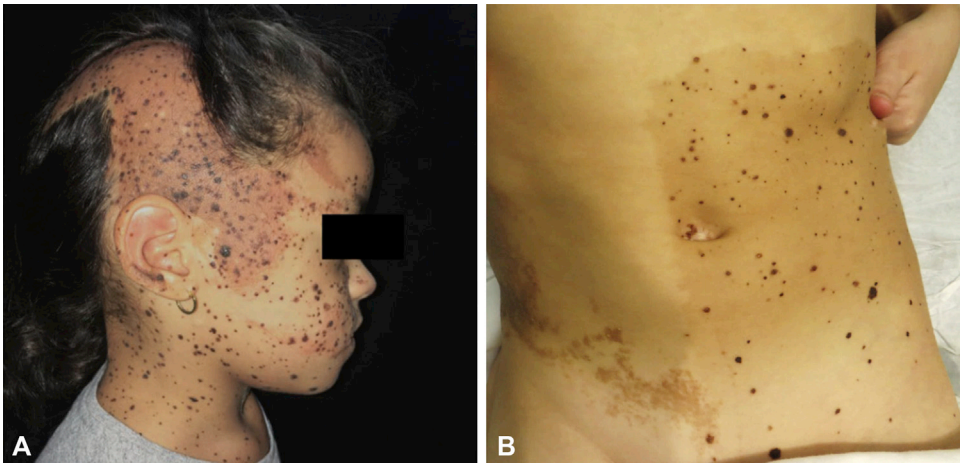

Fig 2. Phacomatosis pigmentokeratotica. **A**, Right-sided, intensely packed macular and papular melanocytic nevi on a hypermelanotic background (papular nevus spilus), which is barely visible because of the dark complexion of the patient and intermingling with an ipsilateral, orange-brown plaque arranged along Blaschko's lines (nevus sebaceus). Modified and reprinted under the Creative Commons Attribution-NonCommercial 4.0 International License from Grana et al.[86] **B**, Flag-like hypermelanotic patch on the left side of the abdomen covered with scattered papular and macular melanocytic nevi (papular nevus spilus). A contralateral, brownish, flat, Blaschkolinear epidermal nevus involves the right side. Modified and reprinted with permission from Elsevier.[93]

Table I. Associated mucocutaneous manifestations of phacomatosis pigmentokeratotica

Mucocutaneous manifestations			Number of occurrences	References
Mucosal involvement by nevus sebaceus		Oral	10	15,23,32,33,51,52,56,59,85,90
		Ocular	2	14,33
Superimposed lesions	On papular nevus spilus*	Spitz nevus	9	31,40,42,48,57,59,68,71,72
		Blue nevus	4	11,25,59,80
		Malignant melanoma	2	29,40
	On nevus sebaceus	Basal cell carcinoma	14	9,22,24,25,30,40,46,49,54,60,64,71,72,90
		Adnexal tumors (syringocystadenoma papilliferum, sebaceous adenoma, trichoblastoma, trichilemmoma, apocrine hidrocystoma)	4	60,72,73
		Squamous cell carcinoma	1	91
		Eccrine carcinoma	1	50
		Apocrine intraductal carcinoma	1	72
Other lesions		Hemangioma	2	10,26
		Collagenous nevus	1	33
		Capillary nevus	1	33
		Segmental dermal melanocytosis	1	52
		Scleral pigmentation	1	21
		Conjunctival melanocytic nevus	1	58

*An alternate designation would be *speckled lentiginous nevus of the papular type*, whereas the simple denomination *speckled lentiginous nevus* is unsuitable because it includes both macular and papular nevus spilus.

Table II. Extracutaneous manifestations of phacomatosis pigmentokeratotica

Manifestations			Number of occurrences	References
Skeletal		Scoliosis	30	10,20,21,26,27,29,32,33,36,41,44,46,47,50-52,55,56,62,63,67,68,73,77,83,85,88
		Hemiatrophy	17	10,11,13,14,22,26,29,33,34,38,41,45,51,63,71,85
		Hemihypertrophy	4	48,53,61,87
		Unilateral hypoplasia	3	34,41,45
		Spina bifida	2	14,40
		Torticollis	2	29,51
		Kypholordosis	1	22
		Pes cavus	1	53
		Talipes equinovarus	1	55
		High arched palate	1	17
		Seventh rib anomaly	1	23
		Impaired dexterity of arm	1	53
Neural	Central nervous system	Developmental delay/intellectual disability	13	11,15,19,29,33,37,43,50,52,53,77
		Structural abnormalities	9	11,12,20,41,52,55,69,74,85
		Electroencephalographic abnormalities	5	11,12,14,92
		Seizures	4	15,37,74,75
		Hemiparesis	3	10,12,37
		Hyperreflexia	2	11,29
		Arachnoid cyst	2	44
		Paroxysmal subcortical dysfunction	1	40
		Hyporeflexia	1	22
		Homonymous hemianopsia	1	53
	Peripheral nervous system	Cranial nerves' lesions (including ptosis and strabismus)	10	14,15,22,29,32,49,50,52,55
		Hyperesthesia	4	26,29,51,53
		Hyperhidrosis	4	29,33,51,83
Endocrine		Rickets	25	15,20,24,28,29,38,41,43,45-47,50,52,67,70,73,75,76,79,81,86,88
		Precocious puberty	2	61,82
		Cryptorchidism	2	74,85
Ocular		Glaucoma	1	29
		Large-vessel abnormalities	1	29
		Microphthalmia	1	44
		Iris heterochromia	1	85
		Corneal dermoid	1	11
		Coloboma	1	15
Cardiovascular		Cardiac arrhythmia	3	62,74,85
		Lymphedema	2	51,69
		Coarctation of the aorta	1	74
Neoplastic		Rhabdomyosarcoma	5	16,48,61,84,85
		Urothelial carcinoma	2	2,41
		Epidermoid carcinoma (metastatic)	1	9
		Pheochromocytoma	1	46
		Nephroblastoma	1	65
		Leiomyoma (bladder)	1	43
		Neural tumors	1	44
Other		Turner syndrome	1	31
		Fragile X syndrome	1	33

intracellular pathways within *HRAS*-mutated cells (which may or may not be harbored within the nevi).[76] These changes would then promote renal excretion of phosphate and inhibit bioactivation of vitamin D, thereby causing rickets. There is little doubt that rickets in PSS depends on the presence of SNs. In fact, there is only 1 single report of an isolated PNS associated with rickets (and of the vitamin D–responsive type).[146] Considering that the number of reported cases of rickets in Schimmelpenning syndrome is comparable to those in PSS[45] and that Schimmelpenning syndrome is much more common than PSS, it can be serendipitously guessed that the latter condition confers a much higher risk of developing vitamin D–resistant rickets.

PSS and internal malignancies

A link between PSS and internal cancer has been suggested by 2 studies in which urogenital malignancies harbored the same *HRAS* mutation of their respective cutaneous lesions.[2,84] In addition to the 10 cases included in our review,[2,9,16,41,46,48,61,65,84,85] nephroblastomas developed in another 2 possible PSS cases.[101,103] Our data further support the view that PSS is a condition definitely prone to developing cancer, confirming a striking predilection for the urogenital tract. Interestingly, other conditions caused by mosaic *HRAS* mutations do not seem to feature the same proneness to malignancy, notwithstanding a predilection for the urogenital tract.[147-150] Hence, based on the available evidence, PSS seems to represent a mosaic RASopathy with a higher risk of malignancies.

Pathophysiology of PSS

A growing body of experimental evidence unequivocally shows that the 2 different PSS nevi, and therefore PSS itself, are caused by a postzygotic missense *HRAS* mutation.[2] However, there have been 4 cases labeled as *PPK* in which the mutation affected the *BRAF* gene instead.[102,105,124,125] We believe that such instances do not feature a clear-cut PNS and, therefore, that the *BRAF* gene is not involved in PSS.

When considering the most significant findings of the present review, a publication bias toward PSS can be discounted at least in part when considering that, in many instances, (1) the rarity of PSS was in itself a reason for reporting and (2) such condition had been diagnosed otherwise. Instead, it can be speculated that the presence of 2 mosaic cutaneous lesions imply that the pathogenic postzygotic mutation might arise earlier during embryogenesis (compared with conditions featuring only 1 nevus), thus increasing the chance that additional cell lines also carry the predisposing mutated gene.[85]

Association of flag-like hypermelanotic nevus and nevus sebaceus

A collateral output of the present review was the identification of a group of patients defined by the coexistence of a flag-like hypermelanotic nevus and an SN. Therefore, in terms of cutaneous manifestations, these cases differ from PSS only in the absence of papular melanocytic nevi superimposed on the hypermelanotic patches. It is well known that the papular nevi of PNS might take years after birth to develop on the congenital hypermelanotic patches. However, 4 (33.3%) patients were 10 years or older, including 2 adults.[133,134,138,140] Additional differential features compared with the bulk of confirmed PSS cases include (1) a frequently severe clinical picture, (2) a relatively high percentage of cases with cardiovascular or ocular manifestations, and (3) a mosaic *KRAS* mutation in 1 instance.[141] As things stand, there are, in our view, not sufficient grounds to call for an independent clinicogenetic variant deserving another specific name.

CONCLUSION

Based on current evidence, we suggest renaming the syndrome defined by the co-occurrence of sizeable PNS and SN (formerly PPK) as *PSS*. PSS is caused by a postzygotic missense *HRAS* mutation.[2] In addition to its hallmark nevi, the most distinctive features of PSS include (1) systemic manifestations that result from varying degrees of intermingling between Schimmelpenning syndrome and PNS syndrome; (2) a relatively high risk of malignancy, most relevantly BCCs and urogenital cancer; and (3) a relatively high frequency of hypophosphatemic rickets. Future clinical and molecular research will hopefully help further refine such knowledge.

Conflicts of interest

None disclosed.

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