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Torchia, Daniele

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Phacomatosis spilorosea and phacomatosis melanorosea: further phenotype expansion

Daniele Torchia MD PhD

Affiliations: Department of Dermatology, James Paget University Hospital, Great Yarmouth, United Kingdom

Corresponding Author: Daniele Torchia MD PhD, Department of Dermatology, James Paget University Hospital, Lowestoft Road, Gorleston-on-Sea, Great Yarmouth NR31 6LA, United Kingdom, Tel: 44-1493-452-313, Email: daniele.torchia@gmail.com

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To the Editor:

Phacomatosis pigmentovascularis (PPV) is a term encompassing a group of disorders characterized by the coexistence of a large, pigmented nevus of melanocytic origin and large capillary nevus. Out of the six known types of PPV, the four characterized by a nevus cesius are phacomatosis cesioflammea (by far the most common variant with hundreds of described cases), phacomatosis cesiomarmorata, phacomatosis cesioflammeomarmorata, and phacomatosis melanocesioflammea. The remaining two types (phacomatosis spilorosea [PSR] and phacomatosis melanorosea [PMR]) feature a nevus roseus, instead. Phacomatosis spilorosea and PMR are exceedingly rare, with 18 and 14 definite cases identified in the literature, respectively [1]. A postzygotic *PTPN11* mutation was recently discovered as the cause of PSR [2].

Beside previously employed search engines [1], the search method was refined by using ResearchGate (researchgate.net), WorldCat® (worldcat.org), Global Index Medicus (https://www.globalindexmedicus.net/), CNKI (https://oversea.cnki.net/index/), China/Asia On Demand (https://caod.oriprobe.com/), and J-STAGE (https://www.jstage.jst.go.jp/).

Two additional cases of PSR [3,4] and seven of PMR [5-11] were retrieved (**Table 1**); none were precisely diagnosed as such at the time of publication. Hence, the total number of known cases of PSR and PMR can be increased to 21 apiece. Two other identified cases probably represent redundant publications [12,13]. In two instances, the diagnosis of PSR was judged to be incorrect [14,15]. Within a large series by Knöpfel et al. concerning individuals affected by *GNAQ/GNA11* mosaicism, at least two cases were briefly mentioned that were characterized genetically by a mosaic mutation of *GNA11* c.547C>T (p.R183C), and clinically by a "capillary malformation" and "café-au-lait macular pigmentation" [16], hence reminiscent of PMR.

This review highlights the first PSR instance in an East Asian patient [4]. Also taking into account the previous data [1], body asymmetry caused by skeletal or soft tissue abnormalities homolateral to the nevus roseus (e.g., Sturge-Weber-Klippel-Trenaunay-like phenotype, lymphedema, scoliosis) represents the most frequent extracutaneous anomaly in PSR and PMR (66.7% and 23.8% of cases, respectively). The occasional, yet relevant co-occurrence of central nervous system malformations (mostly cerebrovascular) was confirmed for both PSR and PMR. Interestingly, two PMR cases featuring retinal arteriovenous anastomoses were brought to light [5,7]. A novel association of PMR with syndactyly was also revealed [6]. Extracutaneous anomalies were not detected in 28.6% of PSR cases and 52.4% of PMR ones, the latter entity seemingly representing a milder phenotype.

As a by-product of this study, the unique case of a 2-year-old Japanese boy was identified, who was characterized by the coexistence of a flag-like hypermelanotic nevus and cutis marmorata telangiectatica congenita, associated with leg length

Table 1. *Additional cases of phacomatosis spilorosea and phacomatosis melanorosea.*

Reference	Age (years)	Sex	Ethnicity	Lateralization of macular nevus spilus	Lateralization of nevus roseus	Extracutaneous abnormalities
Phacomatosis spilorosea						
[3]	55	Female	White	Left (chest)	Left (face)	Cerebrovascular malformations Epilepsy Hypoacousia
[4]	70	Male	East Asian	Bilateral (trunk)	Right (trunk)	
[2]	53	Female	Hispanic	Bilateral (trunk, lower limbs)	Right (trunk, lower limb)	Cerebrovascular malformations Klippel-Trenaunay phenotype (right side)
				Lateralization of flag-like hypermelanotic nevus		
Phacomatosis melanorosea						
[5]	6	Male	White	Right (trunk)	Right (lower limb, genitals)	Klippel-Trenaunay phenotype (right side) Cerebrovascular malformations (right side) Retinal arteriovenous anastomoses (right side)
[6]	2	Male	East Asian	Bilateral (systematized)	Bilateral (trunk)	Megalencephaly Syndactyly of toes (bilateral)
[7]	7	Female	White	Left (trunk, upper limb)	Left (face)	Retinal arteriovenous anastomoses (left side)
[8]	15	Male	White	Bilateral (trunk)	Right (limbs)	Klippel-Trenaunay phenotype (right side)
[9]	24	Male	East Asian	Left (chest, upper limb)	Left (face, trunk, upper limb)	Aneurysm of petrous internal carotid artery (left side)
[10]	4	Female	White	Right (abdomen, limbs)	Right (limbs)	
[11]	10	Female	East Asian	Left (face, neck)	Right (face, neck)	

discrepancy and moyamoya disease [17]. This report adds up to the handful of instances still to be labelled as "unclassifiable PPV" [1].

To sum up, PSR and PMR are confirmed to be exceedingly rare entities. PSR is associated with a macular nevus spilus and is caused by a postzygotic *PTPN11* alteration [4], whereas PMR is associated with a flag-like hypermelanotic nevus and still awaits the unequivocal identification of its causative gene defect.

Potential conflicts of interest

The author declares no conflicts of interest.

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