

Phacomatosis Pigmentovascularis of Cesiioflammea Type in 7 Patients

Combination of Ocular Pigmentation (Melanocytosis or Melanosis) and Nevus Flammeus With Risk for Melanoma

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Objective: To describe the features of phacomatosis pigmentovascularis (cesiioflammea type).

Design: Noninterventional retrospective case series composed of 7 patients.

Results: Nevus flammeus combined with ipsilateral ocular melanocytosis or melanosis was seen in all 7 patients. Additional contralateral nevus flammeus was observed in 3 patients. Nevus flammeus (unilateral in 4 patients and bilateral in 3 patients) was distributed in trigeminal nerves V1 (n=3), V2 (n=7), and V3 (n=5). Related findings included diffuse choroidal hemangioma (n=1) and glaucoma (n=1), with no patients having brain hemangioma or seizures. Ocular pigmentary abnormalities (unilateral in all 7 patients) included congenital ocular melanocytosis (n=6) and conjunctival acquired melanosis (n=1). Pigmentation was sectorial (partial) in 5 patients and complete in 2 patients. Melanocytosis involved the periocular skin in 1 patient, sclera in 2 patients, iris in 2 patients, and choroid in 4 patients. In 3

of 6 patients, melanocytosis was visible in the choroid only on dilated fundus evaluation. Related tumors included choroidal melanoma (n=3), optic disc melanocytoma (n=1), and conjunctival melanoma in situ (primary acquired melanosis) (n=1). Melanoma metastasis developed in 1 patient.

Conclusions: Phacomatosis pigmentovascularis shows features of nevus flammeus and more serious ocular pigmentary abnormalities (uveoscleral melanocytosis and conjunctival melanosis). Melanocytosis may be detected only by dilated ocular fundus examination, as found in 3 of 6 patients. Furthermore, choroidal melanoma can develop from melanocytosis, as noted in 3 of our 6 patients (50%). All patients with nevus flammeus should be examined for phacomatosis pigmentovascularis by an ophthalmologist because ocular melanocytosis and uveal melanoma may remain hidden within the eye.

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PHACOMATOSIS PIGMENTOVASCULARIS represents the coexistence of a cutaneous vascular malformation (most often nevus flammeus [port-wine stain]) with melanocytic nevus (most often ocular or dermal melanocytosis or both).¹ Since phacomatosis pigmentovascularis was first reported in 1947 by Ota et al,² there have been few clinical series published on this rare condition. In the dermatology literature, Cordisco et al³ described 25 patients, Vidaurri-de la Cruz et al⁴ identified 24 patients, and Fernández-Guarino et al⁵ reported on 15 patients. In the ophthalmology literature, Teekhasaene and Ritch⁶ described in 1997 a series of 9 patients with phacomatosis pigmentovascularis, some of whom demonstrated related glaucoma. In 2005, Tran and Zografos⁷ reported 3 cases of phacomatosis pigmentovascularis that were associated with uveal melanoma.

In 2005, Happle⁸ proposed a reclassification of phacomatosis pigmentovascularis with emphasis on creating relevant descriptive nomenclature rather than using the prior numerical system. The previous cumbersome classification devised in 1947 by Ota et al² characterized groups I to V, with *a* and *b* subdivisions, whereas the revised classification proposed in 2005 by Happle⁸ categorized 3 groups descriptively as phacomatosis cesiioflammea, phacomatosis spilorosea, and phacomatosis cesiomarmorata (**Table 1**). Herein, we describe 7 patients with phacomatosis cesiioflammea, all diagnosed following ocular consultation.

REPORT OF CASES

Clinical features of the patients with phacomatosis cesiioflammea are summarized in **Table 2** (**Figures 1, 2, and 3**). All cases were diagnosed following our ocular examination.

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Table 1. Revised Classification of Phacomatosis Pigmentovascularis (PPV)^a

New Classification	Findings	Old Classification
Phacomatosis cesioflammea	Nevus caesius (blue spot) or melanocytosis with nevus flammeus	PPV IIa/b
Phacomatosis spilorozea	Nevus spilus (speckled lentiginous nevus) with pale pink telangiectatic nevus	PPV IIa/b
Phacomatosis cesiomarmorata	Nevus caesius (blue spot) with cutis marmorata	PPV Va/b
Phacomatosis pigmentovascularis unclassifiable	Various pigmentary and vascular nevi	PPV IVa/b and no name

^aRevised classification proposed by Happle.⁸ The old classification of type I was considered not truly present in clinical practice, so it was not included in the new classification. The old type III was also partly type IV, which affected its reclassification to the new types.

CASE 1

A 48-year-old woman was referred with choroidal melanoma. Mild ipsilateral iris melanocytosis was observed. Long-standing ipsilateral unilateral congenital cutaneous nevus flammeus was noted. Phacomatosis cesioflammea was diagnosed. Melanoma subsequently metastasized to the liver.

CASE 2

A 78-year-old man was referred with choroidal melanoma and vitreous hemorrhage (Figure 3C and D). Minimal scleral melanocytosis was found. Prominent bilateral congenital cutaneous nevus flammeus was noted. Phacomatosis cesioflammea was diagnosed.

CASE 3

A 15-year-old Hispanic girl with prominent bilateral congenital cutaneous nevus flammeus was referred for evaluation (Figure 1A and B). Unilateral oculodermal melanocytosis was found. Phacomatosis cesioflammea was diagnosed. Ipsilateral optic disc melanocytoma was noted.

CASE 4

A 13-year-old boy with congenital cutaneous nevus flammeus and visual loss from choroidal hemangioma was referred for treatment (Figure 1C and D). Patchy choroidal melanocytosis was found on dilated examination. Phacomatosis cesioflammea was diagnosed. External radiation therapy was delivered to resolve the retinal detachment associated with the choroidal hemangioma.

CASE 5

A 42-year-old woman with choroidal nevus was referred to rule out melanoma. She was found to have choroidal melanocytosis and long-standing ipsilateral unilateral congenital cutaneous nevus flammeus. Phacomatosis cesioflammea was diagnosed. At a 3-year follow-up visit, growth of the melanoma was confirmed and treated.

CASE 6

A 77-year-old woman with lifelong unilateral congenital cutaneous nevus flammeus was found to have ipsilateral ocular pigmentation that proved on examination

and subsequent excision to be primary acquired melanosis of the conjunctiva with atypia (melanoma in situ) (Figure 3A and B). Phacomatosis cesioflammea was diagnosed.

CASE 7

A 6-week-old girl had been noted after birth to have bilateral congenital cutaneous nevus flammeus and was treated with dermatologic laser photocoagulation (Figure 2). At age 2 years, the tongue showed mild left hyperemia. Amblyopia in the right eye led to the discovery of subtle epiretinal membrane and prominent diffuse choroidal melanocytosis. Phacomatosis cesioflammea was diagnosed.

COMMENT

Phakos is Greek for birthmark or spot. *Phacomatosis* (preferred over *phakomatosis* when a Latin adjective follows⁸) is a term applied to a group of genetically determined conditions with oculoneurocutaneous findings. According to Happle,⁸ phacomatosis pigmentovascularis can be divided into 3 distinct types, including phacomatosis cesioflammea, phacomatosis spilorozea, and phacomatosis cesiomarmorata (Table 1). Phacomatosis cesioflammea is characterized by coexistence of a dermal melanocytosis or blue spot and nevus flammeus (port-wine stain). *Caesius* is Latin for bluish gray, and *flammea* is Latin for flame or fire. Additional findings in phacomatosis cesioflammea include nevus anemicus, focal alopecia, asymmetric limb length, glaucoma, and hypoplastic nails. Phacomatosis spilorozea is characterized by coexistence of nevus spilus (a speckled lentiginous nevus) and a light pink telangiectatic nevus (different from the darker port-wine stain). *Spilo* is Latin for spot or speckled, and *rosea* is Latin for pink. Associated findings include lymphedema, hemiparesis, seizures, and asymmetric limb length. Phacomatosis cesiomarmorata is the association of nevus caesius (blue-gray nevus and mongolian spot) and cutis marmorata telangiectatica congenita. *Marmorata* is Latin for marblelike. Related defects include asymmetric cerebral hemispheres, leg hyperplasia, and blue sclera.

Fernández-Guarino et al⁵ reviewed 216 published cases of phacomatosis pigmentovascularis through May 2007 and classified 77% as cesioflammea, 13% as spilorozea, 1% as cesiomarmorata, and 8% as unclassifiable. Almost all information on this topic in the literature emanates

Table 2. Clinical Features of Patients With Phacomatosis Cesiioflammea

Case No./ Sex/Age, y	Race/ Ethnicity	Unilateral or Bilateral	Eye	Melanocytosis				Age at Uveal Melanoma/ Melanocytoma, y
				Tissue Involved	Complete or Sectorial	Related Glaucoma	Related Uveal Melanoma	
1/F/48	White	Unilateral	Left	Iris	Sectorial ^a	No	Yes	48
2/M/78	White	Unilateral	Left	Sclera	Sectorial	No	Yes	78
3/F/15	Hispanic	Unilateral	Left	Eyelids, sclera, uvea	Complete	No	No, disc melanocytoma	15
4/M/13	White	Unilateral	Left	Choroid	Sectorial	No	No	...
5/F/42	White	Unilateral	Left	Choroid	Sectorial	No	Yes	45
6/F/77	White	Unilateral	Right	Conjunctiva (melanosis)	Sectorial	No	No	87 (melanoma in situ)
7/F/2	White	Unilateral	Right	Choroid	Complete	No	No	...

(continued)

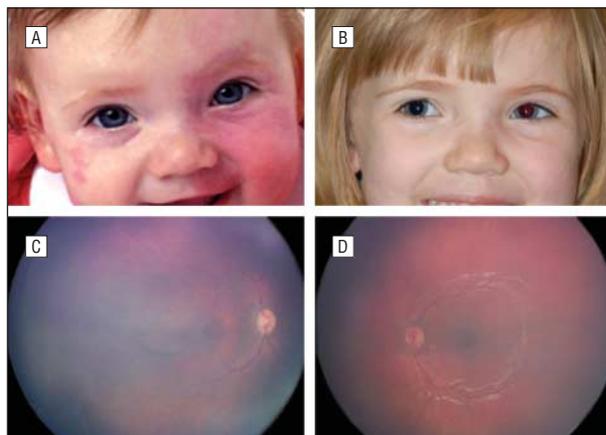


Figure 1. Case 7. Ocular melanocytosis may be found only in the choroid and may not be visible externally. Bilateral facial nevus flammeus in an infant (A) and 3 years later after laser treatment (B). At that time, dilated ocular examination disclosed choroidal melanocytosis in the right eye (C) but not in the left eye (D).

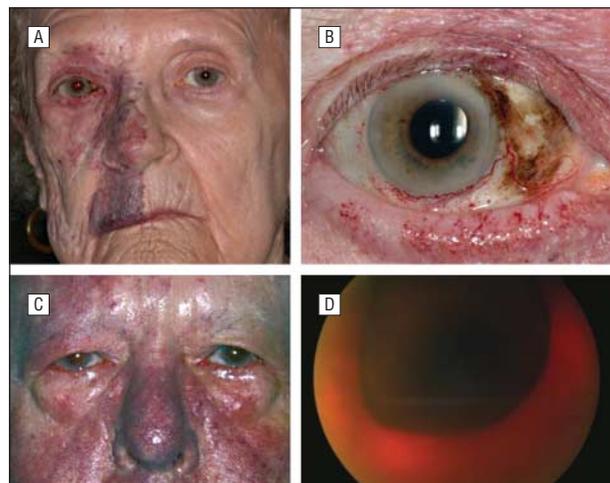


Figure 2. Phacomatosis pigmentovascularis of cesioflammea type with related melanoma. In case 6, a 77-year-old woman with lifelong facial nevus flammeus (A) developed conjunctival primary acquired melanosis (melanoma in situ) (B). In case 2, a 78-year-old man with lifelong facial nevus flammeus (C) developed choroidal melanoma (D). He demonstrated sectorial scleral melanocytosis in the quadrant of the tumor.

from dermatology studies. Few studies exist in the ophthalmology literature. A PubMed survey for the keywords *phacomatosis pigmentovascularis* and *ophthalmology* or *eye* yielded only 9 relevant publications, most of which were case reports. Teekhasaenee and Ritch⁶ described a series of 9 patients with phacomatosis pigmentovascularis from their glaucoma practice and noted melanocytosis bilaterally in 7 of them. They reported that congenital glaucoma occurred in all 10 eyes with both melanocytosis and episcleral vascular malformations of Sturge-Weber syndrome. Eyes with melanocytosis only or episcleral vascular malformations only did not develop glaucoma, so the authors concluded that the coexistence of these 2 conditions in one eye was a strong indicator of the development of glaucoma. They also advised long-term follow-up of all such patients for secondary glaucoma. Tran and Zografos⁷ described 3 patients with phacomatosis pigmentovascularis, classified as type IIb in their study but reclassified by us using the new terminology as phacomatosis cesioflammea. Among patients in that study, melanocytosis was unilateral and nevus flammeus was unilateral, but the conditions were

contralateral to each other in 2 cases and ipsilateral in 1 case. All 3 patients were initially seen with uveal melanoma in the eye with melanocytosis. These authors advised long-term follow-up for melanoma in affected patients.

In our case series, 6 patients had unilateral melanocytosis, and 1 patient had unilateral conjunctival primary acquired melanosis. Nevus flammeus was ipsilateral in all 7 patients and also contralateral in 3 patients. Among a glaucoma-based practice in the study by Teekhasaenee and Ritch,⁶ glaucoma was present in 10 eyes, and no patient showed melanoma. Conversely, in our tumor-based practice, glaucoma was observed in no patient, and 4 of 7 patients demonstrated melanoma. Findings similar to ours were reported by Tran and Zografos⁷ in their tumor-based practice. In fact, none of our patients had been correctly diagnosed as having phacomatosis pigmentovascularis before referral, and the reason for referral was possible melanoma in 5 patients. In our series, case 6 (Table 2) had nevus flam-

Table 2. Clinical Features of Patients With Phacomatosis Cesiioflammea (continued)

Nevus Flammeus									
Unilateral or Bilateral	Right or Left Side	Tissue Involved	Related Brain Hemangioma	Related Seizures	Related Choroidal Hemangioma	Related Glaucoma	Melanocytosis and Nevus Flammeus	Additional Findings	Follow-up Period, mo
Unilateral	Left	V2, V3	No	No	No	No	Ipsilateral	Monosomy 3 malignant melanoma with metastasis	51
Bilateral	Both	V1, V2, V3	No	No	No	No	Ipsilateral, contralateral	Vitreous hemorrhage	119
Bilateral	Both	V1, V2, V3, neck, trunk, extremities	No	No	No	Yes	Ipsilateral, contralateral	Amblyopia in right eye	45
Unilateral	Left	V2	No	No	Yes	No	Ipsilateral	Amblyopia in left eye	39
Unilateral	Left	V2	No	No	No	No	Ipsilateral	...	153
Unilateral	Right	V1, V2, V3	No	No	No	No	Ipsilateral	...	120
Bilateral	Both	V2, V3	No	No	No	No	Ipsilateral, contralateral	Epiretinal membrane, hemitongue erythema	8

Abbreviations: F, female; M, male; ellipsis, not applicable.
^aTrace.

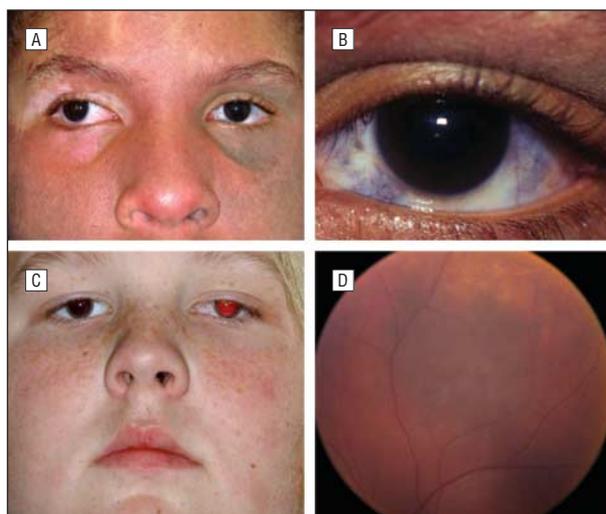


Figure 3. Clinical features of phacomatosis pigmentovascularis of cesioflammea type. Case 3 shows prominent bilateral facial nevus flammeus (A) in a Hispanic girl with obvious episcleral and periocular cutaneous melanocytosis (B). Case 4 shows subtle left-sided facial nevus flammeus (C) of the lower cheek region in a boy of white race/ethnicity, previously treated with laser, and subtle choroidal melanocytosis superiorly (D). There was no episcleral or cutaneous melanocytosis. The left pupil appeared red due to an associated choroidal hemangioma that was treated with external beam radiation therapy.

meus and ipsilateral extensive primary acquired melanosis, a relationship that has not been previously described as a classic feature of phacomatosis pigmentovascularis. We included the patient in this series because of the melanocytic derivation of the precancerous melanosis (melanoma in situ) in the background of nevus flammeus.

Dilated ocular examination is critical in establishing the diagnosis of melanocytosis. Most important, ocular melanocytosis was not visible externally in 5 of 6 pa-

tients herein and was apparent only with close examination of the sclera, iris, and choroid. In 3 of 6 patients, the pigment was solely in the choroid and was found only after dilated ocular examination. For example, 1 child received frequent laser therapy to a facial nevus flammeus and was finally discovered to have choroidal melanocytosis during our dilated ocular examination several years later. Based on our findings, we concur with Tran and Zografos⁷ that all patients with phacomatosis pigmentovascularis should receive dilated fundus evaluation for uveal melanoma. Furthermore, we believe that all patients with Sturge-Weber syndrome or cutaneous nevus flammeus should undergo dilated fundus examination for uveal melanocytosis and possible melanoma.

The association of dermal melanocytosis with cutaneous nevus flammeus is believed to result from a twin-spotting phenomenon.^{9,10} *Twin spotting* is the association of 2 genetically different clones of cells within a region of normal cells, generated by somatic recombination. In other words, twin spotting produces mosaic distribution of lesions, is sporadic and usually without familial occurrence, and affects monozygotic twins discordantly. Moutray et al¹¹ describe monozygotic twins who were discordant for phacomatosis cesioflammea, supporting the twin-spotting theory. In that study, twin 1 had normal findings, and twin 2 had cutaneous nevus flammeus of the arm, maxilla, and periocular region, in addition to mongolian spot and bilateral ocular melanocytosis. The authors concluded that phacomatosis pigmentovascularis resulted from mosaicism related to a postzygotic event.

In summary, we describe 7 patients with phacomatosis pigmentovascularis of cesioflammea type. We observed some new findings in our case series, including epiretinal membrane in 1 patient, primary acquired melanosis (melanoma in situ) in 1 patient,

and related choroidal melanoma in 3 patients. In several patients, ocular melanocytosis was not obvious externally, as it involved primarily the choroid. We advise that all patients with nevus flammeus should have a complete ocular evaluation by an ophthalmologist to search for related melanocytosis and possible melanoma, which may not be clinically evident to the nonophthalmologist.

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REFERENCES

1. Happle R. Neurocutaneous diseases. In: Freedberg IM, Eisen AZ, Wolf K, Austen KF, Goldsmid LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York, NY: McGraw-Hill; 2003:1806-1821.
2. Ota M, Kawamura T, Ito N. Phacomatosis pigmentovascularis [in Japanese]. *Jpn J Dermatol*. 1947;52:1-3.
3. Cordisco MR, Campo A, Castro C, et al. Phacomatosis pigmentovascularis: report of 25 cases. *Pediatr Dermatol*. 2001;18:70.
4. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, de la Luz Orozco-Covarrubias M, Ruiz-Maldonado R. Phacomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. *J Dermatol*. 2003;30(5):381-388.
5. Fernández-Guarino M, Boixeda P, de Las Heras E, Aboin S, García-Millán C, Olasolo PJ. Phacomatosis pigmentovascularis: clinical findings in 15 patients and review of the literature. *J Am Acad Dermatol*. 2008;58(1):88-93.
6. Teekhasaene C, Ritch R. Glaucoma in phacomatosis pigmentovascularis. *Ophthalmology*. 1997;104(1):150-157.
7. Tran HV, Zografos L. Primary choroidal melanoma in phacomatosis pigmentovascularis IIa. *Ophthalmology*. 2005;112(7):1232-1235.
8. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. *Arch Dermatol*. 2005;141(3):385-388.
9. Suzuki K, Ishizaki H, Takahashi H. Phacomatosis pigmentovascularis IIIb associated with porokeratosis, acanthosis nigricans and endocrinopathy in brother and sister [in Japanese, with an English summary]. *Skin Res (Hifu)*. 1990;32:65-70.
10. Danarti R, Happle R. Paradoxical inheritance of twin spotting: phacomatosis pigmentovascularis as a further possible example [letter]. *Eur J Dermatol*. 2003;13(6):612.
11. Moutray T, Napier M, Shafiq A, Fryer A, Rankin S, Willoughby CE. Monozygotic twins discordant for phacomatosis pigmentovascularis: evidence for the concept of twin spotting. *Am J Med Genet A*. 2010;152A(3):718-720.

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