Phacomatosis Pigmentovascularis of Cesioflammea 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 (cesioflammea 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.

Arch Ophthalmol. 2011;129(6):746-750

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). Since phacomatosis pigmentovascularis was first reported in 1947 by Ota et al, there have been few clinical series published on this rare condition. In the dermatology literature, Cordisco et al described 25 patients, Vidaurri-de la Cruz et al identified 24 patients, and Fernández-Guarino et al reported on 15 patients. In the ophthalmology literature, Teekhasaenee and Ritch described in 1997 a series of 9 patients with phacomatosis pigmentovascularis, some of whom demonstrated related glaucoma. In 2005, Happle 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 al characterized groups I to V, with a and b subdivisions, whereas the revised classification proposed in 2005 by Happle categorized 3 groups descriptively as phacomatosis cesioflammea, phacomatosis spilorosea, and phacomatosis cesiomarmorata (Table 1). Herein, we describe 7 patients with phacomatosis cesioflammea, all diagnosed following ocular consultation.

REPORT OF CASES

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

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lateral ocular pigmentation that proved on examination a cutaneous nevus flammeus was found to have ipsilateral cutaneous nevus flammeus. A 77-year-old woman with lifelong unilateral congenital cutaneous nevus flammeus was referred for treatment (Figure 1C and D). Patchy choroidal melanocytosis and long-standing ipsilateral unilateral congenital cutaneous nevus flammeus was noted. Phacomatosis cesioflammaea was diagnosed. Ipsilateral optic disc melanocytoma was noted. Phacomatosis cesioflammaea 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 cesioflammaea 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 cesioflammaea 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 cesioflammaea 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 cesioflammaea 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 photoacoagulation (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 cesioflammaea was diagnosed.

Phakos is Greek for birthmark or spot. Phacomatosis (preferred over phakomatosis when a Latin adjective follows) is a term applied to a group of genetically determined conditions with oculoneurocutaneous findings. According to Happle, phacomatosis pigmentovascularis can be divided into 3 distinct types, including phacomatosis cesioflammaea, phacomatosis spilorosea, and phacomatosis cesiomarmorata (Table 1). Phacomatosis cesioflammaea is characterized by coexistence of a dermal melanocytosis or blue spot and nevus flammeus (portwine stain). Caesius is Latin for bluish gray, and flammea is Latin for flame or fire. Additional findings in phacomatosis cesioflammaea include nevus anemicus, focal alopecia, asymmetric limb length, glaucoma, and hypoplastic nails. Phacomatosis spilorosea 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 al reviewed 216 published cases of phacomatosis pigmentovascularis through May 2007 and classified 77% as cesioflammaea, 13% as spilorosea, 1% as cesiomarmorata, and 8% as unclassifiable. Almost all information on this topic in the literature emanates from Table 1. Revised Classification of Phacomatosis Pigmentovascularis (PPV)*

<table>
<thead>
<tr>
<th>New Classification</th>
<th>Findings</th>
<th>Old Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phacomatosis cesioflammaea</td>
<td>Nevus caesius (blue spot) or melanocytosis with nevus flammeus</td>
<td>PPV IIa/b</td>
</tr>
<tr>
<td>Phacomatosis spilorosea</td>
<td>Nevus spilus (speckled lentiginous nevus) with pale pink telangiectatic nevus</td>
<td>PPV IIa/b</td>
</tr>
<tr>
<td>Phacomatosis cesiomarmorata</td>
<td>Various pigmenitary and vascular nevi</td>
<td>PPV Va/b</td>
</tr>
<tr>
<td>Phacomatosis pigmentovascularis unclassifiable</td>
<td>Nevus caesius (blue spot) with cutis marmorata</td>
<td>PPV Va/b and no name</td>
</tr>
</tbody>
</table>

*Revised classification proposed by Happle. 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.
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 Ritch 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 Zografos 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 Zografos 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 flammeus.}

### Table 2. Clinical Features of Patients With Phacomatosis Cesioflammea

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

(continued)
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 patients 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 Zografos’ 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. 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 al 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 periorbital 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 ipsilateral monosomy 3 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.

Submitted for Publication: July 9, 2010; revision received September 1, 2010; accepted October 7, 2010.

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Author Contributions: Dr C. L. Shields had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Eye Tumor Research Foundation (Dr C. L. Shields).

Role of the Sponsor: The funders had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES