A New Macular Dystrophy With Anomalous Vascular Development, Pigment Spots, Cystic Spaces, and Neovascularization

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Objective: To clinically phenotype an inherited macular dystrophy with peculiar intraretinal pigment spots, cysts, and hemorrhage in a 24-year-old female proband and her family.

Methods: Extended family members of the proband underwent dilated fundus examination, optical coherence tomography, and, in selected cases, fluorescein angiography and electroretinography.

Results: Seventeen family members, representing 3 generations and ranging in age from 5 to 64 years, were clinically examined. Visual acuities ranged from 20/20 to 20/200. Amblyopia and strabismus were frequently present in affected individuals. Consistent with an autosomal dominant pattern of inheritance, 7 family members had multiple central macular cystic spaces and flat, round, densely pigmented spots within the retina. There were right-angle vessels and telangiectasis in the central macula. Two subjects showed evidence of active macular neovascularization with leakage on fluorescein angiography at ages 7 and 24 years, which was responsive to either focal laser or a single injection of bevacizumab. In those cases examined, multifocal electroretinography showed a diminished foveal response.

Conclusions: This spotted cystic neovascular macular dystrophy appears to represent a new autosomal dominant retinal condition. Because these patients are at risk for choroidal neovascularization, identification of the responsible gene may provide insight into the mechanisms of pathological neovascularization.


A 24-YEAR-OLD WOMAN WAS referred to The University of Iowa for evaluation of unusual pigment changes in her maculae associated with a recent retinal hemorrhage. Additional investigation disclosed that several members of her extended family shared characteristic features that included abnormal macular vessels, cystic spaces, and pigment deposition in multiple retinal layers, which suggested the presence of an inherited retinal dystrophy. These fundus findings did not match any previously published description of a macular or retinal dystrophy. Pedigree analysis of the family suggested an autosomal dominant pattern of inheritance.

REPORT OF A CASE

As a child, the female proband (subject V-3) had undergone patching for strabismic amblyopia in her right eye, her parents recalled. By age 14 years, macular pigment clumping was noted in both eyes, and her visual acuity was between 20/30 and 20/50. She was referred to our clinic at age 24 years for evaluation of vision loss and macular “scarring.” She had no systemic medical problems. Two weeks before presentation, she had noticed difficulty reading with her left eye. On examination, her visual acuity was 20/60 OU with a hyperopic refraction of +4.00 + 1.50 × 105 OD and +6.00 + 0.25 × 121 OS. There was no improvement with pinhole correction. There was no relative afferent pupillary defect, and her intraocular pressure was 20 mm Hg OU. Her visual fields were full to confrontation, but she demonstrated a 10– prism diopter alternating exotropia. The results of her anterior segment examination were unremarkable.

A dilated fundus examination demonstrated atypical pigment spots centered in the macula of both eyes (Figure 1A–C). There were cystic spaces and a small retinal hemorrhage in the left eye. The retinal periphery appeared normal without flecks, intraretinal pigment migration (“bone spicules”), or choroidal atrophy. Fluorescein angiography showed early
Figure 1. Fundus imaging in the proband. A, The right macula shows pigment spots and cystic cavities, along with atrophic and fibrotic changes. B, The left macula displays similar features in addition to a retinal hemorrhage. C, High-magnification view of the left macula. D through F, Early, middle, and late fluorescein angiography of the left fundus shows progressive leakage consistent with 2 foci of neovascular membranes. G, Stereo angiogram shows abnormal foveal vasculature. Arterioles dive deep into the retina before they reach the fovea and directly into pigment spots. H, Representative optical coherence tomography line scans of the left eye show high-reflectance regions and shadowing corresponding to the pigment spots. Hyporeflective cysts are present in the inner and outer plexiform layers. I, The left macula shows resolution of the hemorrhage and edema after treatment with intravitreal bevacizumab. J, After treatment, optical coherence tomography shows consolidation of the hyporeflective cysts.
blockage colocalizing with the pigment spots. Late phases demonstrated progressive leakage consistent with 2 foci of neovascular membranes in the left eye (Figure 1D-F). There was also some retinal telangiectasia near the fovea. Of particular note, there were several arterioles that, in their course toward the fovea, passed through the deep retina before supplying more superficial retinal capillaries. Stereoscopic examination and angiography demonstrated abnormal right-angle arterioles diving into the deep retina before reaching the fovea or directly into the pigment spots (Figure 1G). Optical coherence tomography (OCT) showed hyporeflective spaces at the inner and outer plexiform layers and high-reflectance spots with dark shadows corresponding to the pigment spots at various levels of the retina (Figure 1H). There was no subretinal fluid. At the initial visit, the patient elected observation.

Three months later, her visual acuity had decreased to 20/70, and, although much of the hemorrhage had dissipated, OCT confirmed that the intraretinal fluid and macular thickness had increased. At this time, the patient elected to receive an off-label intravitreal injection of 1.25 mg of bevacizumab. Six weeks later her visual acuity had improved to 20/50, and the macular fluid was replaced by a small fibrotic scar (Figure 1I). The central macular thickness had decreased from 329 to 298 μm. It is interesting to note that, after treatment, the small round hyporeflective cavities on OCT seemed to have coalesced with one another, leaving fewer, larger cavities, some of which were just beneath the nerve fiber layer (Figure 1J).

The proband reported that some other members of her family had “scarring” in their eyes. Ranging in age from 5 to 63 years and spanning 3 generations, 16 additional family members were identified and examined.

### METHODS

The study was approved by The University of Iowa’s institutional review board, and informed consent was obtained from study participants. Subjects underwent eye examinations that included slitlamp examination, dilated retinal biomicroscopy and indirect ophthalmoscopy, OCT, and, in selected cases, fluorescein angiography and multifocal electroretinography (mfERG). The mfERG was performed on selected subjects by means of a Burian-Allen contact lens electrode with a 103-hexagon black-and-white stimulus. The mfERG first-order response was analyzed.

### RESULTS

Pigment spots and cystic spaces were present in 7 family members, including both males and females. There were no skipped generations and no history of consanguinity. Thus, the pedigree was most compatible with an autosomal dominant pattern of inheritance (Figure 2).

The proband’s paternal generation (IV) showed less severe phenotypes with better visual acuities. Subjects IV-2 and IV-5 had only 1 or 2 characteristic pigment spots in the macula (Figure 3). Subject IV-5 had abnormal right-angle vessels, including the cilioretinal artery in the right eye that stopped short of the fovea and dove deep into the retina or into the pigment spot (Figure 3G). Moreover, there was no foveal capillary-free area, and temporal to the fovea, a vascular anomaly was identified with connection of the upper and lower retinal vessels. Their OCTs showed characteristic pigment spots with shadowing and milder hyporeflective spaces, and there seemed to exist photoreceptor loss in the macular area of both eyes. There were diffuse, small granular pigment changes throughout the posterior poles. A number of subjects had strabismus, amblyopia, and hyperopia (Table).

Subject IV-3 (Figure 4A-C) had strabismus surgery with visual acuity of 20/70 OD and 20/25 OS. He had only 1 pigment spot adjacent to the disc and only mild granular pigment changes in the macula. The visual fields did not show a central scotoma (data not shown). An mfERG, however, demonstrated a diminution of the relative foveal peak response (Figure 4D and E). The amplitude was decreased in the central ring of the 103 hexagons. The outer ring appeared preserved. There was no significant delay in the implicit time. Some family members in earlier generations I, II, and III were reportedly “blind,” but they either had died or were unavailable for examination.

Generation V, which included the proband, generally showed more severe phenotypes than their parents. Subject V-6 was examined at The University of Iowa at age 7 years for decreased vision in her left eye due to an “idiopathic” neovascular membrane. Her visual acuity at the time was 20/40 OD and 20/70 OS with a hyperopic refraction of +7.50 OU. The results of her anterior segment examination were unremarkable. The fundus examination of the right eye showed mild telangiectasia near the fovea, disc drusen, and an inactive peripapillary choroidal neovascular membrane (Figure 5A). In the left eye, fundus examination showed disc drusen, a large peripapillary choroidal neovascular lesion with fibrosis and atrophy, a maculopathy with a pigment spot, and an abnormal pattern of right-angle vessels and subretinal fluid (Figure 5B and C). Echography confirmed the presence...
of disc drusen. In addition, there was a juxtafoveal pig-
mented lesion with subretinal fluid. Fluorescein angiog-
raphy of the left eye showed anastomosis of right-angle
retinal arterioles to a choroidal neovascular membrane
that displayed focal progressive hyperfluorescence
and leakage. The choroidal neovascular membrane was
successfully ablated with focal krypton red laser
(Figure 5D–F). Her vision stabilized at 20/60 OS within
a few weeks. On recent examination at age 20 years, her
visual acuity was 20/50 OD and 20/200 OS. Interest-
ingly, new pigment clumps and cysts had developed in
each eye (Figure 5G and H). The treated eye showed con-
solidation of the peripapillary fibrosis, extension of at-
rophy, and a flat stable scar. Horizontal OCT confirmed
large cysts in the right eye and new, characteristic pig-
ment spots in both eyes (Figure 5I). Other generation V
subjects had similar findings but without a choroidal neo-
vascular membrane. Subjects V-1 and V-4 showed right-
angle arterioles, telangiectasia, numerous pigment spots,
cystic changes, and mild epiretinal membranes (Figure 6).
Both subjects had strabismus.

Generation VI included children aged 5 to 9 years. Al-
though similar to subject V-6 in age at presentation, none
of these subjects had pigment spots or retinal hemor-
rhages. Nevertheless, subjects VI-5 and VI-6 showed either
telangiectasia near the fovea (Figure 7A and B) or very
mild cystic changes and hypopigmented spots in the
macula. It is difficult to compare the severity of disease
in this generation because of their early age. Their vi-
sual acuities were relatively good, but subject VI-6 did
have strabismus. Because of the progressive nature of the
disorder demonstrated by subjects in previous genera-
tions, we consider these children “at risk,” and they will
require close follow-up. Optical coherence tomography

Figure 3. Fundus imaging in generation IV. A and B, The right macula of subject IV-2 shows a pigment spot; the left shows subtle telangiectasia. C, Hyperreflec-
tive regions are present on optical coherence tomography. D through F, Maculae of subject IV-5 show pigment spots (P), telangiectasia, and cystic structures on fundus
imaging and optical coherence tomography. G, Stereoscopic fluorescein angiographic view of telangiectasia in the right macula. Abnormal arterioles dive deep into the
retina as they approach the fovea, and 2 prominent arterioles dive into the developing pigment spot.

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was not available for either subject. The clinical findings are summarized in the Table.

**COMMENT**

There are several interesting and distinguishing features of this newly reported macular dystrophy. In addition, the broad age range represented by the 7 affected individuals and the 10- and 13-year follow-up fundus images in 2 cases provide some information on the longitudinal natural course, suggesting a chronology of pathological events. The macular findings, which appear among the youngest affected individuals, are foveal telangiectasia, vertical right-angle arterioles, and anomalously deep lamellar location of perifoveal arterioles, and these were identified as early as age 7 years. These features are followed by or associated with irregular cystic spaces in the macula. The spaces increase in size over time, and pigmentation develops in the macula or adjacent to the disc at age 20 years or later. These pigmented spots occur in deep, superficial, or multiple levels of the retina. The number, density, and size of spaces and spots increase over time. Because of the density of black pigmentation and large spot size, we hypothesize that this feature represents migration of retinal pigment epithelium or other melanocytic cells within the cystic spaces. Some clinical manifestations may be secondary changes of the early vascular abnormality.

In 2 individuals, the proband (V-3) and her cousin (V-6), choroidal neovascularization developed. In the paternal generation (IV), affected individuals had no choroidal neovascularization, but they did have pigment spots, cysts, and telangiectasis, and 1 subject had an abnormal mfERG suggestive of underlying photoreceptor dysfunction near the fovea.

We were unable to identify any extraocular consequences of this disorder. Possible explanations could include the limited number of affected individuals examined, ascertainment bias, or absence of extraocular manifestations. Nearly all of the affected subjects demonstrated hyperopia and strabismus at a young age. Because all patients affected by strabismus had visual loss at the time of our examination, we presume that the strabismus is organic in origin. Given the early history of strabismus and telangiectasia and the presence of deep, intraretinal, branching arterioles, we believe that this disorder may involve a gene mutation affecting retinal vascular development in the macula. The findings may be similar to those of the sibling pairs with spastic paraplegia described by Leys et al, who also had macular telangiectasia, right-angle vessels, and choroidal neovascularization, but less obvious deep arterioles and pigmented spots.

There are several features that distinguish this condition from other retinal vascular disorders and reported dystrophies. None of the members of this pedigree, for example, demonstrated vitelliform lesions, flecks,
pisiform deposits, drusen, a bull’s-eye pattern, or pigment changes typical of cone or retinal pigment epithelial pattern dystrophy. The differential diagnosis of hyporeflective spaces among some affected individuals includes fenestrated sheen macular dystrophy, familial internal limiting membrane dystrophy, and idiopathic juxtafoveal telangiectasia (IJT).\textsuperscript{3-6} However, neither of the dystrophies has dense, round pigment spots, nor has either been associated with retinal hemorrhages. Fenestrated sheen–affected maculae develop retinal atrophy. Familial internal limiting membrane dystrophy shows very prominent retinal undulations, not found in any member of this pedigree.

The peculiar deep retinal arterioles found in some of our subjects suggest that anomalous vascular development may be the fundamental abnormality of the dystrophy. This dystrophy shares a subset of phenotypic features, which include juxtafoveal telangiectasia and hyporeflective spaces, with IJT.\textsuperscript{7} However, spotted cystic hemorrhagic dystrophy demonstrates highly penetrant, autosomal dominant inheritance, unique large pigmented spots, and anomalously located central macular...

Figure 4. Fundus imaging and multifocal electroretinography in generation IV, subject IV-3. A and B, There is a pigment spot adjacent to the left disc and small granular pigmentation in the posterior poles. C, The optical coherence tomography line scans in the right macula were normal, but in the left there was a hyperreflective region with shadowing at the pigment spot (P). Other hyperreflective regions and shadowing correspond to blood vessels near the disc. D and E, Multifocal electroretinography in subject IV-3 shows diminished foveal peaks.
arterioles, which distinguish it from IJT. In IJT the acquired and progressive telangiectasia is contiguous with normally located, superficial retinal vessels. There was no predilection for temporally located telangiectasia, as is the usual case with IJT. There was no evidence of atrophy or an inner lamellar foveal cyst, which are the early foveal signatures of that disease. In addition, in IJT, pigment epithelial hyperplasia that proceeds to course
through the middle of the retina may be appreciated as mottling and hyperpigmentation, or as perivascular linear deposits (bone spicules), but not as large, circular intraretinal deposits. Macular pigment analysis and fluorescein angiography could not be performed in generation VI subjects to determine whether early IJT changes, such as reduction in foveal pigment or perifoveal leakage without cystic changes, were present. Nevertheless, these typical IJT features were absent in cases of less advanced disease in which fluorescein angiography was performed. Some members of our pedigree were originally diagnosed as having IJT or idiopathic choroidal neovascularization. Late stages of this condi-

Figure 6. Fundus imaging in generation V. A and B, Stereo images in subject V-1 demonstrate abnormal foveal vasculature, numerous pigment spots at various levels of the retina, and large cysts in both eyes. C and D, Subject V-4 had similar abnormal foveal vessels, pigment spots, and cysts. The fine retinal sheen suggests that epiretinal membranes are present in both eyes. E and F, Optical coherence tomography demonstrates the corresponding cysts and pigment shadows.

Figure 7. Fundus imaging in generation VI. A and B, Nine-year-old subject VI-5 shows telangiectasia (arrows), hypopigmented spots, and small cysts with granular pigment changes near the fovea. C, Five-year-old subject VI-6 had milder telangiectasia (arrow) and hypopigmented spots but no cysts.
Genetic Risk of IJT in Subjects of European American Descend

tions in the recessive ataxia telangiectasia gene confer a was not evident.2,9-11 Further studies suggest that muta-
pathic juxtafoveal telangiectasia with typical features was described in siblings, but multigenerational disease never occurs so early in IJT.

Rare pedigrees that are phenotypically indistinguishing from IJT have been reported, but IJT is usually sporadic without any obvious pattern of inheritance. Idio-
dilated parafoveal capillaries may also be seen in a variety of noninherited retinal vascular diseases such as diabetes.14 None of these conditions, however, shows the atypical features or dominant inheritance pattern of the family we examined. Further understanding of the phenotype and genotype of this dystrophy may provide an additional avenue of insight into retinal vasculogenesis and disorders such as IJT and choroidal neovascularization.

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