Geographic Chorioretinal Atrophy in Pseudoxanthoma Elasticum

SCOTT D. SCHOENBERGER AND ANITA AGARWAL

• PURPOSE: To describe a series of patients with geographic atrophy independent of choroidal neovascularization (CNV) in pseudoxanthoma elasticum and to report progression over time.
• DESIGN: Retrospective observational case series.
• METHODS: Records of all Vanderbilt Eye Institute patients with pseudoxanthoma elasticum and at least 1 set of color fundus photographs were reviewed (41 eyes of 21 patients). Fluorescein angiography, fundus autofluorescence, and optical coherence tomography images were reviewed, when available. In patients with geographic atrophy and at least 1 year of follow-up, atrophy was measured using fundus photographs. Main outcome measures included incidence of geographic atrophy, progression over time, and macular features associated with development or progression of geographic atrophy.
• RESULTS: Eight eyes (20%) of 5 patients had geographic atrophy independent of CNV. Progression was documented in 6 eyes of 4 patients followed for at least 1 year (mean 3.5 years). Mean initial and final area was 2.9 and 9.5 mm², respectively, and growth rate was 1.7 mm² per year. Of the 6 eyes, 3 had a final visual acuity of 20/20 and the other 3 ranged from 20/150 to 20/400. All 8 eyes had pattern dystrophy, and 5 had linear pigment deposits that appeared to predict development or growth of atrophy.
• CONCLUSIONS: Isolated geographic atrophy independent of CNV can develop in pseudoxanthoma elasticum, causing significant vision loss. Linear pigmented pattern dystrophy appears to predate geographic atrophy. Progression is similar to age-related macular degeneration. Recognition of this feature is important, especially if therapies to slow or reverse geographic atrophy become available. (Am J Ophthalmol 2013;156:715–723. © 2013 by Elsevier Inc. All rights reserved.)

PSEUDOXANTHOMA ELASTICUM IS A SYSTEMIC disease that primarily affects the elastic tissue of the skin, cardiovascular system, and eyes. Inheritance is usually autosomal recessive and the causative mutation is in subclass C of the ATP-binding cassette transporter gene, where numerous mutations are reported. Pathologic changes are most pronounced in the dermis, Bruch membrane, and blood vessels. Characteristic fundus lesions include angioid streaks, peau d’orange, optic disc drusen, pattern dystrophy, crystalline bodies, midperipheral “comet-tail” atrophic spots, and choroidal neovascularization (CNV). Numerous retinal pigment epithelium (RPE) alterations have been described, including atrophy along angioid streaks, atrophy associated with CNV, and pattern dystrophy. With CNV, RPE alterations include rips, multilobular areas of atrophy, and broad areas of poorly demarcated thinning/atrophy.

The most common cause of vision loss is CNV and disciform scarring, which occurs in 68%-86% of cases. Little has been reported regarding primary geographic atrophy in the absence of CNV. Identified cases only exist in case reports or hidden in larger studies. Longitudinal follow-up information and proposed mechanisms of pathogenesis of the atrophy are lacking.

The purpose of the current study is to describe a series of patients with geographic chorioretinal atrophy independent of CNV in pseudoxanthoma elasticum. Serial photography allowed for measuring progression rates of geographic atrophy. We also attempt to identify other clinical features of pseudoxanthoma elasticum that may predict the development or progression of geographic atrophy.

METHODS

• PATIENT SELECTION: A retrospective observational study was performed on all patients seen at the Vanderbilt Eye Institute between 2002 and 2012 with a diagnosis of “angioid streaks” or “pseudoxanthoma elasticum” based on ICD-9 coding. Vanderbilt University Institutional Review Board approval was obtained for this retrospective review. Data were collected in accordance with compliance set forth by the Health Insurance Portability and Accountability Act of 1996. The study adhered to the tenets of the Declaration of Helsinki.

All patients with a diagnosis of “angioid streaks” or “pseudoxanthoma elasticum” were identified. Only those with at least 1 set of digital color fundus photographs and medical records were reviewed. Each patient’s diagnosis of pseudoxanthoma elasticum was made based on fundus

Accepted for publication May 23, 2013.
From the Vanderbilt Eye Institute, Vanderbilt University School of Medicine, Nashville, Tennessee.
Inquiries to Anita Agarwal, Vanderbilt Eye Institute. 2311 Pierce Avenue, Nashville, TN 37232; e-mail: anita.agarwal@vanderbilt.edu
findings with or without a skin examination or biopsy. Clinical findings, fundus photographs, fluorescein angiography (FA), optical coherence tomography (OCT), and fundus autofluorescence (FAF) were reviewed.

• IDENTIFICATION AND MEASUREMENT OF GEOGRAPHIC ATROPHY: Geographic atrophy was determined based on fundus photography. Patients who had geographic atrophy distinct from peripapillary atrophy or chorioretinal atrophy that followed angioid streaks were identified. Patients were excluded if geographic atrophy was associated with CNV. This was defined by the presence of subretinal hemorrhage, lipid, fluid, subretinal fibrosis, or pigment epithelial hyperplasia contiguous with geographic atrophy.

Geographic atrophy was measured on color fundus photographs using OIS WinStation XP 5000 software (Ophthalmic Imaging Systems, Inc, Sacramento, California, USA). Fifty-degree images centered at the posterior pole were used in all cases, allowing for standardization of measurements. If present, FA and FAF were used to help identify areas of atrophy, but they were not used for measurements. The magnification obtained on FAF images does not conform to the standard magnification obtained on fundus photographs; hence these images were not used. The lesions were measured separately by each author (S.D.S., A.A.) and the mean value for each eye was used for reporting. Growth per year was determined using the first and last digital fundus photograph showing geographic atrophy.

• OTHER FEATURES OF PSEUDOXANTHOMA ELASTICUM: In addition to geographic atrophy, photographs were also reviewed for angioid streaks, atrophy attributable to CNV, atrophy along angioid streaks, disc drusen, peau d’orange, comet-tail lesions, pattern dystrophy, crystalline bodies, and signs of CNV (subretinal hemorrhage, lipid, fluid, subretinal fibrosis, or pigment epithelial hyperplasia). Patient demographics and other examination findings were reviewed. Main outcome measures included the incidence of geographic atrophy without CNV, progression over time, and other macular features associated with development or progression of geographic atrophy.

RESULTS

• PATIENTS: A total of 41 eyes (21 patients) were identified with a clinical diagnosis of pseudoxanthoma elasticum and at least 1 set of digital fundus photographs. One patient had photographs performed only in 1 eye but had bilateral disease. Mean age of the 21 patients at initial photography was 50 years (range 19-71 years). Signs of active or inactive CNV were present in 24 eyes (59%). Other findings included angioid streaks (41 eyes, 100%), pattern dystrophy (19 eyes, 46%), chorioretinal atrophy along angioid streaks (17 eyes, 41%), peau d’orange (16 eyes, 39%), atrophy with CNV (15 eyes, 37%), disc drusen (10 eyes, 24%), crystalline bodies (9 eyes, 22%), and comet-tail lesions (7 eyes, 17%). All eyes with pattern dystrophy had isolated pigment clumps consistent with fundus pulverulentus. In addition, linear pigment deposits similar to the butterfly-type pattern dystrophy were present in 7 eyes of 4 patients.

• GEOGRAPHIC ATROPHY: Geographic atrophy separate from angioid streaks or CNV was identified in 8 eyes (20%) of 5 patients. Mean age of eyes when geographic atrophy was first identified was 50 years (range 37-53 years). Pattern dystrophy was present in all 8 eyes (100%), compared to 33% without this finding. The type of pattern dystrophy present was clumps of RPE distributed in a random fashion in the macula, typical of fundus pulverulentus, and sometimes arranged in a linear pattern resembling the butterfly type. Those with multiple sets of photographs separated by at least 1 year (6 eyes of 4 patients) were measured for area of geographic atrophy. Two eyes of 1 patient with geographic atrophy had only 3-month follow-up and were excluded from measurement analysis. The mean initial and final area of the 6 eyes was 2.9 mm² (range 0.3-8.1 mm²) and 9.5 mm² (range 0.8-21.2 mm²), respectively, and mean growth rate was 1.7 mm² per year (range 0.4-2.5 mm² per year). Of the 6 eyes measured, 3 had visual acuity (VA) of 20/20 at both initial and final visits. Three other eyes worsened over time, with initial VA ranging from 20/25 to 20/200 and final VA ranging from 20/150 to 20/400. Further characteristics of the 6 eyes measured are described below and in the Table.

Patient 1. Patient 1 was a 50-year-old man with VA of 20/20 associated with paracentral scotomas in both eyes. Fundus photography at presentation showed angioid streaks, pattern dystrophy, comet-tail lesions, and disc drusen in both eyes (Figure 1, Top row). His left eye had a small patch of geographic atrophy in the macula, measuring 2.50 mm². He also had a “plucked chicken skin” appearance on his neck. Two years and five months later, the atrophy had enlarged in his left eye and he developed geographic atrophy in the macula of his right eye (1.50 mm²), but he retained 20/20 vision OU (not shown). At his final visit, four years and five months after initial presentation, VA remained 20/20 OU. The atrophy continued to enlarge in both eyes, with an area of 6.51 mm² OD and 7.13 mm² OS (Figure 1, Bottom row). The atrophy had enlarged by 2.51 mm² per year OD and 1.05 mm² per year OS. Isolated pigment clumps (white arrows) and linear pigment deposits (black arrowheads) were present. FAF revealed numerous intensely hyperautofluorescent areas scattered in the macula corresponding to isolated pigment clumps (Figure 2, Top row; white arrows). Temporal to
geographic atrophy in both eyes were linear areas of mild hyperautofluorescence corresponding to linear pigment deposits (black arrowheads). Infrared and spectral-domain OCT imaging was performed on the right (Figure 2, Middle row) and left (Figure 2, Bottom row) eyes, which showed hyperreflectivity at the level of the outer nuclear layer corresponding to the linear pigment deposits (Figure 2, Middle row and Bottom row, white arrowhead; magnified on left insets). Subretinal hyperreflectivity corresponding to RPE was present in areas of isolated pigment clumps (Figure 2, Middle row and Bottom row, white asterisk; magnified on right insets).

**TABLE.** Demographic Information and Ocular Features Over Time in 6 Eyes With Progressive Geographic Chorioretinal Atrophy Attributable to Pseudoxanthoma Elasticum

<table>
<thead>
<tr>
<th>Patient (Eye)</th>
<th>Age, Sex</th>
<th>Initial Visual Acuity</th>
<th>Initial Area of Geographic Atrophy (mm²)</th>
<th>Length of Follow-up</th>
<th>Final Visual Acuity</th>
<th>Final Area of Geographic Atrophy (mm²)</th>
<th>Growth of Geographic Atrophy (mm²/y)</th>
<th>Linear Pigment Deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (OD)</td>
<td>52, M</td>
<td>20/20</td>
<td>1.50</td>
<td>2 years</td>
<td>20/20</td>
<td>6.51</td>
<td>2.51 mm²/y</td>
<td>Yes</td>
</tr>
<tr>
<td>1 (OS)</td>
<td>50, M</td>
<td>20/20</td>
<td>2.50</td>
<td>4 years, 5 months</td>
<td>20/20</td>
<td>7.13</td>
<td>1.05 mm²/y</td>
<td>Yes</td>
</tr>
<tr>
<td>2 (OD)</td>
<td>53, F</td>
<td>20/200</td>
<td>8.07</td>
<td>6 years</td>
<td>20/400</td>
<td>21.20</td>
<td>2.19 mm²/y</td>
<td>Yes</td>
</tr>
<tr>
<td>2 (OS)</td>
<td>53, F</td>
<td>20/60</td>
<td>3.14</td>
<td>6 years</td>
<td>20/150</td>
<td>17.47</td>
<td>2.39 mm²/y</td>
<td>Yes</td>
</tr>
<tr>
<td>3 (OS)</td>
<td>41, M</td>
<td>20/25</td>
<td>1.92</td>
<td>15 months</td>
<td>20/200</td>
<td>3.71</td>
<td>1.43 mm²/y</td>
<td>Yes</td>
</tr>
<tr>
<td>4 (OS)</td>
<td>37, M</td>
<td>20/20</td>
<td>0.34</td>
<td>15 months</td>
<td>20/20</td>
<td>0.80</td>
<td>0.37 mm²/y</td>
<td>No</td>
</tr>
</tbody>
</table>

*The right eye of Patient 1 developed geographic atrophy 2 years and 5 months after his initial evaluation, whereas atrophy was present in his left eye at initial evaluation.

**FIGURE 1.** Fundus photographs of a 50-year-old man (Patient 1) with pseudoxanthoma elasticum showing the evolution of pattern dystrophy with progressive non-neovascular geographic atrophy. (Top left and Top right) Images at presentation display angioid streaks, disc drusen, and pattern dystrophy that appeared in some areas as isolated pigment clumps (white arrows) and in other areas as linear pigment deposits (black arrowhead). Geographic atrophy is present in the left eye measuring 2.50 mm². (Bottom left and Bottom right) Four years and 5 months later, the right eye has geographic atrophy (6.51 mm²), while the atrophy in the left eye is larger (7.13 mm²). Disappearance of the linear pigment deposits is observed with progression of the geographic atrophy.
Patient 2. Patient 2 was a 49-year-old woman with angioid streaks, peau d'orange, pigment clumps, and linear pigment deposits in the macula consistent with pattern dystrophy in both eyes, without signs of CNV or geographic atrophy. (Figure 3, Top row; linear pigment deposits, black arrowheads). Visual acuity at that time was 20/30 OD and 20/40 OS. At age 53, her vision worsened to 20/200 OD and 20/60 OS. Central geographic atrophy was present in both eyes, measuring 8.07 mm² OD and 3.14 mm² OS (Figure 3, Second row). Over the next 6 years, VA declined to 20/400 OD and 20/150 OS with enlargement of geographic atrophy in both eyes, measuring 21.20 mm² OD and 17.47 mm² OS (Figure 3, Third row). The progression rate was 2.19 mm² per year OD and 2.39 mm² per year OS. FAF showed geographic atrophy to be distinct from peripapillary atrophy and angioid streaks (Figure 3, Bottom row). FAF also showed extensive areas of hyper- and hypofluorescence, indicative of widespread RPE disease. Pigment clumps of pattern dystrophy were more easily seen on FAF than on the photographs (white arrows).

Patient 3. Patient 3 was a 41-year-old man with VA of 20/20 OD and 20/25 OS. Angioid streaks, pattern dystrophy, and midperipheral comet-tail lesions were seen in both eyes on fundus photography. He had
FIGURE 3. Fundus photographs of a 49-year-old woman (Patient 2) with pseudoxanthoma elasticum showing the evolution of pattern dystrophy with progressive non-neovascular geographic atrophy. (Top left and Top right) Fundus photographs at presentation show pigment clumps (white arrows) and linear pigment deposits (black arrowheads) in both eyes without geographic atrophy. (Second row left and Second row right) Four years later there are large areas of geographic atrophy in both eyes, measuring 8.07 mm² OD and 3.14 mm² OS. (Third row left and Third row right) Photographs 6 additional years later demonstrate enlargement of atrophy in both eyes, measuring 21.20 mm² OD and 17.47 mm² OS. (Bottom left and Bottom right) Fundus autofluorescence shows hypoautofluorescence of the geographic atrophy. Pigment clumps are subtle on photography but more evident on autofluorescence (white arrows). The linear pigment deposits gradually disappear with enlargement of the geographic atrophy.
subfoveal fibrosis OD and several distinct areas of atrophy OS measuring a total of 1.92 mm² (Figure 4, Top left) that were also seen on FAF (Figure 4, Top right). Intensely hyperautofluorescent pigment clumps (white arrows) and mildly hyperautofluorescent linear pigment deposits were seen (black arrowheads). Fifteen months later, VA declined to 20/50 OD and 20/200 OS. Fundus photographs (Figure 4, Bottom left) and FAF (Figure 4, Bottom right) showed enlargement of geographic atrophy in the left eye, now measuring a total of 3.71 mm². The rate of enlargement was 1.43 mm² per year. Some pigment clumps remained (white arrows), while the linear pigment deposits evolved into a ring.

**DISCUSSION**

Geographic atrophy may be seen in several diseases, including age-related macular degeneration (AMD), maternally inherited diabetes and deafness, inherited pattern dystrophies, Stargardt macular dystrophy, central areolar dystrophy, extensive macular atrophy with pseudodrusen-like appearance, late-onset retinal macular degeneration, and a resolved vitelliform lesion associated with cuticular drusen. There are scattered reports describing geographic atrophy in pseudoxanthoma elasticum in the absence of CNV. We describe a series of eyes with geographic atrophy in patients with pseudoxanthoma elasticum, their rate of progression over time, and identification of risk factors. These latter
findings have not been previously reported and may aid in understanding the pathogenesis of pseudoxanthoma elasticum.

The primary pathologic site in pseudoxanthoma elasticum is the RPE–Bruch membrane complex. Several types of RPE alteration have been described, including changes along angioid streaks and associated with CNV. Atrophy associated with disciform scarring may be quite extensive, involving the entire macula and nasal to the optic nerve. Cases of geographic atrophy without CNV are present in the literature but are limited to single reports or hidden in a larger series. Long-term follow-up data were not presented and growth rates were not measured. In addition, associated features and risk factors for progression were not ascertained.

In the current series, geographic atrophy was present in 8 eyes of 5 patients. Pattern dystrophy was present in all 8 eyes, whereas in the remaining 33 eyes it was present in 11 eyes (33%). On our review of the images of the 4 reported cases of geographic atrophy without CNV in the literature, 3 were of adequate quality to determine the presence of pattern dystrophy. All 3 had findings on fundus photography, FA, or FAF that were consistent with pattern dystrophy. Pattern dystrophy in pseudoxanthoma elasticum is a common finding, noted in 46% of eyes in this review and 59% of patients in our previous report (4 patients included in both studies). The presence of pattern dystrophy seems to be required for geographic atrophy, though not all eyes with pattern dystrophy develop it. Geographic atrophy and pattern dystrophy in maternally inherited diabetes and deafness and familial pattern dystrophy resemble the current series, suggesting possible overlap in pathophysiology between these entities.

Two types of hyperautofluorescence of the pigment lesions were seen: mild hyperautofluorescence of the linear or radial pigment deposits and bright punctate hyperautofluorescence of the pigment clumps. The former likely represents pigment epithelial migration into the retina, representing a disturbance of the interdigitation of the photoreceptor/RPE complex. This may be the earliest step prior to the development of visible photoreceptor and RPE atrophy. Linear pigment deposits were seen in 5 of 8 eyes that had, or developed, geographic atrophy (Patients 1, 2, and 3), and its presence may predict development of, or worsening, atrophy. Two eyes of 1 patient without geographic atrophy or CNV had linear pigment deposits, but follow-up imaging was not available so progression to atrophic or neovascular disease could not be assessed. OCT imaging of 2 eyes in 1 patient (Patient 1) with geographic atrophy revealed pigment to be at the outer nuclear layer. Intraretinal pigment migration has also been described in type II macular telangiectasia and AMD, where migration occurs over areas of outer retinal or RPE disruption. The imaging findings of linear pigment deposits are in contrast to bright punctate hyperautofluorescence of isolated pigment clumps. The latter clumps are located in the subretinal space and correspond to engulfed fluorophores within native RPE cells remaining at their natural location. This more common finding was seen in several eyes without geographic atrophy and appears less predictive of geographic atrophy than linear pigment deposits. This suggests that disruption of the photoreceptor-RPE complex and migration of RPE cells is a precursor for geographic atrophy.

Rate of growth of geographic atrophy in pseudoxanthoma elasticum has not been previously reported and approximates that in atrophic AMD. Using fundus photographs, Lindblad and associates determined progression of 1.78 mm² per year, and Sunness and associates reported a median enlargement rate of 2.1 mm² per year in AMD. Mean progression in the current series was 1.7 mm² per year. Differences were seen between the 2 etiologies, aside from what is evident on clinical examination. A ring of hyperautofluorescence around geographic atrophy may predict further extension in AMD, and is attributable to increased metabolic stress of the surrounding RPE cells. In the current study, FAF images were obtained in 3 patients (Patients 1, 2, and 3), and none had a ring of hyperautofluorescence. This finding was also absent with multilobular atrophy distinct from CNV and angioid streaks. Metabolic stress at the edge of geographic atrophy does not appear to contribute in pseudoxanthoma elasticum.

The genetic defect in pseudoxanthoma elasticum involves subclass C of the ATP-binding cassette transporter, which is involved in the metabolism and synthesis of the extracellular matrix. Genetic mutations may result in aberrant transport mechanisms in the retina, leading to abnormal elastin accumulation in the RPE–Bruch membrane complex and impaired removal of waste products by the choriocapillaris. The Bruch membrane becomes thickened and calcified and the number of pigment granules in the RPE decreases. The number of remaining RPE cells may be reduced and become dedifferentiated. Retinal changes may occur because of changes in nutrient supply to photoreceptors across a diseased Bruch membrane, resulting in full-thickness atrophy of Bruch membrane, RPE, choriocapillaris, and photoreceptors. RPE dedifferentiation and intraretinal migration appears to precede atrophy of the RPE–Bruch membrane complex.

Although there are no currently approved treatments for geographic atrophy, several therapies are in clinical trials or preclinical testing. Ciliary neurotrophic factor delivered by encapsulated cell technology can slow progressive vision loss attributable to geographic atrophy in AMD. Stem cell technology and fenretinide have also shown some promise in AMD. Clinical trials are ongoing for doxycycline, sirolimus, and fluocinolone acetonide intravitreal implants, among others. It is important to recognize geographic atrophy as a cause of...
severe vision loss in pseudoxanthoma elasticum. Findings such as pattern dystrophy and linear pigment deposits may represent high-risk features that may benefit from earlier intervention, when available. However, it is unclear if different pathophysiologic mechanisms of geographic atrophy formation in pseudoxanthoma elasticum and AMD would result in different treatment responses. It seems plausible that restoration of lost photoreceptors (ciliary neurotrophic factor, stem cells) would be more successful in pseudoxanthoma elasticum than targeting AMD-based pathways (fenretinide).

There are limitations to this study. It is retrospective with variable follow-up. Aside from fundus photography, imaging was not uniform. In addition, atrophy was identified and measured using fundus photography. FAF and high-resolution OCT were not available until recently and were only used as adjunctive studies to aid in outlining atrophy. However, both FAF and color fundus photography are reliable for measuring geographic atrophy in AMD. The incidence of atrophy may have been underestimated, as it could have preceded CNV in some eyes, which excluded the eye from our analysis. Finally, genotyping was not performed on any patients in the study; genotype-phenotype associations have been previously described in pseudoxanthoma elasticum.

In conclusion, geographic atrophy can develop in pseudoxanthoma elasticum independent of CNV, resulting in severe vision loss. Linear pattern dystrophy may predict development of geographic atrophy. Progression is similar to AMD. Some of the future treatments that become available to slow or reverse geographic atrophy in AMD may also benefit patients with pseudoxanthoma elasticum. Early identification of this finding and predisposing factors may be critical when such therapies become available.

**REFERENCES**

19. Charbel Issa P, Finger RP, Holz FG, Scholl HP. Multimodal imaging including spectral domain OCT and confocal near


