Fundus Autofluorescence in Patients with Pseudoxanthoma Elasticum

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Purpose: To evaluate the autofluorescence findings of patients with pseudoxanthoma elasticum, a disease resulting from a defect in a reputed transport protein encoded by the gene adenosine triphosphate–binding cassette subtype C number 6.

Design: Observational case series.

Methods: Color, red-free monochromatic, and autofluorescence photography and fluorescein angiography of patients with pseudoxanthoma elasticum seen in a referral practice were evaluated.

Main Outcome Measures: Cataloging of the abnormalities as detected by autofluorescence photography.

Results: The 8 subjects ranged in age from 26 to 60 years (mean, 55±12), and their best-corrected visual acuity ranged from 20/20 to 5/400 (mean, 20/50). Of the 16 eyes of the 8 patients, all had abnormalities typical of pseudoxanthoma elasticum, including angioid streaks in 14, peau d'orange in 4, and choroidal neovascularization in 11. Angioid streaks appeared as hypoautofluorescent fissures, sometimes showing expansion of the hypoautofluorescence suggestive of retinal pigment epithelium (RPE) absence or atrophy. Peau d'orange had a stippled appearance of autofluorescence, and drusen of the optic nerve appeared as hyperautofluorescent bodies. In addition to the expansion of RPE atrophy around angioid streaks, 3 additional configurations of RPE atrophy were recognized as RPE rips in 6 eyes, multilobular areas of atrophy in 9 eyes, and broad areas of poorly demarcated atrophy in 5 eyes. Some eyes had more than one manifestation of RPE atrophy, but the latter 3 types of atrophy occurred in eyes with, but not necessary contiguous to, concurrent choroidal neovascularization.

Conclusions: Autofluorescence photography demonstrated that patients with pseudoxanthoma elasticum have more widespread areas of RPE disturbance, particularly atrophy, than what is detectable by other means of ocular imaging, which suggests that the RPE disturbance may play a role in the pathogenesis of visual loss in patients with pseudoxanthoma elasticum. *Ophthalmology 2006;113:814–820 © 2006 by the American Academy of Ophthalmology.*

Pseudoxanthoma elasticum has a prevalence of 1 in 25 000 and causes abnormalities chiefly involving the eye, skin, and cardiovascular system.[1] Histopathologic examination shows dystrophic mineralization and fragmentation of elastic fibers, abnormalities of collagen fibers, and defects in the extracellular matrix.[2,3] Because of the histopathologic findings, pseudoxanthoma elasticum was thought at one time to be a primary disorder of the elastic fibers. More recently, the gene defect in pseudoxanthoma elasticum has been characterized as a loss of function mutation in the adenosine triphosphate–binding cassette subtype C number 6 gene (ABCC6).[4–6] This gene is expressed in the liver, kidney, and, to a much lesser extent, in affected tissues such as the eye, skin, and cardiovascular system.[7] The protein encoded by the ABCC6 gene appears to be a transport protein.

There are a variety of ocular manifestations of pseudoxanthoma elasticum, including angioid streaks, peau d'orange, drusen of the optic nerve, and choroidal neovascularization. Autofluorescence photography allows visualization of the lipofuscin that accumulates in functional retinal pigment epithelium (RPE) cells and highlights defects in the RPE that are difficult to image otherwise.[8–10] Because many of the ocular abnormalities of pseudoxanthoma elasticum may directly or indirectly involve the RPE cells, it may be possible to gain increased understanding of visual loss by studying the autofluorescence characteristics.

Patients and Methods

This is a retrospective review of consecutive patients with an established diagnosis of pseudoxanthoma elasticum examined by the authors from 2002 to 2005 in a referral practice. The study was approved by the institutional review board of Manhattan Eye, Ear, and Throat Hospital. All patients underwent a complete ophthalmic examination, including determination of best-corrected visual acuity (BCVA); slit lamp and fundus

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assessment; color, red-free, and fundus autofluorescence imaging; and also fluorescein angiography as needed. Autofluorescent imaging was carried out using a fundus camera (Topcon USA, Paramus, NJ) with an excitation filter centered at 580 nm (bandwidth, 500–610) and a barrier filter centered at 695 nm (bandwidth, 675–715), as previously described.[8,9] The data obtained were analyzed with frequency and descriptive statistics. Categorical analysis was performed using the Fisher exact test. A P value of <0.05 was considered significant. Statistical analysis was performed with SPSS (version 12.0, SPSS Inc., Chicago, IL).

Results

The subjects included 2 males and 6 females ranging in age from 26 to 60 years (mean, 55±12). Their BCVA ranged from 20/20 to 5/400 (mean, 20/50). Choroidal neovascularization in the macular area was seen in 11 eyes. The autofluorescence findings of the pseudoxanthoma elasticum patients could be divided into specific groups: angioid streaks, peau d'orange, drusen of the optic nerve, choroidal neovascularization, and zones of RPE atrophy. Every eye had at least one abnormality.

Angioid streaks appeared as jagged dark lines with a variable amount of hyperautofluorescence at the borders of the crack (Figs 1, 2 [the latter available at http://aaojournal.org]). There was a very high concordance between fundus photography and autofluorescence photography in being able to visualize the angioid streaks. Angioid streaks were found in fundus photographs in 14 eyes (88%). In 1 eye, the angioid streaks did not have the typical brick red color; instead, the streaks appeared as lighter-colored lines. Autofluorescence imaging revealed fine, dark, radiating cracks corresponding to these lines, typical of autofluorescence findings of angioid streaks seen in other eyes, with the exception that they were narrower. The fellow eye of the same patient had fine hypoautofluorescent streaks seen by autofluorescence photography, with no obvious correlate seen by conventional fundus photography. No eye had angioid streaks imaged by color or red-free monochromatic photography or fluorescein angiography that were not also visible by autofluorescence photography. Some angioid streaks appeared to have stippled areas of autofluorescence within them. In other patients, broadening of the hypoautofluorescence was seen associated with the angioid streaks. This apparent expansion of RPE atrophy produced a triangular area of hypoautofluorescence, with the base of the triangle oriented toward the optic nerve. Two eyes of one patient had such widespread abnormalities that no discrete angioid streaks were seen by any imaging modality.

Peau d'orange was seen by fundus photography in 4 eyes (Fig 3 [available at http://aaojournal.org]). Autofluorescence photography showed a granular stippling in each eye, which corresponded to the pattern seen in the fundus photographs. Drusen of the optic nerve were seen in 5 eyes of 4 patients by autofluorescence photography (Fig 4). In only one of these cases were the drusen visible by conventional fundus photography. Areas of choroidal neovascularization had a variable amount of associated autofluorescence. Increased pigmentation secondary to pigment hyperplasia was invariably hypoautofluorescent. Atrophy exposing bare sclera showed slight hyperautofluorescence from the sclera.

In addition to RPE loss associated with angioid streaks, every patient with choroidal neovascularization had associated regions of absent or atrophic RPE, which had 1 of 3 possible configurations: (1) RPE rips, (2) multilobular areas of discrete atrophy, and (3) broader areas of less well-defined atrophy. Definite RPE tears associated with choroidal neovascularization were found in 6 eyes (Fig 5). In 2 eyes with choroidal neovascularization, there was no tear, whereas in the remaining eyes with choroidal neovascularization there was such widespread RPE atrophy and disturbance that it was not possible to distinguish if there were also RPE tears. Some of the RPE tears had rounded borders, as seen in age-related macular degeneration (AMD), whereas other cases had angular outer borders. As opposed to recent RPE tears sometimes seen in choroidal neovascularization secondary to AMD, the denuded areas were not hyperfluorescent during fluorescein angiography, implying atrophy of the underlying choriocapillaris. The second type of RPE atrophy appeared as multilobular regions, which were seen in 9 of the 11 eyes with choroidal neovascularization (Figs 6–8) but in no eyes without neovascularization ($P = 0.0048$, Fisher exact test). The multilobular regions of atrophy were often, but not necessarily, adjacent to the areas involved with neovascularization and were located nasal to the nerve and in the periphery. These multilobular areas of atrophy were not surrounded by as prominent a zone of increased autofluorescence as seen in geographic atrophy secondary to AMD. The third pattern of atrophy encompassed broader but less well-defined regions of decreased autofluorescence. These less well-defined areas were seen in 5 eyes, all of which had choroidal neovascularization (Figs 8, 9 [the latter available at http://aaojournal.org]; $P = 0.12$). This less well-defined atrophy was separated from the area of choroidal neovascularization in 3 eyes. In one patient, the posterior pole of each eye had what appeared to be pigmentary mottling in the color and red-free monochromatic images, but was found to have widespread atrophy of the RPE by autofluorescence photography. This patient also had bilateral but inactive choroidal neovascularization. Of the 11 eyes with choroidal neovascularization, 5 had had previous treatment. One patient had atrophy of the retina, RPE, and choroid in the area of past laser photocoagulation, but otherwise, there were no changes in the autofluorescence findings in these patients that appeared to be attributable to treatment. In particular, the areas of atrophy described above occurred in untreated eyes or in treated eyes outside of any treatment area.

Discussion

In this study of patients with pseudoxanthoma elasticum, we showed the autofluorescence correlates to a number of well-known fundus findings such as peau d'orange, drusen of the optic nerve, and angioid streaks. In addition, we found, rather unexpectedly, that patients with pseudoxanthoma elasticum often have large areas of missing or atrophic RPE. In a past study, drusen of the optic nerve were found by ultrasonography in 21% of patients with pseudoxanthoma.[11] We found drusen in 5 eyes of 4 of 8 patients, a higher proportion, albeit with a different imaging technique. Angioid streaks appeared as fissures with central hypoautofluorescence. Angioid streaks are linear fractures in Bruch's membrane with the dehiscence filled in with varying amounts of fibroblasts, RPE cells, and dedifferentiated RPE cells.[12,13] Histopathologic analysis of angioid streaks showed both an absence of RPE cells and a lack of pigmented granules in remaining RPE cells around angioid streaks.[13] The presence of stippled areas of autofluorescence within angioid streaks implies there is a potential for a few functional RPE cells to repopulate the gap caused by the angioid streak.

In addition to angioid streaks, there were 3 other configurations of absence of autofluorescence signal from the RPE: RPE rips, lobular regions of loss, and larger less well-defined regions of atrophy. The RPE rips invariably