Acute Retinopathy in Pseudoxanthoma Elasticum

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IMPORTANCE Acute retinopathy may partly explain variable disease manifestation and vision loss in patients with pseudoxanthoma elasticum (PXE). The diagnosis of this likely autoimmune process may inform patient counseling and treatment approaches.

OBJECTIVE To characterize acute retinopathy in patients with PXE as a disease manifestation that may be associated with profound visual impairment.

DESIGN, SETTING, AND PARTICIPANTS This single-center case series was conducted from May 2013 to October 2018. It used the patient database of the Department of Ophthalmology at the University of Bonn, a referral center for PXE in Germany. Patients at this center with genetically confirmed PXE and who met the inclusion criteria were included (n = 9). Patients underwent multimodal retinal imaging, including fundus photography, fundus autofluorescence (AF), optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA); in select cases, electroretinography as well as antiretinal and anti–retinal pigment epithelium (RPE) antibody testing were also used.

MAIN OUTCOMES AND MEASURES Clinical presentation and disease course.

RESULTS Nine patients (8 [89%] female; mean [range] age, 43 [19-55] years) with acute retinopathy were identified in a cohort of 167 consecutive patients with PXE (frequency of 5%). Symptoms ranged from light sensations or metamorphopsia to profound vision loss. Visual acuity was reduced in 6 patients (67%), ranging from a best-corrected visual acuity of 20/30 to perception of hand movements at manifestation. All patients revealed characteristic fundus features with temporary appearance of partly confluent outer retinal whitish dots at the posterior pole, which corresponded to areas of hyperautofluorescence on fundus AF, loss of the ellipsoid band on OCT, and associated scotomata. The FA and late-phase ICGA imaging showed associated hyperfluorescence and hypocyanescence. Electroretinography revealed a variable reduction of amplitudes. Changes were fully reversible within 1 month in 3 of 8 patients with available follow-up data. Of the remaining 5 patients, 3 had a prolonged and likely permanent vision loss (observation period, 1-64 months) mainly owing to central subretinal hyperreflective material originating from angioid streaks. In 4 (67%) of 6 tested, antiretinal and/or anti-RPE antibodies were detected.

CONCLUSIONS AND RELEVANCE Acute retinopathy in patients with PXE may occur, with symptoms ranging from short-term, reversible alterations to irreversible vision loss; these findings contribute to understanding the variable ocular disease progression in PXE and provide insights into the autoimmune phenomena of the posterior pole.

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Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive multisystem disease characterized by progressive calcification of tissue rich in elastic fibers. In the eye, calcification of the Bruch membrane is associated with an altered fundus reflex and may eventually result in retinal atrophy with vision loss. Breaks in the calcified Bruch membrane (angioid streaks) may give rise to the development of choroidal neovascularization as another factor in the visual impairment of patients with PXE.

The understanding of pathophysiological mechanisms of PXE has improved over the past 2 decades, and novel treatment options are being explored. At the same time, identification of reliable outcome measures for clinical trials has remained challenging because of the slow disease progression, limited reliability in measuring changes of tissue calcification, variable disease severity between patients, and variable calcification of different organs in the same patient.

Vision loss with its substantial implications for quality of life is one of the most worrying concerns of patients with PXE. Thus, assessment of vision should play a prominent role in describing the natural multisystem history and when defining outcome measures for clinical trials. However, the reason for substantial vision loss sometimes remains obscure.

The aim of this study was to provide a detailed characterization of acute-onset, non-neovascular fundus changes in a large cohort of patients with PXE; these changes are suggestive of outer retinal inflammation and show similarities with multiple evanescent white dot syndrome (MEWDS). Although recovery is possible, marked and partially nonreversible morphologic changes with substantial permanent vision loss may also occur. This ocular phenotype may be a factor in the diversity of fundus alterations and variable vision loss in patients with PXE.

Methods

This single-center case series, conducted from May 2013 to October 2018, followed the tenets of the Declaration of Helsinki. Patients were identified from the PXE database of the Department of Ophthalmology at the University of Bonn, a referral center for PXE in Bonn, Germany. All patients with PXE who were seen in the referral center from May 2013 to October 2018 had consented, in writing, to having additional images taken of their eyes and to the publication of their clinical data. This study and consent process were approved by the institutional review board of the Medical Faculty at the University of Bonn.

Inclusion criteria were the diagnosis of PXE based on the diagnostic criteria for PXE by Plomp et al and sufficient image quality of a standardized imaging protocol consisting of at least fundus photography, fundus autofluorescence (AF), and optical coherence tomography (OCT). Most patients also underwent fluorescein angiography (FA) and indocyanine green angiography (ICGA), and for some patients, results from full-field electroretinography or microperimetry testing were available. In a subset of patients, antiretinal, anti-retinal pigment epithelium (RPE), and anti-angiogenic antibody treatments were analyzed.

Key Points

**Question** Is the ocular disease manifestation in patients with pseudoxanthoma elasticum influenced by processes different from calcification or neovascularization?

**Findings** In this single-center case series of 167 consecutive patients with pseudoxanthoma elasticum, 9 were identified with an acute onset of a characteristic retinopathy, with symptoms ranging from short-term, reversible alterations to irreversible vision loss; all patients showed fundus alterations with similarities to multiple evanescent white dot syndrome.

**Meaning** These findings offer an additional explanation for the variable ocular phenotype and disease progression in patients with pseudoxanthoma elasticum and may suggest a possible ocular autoimmune process.

To prevent a potential identification of participants, no demographic data of individual participants were reported. More detailed information on the methods we followed may be found in the eMethods in the Supplement.

Results

**Patient 1** A patient with PXE presented with a 1-day history of reduced visual acuity and a central relative scotoma in her right eye (best-corrected visual acuity [BCVA]: 20/40 OD, 20/20 OS). Ophthalmoscopy of the right eye revealed outer retinal white dots at the posterior pole (Figure 1A), which were confluent along major vessels, angioid streaks, and the optic disc. These lesions were associated with hyperautofluorescence on AF (Figure 1B), hyperfluorescence on FA, and hypocyanescence on late-phase ICGA (Figure 1C). Corresponding OCT images showed a disruption of the ellipsoid and interdigitation band (white arrowhead in Figure 1D). Along some angioid streaks, focal, subretinal, slightly hyperreflective lesions had formed, which were interpreted as a subretinal fibrovascular proliferation and treated with an intravitreal injection of bevacizumab. Additional phenotypic illustrations at initial presentation are found in eFigure 1A-F in the Supplement.

One month later, after initial improvement of vision, the patient reported a 1-day history of severely reduced vision in the same eye. The patient’s BCVA had dropped to hand movements, and relative afferent pupillary defect and mild vitreous cells were observed. Although the whitish lesions and their correlates on AF, FA, and ICGA had largely disappeared, macular OCT imaging showed loss of the ellipsoid band and some hyperreflective changes within the outer nuclear layer (eFigure 1G-K in the Supplement). Angioid streaks had enlarged considerably. Photopic and scotopic responses were extinguished on full-field electroretinography testing. Under the hypothesis of an inflammatory process, oral corticosteroid therapy (100-mg prednisolone-21-hydrogen succinate tapered over 6 weeks) was initiated. The patient’s BCVA slowly recovered (20/50 at the 2-month, 20/32 at the 5-month, and...
20/20 at the 15-month follow-up), the ellipsoid band re-formed (eFigure 1L-U in the Supplement), and retinal sensitivity improved (eFigure 2 in the Supplement).

Over the subsequent months, the patient received 6 intravitreal anti–vascular endothelial growth factor (VEGF) injections in the right eye owing to recurrent fovea-involving subretinal proliferations, and BCVA was stabilized at around 20/40. Forty-three months after initial manifestation, the patient again experienced an acute reduction of visual function (BCVA 20/640) in the same eye, which was accompanied by intense vitreous floaters and vitreous cells as well as the rapid formation of an extensive subretinal fibrosis without the usual signs of neovascular activity, such as subretinal or intraretinal fluid (eFigure 3 in the Supplement). After a parabulbar triamcinolone acetonide injection, BCVA slowly increased to 20/80. At last review 64 months after baseline, no inflammatory signs were found, but subretinal fibrosis had progressed further (without substantial advantage after repeated intravitreal anti-VEGF injections) and BCVA had stabilized at 20/80 (eFigure 3 in the Supplement).

These dynamic changes were limited to the right eye throughout the observational period, whereas PXE-associated fundus changes in the left eye remained unchanged.

Patient 2
The patient reported a 2-week history of reduced visual acuity, metamorphopsia, and hazy vision in the right eye. Two years earlier, she was treated with 2 intravitreal bevacizumab injections for choroidal neovascularization in each eye. The patient’s BCVA was 20/32 OD and 20/20 OS. Clinical examination revealed subtle outer retinal white dots, which were partly confluent along angiod streaks and larger vessels. Imaging revealed corresponding hyperautofluorescence on AF, hyperfluorescence on FA, and hypocyanescence on late-phase ICGA (Figure 2A-C). The OCT images showed discontinuities in the ellipsoid band (eFigure 4F in the Supplement) and subretinal hyperreflective material with adjacent hyperreflectivity of the outer retina originating from a central angiod streak (Figure 2D), for which an intravitreal anti-VEGF treatment with bevacizumab was performed. Additional phenotypic illustrations at initial presentation are included in eFigure 4A-G in the Supplement.

One month later, BCVA had improved to 20/25. The white-yellowish deep retinal lesions and their correlates on retinal imaging had disappeared, and the subretinal hyperreflective material had regressed (eFigure 4H-K in the Supplement). At this time, electroretinography examination revealed amplitudes in the normal range; however, the amplitudes of the right eye were substantially below those of the left eye. One month later, the patient received 1 additional intravitreal bevacizumab injection for recurrence of the subretinal hyperreflective material. Afterward, BCVA remained stable at 20/25, and no further treatment was required during the observation period of 48 months.

Patient 3
The patient presented with reduced visual acuity for 2 weeks in his left eye, which previously had similar visual acuity as the right eye. At presentation, BCVA was 20/20 OD and 20/
On clinical examination, the left eye revealed mild vitreous cells and extensive whitish, confluent, sometimes dotlike outer retinal lesions centered on the posterior pole and extending along angioid streaks (Figure 3A). Fundus AF imaging showed peculiar dotlike changes with a hyperautofluorescent center and a hypoautofluorescent halo (arrowhead in Figure 3B), confluent hyperautofluorescence at the posterior pole, and more eccentric dotlike hyperautofluorescent lesions. The FA imaging revealed corresponding hyperfluorescent lesions, and ICGA imaging showed hypocyanescent lesions (Figure 3C; eFigure 5 in the Supplement). The OCT imaging showed extensive loss of the ellipsoid band, small and focal hyperreflective lesions with minimal subretinal fluid adjacent to angioid streaks, and appearance of thicker choroid compared with the choroidal thickness on follow-up visits (Figure 3D). The full-field electroretinography amplitudes were within normal range, but amplitudes were lower in the left eye compared with the right eye. Oral corticosteroid therapy was initiated (80-mg prednisolone tapered over 3 weeks). Additional phenotypic illustrations at initial presentation are found in eFigure 5A-G in the Supplement.

One month later, BCVA was further reduced to 20/640, and OCT imaging revealed disease progression with development of subretinal fibrosis and mild intraretinal fluid (eFigure 5H-J in the Supplement). Choroidal thickness was no longer increased. Intravitreal anti-VEGF treatment with bevacizumab was combined with peribulbar triamcinolone. At the 8-week follow-up, intraretinal fluid was reduced, but the subfoveal fibrosis had further progressed. At last review 20 months after the initial presentation, the patient had developed widespread outer retina and RPE atrophy, mainly within the areas of the former dotlike hyperautofluorescent and hypoautofluorescent lesions temporal to the optic disc as well as an inactive subfoveal fibrosis (eFigure 5K-M in the Supplement).

General Observations
Over a period of 13 years, 9 (5%) of 167 consecutive patients with PXE (8 [89%] female; mean [range] age, 43 [19-55] years) were identified with a similar acute retinopathy (eFigure 6 in the Supplement). None of the patients reported a preceding ocular trauma. Symptoms ranged from blurred vision and photopsia to loss of central vision. Visual acuity was reduced in 6 patients (67%), ranging from 20/30 to perception of hand movements at manifestation (Table 1).

In this cohort, several characteristic morphologic findings were consistently observed in acute retinopathy (Table 2). Electoretinography testing was performed in 6 patients (4 recordings during the acute phase of vision loss; 1 recording after 1 week of corticosteroid treatment and 1 recording 4 weeks after the acute onset) and was less consistent: 1 patient showed severely reduced amplitudes in the affected eye, whereas responses were within normal limits in the other 5 patients, although 2 of them showed relatively reduced amplitudes in the affected eye.

Follow-up data were available for 8 (89%) of 9 patients, with an observation period ranging from 1 to 64 months. At the last follow-up, vision had fully recovered in 1 patient (patient 4), and 2 maintained their initial good vision. The remaining 5 patients with initially reduced visual acuity had only a partial recovery of vision. Clinical signs of acute retinopathy...
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye</th>
<th>Symptoms of Autoimmune Retinopathy</th>
<th>Interval Onset to Presentation</th>
<th>BCVA Before Onset</th>
<th>BCVA at Manifestation</th>
<th>Refraction</th>
<th>Vitreous Cells</th>
<th>ERG</th>
<th>Therapy</th>
<th>BCVA Last Follow-up</th>
<th>Observation Period, mo</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>OD</td>
<td>Reduced visual acuity; relative scotoma; haze</td>
<td>1 d</td>
<td>20/20</td>
<td>Hand movements</td>
<td>−5.5/−1.25 × 179°</td>
<td>Positive</td>
<td>Reduced</td>
<td>Corticosteroids, anti-VEGF</td>
<td>20/80</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>OD</td>
<td>Metamorphopsia; dark spots</td>
<td>2 wk</td>
<td>20/20</td>
<td>20/32</td>
<td>+3.75/−1.25 × 138°</td>
<td>ND</td>
<td>Normal range, OD = OS</td>
<td>Anti-VEGF</td>
<td>20/25</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>OS</td>
<td>Reduced visual acuity</td>
<td>3 wk</td>
<td>20/25</td>
<td>20/400</td>
<td>−0.25/−0.5 × 72°</td>
<td>Positive</td>
<td>Normal range, OS &lt; OD</td>
<td>Corticosteroids, anti-VEGF</td>
<td>20/320</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>OS</td>
<td>Reduced visual acuity; glare; relative scotoma; scintillations</td>
<td>3 d</td>
<td>20/20</td>
<td>20/40</td>
<td>−2.25/−0.75 × 97°</td>
<td>Positive</td>
<td>Normal range</td>
<td>Corticosteroids, anti-VEGF</td>
<td>20/20</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>OS</td>
<td>Central gray haze</td>
<td>Some weeks</td>
<td>20/20</td>
<td>20/20</td>
<td>0.0/−0.25 × 141°</td>
<td>ND</td>
<td>NP</td>
<td>None</td>
<td>20/20</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>OS</td>
<td>Reduced visual acuity; glare; relative scotoma; night vision problems</td>
<td>1 wk</td>
<td>20/25</td>
<td>20/200</td>
<td>−1.75/−0.5 × 46°</td>
<td>Positive</td>
<td>Normal range</td>
<td>None</td>
<td>20/40</td>
<td>2</td>
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<tr>
<td>7</td>
<td>OD</td>
<td>Reduced visual acuity; glare; night vision problems</td>
<td>1 wk</td>
<td>20/20</td>
<td>20/640</td>
<td>+3.5/−0.5 × 101°</td>
<td>Positive</td>
<td>Normal range</td>
<td>Corticosteroids</td>
<td>20/63</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>OS</td>
<td>Reduced visual acuity; flashes</td>
<td>3 mo</td>
<td>20/20</td>
<td>20/20</td>
<td>+0.5/−0.25 × 24°</td>
<td>Positive</td>
<td>NP</td>
<td>None</td>
<td>20/20</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>OD</td>
<td>Reduced visual acuity</td>
<td>Some weeks</td>
<td>20/50</td>
<td>20/200</td>
<td>−2.5/−1.5 × 24°</td>
<td>ND</td>
<td>NP</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; ERG, electroretinography; NA, not available; ND, not documented; NP, not performed; VEGF, vascular endothelial growth factor.

* The genotype of all 9 patients is shown in eTable 1 in the Supplement.

b Treatment with corticosteroids consisted of an initial dose of prednisolone-21-hydrogen succinate, 1 mg/kg for 4 weeks.

Figure 3. Retinal Phenotype of Patient 3 With Pseudoxanthoma Elasticum and Acute Retinopathy

A. Fundus color photo  B. Fundus autofluorescence  C. ICGA late phase

D. Optical coherence tomography

The white line in A illustrates the position of the OCT section in D. The white arrowhead in B points to dotlike alterations. ICGA indicates indocyanine green angiography.
resolved within 1 month in 3 patients (patients 5, 6, and 8) without treatment. One patient (patient 2) with only mild proliferation of subretinal hyperreflective material was treated successfully with 2 intravitreal anti-VEGF injections. Patients with more pronounced inflammation and symptoms (patients 1, 3, 4, and 7) were treated with systemic steroids (initial dose: 1 mg/kg prednisolone tapered over 4-6 weeks), with 3 patients (33%) with and 1 patient (11%) without intravitreal bevacizumab injections depending on the presence of potentially vision-threatening subretinal hyperreflective material. Only 1 of these patients regained nearly normal vision; 1 patient had recurrent subretinal hyperreflective material and was treated with multiple anti-VEGF injections, and 2 patients developed fovea-involving subretinal fibrosis (Table 1).

Two patients (22%) had a previous episode of acute retinopathy in the same eye 3 years (patient 4) or 4 years (patient 2) earlier, which had resolved without clinically relevant function loss. Patient 2 also had a comparable episode in the contralateral eye 5 years earlier. One patient (patient 1) had a relapse 36 months after her first onset.

### Occurrence of Autoantibodies

To investigate the hypothesis of an autoimmune involvement in the pathophysiological process of this acute retinopathy, we examined serum antiretinal and anti-RPE autoantibodies in 6 patients with variable time intervals after onset of acute retinopathy (Table 2 in the Supplement). Antiretinal autoantibodies were found in 1 patient (17%) and anti-RPE antibodies against a 62-kDa protein in 4 patients (67%). Two patients (33%) were seronegative for both antiretinal and anti-RPE autoantibodies. One patient (17%) was retested 3 months after first presentation (patient 3). Although the formerly detected anti-RPE autoantibodies against the 30-kDa and 70-kDa proteins were not found any more, the anti-62-kDa RPE autoantibodies persisted (Table 2 in the Supplement).

### Discussion

This study describes an acute retinopathy in patients with PXE that may alter the natural course of the disease. Although symptoms may be transient, some patients may develop permanent vision loss. All patients presented a characteristic phenotype with only partially reversible morphologic changes at the level of the Bruch membrane, the RPE, and the outer retina. We hypothesized that an autoimmune process in the outer retina is associated with the development of such an acute retinopathy in patients with PXE.

### Clinical Presentation

Acute retinopathy in patients with PXE is suggestive of outer retinal inflammation and shares some similarities with MEWDS. These similarities include the rate of visual deterioration, the unilaterality, and specific phenotypic findings on ophthalmoscopy and multimodal imaging. Overall, angiographic features suggest a pathological condition of the inner choroid and/or RPE and could be associated with increased permeability for fluorescein and reduced uptake of ICGA within the RPE. Fundus AF showed hyperautofluorescent lesions that may fade with photopigment bleaching of surrounding retinal areas. Hence, the apparently increased AF is likely associated with the reduced amount of photopigment and unmasking of the underlying AF of the RPE, as described previously in patients with MEWDS, central serous choroidopathy, or macular telangiectasis type 2. Outer segment disruption as indicated by loss of the ellipsoid band on OCT imaging may be associated with such loss of photopigment. These structural changes and the associated functional loss were transient in most patients and may improve over several weeks to months. However, acute retinopathy in patients with PXE also differs in several aspects from typical MEWDS. The fundus lesions are most extensive and often confluent along angioid streaks, blood vessels, and the optic disc. Possible concomitant uveitic reactions (eg, vitreous cells, choroidal thickening) may be a more frequent finding in PXE-associated acute retinopathy, although the true frequency will remain unknown until larger cohorts are identified. Moreover, rapid progression of angioid streaks, development of choroidal neovascularization or RPE atrophy, and development of subretinal hyperreflective material in the subretinal space in PXE-associated acute retinopathy may occur. These unique features of acute retinopathy and the frequency of 5% in this cohort suggest a true association with PXE and not a coincidental co-occurrence of MEWDS. Diagnosing acute retinopathy in patients with PXE may be challenging in eyes with advanced fundus changes, in which many of the signs cannot be observed because of other morphologic changes.
Acute retinopathy may explain previously reported non-recordable electroretinography responses in patients with PXE.9 Although there was variability in the severity of acute retinopathy and inconsistency with the time since onset of symptoms, generalized retinal dysfunction was found in 3 of 6 tested patients. Further studies using more standardized electroretinography recordings will be needed to support these findings.

With regard to the long-term outcome, central subretinal hyperreflective proliferations were important determinates for the visual prognosis in this cohort. These lesions showed no classic characteristics of neovascular tissue, such as associated hemorrhages and clear leakage on FA images or subretinal or intraretinal fluid on OCT images, but they showed some response toward treatment with anti-VEGF drugs. It may be speculated that these lesions represent a cellular reaction to an underlying inflammatory process associated with the secondary formation of fibrovascular tissue similar to a report on lesions in multifocal choroiditis.22 The often-observed small, subretinal hyperreflective lesions associated with angioid streaks could be an early manifestation that potentially may regress.

**Pathophysiological Considerations**

Morphologic changes in acute retinopathy appear to be located between (and including) the photoreceptor layer and the choroid. The phenotypic overlap with MEWDS15,23 suggests common pathogenic pathways. Even though the pathogenesis of MEWDS is currently incompletely understood, it has been associated with pathologic processes of the inner choroid, RPE, and photoreceptor outer segments17 with a possible underlying immune component.17,24 Besides an association with viral infections17 or vaccinations,25,26 MEWDS-like findings have also been observed after traumatic subretinal bleeding,27 choroidal rupture, and contralateral penetrating injury28 or associated with angioid streaks,29 indicating antigen exposure as a possible pathogenic factor.30 Manifestation of PXE-associated acute retinopathy is typically most pronounced along angioid streaks (breaks in the Bruch membrane), in which exposure of retinal, RPE, and the Bruch membrane antigens to the immune system might trigger an autoimmune process.

In line with this hypothesis, 4 (67%) of 6 tested cases revealed autoantibodies against RPE protein. Autoantibodies against a 62-kDa protein were an especially recurrent and characteristic pattern. Only 2 participants were tested in the acute phase of the retinopathy, and antibodies were detected up to 4 years after an episode of the acute retinopathy. However, autoantibodies can persist in the circulation for a long time if the antigen is present and stimulates the immune system.12 One retested participant showed a different antibody profile, underlining the fact that autoantibodies often fluctuate and their repertoire may change over time.12,13 In addition, autoantibody testing for this study was performed on a research basis only, and no detailed information is available on the sensitivity or specificity of the detected antibodies. Therefore, the results of antibody testing need to be interpreted with caution and in the context of clinical findings. Owing to their phenotypic and pathophysiological similarities, patients with MEWDS would be interesting to examine to see if they have similar autoantibodies as patients with PXE.

**Treatment**

Treatment suggestions are difficult to provide owing to the limited number of cases that have been reported. The frequent spontaneous functional recovery indicates that observation only is reasonable in many cases. Under the assumption of an immune or autoimmune phenomenon, systemic steroids might be considered for patients with severe disease manifestation, but the data from this investigation do not provide definitive support to this recommendation. Combined treatment with corticosteroids and intravitreal anti-VEGF agents might be considered in cases with subretinal hyperreflective proliferative lesions because of possible inflammatory and vasoproliferative mechanisms, but these cases also do not provide strong evidence to support this treatment strategy.

**Limitations**

The main limitation of this study is the relatively small number of patients, which is an inherent problem of reporting phenotypic findings in rare diseases. In addition, owing to the retrospective nature of the study, observation intervals and, if applicable, treatments of patients were not standardized. Therefore, the results of this study, especially on treatment, must be interpreted with caution.

**Conclusions**

Acute retinopathy, in addition to choroidal neovascularization and atrophic lesions, may be associated with vision loss in patients with PXE. Acute retinopathy may alter the disease course and may, at least in part, explain the poorly understood heterogeneity of ocular findings among patients with PXE. Similarities with MEWDS may suggest common pathogenic pathways, and improved knowledge of the underlying mechanisms might expand the understanding of both disease entities. Diagnostic awareness about this phenotype may be of value for individual prognostication and the interpretation of ocular outcome (eg, visual function) in interventional trials for PXE.
Acute Retinopathy in Pseudoxanthoma Elasticum

Drs Gliem and Birtel contributed equally to this data and the accuracy of the data analysis.

Charbel Issa.

Acquisition, analysis, or interpretation of data: Charbel Issa.

Bochum, Bad Oeynhausen, Germany (Hendig, University Hospital of the Ruhr University of

Statistical analysis: Herrmann, Holz, Adamus.

Charbel Issa.

The views expressed herein are those of the manuscript for publication.

DISCLAIMER:

We declare that we have no financial or personal relationships that could inappropriately influence our work.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer:

The views expressed herein are those of the authors and do not reflect the official policy or position of the National Health Service, the National Institute for Health Research, or the Department of Health and Social Care.

REFERENCES


Potentially Novel Acute Retinopathy Similar to Multiple Evanescent White Dot Syndrome in Patients With Pseudoxanthoma Elasticum

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In this issue of JAMA Ophthalmology, Gliem et al1 present a case series describing a potentially novel presentation of acute retinopathy in 9 patients with pseudoxanthoma elasticum (PXE). Clinical findings in this disease shared many characteristics with multiple evanescent white dot syndrome (MEWDS): female predominance (8 of 9 patients), unilaterality (9 of 9 patients), blurry visual acuity and/or photopsia (variable symptoms among the cohort), mild vitreous cells (6 of 9 patients), and multiple small punctate outer retinal white lesions that tended to cluster in the posterior pole, particularly around the optic nerve and retinal vessels. Ancillary testing findings that compared similarly with MEWDS included reduced electroretinogram amplitudes in some patients (3 of 6), many more apparent lesions on fundus autofluorescence imaging and indocyanine green angiography, with hypofluorescence of the lesions on indocyanine green angiography, hyperfluorescence of lesions on fluorescein angiography, and outer retinal disruptions on optical coherence tomography.2

Findings that differed from MEWDS were the underlying presence of angioid streaks (due to PXE) and confluence of lesions around angioid streaks (in addition to around retinal blood vessels and the optic nerve). In addition, the resolution of these lesions often led to the progression in size of angioid streaks. The authors did not mention or demonstrate whether their patients had foveal granularity, a common finding in patients with MEWDS.2 The authors also did not discuss the choroidal thickness in their cohort; increased choroidal thickness has been described in some patients with MEWDS and may be associated with the appearance of subretinal hyperreflective material in that disease.3 Enhanced depth imaging might be helpful in the future to characterize the choroidal thickness in patients with this unusual syndrome.

The appearance of subretinal hyperreflective material in some eyes in this series likely indicated the presence of choroidal neovascular membranes, a known consequence of angioid streaks.4 Conversely, this material could represent nonvascularized inflammatory material deposits under the retina. Optical coherence tomography angiography might be useful in future patients to determine whether these lesions are indeed vascularized. The concurrence of subretinal hyperreflective material and acute inflammatory lesions in MEWDS is unusual but has been described, similar to the lesions described in this series, and the pathogenesis may be similar.3

The authors1 found evidence of autoantibodies in 4 of 6 patients tested (1 had both antiretinal and anti-retinal pigment epithelium antibodies, and 3 had anti-retinal pigment epithelium antibodies only). It is unclear whether this finding may be involved in the pathogenesis of the acute PXE-associated retinopathy described here. The formation of antiretinal antibodies has been suggested in other forms of autoimmune chorioretinitis (eg, sympathetic ophthalmitis). Conversely, the formation of antiretinal and anti-retinal pigment epithelium antibodies may form because of a consequence of the retinal degeneration secondary to PXE. Auto-antibodies have been described in patients with retinal degeneration, and other authors have suggested that they may form as a consequence of exposure of the immune system to retinal breakdown products.5,6

It is unclear why this acute PXE-associated syndrome has not been described before, to my knowledge. The authors note there was a rare incidence (5%) of this acute retinopathy among their larger cohort of patients with PXE. Perhaps the syndrome is directly related to PXE, is more common than we think, and may be difficult to detect owing to its transient nature. Perhaps the appearance of this syndrome may be obscured in some eyes in the setting of extensive retinal pigment epithelium abnormalities often seen in patients with angioid streaks from PXE. The genetics of PXE has been ascribed to mutations in the ABC6 gene, which encodes for multidrug resistance-associated protein 6 (MRP6), the function of which is still not clear.4 Perhaps there are genetic variants of ABC6 more prevalent to that region of Germany, which may have predisposed patients to this acute retinopathy. Indeed, 4 of 9 patients in this cohort had identical mutations in the ABC6 gene. Along the same lines, there may be other genes linked to specific polymorphisms of ABC6 that could be associated with this acute retinopathy.

Lastly, the development of this acute PXE-associated retinopathy may occur owing to a combination of genetic predisposition and environmental triggers, as postulated to be the etiology in many autoimmune disorders (such as MEWDS).7