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UNUSUAL PRESENTATION OF PRESUMED POSTERIOR POLYMORPHOUS DYSTROPHY ASSOCIATED WITH IRIS HETEROCHROMIA, BAND KERATOPATHY, AND KERATOCONUS

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Abstract

PURPOSE—To report an unusual presentation of posterior polymorphous corneal dystrophy (PPCD) associated with band keratopathy, iridocorneal adhesions, heterochromia, keratoconus, and confocal microscopic findings suggestive of iridocorneal endothelial syndrome (ICE).

METHODS—Confocal microscopy, corneal topography, electroretinography and genetic analysis were performed in the proband and his siblings.

RESULTS—A 23 year old man presented with decreased vision in both eyes over 9 months. Examination revealed bilateral alterations in corneal endothelial mosaic with corneal edema and beaten metal appearance in the right eye, and cystoid endothelial opacities in the left eye. Marked heterochromia, band keratopathy, and broad peripheral anterior synechiae were present in both eyes. Topographic features of keratoconus were noted. Electroretinography did not detect abnormal retinal function, as has been described with PPCD associated with VSX1 mutations. Diagnosis of PPCD was postulated based on the examination of the three proband's brothers by confocal microscopy. Genetic analysis of three known PPCD genes, VSX1, COL8A2, and TCF8, did not detect any mutations.

CONCLUSIONS—In severe cases, PPCD can resemble iridocorneal endothelial syndromes (ICE) in both clinical appearance and imaging studies (confocal microscopy). There was a strong genetic phenotypic penetrance in the family which was essential in the diagnostic decision-making. A yet undetermined genotype is contributing to this unusual PPCD phenotype.

INTRODUCTION

Posterior polymorphous corneal dystrophy (PPCD) is a hereditary corneal dystrophy affecting Descemet's membrane and the corneal endothelium. It is often, but not exclusively bilateral and frequently asymmetric in clinical presentation.¹ Patients with this condition are usually asymptomatic and the disease course is slowly progressive. However, there is a wide clinical spectrum, and the most aggressive cases can lead to visual disability from corneal edema and

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secondary glaucoma.² Clinically, PPCD is characterized by bilateral endothelial bands, vesicles, and polymorphous opacities at the level of Descemet's membrane and endothelium that can be accompanied by iridocorneal peripheral adhesions, iris atrophy, and corectopia. Glaucoma can often occur with PPCD if there is growth of the abnormal endothelium over the angle impeding aqueous outflow.³ Pathologically, there is an abnormal transformation and migration of the endothelial cells with secondary alterations in Descemet's membrane. This results in a proliferation of epithelial-like cells within the endothelium, resulting in replacement of the normal hexagonal corneal endothelial cells.⁴

Specular and confocal microscopic studies are useful diagnostic tools for evaluating the morphology of the corneal endothelium *in vivo*. With specular microscopy, characteristic features of PPCD are rounded cyst-like or vesicular areas in the endothelial mosaic, larger than guttae. These cyst-like areas have cells in their central base that appear smaller and lighter than normal endothelial cells. The characteristic "snail track" lesions are band-like dark areas enclosing some smaller lighter cells which correspond to the band-like lesions with scalloped irregular edges seen on slit-lamp examination.⁵ Characteristic confocal microscopic findings in PPCD demonstrate craters, streaks, and cracks over the corneal endothelial surface, often with hyperreflectivity at the level of Descemet's membrane around these lesions. Pleomorphism and polymegathism are also present in eyes with PPCD.⁶

The iridocorneal endothelial syndrome (ICE) is a rare ocular disorder encompassing Chandler's syndrome, progressive essential iris atrophy, and the iris nevus (Cogan-Reese) syndrome.⁷ The presentation of ICE can often be confused with PPCD since both share common clinical findings including corectopia, iridocorneal adhesions, elevated intraocular pressure, and a hammered silver appearance to the corneal endothelium.¹ With specular microscopy, characteristic "ICE" cells are larger and exhibit increased pleomorphism compared to the normal endothelium. They show dark/light reversal where cell surfaces are dark (instead of light) and intercellular borders are light (instead of dark).^{8, 9} The ICE syndromes are non-inherited, unilateral, and affect women more frequently.^{10, 11}

Although the inheritance pattern for PPCD has been well-established as autosomal dominant, research on the responsible genes is still ongoing. The first locus (PPCD1) was mapped to chromosome 20q11 using a large 5 generation family¹² and subsequently refined to two mutations (Asp144Glu and Gly160Asp) in the visual system homeobox (VSX1) gene in 2 of 22 patients affected with PPCD.¹³ However, these mutations do not appear to be a common cause of PPCD. A study by Aldave et al. of 14 probands found no Gly160Asp mutation in any of the probands and only one proband (as well as one control) with the Asp144Glu mutation in the VSX1 gene.¹⁴ Two other studies by Gwilliam et al¹⁵ and Hosseini et al¹⁶ similarly excluded VSX1 as the pathogenic gene among their respective probands. A second genetic locus for PPCD, (PPCD2) has been mapped to Chromosome 1p34 in a mutation in the gene encoding collagen type VIII $\alpha 2$ (COL8 $\alpha 2$) as reported in two family members with PPCD.¹⁷ Most recently, a third locus was found in 2004 (PPCD3) on chromosome 10p11 in a mutation in the transcription factor 8 (TCF8) gene, also known as the zinc finger E-box binding homeobox 1 (ZEB1) gene.¹⁸ Unlike the VSX1 and COL8 $\alpha 2$ mutations, which have been identified in 9% and 7% of studied probands, respectively,^{13, 17} mutations in the TCF8/ZEB1 gene have been found responsible for approximately one third of probands in the three studies that have screened for this gene thus far.^{19–21}

The genes responsible for PPCD may also contribute to other inherited corneal disorders. One locus for the autosomal dominant form of congenital endothelial dystrophy (CHED 1) has been mapped to the pericentromeric region of Chromosome 20. The 20q11 loci overlaps with the PPCD1 locus, suggesting that these two conditions may be allelic.²² Mutations in collagen

type VIII $\alpha 2$ (COL8A2) on chromosome 1, have also been identified in Fuchs endothelial dystrophy¹⁷ DNA sequence variants in the VSX1 may also contribute to keratoconus.¹³

In this study, we present a 23-year-old male proband with an unusual case of severe bilateral PPCD with associated findings of keratoconus. We also present data on his three brothers, including screening of genes known to cause PPCD.

METHODS

Ophthalmologic exam was performed on the proband and all living members of his family, which included three brothers and their mother. Examination consisted of slit lamp biomicroscopy, gonioscopy, slit lamp photos, specular microscopy, corneal topography and confocal imaging. The proband also underwent electroretinography (ERG) testing to evaluate retinal function. Family members were classified as having PPCD if they exhibited any of the following corneal findings: vesicular, geographic or band-like lesions at the level of Descemet's membrane and characteristic confocal imaging findings.

In addition, blood samples from the proband and his three brothers and his mother were obtained for genetic analysis after informed consent. Genomic DNA was isolated from peripheral blood samples and screened for mutations in VSX1, TCF8 and COL8A2. All exons and 50 base pairs of the flanking intron sequence were sequenced for each gene using nested PCR strategies for amplification. Oligonucleotides for amplification and sequencing were selected using Primer3 software (provided by Massachusetts Institute of Technology, Cambridge, MA). PCR was performed in a thermal cycler in a total volume of 25 μ l containing 50 ng genomic DNA; 1.5 mM $MgCl_2$; 200 μ M each of dATP, dCTP, dGTP, and dTTP; 100 ng forward PCR primer, 100 ng reverse PCR primer; 20 mM Tris-HCl (pH 8.4); 50 mM KCl; and 0.5 U Taq DNA polymerase (Platinum Taq; Invitrogen-Life Technologies, Rockville, MD). Cycling conditions were as follows: an initial denaturing step of 5 min at 94 °C; 35 cycles of denaturation (94 °C for 45 s), annealing (primer-specific annealing temperature for 60 s), elongation (72 °C for 45 s), and a final elongation step of 5 min at 72 °C. Amplified genomic DNA was directly sequenced using sequencing chemistries (BIGDYE version 3.1; Applied Biosystems Inc.) and an automated sequencer (model 3100; Applied Biosystems Inc.). Sequences were analyzed using Vector NTI sequence alignment tool and compared to the gene sequence in the [public database](http://www.genome.ucsc.edu) (UCSC Genome browser, www.genome.ucsc.edu).

RESULTS

The 23 year old white male proband first presented to the Massachusetts Eye and Ear Infirmary with complaint of painless progressive decrease in vision for 9 months. He had no prior ocular history. He also noted a gradual darkening of his left iris color. His last eye exam was approximately ten years ago and was within normal limits. Family history was negative for ocular diseases.

On clinical examination, best corrected visual acuity was 20/200 in the right eye and 20/40 in the left eye. There was no afferent pupillary defect. Corneal thickness measured by ultrasound pachymetry was 692 μ m in the right eye and 689 μ m in the left eye. Intraocular pressures were 15 mmHg in the right eye and 19 mmHg in the left. Heterochromia was present with a blue iris color in the right eye (Fig. 1A) and hazel-brown iris color in the left eye (Fig 1B). Slit lamp examination of the right eye disclosed diffuse corneal edema with band keratopathy across the central cornea (Fig. 1C). The corneal endothelium had a beaten metal appearance with fine granular lesions centrally. No guttae were noted (Fig. 1B). The cornea of the left eye had mild edema with deep stromal and endothelial opacities (Fig. 1D). No ectropion uveae or iris transillumination defects were present in both eyes. The left eye also had several iris nodules.

Gonioscopy of both eyes revealed an open anterior chamber angle with extensive presence of broad anteriorly placed peripheral anterior synechiae (PAS.) (Fig. 2). There was no evidence of posterior embryotoxon in both eyes. Dilated fundus examination was unremarkable without signs of macular edema or glaucomatous optic nerve cupping.

Specular microscopy could not be performed on the right eye due to band keratopathy and corneal edema. Specular microscopy of the left eye showed enlarged cells with several cells exhibiting pleomorphism and loss of the normal hexagonal configuration. Confocal microscopy on the right eye revealed smaller sized, disorganized endothelial cells with bright, hyperreflective centers, very similar in appearance to characteristic ICE cells (Fig. 3A). Confocal microscopy of the left eye showed an endothelial cell count of 1140 with a decrease in the amount of hexagonal cells and irregularly shaped pleomorphic cells. The cells exhibited hyperreflective nuclei, although fewer in number than the right eye (Fig. 3B). The areas of demarcation of normal and diseased endothelium were noted.

Due to a known association of certain variants of PPCD with corneal ectasia, corneal topography was performed. The right eye revealed moderate astigmatism with corneal powers of 45.2×48.2 diopters and inferior steepening consistent with keratectasia (Fig. 4A). Keratoconus analysis using the built-in Pentacam® program revealed a keratoconus level of 2. The left eye had steep corneal powers (47.8×48.9) but no characteristic inferior steepening was noted (Fig 4B). Corneal thickness maps revealed diffuse edema in both eyes.

Because the patient had calcific band keratopathy, systemic work-up was performed. Laboratory tests revealed normal serum calcium, phosphorus, uric acid, and creatinine levels. ANA, Lyme titers, HLA B27, toxoplasma antibodies and immunological panel were all negative. Liver function panel showed abnormally elevated AST (75.0), ALT (193.0) and total cholesterol (211.0) levels. Upon further questioning, the patient revealed extensive alcohol use over the past couple of years. Further systemic work-up did not reveal any other disorders.

The patient underwent chelation therapy with 1.7% EDTA to remove the band keratopathy in the right eye. The best-corrected visual acuity initially improved to 20/100 in the early postoperative period. However, despite the calcium removal, the patient's vision eventually declined to 20/200 with worsening corneal edema. Due to known association of PPCD, keratoconus, and retinal bipolar cell dysfunction, ERG analysis was performed to evaluate retinal function, and was found to be normal.

Based on slit lamp exam findings, specular and confocal microscopy, it was very difficult to make a definitive diagnosis of ICE versus PPCD since the patient had findings that could be seen in both conditions. Fortunately, this patient had three brothers and a mother who were also available for examination. The 31-year-old brother was asymptomatic, however his slit lamp exam revealed changes in Descemet's membrane consistent with posterior polymorphous dystrophy that was more pronounced in his right eye. Diagnosis was confirmed by confocal imaging, which revealed the characteristic endothelial cellular changes of PPCD (Fig. 5A). Corneal topography with keratoconus analysis revealed corneal ectasia in the right eye with an increased probability of keratoconus. His 29-year-old brother was also asymptomatic, but had band-like and vesicular defects in Descemet's membrane consistent with PPCD. Confocal imaging also showed characteristic PPCD changes (Fig. 5B). Topography revealed corneal steepening of the right eye (46.7×49.2) with evidence of early ectasia. The 22-year-old brother was asymptomatic as well, and had bilateral endothelial scalloping, bands, and vesicles, which was confirmed as PPCD on confocal imaging (Fig 5C). Topography was not performed on this brother. The mother's ophthalmic examination was unremarkable, and the patient's father has passed away without any known history of ocular disease.

Using genomic DNA purified from peripheral blood samples, three genes known to be associated with PPCD (VSX1, COL8A2 and TCF8) were screened in the proband, and his brothers. Biologically significant mutations were not detected in any of these genes in the proband and in the affected family members.

DISCUSSION

Clinical differentiation between PPCD and ICE syndrome can be challenging, especially when the PPCD presentation is particularly severe. Although unusual, ICE syndrome can be bilateral and may also demonstrate concurrent keratoconus and features of PPCD.²³

The presentation of PPCD in our case was unusual as the clinical exam findings and confocal imaging were consistent with ICE syndrome. Also suggestive of ICE syndrome was the corneal decompensation and edema, the presence of broad-based peripheral anterior synechiae, and confocal imaging demonstrating small hyperreflective endothelial cells.

However, there were several factors that favored the diagnosis of PPCD in this patient. Although asymmetric, the bilateral involvement is more consistent with PPCD, since the ICE syndrome is generally unilateral. Most importantly, the ability to examine his three brothers who all exhibited milder manifestations of PPCD helped to confirm the diagnosis, since PPCD is inherited as an autosomal dominant trait in most cases. In addition, the three brothers exhibited topographic changes ranging from corneal ectasia to keratoconus, which corresponded to their clinical severity. The association between PPCD and keratoconus has been previously reported in the literature.^{24–26} Interestingly, genetic analysis performed on the three brothers did not reveal any mutation in the VSX1 gene, nor in the other two previously determined genes associated with PPCD (COL8A2, and TCF8), suggesting that the disease affecting this family may be caused by a novel gene not yet identified.

There is much yet to be learned about the pathophysiology of this corneal dystrophy. As demonstrated by this family, PPCD can present with great phenotypic variability and may involve unidentified genetic associations. Future studies to evaluate the histopathology of the affected corneas will be performed if penetrating keratoplasty is required. This may provide valuable insight into the abnormal biology of the corneal endothelium and the pathophysiology of this condition.

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FIGURE 1.

Slit lamp photos. A. Low magnification. Right eye with diffuse corneal edema and band keratopathy. B. Low magnification. Left eye with mild corneal edema. Note the heterochromia, with blue iris color in the right eye A. and hazel-brown iris color in the left eye B. C. High magnification. Right eye corneal endothelium has a beaten metal appearance centrally with diffuse band keratopathy (arrow). D. High magnification. Left eye showing fine granular endothelial lesions centrally (arrow).

FIGURE 2.
Gonioscopy. Left eye demonstrating area of broad, anterior placed peripheral anterior synechiae.

FIGURE 3.

In vivo confocal microscopy. A. Right eye with abnormal endothelial cells exhibiting indistinct borders and bright, hyperreflective centers, reminiscent of characteristic ICE cells. Note the pleomorphic appearance with smaller sized cells and highly irregular cellular arrangement. Several cells had very bright, prominent nuclei located in the center of the cell (*arrow*). B. Endothelium of the left eye exhibits epithelioid-like pattern with pleomorphic appearance, loss of hexagonal borders, and non-homogenous diversely shaped nuclei, some with hyperreflective centers (*arrow*).

FIGURE 4.

Pentacam topography. A. *Top*, Sagittal curvature map showed inferior steepening of the right eye (OD) consistent with keratoconus. *Bottom*, corneal thickness map showed diffuse corneal edema. B. *Top*, Sagittal curvature map showed diffuse steepening of the left eye. *Bottom*, diffuse corneal edema was noted on the corneal thickness map.

FIGURE 5.

In vivo confocal microscopy of three brothers of the proband showing endothelial findings consistent with posterior polymorphous dystrophy. A. 31 year-old male. B. 29 year-old male. C. 22 year-old male.