developmental glaucoma and polydactyly with trisomy 13 often results in severe ocular development anomaly of angle.6 Although our patient had a normal pupil phenotype, the abnormalities of the eye. Trisomy 13 often results in severe ocular defects, including developmental glaucoma.2 One case of developmental glaucoma and polydactyly with trisomy 13 was reported,7 which is compatible with our case. In a French family with congenital microcoria, axial myopia, and juvenile open-angle glaucoma, genetic linkage to 13q31-32 was suggested to result in these ocular findings.8 Although our patient had a normal pupil phenotype, trisomy 13q31 might be responsible for the developmental anomaly of angle.

Taken together, it is suggested that the abnormalities of chromosome 9p23 and/or 13q31 are associated with developmental glaucoma with other systemic anomalies.

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### Table. Results of Examination Under General Anesthesia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 6 mo IOP, mm Hg</td>
<td>Schiotz tonometer</td>
<td>23.8</td>
</tr>
<tr>
<td>Perkins applanation tonometer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Corneal diameter, mm × mm</td>
<td>14.0 × 14.0</td>
<td>14.0 × 14.0</td>
</tr>
<tr>
<td>Corneal thickness, µm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>572</td>
<td>514</td>
</tr>
<tr>
<td>Axial length, mm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Aged 27 mo IOP, mm Hg</td>
<td>Schiotz tonometer</td>
<td>14.6</td>
</tr>
<tr>
<td>Perkins applanation tonometer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Corneal diameter, mm × mm</td>
<td>13.0 × 14.0</td>
<td>13.0 × 13.5</td>
</tr>
<tr>
<td>Corneal thickness, µm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>509</td>
<td>490</td>
</tr>
<tr>
<td>Axial length, mm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23.8</td>
<td>22.8</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.

<sup>a</sup>The Perkins applanation tonometer was from KOWA (Tokyo, Japan).

<sup>b</sup>The ultrasonic measuring method used an AL-2000 Biometer/Pachymeter (Tomey Corp, Nagoya, Japan).

P araneoplastic retinopathies are rare disorders caused by the immune system’s response to distal tumors. Autoantibodies generated against distant tumor antigens cross-react with different retinal proteins, resulting in retinal degeneration. Paraneoplastic retinopathies are usually divided into 2 major groups, cancer-associated retinopathy and melanoma-associated retinopathy (MAR).

Cancer-associated retinopathy is usually seen in patients with small-cell carcinoma of the lung and is associated with autoantibodies against recoverin and α-enolase.4,5 The autoantibodies in cancer-associated retinopathy induce apoptotic death of the photoreceptors, resulting in a severe retinal degeneration affecting both cones and rods.3 Melanoma-associated retinopathy is usually seen in patients with cutaneous malignant melanoma. The disorder often appears at the stage of metastases with a sudden onset of night blindness, photopsias, shimmering, and a varying degree of visual loss.9 Melanoma-associated retinopathy has been associated with autoantibodies against the retinal bipolar cells, and the typical full-field electroretinogram (ERG) shows a markedly reduced or absent dark-adapted b-wave and a preserved a-wave, confirming a defect in bipolar function.6 Melanoma-associated retinopathy usually has a normal retinal appearance.6 However, more recent studies have described patients with MAR or MAR-like symptoms with posterior uveitis, pigment epithelium changes, paracentral scars, optic disc pallor, and retinal vessel attenuation.4,7,8 A few patients with vitelliform retinal changes or serous retinal detachments resembling Best macular dystrophy (BMD) have also been described.9-12 In 3 of these patients, the primary tumor was a choroidal malignant melanoma.9,11,12

In this article, we describe a patient with a history of choroidal malignant melanoma in the left eye and a vitelliform macular appearance in the right eye, and we show for the first time to our knowledge the presence of circulating autoantibodies against bestrophin-1. The clinical appearance, including that on electro-oculography (EOG), resembled BMD.

### Methods

A 45-year-old man had fluctuations in visual acuity and difficulties in dark night vision of a few months’ duration in his right eye and only eye. Ten years prior, his left eye had been enucleated because of a choroidal ma-
lignant melanoma (spindle B type). One year previously, metastases in the liver and lungs were found and the patient was undergoing treatment with chemotherapy and radiation. There was no family history of night blindness, visual failure, or retinal disorders.

Ophthalmologic examination included assessment of best-corrected Snellen visual acuity, slitlamp examination, fundus inspection, kinetic perimetry with a Goldmann perimeter using standardized light targets Ia, V4e, and Oa (testing for scotoma), Farnsworth D15 testing, dark-adaptation threshold measured with the Goldmann-Weekers adaptometer, dark-adapted full-field ERG, EOG, optical coherence tomography, and ultrasonography of the macular region.

Dark-adapted full-field ERGs and EOG were recorded using the Nicolet analysis system (Nicolet Biomedical Instruments, Madison, Wisconsin) according to the International Society for Clinical Electrophysiology of Vision standards.13,14

The VMD2 gene was screened for mutations by DNA sequence analysis. One serum sample was analyzed for the presence of antiretinal and anti-retinal pigment epithelial (RPE) autoantibodies by Western blotting and immunohistochemistry using human retina as described previously by Adamus et al.15 The RPE was extracted from human RPE and the protein extract was prepared as follows. The RPE from a human eye was homogenized in a lysing buffer containing 1% Triton X-100 (Sigma-Aldrich Co, Stockholm, Sweden) in 50 mM Tris, pH 8.0, 150 mM sodium chloride, 0.5 mM EDTA, and protease inhibitor cocktail. After centrifugation at 10000g at 4°C for 30 minutes to remove debris, the protein concentration of the lysate was determined using a bicinchoninic acid assay (Pierce, Rockford, Illinois). Ten micrograms of proteins was used for gel electrophoresis. Informed consent was obtained from the patient.

Results. At examination, Snellen visual acuity was 0.9. The anterior segment of the eye was normal. There were no signs of uveitis. A central serous retinal detachment as a “pseudohypopyon” vitelliform lesion was seen in the macula (Figure 1 A). The visual field revealed a central scotoma for the Oa object (Figure 1B) and the Farnsworth D15 test showed 2 errors along the tritan axe. The dark-adaptation threshold was normal. There were no signs of a recurrent tumor in the enucleated orbit.

Dark-adapted full-field ERGs were evaluated twice, 1 month apart. On both examinations, normal amplitudes were found regarding the responses to dim blue light, white light single flash (a- and b-wave), and 30-Hz flicker white light. On the first examination, the implicit time to 30-Hz flicker white light was on the upper limit for a normal timing (32.8 milliseconds), and reexamination showed a prolongation in the implicit time (34.1 milliseconds). The EOG showed a pathological Arden ratio of 1.1 (reference range, > 1.5). Optical coherence tomography showed a serous retinal detachment in the macula (Figure 1C). B-scan ultrasonography confirmed the macular retinal detachment, and no pathological findings could be found otherwise.

Based on the clinical appearance in the macula resembling BMD, a blood sample was examined for disease-causing mutations in the VMD2 gene. No mutation was found in exons 2, 4, 6, or 8 of the VMD2 gene.

A serum sample was examined for antiretinal and anti-RPE autoantibodies. Western blot analysis results were positive for antiretinal autoantibodies against α-enolase in a low titer and were negative for antirecoverin autoantibodies. The patient’s serum antibodies mildly labeled the outer limiting membrane in the human retina. Testing serum for anti-RPE autoantibodies revealed the presence of autoantibodies against a 68-kDa protein, which was identified as bestrophin-1 (Figure 2).

After the last ophthalmologic examination, the disease worsened and widespread metastases were found. The patient died 4 months later.

Figure 1. Fundus photograph, Goldmann perimetry, and optical coherence tomography in the patient. A, Fundus photograph demonstrating the vitelliform “pseudohypopyon” macular appearance in the macula. B, Goldmann visual field demonstrating the central scotoma for light target Oa. C, Optical coherence tomography scan of the serous retinal detachment of the macula.
Comment. Our patient had a history of a choroidal malignant melanoma in the left eye. Initially, he had a typical clinical appearance of BMD in the right eye, including a vitelliform pseudohypopyon lesion in the macula, pathological EOG findings, and a normal full-field ERG. Best macular dystrophy is an autosomal dominantly inherited disease caused by mutations in the VMD2 gene encoding the bestrophin-1 protein. The patient had no history of BMD in the family and genetic analysis of the VMD2 gene revealed no mutations.

Besides the BMD appearance in the eye, the patient reported typical MAR-like symptoms with difficulties with night vision. These symptoms together with the history of malignant choroidal melanoma led to the suspicion of MAR. However, repeated ERG examinations 1 month apart could not establish any defect in the bipolar cell function. The full-field ERG results were normal in amplitudes, but on the last examination the cone b-wave implicit time showed a clear prolongation. A prolongation in cone b-wave implicit times has also been reported.22 The presence of anti-α-enolase autoantibodies could explain the prolongation in implicit time in the full-field ERG seen in our patient, but we consider it unlikely that these autoantibodies would produce the abnormal EOG findings.

Bestrophin-1 is a 585–amino acid, 68-kDa putative integral transmembrane protein localized to the basolateral aspect of the RPE.23 This protein has previously been described as a calcium ion–dependent chloride channel and a modulator for voltage-dependent calcium ion channels in RPE cells.24 It is still unclear in what way a dysfunction of bestrophin-1 results in a typical BMD phenotype with a vitelliform macular appearance and a light peak reduction in EOG. Based on the autosomal dominant pattern of inheritance of BMD, dominant negative effects would be expected. However, BMD is known to have a large variability in expressivity, and recent studies showed that the disorder may have a compound heterozygous pattern of inheritance as well.25 The result of autoantibodies to bestrophin-1 action would be expected to cause a loss of protein function. However, mice lacking bestrophin have no retinal abnormalities.26 A previous study has shown the importance of VMD2 encoding bestrophin-1 in ocular development.27 It is possible that bestrophin-1 has different functions in the eye during different stages of life. Our patient would be expected to have an acquired bestrophin-1 dysfunction in adulthood, whereas patients with BMD have a congenital defect to the protein. The function of bestrophin-1 needs to be further elucidated in future studies. We believe that the electrophysiological findings in our patient could be related to autoantibodies against bestrophin-1 as well as against α-enolase.

In conclusion, paraneoplastic retinopathies are complex disorders caused by various antiretinal autoantibodies and possibly by anti-RPE autoantibodies. In patients with choroidal malignant melanoma, the paraneoplastic retinopathy may manifest with the clinical appearance of BMD, possibly owing to circulating autoantibodies directed against bestrophin-1. Whether this expression of disease should be considered as a separate paraneoplastic entity or a variant of MAR remains to be clarified.

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**Figure 2.** Western blotting analysis of the patient’s serum against human retinal (HRE) proteins (A), α-enolase (B), and retinal pigment epithelium (RPE) proteins (C). The patient’s serum diluted 1:100 was incubated with a blot containing proteins as follows: 10 µg of HRE proteins on the blot with molecular standards in lane 1, the patient’s serum in lane 2, anti-α-enolase serum in lane 3, and antirecoverin serum in lane 4 (A); 1 µg of retinal α-enolase on the blot with the patient’s serum in lane 1 and anti-α-enolase serum in lane 2 (B); and 10 µg of RPE proteins on the blot with molecular standards in lane 1, the patient’s serum in lane 2, a negative control in lane 3, and anti-bestrophin-1 antiserum (t 2000) (Abcam, Inc, Cambridge, Massachusetts) in lane 4 (C). *Nonspecific band.

**Figure 2.** Western blotting analysis of the patient’s serum against human retinal (HRE) proteins (A), α-enolase (B), and retinal pigment epithelium (RPE) proteins (C). The patient’s serum diluted 1:100 was incubated with a blot containing proteins as follows: 10 µg of HRE proteins on the blot with molecular standards in lane 1, the patient’s serum in lane 2, anti-α-enolase serum in lane 3, and antirecoverin serum in lane 4 (A); 1 µg of retinal α-enolase on the blot with the patient’s serum in lane 1 and anti-α-enolase serum in lane 2 (B); and 10 µg of RPE proteins on the blot with molecular standards in lane 1, the patient’s serum in lane 2, a negative control in lane 3, and anti-bestrophin-1 antiserum (t 2000) (Abcam, Inc, Cambridge, Massachusetts) in lane 4 (C). *Nonspecific band.
Central Corneal Thickness and Optic Disc Hemorrhages: The Beijing Eye Study

Central corneal thickness (CCT) has been described to be a predictor for the development of primary open-angle glaucoma and the progression of glaucomatous visual field defects in the Ocular Hypertension Treatment Study and other investigations. Correspondingly, a previous investigation by Herndon and colleagues found that CCT was the most consistent predictor of the degree of glaucomatous damage in their hospital-based cross-sectional study. However, CCT also influences application tonometry, so it has remained unclear whether the reported findings are due to the dependence of intraocular pressure measurements on CCT and a corresponding selection artifact of patients or whether a thin cornea may predispose the eye to a higher glaucoma susceptibility. Since optic disc hemorrhages can indicate progression of glaucomatous optic neuropathy and because most of the previous investigations were hospital-based studies with a possible referral bias, it was the purpose of our population-based study to assess whether CCT influences the development of disc hemorrhages.

Methods. The Beijing Eye Study is a population-based cohort study in northern China. The medical ethics committee of the Beijing Tongren Hospital approved the study protocol and all of the participants gave informed consent according to the Declaration of Helsinki. Of 5324 individuals aged 40 years or older residing in the study area, 4439 individuals (2505 women) participated in the eye examination (response rate, 83.4%) in the year 2001 as described in detail previously. In 2006, the same population was invited for a reexamination, with 3251 subjects participating (response rate, 73.3%). All of the participants underwent a standardized ophthalmic examination including CCT measurement by slitlamp optical coherence tomography. Only 1 randomly selected eye was taken for statistical analysis. Glaucoma was defined by the appearance of the optic nerve head as described recently.

Results. Of the 3251 subjects, CCT measurements were available for 3100 subjects (95.4%); 32 of them (1.0%) showed an optic disc hemorrhage. The CCT was slightly greater in the hemorrhagic group (mean [SD] CCT, 569.5 [33.8] µm) than in the nonhemorrhagic group (mean [SD] CCT, 556.0 [33.0] µm) (P = .03; after application of the Bonferroni method to correct for performing multiple statistical analyses, P = .06) (Figure). Including glaucomatous eyes (n = 77) only, the CCT did not vary significantly between the hemorrhagic group (n = 5 eyes [6%], mean [SD] CCT, 571.8 [36.1] µm) and the nonhemorrhagic group (n = 72 eyes [9%], mean [SD] CCT, 549.3 [31.4] µm) (P = .24), with the hemorrhagic group having slightly thicker corneas than the nonhemorrhagic group.

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