Xanthomonas maltophilia Endophthalmitis After Cataract Surgery

Xanthomonas maltophilia, previously known as Pseudomonas maltophilia and Stenotrophomonas maltophilia, is a gram-negative motile bacillus that can be isolated from human, animal, and environmental sources. It may cause potentially life-threatening opportunistic systemic infections. Most isolates demonstrate multidrug resistance, making it a highly virulent organism. Postoperative endophthalmitis caused by X maltophilia is rare. To date, only 2 case reports have been published. We describe 4 additional patients with postoperative X maltophilia endophthalmitis treated between January 1, 1996, and March 31, 1999, at the Bascom Palmer Eye Institute, Miami, Fla (Table 1).

Report of Cases. Case 1. An 80-year-old woman was evaluated for increasing pain and decreased vision in the left eye, 2 weeks after uneventful clear-corneal phacoemulsification and posterior chamber intraocular lens (IOL) insertion. Her medical history was unremarkable. Visual acuity in the affected eye was hand movements. Clinical findings included a 5% hypopyon and marked vitritis. Vitreous tap was performed through the pars plana, and the patient was given intravitreal injections of ceftazidime, 2.25 mg; vancomycin hydrochloride, 1.0 mg; and dexamethasone sodium phosphate, 0.4 mg. On the first day after the initial treatment, a combined regimen was started with topical fortified ceftazidime, vancomycin, and 1% prednisolone acetate, every hour, and 1% atropine sulfate, 3 times daily. No systemic antibiotic therapy was used. Gram stain of the vitreous aspirate revealed many neutrophils, but no organisms were identified. Three days later, X maltophilia was isolated from the culture that was resistant to ceftazidime but sensitive to amikacin sulfate (Table 2). However, her clinical condition continued to improve, with resolution of the hypopyon; visual acuity returned to 20/50 OS. A small amount of retained lens cortex was noted at the 6-o’clock position. Gradual tapering of topical medications was begun.

Three weeks after the initial treatment, she returned with visual acuity in the left eye of light perception and recurrent hypopyon. Vitreous tap was performed and intravitreal injections of amikacin sulfate, 0.4 mg, and dexamethasone sodium phosphate, 0.4 mg, were given. Cultures of the vitreous aspirate were again positive for X maltophilia. During the next 48 hours, she developed worsening intraocular inflammation; the visual acuity remained light perception. Pars plana vitrectomy was performed and intravitreal injections of amikacin sulfate, 0.4

Table 1. Treatment Outcomes of Xanthomonas maltophilia Endophthalmitis*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Surgery</th>
<th>Time to Infection, d</th>
<th>Initial Intravitreal Treatment (Dosage)</th>
<th>Initial PPV</th>
<th>Time to Recurrence, d</th>
<th>Subsequent Treatment (Dosage)</th>
<th>Visual Acuity</th>
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<tr>
<td>1</td>
<td>PE and PCIOL</td>
<td>14</td>
<td>Vancomycin hydrochloride (1.0 mg), ceftazidime (2.25 mg), and dexamethasone sodium phosphate (0.4 mg)</td>
<td>-</td>
<td>21</td>
<td>Intravitreal injection of amikacin sulfate (0.4 mg), followed by PPV, and repeat intravitreal injection of amikacin sulfate (0.4 mg)</td>
<td>HM 20/50</td>
</tr>
<tr>
<td>2</td>
<td>PE and PCIOL</td>
<td>26</td>
<td>Vancomycin hydrochloride (1.0 mg), ceftazidime (2.25 mg), and dexamethasone sodium phosphate (0.4 mg)</td>
<td>-</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>ECCE and PCIOL</td>
<td>6</td>
<td>Amikacin sulfate and cefazolin sodium†</td>
<td>-</td>
<td>45</td>
<td>PPV and intravitreal injection of vancomycin hydrochloride (1.0 mg) and ceftazidime (2.25 mg)</td>
<td>20/200 20/30</td>
</tr>
<tr>
<td>4</td>
<td>ECCE and PCIOL</td>
<td>5</td>
<td>Vancomycin hydrochloride (1.0 mg), ceftazidime (2.25 mg), and dexamethasone sodium phosphate (0.4 mg)</td>
<td>+</td>
<td>7</td>
<td>Intravitreal injection of ceftazidime (2.25 mg) ×2 and subsequent PPV for nonclearing vitreous opacities</td>
<td>LP 20/400</td>
</tr>
</tbody>
</table>

*PPV indicates pars plana vitrectomy; PE, phacoemulsification; PCIOL, posterior chamber intraocular lens implant; minus sign, no initial PPV was performed; HM, hand movements; ECCE, extracapsular cataract extraction; plus sign, an initial PPV was performed; and LP, light perception.

†Dosages not known.
mg, and dexamethasone sodium phosphate, 0.4 mg, were administered. During the vitrectomy, the silicone plate posterior chamber IOL dislocated into the vitreous cavity but was positioned into the anterior chamber with a plan to exchange the IOL at a later date. At the 9-month follow-up visit, visual acuity was 20/50 OS and the vitritis resolved (Figure).

Case 2. A 70-year-old woman was referred with increasing pain and redness in her left eye. One month earlier, she underwent phacoemulsification and insertion of a posterior chamber IOL. Her early postoperative course was uneventful, and she recovered 20/25 OS visual acuity by week 2. However, she had persistent anterior chamber reaction (2+) with retained lens cortex at the 5-o’clock position and was given a sub-Tenon injection of dexamethasone sodium phosphate, 40 mg, by her ophthalmologist. Two days later, the visual acuity in the left eye decreased to hand movements. Clinical findings included a 5% hypopyon, vitritis, and no view of the retina. A vitreous aspirate was performed, and she was given intravitreal injections of ceftazidime, 2.25 mg; vancomycin hydrochloride, 1.0 mg; and dexamethasone sodium phosphate, 0.4 mg. Cultures of the vitreous aspirates were positive for X malophilia that was sensitive to ceftazidime but resistant to amikacin (Table 2). However, the patient had an excellent response to intravitreal ceftazidime treatment and 3 months later, best-corrected visual acuity was 20/30 OS and the vitritis resolved.

Case 3. A 46-year-old man developed pain and irritation 5 days after undergoing extracapsular cataract extraction and posterior chamber IOL implantation in his left eye. In Venezuela, he was diagnosed as having postoperative endophthalmitis and was treated with vitreous tap and intravitreal injections of amikacin and cefazolin sodium. Vitreous cultures were reported to yield gram-negative rods and were read as possible Escherichia coli. Initially, the patient showed improvement in clinical signs but developed recurrent inflammation after 6 weeks and was referred to the Bascom Palmer Eye Institute for further management of his condition.

Best-corrected visual acuity was 20/200 OS. The cornea was slightly edematous, with anterior chamber cells (2+ to 3+) but no hypopyon. The posterior chamber IOL was in the bag with fluffy white cortical material for about 3 clock-hours. Dilated fundus examination revealed vitritis (2+) with optic disc hyperemia and cystoid macular edema. The patient underwent an uncomplicated pars plana vitrectomy, partial capsulectomy, and received intravitreal injections of ceftazidime, 2.25 mg, and vancomycin hydrochloride, 1.0 mg. Several days later, X malophilia was isolated from the culture of vitreous aspirates that was sensitive to ceftazidime but resistant to amikacin (Table 2). The vitritis resolved; visual acuity improved to 20/30 OS at the 8-month follow-up visit.

Case 4. A 48-year-old man underwent an uneventful extracapsular cataract extraction with insertion of posterior chamber IOL in his right eye in Nicaragua. Because of the marked intraocular inflammation on the fifth postoperative day, a clinical diagnosis of postoperative endophthalmitis was made and he was treated with subconjunctival gentamicin and topical tobramycin-prednisone drops every hour. Seventy-two hours after the first treatment, the patient was seen by us. Visual acuity in the operated eye was light perception with a 20% hypopyon and no view of the posterior pole. The patient underwent pars plana vitrectomy with
intravitreal injection of ceftazidime, 2.25 mg; vancomycin hydrochloride, 1.0 mg; and dexamethasone sodium phosphate, 0.4 mg. In addition, he was started on a regimen of topical fortified ceftazidime, vancomycin, and 1% prednisolone acetate, every hour, and 1% atropine sulfate, 3 times daily. Vitreous cultures were positive for *X maltophilia* that was sensitive to ceftazidime but resistant to amikacin (Table 2). The initial favorable clinical response was followed 1 week later by increasing pain, decreased visual acuity in the right eye to hand movements, and increased hypopyon (30%). A second vitreous culture was taken and intravitreal injection of ceftazidime, 2.25 mg, was administered and the patient was given oral ciprofloxacin, 750 mg twice daily. Vitreous cultures were again positive for *X maltophilia* sensitive to ceftazidime. Five days later, the patient returned with increasing pain and subjective decrease in vision in the right eye, but the results of the ocular examination were unchanged. A third course of intravitreal injections of ceftazidime, 2.25 mg, and dexamethasone sodium phosphate, 0.4 mg, was administered and treatment with topical fortified antibiotics was continued. During the next 3 weeks, there was significant improvement in pain and inflammation but visual acuity remained poor at hand movements because of vitreous opacities. Pars plana vitrectomy was performed to clear the vitreous opacities. Vitreous cultures were not obtained and intravitreal antibiotic injections were not administered. Three weeks after the second vitrectomy, the vitritis resolved but visual acuity was 20/400 OD owing to persistent cystoid macular edema. The patient returned to Nicaragua and was lost to follow-up.

**Comment.** The first reported case of *X maltophilia* endophthalmitis was in a patient with acquired immunodeficiency syndrome following implantation of a ganciclovir implant. This patient required multiple injections of amikacin and ciprofloxacin hydrochloride with only partial response. Two different vitreous aspirate cultures yielded *X maltophilia* that was sensitive to ceftazidime but resistant to all aminoglycosides, quinolones, and other β-lactam antibiotics. Treatment included removal of the ganciclovir implant, pars plana vitrectomy, and administration of intravitreal and systemic ceftazidime.

Kaiser et al recently reported a case of *X maltophilia* endophthalmitis 6 days after cataract extraction in an immunocompetent 76-year-old woman. The patient was initially treated with pars plana vitrectomy and intravitreal injections of vancomycin and tobramycin. Vitreous aspirate culture was positive for *X maltophilia* that was resistant to both of the initially administered antibiotics but was sensitive to ceftazidime, gentamicin, ciprofloxacin, ticarcillin, polymyxin B, and sulfamethoxazole-trimethoprim. However, the patient responded extremely favorably to the initial treatment but had recurrence of inflammation 6 weeks later. A second pars plana vitrectomy, intravitreal ceftazidime injection, and treatment with topical and oral ciprofloxacin and sulfamethoxazole-trimethoprim sulfate was successful in clearing the vitritis.

In our study, the clinical course of *X maltophilia* endophthalmitis following cataract surgery in 4 immunocompetent patients is described. Patient 2 responded well to the initial intravitreal antibiotic therapy. The other 3 patients (cases 1, 3, and 4) had a course of recurrent infection similar to previously published cases. The duration between the initial treatment and the first recurrence ranged from 7 to 45 days. In all patients, cure was achieved by pars plana vitrectomy and/or intravitreal antibiotic injection.

In a study by Stern et al, reported risk factors for recurrent postoperative endophthalmitis included infection with a gram-negative bacillus, host immunosuppression, slow-growing organisms, organisms with multi-antibiotic resistance, and inadequate antibiotic exposure time. Antibiotic resistance may in part explain the recurrence in the cases reported by Chen et al and Kaiser et al and cases 1 and 3 in our study. The case by Kaiser et al and patient 1 in our case series did show favorable clinical response to initial intravitreal therapy despite organism resistance. Intravitreal injection of antibiotics provides high initial concentrations of antibiotics that are well in excess of the minimum inhibitory concentrations against susceptible organisms. However, in patient 4, the organism was sensitive to the ceftazidime but endophthalmitis still recurred. Cottingham and Forster hypothesized the concept of eradication time, which was the time after inoculation within which eyes had to be treated to be sterilized. Beyond the eradication time, the organism load is such that pars plana vitrectomy is required in addition to injection of intravitreal antibiotics. Our patient 4 may represent an infected eye treated after the eradication time had elapsed.

Three of the 4 cases (cases 1 through 3) had visible retained lens cortex that may cause intraocular inflammation mimicking endophthalmitis. It is also possible that the retained lens cortex may have played a role in facilitating growth of the organisms as has been described for postoperative *Propionibacterium* endophthalmitis. The antibiotic sensitivities of all vitreous isolates in our study are summarized in Table 2. All 4 isolates were sensitive to polymyxin B and sulfamethoxazole-trimethoprim, while 3 of the 4 isolates were sensitive to ciprofloxacin. All isolates were resistant to gentamicin, while 2 of the 4 isolates were sensitive to amikacin, tobramycin, and ceftazidime; there was no cross-resistance between amikacin and ceftazidime.

The role of systemic antibiotics in the management of *X maltophilia* endophthalmitis is unclear. Kaiser et al used both oral ciprofloxacin and sulfamethoxazole-trimethoprim for treating their patient with *X maltophilia* endophthalmitis. In accord with the findings of the Endophthalmitis Vitrectomy Study Group showing no beneficial effect of systemic antibiotic treatment in the management of postoperative endophthalmitis, no systemic antibiotics were used in our study.

Endophthalmitis associated with gram-negative organisms usually has poor visual prognosis. However, some gram-negative organisms may be less virulent, cause somewhat delayed-onset endophthalmitis, and
have a better visual prognosis.11 Despite the high recurrence rate, endophthalmitis caused by *X maltophilia* seems to be in the latter category since the visual acuity outcomes after treatment were generally favorable.

Our case series and the previously reported cases demonstrate that *X maltophilia* endophthalmitis may have a persistent and recurrent clinical course even when the organism is sensitive to the intravitreal antibiotics used. Hence, it is important to follow up these patients closely for recurrence, possibly repeating treatment with intravitreal antibiotics and pars plana vitrectomy when indicated.

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### Pseudodefects of the Retinal Nerve Fiber Layer Examined Using Optical Coherence Tomography

Glucoma destroys the ganglion cell axons in the retina and may produce localized and/or diffuse damage of the retinal nerve fiber layer (RNFL). Unlike diffuse damage, localized defects are easy to detect. At the location of the RNFL defect the normal striated pattern of RNFL disappears and the localized defect is well outlined against the surrounding healthy nerve fiber bundles. Although single or multiple slitlike defects are probably not a sign of abnormality, they may sometimes be misinterpreted as a localized RNFL defect. This study demonstrates another RNFL finding to be differentiated from a true localized RNFL defect, ie, what we call a “pseudodefect” of the RNFL.

**Report of Cases.** When routine RNFL photographs were examined, pseudodefects were detected in a total of 13 patients (Figure 1). Four patients were found during glaucoma screening and no information was available from the Finnish Glaucoma Patient Association. The remaining 9 patients (7 female and 2 male) had a mean age of 62 years (age range, 41-75 years). We also had the opportunity to measure 6 patients with RNFL pseudodefects using Optical Coherence Tomography (Zeiss Humphrey, San Leandro, Calif). Several optical coherence tomographic scans were taken across the pseudodefect. Using a prototype software version, an estimate of the mean thickness of the RNFL at the pseudodefect was compared with the mean thickness of the adjacent normal retina on both sides of the pseudodefect (Figure 2). The mean of 3 measurements was used for each location.

The pseudodefects were found along the major retinal blood vessels. Within 1 to 4 disc diameters from the optic disc margin, they looked like oblong or braid-shaped chinks or cracks within the normal RNFL structure (Figure 1). In 3 eyes these pseudodefects could be followed far into the periphery (up to 4 disc diameters temporal to the macula) where the pseudodefect no longer looked like a chink but had a flat, beaten appearance. In 1 patient the pseudodefect was seen in the inferior nasal retina; all others were located temporal to the optic disc and/or the macula. In 2 patients pseudodefects were found in both eyes.

In 5 of 6 patients the optical coherence tomographic scan showed a thinning of the RNFL at the pseudodefect. The mean ± SD thickness of the RNFL was 132 ± 49 µm at the pseudodefect, 220 ± 49 µm on the temporal side of the pseudodefect, and 203 ± 70 µm on the nasal side of...
pseudodefects in the literature. In the reference range, 1.1-1.6 mm², the Heidelberg Retina Tomograph disc area of the 6 eyes using the difference, 37%). The mean ± SD optic disc size of 1.4 mm² of the eyes. The differences of the retinal thickness values at the pseudodefect compared with the average retinal thickness values on either side of the pseudodefect were 212, 136, 111, 38, 32, and −53 μm (mean difference, 79 μm). The retinal thickness values at the pseudodefect were also in hyperopes and mild myopes, (2) our patients were all older than 40 years, (3) in 2 patients the changes were seen bilaterally, (4) the mean optic disc size of 2.1 mm² of the pseudodefect was smaller compared with our previously reported mean disc size of 2.1 mm², and (5) the mean decrease in retinal thickness was 79 μm (37%) at the pseudodefect, which is larger than the mean difference of 39 μm reported between glaucomatous and normal eyes.

Chihara and Chihara described 3 patients with what they called a cleavage of the RNFL. They reported that the cleavage was associated with high myopia (−14, −14, and −15 D) and postulated that the number of axons might be insufficient to cover the enlarged posterior segment of these myopic eyes. All of their patients were younger than 35 years. They did not find a cleavage in any of 144 emmetropic or hyperopic eyes. The cleavage was unassociated with any visual dysfunction measured with automated perimetry.

In our larger number of patients we found several differences and new findings compared with the previously published Japanese cases, ie, (1) although most frequent in high myopes, pseudodefects were found also in hyperopes and mild myopes, (2) our patients were all older than 40 years, (3) in 2 patients the changes were seen bilaterally, (4) mean optic disc size of 1.4 mm² of the eyes with pseudodefects was smaller compared with our previously reported mean disc size of 2.1 mm², and (5) the mean decrease in retinal thickness was 79 μm (37%) at the pseudodefect, which is larger than the mean difference of 39 μm reported between glaucomatous and normal eyes.

Figure 1. Within 1 to 4 disc diameters from the optic disc margin the pseudodefects of the retinal nerve fiber layer look like oblong or braid-shaped chinks or cracks in the normal retinal nerve fiber layer structure (small arrows). Further in the periphery, the pseudodefect has a flat, beaten appearance (large arrow).

Figure 2. An Optical Coherence Tomographic (Zeiss-Humphrey, San Leandro, Calif) image of a retinal nerve fiber layer pseudodefect (arrow) adjacent to the blood vessel.

Complications of Systemic Chemotherapy as Treatment of Retinoblastoma

Retinoblastoma is the most common intraocular tumor in children. Historically, the treatment of retinoblastoma was enucleation. However, improvements in diagnosis and treatment of retinoblastoma have led not only to a survival rate well over 90%, but also to an increasing ability to offer globe conservation as a secondary goal of therapy. Globe-conserving therapies include cryotherapy, laser photocoagulation, hyperthermia, and plaque radiotherapy for smaller tumors, and external beam radiation and systemic chemotherapy for larger tumors not amenable to local control.

Recently, multiple-agent chemotherapy with etoposide phosphate, carboplatin, and vincristine sulfate combined with transpulmonary hyperthermia has been demonstrated to achieve excellent local control of retinoblastoma. Further, systemic chemotherapy spares the patient the risk of craniofacial abnormalities and may eliminate or decrease the risk of secondary tumors that have been associated with external beam radiation. However, systemic chemotherapy employed for retinoblastoma has been associated with adverse events such as myelosuppression and subsequent infections and need for transfusion of blood products. To our knowledge, the incidence of such complications and their effect on treatment remain unknown. This study evaluates the adverse events and resultant alterations in treatment protocol during the treatment of retinoblastoma with systemic chemotherapy.

Report of Cases. The study protocol was approved by the Institutional Review Board of the University of Miami School of Medicine, Miami, Fla. The medical records of all patients with retinoblastoma evaluated at Bascom Palmer Eye Institute, Miami, and treated with systemic chemotherapy at Jackson Memorial Hospital, Miami, between July 1, 1995, and May 31, 1999, were reviewed. Outcome measures included chemotherapy cycle delays, adjustment of chemotherapy doses owing to side effects, delays in planned examinations under anesthesia, unplanned hospital admissions, febrile episodes, myelosuppression, transfusions, and port-related complications.

Five (42%) of the 12 patients were male and all 12 had no family history of retinoblastoma. The mean age at diagnosis was 17 months (age range, 2-66 months); the mean duration of chemotherapy was 5.9 months. One of the 12 patients had extraocular disease.

All of the patients received carboplatin (20 mg/kg for patients <12 months, 550-600 mg/m² body surface area for patients >12 months) and etoposide phosphate (5 mg/kg if the patient was <12 months, 150 mg/m² body surface area if the patient was >12 months). 9 (75%) received vincristine sulfate (0.05 mg/kg if the patient was <12 months, 1.5-2 mg/m² body surface area if the patient was >12 months) and 4 (33%) also received cyclosporine (5 mg/kg per hour bolus for 2 hours before chemotherapy started, then a 1.5 mg/kg per hour infusion over the next 30 hours if the patient weighed <12 kg, adjusted to 4 mg/kg per hour and 1.25 mg/kg per hour, respectively, if the patient weighed 12-30 kg, and adjusted to 3 mg/kg per hour, and 1.0 mg/kg per hour if the patient weighed >30 kg). The 1 patient who had extraocular tumor extension also received intrathecal treatment with a combination of methotrexate, hydrocortisone sodium succinate, and cytarabine. The patients underwent a mean of 7.2 cycles of chemotherapy (range, 4-10 cycles).

Nine patients (75%) had at least 1 cycle of chemotherapy delayed during the course of therapy. The 12 patients underwent a total of 86 cycles of chemotherapy, 17 (19.8%) of which were delayed an average of 9 days (range, 1-30 days). Chemotherapy was often delayed owing to a combination of factors, including neutropenia in 11 (65%) of 17 patients, thrombocytopenia in 5 (35%) of 17 patients, and febrile episode in 5 (29%) of 17 patients. Four (33%) of the 12 patients had doses of chemotherapy reduced secondary to treatment-related morbidity.

During the course of therapy, the 12 patients had a total of 91 examinations under anesthesia scheduled, 16 (18%) of which were delayed an average of 10 days (range, 1-21 days). Seven patients (58%) had at least 1 examination under anesthesia delayed. Causes of delay of examination under anesthesia included neutropenia in 11 (69%) of 16 patients, febrile episode in 7 (44%) of 16 patients, and thrombocytopenia in 4 (25%) of 16 patients.

Nine patients (75%) had at least 1 unplanned hospital admission (mean, 1.7 admission; reference range, 0-4 admissions) during the course of chemotherapy. The reasons for unplanned hospital admissions included neutropenia in 5 patients (60%), fever in 4 patients (30%), and thrombocytopenia in 4 patients (45%). Some patients had more than 1 problem leading to their hospital admission. Five patients (42%) required a transfusion of platelets; 3 patients (25%) needed a transfusion of packed red blood cells during the course of therapy.

Each patient had a central intravenous port placed under general anesthesia at the outset of therapy. Surgical time for port placement averaged 47 minutes (range, 35-90 minutes). Two of the patients underwent unplanned port removal secondary to complications (infection and exposure).

None of the patients required discontinuation of the treatment course secondary to treatment-associated morbidity. Outstanding tumor response was achieved in all patients. No patient in our series required enucleation or radiotherapy owing to failure of the planned treatment with systemic chemotherapy.

Comment. Although the use of systemic chemotherapy for retinoblastoma is not amenable to local treatment but is associated with excellent local tumor control, adverse events are likely to complicate the course of treatment. Even though these adverse events are treatable and did not result in the cessation of therapy, physicians administering the treatment and counseling the families of affected patients should be aware of the
potential complications and should communicate the risks to the families.

An additional consideration in planning future systemic chemotherapy regimens for patients with retinoblastoma is the incorporation of granulocyte colony-stimulating factor (Neupogen; Amgen, Thousand Oaks, Calif) in the treatment plan. Granulocyte colony-stimulating factor has been demonstrated to have promyelocytic activity and may help to decrease the incidence of myelosuppression, infection, and need for transfusion of blood products in these patients.6

Further information concerning systemic chemotherapy-associated morbidity among patients with retinoblastoma should become available with the results of the international clinical trial funded by the National Cancer Institute to evaluate systemic chemoreduction in the management of patients with large bilateral retinoblastomas.

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Persistent Hyperplastic Primary Vitreous
Associated With Septo-optic-pituitary Dysplasia and Schizencephaly

Persistent hyperplastic primary vitreous (PHPV), a form of persistent fotal vasculature, occurs infrequently with systemic conditions.1 We report the novel association of unilateral PHPV with septo-optic-pituitary dysplasia (SOPD) and ipsilateral schizencephaly.

Report of a Case. A full-term female neonate was born to a 17-year-old primigravid woman by cesarean delivery. On the third day of life, hypoglycemia and hypotonia raised the suspicion of sepsis, for which intravenous antibiotic therapy was administered. Microbiologic cultures were negative for organisms. The patient's condition stabilized and the neonate was discharged from the hospital.

On the ninth day of life, the patient was found ashen and unresponsive; she had suffered a grand mal seizure. On admission to a neonatal intensive care center, the patient was lethargic, hypotonic, hypoglycemic (1.270 mmol/L [23 mg/dL]), and hyperbilirubinemic (239.4 µmol/L [14.0 mg/dL]). Magnetic resonance imaging scans revealed an absent septum pellucidum, posterior ectopic pituitary gland, absent infundibulum, right closed lip schizencephaly, cortical dysplasia, and ventriculomegaly (Figure 1). Serum endocrinologic evaluation disclosed a low thyrotropin level (4.6 µU/mL), low total thyroxine level (50 ng/mL [3.9 µg/dL]), low morning cortisol level (<55 µmol/L), and subnormal response to corticotropin stimulation (0.66 µg/mL). The patient was treated for thyrotropin deficiency and corticotropin deficiency with levothyroxine sodium and hydrocortisone, respectively.

During ophthalmic examination on the 13th day of life and again in the seventh week of life, the infant did not fixate but briefly followed light. Pupils sluggishly reacted to light and a left-sided beating nystagmus worsened on left gaze. Corneal diameters were 8 mm OD and 10 mm OS. Biomicroscopic examination of the right eye revealed a clear cornea, and a shallow, but formed, anterior chamber. Neither iris vessels nor elongated ciliary processes were noted. A fibrovascular plaque on the superonasal retrolental surface funneled to a vascular band that extended on to a small optic disc. Macular anatomy was absent in this eye (Figure 2).

The left eye was remarkable for a normal anterior segment, engorged retinal veins, and a small, pale optic disc with a double-ring sign. Because improvement in visual function with surgical intervention was not expected, only periodic follow-up was recommended.

Comment. Persistent hyperplastic primary vitreous refers to a form of persistent fetal vasculature in which the posterior tunica vasculosa lentis (or posterior fetal fibrovascular sheath) and the hyaloid artery fail to regress.1 Although traditionally a sporadic, unilateral, and isolated finding, PHPV also has been reported in trisomy 13, Norrie disease, Warburg syndrome, incontinentia pigmenti, cerebro-oculodysplasia-muscular dystrophy,1 and fetal alcohol syndrome.2 Malformations of the macula, such as hypoplasia in our patient, may occur.3

Septo-optic-pituitary dysplasia (de Morsier syndrome) refers to the variable constellation of absent septum pellucidum, complete or partial thinning of the corpus callosum, hypoplastic anterior visual pathways, and pituitary hormone deficiency.3,4 Endocrinologic problems may be life-threatening as in our patient, whose corticotropin deficiency caused apnea, hypotonia, seizures, prolonged jaundice, and hypoglycemia. Absent pituitary infundibulum on the magnetic resonance imaging scan correlates with concurrent endocrinologic deficiency, while an ectopic posterior pituitary, seen as an intense nodule in T1-weighted images, may have sparing of posterior pituitary function5 (Figure 1).

Schizencephaly is a cerebral hemisphere migration anomaly in which an abnormal gray matter—
lined cleft extends through the cerebral hemisphere from the lateral ventricle to the cortical surface. Schizencephaly may accompany SOPD and can lead to seizure disorder and mental retardation.3

The pathogeneses of PHPV, SOPD, and schizencephaly are unclear. Persistent fetal vasculature has been postulated to be an arrest in fetal intraocular vascular development.1 Septo-optic-pituitary dysplasia has been postulated to result from supernormal regression of axons,4 disrupted migration of neurons and axons with failure to make target connections,3 or vascular insult to a developmental field during the first trimester of embryogenesis.5 Although a teratogenic history was not elicited in our patient, coincident optic nerve hypoplasia with PHPV2 and coincident SOPD and schizencephaly have been reported in pa-
tients with a maternal history of gestational substance abuse. Our case of unilateral PHPV with SOPD and ipsilateral schizencephaly is a novel and intriguing association.

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**Combined Choroidal and Retinal Ischemia During Interferon Therapy: Indocyanine Green Angiographic and Microperimetric Findings**

This article presents findings from indocyanine green angiography (ICGA) and microperimetry in a patient with interferon (IFN)-associated combined choroidal and retinal perfusion deficits.

**Report of a Case.** A 40-year-old man was seen for central scotomas and blurred vision during treatment with IFN alfa-2b for metastatic renal cell carcinoma. Findings from retinal examination included cotton-wool spot formation and small hemorrhages. Findings from fluorescein and ICGA demonstrated areas of retinal as well as choroidal nonperfusion. Results of scanning laser ophthalmoscope microperimetry revealed central scotomas corresponding to choroidal perfusion defects. Cotton-wool spots and retinal hemorrhages disappeared during therapy over a 6-month period, but visual impairment and choroidal ischemia persisted. In addition to retinopathy, IFN therapy may also induce persistent choroidal perfusion changes associated with scotomization.

Our patient was seen for blurred vision in both eyes and reading difficulty for several months. Findings from the patient’s medical history revealed renal cell carcinoma, for which he had undergone nephrectomy 3 years earlier. Treatment with IFN alfa-2b was administered for metastasis of the lung with an initial dose of $2 \times 10^6$ IU subcutaneously and increased to the continuos dose of $10 \times 10^6$ IU 5 times per week. His general condition was otherwise good, and he did not take any other medications. Ocular symptoms were noted roughly 1 month after initiation of IFN alfa-2b therapy. On initial examination, visual acuity was 20/20 OU. On ophthalmoscopic examination, cotton-wool spots and small retinal hemorrhages were found scattered throughout the posterior pole in both eyes (Figure 1). The patient was not diabetic, and his blood pressure levels have never been elevated. Other systemic causes of cotton-wool spots were excluded by findings from extensive laboratory examination. Two months later, his visual acuity decreased to 20/50 OD and remained unchanged in his left eye. Results of fluorescein angiography showed a central area of complete absence of choroidal perfusion with overlying intact retinal perfusion and no alteration of the perifoveal capillary net in early-phase fluorescein angiography (Figure 2, A and B). Late-phase fluorescein angiography showed venous dilatation and retinal vessel leakage in both eyes (Figure 2, C). The ICGA revealed a well-demarcated area of confluent and persistent choroidal filling defects (Figure 3, A). The characteristic ICG pattern of the capillary and arteriolar net was missing. Findings from objective testing using scanning laser ophthalmoscope microperimetry revealed central and para-central scotomas (Figure 4) precisely corresponding to the 2 areas of choroidal hypofluorescence consistent
with choroidal ischemia during late-phase ICGA (Figure 3, B). A slight decrease of the Arden ratio was found by whole electroretinography. Within the initial follow-up period of 6 months, the cotton-wool spots and the retinal hemorrhages disappeared. However, there was no recovery of the central choroidal perfusion changes. Functional defects persisted over a 1-year follow-up period, and visual acuity remained 20/63 OD.

Comment. Interferon alfa inhibits vascular endothelial cell proliferation and reveals antitumor activity. Therefore, it is used to treat human neoplasms, including metastatic renal cell carcinoma. Interferon-associated retinopathy has been described previously, mainly in the Japanese literature. Typical retinal findings include cotton-wool spots, hemorrhages, and microaneurysms. Retinal ischemia may be observed in affected areas by fluorescein angiography. Other ocular findings included conjunctival hemorrhage, central retinal vein occlusion, branch retinal artery occlusion, aggravation of diabetic retinopathy, optic disc edema, oculomotor nerve paralysis, and hypertrichosis.

To our knowledge, choroidal perfusion changes have not been described in the literature until now and are documented for the first time in a patient undergoing prolonged systemic IFN therapy. The patient had symptoms of focal retinal capillary dropout as manifested by cotton-wool spots. However, there were no retinal infarctions seen within the area of choroidal nonperfusion itself, and the perifoveal capillary perfusion was intact (Figure 2, A). Choroidal filling defects were substantiated by ICGA (Figure 3) and appeared to be responsible for vi-
sual impairment based on microperimetry. Electrophysiological findings supported the presence of photoreceptor damage, which is responsible for the central functional defect documented by scanning laser ophthalmoscope microperimetry. The central and paracentral scotomas corresponded in size and location to 2 persisting choriocapillar perfusion defects delineated by ICGA. As reported by other authors, symptoms of retinal vasculopathy subsided spontaneously in our patient; the choroidal defects, however, did not resolve.

The pathogenesis of IFN-associated vasculopathy is unclear. It is known that up to 10% of patients treated with recombinant IFN alfa produce autoantibodies. It is therefore postulated that IFN may cause deposition of immune complexes in retinal vessels. However, capillary-type damage is suspected in IFN retinopathy, while choroidal nonperfusion is more likely owing to occlusion of larger-caliber vessels. Occlusive choroidalopathy was seen in malignant hypertension and Harada disease and was associated histopathologically with fibrin platelet clots in the choriocapillaris. Another possible origin of choroidal thrombosis could be the underlying renal cell carcinoma, which might have triggered an embolic event by platelet or tumor clots. Venous choroidal thrombosis mostly induced serous retinal detachment, which was not present in our patient. However, embolization of the choriocapillaris by an arterial route did not result in detachments experimentally. Arterial choroidal occlusion is most likely responsible for intensive functional defects. However, choroidal perfusion changes and photoreceptor function did not recover during long-term follow-up.

Our observation suggests that patients demonstrating retinopathy during IFN therapy should carefully be examined by ICGA and central field testing to recognize additional choroidal nonperfusion. Since there is evidence that vaso-occlusion might not be restricted to retinal capillaries, the risk of ischemia occurring within other organ systems should be taken into account.

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There was a point of leakage located at the inferonasal margin of the RPE tear during the early phase, which leaked profusely during the later stage (Figure 2, right). Electroretinography and electro-oculography of the right eye were abnormal. Amplitudes of the b-wave were 30.5 µV in the right eye and 133.1 µV in the left eye. The Arden ratios were 1.29 OD and 2.24 OS. Focal diode laser photocoagulation to the point of leakage was performed that subsequently resulted in complete resolution of the exudative retinal detachment. The best-corrected visual acuity improved to 20/30 OU 4 months later.

Comment. Krishan et al,\(^3\) using a metal plate model, demonstrated that the bending stress along the RPE detachment was inversely proportional to the radius of curvature. The radius of curvature at the margin of the detachment was much smaller than that at the center. Hence, the bending stress at the edge was greater than that at the center of the RPE detachment, which explained why tears occurred mostly at the margin of the RPE detachment. However, in cases of age-related macular degeneration, the subretinal neovascular membrane may exert a tangential tractional force on one side of the RPE detachment causing an RPE tear at one side. In our patient, the RPE tear occurred at the center of the detachment. This might be due to uneven thickness or strength of the RPE layer. Gradual weakening or thinning of the RPE layer at the center of the detachment might have rendered it unable to sustain high mechanical stresses. Whether a steroid administered for systemic effect or IgA nephropathy itself predisposes the RPE weakness remains speculative.

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**Figure 1.** The right fundus photograph shows a large retinal pigment epithelium tear along the inferotemporal arcade.

**Figure 2.** Left, Composite photograph of early-phase fluorescein angiography of the right fundus demonstrates a hyperfluorescent lesion representing the denuded Bruch’s membrane. It is lined by 2 almost parallel hypofluorescent bands, which represent the rolled retinal pigment epithelium on each side. Right, A late-phase fluorescein angiogram of the right fundus shows a large hyperfluorescent lesion representing the denuded Bruch’s membrane. It is lined by 2 almost parallel hypofluorescent bands, which represent the rolled retinal pigment epithelium on each side. At the nasal tip of the retinal pigment epithelium tear, a leakage point with profuse leakage is evident.