Cystoid Macular Edema Associated with Latanoprost Therapy in a Case Series of Patients with Glaucoma and Ocular Hypertension

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Objective: To identify coexisting ocular diagnoses in a case series of eyes that developed cystoid macular edema (CME) associated with latanoprost therapy.

Design: Retrospective observational case series.

Participants: Seven eyes of seven patients who developed CME possibly associated with latanoprost treatment were studied.

Intervention: When these patients, all of whom were treated with latanoprost in addition to other glaucoma medications, described blurred vision or eye irritation, ocular examination revealed CME, which was confirmed by fluorescein angiography. Latanoprost was discontinued, and in three cases topical corticosteroids and nonsteroidal anti-inflammatory agents were used to treat the CME.

Main Outcome Measures: Visual acuity and intraocular pressure were determined before latanoprost use began, during therapy, and after latanoprost use ceased. In these cases, resolution of CME was documented clinically after discontinuing latanoprost.

Results: Clinically significant CME developed after 1 to 11 months of latanoprost treatment, with an average decrease of 3 lines in Snellen visual acuity. Intraocular pressure decreased an average of 27.9% during treatment. Cystoid macular edema was confirmed in all cases by fluorescein angiography. In these seven patients, the following coexisting ocular conditions may have placed these eyes at risk for prostaglandin-mediated blood–retinal barrier vascular insufficiency: history of dipivefrin-associated CME, epiretinal membrane, complicated cataract surgery, history of macular edema associated with branch retinal vein occlusion, history of anterior uveitis, and diabetes mellitus. In all cases, the macular edema resolved following discontinuation of latanoprost, in some instances with concomitant use of steroidal and nonsteroidal anti-inflammatory agents.

Conclusions: In this case series of pseudophakic, aphakic, or phakic eyes, the temporal relationships between the use of latanoprost and developing CME, and the resolution of CME following cessation of the drug, suggest an association between latanoprost and CME. In all cases, coexisting ocular conditions associated with an altered blood–retinal barrier were present. *Ophthalmology 1999;106:1024–1029*

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In June of 1996, the United States Food and Drug Administration approved latanoprost (Xalatan, Pharmacia & Upjohn, Kalamazoo, MI) as a second-line agent for treatment of elevated intraocular pressure (IOP) and glaucoma. Previously known as PhXA41, latanoprost, an isopropyl ester prodrug of 17-phenyl substituted prostaglandin $F_{2\alpha}$, enhances uveoscleral outflow as the physiological mechanism for lowering IOP.[1] Since latanoprost's approval and widespread clinical use in glaucoma and ocular hypertension management, several new ocular side effects have surfaced, including hypertrichosis and increased eyelash pigmentation,[2,3] hypotony and choroidal effusions,[4] iritis,[5] anterior uveitis,[6] and cystoid macular edema (CME) in eyes with complicated surgical histories.[5,7–10] In our case series of patients who developed CME during latanoprost treatment, we identify coexisting ocular conditions that may place

Table 1. Patient Demographics, Ocular Diagnoses, Lens Status, and Glaucoma Medications of Patients Who Developed CME after Addition of Latanoprost to Their Glaucoma Medical Regimen

Case No.	Age (yrs)/Sex	Ocular Diagnoses	Lens Status in Affected Eye	Intraocular Surgeries in Affected Eye	Glaucoma Medications in Affected Eye
1	79/female	Branch vein occlusion OU Neovascular glaucoma OD Ocular hypertension OS Cataract OU Epiretinal membrane OS History of CME OS (resolved)	Moderate nuclear sclerosis OS	None	Timolol, dorzolamide, dipivefrin, pilocarpine, latanoprost
2	71/male	History of anterior uveitis OD Epiretinal membrane OD Pseudoexfoliation glaucoma OU Diabetes mellitus*	PC IOL OD, intact posterior capsule	Combined cataract removal, IOL, trab ALT Trab with MMC Ahmed tube	Timolol, latanoprost
3	46/male	Secondary OAG OU Marfan syndrome HLA-B27 associated uveitis	Subluxated lens OS	Thermal sclerostomy Bleb revision with anterior vitrectomy	Dorzolamide, apraclonidine, timolol, latanoprost
4	63/male	Primary OAG OU Epiretinal membrane OD	PC IOL OD, open posterior capsule	ALT Combined cataract removal, IOL, PLS VTX and MP Nd:YAG capsulotomy	Timolol, pilocarpine, brimonidine, latanoprost
5	74/male	OAG OU History of dipivefrin-associated CME OD (resolved) Hemiretinal vein occlusion OS	PC IOL OD, open posterior capsule	Cataract removal, IOL Nd:YAG capsulotomy	Latanoprost
6	79/male	OAG Epiretinal membrane OS Diabetes mellitus*	PC IOL OS, open posterior capsule	Cataract removal, IOL Nd:YAG capsulotomy	Timolol, pilocarpine, latanoprost
7	65/male	Secondary OAG OD	PC IOL OD, open posterior capsule	Complicated cataract removal, IOL VTX for retained lens fragment	Timolol, latanoprost

PC IOL = posterior chamber intraocular lens; Trab = trabeculectomy; ALT = argon laser trabeculoplasty; OAG = open-angle glaucoma; VTX = vitrectomy; MP = membrane peeling; PLS = posterior lip sclerectomy; CME = cystoid macular edema; MMC = mitomycin C.

* Neither patient (cases 2 and 6) had a history of diabetic macular edema.

Note: The lens status, intraocular surgeries, and glaucoma medications (i.e., at the time of CME diagnosis) are listed in the particular eye that developed CME ("affected eye").

these complicated eyes at risk for developing blood–retinal barrier breakdown after exogenous prostaglandin challenge.

Materials and Methods

A retrospective review was conducted on seven patients who developed CME after starting latanoprost treatment and were examined by at least one of the authors at their multispecialty university-based institutions. Data collection included patients' age and gender, coexisting ocular diseases, lens status, ocular surgeries, concomitant glaucoma medication therapy, duration of latanoprost therapy, Snellen visual acuity (VA), and IOP determined by Goldmann applanation tonometry before, during, and after latanoprost therapy. Cystoid macular edema was diagnosed on clinical examination and confirmed by fluorescein angiography in all cases. Interventions and patient follow-up were identified.

Results

Seven eyes of seven patients developed CME after adding latanoprost to their medical therapy for glaucoma or ocular hypertension. The patient demographics, ocular diagnoses, lens status of the affected eye, concurrent glaucoma medical therapy in the affected eye at the time of CME diagnosis, and past ocular surgeries in the affected eye are summarized in Table 1. A variety of lens configurations were identified in our series: phakic (case 1); posterior chamber intraocular lens with an intact capsule (case 2); open capsule, either intentionally with neodymium:YAG laser (cases 4–6), or unintentionally, during cataract surgery (case 7); and aphakic (case 3, who had a spontaneously subluxated lens secondary to Marfan syndrome). In our patients, the following coexisting ocular conditions were identified that may place these eyes at risk for prostaglandin-mediated blood–retinal barrier vascular insufficiency: history of dipivefrin-associated CME (case 5), history of anterior uveitis (cases 2 and 3), macular traction associated with a concurrent or previous epiretinal membrane (cases 1, 2, 4, and 6), branch retinal vein occlusion (case 1), and complicated cataract surgery (case 7). Two patients (cases 2 and 6) had diabetes mellitus, which may contribute to changes in the blood–retinal barrier, but neither had a documented episode of diabetic macular edema.

The duration of latanoprost therapy until CME was diagnosed, effect of latanoprost on IOP, change in VA due to CME, and side effects are summarized in Table 2. The seven patients developed clinically significant CME (i.e., all patients noted blurred vision with clinical evidence of CME) after 1 to 11 months of latanoprost therapy. Five of seven eyes developed CME within the first 2

Table 2. Duration of Latanoprost Therapy until Cystoid Macular Edema (CME) Identified, Visual Acuity (VA), and Intraocular Pressure (IOP) before and during Latanoprost Treatment, and Side Effects after Addition of Latanoprost to the Glaucoma Medical Regimen

Case No.	Duration of Latanoprost Rx	Snellen VA in Affected Eye			IOP (mmHg) in Affected Eye			Side Effects
		Before Rx	*During Rx*	*Change*	*Before Rx*	*During Rx*	*% Change*	
1	1 month OS	20/70	20/200	3 lines	28	25	10.7	CME OS
2	2 months OD	20/30	20/60	3 lines	19	13	31.6	Recurrent anterior uveitis OD, CME OD
3	7 months OS	20/30	20/40	1 line	32	13	59.4	Recurrent anterior uveitis OS, CME OS
4	11 months OD	20/25	20/60	4 lines	25	19	24	CME OD
5	1 month OD	20/25	20/30	1 line	17	15	11.8	Recurrent CME OD
6	2 months OS	20/60	20/100	3 lines	13	13	0	CME OS
7	1.5 months OD	20/20	20/80	7 lines	24	16	33	CME OD

OS = left eye; OD = right eye.

months of therapy. The Snellen VA decreased an average of 3 lines and was attributed to CME. The average IOP decreased from 22.6 mmHg to 16.3 mmHg when latanoprost was added to concurrent glaucoma medications, which was an overall average of 27.9% lower IOP on latanoprost therapy. The fluorescein angiograms confirming the CME diagnosis are shown for case 2 (Fig 1), case 5 (Fig 2), and case 7 (Fig 3). The CME diagnoses for the other cases were also confirmed by fluorescein angiography.

The interventions and outcomes are summarized in Table 3. It is important to note that the CME did reverse in each case after stopping latanoprost therapy (Table 3). In cases 2 and 6, topical steroids and nonsteroidal anti-inflammatory agents were used after stopping latanoprost. In case 3, topical and oral steroids were used after stopping latanoprost. In case 5, the VA did not return to the level recorded prior to latanoprost therapy, and this was attributed to macular drusen, which became clinically apparent subsequent to discontinuing latanoprost. These drusen are felt to be age-related changes and not related to latanoprost treatment.

Discussion

Early multicenter, prospective, clinical trials reported several ocular side effects from latanoprost, including increased iridial pigmentation[11–13] and local ocular side effects,[11] including a slight flare and cellular reaction.[14] In clinical trials of glaucoma medications (e.g., Phase I, II, and III), the patient populations (i.e., normal eyes or those eyes with only ocular hypertension or open-angle glaucoma) are very carefully and appropriately selected using stringent inclusion and exclusion criteria in order to interpret results on safety and efficacy without confounding and uncontrolled variables. Hence, it is not surprising that new side effects are identified during the post–marketing surveillance period when there is widespread use of a new medication in a variety of clinical situations.

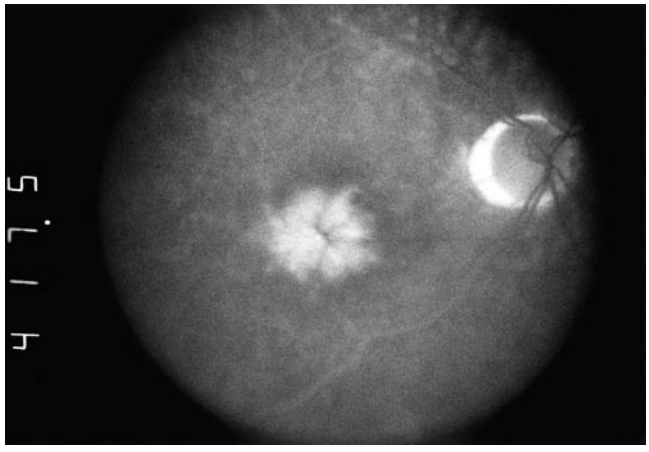

Figure 1. Case 2. Late-phase fluorescein angiogram of right eye at the time of clinically significant CME (VA decreased from 20/30 before drug treatment to 20/60) after 2 months of latanoprost therapy.

Since latanoprost's approval, additional reported side effects attributed to latanoprost include hypertrichosis and increased eyelash pigmentation,[2,3] hypotony and choroidal effusions,[4] iritis,[5] anterior uveitis,[6] and CME.[4,5,7,8] The possibility of latanoprost-induced changes in the blood–retinal barrier has been addressed prospectively in a randomized clinical trial with a 4-week latanoprost treatment period in uncomplicated pseudophakic human eyes.[15] In this study, no eyes treated with latanoprost developed foveal leakage on fluorescein angiogram at the end of 4 weeks, but one placebo-treated eye had angiographic evidence of perifoveal leakage that was not clinically significant. Based on published cases, there is still concern, however, about CME with latanoprost.

In their case report, Rowe et al[4] discuss a susceptibility to CME in their patient, who had a prior resolved episode of postoperative pseudophakic CME; however, there is no statement regarding the posterior capsule status and whether vitreous loss occurred during cataract surgery. In a retrospective study, Warwar et al[5] reported two cases of CME temporally related to latanoprost therapy in 163 eyes of 94 patients. In their two cases, one affected eye had an anterior chamber intraocular lens and a prior resolved episode of CME; the other eye was pseudophakic with an intact posterior capsule but had an episode of anterior uveitis 1 month prior to the start of latanoprost treatment. Six additional cases of CME associated with latanoprost have been reported in pseudophakic eyes with complicated surgical histories.[7–10] In addition to pseudophakic eyes, CME has recently been reported to occur in aphakic eyes.[16]

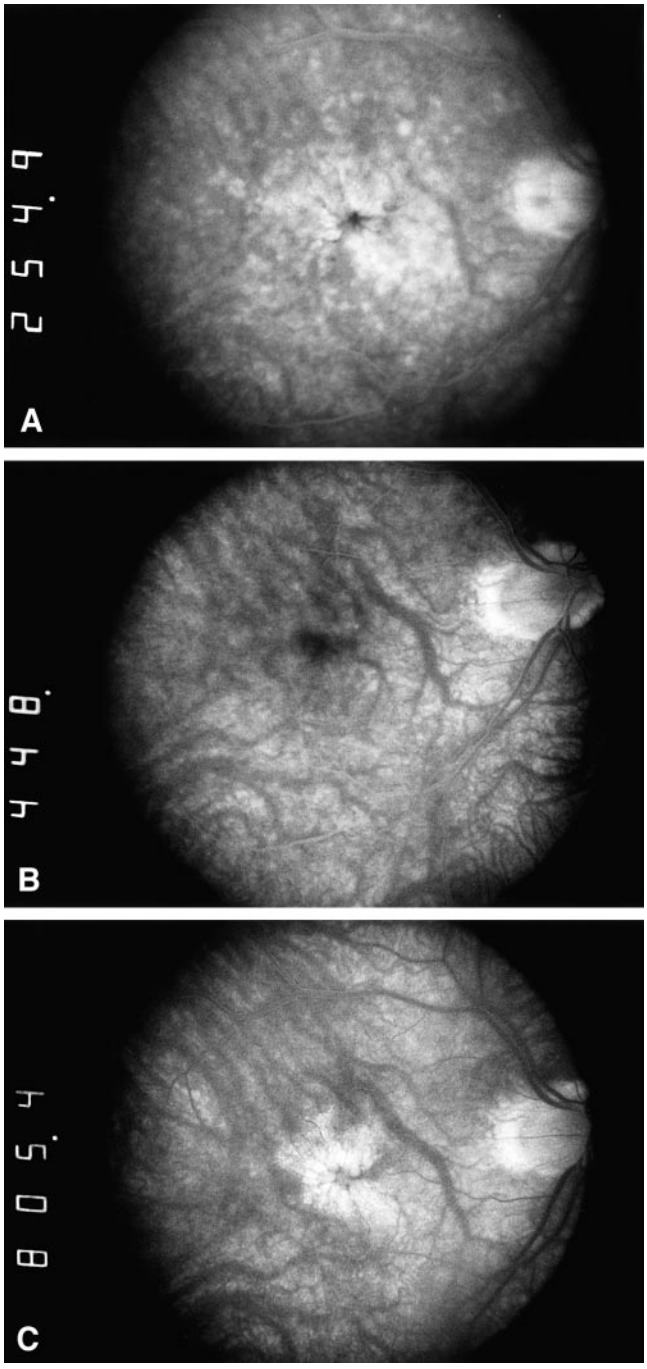

Figure 2. A, case 5. Dipivefrin-associated CME in the right eye confirmed with this fluorescein angiogram. **B,** 1 year later, an angiogram was performed to examine the left eye, and a late-phase view of the right eye showed resolution of the macular edema. **C,** 1 month after starting latanoprost, recurrent florid CME in the right eye is confirmed, and VA dropped from 20/25 to 20/30.

Collectively, these authors propose that CME may occur in eyes that may be "more sensitive or susceptible" to prostaglandin-mediated blood–retinal barrier breakdown, particularly in eyes with prior complicated surgical histories.

In addition to complicated surgical history with vitreous loss, our case series provides evidence to support the intuitive hypothesis that topical exogenous prostaglandins increase the risk of CME in susceptible eyes with coexisting conditions that potentially alter the blood–retinal barrier. Based on the eyes in our study, the following coexisting ocular conditions may place these eyes at risk for prostaglandin-mediated blood–retinal barrier vascular insufficiency: history of dipivefrin-associated CME, history of anterior uveitis, epiretinal membrane, diabetes mellitus, vein occlusion, and complicated cataract surgery. Because this study is limited to a case series, no pharmacoepidemiologic statements may be derived as to the frequency of CME associated with latanoprost in such complicated eyes. These cases came to the attention of the primary author (SEM) from other coauthors, who are also specialists located primarily at university-based practices, so a denominator derived from the referral base of each case would be extremely difficult to determine. Although assessment of risk factors may be more readily determined by a case-control study design, our cases have proved very difficult to match precisely with regard to ocular diagnoses and past surgical histories.

The previously reported cases of CME and our series of CME associated with latanoprost therapy raise the question

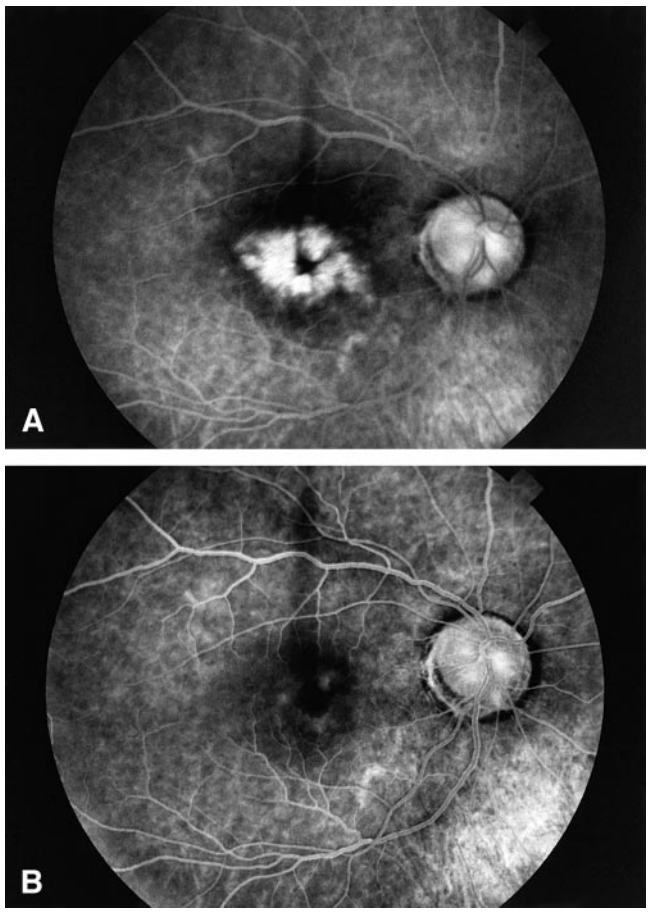

Figure 3. A, case 7. One and a half months after initiating latanoprost therapy, clinically significant CME in the right eye (VA dropped from 20/20 to 20/80) was confirmed with this fluorescein angiogram (385 seconds after fluorescein injection). **B,** 3 weeks after stopping latanoprost, visual acuity improved to 20/20, and follow-up angiography showed near resolution of the CME (312 seconds after fluorescein injection).

Table 3. Interventions and Outcomes in Patients Who Developed Cystoid Macular Edema (CME) after Addition of Latanoprost to the Glaucoma Medical Regimen

Case No.	Intervention	Outcome
1	Stop latanoprost	5 mos off latanoprost, VA 20/70, IOP 30 on timolol, dorzolamide, dipivefrin, pilocarpine, no appreciable CME on biomicroscopy
2	Stop latanoprost, but no change in CME in 11 wks, so prednisolone acetate + ketorolac were added	5 mo follow-up angiogram showed nearly resolved CME; 17 mos off latanoprost, VA 20/30, IOP 15 on timolol and brimonidine, no appreciable CME on biomicroscopy
3	Stop latanoprost; add rimexolone, prednisone, cyclogel	1 yr off latanoprost, VA 20/25, IOP 15 on apraclonidine, timolol, dorzolamide, rimexolone, no appreciable CME on biomicroscopy
4	Stop latanoprost	2 mos off latanoprost, VA 20/40, IOP 21 on brimonidine, timolol, pilocarpine, no appreciable CME on biomicroscopy
5	Stop latanoprost	9 mos off latanoprost, VA 20/40, IOP 14 on betaxalol, brimonidine, no appreciable CME on biomicroscopy, macular drusen noted
6	Stop latanoprost, but no change in CME in 4 wks, so prednisolone acetate + ketorolac were added	15 mos off latanoprost, VA 20/60, IOP 16 on timolol, pilocarpine, no appreciable CME on biomicroscopy
7	Stop latanoprost	3 wks off latanoprost, VA 20/20, IOP 18 on timolol, follow-up angiogram showed nearly resolved CME

VA = visual acuity; IOP = intraocular pressure.

of whether exogenous prostaglandins introduced by topical drops can affect the posterior segment of the eye and lead to CME. Several pharmacokinetic studies in rabbits have examined the distribution of topically applied drugs to various eye tissues. In phakic rabbit eyes, detailed disposition studies of [^{3}H]-labeled prostaglandin $F_{2\alpha}$ esters showed a major role for corneal biotransformation of the drugs and supported corneal penetration with ester modification.[17] Their data showed that the ciliary body prostaglandin drug levels were "remarkably high" at early time points, with similar amounts detected in the anterior sclera. In addition, drug levels were detected in retina and choroid at greater levels than in the vitreous. Although not explicitly discussed by the authors, their data suggested that, in addition to corneal penetration, the prostaglandin $F_{2\alpha}$ esters may also reach the ciliary body, retina, and choroid by penetrating the conjunctival–scleral route. This interpretation is supported by other pharmacokinetic studies involving topical carbonic anhydrase inhibitors,[18] indomethacin,[19] and β-adrenergic receptor antagonists.[20,21] Further, it is reasonable to consider that some proportion of prostaglandins may reach the retina and choroid by the uveoscleral pathway. In short, animal pharmacokinetic studies suggest that topically applied drugs distribute to the retina and choroid. Hence, a topically applied drug could have a biologic effect in the posterior segment, depending on the retinal or choroidal drug concentration and the affinity of the receptor, enzyme, or other target for the drug within the local tissue.

Although the precise pathogenesis of CME is not yet fully understood, a variety of mechanisms are proposed to disrupt the blood–retinal barrier.[22] Numerous clinical trials support the role of inflammatory mediators, such as prostaglandins, in this disruption, with evidence that anti-inflammatory agents may prevent and influence the recovery of CME after cataract surgery.[23] In addition, experimental evidence has demonstrated that the bovine retinal microvasculature can synthesize prostaglandins and that these vessels constrict in a dose-dependent manner to specific prostaglandins mediated by the prostanoid TP receptor subtype.[24] Hence, assuming similar biochemical and physiological processes across species, it appears that the essential elements for mediating the vascular permeability changes in the inner blood–retinal barrier are in anatomic proximity, i.e., prostanoid receptors in retinal microvasculature and availability of prostaglandins. The mechanistic details between prostanoid receptor activation leading to the normal biologic effect versus the pathophysiologic response of a "leaky" blood–retinal barrier and CME in humans are yet to be elucidated.

Another consideration of maculopathy is hypotony; however, in the setting of hypotony, which is typically in the postoperative setting of filtration surgery, the maculopathy is characterized by vision loss, retinal striae, choroidal folds, and no evidence of vascular leakage.[25,26] Hypotony maculopathy is managed by normalizing IOP; however, in instances where the choroidal and retinal folds do not reverse to normal anatomic position, vitreoretinal surgery combined with perfluorocarbon has been used to mechanically flatten the posterior segment.[27] In our case series, there were no other clinical features of hypotony, such as shallow anterior chamber, clinically significant corneal thickening, Descemet's membrane striae, or serous choroidal detachment. Hence, hypotony does not appear to have an obvious role in the CME associated with latanoprost in these complicated eyes.

In summary, our series demonstrates that CME may be associated with latanoprost therapy in complicated eyes that are phakic, aphakic, or pseudophakic with an intact or open posterior capsule. Regardless of lens status, it appears that the described coexisting ocular conditions in our cases (i.e., history of dipivefrin-associated CME, uveitis, epiretinal membrane, vein occlusion, complicated cataract surgery, and possibly diabetes mellitus) may predispose to prostaglandin-associated CME. Hence, the clinician should be aware that the use of latanoprost therapy in patients with pre-existing abnormalities of the blood–retinal barrier may be associated with an increased frequency of CME.

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