CHAPTER 14

Systemic Drug–Induced Retinal Toxicity

Highlights

- Early detection of hydroxychloroquine toxicity is critical and requires the presence of abnormalities on 2 modalities (spectral-domain optical coherence tomography [OCT] and automated threshold visual field testing).
- In Asian patients with hydroxychloroquine toxicity, more peripheral changes may develop, which are best captured with long OCT scans and Humphrey 24-2 or 30-2 visual fields.
- Tamoxifen-related maculopathy can have many of the same features as macular telangiectasia type 2 (MacTel 2) and should be considered in the differential diagnosis of MacTel 2.

Overview

Retinal toxicities caused by systemic therapeutic agents may be categorized according to the retinal level affected and the pattern of toxicity. Broadly, these toxicities manifest as (1) abnormalities at the level of the retinal pigment epithelium (RPE)/photoreceptor complex; (2) occlusive retinopathy or microvasculopathy; (3) ganglion cell and optic nerve damage; and (4) other abnormalities, which include macular edema, crystalline retinopathy, and alterations in color vision and electroretinogram (ERG) responses.

Drugs Causing Abnormalities of the Retinal Pigment Epithelium/Photoreceptor Complex

Chloroquine Derivatives

Although retinal toxicity from *chloroquine* use remains a problem in many parts of the world, it is rare in the United States, where this medication has largely been replaced by the much safer, related drug *hydroxychloroquine*. These medications are used for the treatment of malaria and rheumatologic and dermatologic diseases. Both medications bind to melanin in the RPE, which may concentrate or prolong their effects. Although the

incidence of toxicity is low, it is a serious concern because associated vision loss rarely recovers. Patients and their primary care physicians must be made aware of the ophthalmic risks and the need for regular screening examinations to detect retinal toxicity at an early stage, before vision loss occurs. Typical symptoms include paracentral scotomata, central vision decline, and/or reading difficulty.

The earliest signs of toxicity include bilateral paracentral visual field defects and/or inner segment ellipsoid loss in a paracentral location, which appears as the "flying saucer" sign on spectral-domain optical coherence tomography (SD-OCT) images (Fig 14-1). However, most patients of Asian descent will show initial damage in a more peripheral distribution outside the macular area (Fig 14-2). When there is continued drug exposure, progressive pigmentary changes may develop, and a bilateral atrophic bull's-eye maculopathy may ensue (Fig 14-3). End-stage cases of advanced toxicity may show panretinal degeneration that simulates retinitis pigmentosa. In some patients, corneal intraepithelial deposits, usually referred to as *cornea verticillata,* may also be noted.

Ophthalmic screening of patients receiving chloroquine or hydroxychloroquine is aimed primarily at early detection and minimization of toxicity. As summarized in a 2016 Clinical Statement from the American Academy of Ophthalmology (https://www.aao.org/education/clinical-statement/revised-recommendations-on-screening-chloroquine-h), the risk of toxicity is low for individuals who have no complicating conditions and take less than 6.5 mg/kg/d of hydroxychloroquine or 3 mg/kg/d of chloroquine. The most recent data suggest that a hydroxychloroquine dosage of 5 mg/kg/d or less and a chloroquine dosage of 2.3 mg/kg/d or less based on the patient's real body weight may be safer across all body mass indexes than the dosage recommendation of 6.5 mg/kg/d and 3 mg/kg/d, respectively using the patient's ideal body weight.

Cumulative total doses greater than 1000 g of hydroxychloroquine and 460 g of chloroquine place patients at high risk of toxicity. Additional risk factors include duration of use (>5 years), kidney disease, concomitant use of tamoxifen (fivefold increase), and concomitant

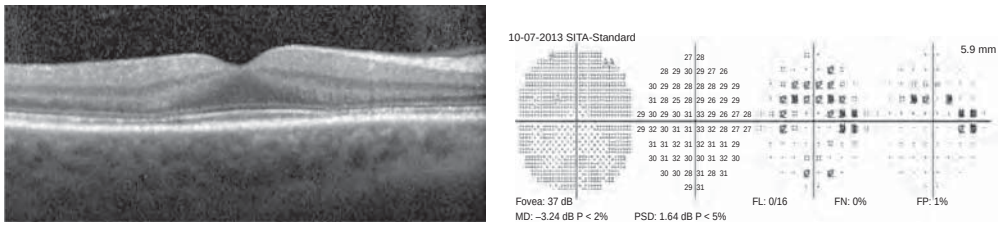

Figure 14-1 Spectral-domain optical coherence tomography (SD-OCT) image and Humphrey visual field (HVF) from a 50-year-old woman who had been using Plaquenil 400 mg daily for 10 years to treat systemic lupus erythematosus. Notably, she also had lupus-related nephrotic syndrome. Her Plaquenil dosage, which was based on actual body weight, was 4.4 mg/kg/d. She was completely asymptomatic. However, SD-OCT *(left)* showed attenuation of the ellipsoid zone and interdigitation zone in a perifoveal pattern, with early "flying saucer" sign with relative preservation of the central photoreceptors. Given the characteristic superior arcuate defect on the 10-2 HVF *(right),* Plaquenil was stopped. It is likely that renal disease accelerated the presentation in this patient despite the dose being within the American Academy of Ophthalmology recommendation of 5 mg/kg/d or less. Therefore, clinicians should maintain heightened vigilance in patients with renal disease, especially when no alternatives to Plaquenil can be safely used. *(Courtesy of Amani Fawzi, MD.)*

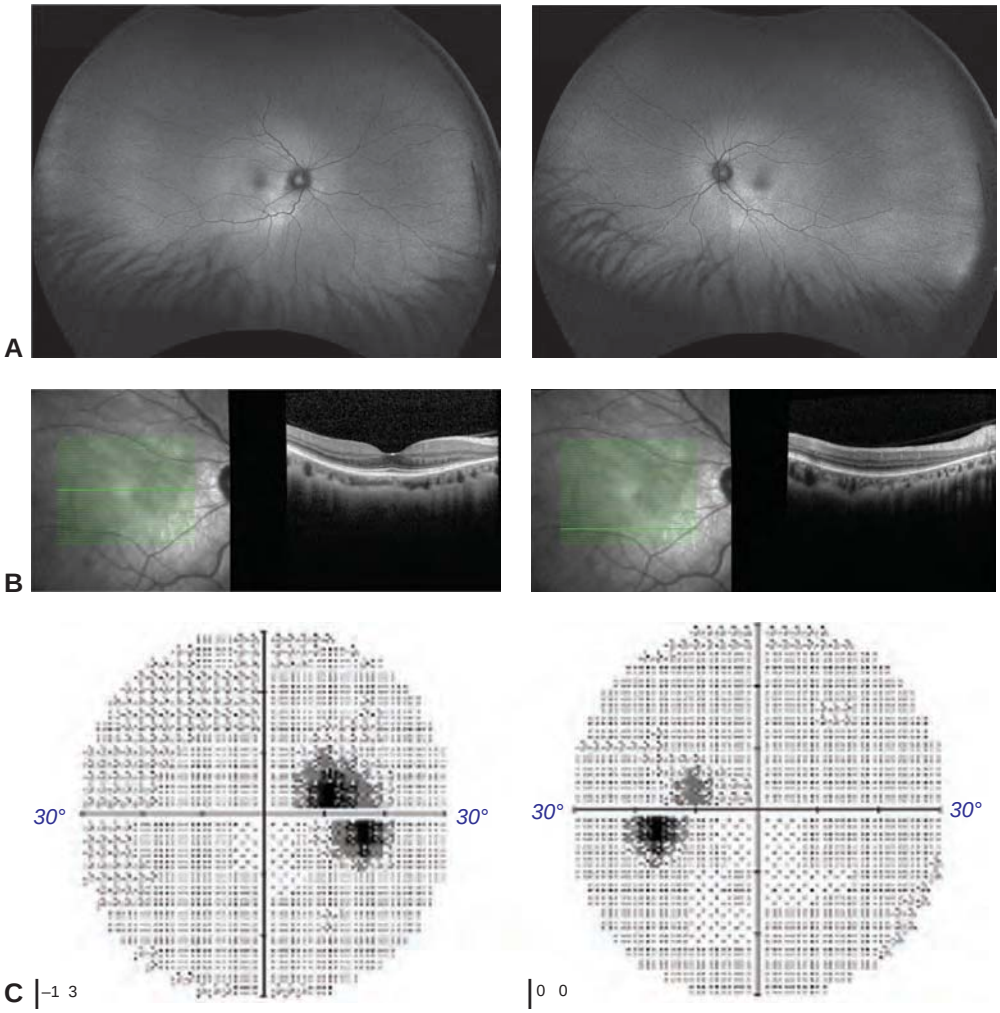

Figure 14-2 Peripheral retinal manifestations of hydroxychloroquine toxicity in Asian patients. **A,** Fundus autofluorescence (FAF) shows hyperautofluorescence along the inferior arcade in both eyes. **B,** OCT scan through the right fovea *(left)* shows disruption of the outer retina and loss of the ellipsoid zone temporal to the optic nerve. More inferior scans *(right)* highlight the extension of this loss along the inferior arcade. This photoreceptor loss explains the unmasking of the retinal pigment epithelium (RPE) autofluorescence and relative hyperautofluorescence in this region. **C,** 30-2 HVF illustrates the peripheral localization of the visual field defects, which would be missed on 10-2 HVF. *(Courtesy of Amani Fawzi, MD.)*

retinal disease such as age-related macular degeneration. The latter can also make early detection of toxicity difficult. Furthermore, well-documented but rare cases of hydroxychloroquine maculopathy have occurred with "safe" daily doses and in the absence of other risk factors.

Baseline evaluation for patients beginning treatment with a chloroquine derivative should include a complete ophthalmic examination. For follow-up comparison, the ophthalmologist can employ SD-OCT as well as automated threshold visual field testing with a white pattern (Humphrey white 10-2 protocol), although some clinicians prefer red for

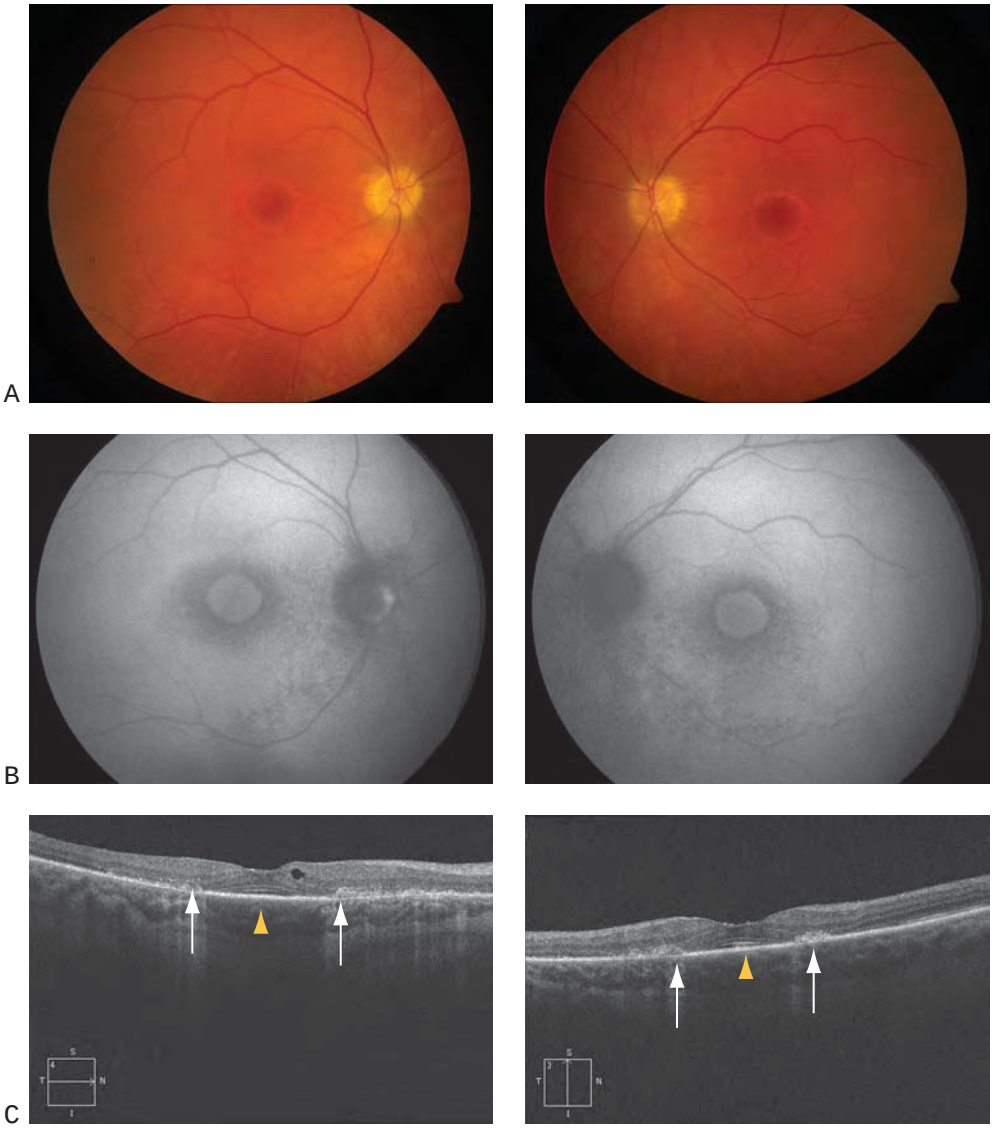

Figure 14-3 Bilateral, symmetric bull's-eye maculopathy in a patient with hydroxychloroquine toxicity. **A,** Fundus photographs of right and left eyes. **B,** Corresponding FAF images. **C,** SD-OCT images demonstrate the characteristic "flying saucer" sign *(arrowhead)*: the ovoid appearance of the central fovea due to preservation of the outer retinal structures in the central fovea surrounded by perifoveal loss of the outer retinal structures. With progression of the toxic effect, pigment migration into the outer retina can be seen *(arrows).* *(Courtesy of Stephen J. Kim, MD.)*

its increased sensitivity. In Asian patients with hydroxychloroquine toxicity, more peripheral changes may develop, which are best captured with long OCT scans and Humphrey 24-2 or 30-2 visual fields.

Current guidelines recommend a baseline fundus examination within the first year of use and then annual screening after 5 years of use in patients at low risk for toxicity.

However, many practitioners screen patients every 6 to 12 months with a combination of Humphrey 10-2 testing and SD-OCT for 5 years and then every 6 months thereafter. Patients who are at risk of toxicity or who have unclear symptoms can be further assessed with fundus autofluorescence and multifocal electroretinography (mfERG). Signs of toxicity include a paracentral ring of hyperautofluorescence or hypoautofluorescence and paracentral mfERG depressions.

Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology.* 2016;123(6):1386–1394.

Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology.* 2015;122(1):110–116.

Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol.* 2014;132(12):1453–1460.

Mititelu M, Wong BJ, Brenner M, Bryar PJ, Jampol LM, Fawzi AA. Progression of hydroxychloroquine toxic effects after drug therapy cessation: new evidence from multimodal imaging. *JAMA Ophthalmol.* 2013;131(9):1187–1197. doi:10.1001/jamaophthalmol.2013.4244

Phenothiazines

Phenothiazines, including *chlorpromazine* and *thioridazine,* are antipsychotic tranquilizing medications that are concentrated in uveal tissue and RPE by binding to melanin granules. High-dose chlorpromazine therapy commonly causes abnormal pigmentation of the eyelids, interpalpebral conjunctiva, cornea, and anterior lens capsule. Anterior and posterior subcapsular cataracts may also develop. However, pigmentary retinopathy from chlorpromazine therapy is unusual.

In contrast, high-dose thioridazine treatment can cause development of a severe pigmentary retinopathy within a few weeks or months of dosing initiation (Fig 14-4). Toxicity is rare at doses of 800 mg/d or lower. Initially, patients experience blurred vision, and the fundus shows coarse RPE stippling in the posterior pole. Eventually, patchy nummular atrophy of the RPE and choriocapillaris may develop. The late stages may be mistaken for choroideremia or Bietti crystalline dystrophy; late-stage signs and symptoms include visual field loss and nyctalopia (night blindness).

Generally, patients receiving thioridazine are not monitored ophthalmoscopically because toxicity is rare at standard doses. However, symptomatic patients or patients suspected of having a toxic reaction, especially those who have taken high doses of the drug, should undergo a full retinal examination.

Miscellaneous Medications

Other systemic medications that can induce toxicity of the RPE include clofazimine, deferoxamine (Fig 14-5), and nucleoside reverse transcriptase inhibitors (NRTIs; Table 14-1). *Clofazimine* is a phenazine dye used to treat dapsone-resistant leprosy and various autoimmune disorders, such as psoriasis and systemic lupus erythematosus. Its toxicity manifests as a bull's-eye maculopathy. *Deferoxamine,* an iron-chelating agent, can cause reticular or vitelliform pigment epithelial changes in the macula (see Fig 14-5B) and can

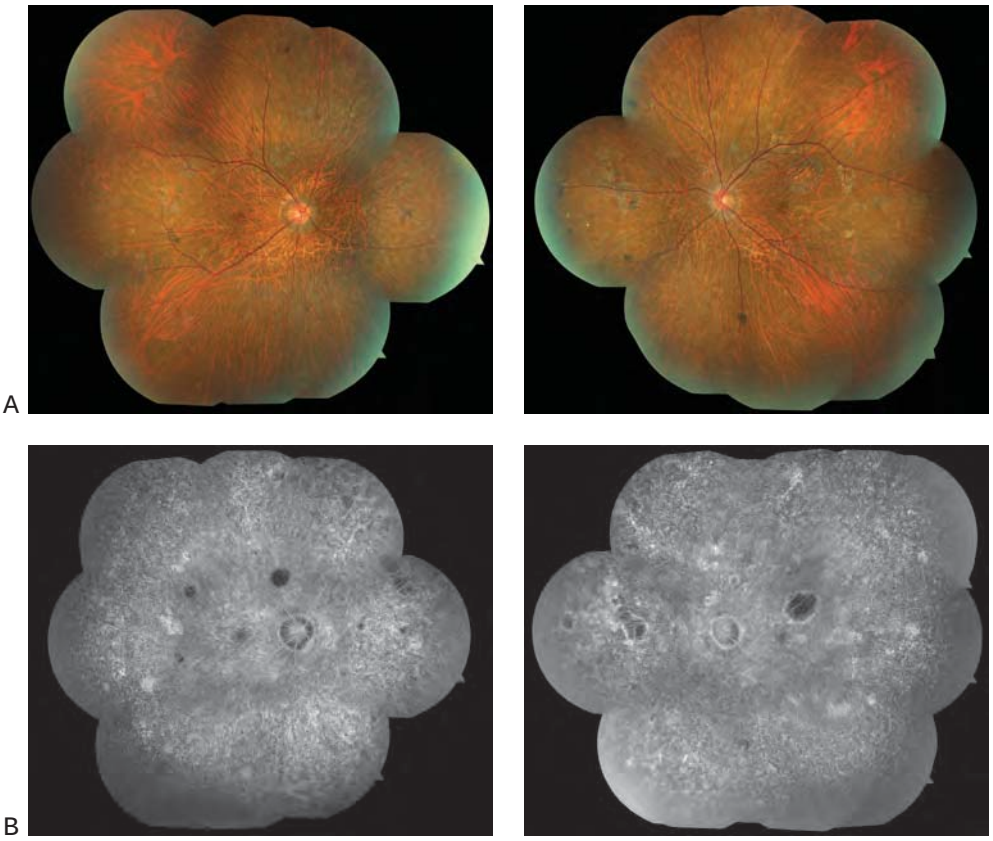

Figure 14-4 Thioridazine toxicity in a patient with schizophrenia. **A,** Fundus photograph montages of right and left eyes. **B,** Corresponding fluorescein angiography montages. Note the diffuse nummular loss of RPE in the posterior pole and periphery of each eye. *(Courtesy of David Sarraf, MD.)*

be associated with macular edema caused by RPE pump failure. NRTIs such as didanosine (formerly, *dideoxydinosine*) have been used in the systemic treatment of patients infected with HIV to inhibit replication of the virus. This class of medications can cause mitochondrial toxicity and damage to tissues with high oxygen requirements, such as the optic nerve and RPE. Patients may develop peripheral vision loss associated with a bilateral, symmetric, and midperipheral pattern of concentric mottling and atrophy of the RPE and choriocapillaris.

Inhibitors of the mitogen-activated protein kinase (MAPK) pathway, including extracellular signal-regulated kinase (ERK), MAPK kinase (MEK), and fibroblast growth factor receptor (FGFR) inhibitors, can cause a condition similar to central serous chorioretinopathy. This condition is characterized by multifocal serous retinal detachments (Fig 14-6). *Immune checkpoint inhibitors,* a class of immunomodulatory drugs for treatment of metastatic cancers, have been associated with a variety of ocular manifestations, including serous retinal detachments, all thought to be related to autoimmune dysregulation. In rare instances, the use of *sildenafil* has been associated with serous macular

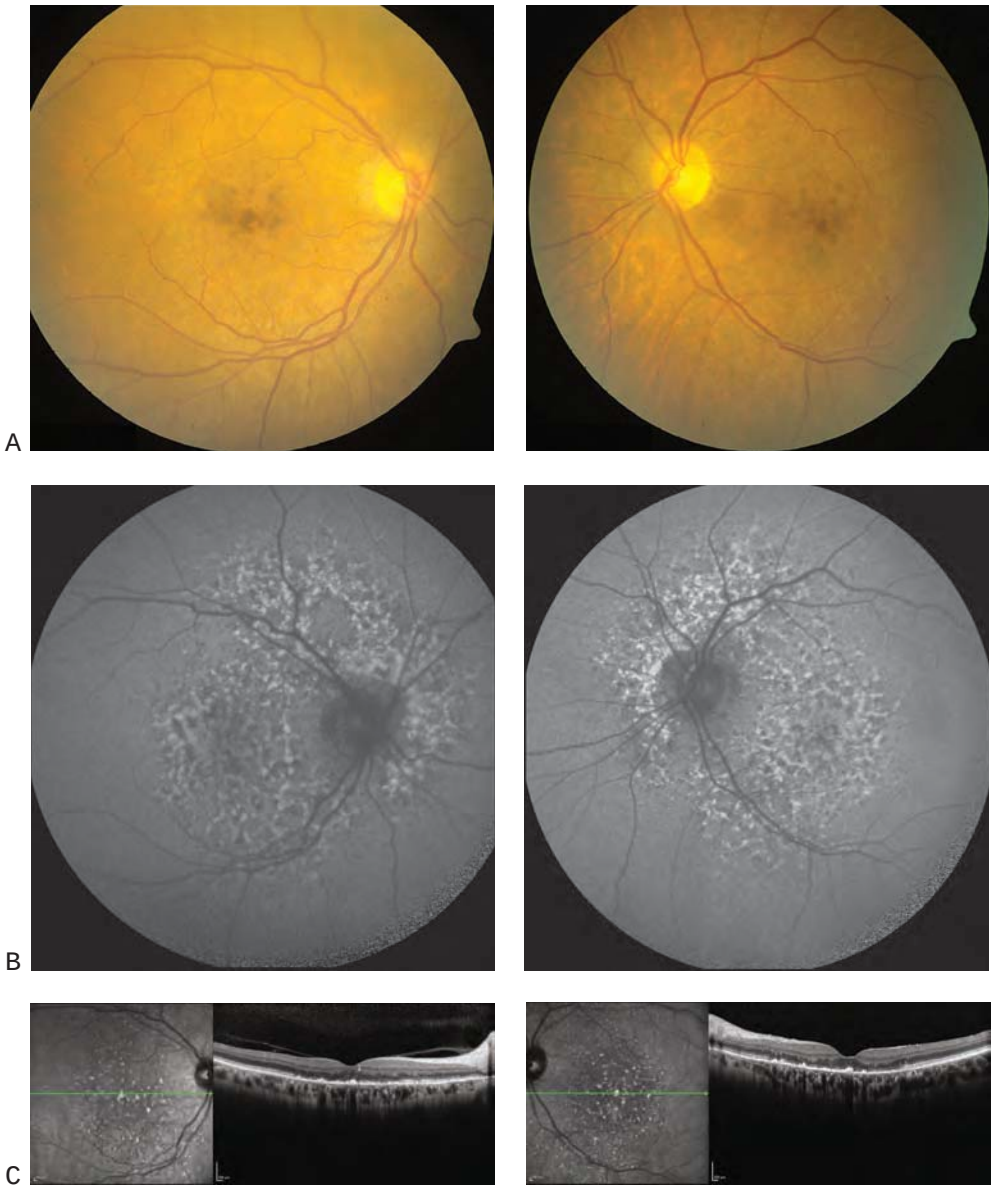

Figure 14-5 Deferoxamine (also called *desferrioxamine*) toxicity. **A,** Fundus photographs show pigmentary macular changes in a patient with sickle cell disease who was receiving deferoxamine for transfusional hemosiderosis. **B,** Corresponding FAF images highlight the classic reticular pigment epithelial changes. **C,** SD-OCT demonstrates ellipsoid loss and hyperreflective deposits at the level of the RPE. *(Courtesy of Kenneth Taubenslag, MD, Edward Cherney, MD, and Anita Agarwal, MD.)*

detachment and central serous chorioretinopathy, presumably caused by choroidal vascular dilation and choroidal congestion manifesting as increased choroidal thickness on enhanced depth imaging (EDI) SD-OCT. *Corticosteroids* are the most common medications to be associated with the development of central serous chorioretinopathy.

Table 14-1 Miscellaneous Medications Causing RPE/Photoreceptor Complex Toxicity

Medication	Use	Complication
Alkyl nitrites (poppers)	Recreational use; euphoric and smooth muscle relaxant usually used in preparation for male-male sexual contact	Foveal outer retinal defect at the photoreceptor level
Clofazimine	Treatment of dapsone-resistant leprosy, autoimmune disorders	Bull's-eye maculopathy
Corticosteroids	Many indications	Central serous chorioretinopathy
Deferoxamine	Iron-chelating agent	Reticular or vitelliform maculopathy Macular edema
Didanosine (dideoxyinosine)	Nucleoside reverse transcriptase inhibitor; inhibit replication of HIV	Mitochondrial toxicity Peripheral pigmentary retinopathy
Immune checkpoint inhibitors	Immunomodulatory therapy for metastatic cancer	Various ocular manifestations, serous retinal detachment, inflammatory
Mitogen-activated protein kinase kinase (MEK) inhibitors	Chemotherapeutic, for metastatic cancer	Multifocal serous retinal detachments, self-limited
Pentosan polysulfate sodium	Treatment of interstitial cystitis	Maculopathy with pigmentary changes and dark-adaptation defects

RPE = retinal pigment epithelium.

Alkyl nitrites ("poppers") are a class of drugs used for recreation and can cause a toxic maculopathy. Patients present with a central scotoma or photopsia. Fundus examination may reveal a yellow spot on the fovea. SD-OCT imaging may reveal focal disruption of the central inner segment ellipsoid band, indicating an abnormality of the foveal cones (Fig 14-7).

Pentosan polysulfate sodium, which is approved by the US Food and Drug Administration for the treatment of interstitial cystitis, has recently been associated with a pigmentary maculopathy with characteristic bilateral findings of parafoveal pigmentary changes, dense hypo- and hyperautofluorescence, and nodular RPE thickening on OCT (Fig 14-8).

Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. *Retina.* 2018;38(6):1063–1078.

Davies AJ, Kelly SP, Naylor SG, et al. Adverse ophthalmic reaction in poppers users: case series of 'poppers maculopathy'. *Eye (Lond).* 2012;26(11):1479–1486.

Gabrielian A, MacCumber MM, Kukuyev A, Mitsuyasu R, Holland GN, Sarraf D. Didanosine-associated retinal toxicity in adults infected with human immunodeficiency virus. *JAMA Ophthalmol.* 2013;131(2):255–259.

McCannel TA, Chmielowski B, Finn RS, et al. Bilateral subfoveal neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer. *JAMA Ophthalmol.* 2014;132(8):1005–1009.

Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology.* 2018;125(11):1793–1802.

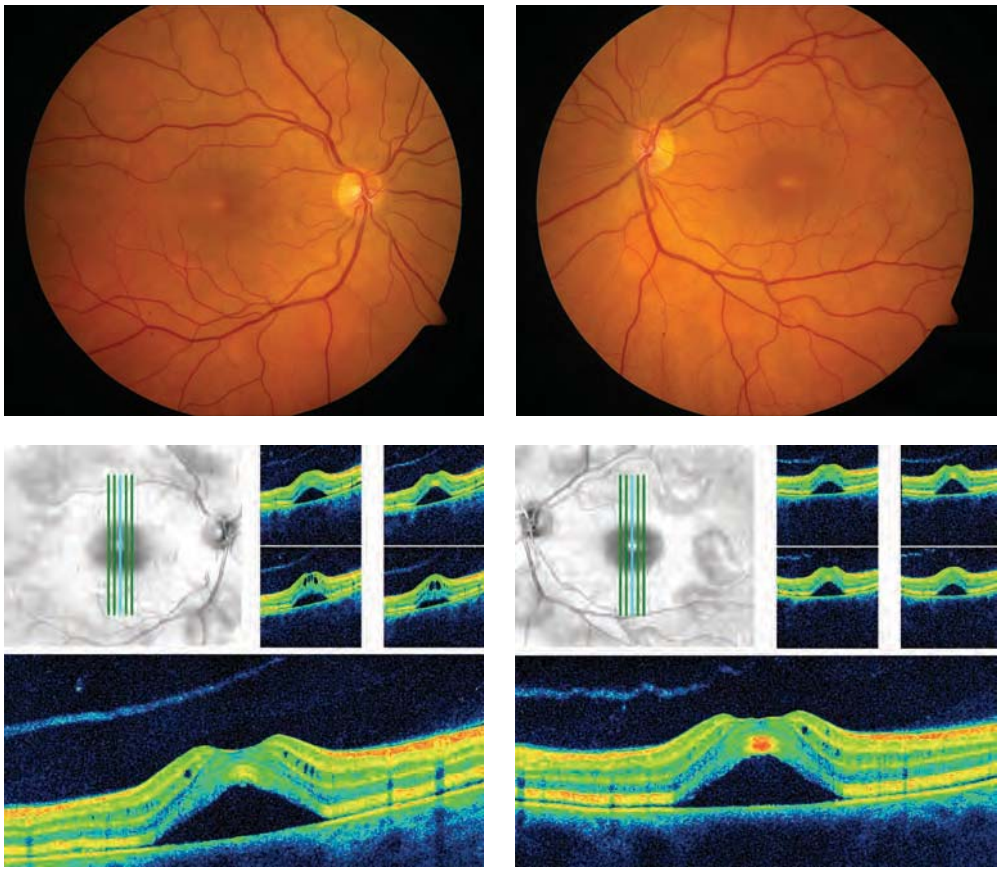

Figure 14-6 MEK toxicity. Fundus photographs and OCT images of both eyes demonstrate multifocal serous detachments involving the fovea and the area around the arcades. The patient reported decreased vision 3 weeks after starting the MEK inhibitor trametinib for metastatic cutaneous melanoma. Subsequent stoppage of trametinib resulted in complete resolution. *(Courtesy of Stephen J. Kim, MD.)*

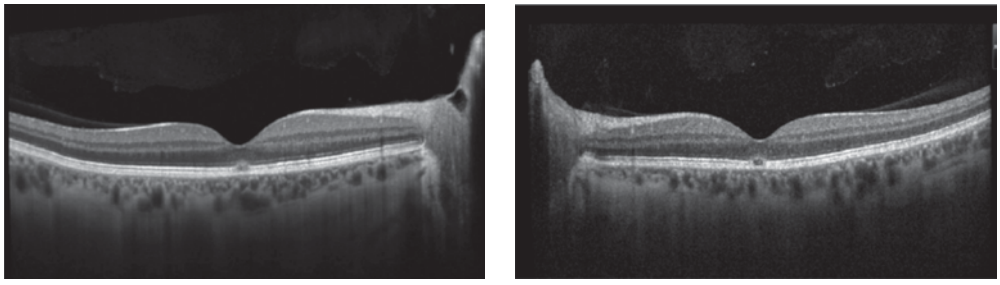

Figure 14-7 SD-OCT images from a 40-year-old man with a 6-month history of blurred vision, who admitted to long-term use of alkyl nitrites ("poppers"). Corrected distance visual acuity (also called *best-corrected visual acuity*) was 20/40 OD, 20/50 OS. SD-OCT of both eyes showed bilateral focal disruption of the central inner segment ellipsoid band in the fovea. *(Courtesy of Manjot K. Gill, MD.)*

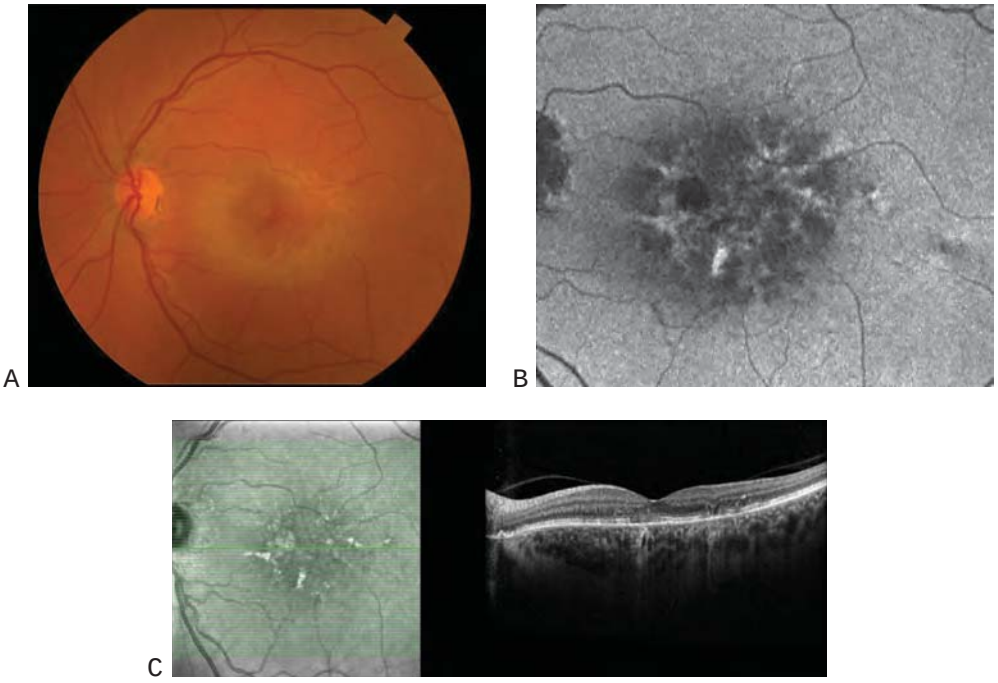

Figure 14-8 Presumed pentosan polysulfate toxicity. A 64-year-old woman reported a yellow discoloration to her vision and difficulties adjusting to light. She had been using pentosan polysulfate sodium for 30 years to treat interstitial cystitis. **A,** Color fundus photograph shows subtle pigmentary changes, while FAF **(B)** and infrared (**C,** *left*) images reveal alternating hyper- and hypoautofluorescent/reflective lesions that are characteristic. **C** *(right),* OCT shows subtle photoreceptor and RPE changes. *(Courtesy of Amani Fawzi, MD.)*

Drugs Causing Occlusive Retinopathy or Microvasculopathy

Interferon alfa-2a is an antiviral and immunomodulatory drug used for the treatment of viral hepatitis. This treatment may be complicated by the development of cotton-wool spots and retinal hemorrhages. *Ergot alkaloids* (vasoconstrictors used to treat migraine) and oral contraceptives have been associated with thrombotic complications, including retinal vein and retinal artery occlusions. *Procainamide* is an antiarrhythmic agent that can induce systemic lupus erythematosus and cause extensive "pruning" of second-order retinal vessels and infarction of the retina, leading to severe vision loss.

A few drugs administered intraocularly but not systemically deserve special mention. The aminoglycosides *amikacin* and especially *gentamicin antibiotics* can cause macular infarction and severe macular ischemia, leading to irreversible central vision loss. Recently, intracameral *vancomycin,* used for prophylaxis of endophthalmitis, has been associated with hemorrhagic occlusive retinal vasculitis (HORV). Postmarketing research studies of *brolucizumab,* a newer anti–vascular endothelial growth factor agent approved for the treatment of neovascular age-related macular degeneration, have reported an association with intraocular inflammation and occlusive retinal vasculitis.

Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. *Ophthalmology.* 2020;127(10):1345–1359.
Narkewicz MR, Rosenthal P, Schwarz KB, et al; PEDS-C Study Group. Ophthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. *J Pediatr Gastroenterol Nutr.* 2010;51(2):183–186.
Raza A, Mittal S, Sood GK. Interferon-associated retinopathy during the treatment of chronic hepatitis C: a systematic review. *J Viral Hepat.* 2013;20(9):593–599.
Witkin AJ, Shah AR, Engstrom RE, et al. Postoperative hemorrhagic occlusive retinal vasculitis: expanding the clinical spectrum and possible association with vancomycin. *Ophthalmology.* 2015;122(7):1438–1451.

Drugs Causing Ganglion Cell Damage and Optic Neuropathy

Quinine is used as a muscle relaxant for leg cramps and as an antimalarial. It has a narrow therapeutic index that is safe at doses under 2 g, but it causes morbidity at doses greater than 4 g and mortality at doses greater than 8 g. At toxic levels, acute severe vision loss may occur as a result of retinal ganglion cell toxicity, mimicking a central retinal artery occlusion. A cherry-red spot may be observed, and SD-OCT imaging may demonstrate ganglion cell layer thickening and hyperreflectivity. Diffuse inner retinal atrophy will ensue, accompanied by retinal vascular attenuation and optic atrophy. Full-field ERG testing will show a negative waveform, similar to that observed with a central retinal artery occlusion (Fig 14-9). Blindness caused by quinine toxicity is permanent.

Methanol toxicity, usually occurring as a result of ingesting contaminated or "cheap" alcohol, causes acute blindness. Posterior segment manifestations include acute transient optic nerve head and macular edema. In histologic studies of acute methanol toxicity, the retina, RPE, and optic nerve demonstrate vacuolization, a sign of cell death. Eventually, optic atrophy and occasionally retinal vascular attenuation caused by diffuse ganglion cell loss may develop. Full-field ERG testing shows a negative waveform. The most commonly reported sequela of methanol toxicity is optic atrophy.

Drugs Causing Macular Edema

The *taxanes* are a class of microtubule inhibitors that include *paclitaxel,* albumin-bound paclitaxel, and *docetaxel.* These drugs are employed as chemotherapeutics for the treatment of various cancers, including breast carcinoma. In rare cases, they are associated with cystoid macular edema (CME) that is visible on examination or SD-OCT but without leakage on fluorescein angiography. Similarly, the cholesterol-lowering agent niacin, also called *nicotinic acid,* can produce angiographically silent CME. Initially, central vision may be impaired, but full recovery follows discontinuation of the drug and resolution of the cystoid edema.

The glitazones *rosiglitazone* and *pioglitazone* are oral hypoglycemics used for the treatment of diabetes mellitus. They can cause severe fluid retention, leading to pulmonary edema, and are occasionally associated with the development or exacerbation of macular edema. *Fingolimod,* an oral agent used in the management of relapsing forms of multiple sclerosis, can

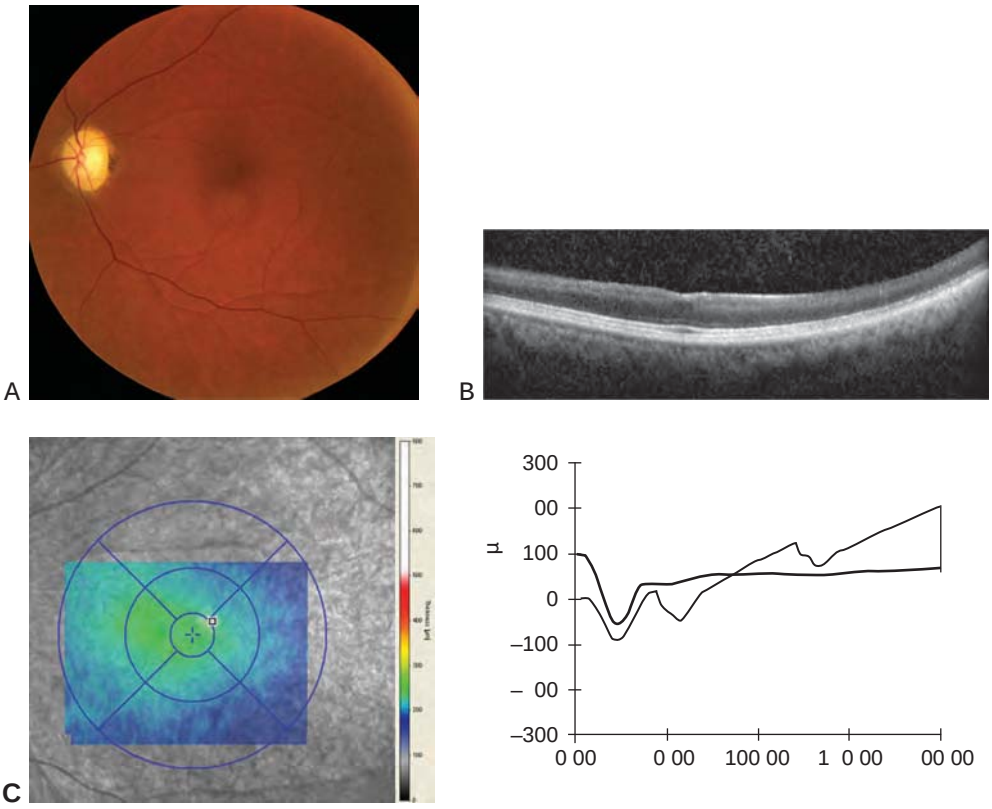

Figure 14-9 Quinine toxicity. **A,** Fundus photograph shows optic nerve head pallor and retinal vascular attenuation. **B,** SD-OCT image demonstrates diffuse inner retinal atrophy. **C,** OCT map analysis shows diffuse retinal thinning. **D,** Full-field electroretinogram shows an electronegative response (the positive b-wave amplitude is less than the negative a-wave amplitude). *(Courtesy of David Sarraf, MD.)*

infrequently cause macular edema, usually within 3 months of initiation of treatment; the edema resolves with cessation but warrants monitoring and differentiation of visual symptoms related to optic neuritis. Topical *prostaglandin $F_{2\alpha}$ analogs,* used in treating glaucoma, have been reported in small case series to cause macular edema. *Deferoxamine* may also cause secondary macular edema due to RPE toxicity, as mentioned earlier in the chapter.

Drugs Causing Crystalline Retinopathy

Crystalline retinopathies can be caused by systemic medications and other agents and can be associated with several ocular and systemic diseases; these diseases are discussed elsewhere in this book or the BCSC series (Fig 14-10, Table 14-2). *Tamoxifen* is an antiestrogen drug used as adjuvant therapy following primary treatment of breast cancer. Retinopathy is rare at typical doses (20 mg daily), but crystalline retinopathy has been reported in patients receiving high-dose tamoxifen therapy (daily doses >200 mg or cumulative doses

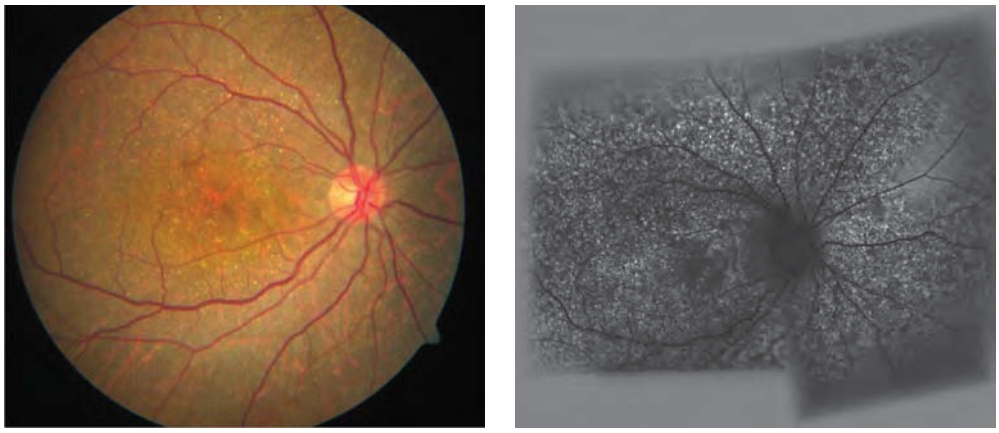

Figure 14-10 Fundus photograph *(left)* shows scattered hyperreflective, crystalline lesions throughout the fundus in a patient with Bietti crystalline dystrophy. FAF image (*right;* same patient) illustrates the hyperautofluorescent crystalline deposits as well as hypoautofluorescence seen in areas of RPE atrophy. *(Reproduced from Berry JL, Fawzi A. Heritable disorders of the retinal pigment epithelium, Bruch's membrane, and the choriocapillaris. In: Wright KW, Strube YNJ.* Pediatric Ophthalmology and Strabismus. *3rd ed. Oxford University Press; 2012, Figures 2 and 28. Copyright 2012, used with permission.)*

Table 14-2 Causes of Crystalline Retinopathy

Systemic diseases
Cystinosis
Primary hereditary hyperoxaluria (primary oxalosis)
Sjögren-Larsson syndrome
Drug-induced causes
Canthaxanthine toxicity
Ethylene glycol ingestion (secondary oxalosis)
Methoxyflurane anesthesia (secondary oxalosis)
Nitrofurantoin toxicity
Talc emboli (caused by long-term intravenous drug use with methylphenidate)
Tamoxifen toxicity (see Fig 14-11)
Triamcinolone acetonide injection–associated crystalline maculopathy (caused by intravitreal triamcinolone injection)
Ocular diseases
Bietti crystalline dystrophy (see Fig 14-10)
Calcific drusen
Gyrate atrophy
Retinal telangiectasia

>100 g). The maculopathy is characterized by brilliant inner retinal crystalline deposits clustered around the fovea and may be associated with CME and substantial vision loss in severe cases; it may be irreversible. In rare instances, SD-OCT imaging has revealed central loss of the inner segment ellipsoid band in patients receiving low-dose tamoxifen therapy, without crystals visible on ophthalmoscopic examination (Fig 14-11). On fluorescein angiography and OCT angiography, eyes with tamoxifen maculopathy may also

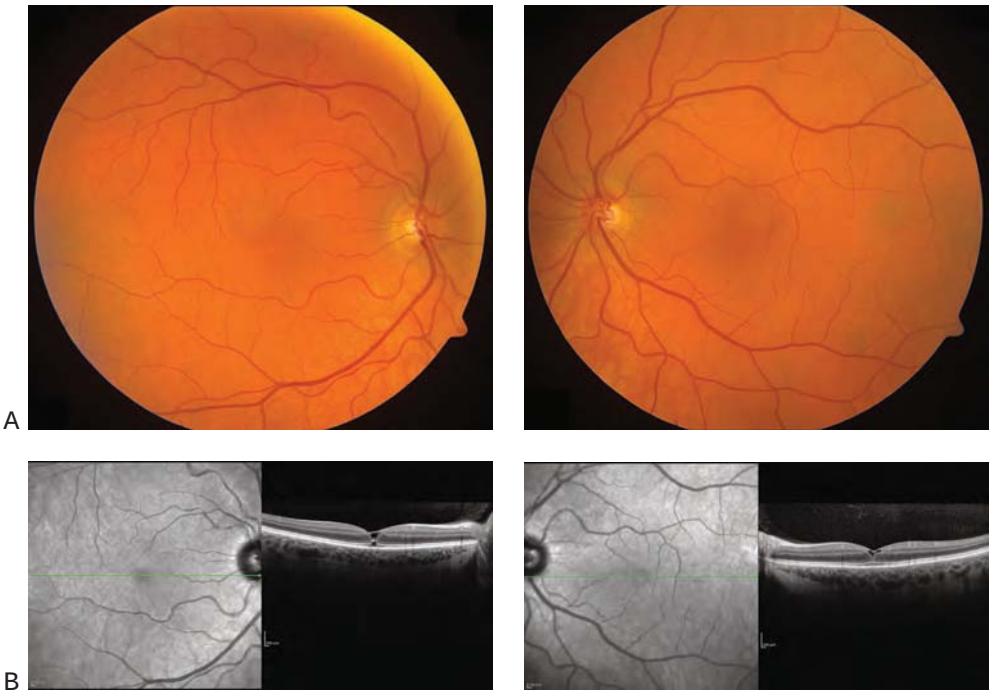

Figure 14-11 Crystalline retinopathy in a woman receiving tamoxifen for treatment of breast cancer. **A,** Fundus photographs show punctate pigmentary changes. Rare inner retinal crystals were noted on slit-lamp biomicroscopy. **B,** SD-OCT of the right eye shows subtle but characteristic inner layer foveal cystic changes with central disruption and loss of the ellipsoid band; the left eye demonstrates inner layer foveal cystic changes only. *(Courtesy of Kenneth Taubenslag, MD, and Stephen J. Kim, MD.)*

show telangiectasia, masquerading as macular telangiectasia type 2 (MacTel 2); thus, this maculopathy should be considered in the differential diagnosis of MacTel 2.

A crystalline maculopathy may also occur after ingestion of high doses of *canthaxanthine,* a widely available carotenoid used to simulate tanning. In the inner retina, canthaxanthine deposits distribute in a doughnut pattern around the macula, with a predilection for the juxtapapillary region. They do not typically cause vision loss and may resolve after the medication is discontinued.

Intravascular crystalline deposits of oxalate have been observed after the ingestion of *ethylene glycol* and after prolonged administration of *methoxyflurane* anesthesia (an agent that is no longer used in the United States) in patients with renal dysfunction. Other retinal crystals that may be deposited intravascularly include talc emboli, which are injected along with drugs such as methylphenidate in persons who inject drugs. The refractile talc deposits usually embolize in the smaller-caliber perifoveal retinal arterioles and may cause peripheral retinal neovascularization in rare cases; they do not typically cause vision loss.

Drenser K, Sarraf D, Jain A, Small KW. Crystalline retinopathies. *Surv Ophthalmol.* 2006;51(6): 535–549.

Drugs Causing Color Vision or ERG Abnormalities

Phosphodiesterase 5 (PDE-5) inhibitors such as *sildenafil* and *tadalafil* can also partially inhibit PDE-6, an integral enzyme in the phototransduction cascade. Transient blue tinting of vision and temporarily subnormal ERG responses (including a delayed cone b-wave implicit time) have been observed in patients taking high doses of sildenafil. These changes may occur in up to 50% of patients ingesting doses greater than 100 mg, but no permanent retinal toxic effects have been reported. Reversible yellow tinting of vision, or *xanthopsia,* may be caused by the cardiac glycoside *digitalis.*

Some patients taking isotretinoin for the treatment of acne have reported poor night vision and have been found to have abnormal dark-adaptation curves and ERG responses. Toxicity seems to be infrequent but is more likely in patients undergoing repetitive courses of therapy. The changes are largely reversible.

The antiepileptic drug vigabatrin can cause visual field constriction and ERG abnormalities, including depression of the 30-Hz cone amplitude.

Drugs Causing Other Ocular Toxicities

The use of *rifabutin* has been associated with vision loss arising from anterior and posterior uveitis with hypopyon and hypotony. Certain sulfur-derived medications such as *acetazolamide* and *topiramate* can cause medication-induced myopia and associated retinal and choroidal folds and macular edema. Vision loss may be mild (caused by isolated macular folds) or severe (caused by ciliochoroidal effusion, leading to angle-closure glaucoma) and may be reversed with early recognition and prompt discontinuation of the drug. There are rare reports of *buproprion* causing choroidal effusion.

Ocular argyrosis may develop after colloidal silver ingestion over a period longer than 1 year; this condition manifests as ocular pigmentation, black tears, and a dark choroid caused by brown-black granules diffusely deposited in Bruch membrane, which can lead to “leopard spotting” and drusenlike deposition.

CHAPTER 15

Diseases of the Vitreous and Vitreoretinal Interface

This chapter includes related activities. Go to www.aao.org/bcscactivity_section12 or scan the QR codes in the text to access this content.

Highlights

- Posterior vitreous detachment occurs commonly with age and can be associated with vitreous hemorrhage or retinal tears.
- There are 3 recognized categories of vitreomacular traction disease: vitreomacular adhesion, vitreomacular traction syndrome, and macular hole.
- Phenotypically similar to retinopathy of prematurity, familial exudative vitreoretinopathy is characterized by failure of the temporal retina to vascularize in an individual born at full term with normal respiratory status.

Posterior Vitreous Detachment

The vitreous is a transparent gel composed mainly of water, collagen, and hyaluronan (hyaluronic acid) that is attached to the basal lamina of the lens, optic nerve, and retina, and fills the vitreous cavity of the eye. A posterior vitreous detachment (PVD) is the separation of the posterior cortical gel from the retinal surface, including its adhesions at the optic nerve head (the area of Martegiani), macula, and blood vessels. At its base, the vitreous remains firmly attached to the retina. Because of this firm attachment, the basal cortical vitreous collagen cannot be peeled off the retina; instead, the vitreous must be "shaved" during vitrectomy, instead of being removed.

With increasing age, the vitreous gel undergoes both liquefaction (synchysis) and collapse (syneresis). The viscous hyaluronan accumulates in lacunae, which are surrounded by displaced collagen fibers. The gel can then contract. With this contraction, the posterior cortical gel detaches toward the firmly attached vitreous base. Clinical studies typically reveal a low occurrence of PVD in patients younger than 50 years. Autopsy studies demonstrate PVD in less than 10% of patients younger than 50 years but in 63% of those older than 70 years. The prevalence of PVD is increased in conditions such as aphakia, pseudophakia with open posterior capsule, inflammatory disease, trauma, vitreous