A Case of Tamoxifen Keratopathy

Tamoxifen citrate (ICI46474) is an antiestrogenic agent used in cases of disseminated breast carcinomas and as adjuvant postoperative therapy. Toxic reactions to tamoxifen, such as decreased visual acuity, bilateral macular edema, and yellow-white dots in the paramacular and foveal areas, are relatively rare (reported incidence between 0.9%-12%).

In 1978, Kaiser-Kupfer and Lippman first reported the occurrence of what has become known as tamoxifen keratopathy and tamoxifen retinopathy in 4 women treated with very high doses (up to 320 mg per day) of tamoxifen citrate for longer than 1 year. The typical findings were bilateral white, whorl-like, central, subepithelial opacities in the cornea. They also found white refractive opacities superficial to retinal blood vessels, forming clusters located in the paramacular and foveal areas, with the highest concentration temporally, and clinical and angiographic evidence of cystoid macular edema. The keratopathy led to decreased visual acuity but was reversible. Despite the decrease in the recommended dose of tamoxifen, retinopathy was reported in patients taking 40 mg of tamoxifen citrate per day and later in patients taking 20 mg of tamoxifen citrate per day. In the majority of cases, however, the toxic effects were reversible. Optic neuritis after tamoxifen use was reported as well.

Report of a Case. A 74-year-old female patient was referred to Kochi Medical School Hospital in March 2005 for further evaluation of a corneal abnormality by a local ophthalmologist. She complained of decreased vision in both eyes during 1 year. Her medical history was significant. In January 1982, she underwent a local buckling for rhegmatogenous retinal detachment in her right eye. She last visited the ophthalmologist in October 1988 and her best-corrected visual acuity was 0.9 OD and 1.5 OS. No retinal detachment was found, but she was diagnosed with an epiretinal membrane in her right eye. In March 2000, she underwent a partial mammectomy for breast cancer and was treated with 20 mg of tamoxifen citrate (Nolvadex D [delayed release]) daily for 5 years (total dose, 36.5 g). The patient was not taking other medications. She stopped taking tamoxifen in March 2005. Her complaints of visual disturbance in both eyes first appeared after 4 years of tamoxifen treatment, and the corneal abnormality was first found at the same time.

On initial examination, visual acuity was 0.7 OD and 1.2 OS. Intraocular pressure was 18 mm Hg in the right eye and 13 mm Hg in the left eye. Slitlamp examination revealed bilateral whorl-like, subepithelial, crystallin-like opacities of different (green, blue, red, white) colors in the corneas of both eyes (Figure 1). Small, relatively clear zones in the paracentral cornea did not contain deposits. The pattern and location of opacities were similar in both eyes. The corneal endothelium was not clearly seen, and therefore, specular microscopy was performed through the relatively clear paracentral zone. Findings were normal for both eyes. The right eye endothelial cell density was 3100, and the left eye endothelial cell density was 3516. Under local anesthesia, a biopsy of the cornea at the limbal area at the 12-o’clock position was performed and the sample was studied using a transmission electron microscope. Foci of electron-dense, granular deposits were observed in the perinuclear areas of the basal cells. These deposits were present mainly in the basal cells of the limbus and resulted in the atrophic

Figure 1. A and B, Slitlamp external photograph of the right eye shows subepithelial crystallin-like substance deposition in the cornea.
and degenerative changes, such as extension of the cellular processes of the subepithelial matrix, and the decreased height of the basal cells. They were closely adjacent to nuclear envelopes. Some of the deposits resembled lipofuscin (Figure 2).

According to ophthalmological examination findings and the patient’s history of tamoxifen use, she was diagnosed as having a tamoxifen keratopathy, and observation every 2 months was recommended. No special treatment for tamoxifen keratopathy has been prescribed so far because the keratopathy is believed to be reversible.

Tamoxifen retinopathy has also been reported as an adverse effect of tamoxifen administration; therefore, the patient underwent special examinations. An epiretinal membrane was diagnosed in the patient’s right eye during fundus examination. No crystallin-like deposits or macular edema were found in either eye. Because of corneal opacities, the fundus photographs by fluorescence angiography were hazy but revealed normal fluorescence, no apparent retinal pigment epitheliopathy, and no dye leakage from retinal vessels or optic discs in either eye. The electroretinogram revealed decreased amplitude of the b wave, with normal oscillatory potentials. Thus, no evidence of tamoxifen retinopathy was found.

Seven months after initial examination, her best-corrected visual acuity was 0.8 OD and 0.7 OS. The distribution of corneal opacities remained unchanged. The decrease of visual acuity from the time of the initial examination is difficult to explain because there are no conclusive findings supporting this observation. We speculate that this may be due to the gradual progress of keratopathy, especially in the pupillary zone.

Comment. Documentation of tamoxifen keratopathy is of big interest, because tamoxifen is a drug used for treatment of disseminated breast carcinomas. The therapy is essential for the patient’s chance of survival. Although its incidence is rare and similar aspects can be found in other disorders, the diagnosis of this keratopathy is not difficult if a careful history is taken and good ophthalmological examination is performed.

Corneal changes similar to those described in patients taking tamoxifen have also been reported in asymptomatic carriers of Fabry disease (Anderson-Fabry disease). Cornea verticillata, a whorl-like opacity, has become one of the hallmarks of Fabry disease.

Corneal deposits were also reported with other antitumor drugs, such as carmustine, in the form of white perlimbal stromal infiltrates, and ulorone hydrochloride, where an increase in the density of the subepithelial opacities, whorl-like clouding of the epithelium, and diffuse and subtle clouding in the epithelium and anterior stroma were found.

The structure of tamoxifen is similar to other cationic amphiphilic drugs known to produce a retinopathy and keratopathy, including chloroquine, chlorpromazine, thiouridazine, and amiodarone hydrochloride. Cases of chloroquine and amiodarone keratopathies have been reported, but, to our knowledge, histopathological features of tamoxifen-induced keratopathy have not been presented to date.

Systemic medications reach the cornea via the tear film, aqueous humor, and limbal vasculature. Amphiphilic medications may produce a drug-induced lipidosis and development of a vortex keratopathy. Corneal changes may result in reduced visual acuity, photophobia, and ocular irritation, which resolve following drug cessation. Corneal manifestations of systemic medications are often dose related. After tamoxifen withdrawal, almost all ocular abnormalities were found to be reversible, except for the retinal opacities. The question remains whether and when patients taking tamoxifen should be systematically examined by an ophthalmologist. An ophthalmological assessment in case of visual complaints for patients taking tamoxifen remains useful, although routine screening seems to be unnecessary.

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Figure 2. Transmission electron microscopy showed foci of electron-dense, granular substances in the perinuclear areas of the basal cells (arrows). Some deposits resemble lipofuscin (arrowhead). Bar = 1 µm.
Ocular Pathologic Features of Hermansky-Pudlak Syndrome Type 1 in an Adult

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease, characterized by a triad of oculocutaneous albinism (OCA), bleeding diathesis due to deficiency of dense bodies in platelets, and lysosomal accumulation of ceroid lipofuscin. Seven genetic subtypes of HPS have been identified in humans; HPS1 on chromosome 10q23 is the most common and represents a founder effect in northwest Puerto Rico. The clinical features of HPS and its ophthalmic involvement are well documented, but no ocular histopathology has been published (to our knowledge). Herein, we describe the ocular histopathology of an adult patient with HPS type 1 (HPS-1).

Report of a Case. This study was approved by the National Human Genome Research Institute and National Eye Institute institutional review boards for human subjects, and informed consent was obtained from the patient. A 43-year-old Puerto Rican man was seen in March 2004. The diagnosis of HPS-1 was confirmed by demonstrating homozygosity for the 16–base pair duplication in exon 15 of HPS1.

Findings from an ophthalmic examination revealed horizontal infantile-onset jerk nystagmus with a torsional component and intermittent exotropia. Best-corrected visual acuity was 20/160 OU (Early Treatment of Diabetic Retinopathy Study), and hyperopic astigmatism was present in both eyes. Posterior embryotoxon, marked iris transillumination, and macular transparency were noted (Figure 1).

The absence of foveal pits and light reflexes indicated foveal hypoplasia, which was confirmed with optical coherence tomography (Figure 2). The patient died of pulmonary fibrosis in April 2005.

Pathologic Findings. Macroscopically, the right globe measured $24 \times 25 \times 22$ mm and the left globe measured $23 \times 24 \times 23$ mm. The cornea, anterior chambers, and optic nerves were normal. The uvea and retinal pigment epithelium displayed marked hypopigmentation. No macula lutea was visible. A focal hemorrhage was noted in the conjunctiva of the right eye.

Microscopically, hemorrhage was present in the temporal conjunctiva of the right eye. A small cluster of mesenchymal cells was adherent to the enlarged and anteriorly located Schwalbe line (posterior embryotoxon) bilaterally (Figure 3A and B). The scleral spur of the right eye was hypoplastic. Only small aggregates of large melanin granules were visible in the pupillary margin (Figure 3C and D). Moderate hyalinization of the ciliary body was observed in both eyes (Figure 3E and F). There was marked depigmentation in the entire uvea (Figure 4). A few fine melanin granules remained in ocular pigment epithelial layers. The fovea showed a lack of differentiation, and the retinal pigment epithelium contained sparse melanin granules (Figure 4B). A few hemorrhages and platelet aggregates were seen in the optic nerve head of the right eye.