The Fine Structure of an Iridectomy Specimen From a Patient With Latanoprost-Induced Eye Color Change

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Herein we report the morphologic and ultrastructural features of an iridectomy specimen taken from a patient whose brown-green iris darkened while participating in the phase 3 trial of latanoprost in Sweden.

A well-documented side effect of latanoprost, an analog of prostaglandin F_{2α} used as an antiglaucoma medication, is iridial color change. The color change is found particularly with green-brown, gray-brown, and blue-brown irides that become progressively more brown with the use of latanoprost. Excessive formation of melanin with stromal release of granules could cause uveitis, exacerbate primary or secondary glaucoma, or lead to precancerous changes.

REPORT OF A CASE

The patient was aged 67 years when she entered the clinical trial. She suffered from ocular hypertension in her right eye with a mean diurnal intraocular pressure of 23 mm Hg. She was treated with 0.025% timolol maleate (Timoptic) for 6 months in her right eye only. Thereafter, she was treated with topical 0.005% latanoprost once daily for 13.5 months. The color change was suspected at 11 months and she was withdrawn from the trial 2.5 months later (Figure 1, right).

In the follow-up, the patient was treated with timolol for only 1 month owing to ocular irritation. Intraocular pressure–lowering medication was not used. She underwent cataract surgery 16 months after withdrawal from the trial and a sector iridectomy was performed via a tunnel incision.

The anterior layer of the specimen was hyperplastic and thickened in the pupillary area. The stroma between the anterior border and the sphincter muscle was hypercellular — these cells contained melanin granules and some were pigmented (Figure 2, right). The fine structure of the posterior epithelial cells was unremarkable, although some nuclear membranes exhibited infolding and invagination. Among the mature melanin granules, some exhibited incomplete melanization or were vacuolated. Spirals of rough endoplasmic reticulum were found in some cells and multilayered basement membrane material was evident in a few local areas.
Ultrastructural investigation of the stroma showed the pigment-containing cells were melanocytes, clump cells, and some fibroblasts (Figure 3). The clump cells were most obvious near the sphincter muscle. Tissue histiocytes were present in small numbers and some had vacuolated cytoplasm. A few mast cells were found. There was no evidence of free melanin granules within the collagen matrix. Qualitative observation of the stromal melanocytes gave the impression that the melanin content was not excessively high (Figure 3).

The anterior border was from 3 to 6 cells wide except in the thickened area in the pupillary zone (Figure 4). The melanocytes were heavily, but not excessively, pig-

Figure 1. Left, Photograph of the right eye before the start of latanoprost treatment. Right, Photograph of the right eye after suspension of latanoprost treatment.

Figure 2. Left, A light micrograph of a semithin section through the specimen (toluidine blue, original magnification ×150). Right, Higher-power light micrograph to show the region of the nevus. Arrows indicate the thickened, pigmented anterior border, and the sphincter muscle (S) is marked (toluidine blue, original magnification ×400).

Figure 3. A transmission electron micrograph of the posterior pigmented epithelium (E), dilator (D), and stroma (ST) that shows no abnormalities. Stromal clump cells can be identified (arrows) (original magnification ×3000).

Figure 4. Anterior border region in the area of the nevus. It is hypercellular and some melanocytes have atypical features (arrows) (toluidine blue, original magnification ×3000).
A mound of cells on the anterior border toward the pupil had the characteristics of a freckle or nevus. The presence of melanocytes with atypical features (nuclear chromatin margination, prominent nucleoli, invagination of the nucleus) was of interest since these characteristics are seen in precancerous lesions.

To our knowledge, this is the first morphologic report of an iris specimen from a patient with latanoprost-induced eye color change. Theoretically, increased pigmentation could result from proliferation of melanocytes, melanogenesis, or migration of melanocytes. In this specimen there is little indication that proliferation took place.

The melanocytes with atypical features did not appear sinister as they were not in the great abundance or in the pronounced form seen in precancerous lesions. Melanocytes exhibiting the nuclear features described above are also found in normal brown irides, and before treatment with latanoprost, the sphincter area was dark brown. The visible change in eye color was in the middle and peripheral parts of the iris where no abnormal morphologic findings were made. Stromal and anterior border melanocytes had abundant melanin granules but did not appear to have excessive pigmentation. The degenerative vacuolation of posterior epithelial melanin granules has been described in the normal aging iris and in the iris of patients with glaucoma.

There is little evidence in this specimen or in studies using cultured melanocytes that latanoprost adversely affected the tissue. The possibility that latanoprost-induced melanogenesis would lead to bursting of melanocytes and extrusion of free melanin into the stroma is not supported by the morphologic features of this specimen. The incidence of mature melanin granules in the stromal melanocytes is in no way remarkable. There did seem to be an abundance of clump cells throughout the stroma, and although the origin and nature of clump cells are not well understood, one of their suspected functions is to mop up loose melanin. Overall, there is little in the way of tissue abnormality in the specimen.

A look at the past . . .

OWL and DORN have shown conclusively by careful tests that the perception of light under the action of the X-ray, which has been described by some authors, belongs in the sphere of subjective light perception, the perceptions occurring even when the visual field is wholly dark. Therefore the reports of the favorable effect of the X-rays on some sorts of blindness are not deserving of credit.