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Clinical, Surgical, and Histopathologic Characteristics of Corneal Keloid

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Purpose. To describe the cause, diagnosis, and management of a case of bilateral corneal keloid. **Methods.** We describe a 17-year-old white boy with enlarging nontraumatic bilateral corneal scars whose growth was exacerbated by a superficial keratectomy. The patient underwent a penetrating keratoplasty (PK) in his left eye. Light and electron microscopy of the corneal button were performed. **Results.** The histopathologic and ultrastructural features of the corneal button were haphazardly arranged collagen fascicles with activated fibroblasts but no inflammatory cells. The clinical outcome was excellent, although there has been continuous growth of the outer margin of the initial lesion not included in the PK. This growth has not affected vision. The unoperated right corneal lesion progressively enlarged during these years. **Conclusion.** A corneal keloid, although unusual, should be suspected in cases of enlarging white glistening avascular corneal scars regardless of a traumatic antecedent. Light and electron microscopy confirmed the diagnosis. Management is by PK when the visual axis is involved and carries an excellent prognosis.
Key Words: Corneal keloid—Electron microscopy—Fibroblasts—Light microscopy—Myofibroblasts—Penetrating keratoplasty.

Corneal keloids are uncommon lesions.[1] Their true incidence has been difficult to establish because they have been frequently reported as part of the hypertrophic scar group.[2,3] However, they are clearly differentiated from said group in that the keloids outgrow their initial boundaries.[1] In the last 6 decades, 69 cases of corneal keloid have been reported,[4,5] but only 5 of these have been confirmed by electron microscopy.[4,6–9] We describe a patient who had no known previous trauma but had exacerbation in the growth of a bilateral corneal keloid after nonpenetrating corneal surgery.

CASE REPORT

A 17-year-old white boy was referred to our clinic with several years' history of bilateral gradual loss of visual acuity. At the age of 12 years, he consulted another institution because of loss of visual acuity and the appearance of "white spots" on both corneas. He had no history of traumatic or inflammatory events. His medical history and family history were unremarkable. His best-corrected visual acuity (BCVA) was 20/20 in the right eye and 20/40 in the left eye. Biomicroscopy of the right eye showed a white, oval, 2 × 2-mm raised lesion, located lateral to the pupil in the superficial corneal stroma. The left cornea showed a whitish, raised, irregularly shaped, 4 × 2-mm lesion located nasal to the pupil in the superficial corneal stroma. The remainder of the ophthalmologic examination was within normal limits. He had regular checkups for approximately 2 years, with gradual enlargement of both corneal lesions together with a slow deterioration of his BCVA to 20/25 and 20/50. A bilateral superficial keratectomy under topical anesthesia was performed with good transparency of the right cornea, but the persistence of a dense leukoma in the left eye, with BCVA of 20/20 and 20/40. Subsequently, there was gradual reenlargement of both corneal lesions, with deterioration of the BCVA.

Two years later, his BCVA was 20/40 in the right eye and counting fingers (CF) at 15 feet in the left eye. Biomicroscopy showed irregular, dense, white, glistening, avascular corneal lesions in both eyes, occupying 50% of the stromal thickness in the right eye (Fig. 1A) and 100% in the left eye (Fig. 2A). In the right eye, the lesion was located temporal to the pupil and had a diameter of 3 mm. In the left eye, the lesion was located in the visual axis and had a mean diameter of 8.7 mm. In the left cornea, an anterior and posterior bulging of the lesion was evident (Fig. 2B). Both lesions had intensely white punctate satellite dots. The epithelium was smooth and glistening and contained irregular iron lines. The remaining ophthalmologic examination was within normal limits. The patient had no keloids on his skin. Based on the evolution and clinical appearance of the lesions, a presumptive diagnosis of bilateral corneal keloid was made. The patient underwent an 8.0- to 8.5-mm penetrating keratoplasty on his left eye, leaving the nasal margin of the lesion because of its proximity to the limbus (Fig. 2C).

The corneal button obtained during surgery showed a prominent bulging in its anterior and posterior surfaces. After sectioning it in half with a blade, the lesion was hard. It was fixed in 3% formalin solution for light microscopy and glutaraldehyde for electron microscopy.

The postoperative course was uneventful with mild cicatrization, except at the entrance point of the running suture at the 4 o'clock position, where a leukoma reappeared with the passage of time. After 6 months, the patient's BCVA was 20/20. In the 4 years after surgery, we noted growth of the nasal margin of the lesion left at the time of the penetrating keratoplasty and the postsuture leukoma at the 4 o'clock position, without invading the donor button or even the penetrating keratoplasty scar (Fig. 2D). In his right eye, we observed a progressive growth of the initial corneal lesion, both in diameter (4 × 5 mm) and in depth (70%) with involvement of the visual axis (Fig. 1B) and a deterioration of his BCVA to counting fingers at 3 feet.

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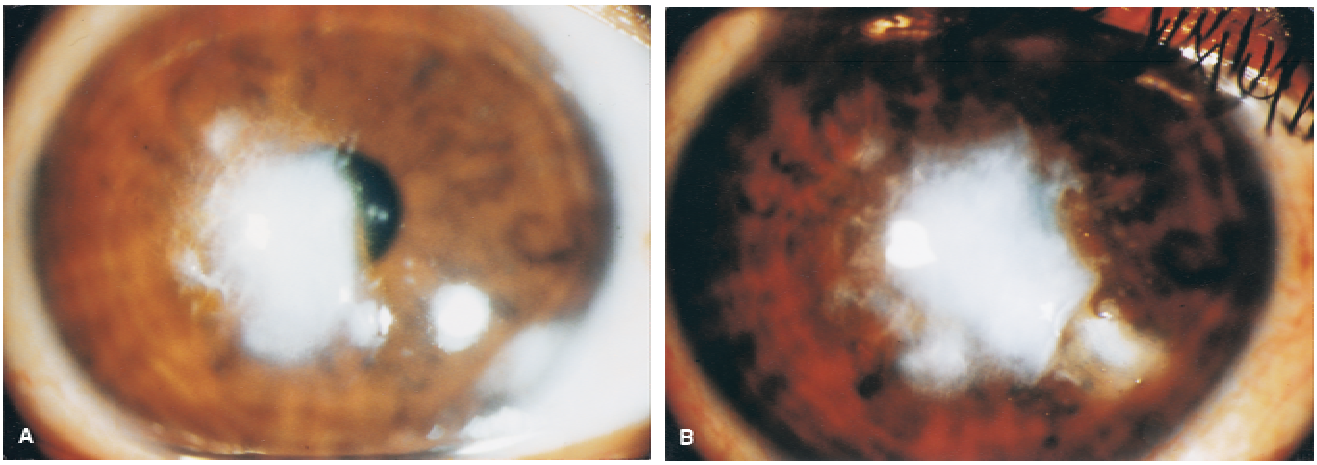

FIG. 1. Right corneal lesion. **A:** August 1995. Note the white, glistening satellite dots. **B:** February 2000. There has been considerable enlargement with involvement of the visual axis.

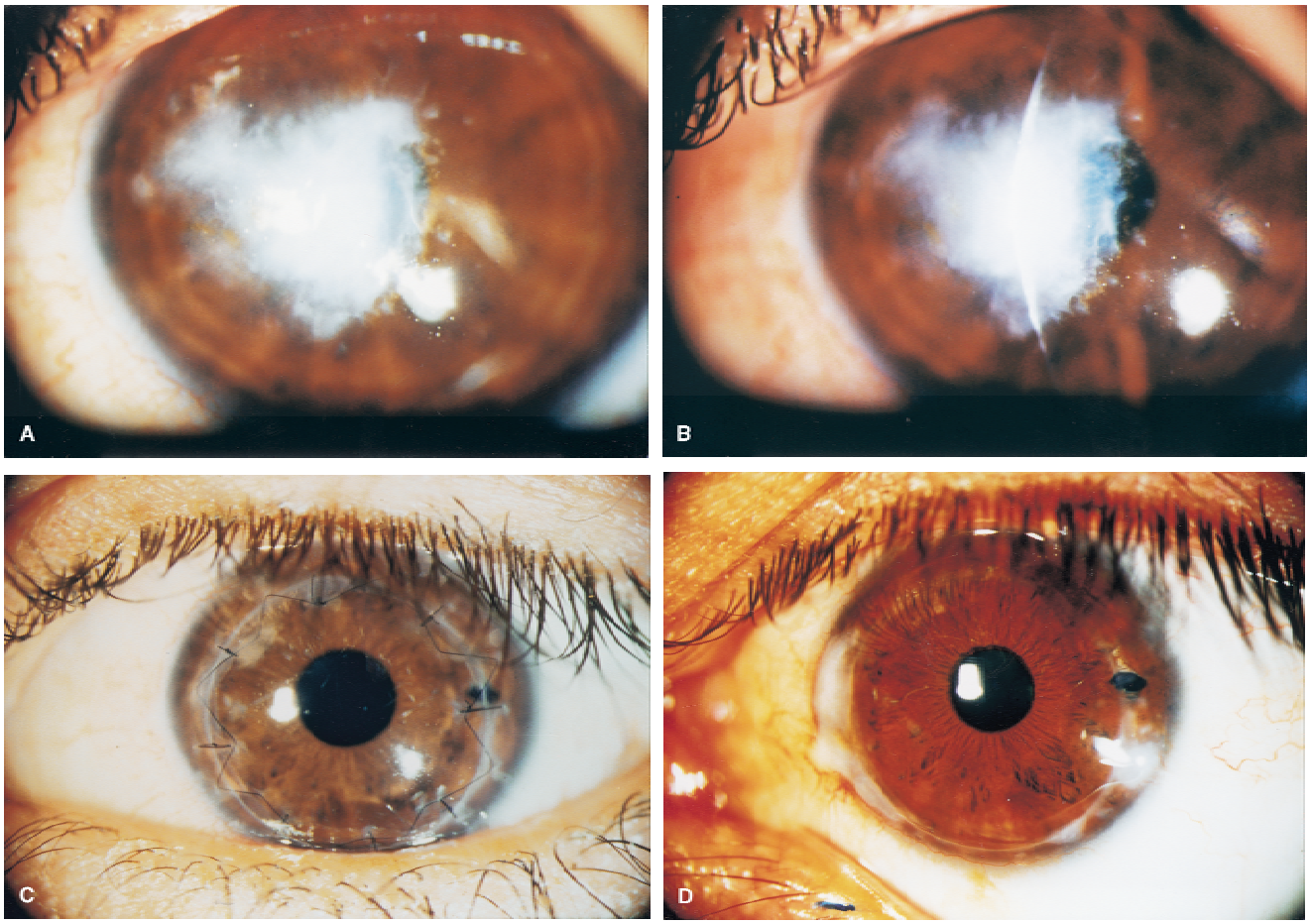

FIG. 2. Left corneal lesion. **A:** August 1995. White, glistening lesion on the visual axis with irregular iron lines. **B:** August 1995. Note the anterior slit bulging. **C:** November 1995. Three months after surgery, the small nasal margin of the keloid (9 o'clock position) was left after surgery because of its proximity to the limbus. **D:** February 2000. Four years and 3 months after surgery, the lateral and volumetric growth of the nasal margin of the keloid left at the penetrating keratoplasty extends from the 7 o'clock to 10 o'clock positions, and the scar left at the entrance point of the continuous suture is seen at the 4 o'clock position.

HISTOPATHOLOGY

Light Microscopy

Half the specimen was submitted for light microscopy. Examination of the paraffin sections stained with hematoxylin and eosin (Fig. 3A), periodic acid–Schiff, and Masson trichrome showed an epithelium of variable thickness with acanthosis, hyperkeratosis, parakeratosis, and an edematous disorganization of its basal layers. There was a localized absence of Bowman's layer. Corneal stromal thickness was markedly increased; birefringent (hyalinized) collagen fibers were erratically interlaced, sometimes perpendicular to the epithelium, forming dense whorls. There were fibroblasts in between these collagen fibers. Cellularity and thinning of the collagen fibers were more evident in the anterior stroma. There were no inflammatory cells. Descemet's membrane and the endothelium were normal

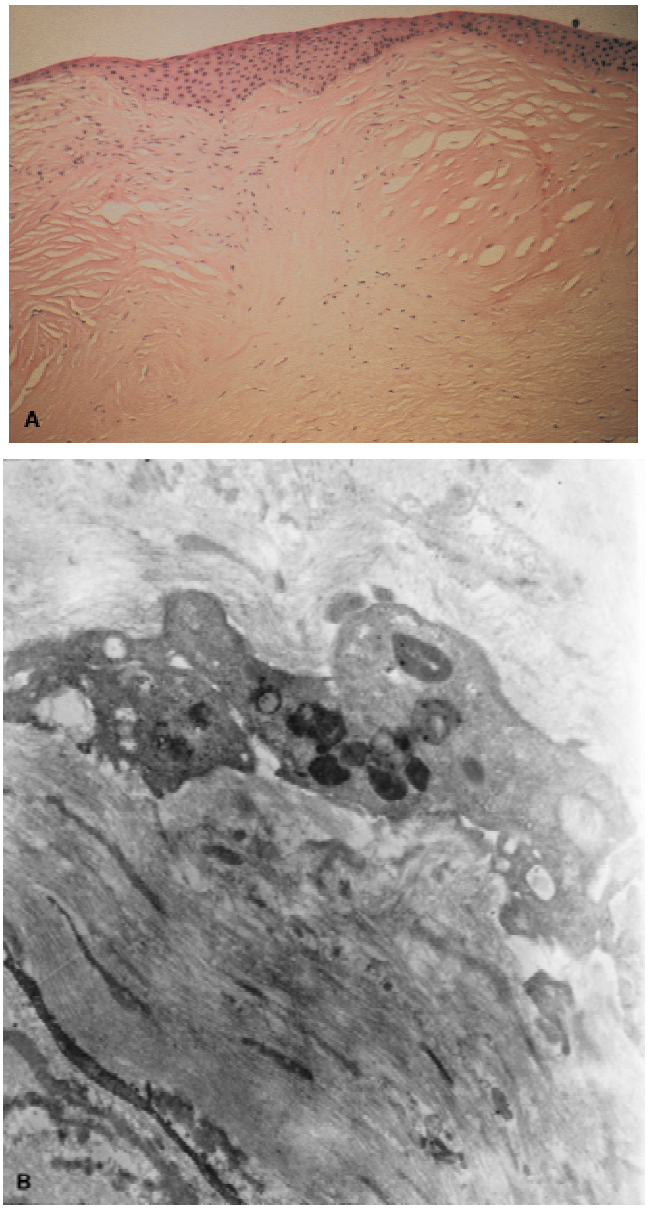

FIG. 3. Histologic examination. **A:** Light microscopy. Note the variably thick epithelium, focal absence of Bowman's layer, and haphazard arrangement of corneal stromal fibers (original magnification, ×25). **B:** Electron microscopy. Note the irregularly oriented collagen and an activated fibroblast with prominent rough endoplasmic reticulum and increase in the number of its organelles (original magnification, ×12,000).

Electron Microscopy

The other half of the specimen was postfixed with osmium and uranic acetate. The epithelium was of varying thickness with focal hyperplasia and acanthosis. The stroma contained crisscrossed and haphazardly oriented lamellae made of collagen fibers with spindle-shaped cells oriented in different directions. These cells had irregular nuclei with compact chromatin, abundant cytoplasm with prominent rough endoplasmic reticula, and a moderate increase in the number of organelles, all of which corresponded to activated fibroblasts (Fig. 3B). There was no active inflammatory process. Descemet's membrane and endothelium were normal.

DISCUSSION

A corneal keloid is a growing white, smooth, glistening lesion on a previously injured cornea of a predisposed patient. Clinically, it does not retract with time, but outgrows its initial boundaries. It can appear months or years after the initial trauma, as opposed to a hypertrophic scar, which appears immediately and does not enlarge.[1,10] However, some authors now question the existence of corneal keloids as a separate entity and consider them a phenomenon in the hypertrophic scar spectrum.[11] Keloids occur more frequently in men, with only a few reports in women.[3,12,13] Sixty-seven percent of patients are symptomatic during the first 2 decades of life,[6–8,12–16] with a mean presentation age of 13 years (range, 2 months–72 years).[6] Among the reported cases, some have been associated with penetrating trauma,[3,17] with nonpenetrating trauma,[1,4] with no trauma at all,[6,13] and as congenital cases.[12,13] The corneal keloid has frequently been associated with Lowe syndrome.[6] In this group of patients, it is the main cause of ocular morbidity after 7 years of age, when glaucoma and cataracts have already been surgically treated. Some authors even consider it characteristic of this syndrome.[7,18] Light and electron microscopy are essential in confirming the clinical diagnosis[1,4,6,7] by establishing the presence of hyalinized collagen, activated fibroblasts, and myofibroblasts.

There are several theories regarding the cause of the corneal keloid. Parson and Fuchs considered that for a corneal keloid to form, there must be a corneal penetrating wound with an incarcerated iris.[12] The inflammatory exudate covering the iris was thought to be responsible for the cellular proliferation. Conversely, Fenton and Tredici[15] suggested that the origin of the lesion is in the corneal stroma itself. Some authors consider that it can appear after subclinical corneal infections, leaving intrastromal antigens that serve as persistent stimuli to the repair process.[6] In the cases of Lowe syndrome, it has been suggested that amino acids can filter into the cornea from abnormal vessels or that substances from within the anterior chamber can get through a defective endothelium.[19]

In skin keloids, it has been found that the process of cicatrization begins when a mechanical stimulus is translated into a cellular response with an inflammatory reaction. This produces vasodilation, edema, and a pink scar with immature fibroblasts, followed

by a biochemical stimulus that induces blood vessel regression and stimulates myofibroblast proliferation, thereby retracting the scar. At some point in this chain of events, a stimulus induces excessive growth. This leads to an exaggerated increase in cellularity and metabolic activity[10] favoring the invasion of the surrounding tissue's healthy borders by the scar. This is the main characteristic of the keloid.[2]

Regarding the corneal cicatrization process, there are several areas of active research: the difference between the proteic chains of the keratocytes and the corneal myofibroblasts[20]; the effect of the cytokines released by the injured epithelium, which apparently produce loss of the anterior stroma keratocytes[21]; the effect of α-interferon and basic fibroblast growth factor, which block α-actin expression and consequently the differentiation of keratocytes into myofibroblasts[22]; and substances, such as transforming growth factor-β, that could be involved in the paracrine and autocrine growth and differentiation of the normal corneal stroma, playing an important role in the corneal response to injury.[22]

On light microscopy, the epithelium is of varying thickness, with hyperplasia, acanthosis, parakeratosis, and an edematous and disorganized basal layer. Bowman's layer is usually absent. In the stroma, the collagen has a whorl-like pattern. There is positive staining for mucopolysaccharides, and basophilic fibroblasts are abundant.[4]

On electron microscopy, the basal epithelial cells are more electron-dense and have more intracytoplasmic tonofilaments than the superficial ones.[4] These cells are arranged in three to six layers, with some areas of hyperplasia. The basal membrane is discontinuous or even absent.[1] In the anterior stroma, the collagen lamellae are randomly distributed, with varying thickness (15–37 nm), and wide interstitial spaces. There is an increase of the extracellular matrix made of water and glycoproteins.[1,4] The cellular compartment is made mainly of fibroblasts, with a moderate increase of macrophages and some lymphocytes. Ultrastructurally, these fibroblasts have different characteristics. The youngest, more metabolically active, have a well-developed rough endoplasmic reticulum, abundant mitochondria and Golgi apparatuses, and one or two prominent nucleoli. Toward the posterior stroma, there are myofibroblasts containing actin filaments[22,23]; their quantity is inversely proportional to the keloid maturity.[3]

The histopathologic findings vary according to the stage of the keloid. In the early stages, there is predominance of type III collagen, abundant myofibroblasts, and new vessel formation. In the later stages, there is predominance of haphazardly arranged collagen type I fascicles and scarce myofibroblasts, with involution of the blood vessels, thus giving a whitish, rigid scar aspect.[1]

In the current case, a patient with a history of bilateral corneal keloid without previous trauma underwent a bilateral superficial keratectomy, which exacerbated the growth of the lesions. The clinical diagnosis was based on the history, growth pattern, and clinical characteristics of the lesions and was confirmed by light and electron microscopy. Penetrating keratoplasty for corneal keloids impinging on the visual axis is a sound and safe option with excellent visual rehabilitation.

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