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Bilateral Congenital Corneal Keloids and Anterior Segment Mesenchymal Dysgenesis in a Case of Rubinstein-Taybi Syndrome

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Purpose. To report the unusual association of bilateral corneal keloids and anterior segment mesenchymal dysgenesis in a child with Rubinstein–Taybi syndrome. **Methods.** Case report of a 2-year-old boy. **Results.** Excision of the epicorneal mass in the right eye was followed by recurrence of the lesion. Multiple penetrating keratoplasties were unsuccessful in reconstructing the anterior segment because of recurrent corneal epithelial breakdown, suggesting limbal stem cell insufficiency. Histopathology and electron microscopy of the excised mass lesion showed features typical of a corneal keloid: thickened keratinized epithelium, absent Bowman's layer, and fibrovascular hyperplasia, with haphazard orientation of the collagen lamellae. Ultrasound biomicroscopy and intraoperative findings suggested a diagnosis of Peter anomaly, but genetic analysis did not show a *PAX6* mutation. **Conclusion.** The findings in our patient add to the spectrum of ocular changes described in Rubinstein–Taybi syndrome and confirm earlier reports of poor ocular prognosis in corneal keloids and Rubinstein–Taybi syndrome.

Key Words: Anterior segment mesenchymal dysgenesis—Corneal keloid—Rubinstein-Taybi syndrome—Ultrasound biomicroscopy.

Corneal keloids are rare lesions that can occur at any age and can appear as a single, solitary nodule or involve the entire corneal stroma.[1] They most commonly occur after ocular injury or perforation, inflammatory disease, in association with rubeola and in Lowe syndrome.[2] Congenital corneal keloids are infrequent, and a review of literature showed six earlier case reports.[2–7] None of the patients had associated systemic disease. Rubinstein–Taybi syndrome (RTS) is characterized by broad thumbs and great toes, short stature, mental retardation, congenital heart defects, constipation, and a characteristic facial appearance including laterally downward slanting palpebral fissures and a beak-shaped nose.[8] Ocular problems are present in as many as 84% of patients and include epicanthi, heavy or highly arched eyebrows, nasolacrimal duct obstruction, ptosis, strabismus and refractive error; glaucoma and corneal lesions are less frequent.[9,10] We describe a patient with a previously unreported constellation of findings, including bilateral corneal keloids, anterior segment mesenchymal dysgenesis (ASMD), and RTS. We describe the clinical and ultrasound biomicroscopic findings, management of the corneal keloids, histopathologic findings, and the results of *PAX6* mutation analysis in our patient.

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CASE REPORT

A 4-month-old male infant was referred to our outpatient clinic in May 1997 for bilateral congenital corneal opacities. The child was delivered after an uncomplicated pregnancy and vaginal birth at 38 weeks' gestation. His birth weight was 4.8 kg. He was diagnosed with RTS, based on the presence of dysmorphic facial features, broad thumbs (Fig. 1) and great toes, congenital heart defects (including atrial septal defect and pulmonic stenosis), and constipation. Magnetic resonance imaging of the brain did not show any abnormalities. Ultrasound evaluation of the abdomen was unremarkable, except for right cryptorchism. Examination of the eyes under general anesthesia showed a horizontal corneal diameter of 12 mm in the right eye and 11.5 mm in the left eye. A fleshy, vascularized, brownish corneal mass, extending to the inferior limbus, was noted in both eyes. The dimensions of the mass were 9 × 10.5 mm in the right eye and 6.5 × 10.5 mm in the left eye for the vertical and horizontal dimensions, respectively (Fig. 2). The superior limbus was poorly defined with superficial vascularization of the corneal periphery, and there was no view of the anterior chamber or fundus in both eyes. Schiotz tonometry showed an intraocular pressure of 24.4 mm Hg in the right eye and 17.3 mm Hg in the left eye. Ultrasound biomicroscopic evaluation showed a thickened cornea (Fig. 3A), iridocorneal touch at multiple sites (Fig. 3B), and poorly defined angle anatomy (Fig. 3C) in both eyes. The anterior chamber was formed, but no discrete lens structures could be identified. All the changes were more marked

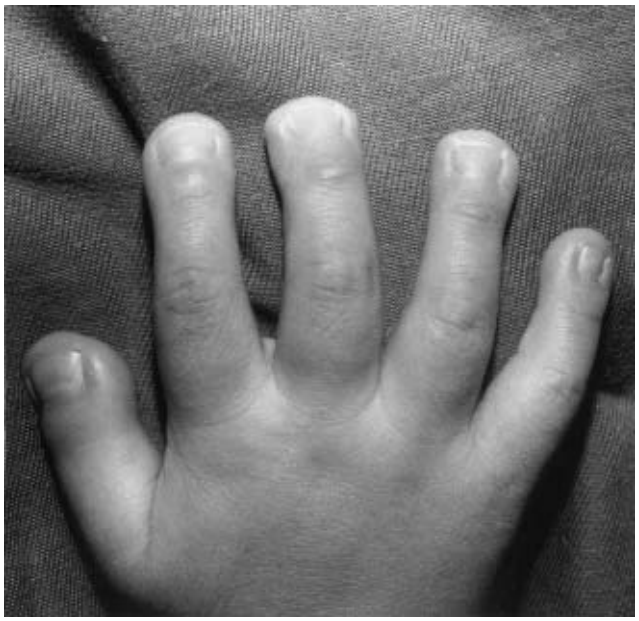


FIG. 1. Right hand of patient showing a broad thumb, characteristic of RTS.

in the right eye. B-scan ultrasonography showed a normal posterior segment in both eyes. Because the diagnosis of the mass was not clear, excision biopsy of the corneal lesion was performed in the right eye. The epicorneal mass was excised with Beaver blade and Westcott scissor. The corneal tissue was preserved and was hazy. Histopathologic examination (Fig. 4) showed thickened corneal epithelium with keratinization. Pigment granules were present in the basal epithelial layer. Bowman's layer was absent. The stroma was thickened with a loss of the normal lamellar pattern. Collagen fibers and lamellae varied in size and coursed irregularly in the stroma. An increase in keratocytes was noted, especially in the anterior layers. Extensive fibrovascular proliferation with blood vessels of varying caliber was noted. Polymorphonuclear leukocytes and lymphocytes were present, but plasma cells and mast cells were not detected. No dermal appendages were evident. Electron microscopy showed the haphazard orientation of the collagen lamellae. The child at the age of 5 months underwent penetrating keratoplasty in the right eye, under general anesthesia, in June 1997. The quality of the donor corneal tissue was fair. During surgery, the entire corneal mass was excised after an inferior peritomy, and a 7-mm corneal button was trephined centrally. Multiple adhesions of the iris to the peripheral corneal endothelium, and a vertically oval, superiorly displaced pupil were noted. The anterior capsule of the crystalline lens was adherent to the central posterior corneal surface, and a significant anterior subcapsular opacity was present (Fig. 5). After anterior capsulorhexis, the cortical material was aspirated and a +30-diopter heparin-surface modified intraocular lens was implanted in the capsular bag. Pupilloplasty was performed with 9-0 polypropylene sutures to tighten the iris diaphragm and centralize the pupil, after which an 8.0-mm donor corneal graft was secured with a continuous 10-0 nylon suture. Histopathologic examination of the excised corneal lesion showed features similar to those noted earlier. The corneal button showed nonspecific degenerative changes.

The right corneal graft had significant corneal edema since the first postoperative day. Topical corticosteroid (Maxidex, Alcon, Puurs, Belgium) was commenced every hour. The graft never became clear after 4 weeks. After surgery, graft edema persisted, and a second penetrating keratoplasty for primary graft failure was performed in July 1997, when the child was 7 months old. The quality of the second cornea was good. Horizontal corneal diameter in the right eye was 12 mm, and intraocular pressure was 20 mm Hg. Examination of the left eye showed features similar to those noted in May 1997. During surgery, inflammatory fibrin membranes on the intraocular lens, segmental iris bombé, exposed iris vessels, and peripheral anterior synechiae were noted in the right eye. The pupillary membranes were excised and peripheral anterior synechiae were released. An 8 × 7 mm penetrating keratoplasty was performed. Histopathologic examination of the excised graft showed features consistent with a failed graft. Immediately after surgery, a persistent epithelial defect developed in the corneal graft and led to graft failure and ectasia.

When the child was 1 year old, in January 1998, examination under anesthesia showed a horizontal corneal diameter of 14 mm in the right eye. A recurrence of the fleshy, vascularized corneal mass was noted. The anterior chamber was shallow and the intraocular lens was in contact with the corneal endothelium. Removal of the corneal mass, 7 × 6.5 mm penetrating keratoplasty, intraocular lens removal, and glaucoma implant surgery with an Ahmed valve were performed. Histopathologic examination of the excised

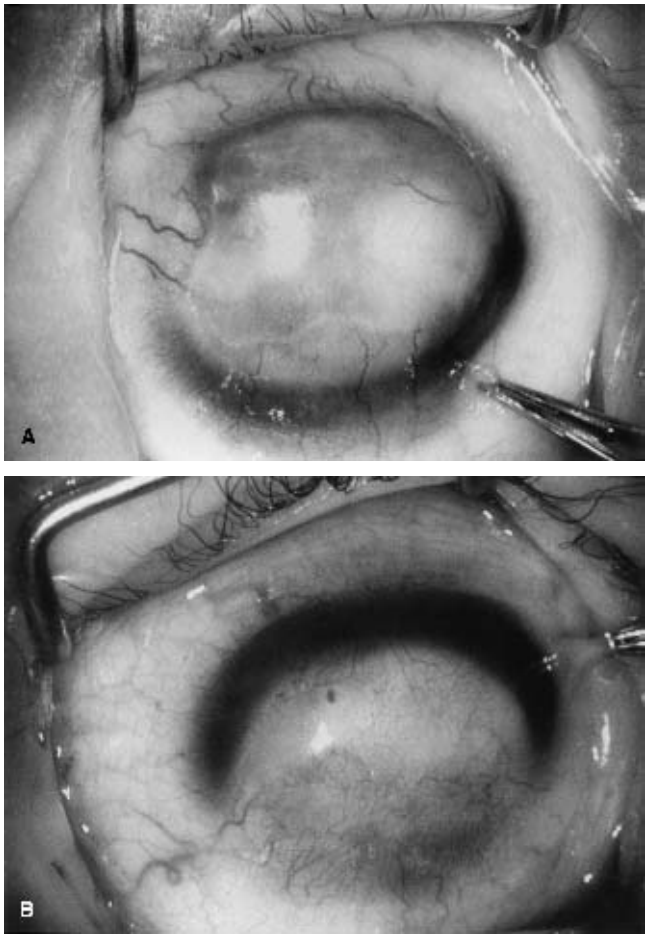
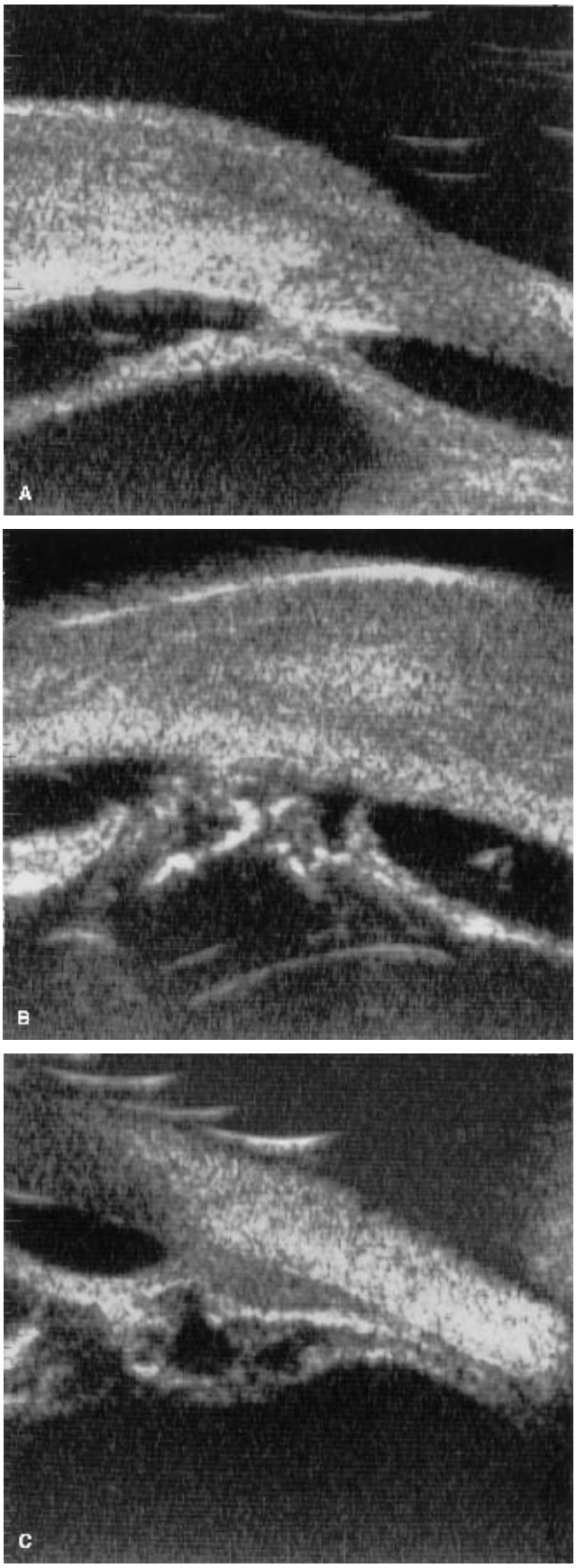


FIG. 2. Appearance of the corneal mass lesion in the right (**A**) and left (**B**) eyes in May 1997.



corneal lesion showed benign stratified squamous epithelium with hyperkeratosis. Fibrosis and interstitial hemorrhage were noted in the stroma. There was no evidence of dysplastic changes. The corneal button showed stromal fibrosis with detachment of basement membrane, and adhesion of iris tissue to the cornea. In March 1998, the child was 14 months old. The IOP was 28 mm Hg, and multiple punctures were performed in the fibrous capsule surrounding the glaucoma implant, with subconjunctival injection of mitomycin-C (0.02% × 0.01 mL). Lateral tarsorrhaphy was also performed for a persisting epithelial defect. In March 1999, when the child was 2 years and 2 months old, the mass lesion had recurred in the right eye. The mass in the left eye had regressed spontaneously. However, the left cornea was hazy. In April 1999, at the age of 2 years and 3 months, limbal stem cell transplantation and penetrating keratoplasty were performed in the left eye, in another center. Postoperative trauma by the child's finger resulted in wound dehiscence, necessitating resuturing of the graft–host junction. Final examination in August 1999 at the age of 2 years and 7 months old showed a large, brown mass protruding from the right cornea and preventing closure of the eyelids (Fig. 6). The left eye showed a failed graft.

PAX6 gene mutation analysis using a standardized method, same as that in our previous publication,[11] was also performed for the patient.

DISCUSSION

The pathogenesis of corneal keloids remains obscure. Earlier theories suggested that they originated from the stromal cells of the iris or from proliferating fibrovascular tissue during the healing stage of corneal perforation.[4] Because corneal perforation is unlikely in congenital corneal keloids, failure of normal differentiation of corneal tissue during embryogenesis, rather than an abnormal reparative process, has been proposed as the mechanism in a recent report.[7]

The clinical appearance of a protuberant, firm, white or brownish, vascularized corneal mass in an infant suggests a differential diagnosis of a keloid or corneal dermoid. A corneal dermoid is a choristoma composed of displaced epithelial and dermislike elements interspersed with hair follicles and sebaceous glands.[12] None of the above features were present in our patient. Histopathologic examination of the excised corneal mass in the right eye did not show the characteristic features of juvenile xanthogranuloma[13] or fibrous histiocytoma[14] of the cornea. Although the lesion recurred after multiple excisions, neither the clinical appearance nor the histopathologic features suggested a malignant lesion.

The histopathologic features described in our patient—thickened, keratinized epithelium, absence of Bowman's layer, fibrovascular hyperplasia, and absence of displaced dermal elements—have been considered pathognomonic of a corneal keloid.[1–7] The tendency of a corneal keloid to recur and grow larger after each excision has also been described.[15]

Management of the lesion by multiple penetrating keratoplasties in the right eye proved unsatisfactory. Repeated epithelial break-

FIG. 3. Ultrasound biomicroscopic appearance of the right eye showing a thickened cornea **(A)**, iridocorneal touch at multiple sites **(B)**, and poorly defined angle anatomy **(C)**.

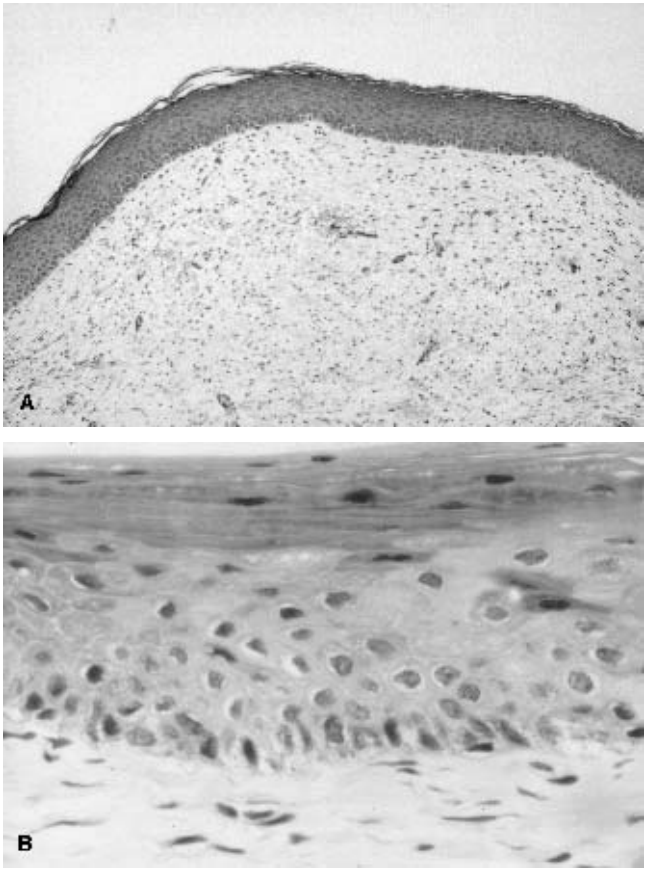


FIG. 4. A: Light microscopy of the mass (hematoxylin and eosin stain) showing thickened keratinized corneal epithelium, misalignment of keratocytes, disorganized connective tissue elements, and fibrovascular proliferation (original magnification, ×100). **B:** Pigment in the basal epithelial cells with absence of Bowman's layer (original magnification, ×400).

down leading to graft failure suggested a possible limbal stem cell deficiency. This is possible considering the extensive anterior segment malformations seen in our patient. Although he underwent limbal stem cell transplantation in the left eye at the time of penetrating keratoplasty, ocular trauma in the postoperative period resulted in graft failure and did not allow evaluation of the efficacy of this approach. An earlier report[16] described encouraging results with sclerokeratoplasty in tectonic reconstruction of such eyes, although the visual prognosis remains guarded because of associated ocular abnormalities and amblyopia. Failure of the keloid to recur after this surgical approach may be the result of complete excision of the lesion. In contrast, penetrating keratoplasty in the initial few months after birth may result in a recurrence of the keloid, as seen in the right eye of our patient. It is interesting that the keloid in the left eye, which did not undergo surgery, regressed spontaneously.

An increased frequency of ocular complications in RTS has led authorities to recommend routine ophthalmologic examination in all patients with RTS.[17] A recent comprehensive review of clinical findings in 614 patients with RTS showed the presence of glaucoma in 32 cases and corneal opacities in 25 cases.[10] The authors concluded that the incidence of glaucoma in RTS exceeds that of the general population and is often congenital or develops in infancy. However, they did not report the occurrence of ASMD in these patients. In this and other reports of congenital[18] and juvenile glaucoma[13,19] in RTS, authors describe a well-formed anterior chamber with a high, flat iris insertion. Features of ASMD were noted in both eyes of our patient on ultrasound biomicroscopic examination. These findings were confirmed by intraoperative visualization of the iris, lens, and corneal relationships during penetrating keratoplasty in the right eye. The role of ultrasound biomicroscopy in characterizing anterior segment changes in patients with dense corneal opacities has been described.[14] ASMD is thought to result from faulty migration of neural crest cells during embryogenesis.[20] Although a number of distinct entities, Axenfeld, Peter, and Reiger anomalies, have been described in ASMD, there is often considerable overlap in the clinical features.[21] The findings in our patient suggested a diagnosis of Peter anomaly in both eyes.

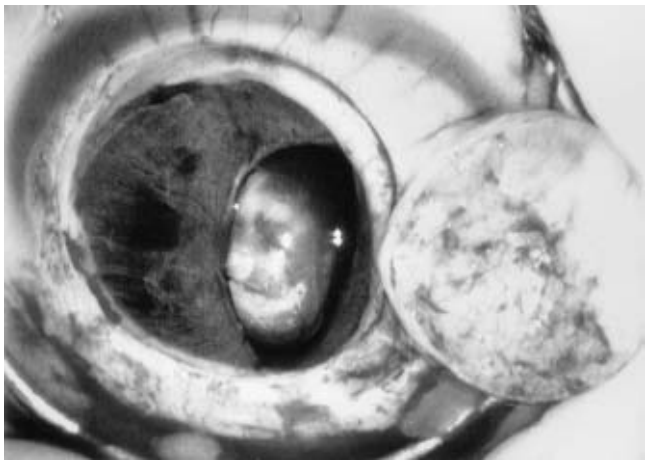


FIG. 5. Intraoperative photograph of the right eye after excision of the corneal button, showing iris changes, distorted pupil, and cataract.

There have been three reports of patients with ASMD who were reported to have small deletions in the short arm of chromosome 11.[22–24] *PAX6* mutation analysis, however, was performed in only one study.[23] The *PAX* genes are thought to function as major controllers in development by switching on and off expression of other genes. Nine *PAX* genes have been identified in humans, and

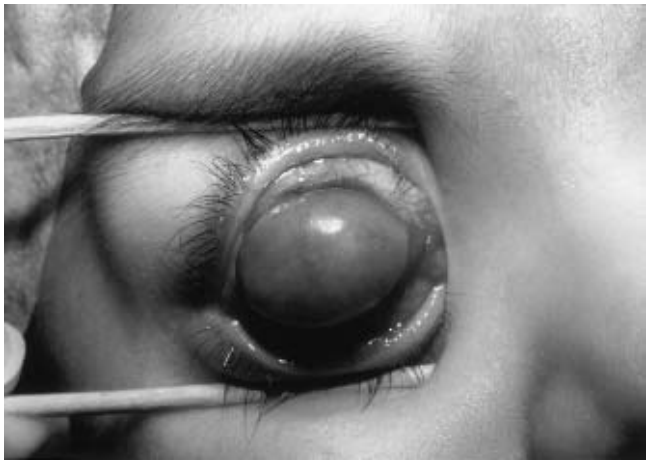


FIG. 6. Aggressive recurrence of keloid in the right eye.

PAX6 is thought to be located on the short arm of chromosome 11.[21] Other evidence from studies in mice also suggests that Peter anomaly, and possibly Reiger anomaly, may result from loss of function of *PAX6*.[23] Thus, although the genetics of ASMD are still being worked out, existing evidence suggests a role for *PAX6* in the cause of this disorder.[21] We looked for, but did not detect, *PAX6* mutation in our patient. Genetic changes in RTS have been localized to the short arm of chromosome 16.[25,26] We are unable to offer a satisfactory explanation for the co-occurrence of these lesions with RTS.

In conclusion, we report hitherto undescribed anterior segment changes in RTS. The clinical course in our patient confirms earlier reports[6] that children with RTS undergo hospitalization and surgery 10 times more often than other children. Our experience also indicates that subtotal excision of a corneal keloid, especially in infants, can result in aggressive recurrence of the corneal lesion.

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