Case report

Are iris mammillations correlated with keratoconus?

Rosalia M.S. Antunes-Foschini, Roberta Martins S. Costa, Sidney Júlio Faria-e-Sousa, Eduardo Melani Rocha

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ABSTRACT

Purpose: To describe the presence of iris mammillations (IM) in keratoconus. Design: Retrospective case series and literature review.

Observations: This is a retrospective case series of eight patients presenting with keratoconus and IM, who were examined between January 2016 and December 2017 in the ophthalmology outpatient clinic. They had a median age of 14 (11 – 30), and all had bilateral keratoconus and diffusely distributed IM. The IM had similar presentations and similar iris colors. None had relevant medical or family diseases associated with IM. Three eyes previously had penetrating keratoplasty. Four (31%) out of 13 eyes had mean keratometry (Km) > 55D, and 4 (31%) had the thinnest pachymetry between 300 and 400μm.

Conclusions and importance: To the best of our knowledge, this is the first time that IM was observed in association with keratoconus patients. The possibility that IM is an early finding in otherwise healthy patients may help to predict the future diagnosis of keratoconus. Future studies are needed to show the frequency and possible association between IM and a keratoconus prognosis. This may also demonstrate that there is a subgroup of patients with a distinct etiology of keratoconus.

1. Introduction

Keratoconus is a corneal ectasia which leads to progressive stromal thinning and protrusion, resulting in irregular astigmatism, visual impairment, and decreased quality of life, with a prevalence of approximately 1:2000, with varying susceptibilities in different ethnic groups. The progression of keratoconus occurs more intensely in the second and third decades of life and is more aggressive at puberty. Its etiology is multifactorial, involving genetic and environmental factors.

Concerning corneal changes, increases in central epithelial thickness, breaks in Bowman's layer, and deformities of Descemet's are prevalent, as well as dramatic changes in collagen fibrils at the apex of the cone were previously described. In addition, many iris abnormalities have been described in keratoconus patients, such as lower tissue resistance during iridotomy, decreases in iris thickness, and iridoschisis.

Iris mammillations (IM) are described as multiple verrucous excrescences, or small elevations, distributed diffusely on the anterior iris surface bilaterally. They have been described previously as iris nodular nevi, or as a dotted Swiss iris, with a clear familial involvement. They are seen in association with various ocular conditions, such as ocular melanosis, oculodermal melanosis associated with uveal melanoma, congenital cataract, neurofibromatosis, congenital ptosis, and other similar ocular conditions. In addition, they have been associated with Cowden's syndrome and congenital adrenal hyperplasia. The goal of this case series is to first describe patients who concomitantly present with keratoconus and IM.

2. Findings

The study was approved by the local Ethics Committee and followed the tenets of the Declaration of Helsinki. A spontaneous and continuous observation of keratoconus patients with IM, who were currently under the care of a corneal ambulatory clinic in Hospital das Clínicas, Medical School of Ribeirão Preto, University of São Paulo, was recorded by a unique examiner (RAF). They were carefully examined with a slit lamp, and the following aspects of the iris of each patient were described: color, IM distribution along the iris surface, laterality, and the presence of iris nevi. Microscopic color photographs were taken at a 16X or 25X magnification. Corneal tomography images were obtained using the
principle of Scheimpflug (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). Best-corrected visual acuity (BCVA), mean (Km) and maximum keratometry (Kmax), medical history, family history of keratoconus, and corneal tomographic parameters were obtained from a review of their medical records. At least one of their eyes had not been surgically treated. A literature review was also undertaken.

Case 1: A 14-year-old white girl (Figs. 1–3), with best corrected visual acuity (BCVA) logMAR 0.5, mean keratometry (Km) 49.1, maximum keratometry (Kmax) 62.3 and thinnest pachymetry (Pachy) 457 μm in the right eye (RE). She presented with iris nevi (Figs. 1–3) and had a prior penetrating keratoplasty in the left eye (LE). He had a family history of keratoconus.

Case 2: A 20-year-old white man (Figs. 1–2), with BCVA logMAR 0.4, Km 49.4, Kmax 60.3 and Pachy 428 μm in the RE and BCVA logMAR > 1.0, Km 57.6, Kmax 65.4 and Pachy 385 μm in the LE. He had a family history of keratoconus.

Case 3: A 14-year-old mulatto boy (Figs. 1–3), with BCVA logMAR 0.2, Km 56.2, Kmax 69 and Pachy 393 μm in the RE. His LE BCVA was logMAR 0.3, Km 51.2, Kmax 61.2 and Pachy 342 μm. He presented with iris nevi and had a prior corneal cross-linking procedure in the LE.

Case 4: A 14-year-old white girl (Figs. 1–4), whose BCVA on the RE was logMAR 0.9, Km 50.6, Kmax 54.8 and Pachy 513 μm. The BCVA in the LE was logMAR 0.0, Km 42.4, Kmax 46.3 and Pachy 579. She presented a pre-papillary membrane and an iris shape that resembled iris atrophy (Figs. 1–4).

Case 5: A 30-year-old white man (Figs. 1–5), who had a prior penetrating keratoplasty in the RE. His BCVA in the LE was logMAR 0.2, Km 51.7, Kmax 69.1 and Pachy 483 μm.

Case 6: A 11-year-old white boy (Figs. 1–6), with BCVA logMAR 0.4, Km 50.4, Kmax 63.0 and Pachy 477 μm in the RE and BCVA logMAR 0.2, Km 50.6, Kmax 63.8 and Pachy 482 μm in the LE. He had previous history of ocular atopy and blepharitis and a prior corneal cross-linking procedure in the RE.

Case 7: A 12-year-old japanese boy (Figs. 1–7), with BCVA logMAR 0.1, Km 46.5, Kmax 49.5 and Pachy 537. The LE BCVA was logMAR 0.4, Km 60.3, Kmax 75.1 and Pachy 412 μm.

Case 8: A 18-year-old black woman (Figs. 1–8), with a prior penetrating keratoplasty in the RE. Her LE had a BCVA of 0.2, Km 69.2, Kmax 81.4 and Pachy 341 μm. She was a rigid contact lenses user.

All of the patients had brown colored irises and bilateral IM, which appeared to be more visible in the upper half of the iris. Seven patients, except for patient 3, had diffusely but relatively uniformly distributed IM. Patient 3 had sparse and more pigmented IM (Figs. 1–3). Funduscopy was unremarkable in all patients.

3. Discussion

To the best of our knowledge, this is the first description of IM in keratoconus patients. Six out of 8 are pediatric patients, and 3 out of 8 had a penetrating keratoplasty, suggesting that these patients have a more aggressive form of the disease.

The etiology of IM and their clinical implications are not clear. As in keratoconus, they can occur sporadically or in familial cases.11,13 The differential diagnosis of IM include all conditions which present with superficial elevations or iris irregularities, such as neurofibromatosis type 1, in which Lisch nodules16,17 are observed, melanoma Tapioca, a rare tumor18 that may present as single or multiple lightly pigmented nodules in the iris, and Cogan-Reese syndrome that presents with iris nevus.19 The differential diagnosis20–22 of IM are displayed in Table 1.

Iris mammillations also have been described in association with other ocular disorders such as bilateral congenital cataract, uveal or dermal melanocytosis, congenital ptosis, Axenfeld and Peters anomaly.11 Similarly, other ocular disorders were already associated with keratoconus, such as posterior polymorphous dystrophy with iris heterochromia and band keratopathy,23 nanophthalmos and pigmentary retinopathy,24 and was also seen in a patient with Noonan syndrome.25 It is interesting that both keratoconus and IM were already associated with anterior segment abnormalities.11,23,24 The presence of IM and other different iris features, such as iris atrophy, associated with other signs of anterior segment malformations, may reinforce the idea that there may be a common genetic pathway which explains both alterations, probably based on extracellular matrix proteins fragility.

Future studies are needed to look for a correlation between keratoconus and IM, as well as other iris abnormalities that may not have been observed during routine examination. This may help to understand the natural history, prognosis, various etiologies, and known conditions associated with keratoconus.

Patient consent

This case series is a retrospective review and had the approval of our local Ethics Committee, and patient consent was not required.

Conflicts of interest

The following authors have no financial disclosures: RA-F, RMSC, SJFS, EMR.

Authorship

Authors attest that they meet the current ICMJE criteria for Authorship.

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**Table 1**

**Differential diagnosis of iris mammillations.**

| Iris mammillations           | Morphology/Localization                                                                 | Clinical features                                                                 |
|------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Iris mammillations           | Multiple verrucous excrescences, or small elevations, distributed diffusely on the anterior iris surface. Usually bilateral. | May be associated with anterior segment malformation. |
| Lisch nodules                | Fluffy texture. Brown colored in blue or green iris and pale in brown iris. Irregularly placed. | Systemic stigmata of neurofibromatosis (cutaneous and central nervous system lesions). |
| Granulomatous iridocyclitis  | Nodules features are widely variable, differing among etiologies (sarcoidosis, infectious, Fuchs'iridocyclitis). | Anterior chamber cells, flare, and hypopyon. Iris dyscoria and posterior uveitis may be present. |
| Juvenile xanthogranuloma     | Nodular, well-circumscribed, thickened, orange-colored mass. Diffuse: thin coating or film, blunting the normal iris crypts. Unilateral. | Presentation in early childhood. Iris, hyphema, secondary glaucoma, neovascularization. May present characteristic skin lesions. |
| Coogan Reese syndrome        | Pigmented, pedunculated nodules surrounded by flat iris stroma, loss of the normal iris architecture. Unilateral. | Peripheral anterior synechiae, dyscoria, iris atrophy and glaucoma. |
| Iris solid tumors            | Tapioca melanoma: Lightly pigmented multiple nodules or irregular large single nodules. Randomly situated (multiple) or inferior situated (single). Melanoma: Usually in inferior quadrant. Nevus: Usually in inferior quadrant. | Rare (1% of melanocytic iris tumors). Slow grow pattern. Glaucoma in 1/3 of patients. |
| Iris cyst                    | Primary: Single or multiple. Regular borders, smooth surface, thin wall, clear fluid content. Usually unilateral (90%), at mid zonal iris (adults) and pupillary margin (children). Secondary: Usually solitary, thick walls, irregular borders and surface, distortion of iris architecture. Unilateral, any local in iris surface. | Rare (4% of uveal melanoma). Primarily in the Caucasian population. Most frequent (60%) melanocytic iris tumor. Low risk for growth into melanoma. Largely asymptomatic, non-progressive. Unusual. History of trauma, surgery, inflammation. Extension occurs over cornea, iris and lens. Iris bombe, secondary glaucoma, iritis, complicated cataracts. |

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