American Journal of Ophthalmology Case Reports 14 (2019) 16–18

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc

Case report

Are iris mammillations correlated with keratoconus?

Rosalia M.S. Antunes-Foschini[a,*], Roberta Martins S. Costa[b], Sidney Júlio Faria-e-Sousa[c], Eduardo Melani Rocha[c]

[a] Hospital das Clínicas, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil
[b] Centro de Saúde Escola, University of São Paulo, Ribeirão Preto, SP, Brazil
[c] Department of Ophthalmology, Otorhinolaryngology, and Head and Neck Surgery, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

ARTICLE INFO

Keywords:
Keratoconus
Cornea
Iris

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.[1] The progression of keratoconus occurs more intensely in the second and third decades of life and is more aggressive at puberty.[2,3] Its etiology is multifactorial, involving genetic and environmental factors.[4]

Concerning corneal changes, increases in central epithelial thickness, breaks in Bowman's layer, and deformities of Descemet's are prevalent,[5] as well as dramatic changes in collagen fibrils at the apex of the cone[6] were previously described. In addition, many iris abnormalities have been described in keratoconus patients, such as lower tissue resistance during iridotomy,[7] decreases in iris thickness,[8] and iridoschisis.[9]

Iris mammillations (IM) are described as multiple verrucous excrescences, or small elevations, distributed diffusely on the anterior iris surface bilaterally.[10] They have been described previously as iris nodular nevi,[11] or as a dotted Swiss iris,[12] with a clear familial involvement.[11–13] They are seen in association with various ocular conditions, such as ocular melanosis,[10] oculodermal melanosis associated with uveal melanoma,[14] congenital cataract, neurofibromatosis, congenital ptosis, and other similar ocular conditions.[11] In addition, they have been associated with Cowden's syndrome[11,15] and congenital adrenal hyperplasia.[13] 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

* Corresponding author. Departamento de Oftalmologia, Otorrinolaringologia e Cirurgia de Cabeça e Pescoço, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes, 3900, Ribeirão Preto, SP, CEP 14049-900, Brazil.
E-mail addresses: antunesfoschini@gmail.com, rmsantunes@hcrp.usp.br (R.M.S. Antunes-Foschini).

https://doi.org/10.1016/j.ajoc.2019.01.011
Received 16 May 2018; Received in revised form 6 July 2018; Accepted 22 January 2019
Available online 02 February 2019
2451-9936/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

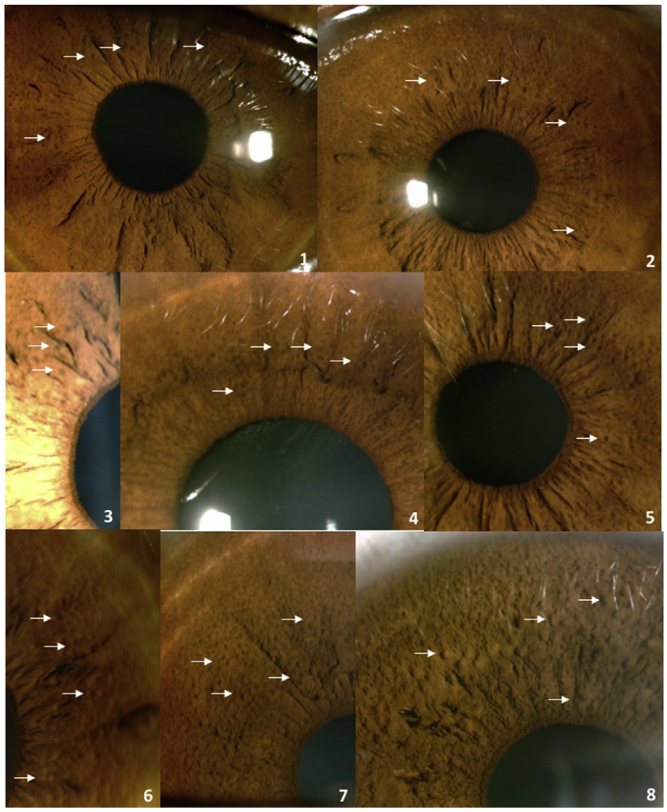

Fig. 1. Patients 1 to 8. The images were obtained during slit lamp microscopy and show diffusely distributed IM. White arrows indicate these structures in all photographs.

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–), with best corrected visual acuity (BCVA) logMAR 0.5, mean keratometry (Km) 49.1, maximum keratometry (Kmax) 62.3 and thinnest pachymetry (Pachy) 457μm in the right eye (RE). She presented with iris nevi (Figs. 1–) and had a prior penetrating keratoplasty in the left eye (LE).

Case 2: A 20-year-old white man (Figs. 1–2), with BCVA logMAR 0.4, Km 49.4, Kmax 60.3 and Pachy 428μm in the RE and BCVA logMAR > 1.0, Km 57.6, Kmax 65.4 and Pachy 385μm 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 393μm in the RE. His LE BCVA was logMAR 0.3, Km 51.2, Kmax 61.2 and Pachy 342μm. 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 513μm. The BCVA in the LE was logMar 0.0, Km 42.4, Kmax 46.3 and Pachy 579. She presented a pre-pupillary 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 483μm.

Case 6: A 11-year-old white boy (Figs. 1–6), with BCVA logMAR 0.4, Km 50.4, Kmax 63.0 and Pachy 477μm in the RE and BCVA logMAR 0.2, Km 50.6, Kmax 63.8 and Pachy 482μm 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 412μm.

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 341μm. 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). Fundoscopy 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 nodules[16,17] are observed, melanoma Tapioca, a rare tumor[18] 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 diagnosis[20–22] of IM are displayed in Table 1.

Iris mammillations also have been described in association with other ocular disorders such as bilateral congenital cataract, oculodermal 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.

Funding

No funding.

Table 1
Differential diagnosis of iris mammillations.

		Morphology/Localization	Clinical features
Iris mammilations		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. Iritis, 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).	Rare (1% of melanocytic iris tumors). Slow grow pattern. Glaucoma in 1/3 of patients.
	Melanoma	Usually in inferior quadrant.	Rare (4% of uveal melanoma). Primarily in the Caucasian population.
	Nevus	Usually in inferior quadrant.	Most frequent (60%) melanocytic iris tumor). Low risk for growth into melanoma.
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).	Largely asymptomatic, non-progressive. Unusual.
	Secondary	Usually solitary, thick walls, irregular borders and surface, distortion of iris architecture. Unilateral, any local in iris surface.	History of trauma, surgery, inflammation. Extension occurs over cornea, iris and lens. Iris bombé, secondary glaucoma, iritis, complicated cataracts.

Acknowledgments

None.

References

1. McGhee CNJ, Kim BZ, Wilson PJ. Contemporary treatment paradigms in keratoconus. *Cornea.* 2015;34:S16–S23.
2. Hamilton A, Wong S, Carley F, Chaudhry N, Biswas S. Tomographic indices as possible risk factors for progression in pediatric keratoconus. *J AAPOS.* 2016;20:523–526.
3. Fujimoto H, Maeda N, Shintani A, et al. Quantitative evaluation of the natural progression of keratoconus using three-dimensional optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2016;57:OCT169–175.
4. McGhee CN, Kim BZ, Wilson PJ. Contemporary treatment paradigms in keratoconus. *Cornea.* 2015;34(Suppl 10):S16–S23.
5. Sykakis E, Carley F, Irion L, Denton J, Hillarby MC. An in depth analysis of histopathological characteristics found in keratoconus. *Pathology.* 2012;44:234–239.
6. Meek KM, Tuft SJ, Huang Y, et al. Changes in collagen orientation and distribution in keratoconus corneas. *Invest Ophthalmol Vis Sci.* 2005;46:1948–1956.
7. Sadoughi MM, Roshandel D, Rezaei J, Einollahi N, Einollahi B. Clinical evidence of decreased Iris resistance in patients with keratoconus. *Cornea.* 2016 Jul;35(7):967–971. https://doi.org/10.1097/ICO.0000000000000878.
8. Bonfadini G, Arora K, Vianna LM, et al. Quantitative analysis of iris parameters in keratoconus patients using optical coherence tomography. *Arq Bras Oftalmol.* 2015;78:305–309.
9. Eiferman RA, Law M, Lane L. Iridoschisis and keratoconus. *Cornea.* 1994;13:78–79.
10. Coats D. Unilateral diffuse melanosis of the uvea, with small elevations on the surface of the iris. *Trans Ophthalmol Soc U K.* 1912;32:165–171.
11. Ticho BH, Rosner M, Mets MB, Tso MO. Bilateral diffuse iris nodular nevi. Clinical and histopathologic characterization. *Ophthalmology.* 1995;102:419–425.
12. Joondeph BC, Goldberg MF. Familial iris melanosis–a misnomer? *Br J Ophthalmol.* 1989;73:289–293.
13. Peyman M, Ong MJ, Iqbal T, Subrayan V. Iris mammillations in two female siblings with congenital adrenal hyperplasia. *BMJ Case Rep.* 2010;2010.
14. Gunduz K, Shields CL, Shields JA, Eagle Jr RC, Singh AD. Iris mammillations as the only sign of ocular melanocytosis in a child with choroidal melanoma. *Arch Ophthalmol.* 2000;118:716–717.
15. Suaiti L, Al-Haseni A, Lee H, Sahni D. Iris mammillations in a pair of twins with Cowden syndrome. *JAAD Case Rep.* 2016;2:323–325.
16. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol.* 2014;13:834–843.
17. Swann PG. Iris mammillations in ocular melanocytosis. *Clin Exp Optom.* 2001;84:35–38.
18. Shields CL, Kancherla S, Patel J, et al. Clinical survey of 3680 iris tumors based on patient age at presentation. *Ophthalmology.* 2012;119:407–414.
19. Eagle Jr RC, Font RL, Yanoff M, Fine BS. The iris naevus (Cogan-Reese) syndrome: light and electron microscopic observations. *Br J Ophthalmol.* 1980;64:446–452.
20. Rao A, Gupta V, Bhadange Y, Sharma R, Shields JA. Iris cysts: a review. *Semin Ophthalmol.* 2011;26:11–22.
21. Samara WA, Khoo CT, Say EA, et al. Juvenile xanthogranuloma involving the eye and ocular adnexa: tumor control, visual outcomes, and globe salvage in 30 patients. *Ophthalmology.* 2015;122:2130–2138.
22. Myers TD, Smith JR, Lauer AK, Rosenbaum JT. Iris nodules associated with infectious uveitis. *Br J Ophthalmol.* 2002;86:969–974.
23. Blair SD, Seabrooks D, Shields WJ, Pillai S, Cavanagh HD. Bilateral progressive essential iris atrophy and keratoconus with coincident features of posterior polymorphous dystrophy: a case report and proposed pathogenesis. *Cornea.* 1992;11:255–261.
24. Sammouh FK, Baban TA, Warrak EL. A patient with keratoconus, nanophthalmos, lipodermoids, and pigmentary retinopathy. *Ophthalmic Genet.* 2016;37:228–232.
25. Lee A, Sakhalkar MV. Ocular manifestations of Noonan syndrome in twin siblings: a case report of keratoconus with acute corneal hydrops. *Indian J Ophthalmol.* 2014;62:1171–1173.