CASE REPORT

Bilateral Chandler Syndrome, Nanophthalmos, and Angle Closure Glaucoma: A Complex Presentation, Challenging Diagnosis, and Pathological Insight—A Case Report

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Abstract

Aim and background: Chandler syndrome (CS) is one of the iridocorneal endothelial syndromes (ICEs) with proliferation of abnormal corneal endothelial cells over the anterior chamber (AC) angle and iris, resulting in complications, for example, secondary angle closure glaucoma (SACG). We report an association between CS and nanophthalmos, highlighting diagnostic and therapeutic challenges and pathological insights.

Case description: A 46-year-old female patient presented with bilateral progressive blurring of vision. Examination revealed bilateral (OU) small corneal diameter, shallow AC, closed AC angle, beaten-bronze appearance of corneal endothelium, and mild iris atrophy in the right eye (OD). Intraocular pressure was 48 mm Hg and 22 mm Hg in the OD and left eye (OS), respectively. Fundus examination revealed optic nerve head cupping. Biometry showed short axial length and microcornea OU, that is, nanophthalmos. Optical coherence tomography and visual field revealed structural and functional evidence of glaucomatous optic neuropathy. Specular microscopy demonstrated reduction of corneal endothelial cell density and the light-dark reversal characteristic of ICE. Therefore, a diagnosis of CS with SACG and nanophthalmos was made. The patient was referred to a specialized glaucoma center with recommendation of clear lens extraction and a glaucoma drainage device with retropupillary tube placement.

Conclusion: This is the first report of an association between CS and nanophthalmos. It highlights the possibility of SACG despite evident risk factors for primary angle closure glaucoma (PACG). Furthermore, it provides a hypothesis about the etiology of ICE. The concurrence of CS and nanophthalmos suggests that a common developmental mechanism could be implicated since periocular mesenchyme, the embryological precursor of corneal endothelium, plays a role in the development of optic cup and stalk.

Clinical significance: SACG should be considered even in the presence of evident risk factors for PACG, such as nanophthalmos. Additionally, the association of nanophthalmos and CS warrants revisiting the yet inconclusive etiology of CS, where a developmental mechanism could be considered.

Keywords: Angle closure glaucoma, Case report, Chandler syndrome, Iridocorneal endothelial syndrome, Nanophthalmos.

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Introduction

Glaucoma is defined as a chronic progressive optic neuropathy characterized by progressive ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) loss, which manifests as optic nerve head (ONH) cupping, and results in progressive visual field (VF) constriction. Elevated intraocular pressure (IOP) is an important modifiable risk factor in glaucomatous optic neuropathy (GON). Glaucoma is classified according to the structural status of AC angle into angle closure glaucoma (ACG) and open angle glaucoma (OAG). ACG is characterized by iridocorneal apposition resulting in AC angle closure, which obstructs the trabecular meshwork (TM) that is the main outflow facility for the aqueous humor resulting in elevation of IOP.[1] ACG can be either primary or secondary. Primary angle closure (PAC) occurs in anatomically predisposed eyes with shallow AC, short axial length (AL), and hyperopia being major risk factors. Conversely, secondary angle closure (SAC) is caused by another ocular pathology, for example, anterior uveitis, uveal effusion.[2] ICE is among the rare causes of SAC, where abnormal proliferation of corneal endothelial cells over the AC angle and iris surface results in variable degrees of progressive angle closure.[3] In this report, we present a case of bilateral ACG secondary to CS, which is an ICE, in a patient with nanophthalmos. This case highlights the possibility of SACG in the presence of evident risk factors for PACG, like nanophthalmos. It also revisits the unsettled debate about the etiology of ICE, suggesting that a developmental mechanism may contribute to the pathogenesis of the condition. The association between nanophthalmos and CS together with the growing body of evidence about the role of periocular mesenchyme (POM) and neural crest cells (NCC) not only as precursors of corneal endothelial cells but also as

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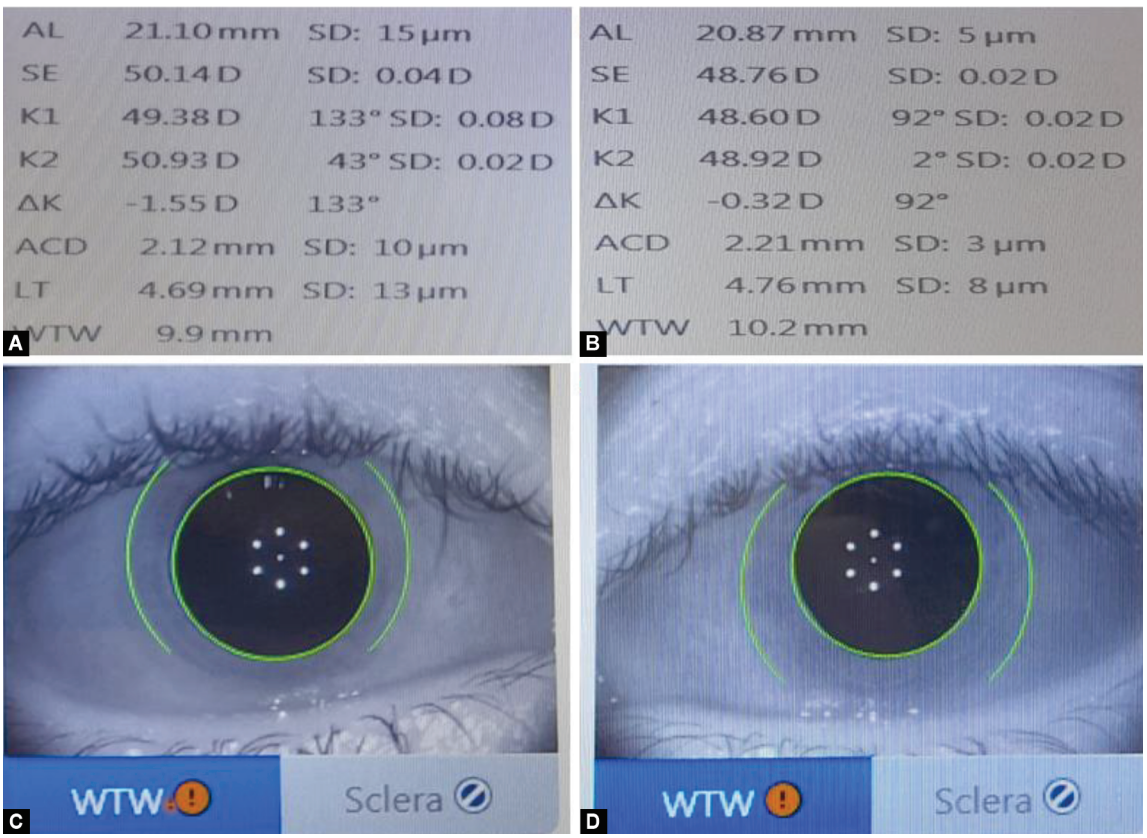
pivotal players in the development of optic cup and stalk,[4] all suggest that a developmental mechanism may contribute to the pathogenesis of ICE.

Case Description

A 46-year-old Caucasian female patient presented with a complaint of bilateral progressive blurring of vision that was more severe in the OD. The patient reported having been diagnosed with PACG 6 years earlier and had been on the topical ocular hypotensive medications dorzolamide-timolol and brimonidine since then. Clinical history was also positive for bilateral photorefractive keratectomy (PRK), which had been performed two years prior to presentation to correct farsightedness. Best corrected visual acuity (BCVA) was 6/24 and 6/9 with −0.50 and +0.50 diopter spherical equivalent in the OD and OS, respectively. Anterior segment examination revealed bilateral microcornea and shallow AC, which were confirmed by optical biometry besides bilateral corneal steepness and short AL (Figs 1A to D). Additionally, examination was remarkable for beaten-bronze appearance of corneal endothelium, which was more prominent OD. Also, there was mild temporal iris atrophy OD. IOP was 48 mm Hg OD and 22 mm Hg OS despite compliance to aforementioned ocular hypotensives. Gonioscopy demonstrated bilateral closed AC angle in all four quadrants with Schwalbe's line being the only visible angle structure (Shaffer grading 1). Fundus examination showed advanced ONH cupping OD and mild cupping OS. Optical coherence tomography of ONH (OCT-ONH), VF, specular microscopy, ultrasound biomicroscopy (UBM), and anterior segment optical coherence tomography (AS-OCT) were performed. OCT-ONH confirmed bilateral asymmetric ONH cupping, RNFL, and GCC thinning, which were more advanced OD (Fig. 2). VF demonstrated bilateral defects consistent with GON with double arcuate scotoma, extensive involvement of nasal hemifield OD and superior arcuate scotoma, nasal step, temporal wedge OS (Figs. 3A to D). UBM and AS-OCT both showed closed AC angle in all quadrants bilaterally (Figs 4A to D). Moreover, AS-OCT demonstrated the right temporal iris atrophy (Figs 5A and B). Furthermore, specular microscopy provided insightful data about the beaten-bronze corneal endothelial appearance. There was bilateral reduction in corneal endothelial cell density (CD), 882 and 1608 cells/mm^2, and increase in coefficient of variation (CV) 39 and 48 OD and OS, respectively. Also, the characteristic appearance of iridocorneal endothelial cells with light–dark reversal was clearly demonstrable, where the cell center and boundary appear bright while the remainder of the cell appears dark (Figs. 6A and B). The clinical signs of bilateral beaten-bronze endothelial appearance, mild iris atrophy OD together with the specular microscopy evidence of reduced CD and light–dark reversal of corneal endothelial cells corroborated a diagnosis of bilateral CS. Moreover, the high IOP, OCT-ONH evidence of cupping, RNFL, and GCC thinning, as well as the characteristic perimetric defects, were diagnostic of GON, which, in light of gonioscopic, UBM, and AS-OCT evidence of bilateral AC angle closure, constituted a diagnosis of bilateral ACG. The bilateral ACG was judged as secondary to CS



Figs 1A to D: Optical biometry of both eyes (OU) using ZEISS IOLMaster; axial length (AL), spherical equivalent (SE), flattest keratometric measurement (K1), steepest keratometric measurement (K2), steep-flat keratometry difference (Δ*K*), anterior chamber depth (ACD), lens thickness (LT), white to white diameter (WTW). (A, C) Optical biometry of the right eye (OD); (B, D) Optical biometry of the left eye (OS) showing small corneal diameter, steep cornea, short AL, and shallow ACD

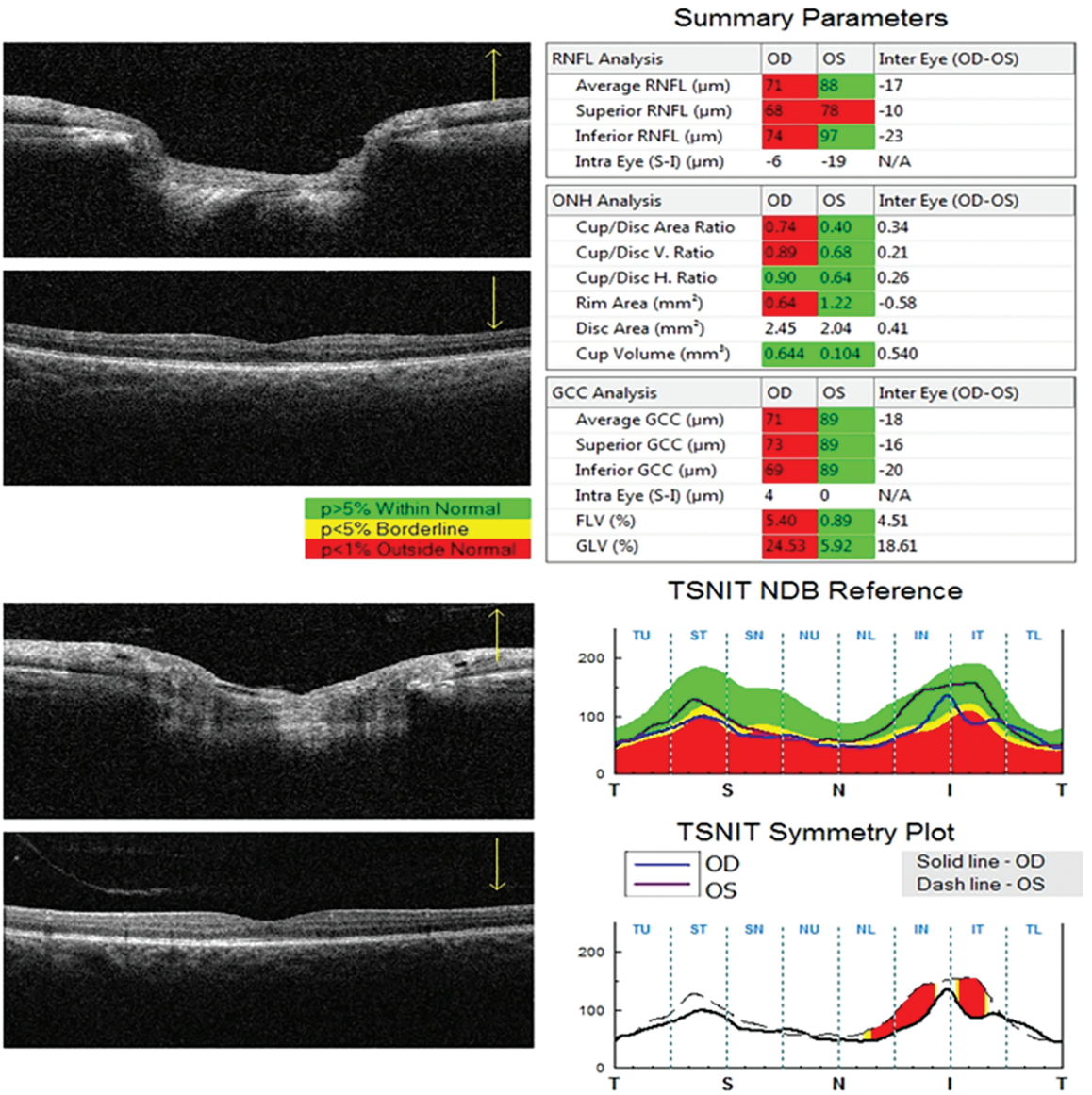
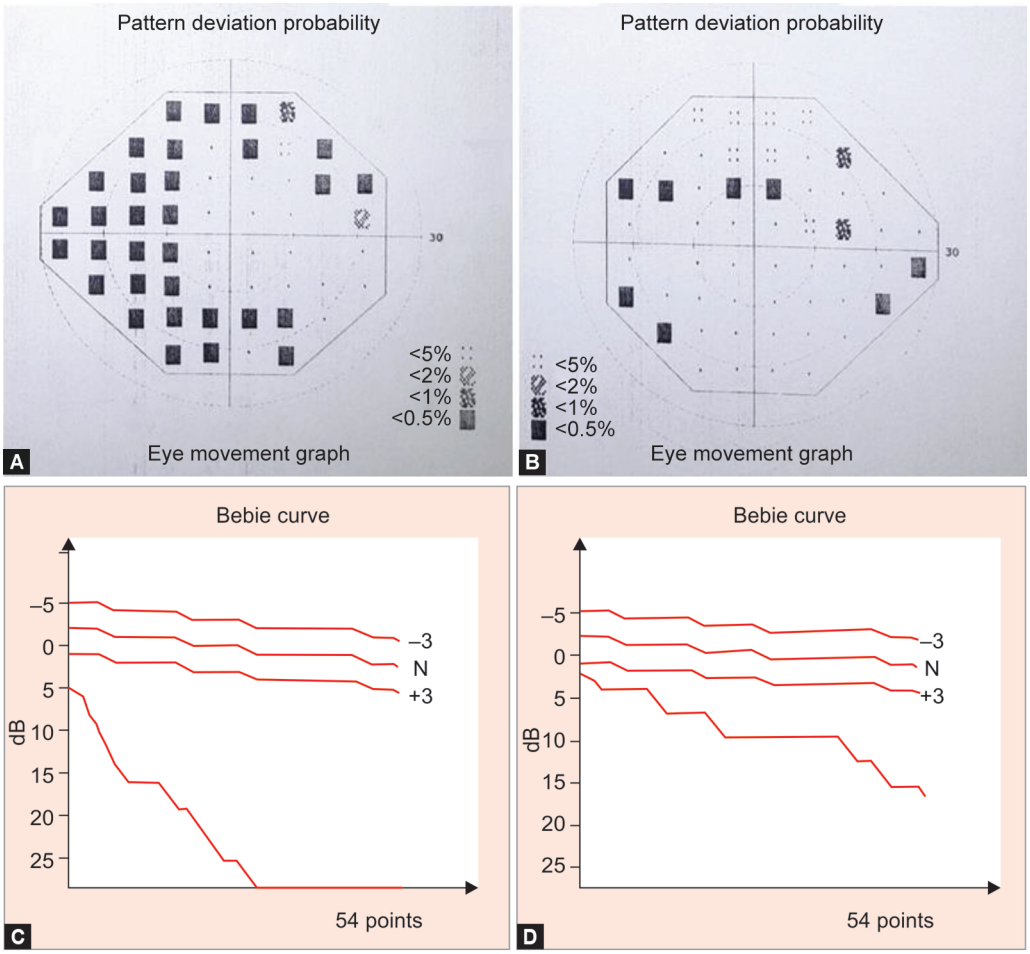


Fig. 2: Optical coherence tomography of optic nerve head (OCT-ONH) of both eyes (OU) using XR AVANTI Optovue; retinal nerve fiber layer (RNFL), ganglion cell complex (GCC). OCT-ONH shows advanced ONH cupping, RNFL and GCC thinning in the right eye (OD) compared to mild superior RNFL thinning in the left eye (OS)

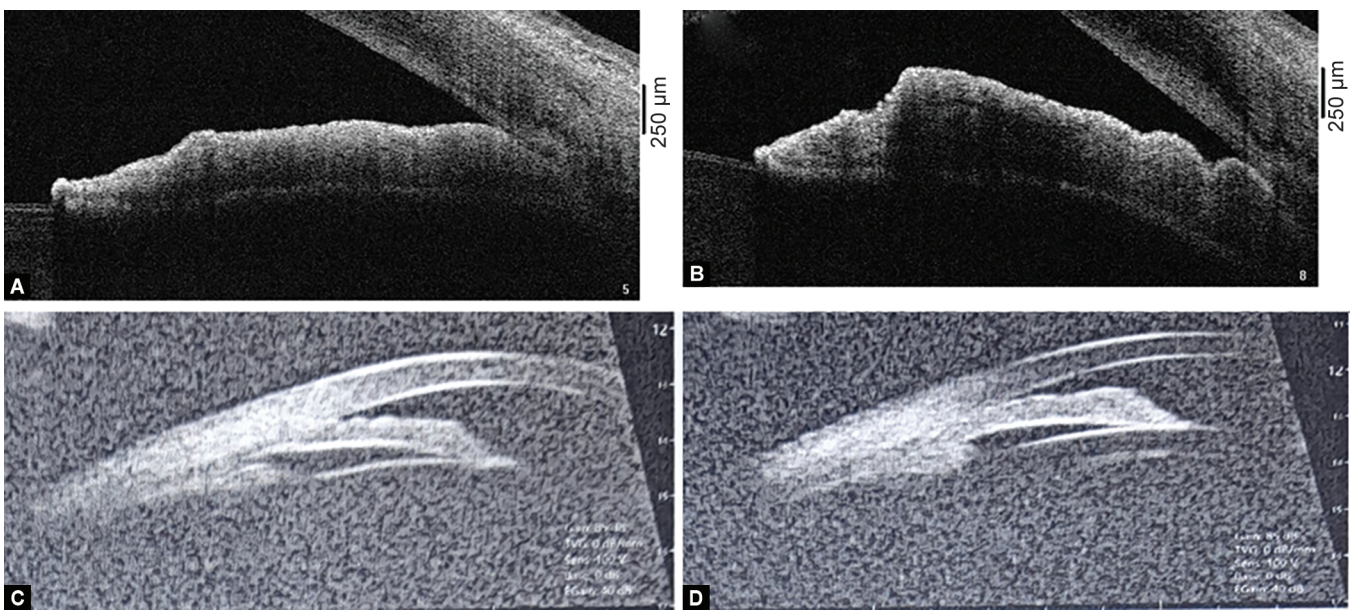
given the absence of history suggestive of acute attacks of PACG as well as the conspicuous lack of signs of acute or chronic PACG, for example, glaukomflecken, pigment deposits on the back of cornea, pigment smudging of AC angle, focal iridocorneal synechiae. Moreover, the severity of glaucoma correlated to the severity of CS with more advanced glaucoma, more severe corneal endothelial changes, and iris atrophy OD compared to OS despite similar AC and AL measurements as well as identical gonioscopic, AS-OCT, and UBM AC angle morphology. Since IOP was poorly controlled, topical prostaglandin, that is, travoprost, was added which nevertheless failed to achieve target IOP. Systemic carbonic anhydrase inhibitor, that is, acetazolamide, was added as a temporizing measure with the lowest recorded IOP being 30 mm Hg OD and 20 mm Hg OS. The patient was referred to a specialized glaucoma center with a recommendation to perform clear lens extraction and implantation of a glaucoma drainage device with retropupillary tube placement. Glaucoma drainage devices have been shown to provide better long-term success in ICE-related glaucoma compared to trabeculectomy with antimetabolites.[5] Furthermore, retropupillary tube placement would decrease the potential detrimental effect of the tube on the already compromised corneal endothelium.

Discussion

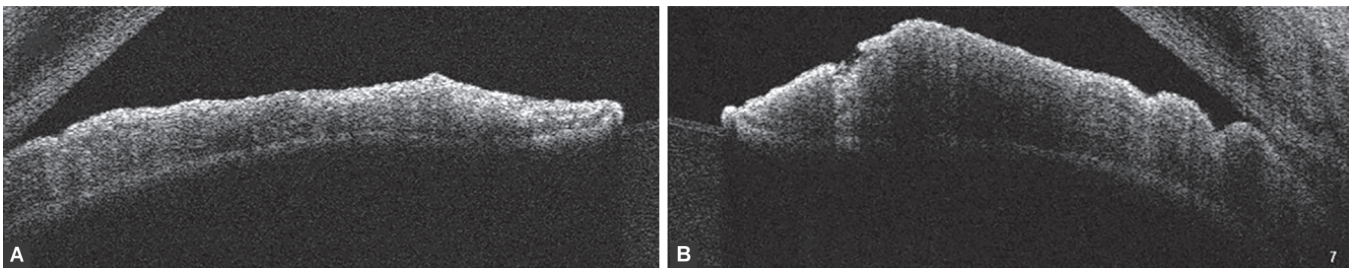
In this report, we present an unusual case of bilateral SACG complicating CS in a patient with nanophthalmos. Such a complex constellation constituted a diagnostic challenge. Prior to presenting to our clinic, the patient was misdiagnosed as PACG. We suggest that this faulty diagnosis was the result of a rather cursory anterior segment examination where the subtle signs of CS, that is, beaten-bronze endothelial appearance and mild iris atrophy, were missed. Moreover, the associated microcornea and nanophthalmos, which are well-established risk factors for PACG due to shallow AC and occludable angle, may have encouraged such a diagnosis.[2,6] The



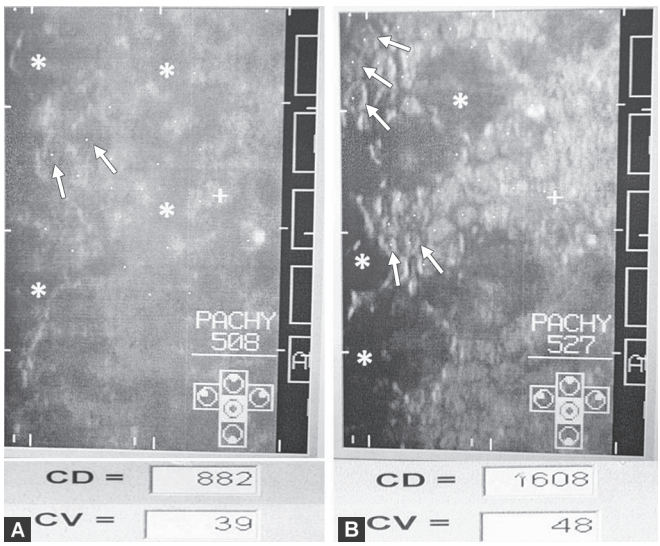
Figs 3A to D: Automated perimetry of both eyes (OU) using OPTOPOL Technology Sp. Z 0.0. (A, C) Automated perimetry (pattern deviation probability and Bebie curve) of the right eye (OD) showing double arcuate scotoma and extensive involvement of nasal hemifield; (B, D) Automated perimetry (pattern deviation probability and Bebie curve) of the left eye (OS) showing superior arcuate scotoma, nasal step, and temporal wedge



Figs 4A to D: Anterior segment optical coherence tomography (AS-OCT) using XR AVANTI Optovue and ultrasound biomicroscopy (UBM) using Sonomed Escalon of both eyes (OU). (A) AS-OCT of nasal quadrant of anterior chamber angle (OD); (B) AS-OCT of temporal quadrant of anterior chamber angle (OS); (C) UBM of the temporal quadrant of anterior chamber angle (OD); (D) UBM of the nasal quadrant of anterior chamber angle (OS) showing iridocorneal apposition and closed angle



Figs 5A and B: Anterior segment optical coherence tomography (AS-OCT) using XR AVANTI Optovue of both eyes (OU). (A, B) AS-OCT showing marked thinning and atrophy of temporal iris in the right eye (OD) (A) compared to the left eye (OS) (B)



Figs 6A and B: Specular microscopy of both eyes (OU) using Konan Noncon specular microscope; specular microscopy of the right eye (OD) (A) and left eye (OS) (B) showing marked decrease in corneal endothelial cell density (CD) and increase in coefficient of variation (CV), white asterisks* represent areas of corneal endothelial cell loss, white arrows point to the light-dark reversal of corneal endothelial cells characteristic of iridocorneal endothelial syndrome (ICE)

differentiation between PACG and CS-related SACG is essential because each entails different management and prognosis. While PACG often benefits from peripheral iridotomy and lens extraction, which both serve to widen the AC angle and prevent pupillary block, CS-related SACG is less likely to benefit from either procedure due to the different underlying pathology where angle closure is irreversible or synechial, secondary to abnormal endothelial cell proliferation and migration over the trabeculum and iris, rather than reversible and appositional.[2,3] Therefore, CS-related SACG is often refractory and requires surgical intervention, for example, trabeculectomy or glaucoma drainage device, more frequently than PACG.[3] In addition to this diagnostic challenge, this case report sheds light on the contentious subject of etiology and pathogenesis of ICE. Three clinical forms of ICE have been described in literature, that is, CS, Cogan–Reese syndrome (CRS), and essential iris atrophy (EIA). CS is the most common of the three forms and is characterized by prominent corneal changes, that is, beaten-bronze endothelial appearance, corneal edema, and mild involvement of the iris, which can sometimes appear normal. It is also more often unilateral and more common in middle-aged females. However, some reports exist of bilateral cases of CS.[7,8] Conversely, CRS, which is also known as iris nevus syndrome, as its name clearly suggests, manifests as iris nodules of variable sizes and shapes ranging from yellowish to dark brown in color resembling iris nevi. In contrast to CS, EIA demonstrates severe iris involvement with pseudopolycoria and iris transillumination together with broad-based iridocorneal adhesions that result in synechial angle closure.[6,9] Despite the existence of three clinically distinct forms of ICE, they all have been attributed to the same pathogenic process of abnormal proliferation and structural alterations of corneal endothelial cells which acquire epithelial features and migrate over AC angle and iris surface with secondary membrane formation, contraction, and variable degrees of scarring resulting in the characteristic clinical signs as well as complications.[10,11] While the exact trigger of abnormal corneal endothelial behavior remains unknown, some studies demonstrated higher prevalence of herpes simplex virus deoxyribonucleic acid (HSV-DNA) in aqueous humor of patients with ICE. Interestingly, patients with unilateral ICE were positive for HSV-DNA only in the affected eye. However, a significant percentage of ICE patients were negative for HSV-DNA, which means that such a hypothesis is not sufficient to explain all cases of ICE. Moreover, the hypothesis, despite demonstrating an association, did not establish a definitive causality.[12,13] In this case report, the association between CS and nanophthalmos bilaterally raises the possibility of a common developmental etiology. This hypothesis is plausible given the fact that corneal endothelial cells originate from the POM and NCC which, at the same time, play an important role in optic cup and stalk development through multiple hypothesized molecular cascades involving the interplay of myriad genes.[4] *PITX* is one such example of a gene that was implicated in both corneal endothelial abnormalities as well as nanophthalmos constituting one potential common developmental basis for both conditions.[4,14] Moreover, an interesting observation is that each of the three clinical forms of ICE, that is, CS, CRS, and EAI, has its analogous developmental form, that is, posterior polymorphous corneal dystrophy (PPCD), ocular melanocytosis with iris mammillations, and Axenfeld–Rieger anomaly (ARA), respectively.[6] In CS and PPCD, corneal endothelial cells acquire epithelial features like filopodia, microvilli, increased expression of cytokeratin, and multilayer cellular organization.[10,15–17] On the other hand, an electron microscopy study of CRS revealed that iris nodules were formed of clumps and aggregates of iris stromal melanocytes which bears a striking similarity to ocular melanocytosis where there is abnormal migration and proliferation of NCC-derived melanocytes.[18,19] Finally, both EIA and ARA are characterized by severe iris involvement with corectopia, polycoria, iris transillumination, broad-based iridocorneal adhesions together with histopathological evidence of corneal endothelium-like cells, and Descemet-like membrane extending on the AC angle and iris surface.[6,20] In conclusion, this case report alludes to the possibility of SACG even in the presence of evident risk factors of PACG, for example, nanophthalmos. Meticulous examination

is therefore necessary so as not to miss subtle signs of ocular conditions associated with SACG, for example, beaten-bronze corneal endothelium in ICE. This was demonstrated in our case by the concurrence of CS-related SACG and nanophthalmos. This case report is also a stimulus to revisit the hypotheses regarding etiology of ICE. The concurrence of CS and nanophthalmos in this case, the aforementioned similarities between the different clinical forms of ICE and analogous congenital conditions, together with the growing evidence of the role of POM not only as a precursor of corneal endothelium but also as a regulator of the development of optic cup and stalk, suggest that a developmental mechanism may contribute to the pathogenesis of ICE and hence should be investigated.

Conclusion

This case is the first report of an association between CS and nanophthalmos. It highlights the possibility of diagnosing SACG despite evident risk factors for PACG, for example, nanophthalmos. Furthermore, it encourages revisiting the etiology of ICE. The concurrence of CS and nanophthalmos suggests that a common developmental mechanism could be the culprit since POM, which is the embryological precursor of corneal endothelium, plays a pivotal role in the development of optic cup and stalk with multiple hypothesized molecular cascades.

Clinical Significance

Secondary angle closure glaucoma should be considered even in the presence of evident risk factors for PACG, that is, nanophthalmos, which requires meticulous examination. Also, the association of nanophthalmos and CS warrants revisiting the yet inconclusive evidence regarding the etiology of CS where a developmental mechanism could be considered and investigated.

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