

Original Article

Successful Treatment of Corneal Opacification with Associated Thickened Epithelium by Simple Peeling Acquired Corneal Subepithelial Hypertrophy (ACSH)



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Abstract

Purpose: To study clinical and histopathological findings of corneal opacification caused by thickened epithelium leading to reduced vision and topographical changes and to evaluate the outcome of its removal.

Methods: Twelve patients (17 eyes) with central, paracentral or peripheral corneal opacification were reviewed to obtain their visual acuity, describe their slit lamp (SL) appearance (depth, extent and density) and document their topographic changes before and after peeling of the epithelium under SL or surgical removal under the microscope. Specimens of six cases were available for histopathological examination and immunohistochemical staining.

Results: Most of the eye opacifications were secondary to corneal procedures in 10 [Penetrating keratoplasty (PKP) in 7 for congenital glaucoma, keratoconus or adherent leukoma – usually over graft-host junction –, Photorefractive keratectomy (PRK) in 2 and Phototherapeutic keratectomy in one], chronic inflammation following trachoma or non-specific causes (3), and herpetic scar (1). Three cases were considered to be idiopathic. All cases presented with decreased vision, astigmatism or changes in topography or refraction. Their vision, clinical symptoms and topography improved after treatment. Histopathologically, all six cases shared findings that are similar to what have been described as peripheral hypertrophic subepithelial corneal degeneration (PHSCD) rather than Salzmann's nodular degeneration. None of the cases showed inflammation or subepithelial pannus formation in the excised tissue. However, our cases did not fit into the diagnosis of PHSCD because of the location of the corneal opacification (being peripheral in 41% of the corneas, the presence of underlying primary etiologic factors in 82% of the eyes and the bilateral occurrence in 5 patients).

Conclusions: Meticulous SL examination aided by corneal imaging may accurately diagnose and determine the depth of corneal opacification as a cause for reduced vision. Histopathologically, the removed tissue is similar to PHSCD, but cases differ in their clinical profile. Peeling the thickened epithelial/subepithelial tissue is curative in most patients, improves visual and clinical outcome and avoids unnecessary corneal grafting.

Keywords: Peripheral hypertrophic subepithelial corneal degeneration, Salzmann's nodular degeneration, Peripheral hypertrophic subepithelial corneal opacification

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Introduction

Peripheral hypertrophic subepithelial corneal degeneration (PHSCD) is an idiopathic entity characterized by fibrosis between the epithelium and Bowman's layer and causes flattening in the cornea which may lead to regular and irregular astigmatism. These patients have bilateral, fairly symmetric, peripheral, hypertrophic and subepithelial corneal opacification.^{1,2} The disorder has been rarely reported in the literature with unknown cause and share clinical and histopathological features of Salzmann's nodular degeneration (SND).^{3,4}

Salzmann's nodular degeneration presents as bilateral white to bluish localized nodules that are located in the mid-peripheral cornea and can be related to multiple causes. Inflammatory conditions have high association with SND, as well as trauma to ocular surface such as surgery or contact lens wear.^{5,6}

Topographic changes in eyes with annular shaped thickened epithelium include irregularity and increased thickness and sometimes increased front elevation.⁷

Our aim is to study the clinical and histopathological findings of corneal opacification caused by thickened epithelium with subepithelial changes that are similar in presentation to PHSCD leading to reduced vision, topographical changes and evaluate the outcome of its removal.

Methods

This is a retrospective case series prepared in concordance with the tenets of the Declaration of Helsinki and it was approved by the institutional review board. Patients were seen in the anterior segment clinic of the departments of ophthalmology at King Khaled Eye Specialist Hospital, Alhokama Center and King Abdulaziz University Hospital in Riyadh between 2008 and 2018. Cases with the impression of a thickened corneal epithelium or scar were included in this study and some cases were referred for corneal grafting. The data collected on these cases included: demographic information (age and gender), and clinical data (presenting complaint, duration of symptom(s), corneal and ophthalmic findings) as well as history of previous eye surgery or other associated ocular conditions. Visual acuity (VA), SL examination and topographic changes (Using Oculus Pentacam) were recorded before and after removing the thickened opacified epithelium in all patients. There were 17 eyes of 12 patients (8 males and 4 females) with a mean age of 51 (range 30–86 years). Clinical photos and tissue for histopathological examination were available for some patients.

Only symptomatic patients were surgically treated by epithelial peeling (13 eyes) under SL using forceps leaving smooth and clear underlying corneal stroma (9 eyes) or superficial keratectomy under the microscope (4 eyes). Adhesions between the opacified tissue and underlying stroma was occasionally encountered that mandated keratectomy.

The obtained tissue was fixed in formalin and submitted for routine processing and staining using Hematoxylin and eosin (H&E) as well as Periodic acid Schiff (PAS). Enough tissue was available for special staining using Masson Trichrome (MT) and immunohistochemical (IHC) staining with Vimentin (as a marker for cells undergoing epithelial to mesenchymal transition and fibrosis) and Reticulin in 2 cases.

Results

Five patients (41%) had bilateral opacified thickened epithelium, ten eyes (59%) had central or paracentral location of these opacifications and seven eyes (41%) showed peripheral location. Peripheral corneal vascularization was seen clinically in two eyes (12%) and one had penetrating keratoplasty (PKP).

The complaint varied from blurring of eye vision in 6 (35%), reduced vision in 3 (17%), and pain in one (6%) while the condition was asymptomatic in 7 eyes (41%).

Ten of 17 eyes (59%) had previous corneal surgery, 6/10 eyes (60%) underwent a single PKP procedure while 1 (10%) had repeated (PKP), 2 eyes (20%) had history of PRK and 1 (10%) had PTK.

The shape of the epithelium thickening following PKP has been observed to be either sectorial as in patient 6 (Fig. 1A and B) or annular as in patient 7 and the left eye of patient 11 (either complete or incomplete donut-shaped) or finally diffuse as in the right eye of patient 11 (Fig. 4A, B and C consecutively). The diffuse ones were following PKP for pseudophakic bullous keratopathy or adherent leukoma in old age, while the annular ones were more commonly seen following PKP for less severe indications like keratoconus, congenital glaucoma or other indications mostly related to retained sutures. It has been also observed that the sectorial-shaped thickened epithelium was found in younger age group following PKP for keratoconus and in other cases with idiopathic or inflammatory causes. Other patchy discrete scar-like opacifications similar to SND were sometimes elevated and irregular and present after PRK, PTK or central inflammation and they were all located centrally or paracentrally.

The topographic findings were interesting and correlated well with the clinical appearance. The increased corneal thickness areas corresponded to the elevated white opacification, where the front elevation is increased but not the back elevation. In the eyes with central corneal opacification topographic changes included steep or irregular cornea centrally or paracentrally without increase in the back elevation. Other eyes such as in patient 5 showed increased corneal thickness by Pentacam imaging corresponding to the area of opacification (Fig. 5).

Similarly, the second case with crescent-shaped corneal opacification, showed corresponding topographic changes that included thickening and increased front elevation.

Opacified thickened epithelium and subepithelial tissue specimens were removed in 13 of the 17 eyes (76%). Nine eyes (69%) were removed by simple epithelium peeling and 4 eyes (31%) required removal by superficial keratectomy and 1 of them had superficial keratectomy twice.

Six cases had available specimens for histopathological examination, all cases shared the findings of an irregular corneal epithelium with variable thickening, absent Bowman's layer (in almost all cases) and the presence of subepithelial hypocellular fibrous tissue with absence of inflammation or subepithelial neovascularization. Immunohistochemically, these cases demonstrated subepithelial fibrosis with strong vimentin staining and focal subepithelial reticulin fibers. Irregular subepithelial fibers were also highlighted using Masson trichrome stain.

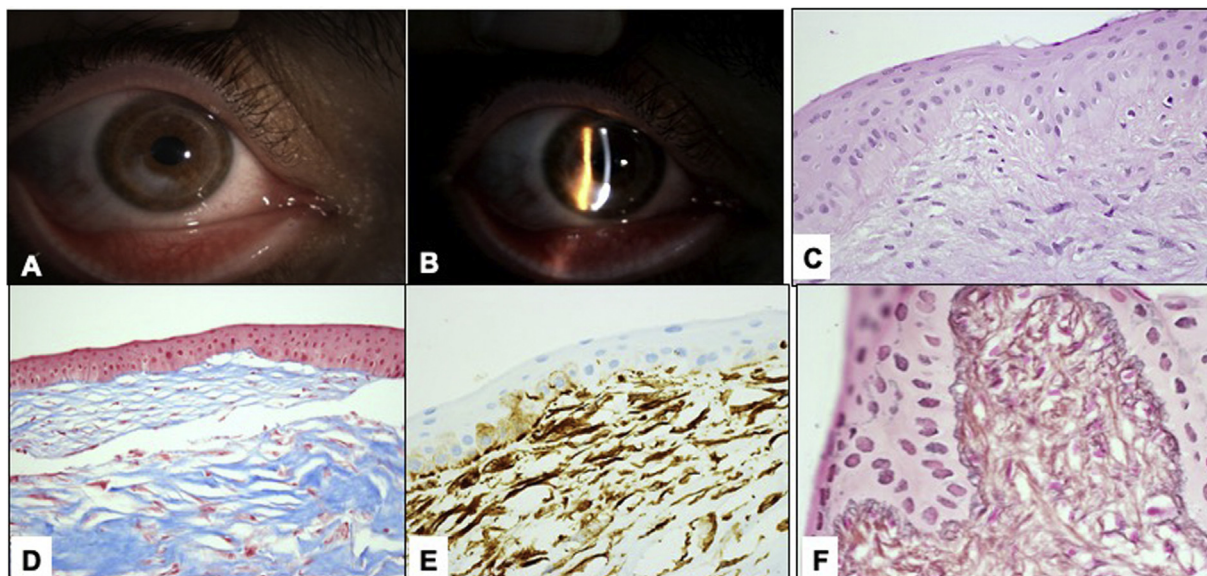


Fig. 1. A & B: The clinical appearance of the right eye peripheral corneal thickened opacification in a 40-year-old male who underwent PKP for keratoconus (Case #6) and regained full vision after peeling. C, D & E: Thick epithelium and absent Bowman's layer with subepithelial fibrosis (Original magnification $\times 400$ H&E in C, MT in D and using Vimentin stain in E). F: Few reticulin fibers in the immediate subepithelial area of the same peeled corneal tissue (Original magnification $\times 400$ Reticulin).

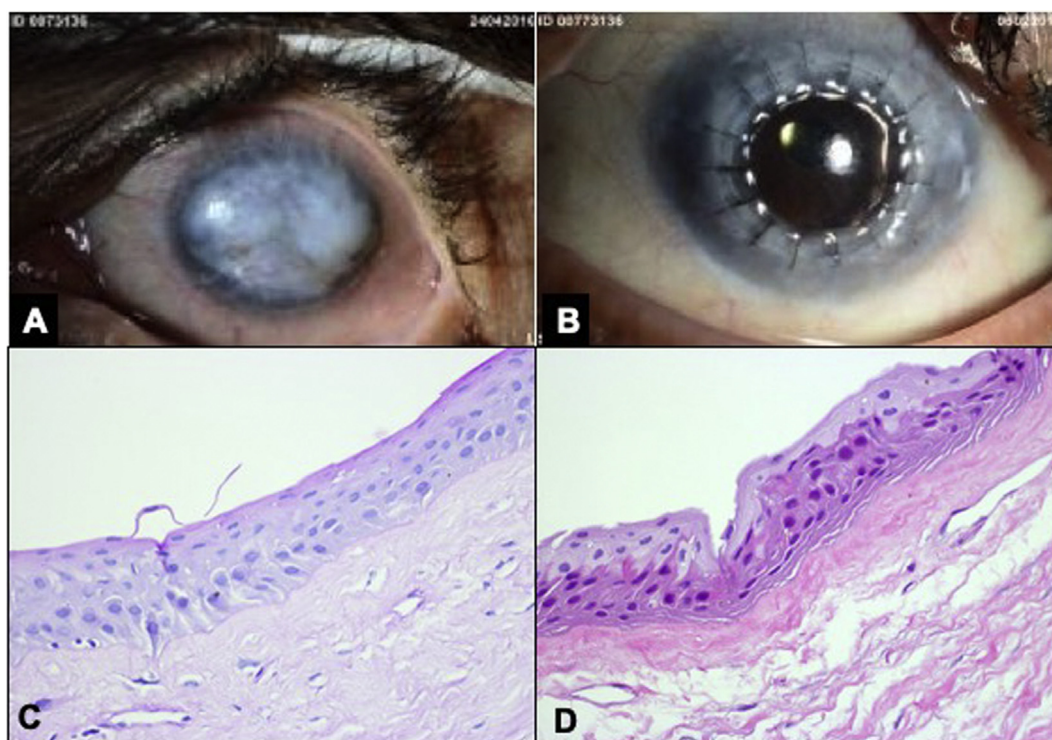


Fig. 2. A: The pre-operative appearance of central extensive diffuse left corneal opacification in a 62-year-old female who underwent repeated PKP (Case #10). B: The appearance of the same left cornea post-surgical keratectomy for removal of the thick epithelial/subepithelial membrane with improved vision from counting fingers to 20/80. C & D: The corresponding histopathological typical findings in the excised corneal tissue showing acanthotic epithelium with irregular basement membrane and thick subepithelial hypocellular fibrous tissue and absent inflammation (Original magnification $\times 400$ H&E in C, and PAS in D).

The clinical and corresponding histopathological appearance of some cases are presented in [Figs. 1–3](#).

The mean follow-up period in 11 patients was 1 year (range 2 weeks to 2 years). Visual acuity improved in all eyes

except one eye, which showed loss of one line. All patients had totally resolved symptoms following treatment and remained asymptomatic in the last follow up without evidence of recurrence. [Table 1](#) shows clinical details of 12

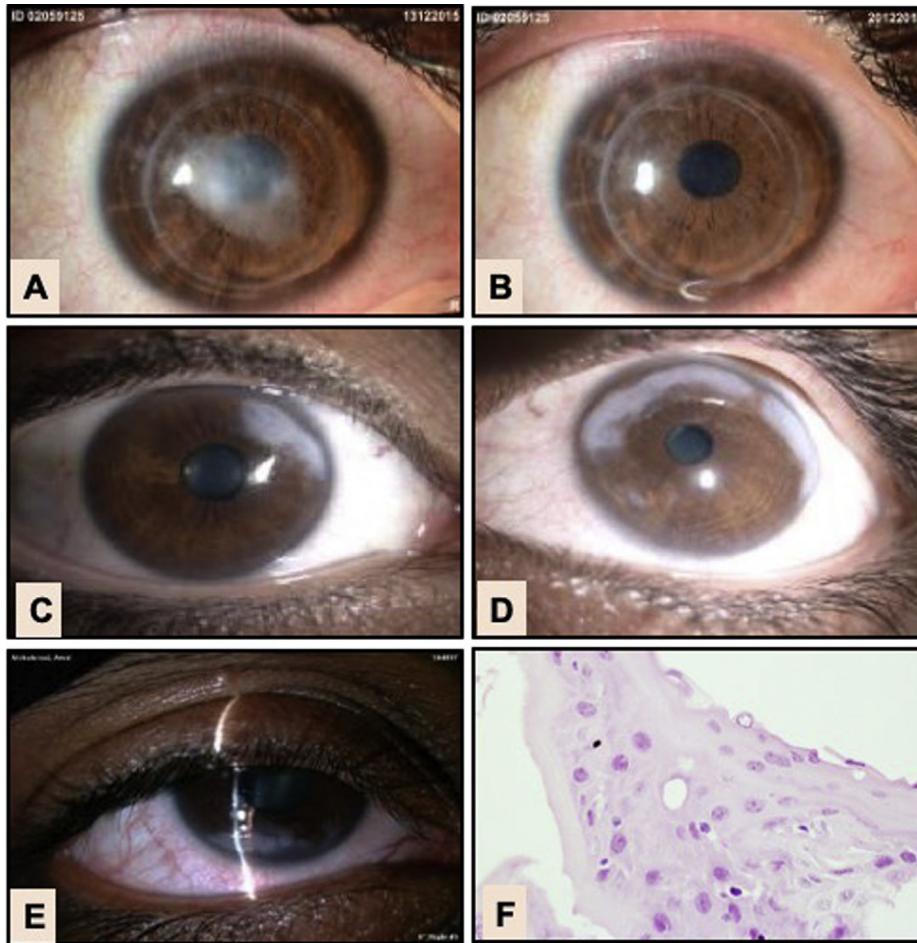


Fig. 3. A & B: Another young patient who is post PKP with less extensive central corneal opacification in comparison to the case in Fig. 2. B: shows excellent outcome following surgical keratectomy with improved vision from CF in to 20/80 in the same eye. C & D: The clinical appearance of bilateral peripheral idiopathic opacification in the right and left eyes (in C & D respectively) in a young female (Case #5). E & F: Similar pre-operative right corneal peripheral opacification in another young female (Case #2) with bilateral corneal involvement, who underwent peeling on the right side only. The corresponding histopathological appearance of the peeled membrane of thick epithelium and irregular interrupted Bowman's layer is shown in F (Original magnification $\times 400$ H&E).

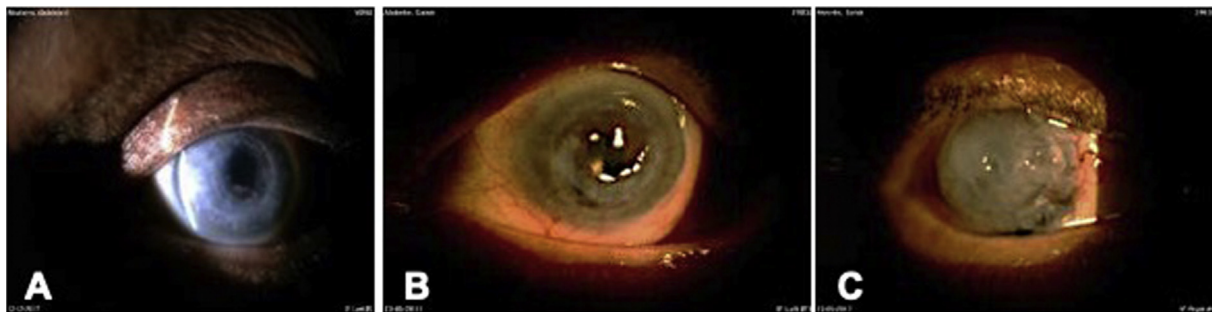


Fig. 4. The clinical appearance of annular or Donut-shaped epithelial thickening (incomplete in patient 7: A, and complete in patient 11 left eye: B) and the diffuse type in the other eye of the same patient #11: C.

patients including preoperative and postoperative visual acuity with an example of dramatic improvement in one of the cases who was treated by superficial keratectomy (Fig. 2B).

Discussion

Peripheral hypertrophic subepithelial corneal degeneration PHSCD is relatively a new entity that can be comparable

to the well-known Salzmann nodular degeneration (SND). It was first described in 2003 in 6 patients and they were all female patients.⁷ Also, Gore and his co-authors described PHSCD ten years later in 22 patients with female predominance in 90% of the cases.² We think that SND is different than PHSCD or this new entity in our patients. The argument that SND is an epithelial dystrophy and same as PHSCD proposed by Eberwein in their correspondence to Gore is not convincing based on unilaterality or history of ocular surface

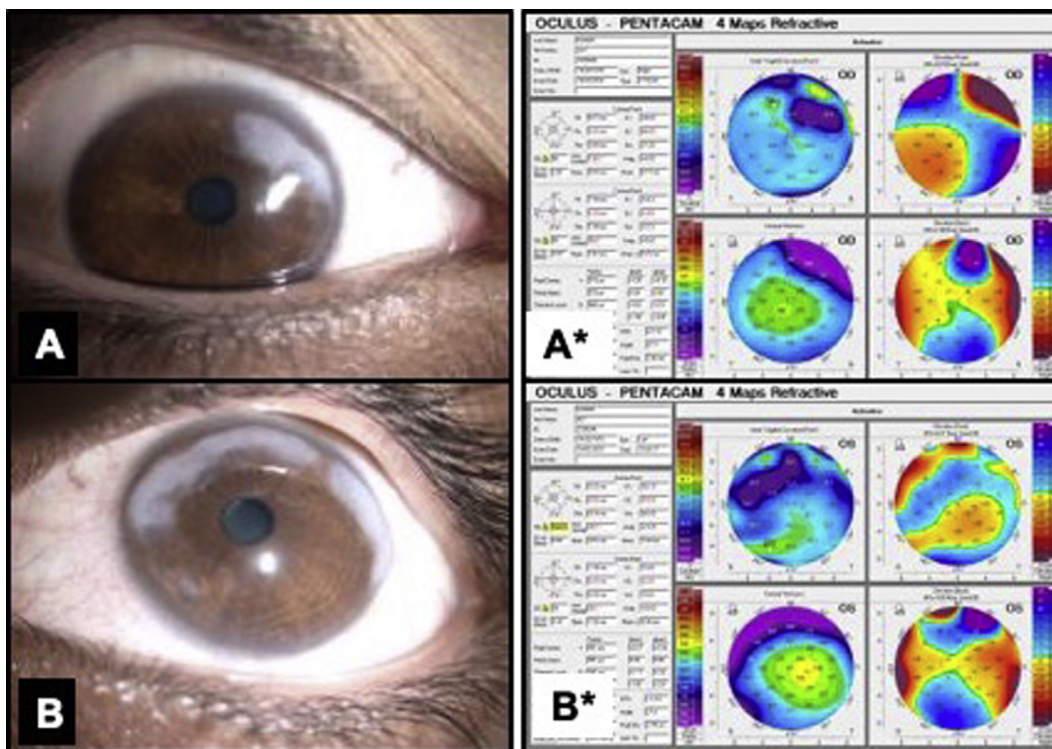


Fig. 5. The clinical appearance of arcuate-shaped opacifications with the corresponding topographic changes in the right and left eyes (A and B consecutively) the topography images are labelled with Asterisk.

Table 1. Clinical details of the 17 eyes of 12 patients.

Patient	Sex	Age (Y)	Eye	Complaint	VA	Previous surgery	Treatment	VA Post Tm
1	M	30	OD	Low VA	20/20	PKP	2 SK	20/20
2	F	34	OD	Blurry VA	20/20	None	Peeling	20/20
			OS	Blurry VA	20/20	None	NR	20/20
3	F	35	OD	Blurry VA	20/25	PRK	SK	20/25
			OS	Blurry VA	20/30	PRK	SK	20/30
4	M	36	OS	Blurry VA	20/60	None	Peeling	20/50
5	F	39	OD	Blurry VA	20/25	PRK	SK	20/25
			OS	None	20/30	None	NR	No F/U
6	M	40	OD	Pain	20/60	PKP	Peeling	20/20
7	M	51	OS	None	20/200	2 PKP	Peeling	20/125
8	M	58	OS	Blurry VA	20/100	PTK	Peeling	20/40
9	M	60	OD	None	20/80	None	Peeling	20/80
			OS	None	20/60	None	Peeling	20/80
10	F	62	OS	Low VA	CF	2 PKP	SK	20/80
11	M	77	OD	None	NLP	PKP	NR	NLP
			OS	None	20/160	PKP	Peeling	20/125
12	M	86	OD	Low VA	HM	PKP	Peeling	HM

M: Male, F: Female, OD: Right eye, OS: Left eye, VA: Visual acuity, CF: Counting fingers, NLP: No light perception, HM: Hand movement, PKP: Penetrating keratoplasty, PRK: Photorefractive keratectomy, PTK: Phototherapeutic keratectomy, SK: Superficial keratectomy.

disease.⁸ Järventausta supported the proposed concept that PHSCD affects predominantly females as 13 females were affected out of total 14 patients included in his study.¹ SND has been also reported to be more prevalent in females (14 out of 19 in one study).⁶ In our study males were more predominantly affected in 67%.

Symptoms of PHSCD were reported to be variable. Gore et al reported that the condition was asymptomatic in 3 (14%) patients, while symptomatic patients complained of ocular surface discomfort (OSD) in 10 (45%), reduced vision in 4 (18%) and both symptoms in 5 (23%).² Another study reported reduced visual acuity in 12 of 14 patients (86%),

OSD in 9 (64%) and 2 (14%) asymptomatic.¹ In our study, 4 (33%) patients were asymptomatic, another 4 (33%) had blurry vision, 3 (25%) with low visual acuity and one (8%) associated with pain.

The association of PHSCD and corneal peripheral neovascularization was found clinically in two eyes only out of 17, however this might have been related to herpetic keratitis in one patient. Regarding the laterality, five of our 13 patients had bilateral thickened epithelium in contrast to Järventausta study, where almost all his patients (12/14) had bilateral disease. In our study, the location of the opacification was peripheral in 7 eyes and central or paracentral in 10 eyes

which is different than what has been reported in PHSCD with predominant peripheral nasal quadrant location in 21 eyes out of 26.¹

In our study, we only treated symptomatic eyes, which constituted 76% of the corneas (13/17). The thickened opacified tissue removed by simple peeling in 9/13 eyes (69%), while superficial keratectomy was needed in 31%. Topical therapy was not tried in any form on our cases. Maust, similarly treated 3/12 PHSCD eyes by superficial keratectomy, while the rest were treated medically by topical lubrication and steroid in addition to oral doxycycline.⁷ On the other hand, treatment modalities for SND has been reported to be successful where 26/30 have received similar medical therapy of ocular lubrication, topical anti-inflammatory and topical prednisolone, while the remaining patients needed surgical treatment.⁶ The surgical procedures reported in the same study were PKP in 2, simple excision and anterior lamellar keratoplasty in one case each.⁶

The lesions in our study were histopathologically different than SND but somehow identical in histopathological appearance and features to the so called PHSCD. However, our cases did not only differ than the typical cases of PHSCD in the location, age range of affected patients and etiology of the opacification but also in the shape, and density, which necessitated surgical treatment. PHSCD has been reported to be associated with human leukocyte antigen genes.⁹ However, we did not do this type of testing for our patients. Topographic changes in PHSCD were previously reported.^{9,10} Peeling or keratectomy of these lesions improved vision by improving the corneal irregularity, astigmatism and refractive error as well as the clarity of the cornea. Our cases had common findings of increased thickness and front elevation with normal back elevation and in certain cases irregular corneal topographic findings. OCT was not in our cases as some of these cases were seen before the availability of the OCT machine. OCT was reported in a single case of PHSCD and revealed focal hyperreflectivity as well as subepithelial nodules.¹⁰ Reidl and his group studied similar peripheral opacifications with vascularization, which were found predominantly nasally and used the terminology: peripheral hypertrophic subepithelial corneal opacification (PHSCO). OCT angiography in their cases was done and revealed better visualization of corneal neovascularization than slit lamp photography.¹¹

We propose to call the described entity in this study: Acquired Corneal Subepithelial Hypertrophy (ACSH) as it has different clinical picture, etiology and unique histopathological findings. ACSH is considered to be an acquired reactive condition secondary to previous surgical intervention and or chronic eye disease. Intra-operatively, these lesions are mostly easily treated by peeling (or surgical removal) with excellent outcome and resolution of vision.

Epithelial peeling in ACSH should be tried first if good separation between the opacified epithelial tissue and the underlying corneal tissue is obtained. This can be done under slit lamp or using a surgical microscope. If adhesions or scarring of the underlying corneal tissue/stroma is encountered, then superficial keratectomy should be tried. Some of these cases are centrally or diffusely located and might be referred for unnecessary corneal transplantation as our case #10

because the actual disease entity of ACSH is not known or being overlooked.

Ophthalmologists should be aware of different presentations and variations in degenerative corneal conditions such as PHSCD/PHSCO and SND as well as this proposed ACSH in order to make the proper diagnosis and management. Corneal imaging play important rule in diagnosing and determining depth and extent of these lesions and for future appropriate treatment planning.

Simple peeling of the thickened epithelial/subepithelial tissue (sometimes associated fibrovascular membrane) has not been described as a treatment modality for the above 2 known degenerative opacifications and we do believe that this procedure in many cases (including our proposed ACSH cases) might be enough to achieve adequate corneal clarity for satisfactory visual outcome. Therefore, meticulous assessment of patients using SL examination and corneal imaging is necessary to diagnose this simply-treated condition and to avoid unnecessary corneal transplantation. The knowledge of this new entity will solve the challenging diagnosis and management of similar cases seen often in our community.

Conflict of interest

The authors have no conflict of interest in relation to this work. This research did not receive any specific fund and authors have no financial interest in relation to any of the equipment or products mentioned in this study.

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