Published in final edited form as:

Am J Ophthalmol. 2011 February ; 151(2): 248–56.e2. doi:10.1016/j.ajo.2010.08.013.

In-vivo Morphological Characteristics of Salzmann Nodular Degeneration with Ultra-High-Resolution Optical Coherence Tomography

Volkan Hurmeric, MD^{*}, Sonia H. Yoo, MD^{*}, Carol L. Karp, MD^{*}, Anat Galor, MD^{*}, Lejla Vajzovic, MD^{*}, Jianhua Wang, MD, PhD^{*}, Sander R. Dubovy, MD^{*}, and Richard K. Forster, MD^{*}

^{*}Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA

Abstract

Purpose—To examine the in-vivo morphological properties of Salzmann nodular degeneration with ultra-high-resolution optical coherence tomography (OCT).

Design—Interventional case series.

Setting: Single-center, academic practice.

Study Population: 19 eyes of 12 patients with Salzmann nodular degeneration were recruited to participate in the study.

Observational Procedure: Subjects were imaged using novel, custom-built ultra-high-resolution OCT. Images were used to describe in-vivo characteristics of subepithelial nodules. Morphometric measurements were made with custom-built software. Ultra-high-resolution OCT findings were compared with histopathological findings in three patients.

Main outcome measures: To demonstrate in-vivo morphological characteristics of Salzmann nodular degeneration with ultra-high-resolution OCT.

© 2010 Elsevier Inc. All rights reserved.

Correspondence to: Sonia H. Yoo MD, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 N.W. 17 Street, Miami, Florida, 33136, Tel: +305-326-6322, Fax: +305-326-6337, syoo@med.miami.edu.

Contribution to authors in each of these areas: Conception and design of the study (VH, SHY, JW)

Analysis and interpretation (VH, SHY, CLK, AG, LV, JW, SRD, RKF)

Writing the article (VH,SHY)

Critical revision of the article (CLK, AG, LV, JW, SRD, RKF)

Final approval of the article (VH, SHY, CLK, AG, LV, JW, SRD, RKF)

Data collection (VH, LV, JW, SRD)

Statistical expertise (VH)

Literature search (VH, AG, LV)

Financial Disclosures: VH, CLK, AG, LV, JW, SRD, RKF: None

SHY: (L) Alcon, Carl Zeiss Meditec, Abbott Medical Optics <10,000, (C) Haag-Streit, Ista, Inspire <10,000; (G) Genentech, Allergan, Carl Zeiss Meditec >10,000.

Statement about Conformity with Author Information: The University of Miami Institutional Review Board reviewed and approved this study, The study and data accumulation were carried out in accordance with HIPAA regulations and the principles of the Declaration of Helsinki. Written informed consent, as approved by University of Miami Institutional Review Board, was obtained from all patients.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—Ultra-high-resolution OCT images demonstrate intraepithelial fibrous nodules with epithelial thinning and corneal surface elevation. Bowman's layer could be differentiated in 9 of 12 patients. The difference between the mean thickness of epithelium above the nodule and the thickness of normal epithelium was statistically significant ($p < 0.0001$). The correlation between thickness of the epithelium and thickness of the nodule was statistically significant ($r = -0.48$; $p < 0.0001$). The correlation between thickness of the nodule and total surface thickness (thickness of the epithelium + thickness of the nodule) was statistically significant ($r = 0.98$; $p < 0.0001$). Ultra-high-resolution OCT findings were consistent with histopathological results.

Conclusions—Ultra-high-resolution OCT can be used to non-invasively image the cornea in Salzmann nodular degeneration. This new imaging technique helps us to demonstrate different in-vivo morphological characteristics of Salzmann nodular degeneration.

Introduction

Salzmann nodular degeneration is a non-inflammatory, progressive corneal degeneration, characterized by elevated, whitish-grey subepithelial nodules (1,2). The nodules are developed by fibrous overgrowth and may appear at any part of the cornea (3). Patients can present with unilateral or bilateral disease and the number of nodules can vary from one to many. It is most commonly seen in females and the majority of the cases are reported in elderly patients. Although Salzmann nodular degeneration can be asymptomatic, it can cause severe pain, irritation, irregular astigmatism and significant decrease in visual acuity (4,5).

Salzmann nodular degeneration may be associated with chronic or recurrent keratoconjunctivitis, surgical trauma or corneal dystrophy. Salzmann nodular degeneration has been associated with, Thygeson's punctate keratitis, vernal keratitis, filamentary keratitis, chronic uveitis, phlyctenular keratitis and epithelial basement membrane dystrophy. (2-9). It can also develop after cataract extraction, pterygium excision, laser-assisted in situ keratomileusis, ocular trauma and hard contact lens wear (1,8). In some cases a specific etiologic factor may not be confirmed (3,8). Manual removal, phototherapeutic keratectomy, penetrating keratoplasty, lamellar keratoplasty or anterior keratectomy have been used in the treatment of symptomatic Salzmann nodular degeneration. Recurrence of the nodules can be seen after the surgical treatment of the degeneration (6).

Optical coherence tomography is a signal acquisition technique used to get detailed images from light scattering tissues. This method is widely used to analyze the structure of anterior and posterior segments of the eye. Ultra-high-resolution optical coherence tomography (OCT) is a new technique, which allows visualization the anterior segment structures with an axial resolution of 3 microns. The images with ultra-high-resolution OCT have the quality of a living biopsy, which allows noninvasive in vivo histological analysis of the morphology of the cornea. This technique has been previously used to analyze the morphological characteristics and the thickness of Descemet membrane (10). In this study we evaluated the in-vivo morphological structure of the cornea with ultra-high-resolution OCT in cases with Salzmann nodular degeneration. We described ultra-high-resolution OCT findings, clinical features and histopathological results.

Methods

Setting

Single-center, academic practice.

Design

Interventional case series.

Study Population

Nineteen eyes of twelve patients with Salzmann nodular degeneration were recruited to participate in the study. All patients with Salzmann nodular degeneration that presented to our clinic between January 2009 and June 2010 were asked to participate in the study. Inclusion criteria included a diagnosis of Salzmann nodular degeneration and ability to provide written informed consent. Patients who did not want to give a written consent were excluded from the study.

Data Collection

Digital slit-lamp pictures of the cornea were taken in all patients before ultra-high-resolution OCT imaging.

A novel, custom-built spectral domain ultra-high-resolution OCT was used for the study. A 3-module superluminescent diode light source (Broadlighter, T840-HP, Superlumdiodes, Ltd., Moscow, Russia) was used with a center wavelength of 840 nm and a full width at half maximum bandwidth of 100 nm. The low coherence light, after passing through a fiber pig-tailed isolator, was coupled into a fiber based Michelson interferometer with a 2×2, 3-dB fiber coupler. The light was splitted into the reference arm and the sample arm. The sample light was connected to a light delivery system which has a telecentric design for imaging the anterior segment of the eye. An X-Y galvanometer scanner was used for delivering the sample light and collecting the reflected light from the eye.

In the detection arm, a spectrometer with a collimating lens ($f=50$ mm), a 1200-line/mm transmission grating, and an achromatic imaging lens ($f=180$ mm) were used. A linear scan CCD camera (Aviiva-M2-CL-2014, 2048 pixels with 14 μ m pixel size operating in 12-bit mode; Atmel, San Jose, CA) sense the light and transfers to the computer. Images were passed through an acquisition board in a computer workstation for signal processing and image display. The A-line (depth scan) rate of the OCT system was set to 24 kHz.

The calibrated axial resolution of the system was ~ 4 μ m in the air and ~ 3 μ m in the water or tissue with a refractive index of ~ 1.39 (11). The ultra-high-resolution OCT radial images were captured at 32 frames per scan. The width of the images varied from 8 to 16 mm according to the extent and the location of the degeneration. The image acquisition was performed relative to the center of the nodule. Custom-built software processed the raw data.

The ultra-high-resolution OCT image with the thickest nodule was selected for each patient and used for thickness measurements. Thickness of the epithelium and thickness of the nodule was measured every 0.1 mm at the entirety of the nodule. Mean thickness of the epithelium, mean thickness of the nodule, minimum thickness of the epithelium overlying the nodule and maximum thickness of the nodule were calculated from these measurements (Figure-1).

Thickness of the epithelium was measured between surface of the cornea and superficial margin of the nodule. Thickness of the nodule was measured between the superficial margin of the nodule and Bowman's layer. In cases with indistinct Bowman's layer (patient 1 OU; patient 2 OU; patient 6 OS) the thickness of the nodule was measured between superficial and deep margins of the nodule. Total surface thickness was measured as the sum of thickness of the epithelium plus thickness of the nodule. The thickness of the normal epithelium was measured at the edge of the nodule at the nearest point to the center of the cornea (Figure-1).

3 eyes of 3 patients who underwent surgical treatment with superficial keratectomy were histologically examined (Table-1). All procedures were performed with topical anesthesia.

The nodules were lifted with a beaver blade and peeled off with a forceps. The dissection plane was prepared in a planar fashion. Bandage soft contact lens was applied for healing and comfort. The specimens were fixed in 10% buffered formalin, dehydrated, and embedded in paraffin. Slides, sectioned at 7 μ , were stained with hematoxylin and eosin, Periodic acid–Schiff, Gomori's one step trichrome staining and analyzed using a microscope (Olympus Optical Co., Tokyo, Japan).

SPSS software version 15.0 (SPSS, Inc., Chicago, IL) was used for statistical analyses. Results are reported as means $\pm$ standard deviation. Differences between thickness measurements were tested for significance by the Mann-Whitney U test. Correlations between thickness measurements were examined with Pearson correlation analysis. $p < 0.05$ was considered significant.

Main outcome measure

Visualization of the in-vivo morphological characteristics of cases with Salzmann nodular degeneration with ultra-high-resolution OCT and to compare ultra-high-resolution OCT results with clinical features and histopathological results.

Results

Table-1 summarizes patient and ocular characteristics. The median age was 61 ± 25 years (range 13 to 82 years). Five patients were male, seven patients were female. Seven patients had a history of dry eye or ocular rosacea. Other Salzmann nodular degeneration related ocular disorders include penetrating keratoplasty, chronic rigid contact lens wear and epithelial basement membrane dystrophy. One patient had a recurrence of Salzmann nodular degeneration 2 years after photo therapeutic keratectomy + superficial keratectomy. Two patients had Salzmann nodular degeneration without any specific ocular history (patients 3 and 8). Best corrected visual acuity ranged from 20/15 to 20/80.

Table-2 summarizes the characteristics of the nodules. Seven patients had Salzmann nodular degeneration in both eyes. 4 patients had Salzmann nodular degeneration in the right eye and one patient in the left eye. 13 eyes had focal nodules, 6 eyes had diffuse/multiple nodules on the cornea.

Ultra-high-resolution optical coherence tomography Images

The ultra-high-resolution OCT imaging displayed the degeneration as prominent bright white deposits in the cornea (Figure-2). The lesions were located under the epithelium and the shape and the distribution of the nodules varied significantly. The nodules extended above Bowman's layer and in some areas induced an anterior corneal surface elevation. These areas were accompanied by significant epithelial thinning. Most of the nodules had uneven surface on the superficial margin. The margins of diffuse nodules demonstrated localized subepithelial triangular spikes. The central parts of the nodules show a heterogeneous signal intensity suggesting a difference in the density of the nodules.

In 9 of 12 patients, Bowman's layer could be differentiated in ultra-high-resolution OCT images (Figure-2). In patients 1 (OD), and 2 (OU) the effect of the degeneration on Bowman's layer seemed to be more prominent and Bowman's layer could not be distinguished from the surrounding nodule (Figure-1). Bowman's layer was not demonstrated in the left eye of Patient 6 who had recurrent Salzmann nodular degeneration after photo-therapeutic keratectomy (Figure-3). The right eye of patient 6 demonstrated thickening at epithelial basement membrane with anterior stromal scarring. In patients 1 (OS), 4 (OU), 5 (OD) and 9 (OS) Bowman's layer could be demonstrated in some of the images.

There was irregular stromal scarring below Bowman's layer in all patients. The posterior margin of this scarring was indistinct and was limited to the superficial layers. The posterior stroma and Descemet membrane were normal in ultra-high-resolution OCT images and were not affected by the superficial pathologies found in our patients.

Thickness Measurements

The mean number of measurements that were taken in each image was 17.5 ± 8.1 (min: 5, max: 31). The epithelial thickness above the nodules and the thickness of the nodules varied significantly in the patients (Table-2). The minimum thickness of the epithelium was measured at patient 6 in the left eye as 3 μm . The mean epithelial thickness above the nodules was $37 \pm 9 \mu\text{m}$ (16-51 μm). The maximum thickness of the nodule was measured in patient 3 in the right eye as 333 μm . The mean nodule thickness was $108 \pm 60 \mu\text{m}$ (31-243 μm). The mean thickness of normal epithelium was $65 \pm 13 \mu\text{m}$ (47-85 μm).

The difference between the mean thickness of epithelium above the nodule and the thickness of normal epithelium was statistically significant ($p < 0.0001$). The correlation between thickness of the epithelium and thickness of the nodule was statistically significant ($r = -0.48$; $p < 0.0001$). The correlation between thickness of the nodule and total surface thickness was statistically significant ($r = 0.98$; $p < 0.0001$) (Figure-4).

Histopathology

The diagnosis of Salzmann nodular degeneration was confirmed in patients 10, 11 and 12 with histopathology. The nodules consisted of moderately dense collagenous material located superficial to the corneal stroma. The surface of the collagenous material was irregular and the overlying epithelium was attenuated. These findings were correlated well with the ultra-high-resolution OCT images (Figure-5).

Discussion

In this study we examined the in-vivo morphologic characteristics of Salzmann nodular degeneration with ultra-high-resolution OCT. We confirmed that the lesions have superficial distribution in conjunction with elevation above the corneal surface and epithelial thinning. We found a weak correlation between thickness of the nodule and thickness of the epithelium. There was a significant correlation between the thickness of the nodule and total surface thickness.

Historically Salzmann nodular degeneration has been diagnosed by its clinical properties (12). In most cases tissue samples are not available for histological examination and previous histological studies have been performed in advanced cases requiring penetrating or lamellar keratoplasty. The only study about the use of OCT imaging in Salzmann nodular degeneration has reported the morphology of a bilateral case, which developed after LASIK (13). However the low resolution of time domain anterior segment OCT prevented the authors from documenting the detailed morphology of Bowman's layer underneath and epithelium overlying the Salzmann nodular degeneration lesions. Ultra-high-resolution OCT provides the opportunity to analyze the in-vivo morphological properties of the cornea with high resolution similar to histological images.

Previous histological studies reported the destruction of Bowman's layer as one of the most significant morphological properties of Salzmann nodular degeneration (1,3,6,9). It was reported that Bowman's layer was partially replaced by a granular PAS-positive material that resembled a basement membrane. Variations in the basement membrane thickness were also reported. In our study 15 of 19 eyes demonstrate a distinctive layer separating the subepithelial nodule from the anterior stroma. It is clear that this layer continues with the

Bowman's layer of the surrounding healthy cornea in ultra-high-resolution OCT images (Figure-2). The histopathological samples in our study group were obtained from superficial keratectomy. Most of our study patients did not require surgical intervention because of good visual acuity and the peripheral location of the lesions. For these reasons we do not have histological proof of the nature of this layer. However the appearance of this layer resembles Bowman's layer. We believe that progressive nature of the degeneration results in the destruction of Bowman's membrane over time. Ultra-high-resolution OCT seems to be a valuable tool in this setting to allow imaging of patients in early stages and get in-vivo morphological images without necessitating tissue sampling.

Some authors report that histological findings in Salzmann nodular degeneration were nonspecific and were not different from a degenerative pannus or an old scar after trauma or inflammation (14,15). The lesions were described as uninflamed dense collagenous tissue elevations located above the normal corneal surface (6,8). The thickness of the epithelium varied especially over the nodules often with only a single layer of flattened cells. Posterior stroma, Descemet membrane and endothelium were reported to be normal in cases with Salzmann nodular degeneration (16). These findings are consistent with the ultra-high-resolution OCT images of our patients (Figure-1). Ultra-high-resolution OCT images demonstrate intraepithelial fibrous nodules with epithelial thinning, and corneal surface elevation. The thickness measurements demonstrate that most of the surface elevation in Salzmann nodular degeneration is a result of the thickness of the nodule. There are indistinct margins of the lesions in the corneal stroma. Posterior stroma and Descemet membrane are within normal limits in our study.

Chronic inflammation or irritation is suggested as the primary causative factor in the development of Salzmann nodular degeneration (2). This primary insult, which leads to over-repair, is thought to be responsible for the formation of excessive keloid-like scar tissue, which is the characteristic histological finding of the degeneration. The fibroblasts are mostly found in the superficial layer of the nodules suggesting a stimulus arising from the epithelium. External irritation due to poor epithelial protection was suggested as a causative factor in these cases. Vannas suggested the interruption of epithelial basement membrane as a factor to allow cell debris and cytoplasmic fibrillar material to be released into the stroma (6). In the right eye of patient 6 ultra-high-resolution OCT images demonstrate thickening of the epithelial basement membrane and anterior stromal scarring at the very early stages of Salzmann nodular degeneration (Figure-3). Our results also reveal uneven surfaces of the nodules in most of the images. Additionally eyes with diffuse Salzmann nodular degeneration demonstrate prominent processes located at the edges of the nodules (Figure-2, bottom left). We believe that the mechanical irritation caused by lid movements over these uneven surface areas could be the reason for the progression of scarring in Salzmann nodular degeneration.

Mechanical removal of the superficial pannus is not achieved easily in all cases and can leave deep defects in the anterior stroma. The recurrence of Salzmann nodular degeneration is reported to be seen in easily treated cases (1). In patient 11 the pannus was excised easily with superficial keratectomy. The ultra-high-resolution OCT images in this case show the superficial involvement of the anterior stroma with an intact Bowman's membrane. We believe that the degree of involvement of the superficial cornea and presence or absence of an intact Bowman's layer in the preoperative ultra-high-resolution OCT could be predictive of the strength of the adhesion of the nodules to the underlying stroma and the likelihood of ease of removal of the nodule with superficial keratectomy.

Limitations of this study are that the ultra-high-resolution OCT findings were compared with histopathological images in three eyes. The histopathological samples were obtained

from superficial keratectomy, which prevented complete comparison of the histological structure of Bowman's layer with ultra-high-resolution OCT images. However our findings suggest that ultra-high-resolution OCT images are useful in morphological evaluation of the patients with Salzmann nodular degeneration. We didn't do a longitudinal study, which can better demonstrate the staging and progress of Salzmann nodular degeneration over time. Another limitation of this study is that we cannot prepare a 3 dimensional map of the corneal surface with our ultra-high-resolution OCT system to date. Because of this reason thickness measurements were made in 2 dimension in a single image with the largest nodule in each patient. Future studies and long-term follow up of the patients are needed to demonstrate the exact role of our findings in the pathogenesis of Salzmann nodular degeneration.

In conclusion ultra-high-resolution OCT can be an effective manner to non-invasively image the cornea in Salzmann nodular degeneration. We found significant correlation between total surface thickness and the thickness of the nodule with ultra-high-resolution OCT imaging. This new imaging technique can be used to demonstrate different morphological characteristics of Salzmann nodular degeneration in various stages of the disease. Ultra-high-resolution OCT also has the potential to be used in the differential diagnosis of corneal degenerations. These observations may help us to better understand the etiology of Salzmann nodular degeneration and to treat the patients before significant destruction of Bowman's layer and stromal scarring occurs.

Acknowledgments

Funding/Support: This research was supported by unrestricted grant from NIH Center Grant P30 EY014801 and Research to Prevent Blindness (RPB).

References

1. Das S, Link B, Seitz B. Salzmann's nodular degeneration of the cornea: a review and case series. *Cornea*. 2005; 24(7):772–777. [PubMed: 16160490]
2. Salzmann M. Über eine Abart der knötchenförmigen Hornhautdystrophie. *Ztschr Augenheilkd*. 1925; 57:92–99.
3. Frising M, Pitz S, Olbert D, Kriegsmann J, Lisch W. Is hyaline degeneration of the cornea a precursor of Salzmann's corneal degeneration? *Br J Ophthalmol*. 2003; 87(7):922–923. [PubMed: 12812904]
4. Werner Leonardo P, Issid K, Werner Liliana P, et al. Salzmann's corneal degeneration associated with epithelial basement membrane dystrophy. *Cornea*. 2000; 19(1):121–123. [PubMed: 10632022]
5. Oster JG, Steinert RF, Hogan RN. Reduction of hyperopia associated with manual excision of Salzmann's nodular degeneration. *J Refract Surg*. 2001; 17(4):466–469. [PubMed: 11472006]
6. Vannas A, Hogan MJ, Wood I. Salzmann's nodular degeneration of the cornea. *Am J Ophthalmol*. 1975; 79(2):211–219. [PubMed: 46719]
7. Abbott RL, Forster RK. Superficial punctate keratitis of Thygeson associated with scarring and Salzmann's nodular degeneration. *Am J Ophthalmol*. 1979; 87(3):296–298. [PubMed: 434089]
8. Wood TO. Salzmann's nodular degeneration. *Cornea*. 1990; 9(1):17–22. [PubMed: 2297989]
9. Moshirfar M, Marx DP, Barsam CA, Mohebbi J, Mamalis N. Salzmann's-like nodular degeneration following laser in situ keratomileusis. *J Cataract Refract Surg*. 2005; 31(10):2021–2025. [PubMed: 16338579]
10. Shousha MA, Perez VL, Wang J, et al. Use of Ultra-High-Resolution Optical Coherence Tomography to Detect in Vivo Characteristics of Descemet's Membrane in Fuchs' Dystrophy. *Ophthalmol*. 2010; 117(6):1220–1227.
11. Lin RC, Shure MA, Rollins AM, Izatt JA, Huang D. Group index of the human cornea at 1.3-microm wavelength obtained in vitro by optical coherence domain reflectometry. *Opt Lett*. 2004; 29(1):83–85. [PubMed: 14719668]

12. Das S, Link B, Seitz B. Salzmann's nodular degeneration of the cornea: a review and case series. *Cornea*. 2005; 24(7):772–777. [PubMed: 16160490]
13. VanderBeek BL, Silverman RH, Starr CE. Bilateral Salzmann-like nodular corneal degeneration after laser in situ keratomileusis imaged with anterior segment optical coherence tomography and high-frequency ultrasound biomicroscopy. *J Cataract Refract Surg*. 2009; 35(4):785–787. [PubMed: 19304107]
14. Yoon KC, Park YG. Recurrent Salzmann's nodular degeneration. *Jpn J Ophthalmol*. 2003; 47(4): 401–404. [PubMed: 12842211]
15. Severin M, Kirchhof B. Recurrent Salzmann's corneal degeneration. *Graefes Arch Clin Exp Ophthalmol*. 1990; 228(2):101–104. [PubMed: 2338247]
16. Linke S, Kugu C, Richard G, Katz T. An in vivo confocal microscopic analysis of Salzmann's nodular degeneration: pre- and post-surgical intervention. *Acta Ophthalmol*. 2009; 87(2):233–234. [PubMed: 19292857]

Biographies

Volkan Hurmeric MD, received his medical degree from Gulhane Military Medical Academy (GMMA) in Ankara, Turkey and completed a medical internship at GMMA in 1997. He completed ophthalmology residency in the Department of Ophthalmology at GMMA in 2003. He has been an assistant professor of ophthalmology at GMMA since 2006. He completed his corneal and refractive surgery research fellowship at Bascom Palmer Eye Institute in 2010. His research interests include corneal imaging, keratoplasty and laser vision correction.

Sonia H. Yoo is currently a Professor of Ophthalmology and cornea fellowship director at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. Dr. Yoo received her B.A. at Stanford University and M.D. at Case Western Reserve University. She completed residency and fellowship at Massachusetts Eye and Ear Infirmary, Harvard Medical School.

Her areas of clinical practice are cornea, cataract and refractive surgery. Her areas of research interest are in laser applications in cornea, cataract and refractive surgery, restoring accommodation, and endothelial keratoplasty.

Figure-1.

Schematic representation of thickness measurements (patient 2, right eye) in Salzmann nodular degeneration. Thickness of the epithelium and thickness of the nodule was measured every 0.1 mm between white lines. a: thickness of the epithelium (46 μm); b: thickness of the nodule (68 μm); total surface thickness= a + b; c: thickness of the normal epithelium (78 μm).

Figure-2.

Slit lamp photo and ultra-high resolution optical coherence tomography images of Salzmann nodular degeneration.

White lines in slit-lamp pictures represent the section of ultra-high-resolution optical coherence tomography image.

White vertical lines in ultra-high-resolution optical coherence tomography images represent 100 microns.

Upper left: Slit lamp photo of patient 11, right eye. Upper right: Ultra-high-resolution optical coherence tomography image of patient 11, right eye. Nodule demonstrates uneven surface on the epithelial margin. Asterix corresponds to the nodule. White arrow: Bowman's layer.

Middle right: Slit lamp photo of patient 3, right eye. Middle left: Ultra-high-resolution optical coherence tomography image of patient 3, right eye. There is significant epithelial thinning and surface elevation above the nodule. Asterix corresponds to the stromal scarring. White arrow: Bowman's layer.

Lower left: Slit lamp photo of patient 1, right eye. Upper right: Ultra-high-resolution optical coherence tomography image of patient 1, right eye. Asterix corresponds to the limbus. White arrow: Heterogeneity in the reflectivity of the nodule with indistinct Bowman's layer. The edge of the nodule has the shape of a triangular spike.

Figure-3.

Slit lamp photo and ultra-high resolution optical coherence tomography images of Patient-6 with Salzmann nodular degeneration.

Upper left: Slitlamp photo of the right eye with early Salzmann nodular degeneration. Upper right: Ultra-high-resolution optical coherence tomography image of the right eye shows thickening at the epithelial basement membrane (EBM) and normal Bowman's layer. Asterix corresponds to EBM. White arrow: Bowman's layer. Maximum thickness of the EBM is 18 μ m.

Lower left: Slitlamp photo of the left eye with recurrent Salzmann nodular degeneration. Lower right: Ultra-high-resolution optical coherence tomography image of the left eye. There is significant thinning in the epithelium above the nodule. Bowman's layer cannot be differentiated (white arrow).

Figure-4.

Scatter plot of relationship between thickness of the epithelium and thickness of the nodule (right) ($r = -0.48; p < 0.0001$), thickness of the nodule and total surface thickness (left) ($r = 0.98; p < 0.0001$) in Salzmann nodular degeneration.

Figure-5.

Comparison of histology with ultra-high-resolution optical coherence tomography in Salzmann nodular degeneration (patient 11, right eye).

Upper image: Hematoxylin-eosin stain (original magnification $\times 100$); middle image: Gomori's one step trichrome stain (original magnification $\times 200$); Lower image: Ultra-high-resolution optical coherence tomography image. Asterix corresponds to the epithelium. Hematoxylin-eosin and trichrome stained sections demonstrate moderately dense, disorganized collagen fibers, with an irregular anterior surface and an overlying variably attenuated epithelium. Histopathology was correlated well with the ultra-high-resolution optical coherence tomography images.

Table-1

Ocular characteristics of patients with Salzmann nodular degeneration

No	Age	Sex	Eye	Ocular History	Ocular Medications	Ocular Surgery	BSCVA		Refraction	
							OD	OS	OD	OS
1	68	F	OU	Dry eye, Fuchs' dystrophy, OU cataract	Topical cyclosporine 0.05%, ATD	Conjunctival biopsy	20/30	20/20	-0.25+0.50×170	+0.50×175
2	13	M	OU	Ocular rosacea	Loteprednol		20/20	20/20	Plano	Plano
3	52	F	OD				20/20	20/15	-1.00 plano	-0.50 plano
4	70	M	OU	EBMD, OS Cataract			20/25	20/50	+4.00 +0.50×45	+0.75 +6.00×55
5	69	M	OD	PBK	Fluoromethalone	OD ECCE IOL (1999), OD PK+IOL Exchange (1999)	20/30	20/25	-4.25 +6.00×0.75	-0.75 +1.75×5
6	54	F	OU	Rosacea, CL wear	ATD	OU PTK+Superficial keratectomy (2008)*	20/25	20/60	-6.00 plano	-7.00 +1.00×25
7	79	F	OS	Dry eye, OU Cataract	ATD	OU Phaco	20/20	20/20	-2.00 +1.00×147	-1.00 +1.50×45
8	82	F	OU	OU Cataract, OU Dermatochalasis, OD CME	Nepafenac, Prednisolone acetate		20/40	20/30	-0.50 +1.25×10	+1.72 +2.00×180
9	43	M	OU	OU KCN, OD PK (1989)		OS PTK (for CL intolerance)	20/20	20/40	-7.50 +3.50×170	-6.00 +8.00×10
10	53	F	OD	Sjogren's disease, Dry eye	ATD	Conjunctival biopsy (to eliminate CIN) + Superficial keratectomy (2009)	20/20	20/20	-3.50 +1.50×180	-2.25 plano
11	82	M	OD	Dry eye, OD ERM	ATD	OD CE+IOL (1992), OS Phaco+AC IOL (2006) + Superficial keratectomy (2010)	20/80	20/40	+075 +3.50×150	-1.75 +1.50×150
12	52	F	OU	Dry eye	ATD	OD Superficial keratectomy (2009)	20/20	20/20	+0.75×180	+0.50×180

AC: Anterior chamber, ATD: Artificial tear drops, BSCVA: Best spectacle corrected visual acuity, CE: Cataract extraction, CIN: Conjunctival intraepithelial neoplasia, CME: Cystoid macular edema, CL: Contact Lens, EBMD: Epithelial basal membrane dystrophy, ERM: Epiretinal membrane, F: Female, IOL: Intraocular Lens implantation, KCN: Keratoconus, M: Male, OD: Right eye, OS: Left eye, OU: Both eyes, Phaco: Phacoemulsification, PK: Penetrating keratoplasty, PBK: Pseudophakic bullous keratopathy, PTK: Photo therapeutic keratectomy, VA: Visual acuity.

* Patient was operated in another institution.

Table-2

Structural characteristics of the nodules in Salzmann nodular degeneration

No	Location and Shape		Eye	BL	Minimum thickness of the epithelium	Average thickness of the epithelium	Thickness of the normal epithelium	Maximum thickness of the nodule	Average thickness of the nodule
	OD	OS							
1			OD	-	36	48	72	183	123
			OS	+/-	32	43	70	41	31
2			OD	-	46	51	78	68	59
			OS	-	40	44	47	66	62

No	Location and Shape		Eye	BL	Minimum thickness of the epithelium	Average thickness of the epithelium	Thickness of the normal epithelium	Maximum thickness of the module	Average thickness of the module
	OD	OS							
3			OD	+	25	37	79	333	243
4			OD	+/-	15	30	81	115	92
			OS	+/-	25	38	76	234	206
5			OD	+/-	26	40	61	86	44

No	Location and Shape		Eye	BL	Minimum thickness of the epithelium	Average thickness of the epithelium	Thickness of the normal epithelium	Maximum thickness of the module	Average thickness of the module
	OD	OS							
6			OD	+	36	38	55	77*	64
			OS	-	3	33	78	200	120
7			OS	+	12	38	71	119	81

No	Location and Shape		Eye	BL	Minimum thickness of the epithelium	Average thickness of the epithelium	Thickness of the normal epithelium	Maximum thickness of the module	Average thickness of the module
	OD	OS							
8			OD	+	14	16	58	149	138
			OS	+	18	36	56	74	49
9			OD	+	13	23	49	67	56
			OS	+/-	20	23	47	188	146
10			OD	+	17	27	72	284	198
11			OD	+	27	43	85	102	84

No	Location and Shape		Eye	BL	Minimum thickness of the epithelium	Average thickness of the epithelium	Thickness of the normal epithelium	Maximum thickness of the module	Average thickness of the module
	OD	OS							
12			OD	+/-	20	42	56	232	158
			OS	+/-	20	43	49	163	99

Grey colored areas demonstrate the location and shape of the nodules on the cornea. Dashed lines demonstrate the graft-host junction in eyes with penetrating keratoplasty. BL (+): Bowman's Layer can be differentiated, BL (-) Bowman's Layer cannot be differentiated, BL (+/-): Some of the images demonstrate Bowman's Layer, OD: Right eye, OS: Left eye.

All values are expressed as microns.

* Thickness of the anterior stromal infiltrate.