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High-resolution optical coherence tomography in the differentiation of inflammatory versus non-inflammatory peripheral corneal thinning

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Abstract

Purpose—To evaluate whether high resolution optical coherence tomography (HR-OCT) can aid in the differentiation of inflammatory versus non-inflammatory causes of peripheral corneal thinning.

Methods—Retrospective chart review of ten patients with peripheral corneal thinning and their respective slit lamp photographs and HR-OCT images.

Results—Ten patients were identified who had peripheral corneal thinning and HR-OCT images. Five had a clinical history consistent with Terrien's marginal degeneration (TMD) while five had thinning thought to be inflammatory in origin. In the eyes with presumed TMD, patients denied pain or inflammation. HR-OCT images demonstrated stromal thinning in the presence of an intact epithelium. The stroma underneath the epithelium in the area of thinning had a similar reflectivity pattern as the non-affected cornea. There was epithelial marsupialization evident in 2 of the 5 images. In the 4 patients with a clinical history of prior inflammation (bulbar hyperemia, pain), and in the one patient with active inflammation at the time of HR-OCT imaging, HR-OCT also demonstrated thinning with an intact epithelium. In contrast to the TMD group, in the group with signs of inflammation, a dense hyper-reflective band was noted in the stroma directly below the epithelium in the area of thinning, suggestive of scarring and/or cellular infiltration.

Conclusion—In patients with a clinical history of inflammation and corneal thinning, HR-OCT revealed a hyper-reflective band directly under the epithelium in the area of thinning which was not seen in patients with presumed non-inflammatory melts and thinning.

Introduction

The peripheral cornea is anatomically and physiologically distinct from the central cornea. Anatomically, the peripheral cornea is thicker than the central cornea¹, while the central

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cornea has a higher density of keratocytes and nerves.² Physiologically, the peripheral cornea is near lymphatics, blood vessels, and inflammatory cells³ and is thus more vulnerable to injury from autoimmune conditions.

Slit lamp biomicroscopy has been mainstay in the examination of the peripheral cornea, and it is still the first step in the approach to peripheral corneal diseases. The presence of injected limbal vessels, stromal thinning, an overlying epithelial defect, corneal opacities, lipid deposition and/or vascularization provide important diagnostic clues to the underlying etiology of the peripheral disease. Specifically, eye care professions use these signs to help differentiate inflammatory diseases such as peripheral ulcerative keratitis (PUK) and marginal keratitis from degenerative conditions like Terrien's marginal degeneration (TMD). Some patients, however, present with peripheral corneal thinning without a clear etiology or diagnosis. In some of these cases, slit lamp examination alone cannot definitely diagnose whether the thinning is inflammatory or degenerative in nature. For example, Terrien's marginal degeneration (TMD), as originally described, was thought to be a non-inflammatory, degenerative condition.⁴ Subsequently, various groups have reported corneal thinning in patients with conjunctival hyperemia, tearing, photophobia and irritation, but without systemic abnormalities, and termed this entity "inflammatory TMD".^{5, 6} Furthermore, systemic inflammatory diseases such as juvenile idiopathic arthritis (JIA)⁷, rheumatoid arthritis (RA)^{8, 9} and vasculitis¹⁰ have been associated with this variant of TMD. In these cases, it is difficult to determine the underlying disease process.

Anterior segment high resolution optical coherence tomography (HR-OCT) provides excellent anatomic resolution of the anterior segment structures and as such has been found clinically useful for the examination, diagnosis, and management of various anterior segment conditions.¹¹ For example, HR-OCT has been used to diagnose and monitor ocular surface squamous neoplasia (OSSN)^{12, 13}, help plan refractive and cornea surgeries¹⁴, and diagnose post surgical complications.¹⁵

Prior studies have demonstrated the ability of HR-OCT to detect morphologic changes in areas of thinning not apparent by clinical exam. For example, Hattori et al used HR-OCT to detect cavity formation in the stroma under the area of thinning in 2 patients with a clinical diagnosis of TMD, only one of which was apparent by clinical examination.¹⁶ Others have proposed a novel staging system based on the curvature of the cornea as assessed by HR-OCT in patients suffering from TMD.¹⁷ In this study, our aim was to evaluate whether HR-OCT could help differentiate between inflammatory versus degenerative peripheral corneal thinning. Herein we evaluated HR-OCT images of 5 patients with a clinical diagnosis of degenerative peripheral corneal thinning and compared them to HR-OCT images of 5 patients with peripheral corneal thinning whose etiology was thought to be inflammatory in nature.

Methods

The peripheral cornea of ten patients with peripheral corneal thinning was evaluated by Heidelberg Spectralis (OCT specifications: 40,000 A-scans/second, axial resolution 3.9 μ m, transverse resolution 14 μ m, scan depth 1.9 mm, average wavelength 870 nm). This was done

after routine ophthalmic examination, which included visual acuity, intraocular pressure [IOP] measurement, and slit-lamp examination. Retrospective chart review was performed to correlate HR-OCT images to clinical data, and the patient's privacy was protected during data collection and analysis. The Miami VA institutional review board approved the retrospective review of patient charts.

Results

We identified 10 patients with peripheral corneal thinning noted on examination that underwent imaging with HR-OCT. Mean patient age was 60.3 years, standard deviation (SD) 20.1, range 27-85 years. Seven patients were male and three female; eight self-identified as white, one as black, and one as Hispanic (Table 1). Demographics and comorbidities were similar between the groups (Table 2). None of the patients had a history of trauma or prior ocular surgery.

Of the ten patients, five had a history of indolent peripheral thinning, with no associated pain, redness or photophobia. None of these patients had a history of systemic autoimmune disorders. All eyes were white and quiet, without evidence of conjunctival hyperemia or corneal epithelial defects over the areas of peripheral corneal thinning, and therefore fit the profile of classic TMD (Figure 1a- c). HR-OCT images of the “non-inflammatory” subgroup (Figure 1d- f) demonstrated various degrees of corneal thinning, associated with focal stromal loss, an intact epithelium and normal stromal reflectivity directly under the epithelium in the area of thinning. Epithelial marsupialization was evident on HR-OCT in two patients (patient 1, Figure 1d and patient 4, Figure 1e), and stromal cavity formation in one (patient 3, picture not shown).

Five patients, on the other hand, had prior inflammatory symptoms and/or signs in the form of pain, photophobia, and injection, which historically had improved with either topical or systemic corticosteroids. None of these patients had a known history of an epithelial defect. Two of the five patients had a history of rheumatoid arthritis (patients 8 and 9), one a history of VZO affecting the right eye (patient 8), and 3 did not have a known systemic autoimmune or infectious disorder (Table 1). At the time of HR-OCT imaging, 1 patient had active symptoms and signs of inflammation in the form of pain, tearing, and conjunctival injection (patient 6) while 4 patients were without symptoms/signs of inflammation. Two were using topical cyclosporine emulsion 0.05%, 1 topical corticosteroid, and 1 both agents at the time of HR-OCT imaging. Patients with a prior history of inflammation had a variety of clinical presentations including inferior (patients 7, 8 and 9), superior (patient 10), and diffuse (patient 6) thinning of various length and depth. One patient had associated bulbar hyperemia (patient 6, Figure 2a), at the time when HR-OCT imaging was performed. In all 5 patients, HR-OCT images were different when compared to those of the non-inflammatory group. Noted were an intact epithelium, broad tissue loss and change in the character of the underlying stroma. Specifically, there was a hyper-reflective band of varying density in the stroma, directly below the epithelium in the area of thinning (white arrows, Figure 2d-f).

Discussion

Corneal thinning can have a multitude of potential etiologies, which may not be evident during the clinical examination. Inflammatory diseases such as rheumatoid arthritis and lupus are examples of conditions that have been associated with PUK, while diseases such as Terrien's marginal degeneration are thought to occur without inflammation in most cases. It can be difficult for the physician to determine the cause of peripheral corneal thinning, especially if no active inflammation is observed and/or the disease course is unknown. The etiology of thinning is an important consideration, as therapy depends on the underlying cause of the condition. Additionally, if inflammation plays a key role in the pathophysiology of a disease process, prognosis and follow up will vary compared to a degenerative condition.

HR-OCT provides a non-invasive, cross-sectional, high-resolution image of the corneal structure.¹⁸ It has been shown to be clinically useful for the examination, diagnosis, and management of various anterior segment pathologies¹¹⁻¹⁵. For the study of diseases leading to thinning of the peripheral cornea, however, the utility of this imaging modality is not well studied.¹⁹ Recently, Hattori et al. used HR-OCT to evaluate morphologic changes in TMD and demonstrated the existence of cavity formation in the peripheral cornea associated with the area of corneal thinning.¹⁶ The authors of this paper hypothesized that progressive stromal abnormalities may induce cavity formation in the peripheral stroma while maintaining intact epithelial and endothelial layers. However, the authors did not elaborate on whether this pattern was exclusive to TMD or whether this could be seen in other peripheral pathologies. Others have employed different imaging modalities such as confocal microscopy to image the corneas of patients suffering from classic TMD^{20, 21} but did not describe any specific patterns of thinning.

Importantly, no reports comment on how HR-OCT or other imaging modalities can help differentiate TMD from other peripheral corneal diseases that also lead to thinning. For example, a report of 14 eyes of 9 patients demonstrated the value of 3D HR-OCT in identifying topographic patterns in eyes with Mooren ulcer.²² However, the authors did not comment on whether there were any distinctive descriptive features of Mooren's ulcer on 3D HR-OCT images that could help differentiate this condition from others with similar physical findings.

In our study, patients with white, quiet eyes and thus presumed "classic" TMD showed an intact epithelium, focal stromal thinning, and the stroma under the epithelium was normal in character. Interestingly, two eyes had epithelial marsupialization and one eye had cavity formation on HR-OCT, consistent with prior literature reports.^{7,16} It is unclear, however, the significance of these patterns of thinning and whether they can point to a degenerative process when encountered. Perhaps the marsupialization occurred as epithelium persisted around a longstanding corneal melting process.

In contrast, patients with a history of inflammation, regardless of its initial trigger, had a bright, hyper-reflective band on HR-OCT imaging directly under the epithelium in the area of thinning, but no groove pattern or cavity formation. Interestingly, this area of hyper-

reflectivity was seen in 4 eyes with no clinical signs of inflammation at the time of HR-OCT imaging. Although the clinical photo for patient 9 shows bulbar hyperemia (Figure 2c), the HR-OCT was obtained 1 month later when the patient was not actively inflamed (Figure 2f). We suspect that this hyper-reflective band may be a clue that prior inflammatory mediators or inflammatory cells were present in that area of the cornea, or it may be stromal scarring associated with prior episodes of inflammation. The hyper-reflective band appears to be a non-specific finding of inflammation as this finding has been described in patients' status post persistent epithelial defect, corneal ulcer and phototherapeutic keratectomy (PTK). None of our patients, however, had a known history of a persistent epithelial defect or PTK. A limitation of our study is that patients with frank PUK or Mooren's ulcer were not included and this is an important avenue of future study.

Our findings are encouraging because, ultimately, treatment is dictated by whether inflammation plays a role in the corneal thinning. Improved understanding of the etiology of thinning could better direct the evaluation and management of the patient. Despite these encouraging initial observations, ours is a preliminary study and larger studies with longitudinal follow up will be needed to validate our findings. In conclusion, we found a difference on HR-OCT imaging in patients with peripheral cornea thinning and signs/symptoms of inflammation when compared to patients in whom the thinning was clinically attributed to a non-inflammatory degenerative process. As such, HR-OCT may be a useful tool in differentiating inflammatory versus degenerative peripheral corneal thinning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Non-inflammatory peripheral corneal thinning

Fig 1a, 1b, 1c: Slit lamp photos from patients without clinical or historical evidence of inflammation (patients 1, 4 and 5), showing a white and quiet conjunctiva, an intact epithelium, and thinning of the peripheral cornea (black arrows).

Fig 1d, 1e, 1f: HR-OCT images from the same patients showing an intact epithelium, varying degrees of stromal tissue loss, and minimal reflectivity changes in the stroma under the epithelium in the area of thinning. Marsupialization in the setting of tissue loss is evident in patients 1 and 4 (Figure 1d and 1e, white arrows). Of note, the reflectivity of normal cornea can vary. In this study, we focused on stromal reflectivity under the epithelium in the area of thinning.

Figure 2. Peripheral corneal thinning associated with inflammation

Fig 2a, 2b, 2c: Slit lamp photographs of the external eye of patients with active inflammation (patient 6 and patient 9) or prior history of inflammation (patient 8) and thinning of the peripheral cornea (black arrows).

Fig 2d, 2e, 2f: HR-OCT of the same patients demonstrating moderate, broad based corneal thinning, with an intact epithelium and a bright, hyper-reflective band (white arrows) in the stroma, directly under the epithelium in the area of thinning. The HR-OCT imaging for patient 9 (Figure 2f) was obtained at a later visit when the patient was not actively inflamed. No evidence of marsupialization or cavity formation is detected in any of these patients at any point.

Table 1

Demographics and clinical characteristics of the study population

#	Age/Gender	Eye(s) involved/Location	Pertinent systemic co-morbidities	Time from inflammation to OCT imaging	Pertinent medications at time of OCT imaging	Other prior therapy
1	81/WM	OU/ 270 degrees 11-9 o'clock	None	N/A	AT	none
2	67/WM	OU/ inferior	None	N/A	AT	none
3	31/WF	OD/ superior	None	N/A	AT	none
4	73/WM	OD/ superior	None	N/A	AT	olopatadine
5	85/WM	OU/ 360 degrees	None	N/A	None	none
6	27/WHM	OU/ 270 degrees 3-12 o'clock	None	Bulbar hyperemia at time of imaging	AT	Topical corticosteroid
7	68/WM	OU/ inferior	None	2 months	AT, topical cyclosporine	none
8	69/WM	OD/ inferior	Rheumatoid arthritis, h/o VZO	2 months	AT, topical cyclosporine, autologous serum tears, doxycycline, tofacitinib	none
9	59/WF	OD/ inferior	Rheumatoid arthritis	1 month	AT, topical corticosteroid, autologous serum tears, omega 3, hydroxychloroquine	Topical cyclosporine, doxycycline
10	43/BF	OS/ superior	None	1 month	AT, topical cyclosporine and corticosteroid, naproxen	none

W=white; B=black; H=Hispanic; M=male; F=female; AT=artificial tears; OD=right eye; OS=left eye; OU=both eyes; VZO=varicella zoster ophthalmicus

Table 2

Comparison of patients with and without a history of ocular inflammation and peripheral corneal thinning

	Patients with no history of inflammation	Patient with history of inflammation	p-value
Age, mean $\pm$ SD	67.4 $\pm$ 21.5 years	53.2 $\pm$ 18 years	0.43
Gender	80% male	60% male	0.62
Race	100% white	60% white	
Systemic autoimmune disorders	None	40%	0.18
Diabetes	20%	0%	0.4
Trauma	0%	0%	1
Glaucoma suspect	20%	20%	1

SD=Standard deviation