It Is All About the Angle: A Clinical and Optical Coherence Tomography Comparison of Corneal Ocular Surface Squamous Neoplasia and Corneal Pannus

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Purpose: The aim of this study was to compare clinical characteristics and high-resolution optical coherence tomography (HR-OCT) findings between corneal ocular surface squamous neoplasia (OSSN) and corneal pannus.

Methods: Retrospective study of 9 individuals, 3 with lesions histologically confirmed to be OSSN, 3 with lesions histologically confirmed to be pannus, 1 with lesions histologically confirmed to be OSSN followed by pannus, and 2 with long-standing, nonchanging lesions clinically diagnosed as pannus. All individuals presented to the Miami Veterans Affairs Medical Center eye clinic or Bascom Palmer Eye Institute between 2015 and 2023. Clinical characteristics and HR-OCT findings were evaluated and compared.

Results: Mean age of the population was 72.8 ± 5.1 years, 100% self-identified as male, 100% as White, and 11.1% as Hispanic. Clinically, all lesions appeared as whitish, opalescent, variably vascularized opacities extending from the limbus. None of the OSSN cases had vessels that extended to the border, whereas 4 cases of pannus (67%) had at least 1 vessel that reached the border. On HR-OCT, epithelial hyperreflectivity was observed in all cases of OSSN and pannus. Epithelial thickening was observed in all cases of OSSN, but in none of the cases of pannus. An important distinction between the 2 groups was the transition between normal and abnormal epithelium. All cases of OSSN had a vertical transition, whereas all cases of pannus had an angled transition.

Conclusions: Corneal OSSN and corneal pannus can both present with clinical findings of an opalescent lesion and may have overlapping findings on HR-OCT. Although both entities may show epithelial hyperreflectivity on HR-OCT, OSSN demonstrates an abrupt transition at a vertical, 90 degrees angle perpendicular to the Bowman layer, whereas pannus appears as an angled transition around 45 degrees. Therefore, the angle of transition between normal and abnormal epithelium can be useful in distinguishing between the 2 entities.

Key Words: ocular surface squamous neoplasia, corneal pannus, corneal lesion, high-resolution OCT, anterior segment, OSSN

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Ocular surface squamous neoplasia (OSSN) is the most common ocular surface malignancy in adults, occurring predominantly in elderly White men.[1] Risk factors for the development of OSSN include exposure to ultraviolet radiation, immunosuppression, and xeroderma pigmentosa.[2,3] The term OSSN encompasses a range of squamous epithelial malignancies, from dysplasia, to carcinoma in situ, to invasive squamous cell carcinoma.[1,4] OSSN arises from limbal stem cells and can involve the cornea and/or the interpalpebral, bulbar, or tarsal regions of the conjunctiva, most commonly in the nasal or temporal quadrants. Typical features of OSSN include irregular borders, variable elevation, and a gelatinous, papilliform, or leukoplakic appearance with accompanying blood vessel abnormalities.[1,5,6] However, OSSN may appear as a white opacity on the cornea without these accompanying features. Corneal pannus can masquerade as corneal OSSN because it commonly presents as a white opacity extending from the limbus, with variable

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vascularization and elevation.[7,8] Pannus is an ingrowth of fibrovascular tissue under the epithelium that can occur in the setting of various ocular surface abnormalities, including inflammation, contact lens use, trauma, and keratitis.[8–10] In some circumstances, it can be difficult to differentiate OSSN from pannus because of similarities in clinical presentation.

Various adjuvant technologies have been investigated to assist in differentiating OSSN from other ocular surface lesions. High-resolution optical coherence tomography (HR-OCT) is one tool that captures an in vivo, cross-sectional image of the anterior segment layers, allowing for differentiation of epithelial and subepithelial lesions.[11] On HR-OCT, features of OSSN include epithelial thickening, hyperreflectivity, and an abrupt transition from normal to abnormal epithelium.[12] In fact, we have previously found that an epithelial thickness cutoff of 120 to 140 μm had a 94% to 100% sensitivity and 100% specificity for differentiating OSSN from pterygium using 2 different HR-OCT platforms (a custom-built ultra-HR-OCT and RTVue HR-OCT).[13,14] However, epithelial thickening is not as prominent of a feature in corneal OSSN as compared to its conjunctival counterpart.[15] In addition to being a helpful diagnostic tool, HR-OCT can help the clinician detect subclinical OSSN (thereby avoiding early termination of topical therapy),[16] assist with surgical planning by examining tumor margins at the time of excisional biopsy,[17] and highlight features of subepithelial lesions such as melanoma, lymphoma, Salzmann nodular degeneration, and amyloidosis.[11,13,14,18] Thus, HR-OCT has become an important adjunct in the evaluation and management of ocular surface lesions, including OSSN.

Although features of pannus on HR-OCT have been previously described as a flat, hyperreflective lesion with normal epithelial thickness,[8] a gap in the literature is a comparison of HR-OCT images in corneal OSSN versus pannus. To bridge this knowledge gap, we present cases of individuals with corneal opacities due to both entities and examine clinical features and HR-OCT findings that may assist in differentiating these entities.

METHODS

A retrospective chart review was conducted of 9 individuals seen at the Miami Veterans Affairs Medical Center or Bascom Palmer Eye Institute with corneal opacities in which the differential included OSSN and/or pannus. Seven individuals underwent biopsy because of atypical corneal lesion features (eg, vessels that did not reach the edge of the lesion or irregular borders). Three individuals were found to have OSSN and 3 had a biopsy that was consistent with pannus. One individual had biopsy-proven OSSN and was later biopsied for a persistent corneal opacity, which was found to be consistent with pannus. Two additional individuals presented with long-standing, stable, fully vascularized corneal lesions, clinically consistent with pannus. A chart review was performed to gather clinical history, examination and imaging findings, histopathologic results (as available), and course in all 9 individuals. Epithelial thickness for OSSN and pannus was estimated on HR-OCT by comparing the thickness within (OSSN) or on top of (pannus) the lesion to the normal epithelium in the same cut. Results were presented as fold increase from the normal epithelium. Institutional Review Boards of the Miami Veterans Affairs Medical Center and the University of Miami approved this retrospective study, and the methods adhered to the tenets of the Declaration of Helsinki.

Descriptive statistics were used to investigate patient demographic and clinical information. The chi square test was used for categorical variables, and the independent samples *t* test was used for continuous variables. *P* values are 2-tailed and $P < 0.05$ is considered significant. Statistical analysis was performed using SPSS, version 28.0 (IBM Corp, Armonk, NYU).

RESULTS

The mean age of the 9 individuals was 72.8 ± 5.1 (range 63–81) years, 100% self-identified as male, 100% as White, and 11.1% as Hispanic. Individuals with either OSSN (n = 3) or pannus (n = 5) were roughly the same age (70.0 ± 6.1 vs. 73.8 ± 5.4; $P = 0.39$). Similarly, the individual with OSSN followed by a pannus was aged 76 years. None of the 9 individuals were current smokers. One individual in the OSSN group and 2 individuals in the pannus group had a history of skin cancer (33% vs. 40%; $P = 0.85$), as did the individual with both lesions. The individual with both lesions also had a history of immunosuppression from chemotherapy and radiation treatment for bladder cancer, but the remaining 8 individuals did not have a history of immunosuppression.

All 9 individuals presented with a whitish, opalescent opacity extending from the limbus onto the cornea. In the OSSN group, 2 lesions were located in the inferonasal quadrant and 1 in the inferotemporal quadrant. In the pannus group, 2 lesions were located in the inferonasal quadrant and 3 lesions were located in the inferotemporal quadrant. The lesion in the patient with OSSN followed by pannus was in the inferonasal quadrant. All lesions in the OSSN group had vascularity that did not reach the border. By contrast, most (4/6) of the lesions in the pannus group had at least 1 vessel that reached the edge of the lesion. In the individual with OSSN then pannus, 1 vessel extended to the border after treatment of the OSSN. Most of the lesions in both OSSN (3/4) and pannus (4/6) groups had irregular borders.

HR-OCT images revealed epithelial hyperreflectivity in all cases of both OSSN and pannus. When measuring the epithelial thickness of the hyperreflective epithelium, thickening was observed in all cases of OSSN. In pannus, a faint line distinguishing a thin hyperreflective epithelium from the underlying pannus could be seen, but in many areas, it was difficult to fully resolve.

The most notable difference between the groups was the transition point between normal and abnormal epithelium. In the OSSN group, the transition was a vertical 90 degrees angle to the Bowman layer, whereas in the pannus group, the transition was sloped at a ~45 degrees angle to the Bowman layer. Clinical findings and subsequent evaluation with HR-OCT and histopathology for each case are presented below.

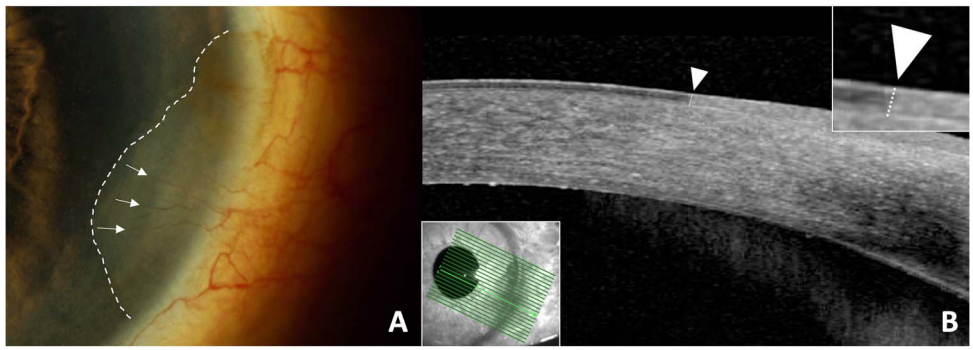

FIGURE 1. A, Slit-lamp photograph of a right, inferonasal opacity at the 3- to 4-o'clock position with irregular borders (dashed white line) and vascularization that did not extend to the edge of the lesion (white arrows). B, High-resolution optical coherence tomography (HR-OCT) demonstrated a hyperreflective, slightly thickened epithelium with an abrupt, vertical (90 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. (The full color version of this figure is available at www.corneajrnl.com.)

Case 1

A 73-year-old White non-Hispanic man with a smoking history was referred for a right, inferonasal (3–4-o'clock position) opacity with irregular borders and vessels that did not reach the edge. HR-OCT was suggestive of OSSN revealing epithelial hyperreflectivity, slight thickening (~×2.6 compared with a normal epithelium), and a vertical (90 degrees) transition between normal and abnormal epithelium (Fig. 1). Biopsy confirmed corneal dysplasia. The patient was treated with topical 5-fluorouracil 1% (5FU) for 4 cycles of 4 times daily for 1 week, followed by 3 weeks off. Owing to minimal response, this was followed by 10 months of daily topical interferon alfa-2b (IFNα2b) with complete resolution. No recurrence was noted over 2 years of follow-up.

Case 2

A 74-year-old White non-Hispanic man with an unknown smoking history was referred for a right, inferotemporal (5–10:30-o'clock position), mildly elevated, opalescent lesion with irregular borders and vascularization not extending to the edge of the lesion. On HR-OCT, epithelial hyperreflectivity, thickening (~×1.4 compared with a normal epithelium), and an abrupt, vertical (90 degrees) transition were noted, suggesting OSSN (Fig. 2). A biopsy of the lesion confirmed corneal intraepithelial neoplasia. To date, the patient has been treated with 6 cycles of 5FU with significant improvement of the lesion.

Case 3

A 63-year-old White non-Hispanic man who was a former smoker with a self-reported history of significant sun exposure and skin cancer was referred for a right, inferonasal (3–4-o'clock position) lesion. The lesion had smooth borders, with some vessels that did not extend to the edge. HR-OCT revealed features suggestive of OSSN with a hyperreflective, slightly thickened epithelium (~×1.7 compared with a normal epithelium) and a vertical (90 degrees) transition (Fig. 3). Biopsy confirmed corneal dysplasia. The patient was treated with 5 cycles of 5FU followed by 2 months of IFNα2b with complete resolution. No recurrence was noted over 1 year of follow-up.

Case 4

A 76-year-old White non-Hispanic man who was a nonsmoker with a history of skin and bladder cancer

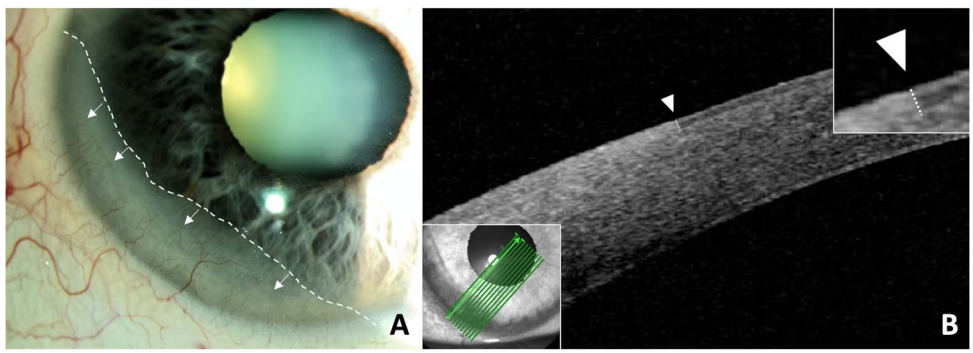

FIGURE 2. A, Slit-lamp photograph of a right, inferotemporal, opalescent lesion at the 5- to 10:30-o'clock position with irregular borders (dashed white line) and vascularization that did not reach the edges (white arrows). B, High-resolution optical coherence tomography (HR-OCT) showed a hyperreflective and slightly thickened epithelium with an abrupt, vertical (90 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. (The full color version of this figure is available at www.corneajrnl.com.)

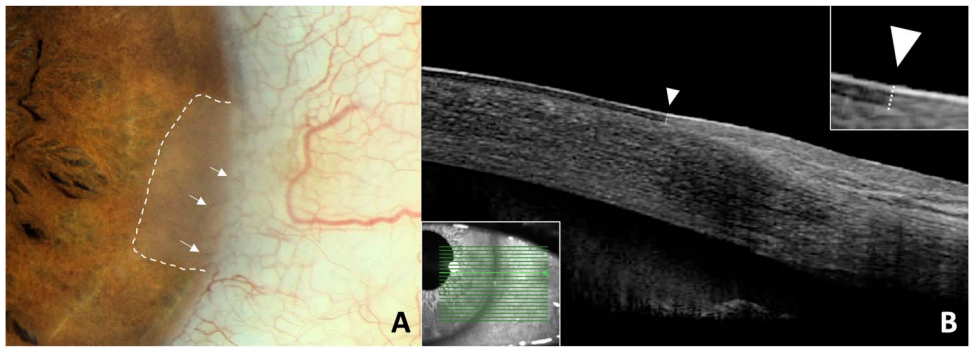

FIGURE 3. A, Slit-lamp photograph of a right, inferonasal, translucent lesion at the 3- to 4-o'clock position with smooth borders (dashed white line) and vessels that did not reach the edge (white arrows). B, High-resolution optical coherence tomography (HR-OCT) revealed epithelial hyperreflectivity, slight thickening, and an abrupt, vertical (90 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. (The full color version of this figure is available at www.corneajrnl.com.)

presented with a left, inferonasal (7–9-o'clock position), irregular, opalescent lesion with vessels that did not reach the border. HR-OCT suggested OSSN with a vertical (90 degrees) transition, but epithelial hyperreflectivity and thickening were minimal (~×1.3 compared with a normal epithelium) (Fig. 4). Biopsy confirmed corneal dysplasia. The patient was treated with 3 cycles of 5FU with improvement of the lesion; however, there remained a residual opacity with some vascularization that extended closer to the border in some areas.

After the medical treatment, the HR-OCT of the residual opacity revealed a thin, hyperreflective epithelium (~×0.8 compared with a normal epithelium) overlying a hyperreflective subepithelial lesion and an angled (~45 degrees) transition (Fig. 5). Repeat biopsy was consistent with pannus.

Case 5

A 77-year-old White Hispanic man with no smoking history was referred for a right, inferotemporal (7:30–8:30-o'clock position) opacity with irregular borders and vessels that did not reach the edge of the lesion. HR-OCT had some features suggestive of OSSN with epithelial hyperreflectivity; however, there was a thin epithelium (~×0.8 compared with a normal epithelium) and an angled (~45 degrees) transition with a hyperreflective subepithelial lesion (Fig. 6). Biopsy was consistent with pannus. The patient was observed for 2 years without a change in the lesion.

Case 6

A 71-year-old White non-Hispanic man who was a nonsmoker with a history of skin cancer and extensive sun exposure was referred for a left, inferotemporal (3–4:30-o'clock position) opacity. The lesion had irregular borders and vessels extending to the edge. HR-OCT suggested OSSN due to epithelial hyperreflectivity; however, the epithelium overlying a hyperreflective subepithelial lesion was thin (~×0.7 compared with a normal epithelium) and the transition of normal to abnormal epithelium was angled (~45 degrees), rather than perpendicular (Fig. 7). Biopsy of the lesion was consistent with pannus. There was no change in the lesion over 2-year follow-up.

Case 7

A 67-year-old White non-Hispanic man who was a former smoker was referred for a right, inferotemporal (6:30–8:30-o'clock position) opacity with irregular borders and some vessels that did not extend to the edge. HR-OCT was concerning for OSSN with epithelial hyperreflectivity;

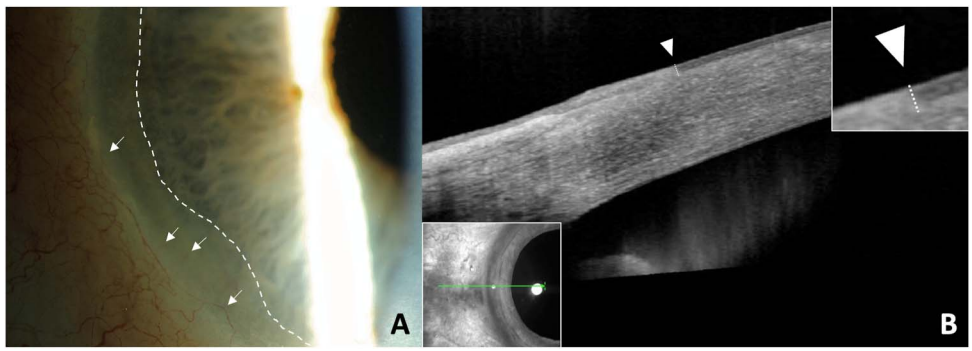

FIGURE 4. A, Slit-lamp photograph of a left, nasal, opalescent, irregular lesion at the 7- to 9-o'clock position (dashed white line) with vessels that did not reach the border (white arrows). B, High-resolution optical coherence tomography (HR-OCT) revealed epithelial hyperreflectivity with minimal thickening and a vertical (90 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. (The full color version of this figure is available at www.corneajrnl.com.)

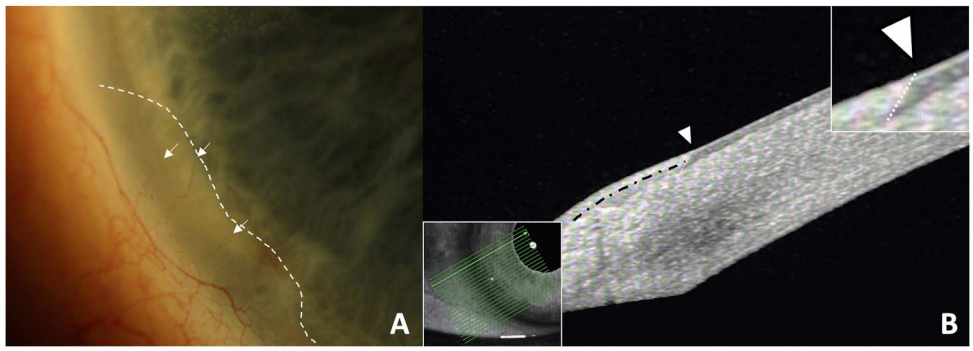

FIGURE 5. A, Slit-lamp photograph of a posttreatment OSSN. Note a nasal, opalescent lesion in the area of the previous OSSN at the 7- to 9-o'clock position with irregular borders (dashed white line) and 1 vessel extending to the edge (white arrows). B, High-resolution optical coherence tomography (HR-OCT) revealed a thin, hyperreflective epithelium over a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (~45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. Biopsy was consistent with pannus. (The full color version of this figure is available at www.corneajrnl.com.)

however, the epithelium was thin (~×0.8 compared with a normal epithelium) over a hyperreflective subepithelial lesion and the transition point was angled (~45 degrees), rather than perpendicular (Fig. 8). Biopsy was consistent with pannus. There has been no change in the lesion over 3-month follow-up.

Case 8

An 81-year-old White non-Hispanic man who was a former smoker with a history of skin cancer presented with a right, inferonasal (5–6-o'clock position) opacity. The lesion had smooth borders and vascularization extending to the edge. HR-OCT revealed epithelial hyperreflectivity and a thin epithelium (~×0.7 compared with a normal epithelium) overlying a hyperreflective subepithelial lesion. The transition from normal to abnormal tissue was angled (~45 degrees) (Fig. 9). No change was observed in the lesion over 1.5 years of follow-up.

Case 9

A 73-year-old White non-Hispanic man who was a never smoker was referred for a left, inferonasal (7–8:30-o'clock position) opacity. The lesion had smooth borders and vascularization extending to the edge. HR-OCT revealed epithelial hyperreflectivity and thinning (~×0.8 compared with a normal epithelium) overlying a hyperreflective subepithelial lesion with an angled (~45 degrees) transition (Fig. 10). The lesion has remained stable over 8-year follow-up.

DISCUSSION

We present 9 illustrations of partially or fully vascularized corneal opacities to examine clinical and HR-OCT

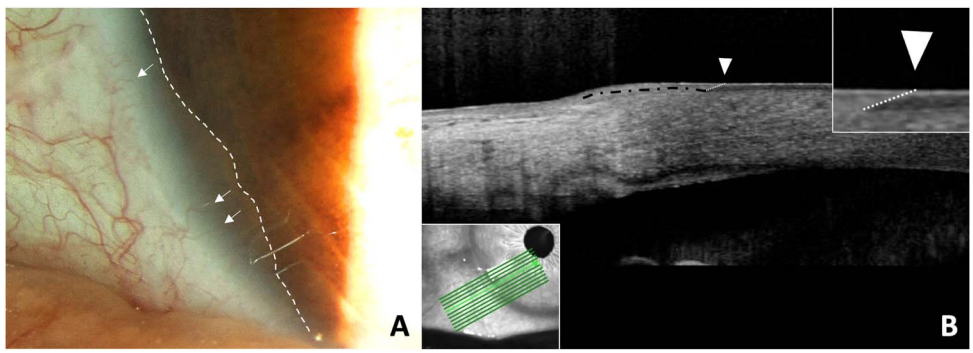

FIGURE 6. A, Slit-lamp photograph of a right, inferotemporal, irregular opacity (dashed white line) with vessels that did not reach the border (white arrows) at the 7:30- to 8:30-o'clock position. B, High-resolution optical coherence tomography (HR-OCT) showed a thin, hyperreflective epithelium over a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (~45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. Biopsy was consistent with pannus. (The full color version of this figure is available at www.corneajrnl.com.)

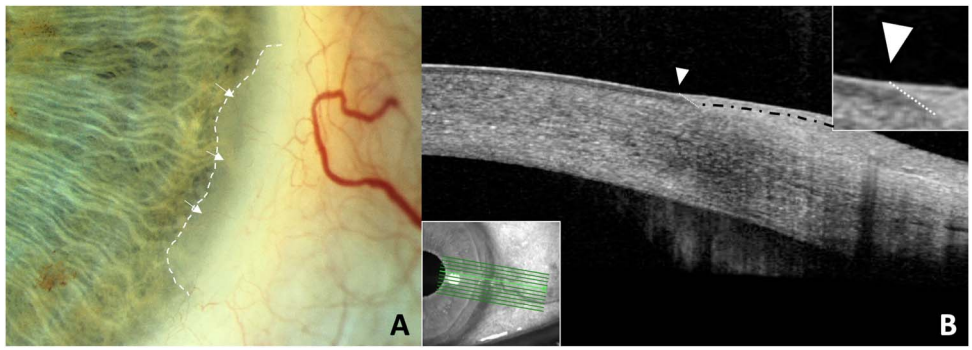

FIGURE 7. A, Slit-lamp photograph of a left, inferotemporal, irregular opacity (dashed white line) with vascularization extending to the borders (white arrows) at the 3- to 4:30-o'clock position. B, High-resolution optical coherence tomography (HR-OCT) showed a hyperreflective, thin epithelium over a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (~45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. Biopsy of the lesion was consistent with pannus. (The full color version of this figure is available at www.corneajrnl.com.)

differences between OSSN and corneal pannus. Clinically, some overlapping features were noted across cases. The opalescent corneal lesions extended from the limbus with some degree of vascularization in all cases. In the OSSN group, none of the lesions had vessels that extended to the border, whereas in the pannus group, the vessels extended to the edge of the lesion in all but 2 cases, which is expected in a "typical" pannus. In addition, in the OSSN group, most of the lesions had irregular borders, whereas 2 of the lesions in the pannus group had smooth borders. On HR-OCT, the most distinctive difference between the groups was the angle of the transition between normal and abnormal epithelium. OSSN lesions had a vertical transition at a 90 degrees angle perpendicular to the Bowman layer. By contrast, pannus lesions appeared as more of a "slope" around 45 degrees to the Bowman layer. Therefore, the main take away point from our 9 cases is that the angle of transition between normal and abnormal epithelium on HR-OCT can help differentiate between corneal OSSN and pannus.

The angle of transition has been found to be a helpful HR-OCT feature in the differentiation of other ocular surface lesions. For example, in a previous study, we compared the HR-OCT findings of conjunctival papilloma (n = 10) and papilliform OSSN (n = 10), which can have shared clinical features (eg, papilliform vessels).[19] On AS-OCT, all papillomas were found to have a "mushroom-shaped" transition with the normal epithelium growing under the abnormal hyperreflective epithelium, whereas all papilliform OSSN lesions had a vertical transition, as seen in our current series as well.[19] The transition zone has also been useful when examining pterygium on HR-OCT.[14] We have previously described features of pterygium on HR-OCT, including a hyperreflective lesion in the space between the epithelium and Bowman layer. Notably, the overlying epithelium was thin with a gradual transition between hyporeflective and hyperreflective epithelium[14] (Fig. 11). However, it is important to note that OSSN may also coexist with benign entities, such as pterygium. In a previous study, we found that 1.7% of

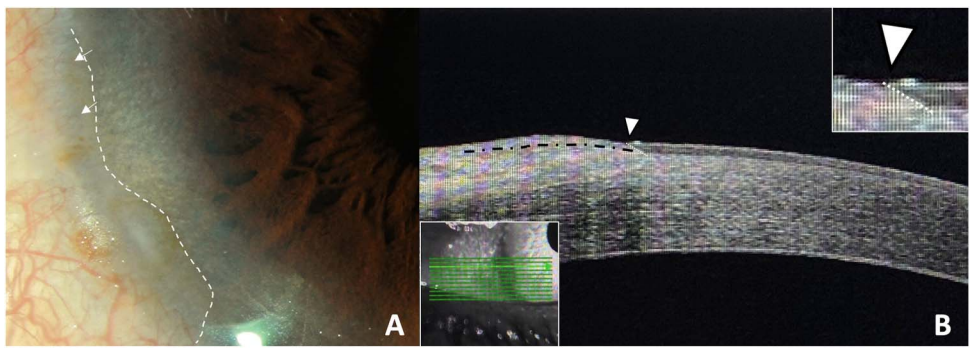

FIGURE 8. A, Slit-lamp photograph of a right, inferotemporal, irregular opacity (dashed white line) at the 6:30- to 8:30-o'clock position with some vessels that did not extend to the edge (white arrows). B, High-resolution optical coherence tomography (HR-OCT) showed a thin, hyperreflective epithelium over a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (~45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. Biopsy was consistent with pannus. (The full color version of this figure is available at www.corneajrnl.com.)

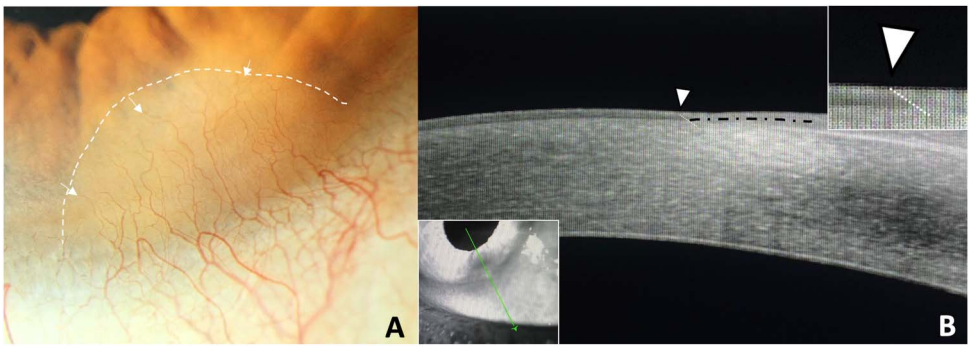

FIGURE 9. A, Slit-lamp photograph of a right, inferonasal opacity with smooth borders (dashed white line) at the 5- to 6-o'clock position with vessels that extended to the edges (white arrows). B, High-resolution optical coherence tomography (HR-OCT) showed a thin, hyperreflective epithelium with a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (~45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. No change was observed in the lesion over 1.5 years of follow-up. (The full color version of this figure is available at www.corneajrnl.com.)

surgically excised pterygia (n = 2005) harbored OSSN.[20] Although uncommon, clinicians should be aware of the possibility of having OSSN within a benign lesion, such as pterygium or pannus, and thus even 1 image with an abrupt 90 degrees transition within a raster that otherwise contains 45 degrees angles of transition should prompt further evaluation for OSSN.

Our current study adds an additional characteristic that can help clinicians differentiate between corneal OSSN and pannus. In pannus, the plane between the hyperreflective subepithelial lesion and thin, overlying hyperreflective epithelium can often be subtle and difficult to differentiate and measure. Furthermore, in cases where the thin epithelium can be differentiated from the underlying pannus, the hyperreflectivity of both may cause difficulty in visualizing the border of the subepithelial pannus. Therefore, the lesion may thus be misinterpreted as epithelial neoplasia. Noting the angle of transition between normal and abnormal epithelium can guide the physician to look for the plane and identify the lesion as subepithelial, which can aid in distinguishing the lesion from OSSN and in treatment monitoring, where a pannus may be seen clinically after OSSN resolution.

As with all studies, our findings need to be considered in light of its limitations. This includes a retrospective chart review with a limited number of patients who were all men, White, and living in South Florida. In addition, 2 of our "classic" pannus cases were not biopsied because this is not our standard of care. However, it is reassuring that their clinical appearance on HR-OCT was similar to the cases that were biopsied and found to be negative for malignancy and that no change was noted in the lesions over time. When evaluating the HR-OCT of a lesion, it is crucial to analyze the angle of transition from normal to abnormal epithelium in all available cuts. Although an angled transition can be used to identify pannus, an abrupt transition in any cut through the lesion should raise suspicion for OSSN. Despite these limitations, this study provides a key distinction between OSSN and pannus on HR-OCT, which can be used for more accurate diagnosis and treatment.

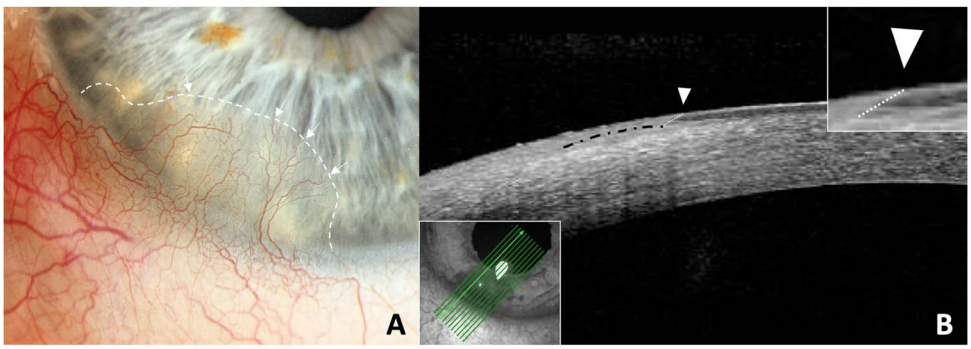

FIGURE 10. A, Slit-lamp photograph of a left, inferonasal, opacity with smooth borders (dashed white line) at the 7- to 8:30-o'clock position and vessels that extended to the edges (white arrows). B, High-resolution optical coherence tomography (HR-OCT) showed a hyperreflective and thin epithelium overlying a hyperreflective subepithelial lesion (black dotted and dashed line) and an angled (45 degrees) transition (white dotted line and arrowhead) between normal and abnormal tissue. The lesion has remained stable over 8-year follow-up. (The full color version of this figure is available at www.corneajrnl.com.)

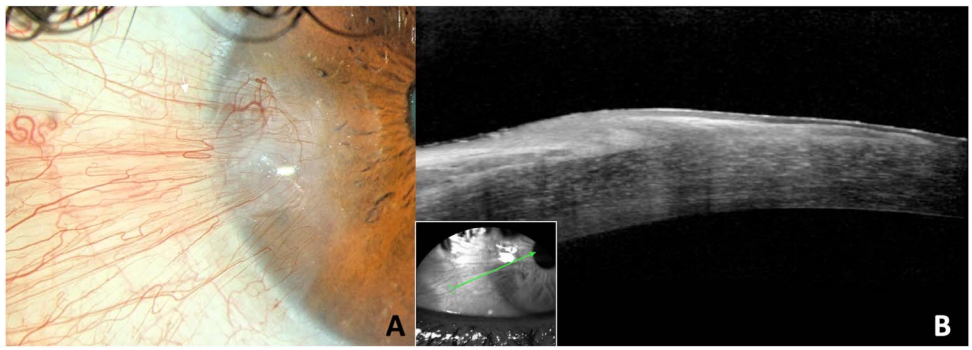

FIGURE 11. A, Slit-lamp photograph of left, nasal pterygium with vascularization that extended onto the cornea at the 8- to 10-o'clock position. B, High-resolution optical coherence tomography (HR-OCT) demonstrated a hyperreflective, subepithelial lesion in between the epithelium and Bowman layer with mild epithelial hyperreflectivity and normal thickness. There is a gradual transition from hyporeflective to hyperreflective epithelium. (The full color version of this figure is available at www.corneajrnl.com.)

To conclude, while both OSSN and pannus may appear as an opalescent limbal opacity with neovascularization, the angle of transition between normal and abnormal tissue on HR-OCT can be used as a differentiating characteristic. Specifically, OSSN has a vertical transition at 90 degrees to the Bowman layer, whereas pannus is angled at around 45 degrees to the Bowman layer. Attention to this detail on HR-OCT can be used to avoid unnecessary procedures and therapies, as well as to highlight cases that may seem more concerning and require incisional biopsy for confirmation.

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