High-Frequency Ultrasonographic Evaluation of Conjunctival Intraepithelial Neoplasia and Squamous Cell Carcinoma

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Objective: To evaluate the high-frequency B-scan ultrasonographic characteristics of squamous conjunctival neoplasia (conjunctival intraepithelial neoplasia and squamous cell carcinoma).

Methods: Each of 11 patients was examined with 20- and/or 50-MHz ultrasonography in a retrospective consecutive case series.

Main Outcome Measures: Ultrasonographic findings with clinical and histopathologic correlations.

Results: Eleven eyes of 11 patients (8 men) were affected. Disease involved the right eye in 6 (55%) of the patients and the left eye in 5 (45%) of the patients; it was multifocal in 5 (45%) of the eyes. All tumors extended to, or primarily involved, the limbal conjunctiva. One patient developed superficial spread overlying a functioning partial-thickness filtering bleb, 1 developed intraocular extension, 1 developed scleral invasion, and 3 developed orbital involvement before treatment. Results of ultrasonographic examinations showed that the superficial aspect of the smaller limbal tumors appeared as fusiform thickening of the conjunctiva. In all patients, the tumor surface was highly reflective in contrast to the characteristically low reflectivity seen within the tumor stroma. Intraocular tumor extension was variably reflective, but evidenced by blunting of the anterior chamber angle and thickening of the uvea. Orbital extension was viewed as low reflective tumor extension into the relatively hyperechoic orbital tissues.

Conclusions: High-frequency ultrasonography may be used to assess the extent of squamous conjunctival neoplasia. While the 50-MHz system offered better resolution, 20-MHz ultrasonography allowed for a wider and deeper field of view. High-frequency ultrasonography was useful in determining tumor thickness, shape, and internal reflectivity, and especially in revealing tumor extension into the sclera, eye, and orbit.

SQUAMOUS CONJUNCTIVAL neoplasia (SCN) can be confined to the conjunctival epithelium (conjunctival intraepithelial neoplasia) or termed squamous cell carcinoma if it invades the conjunctival substantia propria, the sclera, the eye, or the orbit.¹

The most common conjunctival malignancy in the United States, SCN has been causally related to UV-B radiation and human papillomaviruses 16 and 18.¹ Most SCN lesions affect the bulbar conjunctiva at the corneal-scleral limbus, are well demarcated, and can be surgically removed. Adjunct cryotherapy is commonly used to treat the deep and peripheral margins.² Many diffuse or multifocal tumors have been controlled with topical chemotherapy, which has recently become widely used.¹ Before treatment, the extent of most SCN lesions is defined by slitlamp biomicroscopy and documented by photography.

The current method to assess whether the tumor invades the eye wall is to use a probe (eg, a cotton-tipped applicator) to induce movement of the tumor. A freely mobile tumor is less likely to have invaded subjacent tissues. This type of assessment is crude, so posterior margins are typically revealed either during surgery or by histopathologic examination.

The use of high-frequency ultrasonography to examine conjunctival tumors was originally described by Pavlin and Foster.¹ The present study reports the use of high-frequency ultrasonography (20 and 50 MHz) to examine patients with conjunctival intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva. We describe the high-frequency ultrasonographic characteristics of SCN and...
high-frequency ultrasonography’s ability to uncover local invasion.

**METHODS**

Eleven patients were examined with high-frequency ultrasonography for SCN during the consultative examination. No specific consent was needed in that there were no known risks and there were proved potential benefits to ultrasonographic imaging.5-9

The 20-MHz images were obtained using a B-scan probe (Innovative Imaging Inc, Sacramento, Calif) covered with a cap (Tono-Pen) filled with water. Images were acquired, seen on the ultrasound machine (Innovative Imaging Inc), and captured on thermographic paper and in electronic formats. Longitudinal (anterior-posterior) and transverse images were acquired.

The 50-MHz images were obtained using an ultrasound biomicroscope (Paradigm Medical Industries, Salt Lake City, Utah). Photographs were taken and recorded on thermographic paper and in electronic formats. These images had 50-µm resolution.

A transverse scan is acquired when the back-and-forth movement of the transducer occurs parallel (tangential) to the limbus. Depending on how far anterior the probe sweeps, this movement can produce a cross-sectional image of the cornea and iris, the sclera and ciliary body, or the sclera and anterior choroid. For longitudinal scanning, the probe movement is rotated 90° from the position of the transverse scan. The back-and-forth movement can be seen as perpendicular to the limbus. High-frequency longitudinal B-scan cuts are oriented much like the spokes on a wheel with the pupil at its center.10 Longitudinal and transverse B-scan images were acquired in this study.

**RESULTS**

Eleven patients were examined and their results were reviewed by one of us (P.T.F.) between 1999 and 2002. Eight (73%) of the patients were men; 6 tumors (55%) involved the right eye, and 5 (45%) were multifocal (Table).

**GENERAL ULTRASONOGRAPHIC CHARACTERISTICS**

The tumor surface was hyperechoic in all patients (at 20 and 50 MHz). This finding was likely due to the abrupt change in acoustic impedance between the water and the solid tumor surface. In contrast, the tumor stroma was generally hypoechoic. As demonstrated by patient 2, this finding suggests that SCN (conjunctival intraepithelial neoplasia and squamous cell carcinoma) tends to form few intrastromal echogenic interfaces. The perilimbal aspect of the tumor typically appeared as fusiform thickening (Figure 1).

**SPECIFIC ULTRASONOGRAPHIC FINDINGS**

**Intraocular Tumor Extension**

Slitlamp findings consistent with intraocular tumor extension include neovascularization of the cornea and iris (Figure 2A). High-frequency ultrasonography revealed 2 findings suggestive of ocular penetration (blunting of the anterior chamber angle and uveal thickening [patient 4; Figure 2B]). Similarly, these findings were also seen on histopathologic evaluation (Figure 2C and D).

In another patient (patient 6), the tumor covered a functioning filtering bleb (Figure 3). In this patient, although the conjunctiva was covered by the tumor, there was no evidence of intraocular invasion (by clinical examination and ultrasonography) before and during surgery (visual inspection).

When the Corneal Surface Is Obscured by a Tumor

A multifocal tumor (in patient 7) exhibited massive extension of 2-mm-thick SCN onto the cornea (Figure 4A). High-frequency ultrasonographic imaging was used as an adjunctive examination to suggest there was no evidence of intraocular extension. Although no confirmatory histopathologic analysis was (at first) performed, the combination of clinical and ultrasonographic findings strongly argued against intraocular invasion (Figure 4B). These findings allowed for chemoreduction (with topical mitomycin), followed by resection with adjuvant cryotherapy. No evidence of intraocular extension was observed at excision.

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Eye</th>
<th>Focality</th>
<th>Location at the Limbus, Clock Position</th>
<th>Pathologic Findings</th>
<th>Tumor Stroma Reflectivity</th>
<th>USG Intraocular Findings</th>
<th>USG Extension Findings</th>
<th>USG Frequency, MHz</th>
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<tr>
<td>1/F</td>
<td>Left</td>
<td>Multifocal</td>
<td>3</td>
<td>SCC</td>
<td>Too thin</td>
<td>None</td>
<td>Local</td>
<td>20</td>
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<tr>
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<td>20</td>
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<tr>
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<td>20</td>
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<tr>
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<td>Uvea or orbit</td>
<td>20 or 50</td>
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<td>20</td>
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</table>

Abbreviations: CIN, conjunctival intraepithelial neoplasia; SCC, squamous cell carcinoma; USG, ultrasonography.

*Common to all patients: no preauricular or cervical adenopathy was noted; the tumor’s surface displayed high ultrasonographic reflectivity.
Figure 1. Patient 2. A, A slitlamp photograph of perilimbal squamous conjunctival neoplasia. B and C, The tumor's surface (arrows) is highly reflective, and the stroma is hypoechoic (20-MHz transverse [B] and longitudinal [C] sections).

Figure 2. Patient 4. A slitlamp photograph (A) demonstrated a perilimbal tumor with evidence of neovascularization of the deep and superficial cornea. A 20-MHz high-frequency B-scan ultrasonographic image (B) demonstrates blunting of the anterior chamber angle (arrow). This finding is correlated with histopathologic features demonstrating anterior chamber angle (C) and uveal (D) invasion (arrowheads) (hematoxylin-eosin, original magnification ×40).
Scleral Invasion

As in patient 10, high-frequency B-scan ultrasonography can reveal diminished reflectivity within the sclera beneath the tumor, consistent with intrascleral tumor invasion (Figure 5). This patient refused treatment and was unavailable for follow-up.

Orbital Extension

Three patients had orbital extension. In these patients, the relatively low reflective tumor could be differentiated from the relatively amorphous, but more hyperechoic, orbital tissues. High-frequency imaging is limited by the maximum penetration of 20- and 50-MHz ultrasonography. Therefore, it was not always possible to define the posterior margins of these tumors.

COMMENT

High-frequency ultrasonographic imaging (20 and 50 MHz) allowed preoperative imaging of conjunctival tumors. This technology improved our ability to assess ocular invasion before surgery, which proved valuable in the care of patients with SCN. For example, in patient 4, massive intraocular invasion prompted exenteration of the orbit. In patient 6, no evidence of intraocular invasion was present despite a tumor growing over an active sclerotomy site. This patient was treated with excision and cryotherapy. In patient 7, no evidence of scleral or corneal invasion was seen on the ultrasonographic scan, allowing chemoreduction with mitomycin, followed by excision and cryotherapy of the unifocal tumor residue. When documented, the absence of intraocular invasion allowed for the use of less invasive therapies.

Although not performed in this study, high-frequency ultrasonography could also allow for the measurement of tumor thickness. This method could be used in an assessment of tumor response to and treatment planning for conservative treatments (eg, topical chemotherapy and brachytherapy). Primary or recurrent SCN may masquerade as blepharconjunctivitis, uveitis, or orbital disease. Delays in diagnosis put patients at risk for intraocular extension and metastasis. High-frequency ultrasonography’s ability to monitor the sclera, the anterior chamber, and the uvea offers the potential to reduce the number of patients subject to delays in diagnosis.
In this study, we have provided cross-sectional views of the tumor surface, internal reflectivity, borders, and posterior margins of SCN. The tumor stroma was hypoechoic compared with the sclera, iris, and orbital tissues. This finding helps differentiate tumor from healthy tissues. Ultrasonographic evidence of blunting of the anterior chamber angle was correlated to its histopathologic appearance. High-frequency ultrasonographic imaging was clearly helpful for evaluating superficial and invasive SCN.

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REFERENCES