Nondiagnostic Conjunctival Map Biopsies for Sebaceous Carcinoma

Irina V. Koreen, MD, PhD; Andrew Flint, MD; Christine C. Nelson, MD; Bartley R. Frueh, MD; Victor M. Elner, MD, PhD

Objective: To compare the prevalence of nondiagnostic conjunctival map biopsies in patients with extensive pagetoid sebaceous carcinoma (defined as involvement of 3 or 4 quadrants of the ocular surface) and in patients without extensive pagetoid tumor (defined as involvement of 1 or 2 quadrants of the ocular surface).

Methods: Retrospective medical record and pathologic specimen review of 20 patients treated for sebaceous carcinoma at a tertiary care center. Biopsies with artifactual loss of or damage to the epithelium were categorized as nondiagnostic.

Results: One hundred forty-four map biopsies were reviewed, an average of 7.2 (standard deviation [SD], 4.4) biopsies per patient. Sixteen patients had extensive pagetoid tumor, 4 did not. Fifteen percent of biopsies were nondiagnostic. The frequency of nondiagnostic biopsies in patients with and without extensive pagetoid tumor was 37% and 10%, respectively. The odds ratio of nondiagnostic biopsy in the setting of extensive pagetoid tumor was 5.9 (95% confidence interval, 2.3-15.6; P = .004). Six of the sixteen patients (38%) without extensive pagetoid tumor had at least 1 nondiagnostic biopsy, with an average of 1.8 (SD, 1.6) nondiagnostic biopsies per patient (22% of biopsies). Two of the 4 patients (50%) with extensive pagetoid tumor had at least 1 nondiagnostic biopsy, with an average of 5.5 (SD, 3.5) nondiagnostic biopsies per patient (57% of biopsies).

Conclusions: Nondiagnostic, de-epithelialized conjunctival map biopsies are more common in patients with extensive pagetoid tumor than in those with limited or no pagetoid tumor. Artifactual epithelial loss may result from disruption of epithelial adhesion to the basement membrane by infiltrating tumor cells.

mor. At least 4 sections along the long axis of each map biopsy specimen were reviewed. If there was absence of the epithelium or if artifacts rendered the epithelium inadequate for diagnosis, the biopsy was categorized as nondiagnostic. If an epithelium adequate for diagnosis was present, the biopsy was categorized as diagnostic. All statistical analyses were performed using GraphPad (GraphPad software, San Diego, California; http://www.graphpad.com/quickcalcs/contingency1.cfm). Data are presented as mean (standard deviation).

**RESULTS**

The patient population was composed of 8 men and 12 women aged a mean of 69 years (18 years). The mean duration of symptoms was 17 months (21 months). The follow-up period was 26 months (19 months). There were no deaths. Four patients had extensive pagetoid tumor, defined as involvement of 3 or 4 quadrants of the ocular surface. These patients were treated with orbital exenteration.

A total of 144 map biopsies were reviewed; on average, 7.2 biopsies (4.4 biopsies) were sampled from each patient. The histopathologic analysis revealed variable specimen quality (Figure). In diagnostic biopsies, the conjunctival epithelium was well preserved and a diagnosis could be made regarding the presence or absence of pagetoid disease (Figure, A-D). Nondiagnostic biopsies had artifactual loss of or damage to the epithelium, particularly crush artifact, that affected the entire specimen (Figure, E-F).

Fifteen percent of the map biopsies were nondiagnostic. The overall frequency of nondiagnostic biopsies in patients with and without extensive pagetoid tumor was 37% and 10%, respectively. Categorical data analysis using 2-tailed Fisher exact test revealed that the frequency of nondiagnostic biopsies correlated with the presence of extensive pagetoid tumor (Table) (P = .008). The odds ratio of nondiagnostic biopsy in the setting of extensive pagetoid tumor was 5.9 (95% confidence interval, 2.3-15.6; P = .004). Diagnostic map biopsies averaged 3.1 mm (2.5 mm) in greatest dimension, while nondiagnostic map biopsies averaged 5.0 mm (3.2 mm) in greatest dimension. Thus, the propensity for loss of the epithelium is not attributable to inadequate specimen size.

Six of the 16 patients (38%) without extensive pagetoid tumor had at least 1 nondiagnostic biopsy. For these 6 patients, the average number of nondiagnostic biopsies per patient was 1.8 (1.6) (22% of biopsies). In 1 patient, a repeat biopsy in the vicinity of 2 previously nondiagnostic biopsies was negative. The remaining 5 patients did not undergo repeat biopsy because of complete absence of pagetoid disease in their other map biopsies. None of the 6 patients developed tumor recurrence during follow-ups averaging 29 months (range, 15-47 months). Two of the 4 patients (50%) with extensive pagetoid tumor had nondiagnostic biopsies. The average number of nondiagnostic biopsies for these 2 patients was 5.5 (3.5) per patient (57% of biopsies). In both cases, subsequent reexcision, including exenteration, revealed that the conjunctiva was positive for tumor in the vicinity of the previous nondiagnostic biopsies. The difference in the frequency of nondiagnostic biopsies between patients with

**Table. Frequency of Nondiagnostic Biopsies**

<table>
<thead>
<tr>
<th>Biopsy Quality</th>
<th>Extent of Ocular Surface Tumor Involvement, No. (%)</th>
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<tbody>
<tr>
<td></td>
<td>1 or 2 Quadrants</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>103 (90)</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

*Fisher exact test, P = .008.
and without extensive pagetoid disease was statistically significant (2-tailed Fisher exact test, \(P = .004\)).

**COMMENT**

We found that nondiagnostic, de-epithelialized conjunctival map biopsies are more common in patients with extensive pagetoid tumor than in those with limited or no pagetoid disease. Fortunately, our patients with extensive disease requiring exenteration were recognized as such owing to either tumor invasion into the conjunctival stroma of the de-epithelialized biopsies or extensive pagetoid involvement of the remaining specimens that warranted exenteration.

Artifactual epithelial loss may result from disruption of epithelial adhesion to the basement membrane by infiltrating, poorly cohesive tumor cells (Figure). Because these specimens are more fragile, clinicians and pathologists should take great care during specimen harvesting and processing to avoid de-epithelialization. In the context of known pagetoid spread from sebaceous carcinoma, total sloughing of the conjunctival epithelium is nondiagnostic but should not be interpreted as a negative biopsy. Instead, the surgeon should be aware of the fact that artifactual sloughing of the conjunctival epithelium in the context of pagetoid spread may indicate involvement of the conjunctiva in this area by a tumor. The threshold for repeat biopsy should be low if the original specimen is nondiagnostic, especially because of the easy accessibility of the ocular surface.

Recent advances in periocular reconstructive procedures have prompted study of tissue-sparing techniques, including cryotherapy\(^4\) and use of topical mitomycin C\(^3\) to treat pagetoid disease. Our results have implications for these modes of treatment, because the extent of involvement is more likely to be underestimated in patients with greater extent of disease.

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**Correspondence:** Victor M. Elner, MD, PhD, University of Michigan, W. K. Kellogg Eye Center, 1000 Wall St, Ann Arbor, MI 48105 (velner@umich.edu).

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**REFERENCES**


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