High Recurrence Rates of Basal Cell Carcinoma After Mohs Surgery in Patients With Chronic Lymphocytic Leukemia

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Objectives: To estimate and compare the recurrence rates of basal cell carcinoma (BCC) after Mohs surgery in patients with chronic lymphocytic leukemia (CLL) and controls and to evaluate differences among histologic subtypes of BCC.

Design: Retrospective assessment of clinical histories, postoperative notes, and surgical photographs.

Setting: Tertiary-care institution (Mayo Clinic, Rochester, Minn).

Patients: Twenty-four patients with CLL who underwent Mohs surgery for 33 BCCs and 66 controls matched for sex, age, and surgical year who underwent Mohs surgery for BCC of the head and neck from May 1988 through September 1998.

Results: Among the 24 patients with CLL who underwent Mohs surgery for 33 BCCs, there were 4 recurrences. The cumulative incidence of recurrence on a per-tumor basis was 3% at 1 year, 12% at 3 years, and 22% at 5 years. Basal cell carcinoma was 14 times more likely to recur in patients with CLL than in controls ($P = .02$).

Overall, there were no significant differences between patients with CLL and controls in preoperative tumor size (median, 1.6 cm vs 1.4 cm; $P = .18$) and proportion of aggressive histologic subtypes of BCC (58% vs 41%; $P = .12$).

Conclusions: Recurrence rates of BCC are significantly higher after Mohs surgery in patients with CLL. Overall, patients with CLL do not appear to have significantly larger BCCs or more aggressive histologic subtypes of BCC. In patients with CLL, close surveillance is warranted for recurrence of BCC and a decreased threshold is indicated for subsequent biopsies.

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THE AGGRESSIVE NATURE OF nonmelanoma skin cancer in patients with chronic lymphocytic leukemia (CLL), as evidenced by significantly greater subclinical tumor extension, makes Mohs micrographic surgery an optimal technique for management. Use of micrographic surgery routinely results in the highest cure rates, concomitantly maximizing the preservation of normal adjacent tissue to simplify reconstruction of the defect.

Chronic lymphocytic leukemia is the most frequent form of leukemia in adults in Western countries. The estimated incidence rate of CLL in the United States is 8100 new cases per year. However, the true incidence may be up to 37% higher than estimates derived from tumor registries. Because it is relatively indolent, this disease accounts for approximately 0.8% of all cancers and nearly 30% of all leukemias at any time. Patients with CLL have an increased risk of developing subsequent malignant neoplasms because of impaired immune function. Specifically, their risk of developing skin cancer is increased 8- to 13-fold, making cutaneous neoplasms the type of malignancy that is most frequently associated with CLL. Case reports and series suggest a substantially higher potential for recurrence and metastasis of skin cancer in patients with lymphoma or leukemia. The purpose of our study was to estimate and compare, in a controlled, objective manner, recurrence rates for basal cell carcinoma (BCC) after Mohs surgery among patients with CLL. Moreover, we sought to compare differences in the frequency of aggressive histologic subtypes of BCC and clinical tumor size in patients with CLL and controls.

METHODS

The study was approved by the institutional review board of the Mayo Foundation, Rochester, Minn. Patients with a history of CLL who had undergone a Mohs operation were identified from the medical and surgical indexes,
which contain diagnostic and procedure information from the Mayo Clinic medical records. For each patient with CLL and a BCC, we selected 2 residents of the local county, Olmsted County, Minnesota, who were the same sex as the patient, whose ages were within 2 years of the age of the patient, who underwent a Mohs procedure within 1 year of the patient, and who did not have CLL to create the control group. The controls were selected from the local county in an effort to identify patients with long-term and recent follow-up. The patients’ medical records were retrospectively assessed for maximal preoperative tumor diameter, tumor histologic subtype, follow-up after the Mohs operation, and recurrence. Aggressive BCC histologic subtypes were defined by morpheaform, micronodular, and metatypical features. Nodular features classified the tumor as a nonaggressive histologic subtype. Tumors were defined as recurrent if the Mohs operative defect overlaid any portion of the original Mohs excision scar. All tumor recurrences were confirmed by preoperative and postoperative photographic comparisons of the original and follow-up Mohs procedures. Chronic lymphocytic leukemia is diagnosed when the published criteria of the National Cancer Institute–Sponsored Working Group are fulfilled. Typically, in the peripheral blood, the number of small, mature-appearing lymphocytes is more than 5000/µL. Although bone marrow examination is not required for the diagnosis of CLL to be made in general practice, aspirate smears show that more than 30% of all nucleated cells are lymphoid. All study CLL cases had been confirmed by an evaluation in the Division of Hematology and Internal Medicine.

The characteristics, histologic subtype, and maximal preoperative diameter of the BCCs were compared between patients and controls using the Fisher exact test, the χ² test, and the Wilcoxon rank sum test, as appropriate. The Kaplan-Meier method was used to estimate the cumulative incidence of BCC recurrence on a per-tumor basis. Duration of follow-up per tumor was calculated from the date of the Mohs procedure to the date of the latest follow-up (dermatologic evaluation, clinical visit, or death if there were no subsequent evaluations after the Mohs procedure). Associations between patient type (case patient or control patient) or histologic subtype (aggressive or nonaggressive) and recurrence were assessed by fitting Cox proportional hazards models. The correlation between multiple tumors per patient was accounted for in the model by using the robust standard error method of Wei et al. The strength of an association with recurrence was summarized with a risk ratio (RR) and 95% confidence interval. All calculated P values were 2-sided, and P<.05 was considered statistically significant. Statistical analyses were performed using an SAS software package (SAS Institute, Cary, NC).

**RESULTS**

The sample included 24 patients with CLL who were treated with the Mohs procedure for 33 BCCs from May 1988 through September 1998. Seven patients also had squamous cell carcinoma (SCC) and were included in a recent study of SCC recurrence rates among 28 patients with CLL. All the BCCs were located on the head or neck. Twenty (83%) of the 24 patients were male. All but 8 of the study patients are deceased. The mean age of the study patients at the time of the first Mohs procedure for BCC was 74 years (range, 62-86 years). During this period, 1 BCC developed in each of 18 patients, 2 BCCs developed in each of 4 patients, 3 BCCs developed in 1 patient, and 4 BCCs developed in 1 patient. The distribution of the histologic subtypes of the 33 tumors was as follows: 14 nodular (42%), 9 morpheaform (27%), 9 metatypical (27%), and 1 micronodular (3%) (Table). Based on the maximal preoperative diameter of each of the 33 tumors, the mean (SD) size was 1.9 (1.2) cm (median, 1.6 cm; range, 0.7-5.5 cm).

Fifty-eight (88%) of the 66 control patients were male, and 26 are deceased. The mean age of the control patients at the time of the Mohs procedure for BCC was 75 years (range, 60-87 years). All tumors in the control group were on the head and neck. The distribution of the histologic subtypes of the 66 tumors was as follows: 39 nodular (59%), 18 morpheaform (27%), 3 metatypical (5%), and 6 micronodular (9%) (Table). The tumor size was 1.6 (1.0) cm (median, 1.4 cm; range, 0.6-5.5 cm).

Four patients with CLL had recurrences: metatypical tumors in 2 patients at 5 and 23 months, respectively, and nodular tumors in 2 patients at 14 and 55 months, respectively. Among the remaining 20 case patients (29 BCCs) with no known recurrences, the mean duration of follow-up was 4.0 years (median, 3.5 years; range, 14 days to 13.7 years). Among the control pa-

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**Histologic Subtypes and Recurrence Rates of Basal Cell Carcinoma in Patients With Chronic Lymphocytic Leukemia (CLL) and Controls**

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Patients With CLL (n = 33)</th>
<th>Controls (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Tumors</td>
<td>No. of Recurrences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td>19 (58)</td>
<td>2</td>
</tr>
<tr>
<td>Morpheaform</td>
<td>9 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Metatypical</td>
<td>9 (27)</td>
<td>2</td>
</tr>
<tr>
<td>Micronodular</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Nonaggressive (nodular)</td>
<td>14 (42)</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td>33</td>
<td>4</td>
</tr>
</tbody>
</table>

*The cumulative incidence estimates were calculated using the Kaplan-Meier method. The numbers in parentheses are the number of tumors that were still at risk of recurrence.
†Tumors recurred at 5 and 23 months.
‡Tumor recurred at 47 months.
§Tumors recurred at 14 and 55 months.
Patients with CLL with cumulative 3-year recurrence rates greater than 12%, were 13.7 times more likely to have a recurrent BCC after Mohs surgery than controls. The success rate of Mohs surgery in the general population is outstanding, considering that tumors treated by this technique are large and difficult to treat. The patients who are best treated with the Mohs technique are those who have BCCs that are recurrent, incompletely excised, larger than 2 cm, poorly defined clinically, histologically aggressive, or located where they may have a propensity to grow along fascial or embryonic fusion planes. Success rates with the use of Mohs technique for the treatment of primary BCCs are 97% to 99%. For recurrent BCCs, success rates are 96% to 98% with the Mohs technique compared with 50% to 65% with usual methods. Our BCC control group had a 2% recurrence rate, which is similar to prior reported estimates.

Numerous factors contribute to impaired host immune function in patients with CLL, including hypogammaglobulinemia, low levels of complement, impaired granulocyte function, altered leukemic cell expression of class II major histocompatibility complex antigens, altered expression of T-cell receptor variable region genes, and functional defects in bystander and other T-cell subsets. B cells in patients with CLL also contribute to impaired host immune function by elaborating immunosuppressive factors. B cells in patients with CLL can rapidly down-regulate expression of CD40 ligand (CD154) on activated T cells, thereby hindering activated T-cell interaction with bystander normal B lymphocytes or other antigen-presenting cells. Such altered immune function may predispose patients with CLL to increased development of skin cancer and, in turn, to tumors with a greater propensity for aggressive behavior.

The Mohs technique is based on complete extirpation of contiguous tumors through total microscopic visualization. Thus, one would expect uniform recurrence rates regardless of underlying CLL. The most likely reasons for failure of Mohs micrographic surgery in patients with CLL involve a quantitatively exaggerated yet qualitatively inadequate immune response. Dense leukemic infiltrates associated with more than one third of the tumors may pose an intraoperative challenge by obscuring residual BCC tumors during interpretation of histologic margins. Not surprisingly, when reevaluating the original Mohs frozen sections that were available for review from 3 cases of recurrent BCC, we found dense infiltrates present in 1 case (33%); this incidence closely correlated with that reported in a previous study. Furthermore, single or a few malignant cells originating as infiltrating pseudopodlike extensions from the primary tumor may be difficult to identify histologically on frozen section. Such remnants may undergo unopposed proliferation in immunocompromised patients as opposed to being destroyed by a normally effective inflammatory response in patients with competent immune systems. Also, an inadequate or perturbed leukemic immune response may promote incomplete regression in portions of tumor, leading to malignant cell discontinuity that creates false-negative margins during micrographic surgery. A rapidly fixed, permanent section of the peripheral margin for hematoxylin-eosin or cytokeratin staining may assist in assessment of the presence of residual tumor; we have not routinely used these techniques. Rapid cytokeratin antibody staining may enhance the sensitivity of tumor identification and decrease tumor recurrence rates.

The size and histologic classification of the BCC correlate with prognosis. Aggressive tumors tend to be larger or to exhibit infiltrative features, findings that, in turn, predict higher recurrence rates. Because numerous case series anecdotally suggest aggressive histologic behavior of nonmelanoma skin cancer in patients with CLL, larger BCCs with morpheaform, micronodular, and metatypical subtypes would be expected to predominate in such patients. However, in our study, there was no significant difference between the case patients and the control patients in the median preoperative tumor size (1.6 cm vs 1.4 cm, respectively; \( P = .18 \)) or in the overall proportion of aggressive tumors (58% vs 41%, respectively; \( P = .12 \)). Although the difference was not statistically significant, aggressive BCCs were 5 times more likely to recur in the case patients than in the control patients (\( P = .17 \); 95% confidence interval, 0.5-40.2). However, nonaggressive BCCs were significantly more likely to recur in the case patients than in the control patients (\( P = .003 \)). The fact that the difference in the rate...
of recurrence was statistically significant for nonaggressive tumors, but not statistically significant for aggressive tumors, implies that aggressive tumor subtype did not affect tumor recurrence in this cohort of patients with CLL. Furthermore, after a statistical model controlling for histologic subtype (aggressive or nonaggressive) (RR = 13.3) or tumor size (RR = 13.5) was applied, no significant difference was identified between adjusted and nonadjusted (RR = 13.7) recurrence rates. Thus, higher BCC recurrence rates in patients with CLL do not appear to be attributable to larger size or a greater proportion of histologically aggressive tumors.

In conclusion, this study compares the recurrence of BCC in patients with CLL and controls. The significantly greater frequency of BCC recurrence in patients with CLL after Mohs surgery correlates with 1-, 3-, and 5-year SCC recurrence rates of 4%, 15%, and 19%, respectively, in the same population. In many ways, our findings raise more questions than answers. Such questions center around the contiguous tumor theory on which the efficacy of Mohs surgery is based and the role of an intact immune system in clearing tumor remnants. Overall, the proportion of aggressive tumor differentiation or larger tumor size did not differ between patients with CLL and controls, and neither factor significantly contributed to increased recurrence rates in CLL. Yet, the significantly increased propensity of BCC to undergo squamous differentiation and the preponderance of SCC rather than BCC in patients with CLL suggest that an uncompromised, antitumor immune response counters SCC development. A limitation of this study is the relatively small number of patients with CLL and the few number of recurrences in both groups. The sample size affects the precision in estimating risk ratios, which is reflected in the widths of the reported confidence intervals. More prospective future studies in immunosuppressed patients and in animals with skin cancer will aid in revealing the true behavior of malignancy. In the meantime, closer surveillance for BCC recurrence in patients with CLL and a decreased threshold for subsequent biopsies is warranted.

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REFERENCES


