Evaluation of Circulating Malignant Cells Provides Prognostic Information in Cutaneous T Cell Lymphoma

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Peripheral blood lymphocyte morphology was evaluated prospectively by light microscopy of blood smears and E rosette preparations in 160 patients with cutaneous T cell lymphoma (CTCL). Blood involvement was related to the type of cutaneous T-stage, being present in 90% of patients with erythroderma (T4), 27% of those with cutaneous tumors (T3), 9% of those with generalized (T2), and 0% of those with limited skin plaques (T1). Untreated patients with blood involvement (38 of 106) had a higher frequency of CTCL in lymph nodes and viscera and survival inferior to that of patients with normal or nondiagnostic lymphocyte morphology (P < .001). Multivariate analysis showed skin stage and age to be the most important pretreatment risk factors for survival. Although blood involvement was not an independent risk factor for the entire group, it appeared to have some adverse influence in the T2/T3 subsets (P = .051). Both lymphocytosis and size distribution of the circulating CTCL cells at initial diagnosis influenced survival. Patients with "mixed cell" cytology (>20% large [>11 μm] CTCL cells), had a worse survival than those with predominantly small circulating CTCL cells (P = .009). The former were more likely to have aggressive features, including lymph node effacement by tumor (P < .001) and visceral disease (P = .074), than were "small cell" patients. Our data indicate that detailed review of the blood lymphocyte morphology in patients with diagnosed or suspected CTCL is helpful in predicting extent of disease and prognosis.

For many years, mycosis fungoides (MF) was considered primarily a cutaneous disorder, with plaques, cutaneous tumors, and erythroderma recognized as types of skin involvement.1 In 1938, Sézary and Bouvrain described a group of patients with generalized erythroderma who had large, bizarre mononuclear cells in the peripheral blood.2 Similarities between the erythrodermic form of MF and the Sézary syndrome (SS) were soon recognized. In 1970, Crossen and colleagues showed that the abnormal cells of SS were malignant lymphocytes; subsequently, both MF and SS were shown to be malignant proliferations of mature helper T cells.4,5 Because of their similar clinical and histopathologic features, the term cutaneous T cell lymphoma (CTCL) has been used to include both MF and SS5 in a spectrum of disease. At one end of the spectrum is non-erythrodermic MF limited to the skin; at the other extreme is SS with erythroderma and frank leukemia.

Using light microscopy, Clendenning and colleagues reported that up to 20% of advanced plaque/tumor MF patients without erythroderma had circulating convoluted cells similar to those of SS.6 Other investigators reported that these cells could be identified by cytologic features and electron microscopy as well as by cyogenetic and DNA content analyses.7-15

Several studies addressed the clinical implications of blood involvement16-19; however, systematic evaluation prior to therapy was not fully explored until recently. Vonderheid and colleagues showed that prognosis was influenced adversely when there were >10% Sézary cells17 or increased proportions of large convoluted cells.19 We previously reported that peripheral blood involvement had significant impact on prognosis in a small group of prospectively staged patients.20,21 That series has now been extended to 160 patients with CTCL to define the frequency, extent, and morphological variety of circulating CTCL cells detected by light microscopy and to determine the importance of these features for prognosis.

METHODS AND MATERIALS

Patients. The clinical features of the 160 CTCL patients studied by the NCI-Navy Medical Oncology Branch and the Hematology, Dermatology, or Medical Oncology Sections of the Washington Veterans Administration Medical Center between June 1975 and March 1984 are shown in Table 1. Informed consent for the staging procedures and subsequent treatment was obtained for all patients according to the policies of the human studies review boards of the National Naval Medical Center or the Veterans Administration Medical Center and the National Institutes of Health. Group I comprised 105 patients who were staged within 12 months (median 1.4 months) of initial diagnosis and had received no systemic chemotherapy prior to staging. The remaining 55 patients (group II) had received prior chemotherapy or were staged >1 year from diagnosis and were not evaluated for survival. Group I patients were entered into two sequential CTCL treatment protocols. The first 39 patients were treated with total-skin electron-beam radiotherapy and chemotherapy22; the remaining patients were randomized to either intensive combined modality therapy or sequential palliative therapies.23 Group I patients were followed for a median of 54 months.

Staging evaluation. One dermatologist (A.B.F.) characterized the skin lesions using the TNM classification for cutaneous T cell lymphoma.24 In the first 40 patients, a lymph node was biopsied only if lymphadenopathy existed. Subsequently, blind biopsies were also attempted in patients without palpable nodes. The histopathologic features, including lymph node effacement by tumor and visceral involvement, were used to stage the patients. For patients with lymphoma, the presence of lymph node effacement by tumor or visceral disease was used to stage the patients. The extent of disease varied from <20% tumor involvement to frank leukemia.

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findings of the lymph node biopsies were classified according to the number of atypical cells in paracortical node areas and the degree of node effacement.25 This classification describes node involvement as LN1 (no atypical cells), LN2 (small clusters of atypical cells), LN3 (large clusters of atypical cells), and LN4 (partial or total effacement of normal architecture by malignant cells). The initial staging evaluation also included a chest x-ray, lymphangiogram, liver biopsy, and bone marrow biopsy. In the last 60 patients, liver biopsy was performed only if adenopathy, LN3 or LN4 node histopathology, or blood involvement existed.

Peripheral blood studies. Peripheral blood lymphocyte morphology was evaluated by one hematologist (G.P.S.) using light microscopy at x1,500 magnification without knowledge of the type of skin lesions or other physical findings. Every patient had a WBC count and a differential count of a Wright's-Giemsa-stained smear of skin lesions or other physical findings. Every patient had a WBC count and a differential count of a Wright's-Giemsa-stained smear. The morphology of 200 E-rosetted T lymphocytes was determined.26 The morphology of 200 E-rosetted T lymphocytes was then examined on Wright's-Giemsa-stained cytocentrifuge preparations. Fluorescent antiimmunoglobulin antisera (Meloy, Springfield, VA) and fluorescence microscopy were used to determine the percentage of B cells in 90 patients.

The criteria for the diagnosis of CTCL infiltration of the blood were developed during our initial comparisons of lymphocyte morphology of CTCL patients with that of normal individuals and patients with nonmalignant skin disorders or lymphopenia.29 Atypical cells were grouped in the following categories, except for lymphoid cells with cytoplasmic granules which were excluded. Category I describes small convoluted lymphocytes, cells ≤11 μm in diameter, with a nuclear density similar to or greater than that of normal lymphocytes and having nuclear grooves, cleaves, convolutions, or folds (Fig 1a through c). Category 2 describes large convoluted lymphocytes, cells >11 μm in diameter with nuclear abnormalities as described in category 1 or with dense hyperchromatic nuclear chromatin (Fig 2a,b). Category 3 describes "atypical" nonconvoluted lymphocytes, cells >11 μm without nuclear irregularities or convolutions but containing fine nuclear chromatin and/or nucleoli (blastlike or "transformed" cells, Fig 2d, arrow).

A diagnosis of blood involvement by CTCL was made if the sum of the convoluted cells (categories 1 and 2) was ≥20% of the lymphocytes in a blood smear and/or ≥10% of the lymphocytes in the E-rosetted cytocentrifuge preparations (ERCs). Category 3 cells were generally not considered diagnostic, except in one patient with marginal numbers of convoluted cells and numerous nonconvoluted tumor cells.

Thirteen blood smears and 15 ERC preparations from 21 patients with <4,000 lymphocytes/μL, had cells that resembled the small convoluted cell type (category 1) but convolutions were minimal (single folds or small clefts), and category 2 cells were rare or absent. These patients were considered to have abnormal but nondiagnostic lymphocyte morphology. Thus, three groups of patients were identified with respect to their lymphocyte morphology: (a) positive for CTCL, (b) abnormal but nondiagnostic for CTCL, and (c) within normal limits. For purposes of analysis, patients with positive peripheral lymphocyte morphology were in all cases compared with the combined negative and abnormal but nondiagnostic patients.
In patients with positive blood, two groups were identified on the basis of the size distribution of the convoluted cells, a mixed-cell variant and a small-cell variant. Mixed-cell patients had a ratio of category 1 to category 2 cells of <4, with the percentage of large convoluted cells varying between 22% and 67% of all convoluted cells. In the small-cell patients, the ratio was >4, and the median percentage of small convoluted cells was 94%. Tumor cells in the small-cell patients were fairly uniform, with round nuclei and subtle to distinct nuclear grooves, simple folding, or figure 8 shapes (Fig 1). Cells >12 μm were rare. Mixed-cell patients demonstrated greater variability in cytologic characteristics. Frequently, a wide range of cell diameters from 8 to 17 μm existed in the individual patient, with a few patients having predominantly large (>11 μm) cells. Nuclei were often ovoid, with highly bizarre and pleomorphic convolutions and dense chromatin (Fig 2). In some mixed-cell patients, the tumor cells had more finely divided nuclear chromatin and prominent nucleoli (Fig 2d). Cytoplasm was usually scant in the small-cell patients and frequently abundant in the mixed-cell patients. Occasionally, extensive vacuolation occurred in both variants.

The light microscopic findings were compared with those made independently by J.G. using electron microscopy in 78 consecutive patients. The concordance between the light-microscopic and electron-microscopic interpretations was 84%. In 2 of 33 instances, a positive light-microscopic interpretation was not confirmed by electron microscopy; one of these cases was an erythrodermic patient with a frank leukemia of mature T cells with minor nuclear folding. Eleven patients positive by electron-microscopic criteria (>6% convoluted cells) were negative (5 patients) or abnormal/nondiagnostic (6 patients) by light microscopy. The CTCL cells were highly pleomorphic and varied between patients and within the same patient. The diameters ranged between 8 and 17 μm in diameter. Tumor cells containing densely hyperchromatic nuclei (A,B), hyperconvoluted nuclei (B,E,F), nuclei with finely dispersed chromatin without convolutions (D, arrow) or only with vague grooving and rarely with nuclear segmentation were noted.

Concordance of the peripheral smear and ERC evaluation in CTCL. Sixty patients (38%) were identified as having one or both preparations (blood smear or ERC) diagnostic for CTCL blood involvement. The remaining patients had either normal lymphocyte morphology (79 patients, 48%) or abnormal/nondiagnostic morphology on either the smear or ERC (21 patients, 14%). Of 145 patients studied, 45 had both positive smear and ERC preparations. The percentage of convoluted cells on smear (Fig 3) correlated significantly with the percentage of convoluted T cells noted on the ERC preparations (P < .001). In five patients, one of the preparations was considered positive (ERC 4,
smear 1) whereas the other was not. Two patients with positive smears had inadequate ERC preparations due to extremely low percentages of T cells (<12%), and eight did not have an ERC study.

An abnormally low percentage of T cells (<58% AET- or <45% unmodified E rosettes) occurred in 11% of the patients and was associated with blood involvement in 13 of 17 instances. Eleven patients had a low percentage of B cells (<4%); B cell lymphopenia was apparently due to dilution in six patients with frank CTCL cell leukemia. It was explained in five patients with normal lymphocyte counts, three of whom had peripheral blood involvement.

No preparation from the 71 non-CTCL subjects, including 60 blood smears and 24 ERC preparations, met the criteria for infiltration by CTCL cells. Sixty-six non-CTCL subjects had completely normal lymphocyte morphology. Five non-CTCL subjects (7%) had abnormal lymphocyte morphology (smear 4, ERC 2) associated with diagnoses of follicular lymphoma, reaction to phenytoin, severe lymphopenia, and lymphomatoid granulomatosis (Fig 3).

Correlation of circulating CTCL cells with skin, node, and visceral disease. Diagnostic blood involvement was significantly associated with advanced skin disease (Table 2 and Fig 3), with a similar trend for patients with abnormal but not diagnostic morphology. Overall, 90% of erythrodermic (T4) and 13% of the nonerythrodermic (T1 through T3) patients had positive smears and/or ERC preparations. The erythrodermic patients with normal (three patients) or abnormal but not diagnostic (two patients) morphology were all moderately to severely lymphopenic (540 to 1,200/μL).

In patients without erythroderma, blood involvement was always associated with advanced disease, as judged by the presence of adenopathy (if T2) or cutaneous tumors (T3). No patient with limited plaque disease or generalized plaque without palpable adenopathy had circulating CTCL cells detected by light microscopy. There was no difference in the frequency of blood involvement between group I (no prior treatment) and group II (prior treatment or delayed staging).

The association of blood involvement at initial diagnosis of CTCL (group I patients only) with lymphadenopathy, lymph node histology, and visceral involvement is shown in Table 3. Patients with blood involvement were more likely to have adenopathy (P = .002), lymph node involvement (LN3 or LN4) (P < .001), and visceral disease (P < .001) than were patients with normal or nondiagnostic lymphocyte morphology. Visceral involvement and lymph node effacement (LN4)

Table 2. Correlation of Skin Stage With Circulating CTCL Cells

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. With Circulating CTCL Cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I*</td>
</tr>
<tr>
<td>T1†</td>
<td>0/13 (0)</td>
</tr>
<tr>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>Adenopathy absent</td>
<td>0/17 (0)</td>
</tr>
<tr>
<td>Adenopathy present</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td>T3</td>
<td>4/22 (18)</td>
</tr>
<tr>
<td>T1–T3</td>
<td>7/70 (10)</td>
</tr>
<tr>
<td>T4</td>
<td>31/35 (99)</td>
</tr>
<tr>
<td>Total (T1–T4)</td>
<td>38/105 (36)</td>
</tr>
</tbody>
</table>

CTCL, cutaneous T cell lymphoma.

*Group I, no prior treatment; group II, prior treatment or delayed staging.
†T refers to the TNM* staging system for cutaneous T cell lymphoma: T1, <10% plaque; T2, >10% plaque; T3, cutaneous tumors; T4, erythroderma.
CIRCULATING CUTANEOUS T CELL LYMPHOMA CELLS

Table 3. Correlation of Blood Involvement With Lymph Node and Visceral Disease at Initial Diagnosis of CTCL in Group I

<table>
<thead>
<tr>
<th>Blood</th>
<th>Palpable Adenopathy</th>
<th>Node Histology*</th>
<th>Visceral Involvement†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>LN1/2</td>
</tr>
<tr>
<td>Positive (n = 38)</td>
<td>32 (84)</td>
<td>6 (16)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Negative (n = 67)</td>
<td>36 (55)</td>
<td>30 (45)</td>
<td>31 (54)</td>
</tr>
<tr>
<td>P</td>
<td>.002</td>
<td>&lt;.001</td>
<td>.043†</td>
</tr>
</tbody>
</table>

CTCL, cutaneous T cell lymphoma.
*LN1/2 nodes were not diagnostically involved by CTCL. LN3 and LN4 nodes were infiltrated with CTCL, with LN4 nodes showing effacement of the normal architecture.†

Correlation of lymphocyte number and morphology with other prognostic features in patients with positive peripheral blood. The correlation of lymphocyte concentration, proportion of convoluted cells, and cell size distribution with skin class for all patients (groups I and II) with positive peripheral blood is shown in Table 4. Erythrodermic patients (T4) were significantly (P = .043) more likely to have high lymphocyte counts than were plaque/tumor (T2/T3) patients and a higher proportion (>20%) of large cells (mixed-cell type) (P = .043). T4 patients also had higher proportions of convoluted cells noted on smear than did the T2/T3 patients (P = .025).

The correspondence between lymphocyte count or cell size and lymph node biopsy findings and visceral disease in group I patients is shown in Fig 4. Patients with small CTCL cells were unlikely to have node effacement at initial diagnosis of CTCL, whereas 83% of patients with mixed-cell type had lymph node effacement (LN4). Visceral involvement at diagnosis was more closely associated with high lymphocyte counts (>4,000/μL) and, to a lesser extent, with the mixed-cell type (P = .015 and P = .074, respectively). Lymph node effacement (LN4) was also associated with higher lymphocyte counts but more particularly with the mixed-cell type (P = .069 and P < .001, respectively). In group I patients, neither type of skin disease nor adenopathy was associated with absolute lymphocyte counts or cell size.

Mixed-cell patients had a higher frequency of lymphocytosis than did small-cell patients (12 of 20 v 4 of 18, P = .061). They also had higher percentages of convoluted lymphocytes and nonconvoluted tumor cells on smear (P = .008 and P = .003, respectively) and a lower fraction of lymphocytes with normal morphology (in patients with <6,000/μL, P = .046) (Table 6).

Prognostic significance of peripheral blood findings. The actuarial survival of group I patients with diagnostic blood findings is shown in Fig 4. Patients with positive blood, either by smear or cytology, had a survival inferior to that of patients without positive blood (P < .001), with estimated 5-year survivals of 22% and 76%, respectively.

Lymphocyte size influenced survival in the patients with positive lymphocyte morphology. The actuarial survival of the mixed-cell patients was significantly shorter than that of patients with the small-cell type (23 v 51 months, P = .009;
Fig 5A). Similarly, Fig 5B shows that patients with small-cell CTCL involvement of blood and <4,000 lymphocytes/µL had a significantly improved survival in comparison with mixed-cell patients with <4,000/µL (P < 0.001) or all patients with normal cells >4,000/µL (P = 0.032).

**Multivariate analysis of prognostic factors.** To examine the effect on survival of several parameters simultaneously, the Cox life-table regression method was used in conjunction with two distinct ways of determining what variables would form the final statistical model. For the first approach, all variables given in Table 7 and examined in a univariate analysis were included. Using standard likelihood ratio procedures, a backward step-down approach was used to eliminate those variables found not to be significantly associated with survival at the .05 significance level.

Age, skin class, lymph node histology, adenopathy, and visceral disease as well as blood involvement were each significant predictors of inferior survival when analyzed in a univariate fashion (Table 7). In the multivariate analysis, the only significant factors were skin class and age (P < 0.001 and P = 0.025, respectively). A forward step-up procedure was used as the second approach and resulted in the selection of these same two factors. With these two variables in the model, all remaining variables were not significant at the P = 0.05 level. Thus, T-class and age remained the most important and independent prognostic indicators of survival, with T1 and T2 patients and those patients aged <50 years associated with a favorable prognosis. Adjusted Mantel-Haenszel analyses also were used to confirm these findings.

Blood involvement was not a significant factor in the final model once age and T-class were included (P = 0.31). This finding is readily explained by the fact that blood involvement and T-class are highly associated (P < 0.001). The importance of age in this model remains although almost all deaths in this series were relatable to progressive cutaneous T cell lymphoma. Further analyses were made to determine if first including blood involvement in the model would eliminate the need for subsequently introducing T-class or age into the model. Because both T-class and age still entered the model, however, blood involvement appears not to have been an independent prognostic factor for the entire group of patients. In the subset of patients with T2 (generalized plaque) and T3 (cutaneous tumor) skin disease, however, blood involvement was (P = 0.051) associated with inferior prognosis (Fig 6). Although the number of patients in the nonerythrodermic, blood-positive subgroup was small, their inferior survival reinforces the potential usefulness of blood involvement in the prospective evaluation of this subgroup of patients with CTCL.

**DISCUSSION**

In this study of a large number of patients with cutaneous T cell lymphoma, we found that peripheral blood infiltration correlated with established prognostic factors, including advanced skin disease, palpable adenopathy, lymph node and visceral involvement, and older age. In this series, no patient with limited plaque disease or generalized plaques without
adenopathy had blood involvement. Approximately 22% of plaque patients with adenopathy and/or skin tumors had blood involvement on detailed review of the peripheral blood smear or T cell cytology. In contrast, 90% of those with erythroderma had blood infiltration. In patients with blood involvement, we further identified >20% large convoluted cells or an absolute lymphocytosis as poor prognostic features.

The original description of SS directed attention to the importance of peripheral blood involvement in this disorder. Many years later, using electron microscopy, Lutzner and co-workers recognized considerable variation in the size of Sézary cells and described a variant in which small cells predominated. The recognition that mycosis fungoides and the Sézary syndrome were related disorders, malignancies of mature helper T cells, led to the discovery of circulating "mycosis cells" in ~20% of mycosis fungoides patients. Correlation with other clinical and pathologic findings and prognosis have been addressed, however, in only a few of these studies. Our study affirms that the frequency of blood involvement is directly correlated with the type of skin lesion and other features of advanced stage. Tumor cell morphology did not differ between the erythrodermic (T4) or classic Sézary syndrome patients and the T2/T3 mycosis fungoides patients except that lymphocytosis and the mixed-cell type was more prevalent in the T4 patients. The presence of circulating tumor cells in a univariate analysis was associated with an inferior survival; however, multivariate analysis established that whereas both skin class and age >50 years were independent risk factors in this series, peripheral blood involvement was not. When T2 and T3 skin disease patients were evaluated separately, blood involvement appeared to affect survival adversely.

When Lutzner and co-workers described the small-cell variant Sézary cell, no prognostic significance was attributed to cell size. In the B cell lymphomas, nearly all studies show that large cell size is associated with a more aggressive natural history. In this study, we demonstrated that CTCL patients with >20% of large convoluted cells (mixed-cell type) have shorter survival than those with blood involvement having predominantly small cells.

The mixed-cell type was strongly associated with features of aggressive disease, including lymph node effacement, visceral involvement, increased proportions of convoluted cells, and higher absolute concentrations. Vonderheid and colleagues recently reported that survival in a group of erythroderma patients was more closely related to the proportion of large convoluted cells (15 to 20 μm) than to the relative or absolute number of convoluted cells. Our data support earlier results of Vonderheid and colleagues in that
the number of circulating tumor cells also had an effect on outcome. In our series, in addition to cell size, lymphocytosis had an adverse effect on survival. This effect was most clearly seen in a survival advantage for small-cell patients who had an adverse effect on survival. This effect was most clearly seen in a survival advantage for small-cell patients with normal lymphocyte concentrations. For patients with elevated lymphocyte counts, survival was poor irrespective of cell size.

Occasional cells with electron-microscopic morphology similar to that of Sézary cells are frequently found in the skin and blood of patients with benign dermatoses. These findings are not surprising since CTCL represents a malignancy of mature helper T cells, and normal as well as reactive T cells may resemble their malignant counterpart morphologically. In our series, patients with benign disorders did not have cells with the degree of the nuclear abnormalities and density of chromatin found in CTCL. No patient with a benign skin disorder and no normal individual met our criteria for CTCL cell infiltration. Occasional patients with CTCL had increased numbers of cells with minor nuclear irregularities. These patients were predominantly from advanced disease subsets. Determination of whether the lymphoid cells in these patients represent reactive cells or circulating tumor cells with a relatively bland morphology must await techniques that can clearly establish clonality and measure the extent of the infiltration. Use of DNA probes for the β T cell receptor gene has demonstrated clonal rearrangements in tissues histologically involved with CTCL. With the sensitivity to detect 1% to 5% tumor cells in a population, DNA probes also offer promise of detecting CTCL cells in apparently benign lymph nodes with dermatopathic lymphadenopathy and among circulating lymphocytes. In this study, E rosette cytology did not increase the sensitivity of detecting peripheral blood involvement, since only four patients had a positive ERC after a negative or suspicious smear was found. We previously reported similar results with electron microscopy, and probably neither expensive procedure would increase the yield of positive findings. Cytogenetic analysis clearly does increase the sensitivity of detection, and flow cytometry may detect small numbers of cells when aneuploidy is present. The prognostic significance of detecting small numbers of such cells is unclear, however.

Detailed examination of peripheral blood smears is a noninvasive, inexpensive means of assessing extracutaneous involvement by CTCL. In nonerythrodermic CTCL, our results suggest that identification of blood involvement may be useful in identifying a small subset of patients with inferior survival while they are receiving current therapy. Because blood involvement is nearly universal in erythrodermic CTCL, examination of the peripheral blood smear can also be helpful in confirming a diagnosis of CTCL in patients with chronic erythroderma and nondiagnostic skin biopsies. In addition, assessment of the cell size distribution of the circulating CTCL cells will be useful in distinguishing patients with small-cell type whose course is relatively indolent from patients with the more aggressive mixed-cell type.

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circulating cutaneous T cell lymphoma cells


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Evaluation of circulating malignant cells provides prognostic information in cutaneous T cell lymphoma

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