High Incidence of Gastrointestinal Tract Disorders and Autoimmunity in Primary Cutaneous Marginal Zone B-Cell Lymphomas

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IMPORTANCE To our knowledge, this is the first comprehensive study addressing comorbidities associated with primary cutaneous marginal zone B-cell lymphomas (PCMZLs).

OBJECTIVE To determine if patients with PCMZL were at risk for other medical conditions.

DESIGN, SETTING, AND PARTICIPANTS Case-control study at a cutaneous lymphoma clinic and a dermatopathologic consultation service at a single academic institution using an extensive questionnaire of illnesses, symptoms, and environmental exposures for 80 sequential patients with PCMZL and 80 matched controls.

MAIN OUTCOMES AND MEASURES The frequency of several morbidities was obtained in both groups from data gathered from the questionnaire and corroborated by reviewing medical records when available.

RESULTS We found a high incidence of past or present gastrointestinal tract problems in 49 patients (61.2%) with PCMZL compared with 30 participants (37.5%) in the control group (CG) \( P = .003 \). Gastroesophageal reflux was reported in 50.0% (40 vs 27 in the CG, \( P = .04 \)) and gastric ulcers in 10.0% (8 vs 3 in the CG, \( P = .13 \)); 20.0% of the cohort had positive Helicobacter pylori serology (16 vs 2 in the CG, \( P = .003 \)). Colon disorders, including irritable bowel syndrome and inflammatory bowel disease, were more common in the PCMZL cohort (20 vs 7 in the CG, \( P = .01 \)). Autoimmunity was reported in 20.0% of participants (16 vs 6 in the CG, \( P = .03 \)). Eight patients had a history of Hashimoto thyroiditis. Three patients had a positive antinuclear antibody. Two had a diagnosis of lupus erythematosus and 1 had Sjögren syndrome. Sicca syndrome was noted in 12.5% (10 vs 3 in the CG, \( P = .052 \)). A history of noncutaneous malignant neoplasms was observed in 21.3% of the patients (17 vs 8 in the CG, \( P = .050 \)). Other notable morbidities did not reach statistical significance.

CONCLUSIONS AND RELEVANCE Our results indicate a high incidence of systemic conditions in patients with PCMZL, especially involving the gastrointestinal tract, but also autoimmunity and cancer.

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Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is a common subset of low-grade lymphomas of the skin. The reported incidence of PCMZL is variable, ranging from less than 20% to more than 40% of all cutaneous B-cell lymphomas. The reason for this wide variation is unclear but may reflect geographic peculiarities with endemic risk associated with Borrelia burgdorferi exposure. In addition, overlapping features with reactive lymphoid infiltrates and other low-grade B-cell lymphomas pose a common diagnostic challenge, which may also account for some of these variations.

Primary cutaneous marginal zone B-cell lymphoma is included in the broad category of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites, or mucosa-associated lymphoid tissue (MALT) lymphomas. Often triggered by site-specific infections and mutations, MALT lymphomas are associated with chronic inflammation, resulting in the upregulation of the canonical nuclear factor–κB pathway. For instance, a strong association has been found between Helicobacter pylori infection and gastric marginal zone lymphoma. As a result of this discovery, many early cases of gastric marginal zone lymphoma are now effectively treated with antibiotics. Similarly, salivary MALT lymphoma is associated with Sjögren disease, and Campylobacter jejuni infection has been related to intestinal MALT lymphomas. A subset of PCMZL has been correlated with B. burgdorferi infection mostly in European endemic areas, where 18% to 20% of cases also demonstrate evidence of the infection. However, this finding has not been replicated in Asian or American patients, who up until present have had no known risk factors.

It had been our observation that patients with PCMZL often reported a history of gastrointestinal (GI) symptoms and other health problems. Given the known site-specific associations between MALT lymphoma, infectious agents, and autoimmune conditions as well as the lack of Borrelia-induced PCMZL in the United States, we undertook an exploration of possible comorbidities in North American patients with PCMZL.

Methods

Institutional review board approval was obtained from Northwestern University before pursuing this retrospective and prospective study. The prospective component included subjects diagnosed during the study recruitment period following institutional review board approval. Written consent was obtained from those patients who were interviewed by telephone. Participants were selected from the Cutaneous Lymphoma database at Northwestern University as well as the pathology files from the Dermatopathology Laboratory at the Northwestern University Faculty Foundation. Pathologic material was reviewed by 2 pathologists (J.G. and P.G.). In total, 143 skin biopsy specimens were evaluated and found to be consistent with the diagnosis of PCMZL. B-cell clonality was demonstrated in all cases by immunoglobulin heavy chain gene rearrangement polymerase chain reaction using standard BIOMED-1 probes and capillaroscopy analysis methods and/or identification of light chain restriction using immunohistochemistry and/or in situ hybridization or flow cytometry analysis of skin samples. Cases without proven clonality were excluded. Answers to a written questionnaire were obtained from 21 local participants. Fifty-nine participants completed the questionnaire during a telephone interview. The questionnaire included a wide array of questions, including age, sex, and race; duration of lesions; evolution and present status; medical and surgical history; current medication; and review of systems, with a focus on constitutional symptoms and symptoms associated with the GI tract, eyes, liver, endocrine, and connective tissue diseases. The same epidemiologic questionnaire was used for the cohort of control participants matched by age, sex, and race. The control group (CG) was recruited from patients without cancer or relatives of patients visiting the dermatologic clinic.

The medical records were also reviewed for clinical and laboratory data confirmation when possible. Patients with a history of systemic marginal zone lymphoma or other plasma cell dyscrasias or B-cell lymphomas were excluded from the study.

Comorbidities of patients with PCMZL were compared with noncancer controls using the McNemar test of paired proportions. In addition, odds ratios (ORs) and 95% CIs are provided from conditional logistic regression models. The prevalence of comorbidities among patients with PCMZL was also compared by TNM system information—T1 vs T2 and T3, and T1 and T2 vs T3—using χ² or the Fisher exact test. Age was compared using independent t tests. All analyses were run in SAS, version 9.3 (SAS Institute), at a type I error rate of 5%.

Results

The cohort of 80 adult patients with a median age of 54.6 years (range, 18–87 years) included 38 men and 42 women (76 whites and 4 Hispanics). The mean follow-up was 3.8 years, ranging from 3 months to 17 years. Thirty-four patients (42.5%) had multiple lesions at presentation and 46 (57.5%) had a single lesion at presentation. Twenty-two of these 46 patients developed additional lesions over time. Considering the additional lesions and their distribution, patients were classified based on the TNM system as follows: T1 stage, 24 patients (30.0%); T2 stage, 22 patients (27.5%); and T3 stage, 34 patients (42.5%). The most common location of the lesion was the upper extremities (n = 45), followed by the trunk (n = 35), lower extremities (n = 20), and head and neck region (n = 17). The lesions were reported as papulonodular in 47 patients, patches or plaques with or without a papular component in 13, and tumor lesions in 4. A follicular-based papular pattern was often noted within the plaques and patch lesions (Figure 1). Pruritus was the most common symptom noted in 38 patients (47.5%), while 35 (43.7%) were asymptomatic, and pain was reported in 7 (8.7%). Only 1 patient had ulcerated lesions and none had constitutional symptoms.

None of the patients had lymphadenopathy (N0) or evidence of systemic involvement (M0) at presentation. A few patients recalled a history of possible trauma (n = 6), arthropod bite (n = 7), or tattoo (n = 1) close to the site of disease presentation. But in most of these patients, the traumatic event could not be directly associated with the anatomic site, extent of dis-
ease, or time of presentation. One patient had a single marginal zone lymphoma (MZL) lesion (T1) adjacent to a traumatic scar with an adjoining foreign body reaction. One patient developed a few MZL lesions (T2) within a large tattoo extending from the torso to the upper extremity, and 1 patient with a remote history of leprosy developed 2 adjacent MZL nodules within a hypopigmented leprosy patch. *Borrelia* serology was checked on 40 patients with only 1 positive result. The patient had a remote history of Lyme disease treated with doxycycline hydrochloride without improvement of the skin lesions. The patient failed to recall a history of tick bite. Another patient who reported a remote tick bite had an indeterminate *Borrelia* serology and was lost to further follow-up. Neither of the patients recalled previous tick bites at the specific PCMZL site.

Excluding topical corticosteroids, which for the most part were ineffective, 52 patients received additional treatments and 22 received no additional treatment. Good responses were noted with all skin-directed and systemic therapies with variable proportions of complete responses and persistent stable disease (Table 1).

Six patients were treated with systemic rituximab. Two achieved complete remission, 3 remained stable, and 1 had disease progression with multiple tumors with large-cell transformation and regional lymphadenopathy. However, lymph node biopsy specimens revealed reactive changes without lymphoma involvement.

At the time of the survey, 34 patients were alive and in complete remission (42.5%) without current therapies. Forty-five patients had persistent disease localized to the skin.

The statistical values of the questionnaire results in the following paragraphs are summarized in Table 2. Forty-nine (61.2%) of the patients had past or present GI problems, including gastroesophageal reflux disease (GERD) in 40 (50.0%), with 28 still taking medication. Eight (10.0%) had gastric ulcers and 16 (20.0%) had positive *H pylori* serology. Mean duration of GERD was 15.3 years. A history of peptic ulcer disease was elicited in 8 patients with PCMZL compared with 3 in the CG. Six of the 8 patients also had GERD, with 4 having a positive *H pylori* serology. We reviewed reports of 6 upper endoscopies and 29 colonoscopies, which showed for the most part signs of inflammation of the GI tract and other conditions such as polyps and adenomas, but lymphoma was not detected in any.

In toto, symptoms of colon disorders were reported in 20 patients vs 7 in the CG (*P* = .01). Two patients had a history of inflammatory bowel disease, including 1 with Crohn disease and 1 with ulcerative colitis. In addition, a history of irritable bowel syndrome was obtained in 12 patients (15.0%). Nine additional patients related a history of frequent abdominal pain and diarrhea but had not been diagnosed with inflammatory bowel disease or irritable bowel syndrome. None of the patients reported celiac disease or blood or mucus in the stool. These results contrast with the CG, which had 30 participants (37.5%) with GI problems, including 27 (33.8%) with a history of GERD. Sixteen (20.0%) were taking medication, 3 (3.8%) had peptic ulcer disease, 2 (2.5%) had a positive *H pylori* serology, 1 (1.3%) had inflammatory bowel disease, and 6 (7.5%) had irritable bowel syndrome.

Eight patients gave a history of eye infection (10.0%) vs 17 (21.3%) in the CG. Sixteen patients related dry mouth (20.0% vs 12.5% in the CG), and 26 reported dry eyes (32.5% vs 23.8% in the CG). Mean duration of symptoms was 7.2 years for dry eyes and 11.8 years for dry mouth. Both sicca symptoms were present in 10 patients (12.5%) vs 3 in the CG, and the duration...
of the symptoms was longer in the patient group than in the CG. Three of these patients had a positive antinuclear antibody, and only 2 patients were diagnosed with lupus erythematosus and another had Sjögren syndrome. Three patients related a history of hepatitis. Nine patients (11.3%) had thyroid problems, with autoimmune thyroiditis in 8. Two of these patients also developed thyroid cancer with subsequent thyroidectomy, and a third patient also developed thyroid cancer without a known history of thyroiditis. Thyroid lymphoma was not reported in any. Thyroid pathologic findings were not statistically significant since the CG had 10 patients with a history of thyroid disorders ($P = .78$). However, among the subset of patients with extensive skin disease (T3), thyroid disorders were significantly more prevalent within the PCMZL cohort group (20.6% vs 4.3% in the CG, $P = .03$). This was the only significant factor between patients with generalized and localized disease (Table 3). Sicca syndrome was noted in 12.5% of patients with PCMZL (10 vs 3 in the CG, $P = .052$). However, only

Table 1. Comparisons of Therapies and Outcomes

<table>
<thead>
<tr>
<th>Therapeutic Option</th>
<th>Patients*</th>
<th>Disease Status, No.</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complete Remission</td>
<td>Stable Disease or Relapse</td>
<td></td>
</tr>
<tr>
<td>Observation only</td>
<td>22 (27.5)</td>
<td>5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>47 (58.7)</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Intralional corticosteroids</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Combined therapy</td>
<td>11 (13.8)</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Surgery + Intralional corticosteroids</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Surgery + Radiation</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rituximab + Radiation</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + Radiation</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rituximab + CHOP + Intralional corticosteroids</td>
<td>1 (progressive diseases)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

* Data are given as number (percentage) or number.

Table 2. Comparisons of Cases and Controls

<table>
<thead>
<tr>
<th>Trait</th>
<th>PCMZL*</th>
<th>Control*</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>80</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>74 (92.5)</td>
<td>75 (93.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>38 (47.5)</td>
<td>38 (47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>55 (18)</td>
<td>54 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any GI tract pathologic finding</td>
<td>49 (61.2)</td>
<td>30 (37.5)</td>
<td>2.73 (1.37-5.44)</td>
<td>.003</td>
</tr>
<tr>
<td>GERD</td>
<td>40 (50.0)</td>
<td>27 (33.8)</td>
<td>2.0 (1.03-3.89)</td>
<td>.04</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>8 (10.0)</td>
<td>3 (3.8)</td>
<td>2.67 (0.71-10.05)</td>
<td>.13</td>
</tr>
<tr>
<td>Any bowel problem</td>
<td>20 (25.0)</td>
<td>7 (8.8)</td>
<td>3.17 (1.27-7.93)</td>
<td>.01</td>
</tr>
<tr>
<td>Recurrent diarrhea</td>
<td>9 (11.3)</td>
<td>5 (6.3)</td>
<td>2.00 (0.60-6.64)</td>
<td>.25</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3 (3.8)</td>
<td>1 (1.3)</td>
<td>3.00 (0.31-28.84)</td>
<td>.32</td>
</tr>
<tr>
<td>Eye infection</td>
<td>8 (10.0)</td>
<td>17 (21.3)</td>
<td>0.43 (0.17-1.12)</td>
<td>.07</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>2 (2.5)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid pathologic findings</td>
<td>9 (11.3)</td>
<td>10 (12.5)</td>
<td>0.86 (0.29-2.55)</td>
<td>.78</td>
</tr>
<tr>
<td>Systemic malignant neoplasms</td>
<td>17 (21.3)</td>
<td>8 (10.0)</td>
<td>2.50 (0.97-6.44)</td>
<td>.05</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>16 (20.0)</td>
<td>6 (7.5)</td>
<td>2.67 (1.04-6.82)</td>
<td>.03</td>
</tr>
<tr>
<td>Positive Helicobacter pylori serology</td>
<td>16 (20.0)</td>
<td>2 (2.5)</td>
<td>7.00 (1.59-30.80)</td>
<td>.003</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2 (2.5)</td>
<td>1 (1.3)</td>
<td>2.00 (0.18-22.06)</td>
<td>.56</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>12 (15.0)</td>
<td>6 (7.5)</td>
<td>2.00 (0.75-5.33)</td>
<td>.16</td>
</tr>
<tr>
<td>Dry eye symptoms</td>
<td>26 (32.5)</td>
<td>19 (23.8)</td>
<td>1.64 (0.77-3.47)</td>
<td>.19</td>
</tr>
<tr>
<td>Dry mouth symptoms</td>
<td>16 (20.0)</td>
<td>10 (12.5)</td>
<td>1.75 (0.73-4.17)</td>
<td>.20</td>
</tr>
<tr>
<td>Sicca syndrome (dry eyes and mouth)</td>
<td>10 (12.5)</td>
<td>3 (3.8)</td>
<td>3.33 (0.92-12.11)</td>
<td>.05</td>
</tr>
<tr>
<td>Sjögren disease</td>
<td>1 (1.3)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GERD, gastroesophageal reflux disease; GI, gastrointestinal; PCMZL, primary cutaneous marginal zone B-cell lymphoma.

* Data are presented as number (percentage) unless otherwise indicated.

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1 patient with PCMZL had been diagnosed with Sjögren disease. Overall, autoimmunity was reported in 20.0% of patients (16 vs 6 in the CG, \( P = .03 \)). History of systemic malignant neoplasms was observed in 21.3% of the patients (17 vs 8 in the CG, \( P = .050 \)). These included thyroid, breast, and prostate in 3 patients each, and colon, ovary, renal cell, melanoma, endometrial, parotid, and non-Hodgkin lymphoma (NHL) of the breast in 1 patient each. Other notable morbidities did not reach statistical significance.

A total of 143 biopsy specimens from the 80 participants were reviewed. All skin biopsy specimens revealed a deep dermal lymphoid infiltrate without significant epidermal involvement. The infiltrate often had a vertical periadnexal pattern and a nodular pattern with ill-defined germinal centers and frequent aggregates of monocytoid cells and/or plasma cells (Figure 2). The pathologic material was reviewed by 3 of us (M.E.M.-E., P.G., and J.G.) and believed to be consistent with or diagnostic for MZL in at least 1 specimen per participant. Monotypic light chain expression was demonstrated in 72.5% (79 of 109) of the specimens by immunohistochemistry, 62.8% of the cases (49 of 78) by in situ hybridization, and 20.0% of the cases (1 of 5) by flow cytometry of the skin biopsy specimens (Table 4). Interestingly, 7 patients showed different expression of light chain restriction (\( k \) and \( \lambda \)) over time. In addition, molecular studies yielded a monoclonal B-cell population in 60.0% of the specimens (12 of 20) by immunoglobulin heavy chain gene rearrangement analysis.

### Discussion

Primary cutaneous marginal zone B-cell lymphoma was first recognized in the 1980s, when advances in immunohistochemistry allowed for the detection of monotypic B-cell populations as demonstrated by light chain restriction. Until then, such lesions had been diagnosed mostly as reactive lym-
phoid hyperplasia, lymphadenosis benigna cutis, or “pseudo-
lymphomas,” which is not surprising in view of their remark-
ably indolent course.5,10 As part of the group of extranodal
marginal zone lymphomas (ENMZLs), PCMZLs closely re-
semble mucosal lymphomas and are often referred to in
the literature as MALT-like lymphomas or immunocytomas.
Clinically, PCMZLs have localized red to violaceous deep
nodules, papules, or plaques, most frequently distributed on the
extremities or trunk.2 Histologically, PCMZLs are characterized
by a spectrum of cells ranging from small lymphocytes with
folded nuclei (centrocyte-like) to medium cells with an abun-
dant cytoplasm (monocytoid cells), plasma cells, and scat-
tered large blastic cells. Aggregates of centroblasts or centro-
cytes with a germinal center configuration are also frequently
noted. A definitive diagnosis is rendered on detection of im-
munoglobulin light chain restriction by immunohistochem-
istry or in situ hybridization and/or IgH or IgK gene re-arrange-
ment. A definitive diagnosis is rendered on detection of im-
munoglobulin light chain restriction by immunohistochem-
istry or in situ hybridization and/or IgH or IgK gene re-arrange-
ment. However, our results will need to be validated by larger se-
quences and most were from our institution with data obtained be-
cause most nonendemic PCMZLs remain elusive. We
searched for comorbidities in a cohort of 80 patients with
PCMZL and identified a significant association with GI tract di-
orders as well as certain autoimmune conditions and sys-
temic malignant neoplasms. To our knowledge, this is the first
report of such an association, with the exception of rare re-
ports. Positive H pylori serology was detected in 3 of 11 pa-
ients with PCMZL.13 Two of these cases resolved after resol-
uition of gastric H pylori infection following antibiotic therapy.
Two similar PCMZL cases with resolution after treatment of
gastric H pylori infection were also reported by Mandekou-
Lefaki et al.14 Another study failed to detect H pylori DNA se-
quences in 5 cases of PCMZL.15 To our knowledge, GERD has
not been associated with gastric or other ENMZLs.16 An asso-
ciation with Sjögren syndrome has been noted in 2 of 16 Japa-
nese patients with PCMZL.17,18 None of these patients had a his-
tory of B burgdorferi infection or Hashimoto thyroiditis. Magro
et al18 observed similar comorbidities in 8 of 11 cases, including
1 case each of Sjögren disease, rheumatoid arthritis, thy-
roiditis, ulcerative colitis, and colon cancer.

Autoimmunity as a hallmark of chronic inflammatory dis-
order is associated with an increased risk of NHL and, in par-
ticular, MZL.19 The estimated relative risk of NHL in Sjögren
disease has been calculated at approximately 9. Most of these
NHLs are MZLs involving the salivary glands and frequently
also the skin.4 In a case-control study of 829 patients with
Hashimoto thyroiditis, the risk of NHL was estimated at 67,
again mostly MZLs of the thyroid.20 Our cohort includes sev-
eral patients with Hashimoto thyroiditis, Sjögren syndrome,
and related carcinomas of the thyroid and salivary glands, con-
firming this distinct association. Of note, our cohort with only
1 patient with positive B burgdorferi serology and remote his-
tory of Lyme disease and 1 patient with an indeterminate se-
rology following a tick bite confirms the poor association be-
tween PCMZL and B burgdorferi in the United States.

We believe our data may influence our future approach and
recommendations to patients with newly diagnosed PCMZL.
However, our results will need to be validated by larger se-
ries, as well as prospective and more comprehensive future
studies. One of the limitations of our study is that the comor-
bidities data from the control group were extracted exclusively
from interviews using the standard questionnaire and with-
out access to patient medical records for a more comprehen-
sive review, as we did for the PCMZL cohort. Also, some of the
retrospective data obtained could include cumulative comor-
bidities associated with systemic therapies. However, only 8
patients (10.0%) received rituximab or other chemotherapy,
and most were from our institution with data obtained be-
fore systemic therapies.

On the basis of the results of this study and our previous
experience, we recommend a guided workup for all patients
with newly diagnosed cutaneous MZL. A secondary cutane-
ous lymphoma or plasma cell dyscrasias should be excluded
assessing serum lactate dehydrogenase, urine, and serum pro-
tein electrophoresis. We also recommend a detailed history and
physical examination exploring signs and symptoms associ-
ated with other ENMZLs, specifically thyroid, salivary glands,
eyes, liver, and GI tract, which may be accompanied by guided
imaging or exploratory tests. We also routinely check the an-
tinuclear antibody panel, including Ro and La serology, to iden-
tify patients with Sjögren syndrome; B burgdorferi and H py-
lori serology; thyroid and liver function tests; and other
analytes as guided by the evaluation.

Table 4. Results of Clonality Analysis on Skin Specimens by Light Chain Restriction and Molecular Methods

<table>
<thead>
<tr>
<th>Test</th>
<th>Total No. of Biopsy Specimens (N=143)</th>
<th>Negative</th>
<th>Positive</th>
<th>Noncontributory</th>
<th>κ</th>
<th>λ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunohistochemistry</td>
<td>109 (76.2)</td>
<td>23 (21.1)</td>
<td>79 (72.5)</td>
<td>7 (6.4)</td>
<td>36 (45.5)</td>
<td>43 (54.5)</td>
</tr>
<tr>
<td>In situ hybridization</td>
<td>78 (54.5)</td>
<td>21 (26.9)</td>
<td>49 (62.8)</td>
<td>8 (10.2)</td>
<td>26 (53.1)</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>Immunoglobulin H rearrangement</td>
<td>20 (14.0)</td>
<td>8 (40.0)</td>
<td>12 (60.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>5 (3.5)</td>
<td>4 (80.0)</td>
<td>1 (20.0)</td>
<td></td>
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</tbody>
</table>
Conclusions

Our stratification of the cohort into localized (T1/T2) vs generalized cases (T3) did not yield any significant disparities of risk factors other than thyroid conditions, which were more prevalent in T3 patients. However, some patients with limited disease seem to have a possible local trigger event, like a tattoo, acniform facial eruption, previous trauma, surgery, or arthropod bite reaction near the skin site. Therefore, in patients with limited skin involvement, besides exploring the systemic comorbidities encountered in this study, we also recommend careful evaluation for local factors.

Our results confirm the low-grade nature of PCMZL, which tends to recur and persist in the skin with a very low risk of progression or transformation into a large-cell lymphoma.

While the main limitation of our study is the small size of the cohort, we have detected significant comorbidities that should be further investigated and corroborated by other groups.

REFERENCES