Primary B Cell Lymphoma of the Thyroid and Its Relationship to Hashimoto's Thyroiditis

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Twenty-one cases were selected from 236 thyroidectomies with a diagnosis of Hashimoto's disease for detailed clinicopathologic study on the basis of "early" changes in three cases and an unusually heavy lymphoplasmacytic infiltrate in 18 cases. These cases were studied in conjunction with ten cases of high-grade non-Hodgkin's lymphoma of the thyroid. Immunoglobulin light chain restriction was demonstrated in five cases of Hashimoto's non-Hodgkin's lymphoma of the thyroid. Immunoglobulin light chain restriction could be demonstrated in 18 cases. These studies confirmed the close association between Hashimoto's thyroiditis and B cell lymphoma of the thyroid gland and suggest that this tumor belongs to the group of non-Hodgkin's lymphomas derived from MALT. HUM PATHOL 19:1315–1326. © 1988 by W.B. Saunders Company.

Primary lymphoma of the thyroid gland is an uncommon tumor that may cause considerable diagnostic difficulty. Cases of high-grade lymphoma may be confused with small or large cell thyroid carcinoma, but this distinction can easily be made on immunohistochemical grounds using antibodies to cytokeratins and the leucocyte-common antigens. Most, if not all, cases of thyroid gland lymphoma arise in a setting of Hashimoto's thyroiditis, and it is the distinction between florid Hashimoto's thyroiditis and low-grade lymphoma that causes the most difficulty.

In 1984, Isaacson and Wright proposed that thyroid lymphoma shared common histologic and clinical features with B cell lymphomas arising in mucosa-associated lymphoid tissues (MALT). Although the thyroid gland is not strictly a mucosal organ, it is derived from the foregut, and the lymphoid tissue that accumulates in the thyroid in Hashimoto's thyroiditis shares features of MALT. In this way, the thyroid resembles the salivary gland in which the lymphoid infiltrate seen in myoepithelial sialadenitis (MESA) is closely similar to MALT.

The essential difference between a reactive and a neoplastic lymphoid infiltrate is the presence of light chain restriction in the latter. Using monoclonal leucocyte antibodies reactive in paraffin sections with techniques that permit the demonstration of immunoglobulin (Ig) light chain restriction in these sections, we have been able to discriminate between reactive and neoplastic lymphoid infiltrates in gastric mucosa, salivary gland, and lung. These studies have helped to establish morphologic criteria for the diagnosis of lymphoma in these organs and have emphasized the common features of these mucosal lesions. The aim of the present study was similar; namely, to clarify the relationship between Hashimoto's thyroiditis and thyroid gland lymphoma, and to establish whether there were common histologic and immunohistochemical features between thyroid gland lymphoma and other lymphomas of MALT.

MATERIALS AND METHODS

Paraffin blocks were retrieved from the files of the Department of Histopathology at the University College and Middlesex School of Medicine (London). Twenty-one cases that had adequate material from a thyroidectomy specimen were selected for study, from 236 cases of Hashimoto's thyroiditis diagnosed histologically between 1957 and 1987 in which paraffin blocks were available. Three cases that showed mild (early) features of the disease were selected, while the remaining 18 were specifically chosen because they showed the most florid lymphoid infiltration, thought to be difficult to distinguish from low-grade lymphoma. In two of these cases, sections of adjacent lymph nodes were available. During the same period, ten cases of thyroid lymphoma had been diagnosed; sections from sub-total or total thyroidectomy were available in eight cases and from generous biopsies in two cases. Blocks from adjacent lymph nodes were available in two cases. Case notes

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Table 1. Antibodies Used

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>α, k light chain</td>
<td>DAKO Ig a/s</td>
<td>κ light chain</td>
</tr>
<tr>
<td>α, λ light chain</td>
<td>DAKO Ig a/s</td>
<td>λ light chain</td>
</tr>
<tr>
<td>α IgM</td>
<td>DAKO Ig a/s</td>
<td>μ heavy chain</td>
</tr>
<tr>
<td>α IgG</td>
<td>DAKO Ig a/s</td>
<td>σ heavy chain</td>
</tr>
<tr>
<td>α IgA</td>
<td>DAKO Ig a/s</td>
<td>pan B cell</td>
</tr>
<tr>
<td>L26</td>
<td>DAKO Ig a/s</td>
<td>T cells</td>
</tr>
<tr>
<td>UCHL1</td>
<td>P. Beverley</td>
<td>CD35</td>
</tr>
<tr>
<td>El</td>
<td>N. Hogg</td>
<td>Cytokeratin</td>
</tr>
</tbody>
</table>
### Table 2. Clinical Features and Immunohistologic Findings of Cases Diagnosed as Lymphoma Before or After Review

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Presenting Symptoms</th>
<th>Auto-antibodies</th>
<th>Treatment</th>
<th>Initial Diagnosis</th>
<th>Nodes</th>
<th>Follow-Up</th>
<th>Revised Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 RF F/39</td>
<td>Nodule euthyroid</td>
<td>NA</td>
<td>Partial thyroidectomy</td>
<td>HT</td>
<td>NA</td>
<td>Well, after 2 yr lost to follow-up</td>
<td>Low-grade TGL (IgG)*</td>
</tr>
<tr>
<td>18 NJ F/?</td>
<td>Thyroid enlargement</td>
<td>NA</td>
<td>Thyroidectomy</td>
<td>HT</td>
<td>NA</td>
<td>NA</td>
<td>Low-grade TGL (IgG)*</td>
</tr>
<tr>
<td>19 JW M/49</td>
<td>Nodule euthyroid</td>
<td>6 mo</td>
<td>Partial thyroidectomy</td>
<td>HT</td>
<td>Reactive</td>
<td>Well, after 5 yr lost to follow-up</td>
<td>Low-grade TGL (IgGk)</td>
</tr>
<tr>
<td>20 ML F/47</td>
<td>Goiter euthyroid</td>
<td>1.5 yr</td>
<td>Total thyroidectomy</td>
<td>HT</td>
<td>NA</td>
<td>Well, after 12 yr lost to follow-up</td>
<td>Low-grade TGL with extreme plasma cell differentiation (IgGk)</td>
</tr>
<tr>
<td>21 ES F/73</td>
<td>Thyroid enlargement</td>
<td>NA</td>
<td>Thyroidectomy</td>
<td>HT</td>
<td>Involved</td>
<td>NA</td>
<td>Low-grade TGL with plasma cell differentiation (IgGk)</td>
</tr>
<tr>
<td>22 EJ F/52</td>
<td>Thyroid enlargement</td>
<td>NA</td>
<td>Thyroidectomy</td>
<td>L lobe HT, R lobe lymphoma</td>
<td>NA</td>
<td>NA</td>
<td>L lobe, low-grade TGL (IgGk); R lobe, high-grade TGL (IgGk)</td>
</tr>
<tr>
<td>23 WB F/67</td>
<td>Thyroid enlargement euthyroid</td>
<td>3 mo</td>
<td>Within normal range</td>
<td>Subtotal thyroidectomy radiotherapy</td>
<td>Lymphoma</td>
<td>Involved</td>
<td>18 mo well, no evidence of lymhoma</td>
</tr>
<tr>
<td>24 KM F/52</td>
<td>Nodule euthyroid</td>
<td>3 mo</td>
<td>NA</td>
<td>Subtotal thyroidectomy radiotherapy</td>
<td>Lymphoma</td>
<td>NA</td>
<td>3 yr well, no evidence of lymphoma</td>
</tr>
<tr>
<td>25 YS F/62</td>
<td>Thyroid swelling euthyroid</td>
<td>2 mo</td>
<td>NA</td>
<td>Total thyroidectomy radiotherapy</td>
<td>Lymphoma with extra capsular invasion</td>
<td>NA</td>
<td>Well, no evidence of lymphoma; died 7 yr later from unrelated reasons</td>
</tr>
<tr>
<td>26 KS F/50</td>
<td>Goiter recent rapid increase in size, stridor</td>
<td>10-15 yr</td>
<td>+</td>
<td>Total thyroidectomy</td>
<td>Lymphoma</td>
<td>Involved</td>
<td>Well, after 1 yr lost to follow-up</td>
</tr>
<tr>
<td>27 AT M/7</td>
<td>Thyroid enlargement</td>
<td>NA</td>
<td>Thyroidectomy</td>
<td>Lymphoma</td>
<td>NA</td>
<td>NA</td>
<td>High-grade TGL (IgGk)</td>
</tr>
<tr>
<td>28 YN F/68</td>
<td>Thyroid swelling</td>
<td>3 mo</td>
<td>NA</td>
<td>Total thyroidectomy radiotherapy</td>
<td>Lymphoma</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>29 MD F/51</td>
<td>Goiter recent increase in size</td>
<td>6 mo</td>
<td>+</td>
<td>Total thyroidectomy radiotherapy</td>
<td>Lymphoma with extra capsular invasion</td>
<td>NA</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>30 VT F/76</td>
<td>Goiter cervical lymphadenopathy</td>
<td>~1 yr</td>
<td>NA</td>
<td>Diagnostic biopsy radiotherapy chemotherapy</td>
<td>Lymphoma with extra capsular invasion</td>
<td>NA</td>
<td>3 yr later died with generalized lymphoma</td>
</tr>
<tr>
<td>31 JH M/62</td>
<td>Rapid enlargement of thyroid Addison's disease and primary autoimmune hypothyroidism</td>
<td>20 yr</td>
<td>+</td>
<td>Diagnostic biopsy radiotherapy chemotherapy</td>
<td>Lymphoma with extra capsular invasion</td>
<td>NA</td>
<td>At 4 mo died, no evidence of lymphoma at autopsy</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; HT, Hashimoto's thyroiditis; TGL, thyroid gland lymphoma; Ig, immunoglobulin demonstrated.
* No Ig heavy chain demonstrated.

We were retrieved from all cases, but adequate follow-up information was available for only 17 cases. Additional sections, cut at four μm, were prepared from two to five blocks in each case, stained with hematoxylin-eosin, and reevaluated.

**Immunohistochemistry**

The antibodies used and their sources and specificities are given in Table 1. From each block, serial sections were
stained with the different antibodies by a modification of
the Avidin Biotin complex (ABC) method of Guesdon et
al.9 Following deparaffinization, sections were transferred
into industrial methylated spirit and endogenous peroxi-
dase was blocked with H2O2 for ten minutes. Sections were
then washed in tap water, placed in tris-buffered saline
(TBS) at pH 7.6 for five minutes, and the primary antibody
was applied for 30 minutes at room temperature. For the
demonstration of Ig and CD35 antigen (C3b receptors),
prior trypsinization was necessary. Sections were then
washed for five minutes in TBS, and biotinylated rabbit
anti-mouse antibody or swine anti-rabbit antibody (Dako-
patts, High Wycombe, Buckinghamshire, England), de-
pending on the primary antibody, was applied for 30 min-
utes. Following a further wash in TBS, streptavidin peroxi-
dase complex (Dakopatts) was applied for 30 minutes.
Sections were then rinsed in TBS and peroxidase-binding
sites were demonstrated with diaminobenzidine for five to
ten minutes. The sections were then counterstained with
hematoxylin and mounted. Positive control sections of hu-
man tonsils and negative controls, omitting the primary an-
tibody, were studied in parallel in every instance.

RESULTS

Following reevaluation of the histologic features
and immunohistochemical studies, cases were classi-
fied into the following groups: (group 1) Hashimoto's
thyroiditis showing classical histlogic features with-
out any evidence of light chain restriction; (group 2)
cases resembling Hashimoto's thyroiditis, but with
unequivocal demonstration of light chain restriction,
thus diagnosed as low-grade lymphomas; and (group
3) cases with the obvious histologic features of high-
grade B cell lymphoma, confirmed by staining with
L26 and the demonstration of light chain restriction
in eight of the ten cases.

The results for groups 2 and 3 are summarized
in Table 2.

Clinical Features

Hashimoto's thyroiditis (group 1). All patients were
women, with an age range of 34 to 60 years. All pre-
sented with thyroid gland enlargement varying in du-
ration from 3 months to 7 years. Thyroid function
studies had been performed in ten of the 16 patients
in this group; six were hypothyroid and the remain-
der were euthyroid. Thyroid antibodies had been
sought in eight of the 13 cases and were present in all
instances. In each case, treatment consisted of a par-
tial thyroidectomy. Detailed follow-up was available
for nine patients, all of whom had remained well
through periods ranging from 1 to 15 years.

Cases with an initial diagnosis of Hashimoto's thyroid-
itis revised to low-grade lymphoma following demonstration
of light chain restriction (group 2). There were five pa-
tients in this group and their clinical features are
summarized in Table 2. There were four women and
one man, with an age range of 39 to 73 years. All
patients presented with thyroid enlargement with a
duration of 6 months to 1.5 years. Thyroid antibodies
were detected in three of the five patients in whom it
was sought. Four patients underwent partial thy-
roidectomy and one underwent a total thyroidec-
tomy. Follow-up information was available in three
patients who had remained well 2, 5, and 12 years
after thyroidectomy, respectively.

Cases with histologically obvious (high-grade) lym-
phoma confirmed by demonstration of light chain restriction
(group 3). There were ten patients in this group;
eight women and two men, with an age range of 50 to
76 years. All patients presented with recent thyroid
enlargement, which complicated a long-standing goi-
ter in two cases. Of those patients in whom thyroid
antibodies were sought, the titer was normal in one
and elevated in three. Two patients underwent diag-
nostic biopsy followed by radiotherapy and chem-
otherapy; two patients underwent thyroidectomy not
otherwise specified; two patients underwent a sub-
total thyroidectomy followed by radiotherapy; and four
patients underwent a total thyroidectomy, followed in
three cases by radiotherapy. In three cases, follow-up
information was not available, and death from gen-
eralized lymphoma occurred after 3 years in one of
the remaining seven patients. One patient died 4
months after completing a course of radiotherapy,
with no evidence of lymphoma at autopsy, and an-
other patient died 7 years after thyroidectomy and
radiotherapy from unrelated causes. Two additional

FIGURE 1. Early Hashimoto's thyroiditis. Lymphoid nodules containing
follicles are randomly scattered through the gland, beyond
which there is a patchy infiltrate. (Hematoxylin-eosin stain. magni-
fication ×50)
FIGURE 2. Immunohistochemistry of one of the lymphoid nodules illustrated in Fig 1, stained (A) for cytokeratins, (B) for B cells, and (C) for T cells. The lymphoepithelial lesions are highlighted in A (arrows), while the B cell nature of the lymphocytes forming them is emphasized in B (arrows). The distribution of T cells, only a few of which are found within thyroid acini (arrows), is shown in C. (Immunoperoxidase stain; magnification ×100.)
patients have been lost to follow-up with no evidence of disease for 1 and 5 years postoperatively.

Histology and Immunohistochemistry

Hashimoto's thyroiditis. Three cases were categorized as "early Hashimoto's thyroiditis." In these cases, the thyroid parenchyma showed focal oxyphilic change, with nodules of lymphoid infiltration randomly distributed in the gland (Fig 1). These were formed by hyperplastic follicles, around which small- to medium-sized lymphocytes permeating between thyroid acini were found. Beyond this, infiltrate plasma cells were scattered between the thyroid acini and concentrations surrounding individual acini were seen. The lymphocytes around the follicles appeared slightly larger than mantle zone cells and formed well-defined lymphoepithelial lesions. Immunocytochemical staining with anticytokeratin served to highlight these lymphoepithelial lesions (Fig 2A), and staining with L26 confirmed the predominant B cell nature of the cells forming them (Fig 2B). The B cells and the plasma cells beyond them were polytypic with respect to Ig light chains, with IgG being the predominant heavy chain. T cells were admixed within this infiltrate, and, although infiltrating thyroid epithelium as individual cells, did not form the classical lymphoepithelial lesions (Fig 2C).

Malignant Lymphoma

In five cases initially diagnosed as Hashimoto's thyroiditis, a revised diagnosis of lymphoma was made, based on the presence of light chain restric-
tion. This was present in all available blocks in two cases; in three cases, some blocks showed a polytypic lymphoid infiltrate. In a further case in which a diagnosis of high-grade lymphoma was obvious in sections from the right lobe of the thyroid, the diagnosis of sections from the left lobe was similarly revised from Hashimoto's thyroiditis to low-grade lymphoma. In these six cases, follicles were prominent, with a heavy lymphoid infiltrate between them (Fig 4). The plasma cell component was minor (and polytypic in nature, see below) in three cases, but accounted for the majority of the cells in three cases. The cytology of the lymphocytic infiltrate varied within the spectrum of cells previously described as "centrocyte-like" (CCL) in appearance in studies of gastric, salivary gland, and pulmonary lymphoma (Fig 5). Thus, cells slightly larger than small lymphocytes (eg, mantle zone cells), but with slightly irregular nuclei and clear cytoplasm, characterized some of the cases. Occasional transformed "blast" cells were present. In other cases, the cells more closely resembled centrocytes, with irregularly shaped heterochromatic nuclei. These cells formed easily identifiable lymphoepithelial lesions which were particularly striking in cases no. 18 and 22 (Fig 6), and, while forming solid sheets in some areas, were intimately mixed with plasma cells elsewhere. This cell population could also be seen surrounding and infiltrating reactive follicle centers, with replacement of the mantle zones leading to a "follicular" appearance in two cases (Fig 7). Immunocytochemistry revealed clear kappa light chain restriction in every case, with reference to both cytoplasmic immunoglobulin in the plasma cells in three cases and perinuclear space immunoglobulin in the CCL cells in all six cases (Fig 8). No heavy chain was detectable in two cases, and the heavy chain was Y in the remaining four cases. As in Hashimoto's thyroiditis, plasma cells concentrated around thyroid acini and were present within follicle centers in some cases. These plasma cells showed light chain restriction, with the polytypic nature of the colonized follicle center being readily evident (Fig 8). Staining with CD35 demonstrated the dendritic reticulum cells of reactive follicle centers and invasion of these centers by the neoplastic CCL cells was shown (Fig 9). With L26, the proportion of B cells to plasma cells could be more accurately observed (Fig 10). Although plasma cells were found within thyroid acini, the B cells predominantly comprised the lymphoepithelial lesions (Fig 10). As demonstrated with UCHL1, a heavy T cell infiltrate characterized all cases. In one of two cases in which lymph nodes were
available for study, the lymph nodes were involved with parafollicular infiltrates of neoplastic CCL cells (which showed kappa light chain restriction) invading reactive follicles.

In ten cases, a diagnosis of high-grade lymphoma was obvious in routinely stained sections. The infiltrate consisted of large transformed "blast" cells, most closely resembling pleomorphic centroblasts and without plasmacytoid differentiation in eight cases. Smaller CCL cells were also present (Fig 11). Plasma
cytid differentiation was present in two cases, and striking intrafollicular invasion by tumor cells was present in one of these cases (Fig 12). The follicles were preserved to a varying degree. Well-defined lymphoepithelial lesions were formed by both the large tumor cells and smaller CCL cells. Immunocytochemistry confirmed the B cell phenotype of these tumors and showed light chain restriction in seven cases (Figs 11 and 12; IgGk in four, IgGλ in two, and IgAk in one), and staining with CD35 revealed clusters of dendritic reticulum cells, representing follicles overrun by lymphoma. Lymph node involvement was present in two cases in which lymph nodes were available for study. In two cases of high-grade lymphoma, sections from some blocks showed Hashimoto's thyroiditis with a polytypic lymphoplasmacytic infiltrate, as described.

FIGURE 7. Case no. 22: follicular appearance of low-grade thyroid lymphoma caused by invasion of preexisting reactive follicles (as seen in Fig 4) by neoplastic CCL cells. (Hematoxylin-eosin stain; magnification x50.)

DISCUSSION

The first definitive clinicopathologic study of primary malignant lymphoma of the thyroid was that of Woolner et al in 1965. These investigators drew attention to the association of this disorder with Hashimoto's thyroiditis and to the occurrence of two different types of lymphoma composed predominantly of either small (low-grade) or large (high-grade) lymphoid cells. In this series, an advanced stage, as indicated by spread beyond the capsule of the thyroid gland, was the best indicator of prognosis, but it was noted that more of the high-grade tumors fell into this category. Later, Burke et al drew attention once more to the association of thyroid lymphoma with Hashimoto's thyroiditis and noted the similarity of this tumor to those lymphomas developing in other altered immune states, including Sjogren's syndrome. In their series, all the tumors were high-grade (histiocytic), and they noted the importance of stage in evaluating the prognosis of their cases. Despite the high-grade histology, lymphomas confined by the thyroid capsule behaved favorably. Heimann et al were the first to apply one of the newer (Kiel) classifications to a series of thyroid lymphomas. Their low-grade lymphomas were classified as centroblastic/centrocytic in type (i.e., follicle center cell-derived), while the high-grade cases were either centroblastic or immunoblastic. In contrast to previous reports, Heimann et al found that it was the grade rather than the stage of the lymphoma that determined its prognosis. Maurer et al, using the Lukes and Collins classification, once more suggested a follicle center cell origin for the majority of their tumors, including high-grade lymphomas. The prognosis in their series was related to both stage and grade, but, once again, it was the tumors of higher grade that had spread most often beyond the thyroid gland. Similar findings were described by Compagno and Oertel, who were the first to draw attention to the striking lymphoepithelial lesions characteristic of lymphoma rather than Hashimoto's thyroiditis. Following the suggestion of Isaacson and Wright that thyroid lymphoma belonged to the group of MALT-associated lymphomas, Anscombe and Wright, reinforced this concept in a study of 76 cases, especially with regard to the significance of the lymphoepithelial lesions and the relatively favorable prognosis of this tumor, even in the face of a high histologic grade. They, too, suggested that these lymphomas were follicle center cell-derived. Aozosa et al studied 79 cases of thyroid lymphoma and confirmed the strong relationship with Hashimoto's thyroiditis. In classifying their cases according to the working formulation and the Kiel classification, these investigators noted close correlation between the prognosis and tumor grade, although there was no correction for tumor stage. With the exception of lymphoblastic lymphoma, the entire range of the Kiel classification of B cell lymphomas was represented in the cases studied by Aozosa et al. In another immunologic study, Aozosa et al demonstrated kappa light chain restriction in cell suspen-
FIGURE 8. Case no. 20: low-grade thyroid lymphoma stained (A) for kappa light chains and (B) for lambda light chains. Both lymphocytes and plasma cells show kappa light chain restriction, but staining of many follicle center cells for lambda light chain confirms the reactive nature of this follicle. (Immunoperoxidase stain; magnification x100.)

sions prepared from 27 cases of thyroid lymphoma. Kappa light chain restriction predominated in our study, with only two cases expressing \( \lambda \) light chain. In contrast to other lymphomas of MALT, most of which express IgM or IgA, most of our cases of thyroid lymphoma expressed IgG; the significance of this is not clear.

Careful and precise immunostaining in paraffin sections, particularly of Ig, suggests that low-grade thyroid lymphomas are of a uniform cell type and, rather than being of follicle center cell origin, are derived from parafollicular B cells (also known as CCL cells\(^3\,4\)), a finding that is in common with our studies of gastric, salivary gland, and pulmonary lymphoma. Thus, they share a common histogenesis with other MALT lymphomas. As in other MALT lymphomas, a follicular pattern may be evident, but this is due to the colonization of reactive follicles by CCL cells rather than the neoplastic transformation of follicle center cells.\(^4\) This was particularly seen in cases no. 18 and 22 in our study. From our study, it is possible to propose a sequence of changes from "early" Hashimoto's thyroiditis to high-grade lymphoma. In Hashimoto's thyroiditis, particularly those cases categorized as "early," a close similarity of the lymphoid infiltrate with that of normal gut-associated lymphoid tissue is evident. The B cells beyond the follicular mantle zone, which infiltrate acini-forming lymphoepithelial lesions, correspond to similar cells described in Peyer's patches\(^18,19\) and in the lymphoid tissue accumulating in the salivary gland in MESA.\(^3\) It is this population of parafollicular B cells or CCL cells that expands in more "advanced" Hashimoto's disease, accompanied by increasing numbers of plasma cells. It is evident from those cases resembling Hashimoto's disease, but showing light chain restriction, that the tumor is derived from this CCL cell population. The neoplastic CCL cells form lymphoepithelial lesions, surround and invade follicles, and show transformation into both plasma cells and larger blast forms. It is interesting that monotypic collections of plasma cells are readily found around individual acini and within reactive follicle centers. We previously observed the latter phenomenon in other MALT lymphomas, but have not commented on this observation. It is conceivable that plasma cell transformation around acini and within follicle centers is related to intense antigenic stimulation at these sites, a phenomenon similar to the subepithelial plasma cell differentiation seen in MALT lymphomas of the gastrointestinal tract. A morphologic continuum between the low-grade lymphomas that resemble Hashimoto's thyroiditis and the more obvious high-grade lymphomas of the thyroid gland is suggested by common
was available, there was no evidence of recurrence following simple thyroidectomy after 2, 5, and 12 years, respectively, despite the presence of lymph node involvement in one case. Unfortunately, information on staging and follow-up was incomplete in our series of high-grade lymphomas, but survival without disease of 3, 5, and 7 years in three of our cases is noteworthy.

Given the indolent nature of low-grade thyroid lymphoma, as defined by light chain restriction of the B cell and plasmacytic infiltrate arising in Hashimoto's thyroiditis, it is conceivable that its true incidence may be much higher than recognized. Although our cases of Hashimoto's disease were specifically selected because they showed a particularly heavy lymphocytic infiltrate, our finding of light chain restriction in five cases is remarkable. This finding, however, is similar to that in our study of salivary glands, in which we revised an original diagnosis of MESA to one of lymphoma in 12 of 20 cases. These findings found confirmation in the report of Fishleder et al, who were able to demonstrate Ig gene rearrangements in eight cases of “benign” lymphoepithelial lesion of the salivary gland (MESA). It would be of great interest to study cases of Hashimoto's thyroiditis in a similar manner.

Histologic features, such as lymphoepithelial lesions and invasion of lymphoid follicles, and our findings in case no. 22, in which a typical low-grade lymphoma was present in the left lobe of the thyroid with a high-grade lesion present in the right. Our study confirms the relationship between Hashimoto's thyroiditis and thyroid gland lymphoma, the former being a necessary precursor for the evolution of the latter. After studying a series of fine needle biopsies of the thyroid gland, Holm et al estimated that the relative risk of thyroid gland lymphoma in patients with lymphocytic thyroiditis is 80 times greater than in controls. It is conceivable that this risk is even higher if one accepts the presence of a clonal B cell population in the thyroid as evidence of lymphoma. Like lymphomas of other mucosal sites, it would seem that this type of lymphoma is low-grade, remarkably indolent, and may remain localized for many years. However, the evolution into higher grade lymphoma and the spread outside of the thyroid gland is always a risk. The clinical behavior of thyroid gland lymphoma is similar to that of others arising in mucosal sites. Thus, prognosis is closely related to stage rather than grade, and the high-grade tumors may behave favorably provided there is no infiltration beyond the capsule of the thyroid gland. In the three cases of our low-grade lymphomas in which adequate follow-up
FIGURE 11. Case no. 30: high-grade thyroid lymphoma showing large transformed "blast" cells (A). Stain for kappa light chain (B) is positive, while that for lambda light chain (C) is negative. (A, hematoxylin-eosin stain; magnification ×1,000. B and C, immunoperoxidase stain; magnification ×500.)
FIGURE 12. Case no. 25: high-grade lymphoma showing plasmacytoid differentiation. The detailed cytology of these cells is seen in A. In sections stained for (B) kappa light chain and (C) lambda light chain, the presence of the neoplastic (kappa light chain restriction) plasma cells within follicle centers is shown. (Compare with Fig 8.) (A, hematoxylin-eosin stain; magnification ×1,000. B and C, immunoperoxidase stain; magnification ×50.)
REFERENCES


