T-CELL-RICH B-cell lymphoma (BCL) is a recently described histologic variant of BCL characterized by a minor population of clonal B cells distributed in a background of numerically preponderant polyclonal T lymphocytes. While precise histologic criteria have not yet been defined, clonal B cells typically comprise 10% or less of the total cellular constituency. Controversy persists with regard to both the clinical relevance and the proper classification of this histologic variant. The latter is largely a semantic issue, minor population of clonal B cells distributed in a background of numerically preponderant polyclonal T lymphocytes. However, the issue of biologic behavior, and the related question of optimal therapeutic design, must be addressed. With this purpose, we report our experience with 23 patients with T-cell-rich BCL.

MATERIALS AND METHODS

The records of 23 patients diagnosed and encoded as having T-cell-rich BCL at the University of Texas M.D. Anderson Cancer Center between 1988 and 1991 were reviewed. Immunophenotyping was performed after review of the hematologic and clinical sections. Immunophenotypic studies were performed on formalin-fixed tissue sections stained with hematoxylin and eosin. In all but one case, nonneoplastic T lymphocytes constituted 70% or more of the cells; in the remaining case, T lymphocytes comprised slightly more than 50% of lymphoid cells. In all 23 cases, a histologic diagnosis of T-cell-rich BCL was substantiated by the demonstration of a L26+ UCHL-1 phenotype in the atypical large cell population. Staining for Leu-M1 and LCA were negative and positive, respectively, in the seven cases in which they were examined. B-cell clonality was further confirmed whenever possible on fresh tissue by documentation of either light-chain restriction (six cases: IgH in six of six and IgK in two of two) or immunoglobulin gene rearrangement (six cases: IgH in six of six and IgK in two of two). In nine cases, histologic progression to B-cell large cell lymphoma of usual type was observed, either in subsequent biopsies or in biopsies from other sites. One patient had a history of follicular lymphoma. Southern blot analysis was performed as previously detailed using 32P-labeled probes for the (1) Ig heavy-chain joining region gene (JH), (2) \( \kappa \) light-chain joining region gene (JK), and (3) \( \beta \) T-cell receptor constant region gene (CTB) (Oncor, Gaithersburg, MD). BamHI, EcoRI, and HindIII restriction digestions were used for all analyses. Several variables known to have prognostic importance were analyzed, including age, sex, B symptoms, Ann Arbor stage, tumor burden as defined by Jagannath et al initial serum lactate dehydrogenase (LDH), and \( \beta_2 \)-microglobulin values, and number of involved extranodal sites. Staging and definition of extranodal sites were based on the Ann Arbor classification. The spleen was considered to be involved if it appeared enlarged on physical examination or by radiologic studies. First-line therapy included doxorubicin-containing regimens such as CHOP-Bleo (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine] [Eli Lilly Co, Indianapolis, IN], prednisone, bleomycin) (four regimens with additional local radiotherapy), Pro-MACE (methotrexate, Adriamycin [Adria, Dublin, OH], cyclophosphamide, etoposide), MACOP-B (methotrexate, Adriamycin, cyclophosphamide, Oncovin, vincristine).
prednisone, bleomycin), CHOP-Bleo alternating with OPEN (On-
covin, prednisone, etoposide, Novantrone [mitoxantrone] [Le-
derle, Pearl River, NY]), and alternating triple therapy (ATT) with
ASAP (Adriamycin, Solu-Medrol [methylprednisolone] [Upjohn,
Kalamazoo, MI], ara-C [cytarabine], cisplatin], MBACOS (metho-
trexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin,
Solu-Medrol], MINE (mesna, ifosfamide, Novantrone, etoposide).
Initial therapy also included MOPP (mechlorethamine, Oncovin,
procarbazine, prednisone), MOPP-ABVD (Adriamycin, bleomy-
cin, vinblastine, dacarbazine), or ABVD (two of which also in-
cluded local radiotherapy) for patients with a referring diagnosis of
Hodgkin's disease. One patient received cyclophosphamide-pred-
nisone only. Complete remission (CR) was defined as the disappear-
ance of all signs and symptoms of disease as determined by clinical,
radiographic, and laboratory evaluations. Patients who responded
to treatment and had minimal residual radiographic abnormalities
that remained unchanged for more than 6 months after treatment
were considered to be in CR. Partial remission (PR) was defined as
a reduction of 50% or more in measurable disease for at least 1
month. Any other response, including mixed response, stable dis-
gress, progressive disease, early death, or death due to toxicity of
therapy, was considered a failure. Time to treatment failure was
measured from the date of initial treatment to clinical or radi-
graphic evidence of progression.

RESULTS

Clinical features. Clinical features at presentation are
detailed in Table 1. Twenty-three patients comprised 12
women and 11 men, ranging in age, from 21 to 82 years
(median, 58). Eighteen patients presented with peripheral
lymphadenopathy, four with mediastinal adenopathy, and
one with no adenopathy. Eight patients had splenomegaly,
which was characterized as massive in two. Sites of extro-
domal involvement included liver, lung, colon, base of tongue,
central nervous system, and bone marrow. A primary vagi-
nal tumor was observed in one case. One patient had Ann
Arbor stage I disease, nine had stage II, five had stage III,
and eight had stage IV. Only six patients presented with B
symptoms. Tumor burden was assessed in accordance with
previously published institutional criteria. Five patients
were considered to have high tumor burden, eight interme-
diate, and 11 low. Using the same criteria, eight patients
were classified as having bulky disease. LDH was high in
eight of 19 patients in whom it was measured before ther-
apy. Serum β2-microglobulin levels were ≥3 mg/dL in six of
10 patients (normal, ≤2.0 mg/dL).

Response to therapy. Response to therapy is detailed in
Table 2. Of nine patients who were originally diagnosed with
non-Hodgkin’s lymphoma of various histologic types and
who were treated at their referring institutions, eight
received a doxorubicin-based regimen and one received sur-
movia. Of the eight who received chemotherapy, four (50%)
achieved a CR, two a PR, one a minor response, and one
was refractory to treatment. Of the four patients who
achieved a CR, two subsequently relapsed. Neither re-
sponded to second-line therapy, and both died of disease.

The management of 5 of these 9 patients merits further
comment. One patient, diagnosed before referral as having
centrocytic lymphoma, was treated initially with cyclophos-
phamide, prednisone, and interferon, and sustained only a
minimal response. On transfer to our institution, the diag-
nosis was revised to T-cell–rich BCL. The patient was begun
on our standard alternating triple therapy (ATT) regimen.
She achieved a CR and was free of disease at 12 months of
follow-up. A second patient received only a single course of
Pro-MACE from an anticipated Pro-MACE-CytaBOM (cy-
tarabine, bleomycin, Oncovin, methotrexate) regimen be-
cause of a severe allergic reaction. The treatment was
changed to CHOP after referral to M.D. Anderson. The
patient achieved a CR, but subsequently relapsed and re-
fused further chemotherapy. Two patients diagnosed with
large-cell lymphoma received MACOP-B. One patient did
not respond to this therapy, whereas the second achieved a
PR. Both patients’ disease failed to respond to salvage treat-
ment at our institution. Finally, the ninth patient was still in
CR 8 months after a right hemicolectomy and partial ileec-
tomy for intestinal lymphoma that involved regional lymph
nodes. No adjuvant therapy was administered.

Six patients were diagnosed with Hodgkin’s disease at


Table 2. Response to Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment</th>
<th>1st Line</th>
<th>2nd Line</th>
<th>Relapse</th>
<th>Status</th>
<th>Follow-up (mo)</th>
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<tr>
<td>1</td>
<td>CYT/PRED, IFN, ATT</td>
<td>MR</td>
<td>CR</td>
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<td>A, NED</td>
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<td>2</td>
<td>MOPP-Bleo/XRT; MOPP-ABV/XRT</td>
<td>PR</td>
<td>PR</td>
<td>Y</td>
<td>DD</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>DNAP/CHOP</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
<td>36+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CHOP-Bleo/OPEN</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
<td>13+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CHOP/XRT</td>
<td>PR</td>
<td>NR</td>
<td>Y</td>
<td>AWD</td>
<td>18+</td>
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<tr>
<td>6</td>
<td>Surgery</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
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<tr>
<td>7</td>
<td>MACOP-B/MINE/ESHAP</td>
<td>CR</td>
<td>NR</td>
<td>Y</td>
<td>DD</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Pro-MACE/CHOP</td>
<td>NR*</td>
<td>CR</td>
<td>Y</td>
<td>AWD</td>
<td>23+</td>
</tr>
<tr>
<td>9</td>
<td>ATT</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
<td>8+</td>
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</tr>
<tr>
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<td>CR</td>
<td>Y</td>
<td>A</td>
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<td>U</td>
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<td>A, U</td>
<td>4+</td>
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<td>PR</td>
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<td>DD</td>
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<tr>
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<td>7+</td>
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<td>A</td>
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</tr>
<tr>
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<td>CR</td>
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<td>Y</td>
<td>A</td>
<td>8+</td>
</tr>
<tr>
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<td>U</td>
<td>U</td>
<td>A</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>CHOP/OPEN</td>
<td>U</td>
<td>U</td>
<td>A</td>
<td>1+</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A, alive; ATT, alternating triple therapy; AWD, alive with disease; CR, complete response; CYT, cytarabine; DD, dead of disease; IFN, interferon; NED, no evidence of disease; N, no; NR, no response; PR, partial response; PRED, prednisone; U, unassessable (currently receiving treatment); XRT, radiotherapy; Y, yes.

A relatively large series of T-cell-rich BCL composed of 19 cases was recently published by Macon et al. These findings are parallel to ours in regard to the confusion with other histologic types and the favorable response to therapy when treated appropriately. Because of the paucity of neoplastic cells, histologic examination and evaluation of light-chain restriction may be insufficient to establish a diagnosis of T-cell-rich BCL. Osborne et al. found Southern blotting to be a consistently reliable and definitive method of distinguishing such cases from peripheral T-cell lymphoma. However, clonal proliferations accounting for less than 5% of a cell population may be difficult to detect by conventional Southern blot analysis. Special modifications of the polymerase chain reaction using primers for complementary DNA sequences have proven useful in our hands in documenting the presence of B-cell clones that elude detection by Southern blotting (unpublished observations, February 1992).

The patient population reported herein exhibited clinical features and responses to doxorubicin-based regimens that were comparable to those of B-cell large cell lymphoma of usual type. The 35% incidence of splenomegaly was higher than expected and is perhaps a characteristic clinical sign. However, the number of patients was small, and the potential clinical importance of splenomegaly will require examination in larger patient cohorts. A long history of localized peripheral adenopathies, as noted by Cooper et al., was not seen in our series. Conclusions about therapeutic response are limited by the number of patients and the short follow-
up interval. Of 13 patients treated with standard regimens for intermediate-grade lymphomas, 9 (70%) achieved a CR, a result consistent with the norm. The clinical significance of the preponderant T-cell response that characterizes these lymphomas is uncertain. Various investigators have postulated a host-immune response to the neoplastic clone, analogous to that seen in Hodgkin’s disease. In keeping with this hypothesis is the observation by some that the T-cell reaction tends to diminish as the disease progresses and escapes immune surveillance. Alternatively, it could represent a response of the reactive T cells to some cytokine secreted by the tumor cells. In our study, histologic progression to large cell lymphoma of usual type was noted in 9 of 11 cases in which multiple biopsies, either from different sites or from different times, were studied. In four instances, this was observed in concurrent biopsies from different anatomic sites, and in five patients progression was observed over periods ranging from a few weeks to 10 months. Thus, T-cell-rich histology apparently is a highly unstable parameter of this disease. If this is true, it is not surprising that T-cell-rich BCL exhibits a clinical behavior that closely parallels that of B-cell large cell lymphoma of usual type.

Based on the foregoing and the accumulated experience to date, it would seem that the critical issue in T-cell-rich BCL is the need to distinguish it pathologically from Hodgkin’s disease and other non-Hodgkin’s lymphomas, principally peripheral T-cell lymphomas, with which it may be easily confused. Underscoring this imperative is the fact that six of our cases were referred with diagnosis of Hodgkin’s disease. Of the four patients who received treatment based on this diagnosis, three have died of disease. Thus, the administration of inadequate initial therapy may compromise the potential for salvage and long-term survival. In summary, many aspects of T-cell-rich BCL remain unsolved. Among these are the precise immunophenotype and modulatory role of the infiltrating T cells and the question of whether, with longer follow-up, the response to therapy (including time to treatment failure and overall survival) will differ significantly from that obtained in patients with diffuse large-cell lymphomas of usual type. Prospective studies with more patients and sufficient follow-up periods will be required to answer these queries; however, the preliminary data presented herein do not support the contention that the T-cell-rich infiltrate exerts a significant clinical impact on the behavior of large cell lymphomas of B lineage.

REFERENCES

T-cell-rich B-cell lymphoma

J Rodriguez, WC Pugh and F Cabanillas