Immunoblastic Sarcoma of T-Cell Versus B-Cell Origin:
I. Clinical Features


Within the Lukes-Collins classification system of malignant lymphoma, a tumor of large transformed lymphocytes, termed immunoblastic sarcoma (IBS), is described. This morphological type would have been included within the "histiocytic" category of Rappaport. Immunoblastic sarcoma may be of B-lymphocytic or T-lymphocytic origin. Since differences or similarities of these two variants have not yet been described, we reviewed the case histories of 35 such patients, all of whom had immunologic marker studies performed. Nineteen patients had T-cell IBS (T-IBS), whereas 16 had B-cell IBS (B-IBS). Median age for both groups was approximately 50 yr. A history of prior immune disorder was found in 31% of B-IBS and 16% of T-IBS cases. Prior lymphoproliferative malignancy was noted in 21% of T-IBS and 13% of B-IBS patients. All T-IBS patients first presented because of lymphadenopathy, whereas 56% of B-IBS cases initially presented because of extranodal disease. Systemic "B" symptoms were common in both. Similarly, most patients had widespread disease (stage III or IV) at diagnosis. Clinically suspected hepatic (p = 0.05) and retroperitoneal node (p = 0.01) involvement were more often found in T-IBS. Forty-one percent of T-IBS patients demonstrated polyclonal hypergamma globulinemia, a finding seen in no B-IBS patient (p = 0.02). Although not statistically significant because of small numbers of patients, data on therapy and survival suggest that IBS of B-cell type may be successfully treated with aggressive, multiagent chemotherapy, while alternative approaches appear warranted in T-cell disease.

TRADITIONAL concepts of the pathology and classification of malignant lymphomatous changes dramatically within the past 5 yr. The Rappaport system, proposed in 1956, and based solely on morphological description,1 has been challenged conceptually, since it does not consider the thymic (T lymphocyte) or bursal (B lymphocyte) lineage of these tumors and does not recognize the concept of lymphocyte transformation.2-4 Moreover, recent reports have demonstrated that the various subgroups of disease within the Rappaport system are, in fact, heterogeneous, both pathologically and clinically.2-5-8 The subgroup of histiocytic lymphoma is perhaps the most heterogeneous, consisting of several distinct cytologic types, with diverse median survivals in treated patients ranging from less than 1 yr to more than 5 yr.2-4

The Lukes-Collins classification system of lymphoma, proposed in 1974, is based on the newer concepts of immunology.2 Within this system, a tumor of large transformed lymphocytes, termed immunoblastic sarcoma (IBS), was described. This morphological type would have been included within the histiocytic category of Rappaport.2,4 In our previous report of 33 patients with immunoblastic sarcoma, a history of prior immune disorder or lymphoproliferative malignancy was found in 30%, profound lymphopenia was found in 45% and immunoglobulin abnormalities were detected in 68%.9,10 Because of these findings, and similar observations made earlier, we postulated that this tumor might arise in a setting of an altered immune system.2,9,10 Numerous case reports of this disease have recently confirmed the finding of altered immunity in some patients with immunoblastic sarcoma.11-19 Aside from immune abnormalities, the patients in our initial report appeared similar with regards to a high incidence of systemic symptoms, advanced stage of disease at diagnosis, and a relatively short median survival.

In parallel with the functional division of the lymphocytes into B cells and T cells, we proposed that immunoblastic sarcoma may be of B-lymphocytic or T-lymphocytic origin.2,4 Since prior reports have not dealt with the differences or similarities that may exist between these two groups, and since insights into pathogenesis or optimal therapeutic approach may result, we now report the clinical and pathologic characteristics of 35 patients with immunoblastic sarcoma, whose tumor cells were studied and found to be of T-cell (19 patients) or B-cell (16 patients) lineage.

MATERIALS AND METHODS

Criteria for Inclusion

The 35 cases that constitute this report were collected through the Hematology and Hematopathology services at the Los Angeles...
County-U.S.C. Medical Center and the participating physicians of the Southern California Lymphoma Group during a 5-yr period from January 1975 to December 1979. Twelve of these patients have been reported previously.6,9 Cases were considered for inclusion in this study on the basis of a tissue diagnosis of immunoblastic sarcoma, as well as the availability of fresh cell suspensions prepared from the diagnostic material, to enable performance of immunologic marker studies, or alternatively, the demonstration of cytoplasmic immunoglobulin by immunoperoxidase studies of fixed paraffin sections. All biopsy material was obtained prior to the institution of therapy.

Support for the designation as T-cell IBS was the formation of spontaneous sheep erythrocyte rosettes by the critical malignant cell when viewed on cytospin preparations. If such a finding was not demonstrated, the case was not accepted as a T-cell case for purposes of this study. A diagnosis of B-cell IBS was confirmed when the tumor cells were demonstrated to have immunoglobulin on the cell surface and/or intracytoplasmic immunoglobulin, as demonstrated by the immunoperoxidase technique.2

Cases diagnosed morphologically as B-IBS or T-IBS were so designated on the basis of the morphological criteria described below, but were only included in this study when immunologic surface marker studies, performed on the diagnostic material, were available and confirmed the morphological opinion.

Of 59 cases of immunoblastic sarcoma in which fresh cell suspensions were available, 11 cases were excluded from this study because immunologic marker studies could not be performed due to insufficient numbers of viable tumor cells for testing, and 5 cases were excluded because marker studies were inconclusive, revealing only low levels of immunoglobulin or E-rosette marking cells, which did not permit designation into T-cell or B-cell subtype. These aforementioned cases were excluded from this study because our prime purpose was to describe differences or similarities, if any, between defined B-cell and T-cell cases. Eight cases were excluded because complete clinical information was not available.

**Immunologic Methods**

Lymphocyte suspensions were prepared from fresh samples of the diagnostic material by teasing through stainless steel wire mesh in RPMI-1640 culture medium. Separated cells were washed and incubated for 1 hr in serum-free medium to elute absorbed surface immunoglobulins.7 Cell surface immunoglobulin was determined using whole rabbit anti-human immunoglobulin antisera (antipolyvalent PV, anti-α, anti-γ, anti-κ, anti-λ) and anti-μ and, in most cases, the corresponding F(ab)2 reagents. In all cases specificity of antisera was checked by two-dimensional immunodiffusion, and working dilutions were selected by titration to the plateau end-point. Percentage scores were determined by counting 200 cells in suspension using a Zeiss photomicroscope III with a Ploem illuminator and phase contrast to distinguish granulocytes and monocytes.

A part of the cell sample was also assayed for spontaneous rosette formation with sheep red blood cells using Ficol as a stabilizer.3,21 Cells were pelleted for 2 hr at 4°C prior to gentle resuspension; lymphocytes bearing three or more attached red cells were scored as positive. In addition, slide preparations of E-rosette suspensions were prepared by centrifugation (Shandon Instruments, Sewickley, Pa.), and were stained with Wright stain to facilitate identification of rosette formation about morphologically recognizable neoplastic cells in cases of suspected T-cell IBS.

Cytoplasmic immunoglobulin was analyzed in B5-fixed paraffin-embedded sections of the diagnostic material using an immunoperoxidase method described in detail elsewhere.20,21 Dilutions of antisera were determined by checkerboard titration using sections of myeloma tissue as positive and negative biologic controls (anti-α and anti-μ 1/2000, anti-γ, anti-κ, anti-λ 1/600). Stains of morphologically recognizable neoplastic cells were assessed for monoclonality by the pattern of staining with different light and heavy chain antisera.

Immunoglobulin antisera and peroxidase reagents were obtained from Dakopatts (Santa Barbara, Calif.); F(ab)2 reagents were obtained from Kallestad, Inc. (Chaska, Minn.).

Cell surface immunoglobulin and spontaneous rosette formation with sheep erythrocytes on cases 17 and 18 were performed by the Department of Anatomic Pathology at the City of Hope National Medical Center, Duarte, Calif.

**Statistical Methods**

Differences in the proportion of various characteristics between T-cell and B-cell groups were tested using the Chi-square test. Differences in age, lymphocyte count, and hemoglobin level were tested using the Student's t test and the Mann-Whitney test.24 Survival data were analyzed using life tables and the logrank test.29 All p values were two-sided.

**RESULTS**

**Histopathology**

Immunoblastic sarcoma formerly was included under the designation of reticulum cell sarcoma, or malignant lymphoma, histiocytic.2,3,4,8,20,26 While B-cell and T-cell immunoblastic sarcoma show a number of morphologic resemblances, permitting a common designation of immunoblastic sarcoma, they do show, in many instances, distinct morphological differences that permit their separation into B-cell and T-cell disease.3,4 Using the following criteria, our (C.R.T., D.R.S., R.J.L.) ability to distinguish T-IBS from B-IBS, in the majority of cases, based on morphological criteria alone has been reported.27

In tissue sections of B-cell immunoblastic sarcoma, the predominant neoplastic cell is a large round or ovoid cell, with a large round vesicular nucleus, distinct nuclear membrane, and one or more conspicuous nucleoli. The cytoplasm is moderate in amount and shows variable, but often intense amphophilia, which is reflected as pyroninophilia in methyl-green–pyronin stains. Amphilophia or pyroninophilia alone do not distinguish B-IBS from T-IBS, for both may demonstrate the basophilic characteristic of rapidly proliferating cells. It is the observation of varying degrees of plasmacytoid differentiation, evidenced by the occurrence of a juxtanuclear hof and amphophilia of the cytoplasm, which is of particular value in recognizing the B-cell form (see Fig. 1).

In histologic sections of T-cell immunoblastic sarcoma, the majority of the neoplastic cells are also large, round, or ovoid cells. Plasmacytoid differentiation of neoplastic cells is not present, although reactive plasma cells may be scattered through the lesion. In IBS of T cells, the cytoplasm of the neoplastic cells is characteristically pale and water clear. Irregular folding of the nuclear envelope is present, and nuclear
Immunoblastic sarcoma of B-cell type. Immunoblasts, plasma cells, and intermediate forms are distributed diffusely throughout the node. Small lymphocytes are typically few in number. The immunoblastic forms often contain a single nucleus, with peripheral margination of the chromatin. The cytoplasm is typically amphophilic. (B5 paraffin section, hematoxylin and eosin stain; magnified x325.)

The chromatin is often more finely dispersed than in B-IBS. The neoplastic T immunoblasts may be admixed with a population of small or intermediate-sized lymphocytes, many of which also demonstrate contortions of the nucleus, as demonstrated in Fig. 2. In some cases, epithelioid histiocytes are scattered through the lesion, a finding particularly noted in those cases arising from preceding lymphoepithelioid cell lymphomas.28

A panel of cytochemical markers was performed on tumor imprints from all cases. The stain for nonspecific esterase, a histiocyte marker, was negative in tumor cells from every case.

**Table 1. Immunologic Marker Data: 35 Patients With IBS**

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>E</th>
<th>PV</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>κ</th>
<th>λ</th>
<th>IMPX</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73 22 4 9 2 22 11 11</td>
<td>Neg.* Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72 24 —† — — — 16 10</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>90 11 2 1 6 2 4 2</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50 7 — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>54 6 0 0 0 2 3 0</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>86 5 — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34 16 — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>54 — — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>57 31 1 16 10 12 22 17</td>
<td>Neg Pleura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>68 21 0 10 7 14 17 12</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>† — — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>50 5 0 4 2 5 6 2</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>74 — — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>47 20 3 9 8 11 12 5</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>41 24 9 5 9 15 14 10</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>32 — — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>50 0 — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>47 0 — — — — — — —</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>33 12 1 7 2 11 6 8</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>— — 87 — — 83 — 87 — κ</td>
<td>Lung mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>5 34 — — 13 0 0 29 γλ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>3 91 0 0 3 82 90 0 —</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>— — — — — — — — —</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>0 12 0 0 19 1 14 0</td>
<td>Neg Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>4 91 0 0 89 0 0 84</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>— — — — — — — — αλ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>20 58 51 8 3 14 40 7 ακ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>0 — — — — — — — — κ</td>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>— — — — — — — — λ</td>
<td>Stomach mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>— — — — — — — — κ</td>
<td>Stomach mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>9 20 2 0 0 0 0 0 κ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>21 53 — — — 32 0 50 μλμ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>— — — — — — — — λ</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>— — — — — — — — α</td>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>— — — — — — — — αλδ§</td>
<td>Jejunal mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α, Anti-alpha; γ, anti-gamma; κ, anti-kappa; λ, anti-lambda; μ, anti-mu.

E, Sheep erythrocyte rosette; IMPX, immunoperoxidase; PV, polyvalent antiserum.

*Negative to anti-lambda and to anti-kappa.
†Study not performed.
‡Insufficient cells for sheep erythrocyte rosette assay; E-rosette-forming tumor cells were easily found on the cytospin preparation.
§The critical malignant cells were noted to contain both kappa and lambda light chains by immunoperoxidase technique.
in three, and IgM in two. Light chain analysis revealed kappa determinants in seven cases, lambda in seven, and both kappa and lambda in one. Light chain analysis was not performed in one case.

**Age and Sex**

The 19 cases of T-IBS included 7 males and 12 females. The mean age was 52, with a range from 22 to 85 yr. The 16 B-IBS cases included 8 males and 8 females. The mean age was 50 yr, with a range from 14 to 86 yr.

**Past Medical History**

A history of prior immune disorder or lymphoproliferative malignancy was found both in B-cell and T-cell IBS. Five of 16 (31%) of B-cell cases presented with histories of immune disorders, including one patient with celiac disease who developed IBS in the jejunum, and one patient with biopsy proven chronic atrophic gastritis who developed IBS in the stomach. In addition, one patient had Sjögren’s syndrome and rheumatoid arthritis, one patient (who presented with erythema nodosum) had a history of an unclassifiable abnormal immune reaction in an enlarged spleen (which was removed for diagnostic purposes 3 yr prior to diagnosis of IBS), and one patient had chronic urticaria. A history of prior immune disorder was found in 3 of 19 (16%) of T-IBS cases; these included one patient with Hashimoto’s thyroiditis and idiopathic thrombocytopenic purpura, one with hay fever, and a third with life-long asthma and sarcoidosis.

In addition to immune disorders, a number of patients in each group presented with histories of prior lymphoproliferative malignancies. Two of 16 (13%) B-IBS cases had such a history, including one patient with chronic lymphocytic leukemia (CLL) and one with multiple myeloma. In 4 of 19 (21%) T-cell cases, there was a prior lymphoproliferative malignancy, including 1 patient with small cell lymphoma and 3 patients with lymphoepithelioid cell lymphoma or so-called Lennert’s lymphoma.28 The time interval from prior malignancy to the development of IBS varied from 30 mo (CLL) to simultaneous diagnosis in 2 patients with lymphoepithelioid cell lymphoma. In all, 7/19 (37%) of T-IBS and 7/16 (44%) of B-IBS patients had histories of a prior immune disorder or lymphoproliferative malignancy.

**Method of Presentation**

All of the patients with T-IBS presented to the physician because of lymphadenopathy, including 16 patients with peripheral lymph node enlargement and 2 patients with mediastinal adenopathy. One patient (number 7) presented with ascites and mesenteric lymphadenopathy. In contrast, 9 of 16 (56%) patients with B-IBS initially presented because of disease in extranodal sites. These included four patients with gastric masses, one with a jejunal mass, one with a mass in the clavicle, and three patients with pulmonary parenchymal masses, in whom two had associated mediastinal adenopathy. This difference in the mode of presentation in the two variants was highly significant \( (p = 0.001) \).

Both types frequently presented with systemic “B” symptoms, occurring in 58% of T-cell and 63% of B-cell cases.

**Initial Staging**

Determination of the stage in these patients was accomplished in several different institutions and was not entirely consistent. Staging laparotomy was performed in one case of T-IBS and five cases of B-IBS. Lymphangiogram or abdominal CT scan was performed in 14 T-IBS cases and 11 B-IBS patients. Of the ten cases in whom these procedures were not performed, three had pathologic stage IV disease based on positive bone marrow biopsies, one had pathologic stage IV based on laparotomy with involvement of mesenteric nodes and stomach, one had pathologic stage IV based on a positive pleural biopsy, one had clinical stage IV based on massive hepatomegaly with filling defects seen on technetium sulfur colloid scan of the liver, one had clinical stage I, one had clinical stage II, and two had clinical stage III. Bone marrow biopsy was obtained in 15 T-IBS and 13 B-IBS patients.

Staging work-up revealed advanced stage disease at diagnosis in IBS of both types, with 17/19 (89%) of T-IBS and 13/16 (81%) of B-IBS staged as III or IV at initial presentation (Table 2). A mediastinal mass, detected on chest x-ray, chest tomograms, or CAT scan, was found in 9/19 (47%) of T-IBS patients and 6/14 (43%) of patients with B-cell IBS.

Retroperitoneal adenopathy was detected in 11/14 (78%) T-IBS cases, compared to only 2/11 (18%) of B-IBS patients. The difference was statistically significant \( (p = 0.01) \).

Similarly, clinically suspected hepatic involvement was significantly different, occurring in 8/19 (42%) of T-cell cases and only 1/16 (6%) of B-cell cases \( (p = 0.05) \). Hepatic involvement was defined on the basis of liver biopsy in two of these cases, on the basis of elevated alkaline phosphatase with massive hepatomegaly without focal filling defects on the technetium-sulfur colloid liver scan in four cases, and on the basis of elevated alkaline phosphatase with hepatomegaly and filling defects on technetium-sulfur colloid liver scan in three cases.
Table 2. Stage, Response to Therapy, and Survival: 35 Patients With IBS

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Therapy</th>
<th>Stage</th>
<th>Extranal Site</th>
<th>Response (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COPP</td>
<td>PS IV B</td>
<td>BM†</td>
<td>PR 26</td>
</tr>
<tr>
<td>2</td>
<td>BACOP</td>
<td>PS IV B</td>
<td>BM, liver</td>
<td>PR 20</td>
</tr>
<tr>
<td>3</td>
<td>4000 rads mantle radiotherapy</td>
<td>PS I A</td>
<td>CR</td>
<td>46*</td>
</tr>
<tr>
<td>4</td>
<td>COP, BCNU, mantle radiotherapy</td>
<td>PS IV B</td>
<td>Lung; CS: liver‡</td>
<td>PR 4</td>
</tr>
<tr>
<td>5</td>
<td>COP + ABOP + chlorambucil</td>
<td>PS IV A</td>
<td>BM; CS: liver</td>
<td>PR 28</td>
</tr>
<tr>
<td>6</td>
<td>COPP</td>
<td>PS IV B</td>
<td>BM; CS: liver</td>
<td>PR 9</td>
</tr>
<tr>
<td>7</td>
<td>COPP</td>
<td>CS III A</td>
<td>PR 37</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>BACOP</td>
<td>CS III B</td>
<td>CR 22+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>COPP</td>
<td>PS IV A</td>
<td>Pleura</td>
<td>PR 4</td>
</tr>
<tr>
<td>10</td>
<td>Cyclophosphamide</td>
<td>CS II A</td>
<td>CR 41+ (lost F/U)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CHOP</td>
<td>PS IV B</td>
<td>Lung, pleura</td>
<td>NR 4</td>
</tr>
<tr>
<td>12</td>
<td>BACOP</td>
<td>CS III A</td>
<td>PR 7.25</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>PS IV A</td>
<td>BM; CS: liver</td>
<td>PR 31+</td>
</tr>
<tr>
<td>14</td>
<td>BACOP</td>
<td>PS IV B</td>
<td>BM</td>
<td>NR 9</td>
</tr>
<tr>
<td>15</td>
<td>CHOP, 4000 rads to neck</td>
<td>CS III A</td>
<td>PR 23+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>COPP</td>
<td>CS IV B</td>
<td>Liver</td>
<td>NR 2.5</td>
</tr>
<tr>
<td>17</td>
<td>BACOP</td>
<td>CS IV B</td>
<td>Liver</td>
<td>NR 4</td>
</tr>
<tr>
<td>18</td>
<td>BACOP</td>
<td>PS IV B</td>
<td>BM, liver</td>
<td>NR 4</td>
</tr>
<tr>
<td>19</td>
<td>BACOP</td>
<td>CS III B</td>
<td>PR 12+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>LSA2-L2 + 4500 rads to mantle</td>
<td>PS IV B</td>
<td>Lung</td>
<td>CR 30.25</td>
</tr>
<tr>
<td>21</td>
<td>BACOP + 1200 rads to mediastinum</td>
<td>CS III B</td>
<td>NR 3.25</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Left upper lobe resection + 2250 rads to lung + BACOP</td>
<td>PS IV A</td>
<td>Lung</td>
<td>CR 55+</td>
</tr>
<tr>
<td>23</td>
<td>COPP</td>
<td>PS IV B</td>
<td>Kidney</td>
<td>NR 5</td>
</tr>
<tr>
<td>24</td>
<td>BACOP</td>
<td>CS IV B</td>
<td>Liver</td>
<td>CR 16+</td>
</tr>
<tr>
<td>25</td>
<td>AOP</td>
<td>PS IV B</td>
<td>BM</td>
<td>NR 0.5</td>
</tr>
<tr>
<td>26</td>
<td>4100 rads to mediastinum</td>
<td>CS IA</td>
<td>CR 20</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Gastrectomy + BACOP</td>
<td>PS IIE B</td>
<td>Stomach</td>
<td>CR 22+</td>
</tr>
<tr>
<td>28</td>
<td>BACOP + 2400 rads to clavicle</td>
<td>PS IV A</td>
<td>BM, bone</td>
<td>PR 17.75</td>
</tr>
<tr>
<td>29</td>
<td>Gastrectomy + cyclophosphamide</td>
<td>PS IV B</td>
<td>Stomach</td>
<td>PR 17.75</td>
</tr>
<tr>
<td>30</td>
<td>BACOP</td>
<td>PS IV B</td>
<td>Stomach</td>
<td>NR 2.75</td>
</tr>
<tr>
<td>31</td>
<td>COP + 4500 rads to stomach</td>
<td>PS IV B</td>
<td>Stomach</td>
<td>NR 3</td>
</tr>
<tr>
<td>32</td>
<td>BACOP</td>
<td>PS IV A</td>
<td>BM</td>
<td>NR 8</td>
</tr>
<tr>
<td>33</td>
<td>COPP</td>
<td>CS III B</td>
<td>CR 61+</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Cyclophosphamide</td>
<td>CS III A</td>
<td>PR 54</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Jejunal resection + Adriamycin + cyclophosphamide</td>
<td>PS IIE A</td>
<td>Jejunum</td>
<td>CR 51+</td>
</tr>
</tbody>
</table>

ABOP, Adriamycin, bleomycin, vincristine, prednisone; BACOP, bleomycin, Adriamycin, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, Adriamycin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete remission; LSA2-L2, see reference 53; NA, no response; PR, partial remission.

*Patient died of infection, no evidence of lymphoma at autopsy.
†Bone marrow.
‡Clinically suspected liver involvement.

Bone marrow was found positive for IBS in 7/15 (46%) of T-cell cases and 3/13 (23%) of B-cell cases (p = NS).

**Hematologic Data**

Both variants manifested comparable degrees of anemia at diagnosis, with a mean hemoglobin of 10.7 g/dl in the T-cell type and 11.8 g/dl in B-IBS. Mean lymphocyte count in T-IBS was 1852/dl, compared to 1183/dl in the B-IBS patients. Lymphopenia (less than 1000/dl) was common in both, occurring in 8/19 (42%) of T-IBS and 5/15 (33%) of B-IBS cases. One patient with B-IBS had a white count of 474,000/dl, of which over 90% were immunoblasts. Thrombocytopenia (less than 150,000/dl) was found in 4/19 (21%) of T-cell patients and in 1/16 (6%) of B-IBS cases. With one exception, all patients with thrombocytopenia had bone marrow involvement with IBS.

**Immunoglobulin Data**

Serum protein electrophoresis and/or immunoelctrophoresis was performed on 17 T-IBS patients and 13 B-IBS cases. Comparison of the immunoglobulin data revealed a very significant difference in the two variants. Seven of 17 (41%) of T-IBS cases demonstrated diffuse polyclonal hypergammaglobulinemia (mean 2.2 g/dl, range 1.7–2.8 g/dl). This was not found in any patient with B-IBS (p = 0.02). Monoclonal serum paraproteins were detected in two patients with B-IBS and in none with the T-cell variant. Hypogammaglobulinemia was found in 2/17 (12%) of T-cell cases and 1/13 (7%) of B-cell cases.
Response to Therapy

The therapy of these patients was administered in several different institutions and was neither uniform nor optimal. In addition, systemic restaging was not performed consistently in determining response to therapy. Complete remission was defined as the disappearance of all existing symptoms and signs of disease (100% tumor reduction), with a return to a normal state of well-being. Partial remission indicated a reduction of at least 50% in tumor mass, with residual disease remaining at completion of therapy.

The five patients with localized disease were treated either with radiotherapy or surgery, with or without adjuvant chemotherapy. All achieved complete remission, and the only relapse occurred in a patient with clinical stage I disease, treated with local radiotherapy alone (patient 26).

The results of therapy in all patients in this series are summarized in Table 2. Fourteen patients received combination chemotherapy consisting of bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP), and two received cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP). Only one of the nine T-IBS patients attained complete remission with these regimens, and the median survival for the T-IBS patients was 9 mo. Of the seven B-IBS patients who received BACOP, three attained complete remission. The median survival for all B-cell patients receiving BACOP was 17 mo, whereas all complete remitters remain alive from 16+ to 55+ months from diagnosis. The difference in survival between T-cell and B-cell disease was not statistically significant, perhaps because the numbers of patients were small. Five T-IBS and two B-IBS patients received cyclophosphamide, vincristine, procarbazine, and prednisone (COPP). No patient in the T-cell group attained complete response, and median survival for this group was 9 mo. One patient with B-IBS attained complete remission with COPP (patient 33), and is currently alive at 61+ mo from diagnosis.

Survival

The overall survival in this series is demonstrated in Fig. 3. Median survival for T-cell IBS was 20 mo, compared to 17 mo in the B-cell variant. Aggressive multiagent chemotherapy (BACOP, COPP, or CHOP) resulted in complete response in only 1 of 14 T-cell cases (7%), and a median survival of 9 mo for the group. Of 9 B-cell cases similarly treated, 4 attained complete remission (44%), with all complete remitters remaining alive from 16+ to 61+ mo from diagnosis and a median survival for the group of 17 mo. These differences are not statistically significant, possibly because numbers of patients were small. It is apparent, however, that all partial or nonresponders with disseminated B-cell disease have died, whereas two such T-cell patients remain alive at 12+ and 23+ mo from diagnosis. Moreover, one T-cell case (13; stage IVA) who has never received specific therapy for her disease remains alive, with disease, at 31+ mo from diagnosis.

In attempting to identify characteristics that might predict prognosis, presence of systemic “B” symptoms was found to be associated with shorter survival. The median survival of patients presenting with systemic symptoms was 9 mo, compared to 37 mo in patients lacking these symptoms ($p = 0.05$). Median survival
of patients with disseminated disease was 17 mo, compared to a survival greater than 46 mo in patients with localized disease. This was not statistically significant, possibly because such few patients presented with stage I or II disease.

**DISCUSSION**

In this series, we have compared the clinical features of B-cell versus T-cell immunoblastic sarcoma. Although approximately equal numbers of each subtype have been reported, the cases were not accrued consecutively, and only carefully defined proven B-cell or T-cell cases were included. Thus, the actual incidence of B-cell versus T-cell immunoblastic sarcoma remains to be defined. It should be mentioned, however, that other investigators have reported relatively large series of B-cell or T-cell disease, thus confirming that these two subtypes of immunoblastic sarcoma do exist and are separable by morphological and immunologic means.30–34

As demonstrated in the present series, immunoblastic sarcoma of B-cell and T-cell origin share certain common features, whereas other characteristics appear to differ. The two variants appear similar to one another with regards to the frequent occurrence of an abnormal immune disorder or lymphoproliferative malignancy prior to the development of IBS. Such a history was obtained in 37% of T-IBS and 44% of B-IBS patients. Other indications that these patients are not normal immunologically included the findings of profound lymphopenia in approximately 40% of both variants and serum immunoglobulin abnormalities in a total of 12/30 (40%) of these patients. The development of lymphoma in patients with abnormal immune disorders has been reported sporadically for years. Only recently, however, has such an association been recognized as more than a chance occurrence. For example, in 1971, Anderson and Talal noted a spectrum of lymphoproliferative disorders occurring in patients with Sjogren’s syndrome.35 In some instances, lymphoproliferative processes were confined to salivary glandular structures alone, whereas in others, the proliferation of benign appearing lymphocytes extended into extraglandular regions. The authors also noted that over 30 cases of true lymphoma had been reported to arise in patients with Sjogren’s syndrome,35,36 a finding confirmed by Kassan et al. who noted a 43.8 times greater frequency of this occurrence than would be expected by chance.37 In 1978, Zulman et al. studied the types of malignant lymphomas developing in nine patients with Sjogren’s syndrome, and found that seven of the tumors were monoclonal B-cell neoplasms.38 Although the individual histopathology of these lesions was described as problematic and varied, the authors noted that areas of immunoblastic sarcoma of B-cell type were found in seven of the nine cases. Since patients with Sjogren’s syndrome have a significantly increased frequency of the Dw3 haplotype,39 it is intriguing to speculate that the pathogenesis of immunoblastic sarcoma in these patients may involve the interaction of genetic predisposition, abnormal immune function, and chronic antigenic stimulation.2 A similar progression, from abnormal immune disorder to immunoblastic sarcoma, has now been reported in patients with immunoblastic lymphadenopathy (angioimmunoblastic lymphadenopathy with dysproteinemia),9,10,13,14,16–19 celiac disease,9,10,18,20,40 Hashimoto’s thyroiditis,9,10,11,18,19 and in renal transplant recipients.12,13,20,41 Likewise, as found in our patients, the progression from lymphoproliferative malignancy to IBS has been reported in patients with chronic lymphocytic leukemia,9,10,20,42 multiple myeloma,20,43 alpha chain disease,20,44 Hodgkin’s disease,9,10,45 and macroglobulinemia of Waldenström.9,10,20,46 As noted in the present series, the progression from abnormal immune disorder or lymphoproliferative malignancy may occur in immunoblastic sarcoma of both B-cell and T-cell origin. Interestingly, a similar sequence of progression from lymphoproliferation to frank lymphoma has been observed in a number of animal lymphoma models, again in association with chronic antigenic stimulation and abnormalities of immune response.47–49

Aside from the common finding of disturbed immune function in both variants, patients with IBS of T-cell and B-cell origin appear similar with regard to advanced stage of disease and presence of systemic symptoms at diagnosis. The occurrence of widespread symptomatic disease in patients with IBS is similar to that which has been reported in diffuse histiocytic lymphoma,50 the category in which these patients would be classified using the Rappaport system.1,2,4,8 It is of interest that in both variants, the presence of systemic symptoms at diagnosis was associated with shorter survival.

Although the vast majority of all patients in this series were found to have widespread disease upon routine staging, it is noteworthy that the method of initial presentation differed significantly between the two variants, with all T-IBS patients presenting because of lymph node enlargement, whereas approximately half of the B-cell patients presented because of extranodal disease in the gastrointestinal tract or lung. It is not altogether surprising that patients with IBS of B-cell origin would have tumors arising in these regions, since lung and gastrointestinal tract are regions in which B-cell proliferation normally occurs. Moreover, the ingestion or inhalation of foreign envi-
IMMUNOBLASTIC SARCOMA

environmental factors may serve to provide the antigenic stimulation that may be contributing to the development of this neoplasm.

Another difference between the two variants of IBS is the type of immunoglobulin abnormality encountered, with 41% of T-IBS cases demonstrating diffuse hypergammaglobulinemia, while no patient in the B-cell group demonstrated such an abnormality. The finding of diffuse, polyclonal hypergammaglobulinemia in a significant number of T-cell cases is of interest, since hypergammaglobulinemia is not usually found in lymphomatous malignancies. It is possible that the malignant T lymphocytes in our cases functioned as helper cells for immunoglobulin biosynthesis by normal B-cells. In this regard, Lawrence et al. have recently reported a patient with Sézary’s syndrome whose malignant T lymphocytes were shown to have helper cell activity. Five months after initial diagnosis, the patient presented with lymphadenopathy; biopsy revealed an evolution to immunoblastic sarcoma of the T-cell type. The malignant T immunoblasts in this case were demonstrated to have retained their helper cell activity.

Although this study demonstrates many similarities and only a few differences in the clinical manifestations of B-cell and T-cell disease, the critical question relates to possible differences in therapeutic outcome between the two variants. It is clear that IBS of either type, when localized, may be treated with radiotherapy with excellent results. In contrast, differences in response to multiagent chemotherapy are apparent in disseminated T-cell versus B-cell disease. Aggressive multiagent chemotherapy (BACOP, CHOP, or COPP) resulted in complete response in only 7% of T-cell cases, compared to 44% of patients with B-cell disease. All such complete remitters remain alive at this time. Although these differences are not statistically significant (because the numbers of patients are small), the data suggest that disseminated IBS of B-cell type can be successfully treated with aggressive combination chemotherapy, whereas alternative approaches appear warranted in IBS of T-cell type. This concept may be supported by similar observations regarding T-cell disease that have recently been reported by Waldron et al. and by Watanabe et al. In contrast to the difference in complete response rate, the overall survival for the two groups is similar, with a median survival of 20 mo for T-cell cases, and 17 mo for B-cell patients. This can be explained by the finding that some T-cell patients may survive for prolonged periods in the presence of active disease, after attaining partial response to therapy, or as in one patient, after receiving no specific therapy at all. This finding again has recently been confirmed by Palutke et al., who, in describing the clinical courses of seven patients with “T-cell lymphoma of large cell type,” note that two distinct subgroups could be identified: one with survival times no longer than 10 mo and another group with considerably longer survival. This information should be considered in planning new strategies for the therapy of immunoblastic sarcoma of T-cell type.

ACKNOWLEDGMENT

The authors would like to thank the following pathologists and clinicians of the Southern California Lymphoma Group who contributed their patients to this study. Thompson Adams, Peter D. Boasberg, Donald L. Bogdon, James S. Bonorris, J. Gary Davidson, Sheldon J. Davidson, Jerry Z. Finkenstein, H. Russell Fisher, N. Rune Forsen, Kenneth Frankel, Frank J. Glassy, John C. Gunnell, Richard M. Hollcraft, Gilbert J. Hum, Paul Jernestrom, Robert H. Joseph, Moyeen Khaleeli, James Meltzer, Bharat N. Nathwani, Natalie Orloff, Leo E. Orr, Frances E. Pincus, Robert Pink, Darlene Powars, Marvin I. Retsky, A. P. Richardson, Victor J. Rosen, Rea M. Schneider, Richard Shapiro, William C. Smith, Benjamin Stafford, Stephen B. Strum, John H. Toh, John K. Wakin, Leo Weiss, Lee A. Woods, and Bruce H. Zeitz. In addition, the authors would like to thank Annalia Paganini-Hill, Ph.D. for her help in the statistical analysis, and Rebecca Skibinski for her help in preparing the manuscript.

REFERENCES

1. Rappaport H: Tumors of the hematopoietic system, in Atlas of Tumor Pathology, section III, fascicle 8. Washington DC, Armed Forces Institute of Pathology, 1966


Immunoblastic sarcoma of T-cell versus B-cell origin: I. Clinical features

AM Levine, CR Taylor, DR Schneider, SC Koehler, SJ Forman, A Lichtenstein, RJ Lukes and DI Feinstein