This study compares the histologic and immunophenotypic features of 71 cases of primary CD30+ diffuse large-cell lymphomas (DLCL) and 128 cases of Hodgkin’s disease (HD) and discusses the clinical features of 52 patients with CD30+ DLCL. It includes analysis of sites of involvement, staging, response to treatment, sites and treatment of recurrences, and disease-free and overall survival. Diagnostic immunophenotypic differences were found between CD30+ DLCL and HD. All cases of CD30+ DLCL were positive for one or more common or lineage-specific lymphocyte antigens or for EMA. In contrast, 96.9% of HD cases were negative for CD45, CD45RO, CD43, and CD20. The four exceptions are discussed. All cases of HD were negative for EMA. In patients with CD30+ DLCL, a T-cell phenotype was found in 60%, a null-cell type in 22%, and a B-cell type in 18% of the cases. The median age of patients with T- and null-cell phenotype was 22 years (range, 4 to 72). Fifty-two percent of them had high-stage (III and IV) disease and 61% had extranodal involvement at presentation, including 25% with skin lesions. Lymph nodes draining the skin lesions became involved in seven of 11 patients. No patient had initial bone marrow involvement. Most patients were treated with chemotherapy, and 83% had a complete remission. Fifty-four percent remain free of disease with a median follow-up of 47 months. Thirteen patients (29%) had one or more recurrences and five of them remain free of disease after salvage therapy, with a median follow-up period of 79 months. The clinical stage did not affect survival, probably as a result of different therapy. The t(2;5) translocation was found in five of 15 patients who had cytogenetic abnormalities. Of the other 10 cases, the translocation was detected by reverse transcriptase–polymerase chain reaction (RT-PCR) in four of five cases studied. All nine cases were of T- or null-cell phenotype. The cases of B-cell CD30+ DLCL had a characteristic immunophenotype. All were negative for EMA. These patients were older and had frequent bone marrow involvement but no skin infiltration by lymphoma. All three patients who were human immunodeficiency virus–positive (HIV+) had lymphomas of B-cell lineage. Detection of the t(2;5) translocation by molecular genetics is a useful and highly specific marker in the differential diagnosis between HD and CD30+ DLCL.

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MATERIALS AND METHODS

From 1975 to the present, more than 1,000 cases of malignant lymphoma have been studied in our laboratory in cell suspensions using conventional antibodies and rosetting techniques, and later, panels of MoAbs. Within these series, occasional cases of DLCL were interpreted as T-cell or null-cell phenotypes, or true histiocytic lymphomas. These cases were studied again in paraffin sections using a panel of MoAbs and added to a prospective and retrospective series begun in 1989 using the same MoAb panel to define the immunophenotype of malignant lymphomas by this technique. This series is not representative of the frequency of CD30+ DLCL at this Center, but of the number of cases with available material for these studies. Patients with the diagnosis of HD who have biopsies at the Center and most of those with submitted material are actively studied in our laboratory with the same panel of MoAbs. The biopsy material of 128 consecutive patients with the diagnosis of HD, in which these studies were performed, was analyzed simultaneously with that of patients with CD30+ DLCL reported in this study. The diagnosis of HD was made following the criteria established by Lukes and Butler.26 Malignant lymphomas were classified according to the Working Formulation (1982), and all cases in these series were classified as DLCL. We have excluded those occasional cases in which the primary diagnostic material, although discussed under the differential diagnosis of CD30+ DLCL or HD because of clinical necessity, was not optimal for the identification of features relevant to this series. These cases include minute biopsies, tissues with widespread necrosis, and tissues previously used for frozen-section diagnosis. We also excluded from study those patients with the histologic and immunophenotypic diagnosis of lymphocyte-predominant HD.

The clinical data of patients in these series were collected by chart review. In some cases, physicians of other hospitals provided follow-up information. The patients underwent chest x-rays, computed tomographic scans of chest, abdomen, and pelvis, bone marrow biopsies, and routine studies of peripheral blood, and were clinically staged according to the Ann Arbor system.

Seventy-one patients had histologic and complete immunophenotypic studies. Nineteen patients were excluded from our clinical analysis. Seventeen of these patients had incomplete or no follow-up data, one patient with advanced disease died 1 day after diagnosis, and one patient was originally treated with a different diagnosis. The remaining 52 patients are the subject of our clinical report. Combination chemotherapy with first-, second-, or third-generation regimens (Table 1) was administered as initial treatment to 49 patients, and radiotherapy to two patients. One patient was observed with no treatment for 15 months. Overall survival was calculated from the time of the original diagnosis. Standard criteria for assessing response were used: partial response if there was greater than 50% reduction of tumor size, and complete response (CR) if there was no evidence of disease after restaging at the end of treatment. Disease-free survival was calculated from the time of termination of therapy or, in those patients with protocols that contained a maintenance period, from the end of consolidation and restaging.

Histopathology and immunophenotypic studies. For routine histology, tissue fixed in B33 (3% mercuric chloride in 4% formaldehyde), Formalin, or both were used. The paraffin-embedded sections were stained with hematoxylin and eosin. Immunoperoxidase studies were performed on paraffin sections, using an avidin–biotin peroxidase complex method.27 A panel of MoAbs against CD30, CD15, CD20, CD45, CD45-RO, CD43, and EMA was used in all cases. Other antibodies used include those against CAM 5.2 (Keratin) in 39 cases, S-100 in 28 cases, Ham-56 in 12 cases, and vimentin in 41 cases. BerH2 (anti-CD30) was routinely used in two concentrations, usually 1:50 and 1:200, and often sections from both B3-fixed and Formalin-fixed tissue were studied.

Cytogenetic analysis. Chromosome preparations were obtained following conventional methods, as previously described.28 The preparations were stained to reveal G-banding or Q-banding patterns, or both. Chromosomal aberrations were described according to the International System for Human Cytogenetics Nomenclature (ISCN, 1985). Chromosome abnormalities were defined as clonal if at least two cells had the same structural abnormalities, or if at least three cells had the same nonrandom gain of a chromosome or nonrandom loss of a chromosome.

Gene rearrangement studies. DNA extraction, digestion, Southern blotting, and hybridization were performed as previously described.16 The probes used were as follows: for the Ig heavy-chain gene, a 5.6-kb HindIII-BamHI fragment spanning the entire J region, and for the T-cell receptor (TCR)-β gene, either a 0.6-kb EcoRI fragment of the constant region or a Jβ1 and Jβ11 probe cocktail (Oncor, Gaithersburg, MD). Selected cases were also studied for TCR-γ gene rearrangement using a HindIII-EcoRI fragment of the constant region, and for TCR-δ gene rearrangement using both the J-δ1 and J-δ-2 probes (gift of T. Mak, Ontario Cancer Institute, Toronto, Canada).

RESULTS

Clinical Features

Seventy-one patients with the diagnosis of CD30+ DLCL had complete histologic and immunochemical studies. These patients had primary disease, with no history of preexisting malignant lymphoma. As stated earlier, 19 patients (12 with T- or null-cell and seven with B-cell phenotype) were excluded. The clinical features, treatment, and outcome of the remaining 52 patients are discussed in this section.

Detailed data of these 52 patients are listed in Tables 1 and 2. These CD30+ DLCL were of T-cell or null-cell phenotype in 44 patients, and of B-cell phenotype in five patients. Three additional patients, who were human immunodeficiency virus–positive (HIV+) at the time of diagnosis, are listed as a third group. These three groups of patients will be discussed separately.

Patients with T- and null-cell CD30+ DLCL. These 44 patients had a median age of 22 years, with a range of 4 to 72 (Fig 1). The male to female ratio was 24 to 20. The ratio was similar in those below or above the median age. The disease at diagnosis was high stage (III and IV) in 23 patients and low stage (I and II) in 21 patients. High-stage disease was more often seen in younger patients, and 15 of 21 patients younger than the median age had stage III or IV lymphoma. Skin involvement was seen initially in 11 patients (25%), nine of T- and two of null-cell phenotype. The disease in children often began with fever and generalized lymphadenopathy, mimicking an infectious disease. In four of them, nodules involving skin and subcutaneous tissue appeared in the trunk, face, or scalp. Some of these nodules disappeared spontaneously, while others grew in other parts of the body. These nodules measured between 2 and 8 cm and involved deep dermis and extended deep into the subcutaneous adipose tissue. They had ill-defined margins, were covered by erythematous skin, and were often diagnosed and treated, sometimes for weeks, as inflammatory lesions. The lymph nodes draining these single or multiple skin nodules were simultaneously involved or became involved by lymphoma within a few weeks in seven of 11 patients. In another patient with stage I lymphoma involving the skin of the cheek (Table 1, patient no. 22) and treated with radiation
### Table 1. CD30+ Malignant Lymphomas of T and Null Immunophenotype

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>IP</th>
<th>Site(s) of Involvement</th>
<th>Treatment</th>
<th>Time (mo)</th>
<th>Recurrence</th>
<th>Follow-up (mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>M</td>
<td>N</td>
<td>Skin-R-C LN-R-C</td>
<td>LN-P A</td>
<td>III-A</td>
<td>—</td>
<td>PR DWD (52)</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>T</td>
<td>LN-R-C LN-R-A</td>
<td>I-A</td>
<td>MACOP-B</td>
<td>—</td>
<td>A-NED (27)</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>F</td>
<td>T</td>
<td>Scalp-L LN-L-C Bones</td>
<td>Multiple</td>
<td>IV-A</td>
<td>2,000</td>
<td>A-NED (193)</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>M</td>
<td>T</td>
<td>LN-R-C LN-L-C LN-MD LN-PA</td>
<td>III-B</td>
<td>L-10M 3,500 MD</td>
<td>PR 5</td>
<td>Lung Pericard, CSF+ CT (L-10M) RT-MD CR DWD-T (98) cardiopathly</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>F</td>
<td>N</td>
<td>LN-L-C I-A CHO P 4,000 LN-C</td>
<td>CR</td>
<td>87 LN-R-C CT (L-17) PR A-NED (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>M</td>
<td>T</td>
<td>LN-R-C LN-L-C LN-R-A LN-L-A</td>
<td>II-B</td>
<td>CCG-551 2,000 LN-C LN-A</td>
<td>CR 25</td>
<td>LN-C LN-A CT (LSA_L-A) RT (LN) CR DWD-T (107) sepsis</td>
</tr>
<tr>
<td>7</td>
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<td>M</td>
<td>T</td>
<td>LN-R-C LN-L-C Spleen</td>
<td>II-B</td>
<td>M-2</td>
<td>CR</td>
<td>A-NED (82)</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>M</td>
<td>N</td>
<td>ST Shoulder LN-R-A</td>
<td>II-A (E)</td>
<td>Pro-MACE Cyt-BOM</td>
<td>CR</td>
<td>A-NED (54)</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>M</td>
<td>T</td>
<td>Skin-SCT (Ab) I-A</td>
<td>NY-1</td>
<td>1,690 skin-SCT</td>
<td>CR 56</td>
<td>Skin-SCT Bone Aut-BMT CR A-NED (72)</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>M</td>
<td>T</td>
<td>LN-MD CNS (CSF+) IV-B</td>
<td>L-17 1,800 brain</td>
<td>CR 105</td>
<td>Lungs LN-C None DOD (108)</td>
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<tr>
<td>11</td>
<td>62</td>
<td>M</td>
<td>T</td>
<td>Skin-SCT (foot) LN-L-L</td>
<td>II-A (E)</td>
<td>CHO P 3,500 foot</td>
<td>CR 40</td>
<td>LN-C LN-A CT (Vin-Pred) NR DOD (47)</td>
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<tr>
<td>12</td>
<td>32</td>
<td>M</td>
<td>N</td>
<td>LN-L-L LN-P A</td>
<td>II-A</td>
<td>MACOP-B</td>
<td>CR</td>
<td>DOD (34)</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>M</td>
<td>T</td>
<td>LN-R-C LN-L-C LN-MD LN-PA</td>
<td>III-B</td>
<td>LSA_L 2,000 LN-C</td>
<td>CR 30</td>
<td>LN-C CT (NY-1) CR A-NED (69)</td>
</tr>
<tr>
<td>14</td>
<td>35</td>
<td>F</td>
<td>T</td>
<td>LN-C LN-L Spleen</td>
<td>III-B</td>
<td>MACOP-B</td>
<td>CR</td>
<td>A-NED (79)</td>
</tr>
<tr>
<td>16</td>
<td>53</td>
<td>F</td>
<td>T</td>
<td>Skin-SCT (Leg) LN-R-I</td>
<td>II-A (E)</td>
<td>CHO P-BLEO Alt. TOPP</td>
<td>CR 32</td>
<td>LN-C, A, I CT (ABVD) Atl. C-TOPP PR AWD (110)</td>
</tr>
<tr>
<td>17</td>
<td>50</td>
<td>M</td>
<td>T</td>
<td>LN-C LN-A LN-PV LN-L</td>
<td>III-A</td>
<td>CHOP-BLEO Alt. TOPP</td>
<td>CR</td>
<td>80 Skin CT (CHO P) CR</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>M</td>
<td>T</td>
<td>Skin-SCT Shoulder-R</td>
<td>I-A (E)</td>
<td>—</td>
<td>3,500 should</td>
<td>CR 20 LN-P LN-PV LN-L</td>
</tr>
<tr>
<td>19</td>
<td>13</td>
<td>F</td>
<td>T</td>
<td>LN-C LN-A LN-L LN-PV Pleura</td>
<td>IV-B</td>
<td>LSA_L 2,000 mant.</td>
<td>CR 29 LN-C LN-MD LN-PA CR DWD-T (192) sepsis</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>F</td>
<td>T</td>
<td>LN-RP &amp; Pecus (massive)</td>
<td>II-B</td>
<td>Pro-MACE Cyt-BOM</td>
<td>CR 191 LN-A CT (COTAP) PR A-NED (51)</td>
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</tr>
<tr>
<td>21</td>
<td>47</td>
<td>M</td>
<td>T</td>
<td>Skin-SCT R-cheek</td>
<td>I-E (A)</td>
<td>—</td>
<td>2,500 R-cheek</td>
<td>CR 18 LN-R-C M-BACOD CR A-NED (80)</td>
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<tr>
<td>22</td>
<td>33</td>
<td>F</td>
<td>T</td>
<td>ST paraspinal subdural excision</td>
<td>I-B</td>
<td>CHO P  CR 18 LN-R-C CR A-NED (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>22</td>
<td>F</td>
<td>T</td>
<td>LN-L-L LN-R-C</td>
<td>—</td>
<td>CHO P 3,000 LN-L CR 25 LN-R- CR A-NED (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>26</td>
<td>M</td>
<td>N</td>
<td>LN-R-I</td>
<td>—</td>
<td>CHO P 2,000 LN-L CR 25 LN-R- CR A-NED (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>9</td>
<td>M</td>
<td>T</td>
<td>Skin (trunk) LN-C LN-A LN-L LN-PV Pleura</td>
<td>IV-B</td>
<td>LSA_L 2,000 maint.</td>
<td>CR 25 LN-R-C CR A-NED (77)</td>
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Table 1 (Cont’d). CD30+ Malignant Lymphomas of T and Null Immunophenotype

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>IP</th>
<th>Sites of Involvement</th>
<th>Other</th>
<th>Stage</th>
<th>CT</th>
<th>RT</th>
<th>Resp</th>
<th>Time (mo)</th>
<th>Site(s)</th>
<th>Treatment</th>
<th>Resp</th>
<th>Follow up (mo)</th>
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<tbody>
<tr>
<td>27</td>
<td>53</td>
<td>M</td>
<td>T</td>
<td>LN-R (massive)</td>
<td>—</td>
<td>IIA</td>
<td>—</td>
<td>FR</td>
<td></td>
<td>8</td>
<td>LN-RP</td>
<td>Aut-BMT</td>
<td>CR</td>
<td>A-NED (91)</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>F</td>
<td>N</td>
<td>LN-R-P Pelvic wall</td>
<td>—</td>
<td>II-B (E)</td>
<td>—</td>
<td>CR</td>
<td></td>
<td>4</td>
<td>LN-R-P</td>
<td>Pro-MACE Cytox-BOM</td>
<td>CR</td>
<td>A-NED (22)</td>
</tr>
<tr>
<td>29</td>
<td>22</td>
<td>F</td>
<td>T</td>
<td>Skin-SCT (scalp, Ab, thorax)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td></td>
<td>4</td>
<td>LN-R-P</td>
<td>Bases</td>
<td>Multiple</td>
<td>IV-A</td>
</tr>
<tr>
<td>30</td>
<td>19</td>
<td>F</td>
<td>N</td>
<td>LN-R-P LN-R-PV Spleen</td>
<td>—</td>
<td>II-B</td>
<td>—</td>
<td>PR</td>
<td></td>
<td>6</td>
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<td>Skin</td>
<td>RT (Ab)</td>
<td>CR</td>
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<tr>
<td>31</td>
<td>16</td>
<td>M</td>
<td>N</td>
<td>LN-L-PV (massive) LN-MD Bone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
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<td>(sepsis)</td>
<td>LSA-4</td>
<td>CR</td>
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<tr>
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<td>M</td>
<td>T</td>
<td>LN-PA LN-MD Pleura</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td></td>
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<td>Lung</td>
<td>Pericard</td>
<td>IV-B</td>
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<td>M</td>
<td>T</td>
<td>LN-MD (massive) LN-MD Bone</td>
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<td>—</td>
<td>—</td>
<td>CR</td>
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<td>5</td>
<td>LN-MD</td>
<td>Lung</td>
<td>Pericard</td>
<td>IV-B</td>
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<td>F</td>
<td>N</td>
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<td>II-B</td>
<td>—</td>
<td>CR</td>
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<td>LSA-1</td>
<td>—</td>
<td>CR</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
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<td>LN-MD</td>
<td>LSA-1</td>
<td>—</td>
<td>CR</td>
</tr>
<tr>
<td>37</td>
<td>10</td>
<td>M</td>
<td>T</td>
<td>LN-C LN-MD Liver Spleen Pleura</td>
<td>IV-B</td>
<td>LSA-1</td>
<td>—</td>
<td>PR</td>
<td>—</td>
<td>—</td>
<td>LN-MD</td>
<td>LSA-2</td>
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<td>38</td>
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<td>LN-C LN-MD Liver Spleen</td>
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<td>LSA-1</td>
<td>—</td>
<td>PR</td>
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<td>LN-C LN-A LN-MD LN-I</td>
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<td>—</td>
<td>—</td>
<td>CR</td>
<td></td>
<td>6</td>
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<td>LSA-1</td>
<td>—</td>
<td>CR</td>
</tr>
<tr>
<td>40</td>
<td>11</td>
<td>F</td>
<td>T</td>
<td>Skin-SCT Trunk LN-C LN-MD</td>
<td>IV-B</td>
<td>LSA-1</td>
<td>—</td>
<td>PR</td>
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<td>LSA-2</td>
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<td>LN-C LN- A LN-I</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CR</td>
<td></td>
<td>5</td>
<td>LN-MD</td>
<td>LSA-1</td>
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<td>CR</td>
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<td>42</td>
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<td>LN-C LN- N LN-MD LN-RP Pleura</td>
<td>IV-B</td>
<td>LSA-1</td>
<td>—</td>
<td>PR</td>
<td></td>
<td>5</td>
<td>LN-MD</td>
<td>LSA-2</td>
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<td>31</td>
<td>F</td>
<td>T</td>
<td>LN-C LN-MD LN-MD LN-RP Pleura</td>
<td>IV-B</td>
<td>LSA-1</td>
<td>—</td>
<td>PR</td>
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<td>LN-MD</td>
<td>LSA-2</td>
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<td>CR</td>
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<tr>
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<td>N</td>
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<td>II-B</td>
<td>—</td>
<td>—</td>
<td>CR</td>
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<td>5</td>
<td>LN-R-P</td>
<td>Bones</td>
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**B-CELL IMMUNOPHENOTYPE**

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<th>IP</th>
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<th>Site(s)</th>
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<td>LN-L-C LN-MD BM+</td>
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<td>c-MOPP Aut-BMT</td>
<td>—</td>
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**HIV+ PATIENTS**

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<th>RT</th>
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<td>—</td>
<td>PR</td>
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<td>—</td>
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<td>RT</td>
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**Abbreviations:** IP, Immunophenotype; CT, chemotherapy; RT, radiotherapy; PET, positron emission tomography; L, lymph node; R, right side; L, left side; C, cervix; A, axillary; I, inguinal; PL, paraaortic; MD, mediastinal; RP, retroperitoneal; PV, pelvic; ST, soft tissue; SCT, subcutaneous tissue; Ab, abdomen; should, shoulder; man, mantle; Vis, viscera; Pred, prednisone; Cytox, cyclophosphamide; BMT, bone marrow transplantation; RT, partial response; PR, partial response; NR, no response; A-NED, alive with no evidence of disease; AWD, alive with disease; DOD, died of disease; DWD, died with disease; DWD-T, died with disease of therapy complications.
therapy to the skin, the disease recurred twice, at 18 and 39 months, in lymph nodes satellite to the lesion, which did not recur. In one child, the disease presented as an ovarian mass. Only one patient had positive cerebrospinal fluid at the time of initial staging, and in only one did the disease recur with meningeal involvement. Although one or multiple bones were initially involved in three patients, the bone marrow biopsy and smears from the routinely sampled posterior iliac crest were negative in all patients. Lactate dehydrogenase was within normal limits (1 to 200 IU/dL) in 15 cases, slightly to moderately elevated (200 to 500 IU/dL) in 18 patients, and markedly elevated (>500 IU/dL) in one of 34 patients tested.

*Patients with B-cell CD30+ DLCL.* These five patients (Table 1) were older than those with T-cell or null-cell lymphoma, with a median age of 56 years and a range of 28 to 78. Four of them had high-stage (II or IV) disease and three had bone marrow involvement at initial staging. Two patients had soft-tissue and bone involvement. No patient had skin infiltration by lymphoma.

*Patients with CD30+ DLCL who were HIV+.* Two patients were male and one was female. Two patients presented with initial involvement of paranasal sinuses and nasopharynx, respectively, and one with lymph node involvement only (Table 1). Two patients had lymphomas of B-cell type, and in one the immunophenotype could not be established with certainty. All patients had B-symptoms, and one had bone marrow involvement by lymphoma.

**Histopathology and Immunocytochemistry**

*Patients with T- or null-cell CD30+ DLCL.* Fifty-six patients with this phenotype had histologic and complete immunohistochemical studies. The lymph nodes were largely replaced by tumor in most cases. In a few samples, there was partial involvement of the nodes by cohesive sheets of tumor cells, often in irregular patches within sinusoids or long narrow bands along the subcapsulated sinus. Areas of necrosis were uncommon. In some cases, there was a diffuse infiltration of the tumor by polymorphonuclear leukocytes and single-cell necrosis. Marked erythrophagocytosis by the neoplastic cells was observed in one case. There were rare plasma cells, and in all but one case, eosinophilic leukocytes were practically absent in the lesions. In most cases and within individual cases, a cell type was characteristic. These typical cells were large, with well-defined cytoplasmic borders and C-shaped, eccentric nucleus. This "histiocytoid" cell was the dominant cell type in some cases and characteristic of these lymphomas (Fig 2). In most samples, there were a variable number of giant tumor cells, with polylobulated nucleus or with multiple small nuclei often aligned along the periphery of the cell. These areas of marked pleomorphism were often focal. In three cases, these giant tumor cells, often with
bizarre forms, predominated, giving the tumors a striking polymorphous appearance (Fig. 3).

The skin, when involved by lymphoma, showed infiltration of deep dermis and subcutaneous adipose tissue. The typical band-like infiltration of superficial dermis and dermoeidermal junction, seen in mycosis fungoides and lymphomatoid papulosis, or the perivascular infiltrates in the latter, was not seen in these cases. In large tumors, the skin was ulcerated, but lateral to the ulcer there was no junctional or epidermal involvement by lymphoma.

By definition, all 56 cases were positive for CD30. All of them were negative for CD20. The pattern of reactivity with different antibodies can be seen in detail in Table 3. Forty-nine of the cases (83.9%) had a T-cell phenotype: 26 of these cases were positive for both CD45-RO and CD43, 12 for CD43, and two for CD45-RO only. The other 15 cases (26.7%) were negative for both antibodies and were classified as null-cell type. We found no morphologic features to allow a histologic differentiation between lymphomas of T- and null-cell phenotype.

Forty-seven cases (83.9%) were positive for EMA (32 cases of T-cell type and 15 null-cell type). Thirty cases were positive for CD45, and three cases (two of T-cell type) were positive for CD15.

**Patients with B-cell CD30⁺ DLCL.** Twelve patients had CD30⁺ DLCL with a B-cell phenotype. The most common cell type was a large cell with dense, abundant cytoplasm and round nucleus with several large nucleoli, often called large noncleaved cells, or centroblasts. However, these cells were of different sizes and intermixed with a variable number of similar cells with a large central nucleolus. Multilobulated giant forms of both cell types were common, some of them resembling RSC. In two cases, there were dense irregular clusters of epithelioid cells, and in one case, a marked infiltration by mature eosinophilic leukocytes. Two cases showed plasmacytoid differentiation, one of them with marked polymorphism and numerous giant tumor cells. In those cases with bone marrow involvement by lymphoma, large areas of the marrow were replaced by cells identical to those in the lymph nodes. The immunophenotype was CD30, CD20⁺ in 11 and CD30, CD20, CD45-RO in one (no. 49). Nine (75%) were also positive for CD45. All cases of CD30⁺ DLCL, with a B-cell phenotype were negative for EMA (Table 3).

**Patients with CD30⁺ DLCL who were HIV⁺.** These three cases were characterized by frequent pleomorphic immunoblasts and large areas of necrosis. Two cases had a CD30, CD20 immunophenotype, and in one case, CD30, CD45⁺, the cell lineage could not be established with certainty (Table 3). All three cases were CD15⁻ and EMA-negative.

**Patients with HD.** Immunocytochemical studies using the same panel of MoAbs used in the study of CD30⁺ DLCL were performed in 128 consecutive cases of HD. Ninety-one were classified as nodular sclerosis and 37 as mixed-cellularity type. As mentioned earlier, we excluded patients with lymphocyte-predominant HD from the study.

In all cases, a variable number of RSC and variants were positive for CD30. Most cells showed staining of the membrane and a parancicular dot-like region, but in some cases there were areas with membrane staining or paranuclear staining only. This feature may be because of different functional stages of the cells, or may be processing artifacts. In 99 cases (77.1%), RSC and variants also stained for CD15 (Leu M-1) with a pattern similar to that of CD30. In 81 cases (67%), RSC were positive for vimentin. These cells were negative for EMA, CD43, CD45, and CD45-RO in all cases. They were also negative for CD20 (L26) in 124 cases. In four cases, irregular cohesive patches of RSC and variants were positive for CD20, CD30, and CD15. In these cases, the rest of the sections showed RSC with a CD30⁺, CD15⁻, CD20⁻ phenotype. These four cases showed numerous RSC and variants, with a paucity of lymphocytes, most of which were T cells. There were areas of sclerosis and foci of necrosis associated with these lesions.

**Genetics**

Cytogenetic abnormalities were identified in 15 patients. Five of them (patients no. 9, 10, 13, 14, and 28) had the previously described translocation, t(2;5)(p23;q35), or a variant thereof (Table 4). Of the remaining 10 cases that did not show a cytogenetic 5q35 abnormality (patients no. 11, 12, 15, 16, 20, 21, 22, 30, 32, and 50), five were studied by reverse transcriptase–polymerase chain reaction (RT-PCR) for the chimeric NPM-ALK transcript resulting from the t(2;5).17 Four were positive (patients no. 12, 15, 20, and 22) and one was negative (patient no. 11) (Ladanyi M, unpublished results, March 1995). No material was available to study the five cases of B-cell phenotype (patients no. 45 to 49) or the three remaining HIV⁺ patients (patients no. 50 to 52) by this technique. Immunogenotyping data were available in 21 cases. Only one of 21 cases showed clonal IgH gene rearrangement. This patient was HIV⁺ (patient no. 50). One patient with a T-cell phenotype on the initial biopsy and a germline configuration for IgH and TCR-β and -γ (patient no. 21) showed a clonal IgH gene rearrangement in the biopsy of the recurrence. Eight cases showed clonal rearrangement of one or more TCR genes (β, γ, or δ; patients no. 10, 11, 12, 13, 14, 16, 28, and 32), and in the remaining
Table 3. Immunophenotype of CD30+ DLCL

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Abbreviations: IP, immunophenotype; T, T cell; N, null cell; B, B cell.

12 cases genotyping studies were all germline (patients no. 9, 15, 18, 20, 21, 22, 24, 25, 26, 27, 30, and 31).

Therapy, Response, and Survival

Patients with CD30+ T- or null-cell phenotype. Forty-one of 44 patients with this phenotype were initially treated with combination chemotherapy (CT) only (19 patients) or with CT and radiotherapy (RT) [22 patients; Table 1]. Thirty-five patients (85.3%) had a CR. Of these 35 patients, 22 (53.7% of all those treated with CT or with CT and RT) had no recurrence and remain alive with no evidence of disease (A-NED), with a median follow-up period of 47 months since the time of diagnosis and 40.5 months since the end of therapy.

Eight of 35 patients with initial CR had one recurrence. Of these, four patients (no. 9, 13, 25, and 39) are A-NED after treatment with autologous bone marrow transplant (Aut-BMT) in two cases and with LSA1L2 or a variant of it, the NY-1 protocol, in the remaining two cases. The other four patients with one recurrence (at 8, 9, 40, and 105 months) did not respond to chemotherapy and died of disease soon after.

Four of 35 patients with initial CR had two recurrences. One (no. 14) is A-NED at 79 months after diagnosis, two died of sepsis during induction at 107 and 192 months after diagnosis (no. 6 and 19), and one (no. 12) did not respond to chemotherapy and died 34 months after diagnosis.

One patient had more than two recurrences. This patient (no. 17) is alive with disease after multiple recurrences, 110 months after diagnosis.

Of six patients treated with combination CT who did not have an initial CR, three (no. 30, 37, and 43) died of progressive disease in a few months, one (no. 4) died of myocardopathy after mediastinal RT and Adriamycin (Adria Pharmaceuticals, Columbus, OH) containing CT, and one (no. 38) died of sepsis during induction. One patient (no. 27) who had a partial response and was then treated with Aut-BMT is A-NED at 30 months.

Two of 44 patients in this group were initially treated with RT. One of these (no. 21) had a single lesion in the skin and subcutaneous tissue of the cheek, which recurred twice in the draining cervical lymph nodes and was treated with CT and Aut-BMT, and is A-NED at 80 months. The second patient (no. 18), with a skin and subcutaneous tissue lesion, was treated successfully for a nodal recurrence, had spontaneous remission of a skin recurrence, and is A-NED at 77 months. One patient (no. 1) was evaluated with no treatment for 15 months, treated with RT, and died of massive pulmonary embolism 52 months after diagnosis of progressive lymphoma.

The overall median survival in 44 patients with T or null phenotype in this series was 192.8 months after diagnosis and 171 months after completion of treatment, with a median follow-up period of 51.1 months (Fig 4). The median disease-free survival for 37 patients treated with CT alone (two patients) and CT alone or combined with RT (35 patients) who had a CR was 101.4 months (Fig 5). The initial clinical stage did not affect the outcome, and patients with high-stage (III and IV) disease responded as well and survived as long as patients with low-stage (I and II) disease (Fig 6).
Table 4. Immunophenotype, Genotype, and Cytogenetics of CD30' DLCL

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Abbreviations: IP, immunophenotype; G, germline; R, rearranged; T, T cell; N, null cell.
* t(2;5)-negative by cytogenetics, shown by RT-PCR.

and Table 1). The percentage of patients who had high-stage (III and IV) disease was 71.4% (15 of 21) among patients younger than the median age of 22 years, in comparison to 34.8% (eight of 23) among patients 22 years or older. Despite this significant ($P = .015$) concentration of patients with high-stage disease among the younger group, there was a tendency for them to have a better survival, although the difference was not significant (Fig 7). Eighteen of 21 younger patients were treated with protocols that include 12 to 24 months of maintenance CT, and in 15 of them, also RT.

The influence of immunophenotype on survival was not statistically significant ($P = .30$), although there was a slight advantage for patients with a T-cell phenotype (Fig 8). When patients were stratified by both age (above and below the median age of 22) and immunophenotype (T- and null-cell), the log-rank test comparing the four groups showed a significant difference in survival (Fig 9). Older patients with a null-cell phenotype had the worst survival as compared with the rest of the patients ($P = .0067$).

**Patients with CD30' B-cell phenotype.** Three of five patients (no. 45 to 47) with this phenotype had involvement of the bone marrow at the time of diagnosis (Table 1). Two of them, treated with Aut-BMT and CT, respectively, are A-NED at 40 and 19 months after diagnosis; the third patient had a local recurrence, did not respond to Aut-BMT, and died of disease at 15 months. Two patients (no. 48 and 49) with no marrow involvement were treated with CT; one had a recurrence, did not respond to further CT, and died at 17 months. The other, treated with CT, is A-NED at 12 months after diagnosis.

**Patients with CD30' DLCL who were HIV'.** These three patients (Table 1) were treated with the same combination CT, had partial remission only, and died of progressive disease within 23 months.

**DISCUSSION**

There is a growing consensus on the recognition of CD30' DLCL as a disease with distinct biologic and clinical fea-
tinctures, and on these features as sufficiently different from those of classic HD and other lymphomas to justify a different clinical and possible therapeutic approach. It has also been a common experience that these tumors are heterogeneous in their histologic and immunohistochemical characteristics, and that this polymorphism is one of their characteristic diagnostic features. Previous studies have emphasized the histologic variety of these pleomorphic lymphomas. Although subclassifications are useful to emphasize the wide range of histologic variability of CD30+ DLCL, they also distract from and disperse the experience of what these lymphomas have in common.

In the current study, we have analyzed histologic and immunohistochemical findings in 71 cases of CD30+ DLCL and 128 cases of HD. We have not made the diagnosis of Hodgkin’s sarcoma, included in the original classification. Some of these cases are currently described in the literature as "Hodgkin’s disease with numerous Reed-Sternberg cells," and the original descriptions probably included cases now diagnosed as CD30+ DLCL. There has been general agreement in the literature about the importance of immunocytochemistry in the identification of cases with ambiguous histologic features. These reports have often stressed the relative importance of particular antibodies or the lack of specificity of certain antibodies in the differential diagnosis of CD30+ DLCL and HD.

The most significant diagnostic findings in the current series were the consistent lack of expression by RSC and variants in HD of common and lineage-specific lymphocyte antigens, and the definition of several patterns of expression of these antigens and of EMA, in CD30+ DLCL. Thus, in 124 of 128 cases of HD (96.9%), RSC and variants were positive for CD30 and CD15 (79.8%) or CD30 only (20.2%) and negative for CD45, CD45-RO, CD43, and CD20. In the other four cases (3.1%), these cells were positive for CD30, CD15, and, in ill-defined clusters and scattered single cells, CD20, a pan B-cell antigen. We found no case of HD in which RSC and variants were positive for EMA. On the other hand, all cases of CD30+ DLCL were positive for one or more common or lineage-specific lymphocyte antigens or for EMA in addition to CD30, the defining marker for these lymphomas.

Experience with CD15, originally proposed as a specific marker for RSC in HD, has been discussed in numerous recent publications. Although easily demonstrated in approximately 70% of cases of HD, it is also seen in about 5% to 20% of cases of CD30+ DLCL. This was our experience with the cases discussed in these series, where 4.2% of the cases were positive for CD15. However, in association with CD30 and in the absence of other lymphocyte markers and EMA, CD15 is a useful confirmatory marker in the diagnosis of HD.

Our results in the current series confirm the useful role of CD43 (Leu22) as a sensitive T-cell-associated marker. The epitope detected by this antibody is not by itself a marker restricted to cells of T-lymphocyte lineage. CD43 is expressed on granulocytes in all stages of maturation, circulating and fixed monocytes (histiocytes), and a small percentage of B lymphocytes. It is also detected on neoplastic cells in low-grade centrocytic lymphomas and chronic lymphocytic leukemia. However, when used as part of a panel, it is a reliable marker for T cells and was positive in 38 (53.5%) of 71 cases of CD30+ DLCL in these series.

In the context of the current study, inclusion of EMA was of crucial importance in the differential diagnosis of CD30+
DLCL and HD. This antigen has often been discussed as a useful marker for CD30+ DLCL. However, it has not been used often as a part of a discriminating panel in a simultaneous study of CD30+ DLCL and HD.

As discussed earlier, EMA was negative in all cases of HD. It may be significant that this marker, positive in 47 of 56 cases (83.9%) of T- or null-cell phenotype, was negative in all cases of CD30+ DLCL of B-cell phenotype.

Four cases (3.1%) in these series with the histologic features of HD showed polymorphous neoplastic cells, including RSC with the ambiguous CD30, CD15, CD20 immunophenotype (discussed earlier). We have interpreted these cases as a simultaneous occurrence of HD and CD30+ large-cell lymphoma in the same sample. A hypothetical model to account for the simultaneous or successive occurrence of HD and CD30+ malignant lymphomas would postulate a common neoplastic precursor stem cell in both diseases. The proliferating cells, because of an intrinsic genetic lesion, a suppressor effect of the immunologic constitution of the host, or both, would be unable to express common or lineage-specific lymphocyte antigens, resulting in the histologic, immunophenotypic, and clinical picture of classic HD. Clonal evolution of a neoplastic subpopulation with expression of lymphocyte antigens, coincidental with the onset of HD or occurring during its course, would account for those cases with the histologic and immunophenotypic features of both HD and CD30+ lymphomas of B- or T-cell phenotype. Exploration of the role of the t(2;5)(p23;q35) translocation and possible lesions at other sites, such as chromosome band 1p36, by systematic study of the evolution of these genetic lesions in successive recurrences may help to clarify the genesis of these diseases.

The nonrandom translocation t(2;5)(p23;q35) is a characteristic cytogenetic marker for CD30+ DLCL of T- and null-cell phenotype. Its positivity in approximately 60% of these tumors, regardless of histologic subtype, is a useful tool in the differential diagnosis of CD30+ DLCL and HD.

In a recent study of 40 patients with HD using the same assay, t(2;5) was negative in all patients. Amplification by RT-PCR of the hybrid product resulting from this translocation appears to be a sensitive assay in the differential diagnosis of CD30+ DLCL and HD. It should be useful in further studies of the specificity of t(2;5) and its link with the phenotypic expression of the CD30 (Ki-1) antigen. It may also help in elucidating the clinical and biologic significance of the occasional secondary expression of CD30 in other lymphomas. The correlation between immunophenotype, genotype, and the t(2;5) translocation in CD30+ DLCL is complex. Of nine patients in whom t(2;5) could be demonstrated by cytogenetic or molecular genetic techniques, six had a T-cell and three a null-cell phenotype.

Clinical Features, Treatment, and Survival

This study confirms the large number of cases with extranodal disease at initial presentation, emphasized in numerous recent reports. In 27 cases (63.6%) of CD30+ DLCL with T- or null-cell phenotype, there was initial involvement of extranodal sites, including skin (25%), bones (7%), soft tissues (14%), lungs, pleura, pericardium, liver, and ovary. A single case showed involvement of the central nervous system as demonstrated by a positive CSF.

Most studies, with few exceptions, have stressed the low frequency and even rarity of bone marrow involvement in CD30+ DLCL, a feature that these lymphomas share with HD. In the present series, although one or multiple bones were involved at presentation in three patients, the bone marrow was negative in all cases of CD30+ DLCL of T- or null-cell phenotype. However, it may be significant that the bone marrow was involved in three of five cases of CD30+ DLCL of B-cell phenotype, and among the three patients who were HIV+, in one case. The tendency to involve bones in discrete well-defined foci, rather than the diffuse pattern of bone marrow infiltration seen in other lymphomas, may be due to the tendency of CD30+ DLCL to grow in cohesive patches, often mimicking metastatic carcinomas, frequently described as a characteristic feature of these lymphomas. Local interleukin-6 production at the site of osseous metastases may be a factor in bone destruction.

The rarity of bone marrow involvement in CD30+ DLCL of T- or null-cell phenotype is of particular importance, since autologous bone marrow infusion is an available therapeutic option in recurrent lymphomas. Four patients in this series (no. 9, 21, 25, and 27) with CD30+ DLCL of T-cell phenotype were treated with intensive CT and Aut-BMT after one or two recurrences, and remain A-NED with a follow-up period of 8, 16, 22, and 41 months.

In most reports, the skin was found to be the most frequent site of extranodal involvement. The prognostic significance of skin involvement has been discussed by several investigators. In a recent report, Beljaards et al discuss the clinical features and outcome of 47 patients with primary cutaneous CD30+ DLCL, in whom no sign of extracutaneous involvement was found at initial staging. They emphasize the favorable prognosis of these patients, most of whom were treated with surgical excision, local RT, or both. The majority of these patients presented with solitary (30 patients) or regional (12 patients) lesions. Approximately 31% of the patients developed one or more skin recurrences, often in the region of the original lesion, and 25% developed extracutaneous nodal disease after a median follow-up period of 27 months.

In the present series, skin involvement was seen initially in 11 patients (25%). In three of them, the disease was limited to a single lesion, with no extracutaneous involvement; two were treated with excision and local RT and one with RT and CT. In all three, extracutaneous disease developed after 18, 20, and 56 months (patients no. 9, 18, and 21). In 7 of the 11 patients, lymph nodes draining these single or multiple skin lesions were initially involved or became involved by lymphoma, within a few weeks or months after diagnosis.

The treatment of malignant lymphomas, limited at presentation to a single skin lesion, is often a source of perplexity for the clinician. When the lesion is small and superficial, local excision and RT to the affected area appear indicated, in view of the frequent local and regional recurrences.
patients with large or infiltrative tumors, it is probably prudent, if RT is used, to include the regional draining nodes in the initial treatment. The role of combination CT to prevent extracutaneous, especially nodal, recurrences, which may occur in at least 25% of the patients, is untested.

The finding that clinical stage of the disease in patients with T- or null-cell CD30+ DLCL did not affect survival is at variance with other published reports. In this series, the majority of patients with high-stage (III and IV) lymphoma (71.4%) was found among those younger than the median age of 22 years. However, these patients had a slightly better survival than those in the older group. The immunophenotype of the lymphomas (T or null cell), which marginally affected survival in favor of those patients with a T-cell type (Fig 8), was almost identical in both groups. The only significant difference among factors discussed in this report, besides age itself, was therapy. Eighteen of 21 younger patients were treated with protocols that included 1 to 2 years of maintenance therapy, and in 15 of those patients, RT to bulky sites of disease. Only five patients in the older group were treated with combination therapy, and only one received maintenance therapy.

In agreement with most other series, we find that patients with T and null phenotype expressing the CD30 antigen have a high frequency of extranodal involvement, particularly skin infiltration, a feature that differentiates them from HD. However, involvement of the bone marrow is rare, in contrast to the more common CD30- B-cell lymphomas. They have a high rate of initial complete remission and better overall survival than CD30+ large-cell lymphomas, due, in part, to better response of recurrences. The CD30+ DLCL also have a highly specific genetic marker, the t(2;5) translocation, besides the characteristic immunophenotype. These features appear to justify the recognition of CD30+ DLCL of T- and null-cell phenotype as a well-defined disease.

Reports on the clinical, immunophenotypic, and genetic features of CD30+ DLCL with a B-cell phenotype have been infrequent and incidental to the more prevalent CD30- DLCL of T and null phenotype. They have a distinct immunophenotype and clinical features different from both HD and T- and null-cell CD30+ DLCL. Of five patients in the current series with a B-cell phenotype, all treated with combination CT, four had a CR. Three of these five (one treated with Aut-BMT) remain A-NED after a follow-up period of 10, 12, and 40 months after diagnosis. The other two patients, one with initial bone marrow involvement and treated with Aut-BMT after a recurrence in the scapula, died of disease after 15 and 17 months. Although these findings should be confirmed in larger series, CD30+ DLCL with a B-cell phenotype appear to involve the skin rarely and to have a high frequency of bone marrow involvement. This last feature may be relevant in view of the increasing use of Aut-BMT in the treatment of patients with malignant lymphomas.

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CD30 (Ki-1)-positive malignant lymphomas: clinical, immunophenotypic, histologic, and genetic characteristics and differences with Hodgkin’s disease

DA Filippa, M Ladanyi, N Wollner, DJ Straus, JP O’Brien, C Portlock, M Gangi and M Sun