Nonnasal Lymphoma Expressing the Natural Killer Cell Marker CD56: A Clinicopathologic Study of 49 Cases of an Uncommon Aggressive Neoplasm


Expression of the natural killer (NK) cell antigen CD56 is uncommon among lymphomas, and those that do are almost exclusively of non-B-cell lineage and show a predilection for the nasal and nasopharyngeal region. This study analyzes 49 cases of nonnasal CD56⁺ lymphomas, the largest series to date, to characterize the clinicopathologic spectrum of these rare neoplasms. All patients were Chinese. Four categories could be delineated. (1) Nasal-type NK/T cell lymphoma (n = 34) patients were adults 21 to 76 years of age (median, 50 years), including 25 men and 9 women. They presented with extranodal disease, usually in multiple sites. The commonest sites of involvement were skin, upper aerodigestive tract, testis, soft tissue, gastrointestinal tract, and spleen. Only 7 cases (21%) apparently had stage I disease. The neoplastic cells were often pleomorphic, with irregular nuclei and granular chromatin, and angiocentric growth was common. The characteristic immunophenotype was CD2⁺ CD3⁻/Leu4⁺ CD3e⁻ CD56⁺, and 32 cases (94%) harbored Epstein-Barr virus (EBV). Follow-up information was available in 29 cases: 24 died at a median of 3.5 months; 3 were alive with relapse at 5 months to 2.5 years; and 2 were alive and well at 3 and 5 years, respectively. (2) Aggressive NK cell leukemia/lymphoma (n = 5) patients presented with hepatosplenomegaly and blood/marrow involvement, sometimes accompanied by splenomegaly or lymphadenopathy. The neoplastic cells often had round nuclei and azurophilic granules in the pale cytoplasm. All cases exhibited an immunophenotype of CD2⁺ CD3⁻/Leu4⁺ CD56⁺ CD16⁻/CD57⁻ and all were EBV⁺. All of these patients died within 6 weeks. (3) In blasticoid NK cell lymphoma (n = 2), the lymphoma cells resembled those of lymphoblastic or myeloid leukemia. One case studied for CD2 was negative and both cases were EBV⁺. One patient was alive with disease at 10 months and one was a recent case. (4) Other specific lymphoma types with CD56 expression (n = 8) included one case each of hepatosplenic γδ T-cell lymphoma and S100 protein⁺ T-cell lymphoproliferative disease and two cases each of T chronic lymphocytic/prolymphocytic leukemia, lymphoblastic lymphoma, and true histiocytic lymphoma. All of these cases were EBV⁺. Six patients died at a median of 6.5 months. Nonnasal CD56⁺ lymphomas are heterogeneous, but all pursue a highly aggressive clinical course. The nasal-type NK/T cell lymphoma and aggressive NK cell leukemia/lymphoma show distinctive clinicopathologic features and a very strong association with EBV. Blastoid NK cell lymphoma appears to be a different entity and shows no association with EBV.

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### Table 1. Clinical Data on CD56<sup>+</sup> Lymphomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age</th>
<th>Major Sites of Disease at Presentation</th>
<th>EBER In Situ Hybridization</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nasal-type NK/T-cell lymphomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>F/63</td>
<td>Skin</td>
<td>+</td>
<td>Chemotherapy (BACOP, then BVP)</td>
<td>DOD 6 mo</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>M/47</td>
<td>Testis</td>
<td>+</td>
<td>Orchiectomy and chemotherapy (MECOP-B)</td>
<td>Developed disease in gastrointestinal tract and nasal cavity. DOD 4 mo</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>M/71</td>
<td>Testis, gastrointestinal tract</td>
<td>+</td>
<td>Orchiectomy</td>
<td>DOD 1 wk</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/55</td>
<td>Testis</td>
<td>+</td>
<td>Orchiectomy</td>
<td>Developed skin lesions and hepatosplenomegaly at 1 mo. Given chemotherapy. DOD 5 mo</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/63</td>
<td>Salivary gland</td>
<td>+</td>
<td>Excision and chemotherapy (CHOP)</td>
<td>Relapsed in pharynx and palate at 2.5 yr</td>
</tr>
<tr>
<td>6&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/47</td>
<td>Oropharynx, liver, spleen, marrow</td>
<td>+</td>
<td>Chemotherapy (ProMACE-CytaBOM)</td>
<td>DOD 1 wk</td>
</tr>
<tr>
<td>7&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/21</td>
<td>Liver (RHS)</td>
<td>+</td>
<td>Nil</td>
<td>DOD 1 month</td>
</tr>
<tr>
<td>8&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/41</td>
<td>Breast, nasopharynx</td>
<td>+</td>
<td>Excision and chemotherapy (ProMACE-CytaBOM)</td>
<td>Developed peri orbital edema, lower limb edema and chest wall nodule. DOD 3 mo</td>
</tr>
<tr>
<td>9&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/39</td>
<td>Gastrointestinal tract, spleen</td>
<td>+</td>
<td>Colectomy</td>
<td>DOD 3 wk</td>
</tr>
<tr>
<td>10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/23</td>
<td>Marrow (RHS)</td>
<td>+</td>
<td>Chemotherapy</td>
<td>DOD 4 mo</td>
</tr>
<tr>
<td>11&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/76</td>
<td>Skin</td>
<td>+</td>
<td>Chemotherapy (IMVP-16)</td>
<td>Repeated relapses in skin and soft tissues; DOD 3 yr</td>
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<tr>
<td>12&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/68</td>
<td>Soft tissues</td>
<td>+</td>
<td>Amputation of limb and chemotherapy (ProMACE-CytaBOM)</td>
<td>AW 3 yr</td>
</tr>
<tr>
<td>13&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/73</td>
<td>Soft tissues</td>
<td>+</td>
<td>Chemotherapy (CEOP) and radiotherapy</td>
<td>Relapsed as multiple skin nodules; DOD 9 mo</td>
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<tr>
<td>14&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/41</td>
<td>Lymph nodes, tonsil, marrow (RHS)</td>
<td>+</td>
<td>Chemotherapy (ProMACE-CytaBOM)</td>
<td>DOD 6 mo</td>
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<tr>
<td>15&lt;sup&gt;th&lt;/sup&gt;-&lt;sup&gt;21&lt;sup&gt;nd&lt;/sup&gt;&lt;/sup&gt;</td>
<td>M/64</td>
<td>Salivary gland, tonsil, testis, gastrointestinal tract</td>
<td>+</td>
<td>Chemotherapy (mBACOD)</td>
<td>DOD 5 mo</td>
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<tr>
<td>16&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/61</td>
<td>Marrow, liver, spleen (RHS)</td>
<td>–</td>
<td>High dose steroid</td>
<td>DOD 2 wk</td>
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<tr>
<td>17&lt;sup&gt;th&lt;/sup&gt;-&lt;sup&gt;21&lt;sup&gt;nd&lt;/sup&gt;&lt;/sup&gt;</td>
<td>F/28</td>
<td>Skin</td>
<td>+</td>
<td>Chemotherapy (CHOP, then MACOP-B) and radiotherapy</td>
<td>Relapsed in spleen, liver, mediastinum and meninges; DOD 7 mo</td>
</tr>
<tr>
<td>18&lt;sup&gt;th&lt;/sup&gt;-&lt;sup&gt;21&lt;sup&gt;nd&lt;/sup&gt;&lt;/sup&gt;</td>
<td>M/24</td>
<td>Salivary gland, skin</td>
<td>+</td>
<td>Surgery</td>
<td>DOD 6 wk</td>
</tr>
<tr>
<td>19&lt;sup&gt;th&lt;/sup&gt;-&lt;sup&gt;21&lt;sup&gt;nd&lt;/sup&gt;&lt;/sup&gt;</td>
<td>F/39</td>
<td>Jejunum</td>
<td>+</td>
<td>Surgery and chemotherapy (ACOMLA)</td>
<td>Developed pleural effusion; DOD 1 mo</td>
</tr>
<tr>
<td>20&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/57</td>
<td>Skin, lymph nodes</td>
<td>+</td>
<td>Chemotherapy (CVP)</td>
<td>DOD 4 mo</td>
</tr>
<tr>
<td>21&lt;sup&gt;st&lt;/sup&gt;</td>
<td>M/67</td>
<td>Skin</td>
<td>+</td>
<td>Information not available</td>
<td>Not available</td>
</tr>
<tr>
<td>22&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>M/52</td>
<td>Skin</td>
<td>+</td>
<td>Information not available</td>
<td>Not available</td>
</tr>
<tr>
<td>23&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>M/34</td>
<td>Skin, maxillary antrum, lymph nodes</td>
<td>+</td>
<td>Radiotherapy</td>
<td>DOD 1 mo</td>
</tr>
<tr>
<td>24&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/61</td>
<td>Skin</td>
<td>+</td>
<td>Radiotherapy</td>
<td>Systemic relapse (soft tissue, lungs, spleen, lymph nodes) and complicated by RHS; DOD 1 yr</td>
</tr>
<tr>
<td>25&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/69</td>
<td>Skin, lungs, lymph nodes</td>
<td>+</td>
<td>Nil</td>
<td>DOD 1 mo</td>
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<tr>
<td>26&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/44</td>
<td>Skin (RHS)</td>
<td>+</td>
<td>Chemotherapy (vincristine, bleomycin)</td>
<td>DOD 1 mo</td>
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<tr>
<td>27&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/35</td>
<td>Lip</td>
<td>–</td>
<td>Chemotherapy (CHOP)</td>
<td>Relapsed in epiglottis at 3 yr; AW at 5 yr</td>
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<tr>
<td>28&lt;sup&gt;th&lt;/sup&gt;</td>
<td>F/30</td>
<td>Skin</td>
<td>+</td>
<td>Information not available</td>
<td>Not available</td>
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<tr>
<td>29&lt;sup&gt;th&lt;/sup&gt;</td>
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<td>Not available</td>
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<td>30&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/43</td>
<td>Spleen</td>
<td>+</td>
<td>Information not available</td>
<td>Not available</td>
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<tr>
<td>31&lt;sup&gt;st&lt;/sup&gt;</td>
<td>M/26</td>
<td>Soft tissue (root of penis)</td>
<td>+</td>
<td>Chemotherapy (ProMACE-CytaBOM)</td>
<td>Relapsed in marrow, spleen and liver, and DOD 6 mo</td>
</tr>
<tr>
<td>32&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>M/48</td>
<td>Soft tissue, pancreas, nasopharynx, palate, testis</td>
<td>+</td>
<td>Chemotherapy (M-BACOP)</td>
<td>DOD 7 wk</td>
</tr>
<tr>
<td>33&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>M/56</td>
<td>Larynx</td>
<td>+</td>
<td>Chemotherapy (ProMACE-CytaBOM) and radiotherapy</td>
<td>Relapsed in terminal ileum (perforation) and mesenteric lymph nodes at 2 yr</td>
</tr>
<tr>
<td>34&lt;sup&gt;th&lt;/sup&gt;</td>
<td>M/67</td>
<td>Skin</td>
<td>+</td>
<td>Nil (misdiagnosed as vasculitis)</td>
<td>Developed disease in larynx at 5 mo</td>
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### Table 1 (Cont'd). Clinical Data on CD56⁺ Lymphomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age</th>
<th>Major Sites of Disease at Presentation</th>
<th>EBER In Situ Hybridization</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td><strong>Aggressive NK cell lymphoma/leukemia</strong></td>
<td></td>
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<tr>
<td>35²⁴</td>
<td>F/39</td>
<td>Blood, marrow, lymph nodes, liver, spleen</td>
<td>+</td>
<td>Nil</td>
<td>DOD 4 d</td>
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<tr>
<td>36²⁵,²⁶,³⁴,³⁵</td>
<td>M/50</td>
<td>Blood, marrow, liver, spleen, pleura, skin</td>
<td>+</td>
<td>Prednisone</td>
<td>DOD 1 mo</td>
</tr>
<tr>
<td>37</td>
<td>M/37</td>
<td>Lymph nodes, blood, marrow, liver</td>
<td>+</td>
<td>Chemotherapy (mBACOD)</td>
<td>DOD 6 wk</td>
</tr>
<tr>
<td>38³⁴</td>
<td>F/41</td>
<td>Blood, marrow, liver, spleen⁺</td>
<td>+</td>
<td>Chemotherapy (BACOP, then mBACOP)</td>
<td>Initial partial response, followed by rapid progression; DOD 1 mo</td>
</tr>
<tr>
<td>39</td>
<td>M/54</td>
<td>Blood, marrow, liver (RHS)</td>
<td>+</td>
<td>Nil</td>
<td>DOD 3 d</td>
</tr>
<tr>
<td><strong>Blastoid NK cell lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>M/21</td>
<td>Blood, marrow, tonsils, lymph nodes</td>
<td>–</td>
<td>Chemotherapy (ProMACE-CytaBOM)</td>
<td>Partial response, then changed to German protocol for acute lymphoblastic leukemia, with good response; alive at 10 mo</td>
</tr>
<tr>
<td>41</td>
<td>M/4</td>
<td>Chin</td>
<td></td>
<td></td>
<td>Recent case</td>
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<td><strong>Other specific lymphoma types</strong></td>
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<td></td>
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<tr>
<td>4²⁵,²⁶,³⁴,³⁵</td>
<td>M/12</td>
<td>Spleen, lymph nodes, liver, marrow</td>
<td>–</td>
<td>Steroid and splenectomy</td>
<td>DOD 11 wk</td>
</tr>
<tr>
<td>4³⁶,³⁷</td>
<td>M/50</td>
<td>Skin</td>
<td>–</td>
<td>Chemotherapy (chlorambucil) followed by radiotherapy</td>
<td>DOD 1 yr</td>
</tr>
<tr>
<td>4⁴²,⁴³,⁴⁴</td>
<td>M/67</td>
<td>Skin, spleen, blood, marrow</td>
<td>–</td>
<td>Nil</td>
<td>DOD 4 d</td>
</tr>
<tr>
<td>4⁵⁻⁴,⁴¹</td>
<td>M/39</td>
<td>Spleen, liver, marrow, blood, lymph node</td>
<td>–</td>
<td>Chemotherapy (chlorambucil, COP, then m-BACOP)</td>
<td>DOD 2.5 yr</td>
</tr>
<tr>
<td>4⁶</td>
<td>F/46</td>
<td>Lymph nodes, marrow</td>
<td>–</td>
<td>German protocol for acute lymphoblastic leukemia</td>
<td>Recent case</td>
</tr>
<tr>
<td>4⁶</td>
<td>F/15</td>
<td>Soft tissue of face</td>
<td></td>
<td></td>
<td>AW 4 yr</td>
</tr>
<tr>
<td>4⁶⁻³,⁴⁴</td>
<td>M/31</td>
<td>Skin, liver, spleen, lymph nodes</td>
<td></td>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td>4⁹</td>
<td>M/6 mo</td>
<td>Cervical lymph node</td>
<td></td>
<td></td>
<td>Systemic relapse at 6 mo, and DOD 10 mo</td>
</tr>
</tbody>
</table>

Abbreviations: DOD, died of disease; AW, alive and well; RHS, reactive hemophagocytic syndrome.

* Immunophenotype reinterpreted as being CD3⁻/CD5⁺/CD7⁻/CD8⁻ instead of CD3⁻/CD5⁻/CD7⁻/CD8⁻ as originally reported in Tsang et al.²⁴

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sections or cell smears using the antibody NKH1 (Coulter, Hialeah, FL) or on paraffin sections using the antibody 123C3 (Monosan, Uden, The Netherlands). In a previous study, we have shown that 123C3 can reliably detect CD56 expression in lymphomas on paraffin-embedded tissues.⁎ Forty-nine cases were identified, including 40 cases treated at the Queen Elizabeth Hospital and 9 cases in which the pathologic materials were seen in consultation. Twenty-six of these cases have previously been included in studies on angiocentric T-cell lymphomas (the CD56 status being known in only a small percentage of cases then), large granular lymphocytic leukemia, various aspects of CD56⁺ lymphomas, and various lymphoma types.²⁵,²⁷,³⁴,³⁶,³⁷

The clinical data and follow-up information were collected. Available histologic materials were reviewed together with the immunophenotypic data. EBV was demonstrated using nonisotopic in situ hybridization for EBV-encoded small RNAs (EBERs), as previously described.⁶

### RESULTS

Several groups with different clinicopathologic features can be delineated among these 49 cases (Table 1).

**Nasal-type NK/T-cell lymphoma (n = 34).** This group included 25 men and 9 women, 21 to 76 years of age, with a mean age of 50.2 years and a median age of 50 years. All except 1 patient presented with extranodal disease, often involving more than one site. Case no. 14 presented with cervical lymphadenopathy, but there were also a tonsillar mass and bone marrow involvement at presentation. Lymph node enlargement accompanied extranodal disease in 4 cases. The commonest major sites of involvement at diagnosis were skin (14 cases), upper aerodigestive tract (8 cases), testis (5 cases), soft tissues (4 cases), gastrointestinal tract (4 cases), and spleen (4 cases). For those presenting with skin disease, the lesions were generalized or distributed over multiple anatomic locations. Only 7 (20.6%) patients (cases no. 5, 13, 18, 24, 27, 31, and 33) had possible stage I disease at presentation, but 4 of them developed additional sites of disease within 1 year, and the other 3 relapsed at 2 to 3 years. Five patients had reactive hemophagocytic syndrome at presentation, resulting in marked pancytopenia, and 1 further patient developed the syndrome terminally.
The disease often pursued a rapidly progressive course, with additional sites of disease appearing rapidly within weeks to months. The new sites of involvement were also mostly extranodal and were similar to the predilection sites at presentation. Response to multiagent chemotherapy (such as CHOP, BACOP, or ProMACE-CytaBOM) was often poor; even if complete remission could be attained, relapse developed soon after. Among 29 patients with follow-up information, 24 died in 1 week to 3 years, with a median of 3.5 months. Five were alive, with 2 being disease-free at 3 years and 5 years, respectively, and 3 with relapse at 5 months, 2 years, and 2.5 years, respectively.

Histologically, the lymphomatous infiltrate was diffuse or patchy, with angiocentric and angiodestructive growth being observed in 30 cases (88.2%) (Figs 1 and 2). The cytologic composition was variable from case to case, including predominance of small cells, medium-sized cells, or large cells, or a mixture of these cell types (Fig 2 and 3). The tumor cell nuclei frequently showed irregular foldings and granular chromatin (Fig 2B). The larger cells possessed distinct nucleoli. The cytoplasm was moderate in amount and often pale. Karyorrhexis was usually prominent. Zonal tumor cell death, focal or confluent, was evident in 27 cases. In the 14 cases for which Giemsa-stained touch preparations were available, azurophilic granules could be identified in at least some of the neoplastic cells.

By definition, the neoplastic cells showed CD56 expression (Fig 4). All except 2 cases (cases no. 7 and 12) reacted with the polyclonal CD3e antibody on paraffin sections, but both CD3e− cases were immunoreactive for CD43 and CD45RO. Among 18 cases in which frozen tissue was available for analysis, all were CD2−; 1 case each stained for CD3/Leu4 (weak staining), CD7, and CD8 and all cases were negative for CD4, CD5, CD16, CD57, and B-lineage markers. Thirty-two (94.1%) cases showed labeling for EB-ERs in practically all neoplastic cells (Fig 3B); 2 cases were negative.

**Aggressive NK cell leukemia/lymphoma (n = 5).** These 5 patients were adults 37 to 54 years of age, with a mean age of 44.2 years and a median age of 41 years. They presented with fever and systemic symptoms and were found to have hepatomegaly, anemia, leukopenia, and thrombocytopenia (Table 2). Enlarged spleen was detected in 3 patients and enlarged lymph nodes in 2. Only 1 patient had skin rash. One patient had features of reactive hemophagocytic syndrome. The disease pursued a fulminant course, with rapid development of multiorgan failure. All 5 patients died within 6 weeks, some before a definitive diagnosis could be made or before treatment could be initiated. Postmortem examination was performed in 2 patients (cases no. 35 and 36), showing tumor involvement of multiple organs.

There were very few to numerous granular lymphocytes in the peripheral blood. Some of the granular lymphocytes were indistinguishable from normal large granular lymphocytes, with round nuclei, dense chromatin, and pale cytoplasm with fine azurophilic granules (Fig 5A). Some granular lymphocytes had larger nuclei with more open chromatin and distinct nucleoli (Fig 5B); occasional nuclei could show indentations. The azurophilic granules were sometimes large and coarse. There were also circulating normoblasts and immature myeloid cells. Marrow involvement ranged from subtle to extensive. In histologic sections, irrespective of site, there was a monotonous infiltrate of medium-sized cells with round nuclei and fairly condensed chromatin (Fig 6). Karyor-
Fig 2. Laryngeal nasal-type NK/T-cell lymphoma relapsing as perforation of the terminal ileum (case no. 33). (A) The small bowel mucosa shows extensive necrosis and ulceration in the right field. There is also transmural lymphomatous infiltration. Note the vascular occlusion by lymphoma (arrow). (B) Higher magnification shows large and medium-sized lymphoma cells with irregular nuclear contours. The chromatin is fairly dense.

Fig 3. Cutaneous nasal-type NK/T-cell lymphoma (case no. 34). (A) This biopsy was initially misinterpreted as vasculitic lesion because of the small size of the lymphoid cells and the minimal cellular atypia. (B) Large numbers of lymphoid cells in the skin show positive labeling for EBERs on in situ hybridization. The sweat gland in the left field is negative.
Table 2. Peripheral Blood Counts of Patients With Aggressive NK Cell Leukemia/Lymphoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Hb (g/dL)</th>
<th>WBC (&gt;10^9/L)</th>
<th>% Granular or Abnormal Lymphoid Cells</th>
<th>Platelet (&gt;10^9/L)</th>
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<tbody>
<tr>
<td>35</td>
<td>4.5</td>
<td>46.6</td>
<td>99%</td>
<td>57</td>
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<td>36</td>
<td>10.3</td>
<td>15.3</td>
<td>39%</td>
<td>56</td>
</tr>
<tr>
<td>37</td>
<td>8.8</td>
<td>3.3</td>
<td>1%</td>
<td>10</td>
</tr>
<tr>
<td>38</td>
<td>9.7</td>
<td>5.1</td>
<td>2%</td>
<td>29</td>
</tr>
<tr>
<td>39</td>
<td>6.8</td>
<td>2.8</td>
<td>1%</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; WBC, white blood cell count.

rhesis was prominent. The infiltrate was diffuse, interstitial, or angiocentric.

The immunophenotype as analyzed on fresh/frozen tissues was CD2⁺ CD3⁻ Leu4⁺ CD4⁻ CD5⁻ CD7⁻ CD8⁻ CD16⁻ CD56⁻ CD57⁻ (Fig 7). In paraffin sections, the neoplastic cells showed reactivity with the polyclonal CD3e antibody. In all cases, nuclear labeling for EBER was observed in the majority of neoplastic cells.

Blastoid NK cell lymphoma (n = 2). One patient presented with systemic disease, whereas 1 had localized dis-

Fig 4. Cutaneous nasal-type NK/T-cell lymphoma, with the lymphoma cells showing cell membrane staining for CD56 on paraffin section. The sweat gland in the lower field is not stained.

Fig 5. Two different cases of aggressive NK cell leukemia/lymphoma. (A) Peripheral blood shows increased large granular lymphocytes, most of which are mature-looking (case no. 36). The cell in the center is slightly less mature. (B) Buffy coat smear shows immature large granular lymphocytes with more open chromatin and distinct nucleoli (arrows) (case no. 37). Myeloid cells are seen in the background.
AID Blood 0025 / 5h37$$$481 05-15-97 12:17:18 blda WBS: Blood

CD68

this case resemble plasmacytoid monocytes. short median survival observed in this study corroborates

strate of medium-sized cells with round nuclei. The neoplastic cells in

lymphoma (case no. 37). There is a fairly monotonous, diffuse in®l-

ation with CD56 expression, hence the noncommittal lin-

It is currently unclear whether the nasal-type NK/T-cell

lymphoma. For comparison, although the nasal CD56

lymphomas tend to dissemi-

tion as T-cell lymphomas are more aggressive than the nasal T-

tions. In case no. 41, the immunophenotype as assessed on

paraffin section was CD3

/e

CD3/

CD56

NK/In case no. 40, the immunophenotype was CD2

Leu4

CD4

CD5

CD7

CD8

CD13

CD33

CD56

TdT

and myeloperoxidase-negative on paraffin sections. In case no. 41, the immunophenotype as assessed on

paraffin section was CD3e

CD43

CD56

TdT

and myelo-

peroxidase-negative. Both cases were EBERs-negative.

Specific lymphoma types with CD56 expression (n = 8).
The clinical findings, diagnoses, and immunophenotype of

the 8 cases of specific lymphoma types with CD56 expres-

sion are listed in Tables 1 and 3. Six of the patients have
died at a median of 6.5 months. One patient is alive at 4

years after chemotherapy, and 1 is only recently diagnosed

as having lymphoma.

For case no. 46, the neoplastic cells showed classical fea-
tures of lymphoblasts and strong staining with the polyclonal

CD3e antibody on paraffin section, but they also showed

reactivity with two myeloid-associated markers, CD13 and

CD33, but not myeloperoxidase. This could represent a hy-

bird T-cell/myeloid immunophenotype. All 8 cases were

EBERs-negative.

DISCUSSION

CD56

malignant lymphomas are uncommon. The 49

cases of nonnasal examples included in this series were col-

lected over a 16-year period in a geographic location where

this lymphoma type appears to be more prevalent than most

other places of the world. Over the same period, we have

encountered approximately 70 cases of nasal/nasopharyngeal

CD56

lymphomas. Nonnasal CD56

lymphomas comprise

at least four different entities, and their salient features are

summarized in Table 4, based on information from the cur-

rent study and the literature.

Nasal-type NK/T-cell lymphoma is the commonest type

of CD56

lymphoma occurring outside the nasal or nasopa-

ryngeal region. It is morphologically and immunohistochem-

ically identical to nasal NK/T-cell lymphoma. This study con-

firms it to be a form of extranodal lymphoma with predilec-

tion for the skin, upper aerodigestive tract, testis, gastroin-

testinal tract, soft tissues, and spleen. It is of interest that

these are also the same sites that both the nasal/nasopa-

ryngeal and nasal-type CD56

lymphomas tend to dissemi-

nate to. It has been postulated that these sites may richly

express CD56 (N-CAM), favoring homing of CD56

lymphoma cells, because N-CAM shows homophilic binding

properties.1 This lymphoma type is associated with an in-

creased risk of developing hemophagocytic syndrome

(17.6% [6 of 34]); the systemic histiocytic activation presum-

ably results from cytokines or other products released by the

lymphoma cells.42 The high mortality rate (82.8%) and very

short median survival observed in this study corroborates

the aggressive behavior documented in the small series and

case reports in the literature.7,9,16,25-33,43 This is probably the

most aggressive currently known lymphoma type. Even pa-

tients receiving third-generation combination chemothera-

py have an unfavorable outcome. Despite initial response to

therapy in some patients, relapse usually occurs within a

short time. There are thus strong reasons to design new

strategies of treatment for this group of highly aggressive

lymphoma. For comparison, although the nasal CD56

NK/T-cell lymphomas are more aggressive than the nasal T-

cell or B-cell lymphomas, the 2-year actuarial disease-free

survival of 31% ± 13% (unpublished observation) appears
to be much better than that of nasal-type NK/T-cell lympho-

mas. Nonetheless, the difference can be attributed to the

predominance of stage I/II disease (82.3%) for the nasal

NK/T-cell lymphomas and predominance of advanced stage
disease at presentation for nasal-type NK/T-cell lymphomas.

It is currently unclear whether the nasal-type NK/T-cell
lymphomas are bona fide NK cell neoplasms or T-cell neo-

plasms with CD56 expression, hence the noncommittal lin-
eage designation NK/T.7 This designation is descriptively

more accurate than angiocentric lymphoma because angio-
centric growth is not invariably seen in this lymphoma type

and angiocentricity can be observed in other lymphoma

types, including B-cell lymphomas.44-46 It is not surprising

that there are great difficulties in distinguishing between NK

Fig 6. Lymph node biopsy of aggressive NK cell leukemia/

lymphoma (case no. 37). There is a fairly monotonous, diffuse in®l-

trate of medium-sized cells with round nuclei. The neoplastic cells in

this case resemble plasmacytoid monocytes.
Fig 7. Immunocytochemical staining of aggressive NK cell leukemia/lymphoma (case no. 39), using the labeled avidin-biotin alkaline phosphatase system. The smears were prepared from mononuclear cells separated by density gradient centrifugation using Ficoll-Isopaque. (A) The cells are positive for CD2. (B) There is no reactivity for Leu4/CD3; the strongly stained small lymphocytes serve as internal positive controls. (C) The cells are reactive for CD56 (NKH1).

and T-cell lineage, because these two lineages are so closely related; in fact, a bipotential T/NK progenitor cell probably exists.²⁷ Features favoring an NK cell lineage are the lack of surface CD3 (Leu4) expression, lack of expression of T-cell antigen receptors, presence of azurophilic granules, and lack of T-cell receptor gene rearrangements in the great majority of cases studied.¹⁶,³⁰,³³,⁴⁶,⁴⁸,⁴⁹ Nonetheless, lack of expression of other NK cells markers such as CD16 and CD57 is somewhat unusual for cells of NK lineage. This study also establishes a strong association of this lymphoma type with EBV (94.1% [32 of 34]), comparable to the nasal counterpart. NK/T-cell lymphoma (nasal and nasal-type) is the malignant lymphoma type most strongly associated with EBV in all geographic areas studied.²⁴ The strength of association as reported in our previous study on 15 cases was lower (67%) because of inclusion of specific types of T-cell lymphomas with CD56 expression; if only the nasal-type NK/T-cell lymphomas are considered, the positivity rate is 100% (7 of 7).³⁴ The low figure of 33% recently reported from Japan by Kobashi et al²⁹ is due to the inclusion of 5 cases of blastoid NK cell lymphoma (all EBV-negative); if such cases are excluded, the EBV positivity rate for the nasal-type NK/T-cell lymphomas is 75% (3 of 4). Some recent studies on nasal-type NK/T-cell lymphomas in caucasian populations, albeit small in size, also support a strong although not invariable association with EBV.³³,³⁴

Although aggressive NK cell leukemia/lymphoma is identical to nasal-type NK/T-cell lymphoma in the presence of azurophilic granules, immunophenotypic profile (CD2⁺ CD3/Leu4⁻ CD56⁺ CD16⁻/³⁴ CD57⁻), genotype (lack of T-cell receptor gene rearrangements), and strong association with EBV,¹⁹,⁵⁰,⁶⁰ it does show some distinguishing features: (1) younger age group (mean age for this series was 44.2 years, and for a Japanese series of 11 cases was 29.5 years¹⁰); (2) the presence of peripheral blood involvement (albeit minimal in some); (3) more frequent occurrence of superficial lymphadenopathy; (4) very infrequent skin involvement; (5) more monotonous-appearing neoplastic population; and (6) predominantly round nuclear contour.²¹,⁵⁰,⁵¹,⁵³,⁶¹ However, admittedly some cases with systemic disease cannot be reliably classified as nasal-type NK/T-cell lymphoma or aggressive NK cell leukemia/lymphoma. Patients with nasal NK/T-cell lymphoma have also been rarely reported to develop features of aggressive NK cell leukemia/lymphoma.⁶²

Aggressive NK cell leukemia/lymphoma is not a usual form of leukemia, because bone marrow involvement is often patchy and may even be minimal; thus a designation of leukemia/lymphoma is justified. The clinical course is usually fulminant, with the patients dying shortly after presentation from multiorgan failure. Like nasal and nasal-type NK/T-cell lymphomas, it may also be associated with reactive hemophagocytic syndrome.³²,⁶³ The tumor cells can exhibit a spectrum of cytologic appearances from mature-looking cells to larger cells and cells with prominent nucleoli. Those cases composed of mature-looking granular lymphocytes are indistinguishable from T-cell large granular lymphocytic (LGL) leukemia on morphologic grounds, but a distinction is important because of many important differences. T-cell LGL leukemia is associated with severe neutropenia and rheumatoid arthritis and pursues an extremely indolent course. Special studies are
most helpful for making a distinction, because T-cell LGL leukemia frequently exhibits an immunophenotype of CD3/Leu4+/CD8+/CD57-/CD16+/-/CD56+, clonal rearrangements of T-cell receptor genes, and lack of association with EBV.64-68 It has been suggested that lack of CD57 expression or expression of CD56 may be associated with a more aggressive course in T-cell LGL leukemia,69,70 but this is not a universal finding.71 On the other hand, not all proliferations of CD3/Leu4+ CD56+ large granular lymphocytes pursue an aggressive course.64 The indolent examples differ from the aggressive ones in absence

Table 3. Summary of Immunophenotype of the Specific Lymphoma Types With CD56 Expression

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>CD2</th>
<th>CD3/Leu4</th>
<th>CD3+</th>
<th>CD4+</th>
<th>CD5+</th>
<th>CD7+</th>
<th>CD8+</th>
<th>CD16+</th>
<th>CD57+</th>
<th>CD68+</th>
<th>TCR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>S-100 protein-positive T-cell lymphoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>βF1+</td>
</tr>
<tr>
<td>43</td>
<td>T-cell small lymphocytic lymphoma/chronic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>βF1+</td>
</tr>
<tr>
<td></td>
<td>lymphocytic leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>T-cell prolymphocytic leukemia/lymphoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>45</td>
<td>Hepatosplenic γδ T-cell lymphoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>βF1+</td>
<td>TCRδ1+</td>
</tr>
<tr>
<td>46</td>
<td>T-lymphoblastic lymphoma*</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>47</td>
<td>B-lymphoblastic lymphoma*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>48</td>
<td>True histiocytic lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>49</td>
<td>True histiocytic lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

CD3+: immunoreactivity is demonstrated on paraffin section.
Abbreviation: ND, not determined.
* Both cases of lymphoblastic lymphoma show TdT immunoreactivity.
Table 4. Summary of the Major Types of Nonnasal CD56+ Lymphomas, Based on Information From Current Series and Cases Reported in the Literature

<table>
<thead>
<tr>
<th>Nonnasal Type</th>
<th>Nasal-Type NK/T-Cell Lymphoma</th>
<th>Aggressive NK Cell Leukemia/Lymphoma</th>
<th>blastoid NK Cell Lymphoma</th>
<th>Other Specific Lymphoma Types With CD56 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Usually adults</td>
<td>Usually young or middle-aged adults</td>
<td>Adults</td>
<td>Variable</td>
</tr>
<tr>
<td>Sex</td>
<td>M &gt; F</td>
<td>M = F</td>
<td>?</td>
<td>Variable</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Presenting with extranodal disease, often involving multiple sites (high stage disease at presentation). Skin, upper aerodigestive tract, soft tissues, testis and gastrointestinal tract are commonest sites of involvement.</td>
<td>Presenting with fever and systemic symptoms. Often have hepatosplenomegaly and sometimes lymphadenopathy.</td>
<td>Presenting with extranodal disease, especially skin</td>
<td>Variable; either nodal or extranodal presentation. Distinctive features may be seen in some specific lymphoma types, such as hepatosplenic γ-δ T-cell lymphomas.</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Lymphoma cells often show irregular nuclear foldings and granular chromatin. They can be small, medium-sized or large; either a single cell type predominates, or a mixture of cell types. May be variably admixed with inflammatory cells. Necrosis common. Angiocentric growth may be identified.</td>
<td>Diffuse, monotonous infiltrate of medium-sized cells with condensed chromatin. Nuclei often appear round. May show angiocentric growth and necrosis.</td>
<td>Diffuse, monotonous infiltrate of medium-sized cells with fine chromatin and frequent mitoses. Resembling lymphoblastic lymphoma or granulocytic sarcoma.</td>
<td>Variable, corresponding to the specific lymphoma types.</td>
</tr>
<tr>
<td>T-cell receptor genes</td>
<td>Germline</td>
<td>Germline</td>
<td>Germline</td>
<td>Rearranged</td>
</tr>
<tr>
<td>Association with EBV</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>0%</td>
<td>Variable, usually negative</td>
</tr>
<tr>
<td>Clinical behavior</td>
<td>Aggressive, with early dissemination. Relapse is very common despite initial response to chemotherapy.</td>
<td>Fulminant course</td>
<td>Aggressive</td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

of fever, lack of hepatosplenomegaly or lymphadenopathy, frequent expression of CD16 and CD57, and lack of EBV association. 

Blastoid NK cell lymphoma has only been recently characterized. It shows extranodal presentation and can also rarely arise in the nasal cavity. The case reported by Kawano et al may represent another such example. This entity appears to be biologically distinct from the NK/T-cell lymphomas in the lymphoblastoid or myeloid leukemia-like morphology, often CD2- immunophenotype, and lack of EBV association. The behavior of this tumor remains to be clarified, because very few cases have been reported so far. The relationship with the entity myeloid/NK cell leukemia also requires clarification.

Various specific lymphoma types can uncommonly express CD56, such as lymphoblastic lymphoma, peripheral T-cell lymphoma, and true histiocytic lymphoma. The basis for this phenomenon is unclear. For lymphoblastic lymphoma, a previous study has shown expression of the NK cell-associated markers CD16 and CD57 to be associated with a worse prognosis, although CD56 expression has not been analyzed in that study. T-lymphoblastic lymphoma expressing CD56 has indeed been recently reported by Ichihama et al. Peripheral T-cell lymphoma expressing CD56, sometimes referred to as NK-like T-cell lymphoma, are bona fide T-cell neoplasms because they often (but not invariably) express CD3/Leu4+ and show rearrangements of the T-cell receptor genes. The aggressive behavior of these CD56+ peripheral T-cell lymphomas has also been documented in a number of studies.
among peripheral T-cell lymphomas is in fact very rare, but two specific subtypes show a very high frequency of CD56 expression, at least in the small number of cases in which this marker has been studied, namely hepatosplenic γδ T-cell lymphoma and S100 protein+ T-cell lymphoma. These lymphoma types show overlapping clinical and pathologic features and are known to be aggressive. Another interesting finding from this study is that some true histiocytic lymphomas can also express CD56; thus, CD56 expression among lymphomas is not strictly limited to those of T-cell or putative NK cell lineage.

In conclusion, a number of entities are encompassed in the family of CD56+ malignant lymphomas, including some distinctive putative NK cell neoplasms and CD56-expressing peripheral T-cell lymphomas. Nonetheless, they are unified by the common theme of highly aggressive behavior. Therefore, in the immunophenotypic analysis of T-cell lymphomas, routine application of the CD56 marker may help to identify this group of neoplasm.

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Nonnasal Lymphoma Expressing the Natural Killer Cell Marker CD56: A Clinicopathologic Study of 49 Cases of an Uncommon Aggressive Neoplasm