Natural Killer (NK) cells represent a distinctive lineage of lymphocyte that is closely related to T lymphocytes. NK cells possess many immunophenotypic and functional similarities with cytotoxic T lymphocytes, but differ in the lack of expression of surface CD3 molecule and T-cell receptor, and the germline configuration of the T-cell receptor genes. These cells characteristically express CD56 (neuronal cell adhesion molecule [N-CAM]), which is also expressed in a subset of cytotoxic T lymphocytes. NK cells can lyse target cells without prior sensitization (spontaneous antibody-independent major histocompatibility complex [MHC]-unrestricted cytotoxicity), mostly via the NK receptors.

Neoplasms of NK cells are rare, and have only been well characterized during the past 10 to 15 years. Recognition of the NK cell lineage of a lymphoma is important, because NK cell neoplasms are generally highly aggressive. The new World Health Organization (WHO) classification of hematolymphoid tumors, recognizes three categories of NK cell neoplasms. The first category, extranodal NK/T-cell lymphoma, replaces “angiocentric lymphoma” in the Revised European-American Lymphoma (REAL) classification. It is called “NK/T” rather than simply “NK” because while most cases are genuine NK cell neoplasms, some appear to be cytotoxic T-cell neoplasms. The qualifier “nasal” is appended when the nasal cavity is the primary site of involvement, and “extranasal” or “nasal-type” when other sites are involved.

The second type is aggressive NK cell leukemia, which will be discussed here and is also briefly addressed by Lamy and Loughran elsewhere in this issue.

There is little compelling evidence that the final type, described as “blastic NK cell lymphoma,” truly represents an NK cell neoplasm. In fact, this may be a neoplasm of precursor dendritic cells related to plasmacytoid monocytes (plasmacytoid dendritic cells). This entity is covered by Béné et al in this issue.

Extranodal NK/T-Cell Lymphoma
Clinical Features and Behavior
Extranodal NK/T-cell lymphomas show a predilection for Asians, Mexicans, and South Americans. Recognition of the NK cell lineage of a lymphoma is important, because NK cell neoplasms are generally highly aggressive. The new World Health Organization (WHO) classification of hematolymphoid tumors, recognizes three categories of NK cell neoplasms.

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cavity, which is the prototype of this form of lymphoma. The median age of patients is 53 years, and the male to female ratio is about 3:1.3,14

**Nasal NK/T-cell lymphoma.** Nasal NK/T-cell lymphoma is the predominant histologic type of primary nasal lymphoma, at least in the Asian population.13 The most common presenting symptoms are nasal obstruction, nasal discharge, and epistaxis.13 The full-blown midfacial destructive and ulcerative lesions are much less commonly seen now, probably due to earlier presentation.10,13,14 Extension to the nasopharynx and paranasal sinuses occurs in 37% to 50% of patients with stage I disease.14,40 In a detailed study using computed tomographic (CT) scan and magnetic resonance imaging, the tumor was found to be locally destructive, with frequent erosion of bones (78% of cases).70 including the medial maxillary wall, orbital floor, lamina papyracea, palatal bone, and alveolar bone. Besides demonstrating subtle bone destruction, magnetic resonance imaging is superior to CT scan in delineating the extent of soft-tissue infiltration and in distinguishing tumoral tissue, inflamed tissue, and accumulated fluid.

Although nasal NK/T-cell lymphoma is usually localized at presentation (82% to 92%).13,43,47,49 systemic progression often occurs, usually early in the course of disease. Common distant sites of involvement are the skin, liver, lung, gastrointestinal tract, and testis.13 In our retrospective study of 79 cases, 60% of all failures in patients presenting with localized disease were due to systemic progression alone, and almost all occurred within 12 months after treatment, mainly chemotherapy.14 Similarly systemic failures have been reported in patients treated with radiotherapy alone at a median time of 7 months after treatment.40 Local resistant disease or relapse is also common and has been reported in 50% of patients with localized disease who had achieved complete remission with radiotherapy.40 In our series, local relapse occurred in 31% of all patients who had achieved complete response.14 On the other hand, neck node involvement at presentation or relapse is relatively rare; regional failure as the sole site of failure occurs in only 4% to 11% of cases.14,40 Hemophagocytic syndrome may develop during the course of disease, characterized by fever, precipitous and otherwise unexplained drop in blood counts, presence of hemophagocytic histiocytes in the bone marrow, coagulopathy, and rapid deterioration in liver function.13,14,40,64

**Extranodal NK/T-cell lymphoma.** Extranodal NK/T-cell lymphoma involving sites outside the nasal cavity or upper respiratory tract is rare.1,3,37,39,56 Most patients have multiple anatomic sites of disease at presentation, in the absence of lymphadenopathy. The predominant sites of involvement are skin, gastrointestinal tract, testis, and soft tissues, similar to the sites to which nasal NK/T-cell lymphoma tends to disseminate during the course of disease.1,3,5,7,26,37,55,56,80,93,94 The skin lesions often appear as nodules or plaques with ulceration and necrosis, and occasionally manifest as diffuse erythematous swelling. When the intestines are involved, perforation is the most frequent presenting symptom due to prominent tissue necrosis, thus differing from conventional intestinal lymphomas, which usually manifest as bowel obstruction. Other sites of involvement appear as mass lesions.

Systemic symptoms such as fever, malaise, and weight loss are common. For patients presenting with apparently localized disease, additional sites of disease are often identified on staging, or appear early in the course of disease. Hemophagocytic syndrome may complicate the disease at presentation or in the terminal phase.85

The disease pursues a highly aggressive clinical course, with most patients dying within 6 months. According to one series, the 2-year disease-free survival was only 10%.3 The worse prognosis compared with nasal NK/T-cell lymphoma may be attributable to the high-stage disease in most patients.3,5,39,60,63

**Pathology**

The involved tissue commonly shows extensive coagulative necrosis and ulceration (Fig 1). The diffuse lymphomatous infiltrate varies in cytologic composition from case to case, ranging from small, to medium, to large cells (Figs 2 and 3).3,10 While the small cells often exhibit nuclear irregularities and pale cytoplasms, they can be indistinguishable from normal small lymphocytes, causing great difficulties in diagnosis using morphologic criteria alone.3,16,82 In Giemsa-stained cytologic smears, azurophilic granules can be identified in the cytoplasm of the tumor cells, as expected of the NK or cytotoxic T-cell nature of the neoplastic cell.

Angiocentric-angiodestructive growth is common, although it may not be identified in small biopsies (Fig 4).3,36 Necrosis and apoptosis are also prominent features (Fig 5). Prominent necrosis sometimes mandates repeated and multiple biopsies to procure sufficient viable tissue in order to determine a histologic diagnosis (Fig 6).

**Immunobiologic Features**

The most common immunophenotype of extranodal NK/T-cell lymphoma is CD2+, surface CD3+, cytoplasmic CD3e+, and CD56+ (Table 1).3,5,11,19,21,27,29,60,68,73 The discrepancy in expression of surface CD3 (requiring fresh or frozen tissue for demonstration) and cytoplasm CD3 (demonstrable in fresh, frozen, or paraffin-
embedded tissue) is a distinctive feature, as expected of NK cells; subunits of the CD3 molecules are present in the cytoplasm, but the complete molecule is not assembled on the cell surface. The most consistently expressed NK-associated marker is CD56 (Fig 7). Cytotoxic molecules are, as expected, positive. Nasal CD3+/H9280/H11001 lymphomas that are CD56+/H11002 are currently also placed within the category of NK/T-cell lymphoma provided that they also express cytotoxic molecules and harbor Epstein-Barr virus (EBV). However, if cytotoxic molecules and EBV are negative, the cases should be diagnosed as peripheral T-cell lymphoma unspecified. While one study reported more favorable outcome of the CD56+/H1902 nasal lymphomas compared with CD56− nasal lymphomas, cytotoxic markers and EBV status were not applied to delineate the possible NK/T-cell subgroup from the peripheral T-cell lymphoma unspecified. Since information on the CD56− subgroup of NK/T-cell lymphoma is limited, it would be helpful in the future to identify this subgroup separately to determine its prognostic significance.

The T-cell receptor genes are usually not rearranged. For nasal NK/T-cell lymphoma, EBV is nearly always positive, irrespective of the ethnic origin of the patient. For extranasal NK/T-cell lymphoma, EBV association is strong in Oriental patients, but less consistent in Caucasians. Not much is known about the genetic changes in extranodal NK/T-cell lymphoma. So far, the most commonly observed changes are del(6)(q21-q25), del(17)(p12-p13), del(13)(q14-q34), and gain of 1p32-pter.

**Treatment and Outcome**

Owing to the rarity of the disease, all recently reported clinical studies are based on retrospective patient series (Table 2). This discussion will be limited to the nasal form, because information on extranasal disease is extremely limited. Reports in the literature often have not included complete immunophenotypic data, and
thus the results may apply to nasal lymphomas as a whole and not just to NK/T-cell lymphomas.

All recent publications, with the exception of one Western study, reported no convincing clinical benefit of adding chemotherapy to radiation therapy. The latter series reported a 5-year freedom from progression rate of 71% with chemotherapy compared to 38% with radiotherapy alone. However, immunophenotype was not reported, and most of the patients showed involvement of the maxillary sinuses; thus likely most of the lymphomas were of B-cell lineage.

Most series have reported poor results with initial application of conventional chemotherapy, while radiotherapy alone or radiotherapy combined with chemotherapy produced better or equivalent results. Kwong et al reported a complete remission rate of 75% among 20 patients with localized nasal NK/T-cell lymphomas treated with anthracycline-containing chemotherapy followed by radiation therapy, but two thirds of the patients relapsed, resulting in a poor median overall survival of 12 months. Sakata et al treated 16 early-stage nasal “T-cell” lymphomas mainly with chemotherapy and reported a poor 5-year cause-specific survival of 22% and distant dissemination rate of 75%. In the Shikama et al series of 20 nasal “T-cell” lymphomas treated primarily with radiotherapy (with 64% patients receiving post-radiotherapy chemotherapy), the 5-year survival rate was 72%. Li et al studied the outcome of 175 patients according to stage and treatment. Stage I disease was treated either with radiotherapy alone (more so for limited stage I disease confined to the nose) with or without chemotherapy. There was no difference in 5-year survival between those treated with radiotherapy alone and patients undergoing radiotherapy and chemotherapy, indicating lack of advantage in adding drugs to radiation. Kim et al reported apparent lack of efficacy of chemotherapy in treatment of 17 nasal NK/T-cell lymphomas; frequent primary resistance to chemotherapy was noted, and only six of 15 patients given chemotherapy achieved complete remission. On the other hand, eight of 10 patients who were alive and well had received primary radiation therapy. Ribrag et al reported only

Figure 3. Nasal NK/T-cell lymphoma. (A) This example is predominated by small cells with irregular-shaped and angulated nuclei. Distinction from reactive lymphoid infiltrate can be difficult. (B) This example is predominated by medium-sized cells, and thus a diagnosis of lymphoma should be obvious.
three complete remissions among 12 patients treated initially with chemotherapy, while seven of eight patients treated with initial radiation therapy or alternating chemotherapy-radiation therapy remained free of disease.75 Yamaguchi et al treated 12 nasal NK/T-cell lymphomas, with all five patients who received initial radiotherapy achieving complete remission and four of them remaining alive and well, but only one of seven patients treated with conventional chemotherapy achieved complete remission.75 In our analysis of 79 early-stage nasal NK/T-cell lymphomas according to intent to treat, there was no statistically significant survival difference between patients treated with radiotherapy (5-year disease-free survival, 31%) compared to chemotherapy (5-year disease-free survival, 36%). In this series, the total resistance rate to conventional chemotherapy was 67%.14 In summary, anthracycline-containing combination chemotherapy given before radiotherapy confers no survival benefit, at least for stage I disease.

The high rate of resistance to conventional chemotherapy may be related to frequent expression of P-glycoprotein, the product of the multidrug resistance (MDR) 1 gene, and poor drug delivery owing to the prominent tissue necrosis.14,23,96 Attempts to overcome this problem have used MDR-unrelated anticancer agents or high-dose therapy with peripheral stem cell rescue. Among three patients treated with combination dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) (two concurrently with radiotherapy and one after radiotherapy), all were alive and well at 12 to 96 months.97 In case reports and small series, l-asparaginase as single agent or combined with vincristine and dexamethasone has been reported to be effective as salvage treatment for refractory diseases including failure after autologous marrow transplant, producing response rates up to 50%, including complete remissions.61,67,98,99 Among three relapsed patients treated with marrow transplant in one series, there were two survivors at 12 and 44 months.50 In a pilot study of 20 consecutively treated early-stage nasal NK/T-cell lymphomas, six consolidated with high-dose therapy and peripheral stem cell support, outcome compared favorably to a historical cohort of patients treated at the same institute. The 2-year disease-free survival of
this group was 63% and that of the historical cohort, 38% (P = .083).15

While systemic progression is the usual mode of

Table 1. Immunobiologic Profile of Extranodal NK/T-Cell Lymphoma

- CD2: positive
- Surface CD3/Leu4: negative
- Cytoplasmic CD3 (polyclonal antibody to CD3ε or PS1): positive
- CD56: positive (most cases)
- T-cell receptor: negative
- Other T-cell markers (CD4, CD5, CD7, CD8): usually negative
- CD43 and CD45RO: usually positive
- Other natural killer cell markers (CD16, CD57): usually negative
- Cytotoxic molecules (perforin, granzyme B, TIA-1): positive
- Some cases may express CD25 or CD30
- NK cell receptors: variable expression
- Fas and Fas ligand: commonly positive
- Epstein-Barr virus: positive

failure, local recurrence is also common despite radiotherapy. Studies on the relationship between local control and dose suggest that a total radiation dose higher than that generally recommended for non-Hodgkin’s lymphomas might be needed for disease control. One group reported complete remission in all five patients given time-dose-factor (TDF) values of 80 or over (equivalent to 50 Gy or more given in 2 Gy/fraction, 5 fractions/wk), and only in two of 11 patients given a lower total dose.78 Another group reported a significantly higher 5-year local control rate with total dose greater than 50 Gy compared with a lower dose (100% vs 67%, P = .013).80 In our study, the in-field failure rate (12%) in patients given a total dose greater than 50 Gy and/or concomitant chemoradiation with cisplatinum and having imaging scans done to assist treatment was lower compared with those who were not (28%).14 Thus meticulous CT conformal planning with the aid of magnetic resonance imaging is recommended to delineate the extent of disease and hence the field of radiation therapy.
Prognostic Factors

The clinical factors reported to have prognostic significance in nasal NK/T-cell lymphomas include stage, performance status, B symptoms, age, and bulk. Advanced-stage disease (III and IV) was associated with a very poor outcome (2-year overall survival, 13%). In our study, the 5-year overall survival rates for stage I and II disease were 42% and 19%, respectively. In a series of 92 patients treated by radiotherapy alone, the 5-year overall survival rates were 64% for stage I disease and 25% for stage II disease. A study of 175 patients with predominantly early-stage disease reported significantly different 5-year overall survival rates for stage I (75%) and stage II (35%) disease.

The International Prognostic Index (IPI) has not been adequately examined for predictive value in this disease. We did not find it to be of independent significance. However, since more than 80% of the patients have low-risk IPI (0 or 1), there may not have been a wide enough spectrum of disease to detect a difference.

**Table 2. Major Recent Series of Primary Nasal Lymphomas Reported in Recent 5 Years**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Patients (stage)</th>
<th>Subtypes, No.</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwong et al</td>
<td>20 (I)</td>
<td>NK/T</td>
<td>All CMT</td>
<td>High relapse (67%) with CT, median OS 12 mo</td>
<td>Poor outcome</td>
</tr>
<tr>
<td>Shikama et al</td>
<td>25 (all I)</td>
<td>20 T*, 5 B</td>
<td>9 RT, 16 RT + CT</td>
<td>5-yr-DFS 72% (T* only)</td>
<td>RT dose important; CT adds nothing</td>
</tr>
<tr>
<td>Sakata et al</td>
<td>16 (I=10, II=6)</td>
<td>All T*</td>
<td>2 RT, 14 CMT</td>
<td>7/16 CR, 12/16 systemic progression, 5-year cause-specific survival 22%</td>
<td>RT dose important; very heterogeneous chemotherapy</td>
</tr>
<tr>
<td>Li et al</td>
<td>175 (I=133 II=28 III, IV=14)</td>
<td>46 T*</td>
<td>58 RT, 117 CMT or CT</td>
<td>Stage I 5-yr DFS 68%, 5-year OS 75%</td>
<td>Stage and extent in stage I prognostically important; chemotherapy adds no benefit in stage I</td>
</tr>
<tr>
<td>Lei et al</td>
<td>44 (I, II=40, III, IV=4)</td>
<td>25 nasal (75% T*)</td>
<td>19 NP (33% T*) (6 NK/T)</td>
<td>CMT 64%, RT 14%, CT 23%</td>
<td>5-yr OS 54%; Nasal 33%, NP 82%</td>
</tr>
<tr>
<td>Cuadra-Garcia et al</td>
<td>17</td>
<td>5 NK/T</td>
<td>Unknown</td>
<td>73% NED (&quot;NK/T-cell type&quot;)</td>
<td>Outcome of NK/T-cell type similar to diffuse large B cell</td>
</tr>
<tr>
<td>Kim et al</td>
<td>92 (I=62, II=30)</td>
<td>80% T*</td>
<td>RT alone</td>
<td>66.3% CR, 5-yr OS 40.1%</td>
<td>Common early local failure; stage prognostically important</td>
</tr>
<tr>
<td>Ribrag et al</td>
<td>20</td>
<td>7 NK/T</td>
<td>CMT (8 initial RT, 12 CT)</td>
<td>10 alive with no relapse</td>
<td>Initial RT better; high CT failure rate</td>
</tr>
<tr>
<td>Yamaguchi et al</td>
<td>12 (I=9, II=3)</td>
<td>All NK/T</td>
<td>7 conventional CMT, 5 RT (3 +DeVIC, 2 concurrent DeVIC)</td>
<td>CMT: 1/7 CR, 5-yr OS 13%, RT: 5/5 CR, 5-yr OS 73%</td>
<td>Resistant to conventional CT; DeVIC, RT good</td>
</tr>
<tr>
<td>Kim et al</td>
<td>17</td>
<td>All NK/T</td>
<td>CMT (15 initial CT)</td>
<td>3-yr OS 59%,</td>
<td>High CT-resistance; B-symptom, stage prognostically important</td>
</tr>
<tr>
<td>Cheung et al</td>
<td>79 (I=63, II=16)</td>
<td>All NK/T</td>
<td>18 RT, 61 CMT (intend to treat)</td>
<td>5-yr DFS 35.5%, 5-yr OS 37.9%</td>
<td>CMT no better than RT; stage and performance status prognostically important</td>
</tr>
</tbody>
</table>

Abbreviations: Subtypes, immunophenotypes; NK/T, CD56+ tumors; T* = T or NK/T, but CD56 status unknown; CMT, combined modality treatment; RT, radiation therapy; CT, chemotherapy; NED, no evidence of disease; OS, overall survival; DFS, disease-free survival; IPI, International Prognostic Index; NP, nasopharynx; CR, complete remission; DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin.
**Recommended Treatment**

For stage I disease, radiation therapy is the mainstay; the total dose should be over 50 Gy. Prophylactic radiation of the central nervous system is not necessary because relapse in this site is rare. If chemotherapy is to be added in view of the high rate of systemic progression or to spare essential organs from radiation (such as the eyes) by debulking an originally voluminous tumor, radiation should be applied early.

Theoretically, chemotherapy should play an important role in the treatment of higher stage disease. Regimens employing MDR-unrelated drugs that have been shown to be effective in refractory disease should be tested in prospective protocols. In fact, since outcome has been poor even in stage I disease treated with radiotherapy alone, all medically fit patients should be offered the choice of these latter regimens or intensified therapy with concurrent chemoradiation and high-dose therapy.

To monitor disease activity, the value of plasma or serum circulating EBV DNA as a surrogate marker for minimal residual disease or early relapse requires large-scale and prospective evaluation. P73 gene hypermethylation assay in biopsies also appears to be a promising technique for determining the presence or absence of minimal disease, since this is a common feature in NK/T-cell lymphomas (94%).

**Aggressive NK Cell Leukemia**

**Clinical Features and Behavior**

Aggressive NK cell leukemia represents the leukemic end in the range of NK cell neoplasms, analogous to the acute lymphoblastic leukemia–lymphoblastic lymphoma spectrum and chronic lymphocytic leukemia–small lymphocytic lymphoma spectrum. While there are usually easily identified neoplastic cells in the peripheral blood and bone marrow, involvement can be subtle, rendering a distinction from disseminated extranodal NK/T-cell lymphoma difficult. Hypersensitivity to mosquito bites may represent a precursor lesion of aggressive NK cell leukemia.

Similar to extranodal NK/T-cell lymphoma, aggressive NK cell leukemia is much more common in Asians than in Caucasians and there is a strong association with EBV. In contrast to extranodal NK/T-cell lymphoma, patients are often younger (mean age, 36 years). They are typically very ill, and present with fever, hepatosplenomegaly, lymphadenopathy, and a leukemic blood picture, sometimes accompanied by hemophagocytic syndrome. Coagulopathy, bleeding tendency and multi-organ failure are common. Serum levels of lactate dehydrogenase and Fas ligand are often markedly elevated. A highly fulminant course is usual, with patients succumbing in days to weeks. Response to chemotherapy is poor, and the curability of the disease with bone marrow transplantation remains unproven.

**Pathology**

In the peripheral blood, there are few to numerous circulating large granular lymphocytes, which range in appearance from normal-looking to immature or atypical (Fig 8). The nuclei are often round, and show condensed or loose chromatin, sometimes with discernible nucleoli. The lightly basophilic cytoplasm contains fine or coarse azurophilic granules. In the bone marrow aspirate smears, loose aggregates or sheets of similar cells are present (Fig 9).

**Immunobiologic Features**

The immunophenotype is indistinguishable from extranodal NK/T-cell lymphoma—CD2, surface CD3/Leu4, cytoplasm CD3ε+, CD56+, and cytotoxic...
markers, except that CD16 is expressed in approximately half of the cases. EBV is almost always demonstrable in the neoplastic cells. The T-cell receptor genes are not rearranged. Similar to extranodal NK/T cell lymphoma, deletion of 6q21-q25 is common, but in addition there is commonly loss of 17p13.

Differential Diagnosis

It is most important not to confuse aggressive NK cell leukemia with T-cell large granular lymphocyte leukemia, which is an indolent condition. The latter occurs in older patients, who are asymptomatic or present with infection, hepatosplenomegaly, pure red cell aplasia, or neutropenia.

Not all NK cell lymphoproliferative disorders are aggressive. The indolent form of NK lymphoproliferative disorder is clinically and morphologically similar to T-cell large granular lymphocyte leukemia, but shows an NK phenotype (surface CD3<sup>-</sup>, CD56<sup>+</sup>/−, and germline T-cell receptor genes). The patients are often asymptomatic, there is no hepatosplenomegaly, CD16 and CD57 are commonly expressed, and there is no association with EBV.

References


Figure 9. Aggressive NK cell leukemia, bone marrow aspirate smear. (A) The marrow is normocellular, and the neoplastic infiltrate is still admixed with many normal hematopoietic cells. (B) Mature-looking large granular lymphocytes (leukemic cells) are seen among the hematopoietic cells.
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