Natural Killer Cell Neoplasms

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Natural killer (NK) cell tumors are an uncommon and heterogeneous group of disorders. The World Health Organization (WHO) classified mature NK cell neoplasms into 2 types: 1) extranodal NK cell lymphoma, nasal type and 2) aggressive NK cell leukemia. The mature NK cell tumors are prevalent in Asia and Central and South America. These tumors show polymorphic neoplastic infiltrate with angioinvasion and/or angiodestruction, cytoplasmic azurophilic granules, CD2-positive (CD21)/CD3-negative (CD32)/cCD3e1/CD561 phenotype, and strong association with Epstein-Barr virus (EBV). Loss of chromosomes 6q, 11q, 13q, and 17p are recurrent aberrations. Although blastic NK cell lymphoma, currently referred to as CD41/CD561 hematodermic neoplasm, also was included in the NK cell lymphoma category in the WHO classification scheme, existing evidence indicates a plasmacytoid dendritic cell derivation as opposed to an NK cell origin. Recently, rare cases of CD561 immature lymphoid tumors have been reported in the literature. These tumors are characterized by blastic appearance, CD32/CD42/CD561/CD132/CD332 phenotype, T-cell receptor and immunoglobulin genes in germline configuration, and no evidence of EBV, suggesting a true immature NK cell derivation. For this article, the authors reviewed the recent concepts and progress in clinicopathologic features, pathogenesis, genetic characteristics, diagnosis, differential diagnosis, treatment approaches, and outcomes of all subtypes of NK cell neoplasms. Cancer 2008;112:1425–36. © 2008 American Cancer Society.

KEYWORDS: natural killer cell lymphoma, natural killer cell leukemia, natural killer cell, natural killer cell tumor, CD56.

Natural killer (NK) cells represent a lineage of non-T lymphocytes and non-B lymphocytes that mediate a major histocompatibility complex, nonrestricted cytotoxicity against tumor cells and bacterial or viral infected cells.1 NK cells constitute <5% of peripheral blood lymphocytes with large granular lymphocyte (LGL) morphology. NK cells are derived in bone marrow from hematopoietic stem cells through the intermediate developmental stages of lymphoid stem cells, bipotential T/NK progenitor cells, and committed NK progenitor cells.2-4 Therefore, NK cells express variably T-lineage-associated antigens (CD2 and/or CD7). By definition, NK cells are surface CD3-negatiave (CD31) and myeloperoxidase (MPO)1, and have germline configuration of T-cell receptor (TCR) and immunoglobulin (Ig) genes.5-7 CD16, CD56, and CD57 are NK-associated antigens. Among these 3 markers, CD56 (neural cell adhesion molecule) is expressed most consistently.8

NK cell neoplasms are a rare and heterogeneous group of disorders with a broad spectrum of morphologic, immunophenotypic, and clinical features. The World Health Organization (WHO) classification encompasses 3 distinct entities: 1) aggressive NK cell leukemiation5; 2) extranodal NK/T-cell lymphoma, nasal type10; and 3) blastic
NK cell lymphoma. In recent years, the conceptual view of NK cell neoplasms has changed as the result of further understanding of the cell derivations and the characteristics of the malignant counterparts. Currently, it is believed that blastic NK cell lymphoma derives from plasmacytoid dendritic cells (pDCs) rather than NK cells. In this article, we review the recent concepts and progress in clinicopathologic features, pathogenesis, cytogenticics, diagnosis, differential diagnosis, treatment strategies, and outcomes of this group of uncommon neoplasms.

Clinicopathologic Categorizations and Features
On the basis of morphology, immunophenotype, functional NK cell activity, and expression of cytotoxic molecules, NK cell neoplasms can be divided into immature and mature categories. 

Precursor NK cell neoplasms and other historically related entities
Precursor lymphoblastic lymphoma/leukemia (LBL) expressing NK cell-associated antigens was recognized first by Sheibani et al. in 1987. Six tumors that expressed CD16 and CD57 in addition to terminal deoxynucleotidyl transferase (TdT), CD2, and CD4 were identified among 38 patients who were screened for LBL. These tumors, as a group, were designated "NK-LBL." Subsequently, CD56 has been recognized as a sensitive marker for NK cells and has become popular for identifying NK cell neoplasms. There are approximately 200 CD56+ hematopoietic neoplasms with immature features reported in the literature using an array of names. However, CD56 is not a NK cell-specific marker and can be expressed by other neoplasms, and it has been difficult to determine whether these tumors are of a true NK cell derivation.

Blastic NK cell lymphoma (CD4+/CD56+ hematodermic neoplasm). Starting in 1994, several individual cases or small series of lymphoblastoid-appearing tumors that expressed CD4 and CD56 and involved the skin, bone marrow, and lymph node were reported that described such tumors as a distinct entity. An NK cell origin was suggested for many of these lesions based on CD56 expression in the absence of markers of T-cell, B-cell, and myeloid lineage-specific antigens. Consequently, these tumors were classified provisionally as blastic NK cell lymphoma in the WHO classification scheme of hematopoietic tumors. However, CD56 is not a specific marker for NK cells. CD4 expression is not typical of NK cell development, and previous attempts to differentiate CD4+/CD56+ tumors into NK cells were not successful. In searching for an alternative to an unlikely NK cell origin, an important discovery of strong expression of surface CD123, a molecule mainly expressed by dendritic cells (DCs) and pDCs, by these CD4+/CD56+ tumors suggested an origin from pDCs. Further progress came with the immunophenotypic and functional evidence that most CD4+/CD56+ tumors are related to the pDC lineage. Immunophenotypically, they share expression of CD4, CD43, CD68, CD123, and human leukocyte antigen-D related (HLA-DR), TCL-1, and the cutaneous lymphocyte associated antigen (CLA). They are negative for the major T-, B-, and myeloid cell differentiation antigens (CD3, CD19, CD20, and MPO). Functionally, Chaperot et al. demonstrated that cultured CD4+/CD56+ tumor cells exhibited features of pDCs like secreting interferon-\(\alpha\), undergoing differentiation to DCs with interleukin-3 stimulation, and being able to stimulate naïve T lymphocytes. More recently, it was demonstrated that a more specific DC marker, blood DC antigen 2 (BDCA-2), is expressed in a subset of these CD4+/CD56+ tumors, which further supports the pDC derivation of this type of tumor. However, some issues remain undecided, such as an association of this type of CD4+/CD56+ tumor with precedent, concurrent, or subsequent myelomonocytic tumors and lacking expression of CD56 on nonneoplastic pDCs. More investigation is required to establish the definitive nature of this type of CD4+/CD56+ tumor.

The term agranular CD4+/CD56+ hematodermic tumor originally proposed by Petrella et al. has the virtues of describing a key diagnostic feature, the most common pattern of clinical manifestation, and the defining immunophenotype. Therefore, it seems suitable as a provisional name to replace the misnomer blastic NK cell lymphoma. In the recent WHO-European Organization of Research and Treatment of Cancer classification of cutaneous lymphoma, the term blastic NK cell lymphoma was replaced with CD4+/CD56+ hematodermic neoplasm.

CD4+/CD56+ immature NK cell tumors (provisional precursor NK cell neoplasms). There are rare cases of CD56+ immature lymphoid tumors reported in the literature that do not match the features of blastic NK cell lymphoma (CD4+/CD56+ hematodermic
Recent advances in the developmental biology of T cells and NK cells indicate that both cell types are derived from a common T/NK cell thymic precursor. Interleukin 15 (IL-15) and transcription factor ID2 are essential for the NK cell lineage to diverge from the T cell lineage. CD94 1A, a distal promoter of the CD94 molecule (an NK cell receptor), is activated only by IL-15. Lin et al. recently reported that CD94 1A is the predominant form expressed in immature NK cells and is expressed in TCR– LBL (NK-LBL) but not in TCR+ LBL (T-LBL). On the basis of the expression of CD94 1A transcripts and negative TCR, those investigators identified 7 patients with LBL of immature NK cell origin (CD94 1A+, TCR–) by studying 21 patients with LBL. It is noteworthy that those NK-LBLs occurred in younger patients and had better outcomes compared with patients who had T-LBL (CD94 1A–, TCR+), and none of the tumors were positive for CD56. Because CD56 is not lineage-specific, it is not surprising that neither its presence nor its absence implies commitment to NK cell lineage. Thus, the use of CD94 1A in conjunction with TCR appears to be more precise for identifying an immature NK cell neoplasm than CD56 alone.

### Myeloid/NK cell leukemia/lymphoma.

In 1994, Scott and colleagues described a distinct form of acute leukemia that shared features of both myeloid and NK cells and designated it myeloid/NK cell acute leukemia. These tumors have the following characteristics: 1) acute promyelocytic leukemia-like morphology; 2) the presence of MPO+/Sudan Black+ cytoplasmic, fine, azurophilic granules; 3) lack of t(15;17) and the resultant PML/RARα fusion transcript; 4) a unique immunophenotype (HLA-DR+/CD34+/CD56+/CD13+/CD33–), and 5) functional NK cell-mediated cytotoxicity in a subset of tumors. Furthermore, those investigators also identified normal CD33+/CD56+/CD16– counterpart cells in peripheral blood from healthy individuals and proposed that this type of acute leukemia may arise from transformation of a precursor cell that is common to the myeloid and NK cell lineage.

Later, Suzuki et al. proposed another disease entity, CD7+ and CD56+ myeloid/NK cell precursor acute leukemia, based on its phenotypic similarity to the myeloid antigen-positive NK cell precursors. This entity is characterized by extramedullary involvement, blastic morphology without cytoplasmic granules and MPO reactivity, CD7+/CD56+/CD33+/CD34+/CD3− phenotype, and poor prognosis. Several more patients with this type of leukemia were reported in the literature after its initial
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<th>Age, y</th>
<th>Race</th>
<th>Organ involvement</th>
<th>Immunophenotype</th>
<th>EBV status</th>
<th>TCR/IgH genes</th>
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<td>ND</td>
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<td>Caucasian</td>
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<td>G/G</td>
<td>43.XXdel(2)(p23), add(3)(p12), del(6)(q23), -9, -11, -13, add(19)(q13.3), -20, add(21)(p11.2), +mar</td>
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<td>Neg</td>
<td>G/G</td>
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EBV indicates Epstein-Barr virus; TCR, T-cell receptor; IgH, immunoglobulin heavy chain; BM, bone marrow; LN, lymph nodes; +, present; -, negative; TdT, terminal deoxynucleotidyl transferase; MPO, myeloperoxidase; HLA-DR, human leukocyte antigen D-related; Neg, negative; ND, not done; TEL, translocation e.t. leukemia; FISH, fluorescence in situ hybridization; NHL, non-Hodgkin lymphoma; BMT, bone marrow transplantation; G, germline; del, deletion; add, addition; mar, marker chromosome; ALL, acute lymphoblastic leukemia; DOD, died of disease; TIA-1, T-cell intracellular antigen; ara-C, cytosine arabinoside; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone. 

*All 5 patients represented in this table were girls or women.
identification. However, because CD56 expression has been identified in approximately 20% of patients with acute myeloid leukemia (AML), the features of immature cytologic appearance and the presence of myeloid antigen without light-microscopic MPO reactivity in this type of leukemia overlap with those in AML with minimal differentiation (French-American-British classification, AML-M0). Because there were only a small number of patients studied and the terminology of CD7\(^+\) and CD56\(^+\) myeloid/NK cell precursor acute leukemia has not been recognized widely, currently, it is believed that this subset of leukemia falls into the category of AML-M0.\(^{60}\) Comparing CD7\(^+\)/CD56\(^-\) M0 with other M0 (CD7\(^-\)/CD56\(^-\), CD7\(^-\), or CD56\(^-\)), Suzuki et al. observed a significantly younger age of onset, no 5q abnormalities, more frequent extramedullary involvement, and worse disease-free survival in the patients with CD7\(^+\)/CD56\(^-\) M0 disease. Multivariate analysis demonstrated that the CD7\(^+\)/CD56\(^+\) phenotype was a significant and an independent poor prognostic factor for patients with AML-M0.\(^{60}\) Additional clinicopathologic studies are needed to elucidate whether this subtype of acute leukemia represents a distinct entity.

**Mature NK cell neoplasms**

The distinct nature of NK cell tumors was acknowledged formally at the Hong Kong workshop in 1996.\(^{15}\) Several clinicopathologic entities have been recognized.

**Extranodal NK cell lymphoma, nasal type.** Both nasal and nasal-type (extranasal) NK cell lymphomas are more prevalent in Asia, Mexico, and Central and South America\(^{10,61}\) and are characterized by extranodal presentation and an aggressive clinical course. Because nasal NK cell lymphoma and extranasal NK cell lymphoma share the same histology, the WHO classification groups both nasal NK cell lymphoma and extranasal NK cell lymphoma in the same category.\(^{10}\) However, nasal and extranasal NK cell lymphomas have different clinical manifestations, treatment approaches, and prognoses.\(^{61}\)

Nasal NK cell lymphomas refer to tumors that occur in the nose and the upper aerodigestive tract.\(^{62-67}\) They are the most common type among primary lymphomas of the nasal cavity.\(^{8}\) Men are affected more than women, and the median age at diagnosis in the fifth decade. The location is primarily in the midline and includes the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx. Common symptoms include nasal discharge, nasal obstruction, purulent rhinorrhea, epistaxis, and local swelling of the nasal bridge. In patients with more advanced disease, there may be erythema, swelling of the face, proptosis, and impairment of extracocular movement.\(^{8,62,67}\) The tumors may be destructive, leading to the highly characteristic midline perforation.

Extranasal NK cell lymphomas represent the counterpart of nasal NK cell lymphomas and involve any other part of the body. Men are affected predominantly, and the median age of presentation is in the fifth decade. Primary sites of involvement include the skin, gastrointestinal tract, salivary glands, spleen, and testis.\(^{7}\) The diagnosis of extranasal NK cell lymphoma requires the exclusion of nasal involvement at presentation. A nasal panendoscopy with random biopsies should be performed to rule out occult involvement.\(^{61}\) Patients with extranasal NK cell lymphoma are more likely to exhibit a more advanced stage of disease with significantly higher International Prognostic Index and lactate dehydrogenase levels and with significantly lower hemoglobin and platelet levels compared with patients who have nasal NK cell lymphoma.

The histologic features are similar regardless of the involved sites. Mucosal sites often show ulceration. The lymphomatous infiltrate is diffuse (Fig. 2 [Top]). An angiocentric and angiodestructive growth pattern with associated fibrinoid changes in the blood vessels is observed frequently. Coagulative necrosis and apoptosis are common. In most patients, the tumor is composed of medium-sized cells or a mixture of small and large lymphoid cells with moderate amount of cytoplasm, irregular or elongated nuclei, granular or vesicular chromatin, and inconspicuous, small nucleoli (Fig. 2 [Bottom]). Mitotic figures are found easily. In Giemsa-stained touch preparations, azurophilic cytoplasmic granules commonly are detected. There may be admixture of inflammatory cells consisting of small lymphocytes, plasma cells, histiocytes, and eosinophils in some patients.\(^{10}\)

**Aggressive NK cell leukemia.** Aggressive NK cell leukemia was characterized first by Imamura et al.\(^{68,69}\) This is a catastrophic, systemic disease and also is more prevalent in Asians than in Caucasians.\(^{9}\) It is characterized by the presence of neoplastic NK cells mainly in the peripheral blood and bone marrow and by a rapidly progressive clinical course. There is an equal sex incidence in men and women. The disease typically affects young to middle-aged adults with a median age in the third decade. Patients usually are very ill at presentation with fever, systemic symptoms, liver dysfunction, and hepatosplenome-
gally sometimes accompanied by systemic lymphadenopathy. In contrast to extranasal NK cell lymphoma, skin lesions are uncommon. Some patients may have disease that is complicated by a reactive hemophagocytic syndrome.8 Severe anemia and thrombocytopenia are common because of bone marrow involvement or active hemophagocytosis.70 The clinical progression is inexorable despite treatment, and most patients survive for only days to weeks.

Morphologically, the leukemic cells in aggressive NK cell leukemia are slightly larger than normal LGLs. There is an ample amount of pale or slightly basophilic cytoplasm that contains fine or coarse azurophilic granules. Nuclei show slightly immature chromatin pattern and inconspicuous or distinct nucleoli (Fig. 3 [Top]). Hemophagocytosis is common (Fig. 3 [Bottom]). In tissue sections, the neoplastic infiltrate is diffuse, destructive, and permeative. The lymphoid cell population often appears monomorphous.8 Necrosis, apoptosis, angioinvasion, and angiodestruction are common findings.7–9,71–73

Chronic NK cell lymphocytosis. Chronic NK lymphocytosis is defined as chronic expansion of mature-looking NK cells (≥600/μL) in the peripheral blood for ≥6 months.18,74,75 The median age of 16 patients in 1 study was 60.5 years (range, 7–77 years).18 Most patients present with a chronic, indolent course.18 Associated severe neutropenia, pure red cell aplasia,
vasculitic syndromes, and fever with undetermined origin are reported in some patients.76,77 Occasionally, patients present with a slowly progressive increase of peripheral blood NK cells and with organ involvement. These cases may be labeled chronic NK cell leukemia, but the clonality of the NK cells must be proven. In rare cases, the disease transforms to aggressive NK cell leukemia.18 Cytologically, the circulating neoplastic cells show LGL morphology. There is a moderate amount of pale cytoplasm that contains azurophilic granules (Fig. 4).76,77

All subtypes of mature NK cell neoplasms share a typical immunophenotype of CD2+/CD3-/cCD3+/CD56+/MPO- and are cytotoxic molecule-positive.9,10,76-79 The TCR gene typically is in germ-line configuration. Another characteristic feature of mature NK cell neoplasms, in contrast to immature NK cell neoplasms, is the strong association with EBV.79-81 Nasal NK cell lymphoma is associated almost invariably with EBV infection (Fig. 5). Most patients with aggressive NK cell leukemia, extranasal NK cell lymphoma, and chronic NK cell lymphocytosis also are positive for EBV. A large comprehensive study of NK cell neoplasms in Japan by Oshimi et al. indicated that EBV was detected in all patients with nasal NK cell lymphoma (101 of 101 patients), in 22 of 25 patients with extranasal NK cell lymphoma, in 10 of 12 patients with aggressive NK cell leukemia, and in 6 of 7 patients with chronic NK cell lymphocytosis.79 Analysis of the terminal repeat region of the EBV genome indicated that the virus is in a clonal episomal form. This finding, in addition to providing an indirect proof of the clonal nature of the lymphoid proliferation, also implies that the EBV may play an etiologic role in mature NK cell neoplasms rather than being a bystander.8,82,83

Conventional cytogenetic analysis of mature NK cell neoplasms is difficult, partly because of necrosis and the scarcity of specimens.8 A study by Wong et al.84 demonstrated that 77% (23 of 30) of patients with mature NK cell neoplasms had abnormal clonal karyotypes. Most patients exhibited pseudodiploidy (57%; 13 of 23 patients), hypodiploidy (<46 chromosomes) was identified in 3 of 23 patients (13%), and 7 patients (30%) were hyperdiploid (>46 chromosomes).84 Abnormalities of chromosome 6 were the most frequent findings. A common deletion on 6q in the target area 6q21-25 has been defined by fluorescence in situ hybridization and molecular genetic methods.85,86 Comparative genomic hybridization and loss of heterozygosity studies have indicated that, in addition to deletion of 6q21-25, deletions in chromosome 11q, 13q and 17p also were present.8,87,88 The putative genes implicated in these deletions have not been identified.

**Diagnostic Criteria and Differential Diagnosis**

Diagnosis of NK cell neoplasms requires the integration of clinical presentation, morphology, immunophenotype, and genotype. Expression of at least 1 NK cell marker (CD56, CD16, or CD57); lack of expression of surface CD3, B-cell antigens (CD19 and CD20), MPO, and other lineage markers; and/or TCR and Ig genes in germline configuration in tumors are
TREATMENT AND PROGNOSIS

**CD4-CD56* IMMATURE NK CELL TUMORS (PROVISIONAL PRECURSOR NK CELL NEOPLASMS)**

A standard treatment protocol for immature NK cell neoplasms has not been established because of the paucity of patients. Chemotherapy, non-Hodgkin lymphoma, or acute lymphoblastic leukemia (ALL) therapeutic strategies were the most common. However, the overall outcomes were dismal. Two pediatric patients (Patients 1 and 3) who received non-Hodgkin lymphoma therapy and ALL therapy, respectively, followed by allogeneic hematopoietic stem cell transplantation (HSCT) achieved complete remission for 3 years. Three other patients (Patients 2, 4, and 5) who did not undergo bone marrow transplantation died of disease between 6 months and 35 months. Further studies are necessary to determine whether increased survival can be obtained with aggressive chemotherapy followed by HSCT. It is possible that allogeneic HSCT could provide additional graft versus leukemia/lymphoma benefit. The age of disease onset also appears to be an important prognostic factor. Two patients who were in remission were pediatric patients (Patients 1 and 3). This observation is consistent with other studies. In the study on CD56+ blastic tumors by Suzuki et al., patients aged >30 years had worse outcomes than patients aged <30 years.

**MATURE NK CELL NEOPLASMS**

The clinical outcome of patients with nasal NK cell lymphoma is variable. Most observational studies have demonstrated consistently that radiotherapy is superior to chemotherapy alone in patients with stage I/II disease. Some patients with early-stage disease are cured by radiation therapy. It has been demonstrated that radiotherapy, either as initial treatment or as part of the chemotherapy regimen, is the single most important key to a successful outcome. However, some patients with early-stage disease have early local or systemic recurrences and die of disease. For patients with stage III/IV disease, chemotherapy is the mainstay of treatment. In several published series, the median survival of patients with advanced-stage disease was approximately 12 months.

Extranasal NK cell lymphomas are clinically aggressive. Because the disease may be disseminated, chemotherapy usually is the initial choice of treatment. The response is poor, and most patients die within 6 months after diagnosis. The long-term remission rate with allogeneic HSCT reportedly is <10%. Aggressive NK cell leukemia is a catastrophic disease with an almost uniform mortality. A few patients have a clinical response with conventional chemotherapy, although the response typically is transient. Survival is measured in days to weeks. Allogeneic HSCT reportedly results in short-term remission in a few patients. To our knowledge, no survival >1 year has been recorded.

Patients with chronic NK cell lymphocytosis usually have an indolent clinical course and respond to immunosuppressive therapy. Because of the potential long-term side effects of immunosuppressive therapy, limiting specific therapy only to patients with symptomatic disease is recommended.

**NEW THERAPEUTIC STRATEGIES**

Because of the inferior outcomes with current therapies for NK cell neoplasms, novel approaches must be considered to improve survival. Chemotherapeutic agents currently being tested in cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) provide possible new agents to consider for NK cell treatment protocols. Examples of such agents with efficacy in CTCL and/or PTCL include gemcitabine and liposomal doxorubicin as well as the purine analogs, such as fludarabine and cladribine. Furthermore, the use of histone deacetylase inhibitors (depsipeptide and vorinostat) is being tested in CTCL. Monoclonal antibodies like alemtuzumab have some activity in PTCL and are being investigated in combination with other therapy. Although no NK cell-specific antibodies are under active development, the future availability of such antibodies may offer novel treatment options. In addition, a greater understanding of the signaling pathways activated in NK cell neoplasms could make other biologically targeted agents potential candidates for inclusion in NK cell treatment protocols.

**SUMMARY**

Overall, NK cell tumors are an uncommon, aggressive, and heterogeneous group of disorders. Precursor NK cell lymphoma/leukemia is an extremely rare clinicopathologic entity that is characterized by blastic morphology, expression of CD3-CD4-CD56+CD13-CD33- immunophenotype with predominant CD94 1A expression, TCR germline configuration, and lack of
<table>
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<th>Variable</th>
<th>Precursor NK cell neoplasms (provisional)</th>
<th>CD4⁺CD56⁺ hematodermic neoplasm</th>
<th>Myeloid/NK cell precursor acute leukemia (CD7⁺CD56⁺ M0)</th>
<th>Myelomonocytic/monocytic tumors</th>
<th>T-LBL</th>
<th>Extranodal NK cell lymphoma, nasal type</th>
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<tr>
<td>Cell origin</td>
<td>Immature NK cell</td>
<td>Plasmacytoid dendritic cell</td>
<td>Myeloid precursor</td>
<td>Myeloid and/or monocytic cell</td>
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<td>BM, extramedullary sites</td>
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<td>TCR gene</td>
<td>Germline</td>
<td>Germline</td>
<td>Germline</td>
<td>Germline</td>
<td>Rearranged</td>
<td>Germline</td>
<td>Germline</td>
</tr>
<tr>
<td>EBV</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NK cell indicates natural killer cell; T-LBL, T-cell lymphoblastic lymphoma leukemia; BM, bone marrow; LN, lymph node; -; negative; +, positive; MPO, myeloperoxidase; BDCA-2, blood dendritic cell antigen 2; TCR, T-cell receptor; EBV, Epstein-Barr virus.
EBV positivity. Extranodal NK cell lymphoma, nasal type; aggressive NK cell leukemia; and chronic NK cell lymphocytosis originate from mature NK cells and have distinct geographic distribution. A consistent association with EBV infection suggests that the virus may be of pathogenetic significance in these subtypes. Further studies are needed to define the molecular pathogenesis and biologic markers that aid in the diagnosis of NK cell neoplasms. Furthermore, clinical trials and/or multi-institutional cooperation are necessary to define the optimal therapeutic strategies that will lead to better outcomes in patients with this uncommon group of disorders.

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