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REVIEW

Leukemia and Lymphoma of Natural Killer Cells

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Malignant hematolymphoid disorders arising from NK cells have become widely recognized over the past decade. The two forms of NK-cell malignancy, aggressive NK-cell leukemia (ANKL) and extranodal NK-cell lymphoma of nasal type (ENKL) are both characterized by the proliferation of tumor cells with an NK-cell like immunophenotype. ANKL usually presents with bone marrow tumor cells accompanied by circulating leukemic cells, and hepatosplenomegalay is a common clinical feature. ENKL most frequently affects the nasal or paranasal regions, with cutaneous involvement also being common. Approximately 70 percent of ENKL present with localized tumor cells, and follow an indolent clinical course, but, in advanced cases, tumors rapidly expand and are frequently fatal. Tumor cells from both ANKL and ENKL are surface $CD3^-$ and $CD56^+$ but differ in their expression of CD16. Epstein-Barr virus (EBV) is found in most cases of NK-cell leukemia/lymphoma, suggesting an oncogenic role, but patients may have biclonal or polyclonal populations of malignant cells based on differential EBV genome incorporation. NK-cell neoplasms are frequently resistant to chemotherapy due to p-glycoprotein expression and associated multidrug resistance. The prognoses of both localized and advanced stages of NK-cell malignancies are worse than most other lymphoid malignancies, but studies are currently underway to assess the safety and efficacy of novel chemoradiotherapy regimens for the treatment of these neoplasms.

INTRODUCTION

The classification of lymphoid neoplasms has changed much in recent years. In the Working Formulation[1], lymphocyte lineage was not a factor in neoplasm classification, but the Revised-European-American Classification for Lymphoid Neoplasms (REAL Classification) once again adopted these standards, originally in place in the Kiel Classification[2,3]. However, neoplasms arising from NK-cells were not correctly defined in the REAL Classification, and inclusion of NK-cell neoplasms did not occur until the new World Health Organization (WHO) Classification[4]. In addition to aggressive NK-cell leukemia (ANKL) and extranodal NK-cell lymphoma, nasal type (ENKL), which are listed in the WHO Classification, there are several provisional categories of NK-cell neoplasms (Table 1). In this review, I describe the history of NK-cell neoplasms and the future prospects for disease management and treatment for these malignancies with extremely poor prognoses.

Definition of NK-cells

NK-cells were first recognized as a functional subset of lymphocytes mediating major histocompatibility complex-nonrestricted cytotoxicity[5]. NK-cells are morphologically large granular lymphocytes (LGLs), with germline T-cell receptor (TCR) and immunoglobulin gene configurations. Additionally, they are surface CD3 (sCD3)-negative and CD56-positive[6]. Based on these results, NK-cells are considered as the third lineage of lymphocyte distinct from T- and B-cells. Currently, two types of NK-cells are now proposed, cytotoxic NK-cells and immunoregulatory NK-cells[7]. It remains unclear whether these are distinct NK-cell subtypes or if differential cytokine exposure causes phenotypic interchangeability. During development, NK-cells arise from T/NK bi-potential common progenitors[8,9]. Therefore, NK-cells are functionally and phenotypically very similar to T-cells, particularly cytotoxic T-cells; this renders the differential diagnosis of NK-cell neoplasms difficult.

Table 1. List of NK-cell neoplasms

Disease	Abbreviation
1. Precursor NK-cell neoplasms	
(1) Myeloid/NK cell precursor acute leukemia	MNKL
(2) Blastic NK cell lymphoma	BNKL
2. Mature NK-cell neoplasms	
(1) Aggressive NK-cell leukemia	ANKL
(2) Extranodal NK-cell lymphoma, nasal type	ENKL
(3) Chronic NK-cell lymphocytosis*	CNKL

* Uncertain malignant potential.

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Recognition of NK-cell leukemia and lymphoma

Leukemia of NK-cells was first described by Fernandez *et al*. and Koizumi *et al*. in 1986 as "aggressive NK-cell leukemia (ANKL)" (Fig. 1)[10,11]. Both groups demonstrated NK-activity and IL-2 responsiveness in the leukemic cells and concluded the neoplasms were of NK-cell origin. Imamura *et al*. also identified leukemia of NK-cell origin, but their findings were not published for several years[12]. Based on cellular morphology, these malignancies were considered a type of LGL leukemia[13], but we now know that this classification encompasses a very heterogeneous collection of diseases. Alternative names for ANKL were aggressive LGL leukemia, non-T LGL leukemia, and NK-LGL leukemia, and in the REAL Classification this disease entity was given the new category LGL leukemia, NK-cell type (Fig. 1)[3]. However, this categorization emphasized the morphological features of the leukemic cells, rather than cell origin. Chronic T-LGL leukemia, also classified as an LGL leukemia, exhibits the same cellular morphology as ANKL, but dramatically differs in cell origin, phenotype, genotype, function and clinical course, and these differences are summarized in Table 2[13,14]. These differences led to the recognition of ANKL as a separate entity from T-LGL leukemia in the WHO Classification[4].

Lymphoma of NK-cells was originally incorrectly identified as T-cell lymphoma of nasal origin because of the phenotypic similarity of T-cells and NK-cells[15]. Lethal midline granuloma was a disease of undetermined neoplastic significance occurring in the mid facial area, and biopsied specimens from these lesions exhibited marked necrosis with inflammatory changes. Ishii *et al*. first recognized the presence of tumor cells expressing CD3 in this lesion and termed this disease "nasal T-cell lymphoma"[15]. Further characterization of this tumor revealed angiocentric infiltration of tumor cells, and the terminology of "angiocentric T-cell lymphoma" was proposed[16-18]. In the REAL Classification, this type of nasal lymphoma was considered an angiocentric lymphoma, together with pulmonary lymphomatoid granulomatosis of B-cell origin, based on morphological features[3]. However, Suzumiya *et al*. demonstrated that tumor cells of this nasal lymphoma express cytoplasmic CD3 and CD56, but not T-cell receptors, suggesting their NK-cell origin[19]. On November 11-14, 1994, a workshop on NK-cell lymphomas was held in Hong Kong[20]. At this meeting, tumor angiocentricity was not considered an absolute characteristic of nasal NK-cell lymphomas, and similarities with non-nasal NK-cell lymphomas were confirmed. Thus, the nomenclature of "nasal and nasal-type T/NK-cell lymphoma" was employed. In the WHO Classification, the extranodal origin of this lymphoma was emphasized, and the terminology "extranodal NK/T-cell lymphoma (ENKL), nasal-type" was adopted[4].

Clinical characteristics of aggressive NK-cell leukemia

ANKL is characterized by the systemic proliferation of NK-cells, with a highly aggressive clinical course. It

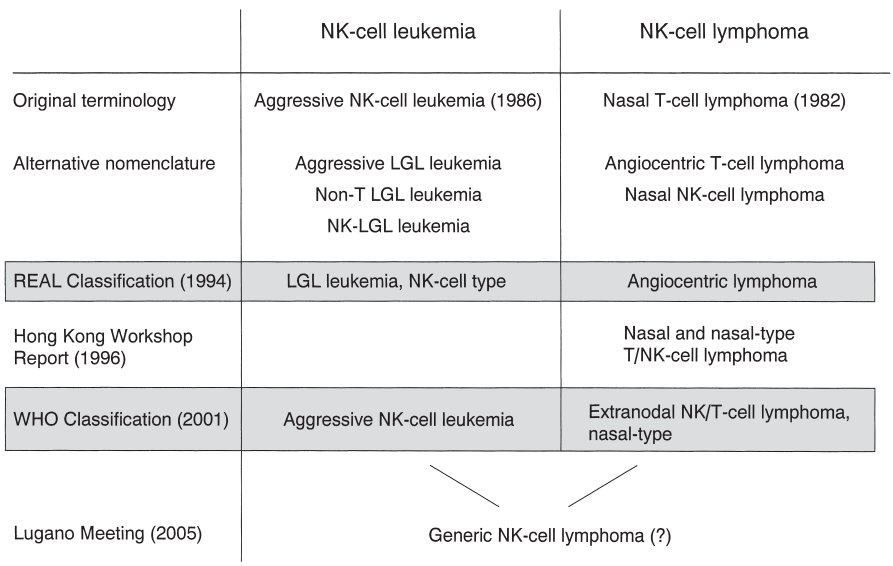

Fig. 1. History of NK-cell leukemia/lymphoma nomenclature.
The classification and nomenclature of NK-cell leukemia and lymphoma have changed over time, and different classification schemes have been proposed. Aggressive NK-cell leukemia and extranodal NK-cell lymphoma, nasal-type are separate entities in the new WHO Classification, and the "generic NK-cell lymphoma" category was recently proposed to integrate these two diseases by Weisenbuerger in the 9th International Conference on Malignant Lymphoma 2005.

Table 2. Phenotypic profile of NK-cell neoplasms and other related/CD56$^+$ T-cell lymphomas

	Aggressive NK-cell leukemia	Extranodal NK-cell lymphoma	Hepatosplenic T-cell lymphoma	Enteropathy-type T-cell lymphoma	T-LGL leukemia
CD2	+	+	+	+	+
sCD3	−	−	+	+	+
cyCD3	+	+	+	+	+
CD4	−	−	−	−	−
CD5	−	−	+/−	−	+
CD7	+/−	+/−	+/−	+	+
CD8	+/−	+/−	+/−	+	+/−
CD16	+(/−)	−	+/−	−	−
CD43	+	+	+	+	+
CD45RO	+	+	+	+	+
CD56	+	+	+(/−)	+/−	−
CD57	−	−	−(/+)	−	+
TCR	−	−	+	+/−	+
Granzyme B	+	+	+/−	+	−
TIA-1	+	+	+	+	−
EBV	+	+	−	−	−

accounts for less than 1% of lymphoid malignancies in Japan[21], and is also rare in Hong Kong, Korea and Taiwan (personal communications). The NK-cell Tumor Study Group in Japan reported the largest series in the literature, examining 22 patients[22]. When data from several reports are considered together, ANKL predominantly occurs in younger patients with a median age around 40 years without any sex predilection[12,14,22-32]. Patients frequently present with B-symptoms, such as fever, night sweat or weight loss, and hematological findings are consistent with leukemia, including circulating and bone marrow leukemic cells, neutropenia, anemia and thrombocytopenia. Hepatosplenomegaly frequently occurs, but does not affect all patients. Cutaneous or central nervous system involvement is uncommon. Interestingly, hypersensitivity to mosquito bites is sometimes a preceding feature of NK-cell leukemia, particularly in younger patients[33-35]. Additionally, leukemic progression of nasal NK-cell lymphoma was also reported[36]. Leukemic cells exhibit a LGL morphology, surfaceCD3$^-$ CD2$^+$ CD56$^+$ immunophenotype, and germline configurations of T-cell receptor genes[22,23,29]. CD16 and cytoplasmic CD3 are positive in many cases. Expression of CD122 and the lack of CD25 suggest ANKL cells originate as cytotoxic NK-cells[22], rather than immunoregulatory NK-cells[7]. As with ENKL of nasal type, tumor cells are Epstein-Barr virus (EBV) positive[22-24,27,29-31]. Although no recurrent cytogenetic abnormalities have been identified, alterations in chromosome 7 occur relatively frequently in ANKL[22]. Chemotherapy for acute leukemia or aggressive lymphoma is not highly effective, resulting in poor prognosis for this disorder. Resistance to chemotherapy is likely mediated by p-glycoprotein, a product of *MDR1* gene[37], that is expressed in this type of lymphoma[38-40]. Most affected patients die within 2 years, many within 6 months after diagnosis[22,23].

Clinical characteristics of extranodal NK-cell lymphoma, nasal type

ENKL is characterized by extranodal involvement, particularly the nasal/paranasal area, and is referred to as "nasal NK-cell lymphoma" in this situation. ENKL is rare in Western countries, but is more frequent in East Asia and Central and South America[41-46]. It represents 3.3% of all non-Hodgkin's lymphoma in Japan[21], 6% in Hong Kong[47], 8% in Korea[48], and 5% in Taiwan[49]. ENKL predominantly occurs in middle-aged patients, and it is significantly more prevalent in men. This type of lymphoma, particularly advanced-stage cases, is associated with hemophagocytic syndrome, and some patients develop the sudden onset of pancytopenia or multi organ failure[41-45]. Histopathologically, the lymphoma cells are polymorphous and show an angiocentric growth pattern, with subsequent vascular obstruction and prominent necrosis. The immunophenotype of tumor cells resembles that of NK-cells (surfaceCD3$^-$ cytoplasmicCD3ε^+ CD56$^+$) in

most cases[19,50-52], but, in rare circumstances, is more consistent with a T-cell phenotype. Most ENKL cells also express cytotoxic granule-associated proteins, such as perforin, granzyme B, TIA-1, and granzyme M[53-59]. Increased expression of Fas-ligand is commonly seen in ENKL, but this is non-specific and seen in a number of aggressive lymphomas[55,60-62]. NK inhibitory receptors, such as CD94 or NKG2A are also expressed in NK-cell neoplasms, but such expression is not uniform or consistent[63-67]. However, expression of CD94 is reported to confer a better prognosis in ENKL[67]. EBV is found in the tumor cells in virtually all cases, and ENKL, nasal-type is now regarded as an EBV-related neoplasm[68-70]. Deletions of the long arm of chromosome 6 are frequently seen in ENKL[71,72], but this abnormality is also commonly seen in other types of lymphoma[73,74]. Approximately 70% of ENKL patients present with limited stage I or II disease[52,75-82]. In addition to the paranasal area, tumors frequently occur in the skin and soft tissue[29,83-90]. Regional lymph nodes may be involved, but restriction to nodal disease is extremely rare[91]. The clinical course of NK-cell lymphoma varies with the clinical stage. Patients with limited stage disease (usually nasal disease) typically have an indolent course with tumor restriction to the original site, but others suffer rapid progression to systemic dissemination often accompanied by hemophagocytosis or disseminated intravascular coagulation. Radiotherapy is effective in the treatment of ENKL, but, as with ANKL, chemotherapy is of limited effectiveness due to the expression of p-glycoprotein[37-40], which mediates the active transport of anthracyclines and vinca alkaloids. Therefore, radiotherapy is typically undertaken in patients with limited stage diseases[92-101], with or without subsequent chemotherapy. No effective therapies exist for advanced cases, however.

Putative precursor NK-cell neoplasms

At the Hong Kong Workshop for Extranodal T/NK-cell lymphoma in 1994, Drs. Suchi and Mori presented two previously unrecognized forms of CD56-positive lymphoma[20]. These cases were characterized by unusual skin involvement, blastic morphology, $sCD3^{-}$ $CD56^{+}$ TdT^{+} phenotype without B-cell markers, and the lack of Epstein-Barr virus (EBV), and the nomenclature of "blastic NK-cell lymphoma" was assigned to this disease[20]. There are several reports of this type of lymphoma, which were not specifically diagnosed due to their unusual phenotype that is not consistent with a clear cellular origin[87-89,102-108]. These tumors were hypothesized to originate from precursor NK-cells due to their phenotypic similarity (Fig. 2), but many blastic NK-cell lymphoma (BNKL) express CD4[87-89,104-108]. Recently, many clinicopathologic differences between CD4-positive and -negative BNKL have been described, suggesting that these two subgroups constitute distinct diseases[109,110]. However, it remains unclear whether CD4 expression or anatomic location (i. e., cutaneous vs. non-cutaneous) should be the primary factor determining categorization. Occasionally, leukemic cases of

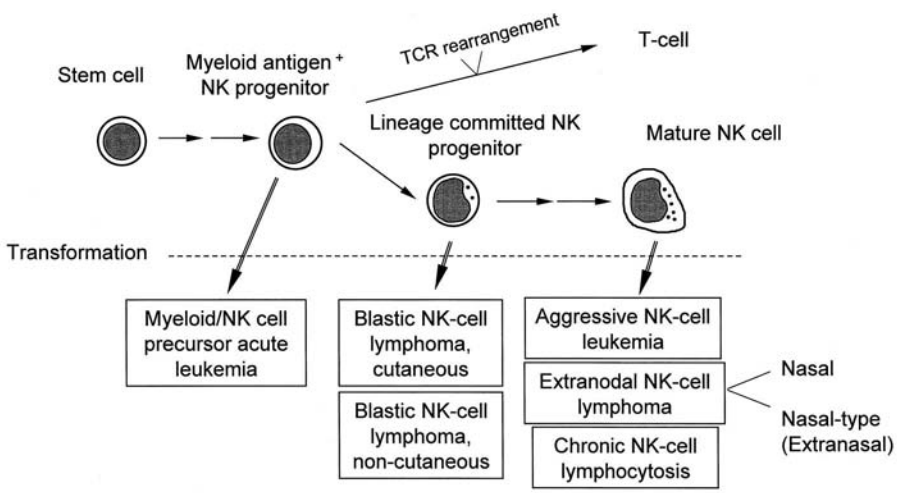

Fig. 2. Differentiation pathway of NK-cells and corresponding NK-cell neoplasms.

NK-cells differentiate from stem cells through the myeloid antigen positive NK/ T bi- potential progenitor and the lineage committed progenitor. The myeloid/NK cell precursor acute leukemia originates from the myeloid antigen positive progenitor, and blastic NK-cell lymphoma are derived from a relatively mature, NK-cell lineage committed progenitor. Mature NK-cell neoplasms, aggressive NK-cell leukemia, extranodal NK-cell lymphoma of nasal and extranasal origin, and chronic NK-cell lymphocytosis arise from transformed mature NK-cells.

this tumor have been reported[111-116], but no prominent clinicopathologic differences between the leukemic and lymphomatous types have been identified[110]. Several groups have proposed that $CD4^+$ BNKL arise from the precursors of plasmacytoid dendritic cells (pDCs)[117,118] or plasmacytoid monocytes[119], on the basis of CD123 expression and interferon production by the tumor cells. However, pDCs are normally present in lymph node and are rare in the skin. Additionally, CD56 is not expressed on normal pDCs[120,121] except for a very minor population[122,123], and CD123, which is expressed on a variety of normal and malignant hematopoietic cells is not a specific marker for pDCs[124,125]. $CD4^{+/-}$ $CD56^-$ $CD123^+$ leukemia/lymphoma with pDC features is the real pDC malignancy[126,127]. Thus, the true origin of BNKL needs further studies.

In 1997, another type of immature CD56-positive hematologic tumor was identified as "myeloid/NK cell precursor acute leukemia" (Fig. 2)[128]. This leukemia was characterized by pronounced extramedullary involvement, immature lymphoblastoid cellular morphology without myeloperoxidase reactivity, a $CD7^+$, $CD33^+$, and $CD56^+$ phenotype, myeloid chemosensitivity and poor prognosis. These cases were classified as AML M0 according to the FAB classification[129,130], and were distinct from CD56-positive tumors of myeloid/NK cell acute leukemia with mature promyelocytoid morphology[131], as well as BNKL[99]. However, this form of leukemia was later found to exhibit different clinical characteristics from $CD7^-$ or $CD56^-$ AML M0[132], and was thus a distinct disease entity among AML subclasses.

These CD56-positive immature leukemia/lymphomas are included in the NK-cell Tumor Study Group classification scheme, but have not yet been shown to originate from precursor NK-cells. Strictly, these diseases should be regarded as CD56-positive immature hematolymphoid tumors, but the phenotypic similarities to NK-cell precursors may facilitate our understanding of these tumors. The NK-cell Tumor Study Group has proposed a provisional classification scheme of NK-lineage malignancies including these ill-defined diseases[44,133].

Other CD56-positive malignancies to be differentially diagnosed

CD56 is not a specific NK-cell marker, and several CD56-positive tumors have been identified (Table 3). In acute myeloid leukemia (AML), CD56 is expressed in approximately 20% of cases, particularly those of the monocytic lineage[134-136]. Although AML is a heterogeneous disease, the expression of CD56 suggests a poor prognosis in AML in general[137-139], or for several specific subtypes[140-144]. CD56 was first reported as a prognostic factor for patients with AML M2 with the t(8;21)(q22;q22) translocation[140], but this has not been verified by other groups. In the meantime, several groups have shown the prognostic significance of CD56 expression in acute promyelocytic leukemia with the t(15;17)(q22;q21) translocation[141-144]. Differentiation of nonnasal NK-cell lymphomas occurring in the skin or soft tissue from extramedullary AML is particularly important for prognostic and therapeutic decisions. However, in acute lymphoblastic leukemia CD56 expression is relatively rare[134,145-147].

CD56 is also expressed in a subset of T-cells, as well as 5-20% of peripheral T-cell lymphomas[148-153]. Some conditions have been described as "NK-like T-cell lymphoma"[86,90,154,155], but this label does not accurately reflect the T-lymphocyte origin of this lymphoma and was therefore not included in the current WHO classification[156]. Because NK-cell and T-cell lymphomas share the $cyCD3^+$ $CD56^+$ phenotype, and the expression of sCD3 and cyCD3 is usually indistinguishable on paraffin sections, appropriate diagnosis is

Table 3. CD56-positive tumors other than NK-cell lineage

Category	Frequency	Subtype	Significance of CD56 expression
Acute myeloid leukemia	20%	Monocytic leukemia (FAB M4/M5)	
		M2 with t(8;21)	Possible prognostic factor
		Acute promyelocytic leukemia	Prognostic factor
Peripheral T-cell lymphoma	5-10%	Anaplastic large cell lymphoma	Possible prognostic factor
		Peripheral T-cell lymphoma, unspecified	Not prognostic
Multiple myeloma	50-70%		Not prognostic
Small round cell tumor	Most cases	Neuroblastoma	
		PNET	
		Ewing sarcoma	
		Wilms tumor	
		Rhabdomyo sarcoma	
		Small cell lung cancer	

essential[50,51,157]. Cells derived from hepatosplenic T-cell lymphoma and enteropathy-type T-cell lymphoma are usually CD56 positive (Table 2)[150,158-161] but other T-cell lymphomas do not display consistent CD56 expression. On the other hand, CD56 expression is a strong prognostic factor for anaplastic large cell lymphoma[152], but not peripheral T-cell lymphoma, unspecified[153].

As CD56 is a neural cell adhesion molecule, it is also expressed in non-hematologic tumors, including neuroectodermal tumors. Its expression has been documented in neuroblastoma[162,163], PNET[162], Ewing sarcoma[162], Wilms tumor[164], rhabdomyosarcoma[162], malignant schwannoma[163] and small cell lung cancer[165,166]. As these tumors can also exhibit a small round morphology, proper exclusion of these tumors from the differential diagnosis is essential.

Genetic features and oncogenes

Currently, no genetic abnormalities specific for NK-lineage neoplasms have been identified. Deletion of the long arm of chromosome 6 was reported to be the most frequent cytogenetic aberration[71,72], but no target or tumor suppressor genes have been identified in this region to date[167-169]. Additionally, no consistent oncogenes or tumor suppressors have been identified for NK-cell lymphoma (Table 4). Homozygous deletion of p15 and p16/p14 were identified in approximately 30% of the cases studied[170,171], and mutation of the *FAS* gene[172,173] and methylation of p73[174], SHP1[175], hMLH1[176], p16[176], and RARβ[176] have been identified in more than half of the cases. Mutation of β-catenin[177-179] and methylation of p21 and p15 were observed less frequently[177,180], but mutation of *N/K/H-RAS* and *N/c-MYC* genes were found in only a small minority of cases[171,177-179]. Ethnicity also affects genetic alterations in NK-cell lymphoma including differences between Japanese and Chinese patients for p73[174,180], p53[178,179,181], and c-Kit[182] alterations. A more precise characterization of the genetic changes associated with NK-cell lymphoma, as well as any role for EBV infection, needs further clarification.

Complementary genetic hybridization (CGH) has been used to investigate genetic aberrations in NK-cell lymphoma[175,183-186]. These studies identified the gain of 1p, 6p, 11q, 12q, 17q, 19p, 20q and Xp, and the loss of 6q, 11q, 13q and 17p in several different samples, but several differences were also identified between the cases examined. Recently, an array-based CGH study was performed and identified new gain/loss regions, which could not be identified using conventional CGH analyses[187]. This study also demonstrated clear genetic difference between ANKL and ENKL, suggesting that these are two distinct disease entities. This data supports the clinicopathologic features identified between ANKL and ENKL[188]. These differences may represent differences in ENKL between localized and advanced cases, but further studies are needed to clarify this issue.

Epstein-Barr virus (EBV)

In most mature NK-cell leukemias and lymphomas, clonal EBV proliferation has been found in tumor cells[23,24,41-44,68,189,190]. Most tumors are associated with EBV with latency II with the occasional absence of LMP-1[30,191,192]. Binding of EBV to target cells is mediated by CD21 in B-cells[193] and NK/T-cells[194], but recent studies suggest the existence of other binding pathways, particularly in epithelial cells[195]. Although the EBV-receptor remains unclear in CD21-negative NK-cell tumors, human leukocyte antigen class II β plays an important role for the internalization of EBV in NK-cells[196]. The EBV genome is linear in the viral particles, but circularizes in an episomal form after infection with a uniquely sized terminal repeat[197]. Therefore, EBV can

Table 4. Aberrations of oncogenes in NK-cell leukemia/lymphoma

Gene	Type of aberration	Frequency	Reference
p73	Methylation	94% (China, Hong Kong), 10% (Japan)	174, 180
hMLH1	Methylation	60-70% (China, Hong Kong)	176
RARb	Methylation	56%	176
SHIP1	Methylation	91%	175
p16	Methylation	63%	176
p15	Methylation	48%	176
p15/p16	Homozygous deletion	38%	170, 171
Fas	Mutation	50-60%	172, 173
p53	Mutation	20-60%	178, 179, 181
c-KIT	Mutation	5-71% (China), 16-22% (Japan)	178, 182
b-catenin	Mutation	16-30%	177-179
N/K/H-Ras	Mutation	Rare (< 5%)	171, 177-179
N/c-*Myc*	Amplification/Mutation	None	171

be detected by Southern blotting as a single band, but genomic integration of EBV occurs in approximately 10% of the cases[198]. Meanwhile, biclonal or polyclonal EBV genomes are found in occasional cases, and the lytic phase of EBV infection has been seen in some overlapping cases. HANK-1 is a cell line established from tumor cells of disseminated NK-cell lymphoma[199]. Southern blot analysis using a probe specific for the EBV terminal repeat demonstrated that this cell-line was derived from a minor clone in original tumor cells (Fig. 3). In most cases, isolated tumor cells have the same phenotype of typical NK-cell neoplasms, suggesting a common tumor origin with differential EBV clonality. Because the EBV genome exists within cells as an episome without integration in most cases, cellular reinfection is possible causing the appearance of different EBV clones. This has been demonstrated in other cases[167,200,201], and therefore, EBV monoclonality is not always required for the diagnosis of NK-cell malignancies.

The presence of EBV-DNA in the serum/plasma of patients was first recognized in nasopharyngeal carcinoma using polymerase chain reaction (PCR)[202]. Later, it was also found in other EBV-associated tumors including NK-cell lymphoma[203]. Spontaneous death of tumor cells leads to the release of EBV DNA, and the presence of EBV DNA in the serum does not necessarily indicate the presence of active EBV in the circulating blood. Therefore, the upper size limit of detectable EBV-DNA is 500 bp, and the size less than 300 bp is desirable for diagnosis or detection of minimal residual disease[204]. Infection-competent EBV is found in the lymphocytes of patients with acute or chronic EBV infection[205], and PCR using peripheral mononuclear cells or whole blood is applied for these patients[206]. Although this is a more sensitive method than serum/plasma PCR[207,208], it is not suitable because it can also detect bystander EBV in immunocompromised patients. A prospective study comparing the prognostic significance between plasma and whole blood as templates for real-time PCR is now under way.

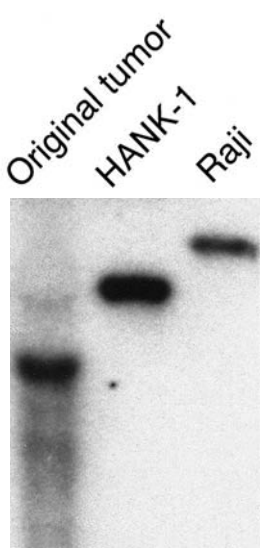

Fig. 3. Southern blotting of EBV terminal repeat in the HANK-1 cell line.
Southern blot analysis was performed using a probe targeting the EBV terminal repeat. The nasal-type NK-cell lymphoma cell line HANK-1 was derived from a minor lymphoma clone, which differed from the major clone in the size of the EBV terminal repeat. Monoclonality with respect to EBV is not always required for the diagnosis of extranodal NK-cell lymphoma.

Cell lines

After the initial recognition of NK-cell leukemia/lymphoma, many cell lines were established from primary tumors that have been invaluable research tools[209,210]. The cell lines derived from NK-cell neoplasms and related disorders are listed in Table 5[10,199,200,211-220]. The first NK-cell tumor line was established by Yodoi *et al*. in 1983 from a boy with mediastinal lymphoblastic lymphoma[211]. Although much relevant clinical information from this case was not provided, the diagnosis according to the current classification scheme seems to fall within the category of ENKL. Likewise, various diagnostic terms were used in the original description of different cell lines, but all can be sorted into three categories, ANKL cell lines[10,212-214,217,220], ENKL cell lines[199,200,211,215,218,219], and other NK-cell lines[216,219]. Several NK-cell lines with abnormal karyotypes have been established from patients without defined malignancies, such as hypersensitivity to mosquito bite, chronic active EBV infection (CAEBV) and hydroa vacciniforme-like eruption. The ability to establish cell lines from these patients supports the hypothesis these diseases are premalignant conditions that may progress to NK-cell leukemia/lymphoma. Most of these cell lines were established from Japanese patients, and are phenotypically similar to the original neoplasms, being positive for CD56 and EBV, and IL-2 dependent. Cell lines derived from ENKL and other categories were all established from Japanese patients and are uniformly positive for CD56 and EBV. In contrast, several lines were established from non-Oriental subjects, and these are occasionally negative for CD56[213,214] or EBV[217,220]. Existence of CD56 may not be essential for the leukemogenesis of NK-cell leukemia. The absence of EBV is consistent with a diagnosis of ANKL and further differentiates it from ENKL[22,25,28,32]. These cell lines are faithful replicas of the actual *in vivo* NK-cell leukemias/ lymphomas. Further studies, particularly genetic investigations, on these cell lines will provide invaluable information on the diagnosis and treatment of NK-cell neoplasms.

Relationship to chronic active EBV infection

CAEBV is a peculiar situation mainly occurs in children

Table 5. Cell lines derived from NK-cell neoplasms and related disorders.

Cell line	Age, sex	Ethnicity	Original description of disease	CD56	EBV	Cytokine dependency	Ref.
Aggressive NK-cell leukemia cell line							
(Unnamed)	71 M	White	Aggressive NK-cell leukemia	ND	ND	IL-2	10
NK-92	50 M	Unknown	LGL-NHL with BM involvement	+	+	IL-2	212
TKS-1	21 M	Japanese	Aggressive LGL leukemia	−*	ND	IL-2	213
NKL	62 M	White	NK-LGL leukemia	−*	−	IL-2	214
KYHG-1	45 F	Japanese	Aggressive NK-cell leukemia	+	−	IL-2	217
IMC-1	42 M	Native American	Aggressive NK-cell leukemia	+	−	IL-2	220
Extranodal NK-cell lymphoma cell line							
YT	15 M	Japanese	Acute lymphoblastic lymphoma with thymoma	+	+	No	211
HANK-1	46 F	Japanese	Nasal-type NK-cell lymphoma	+	+	IL-2	199
NK-YS	19 F	Japanese	Nasal NK-cell lymphoma	+	+	IL-2	215
SNK-1	24 F	Japanese	Nasal NK-cell lymphoma with CAEBV	+	+	IL-2	200
SNK-3	44 M	Japanese	Nasal NK-cell lymphoma	+	+	IL-2	219
SNK-6	62 M	Japanese	Nasal NK-cell lymphoma	+	+	IL-2	218
Other NK-cell line							
KAI3	13 M	Japanese	Hypersensitivity to mosquito bite	+	+	IL-2	216
SNK-5	14 F	Japanese	CAEBV	+	+	IL-2	219
SNK-10	17 M	Japanese	CAEBV	+	+	IL-2	219
SNK-11	16 F	Japanese	Hydroa vacciniforme-like eruption	+	+	IL-2	219

* CD56 was positive in the patients' original leukemic cells.

or young adults with waxing and waning symptoms[205,221-223]. Most patients present with fever, fatigue, lymphadenopathy and/or hepatosplenomegaly, and the EBV genome can be found in peripheral lymphocytes. These symptoms resolve with or without treatments such as anti-inflammatory drugs or steroids but recur after months or years. Occasionally, *bona fide* NK- or T-cell malignancies develop, and pursue fatal clinical course[201,224]. Etoposide-containing chemotherapy is effective[225] and a cure can be obtained with hematopoietic stem cell transplant[192,226], but the timing of treatment is difficult because of the fluctuating clinical course. CAEBV is not simply an EBV infection, but it represents an indolent lymphoproliferative disorder. Young patients with CAEBV need careful observations to judge the timing of treatment. In the future, optimal therapeutic strategies for CAEBV need to be further explored.

CAEBV typically develops in younger patients after an initial EBV infection, but cases in older individuals are sometimes reported[219,223,224,227]. The diagnosis of such cases relies on the presence of the EBV genome in peripheral blood as detected by PCR. However, the EBV genome is also present in the plasma of patients with EBV-positive malignancies including NK-cell neoplasms, and often indicates of the presence of occult malignancies, particularly in older patients. A comprehensive examination for malignancies is essential in elderly patients before a confident diagnosis of CAEBV can be made.

Chronic NK-lymphocytosis

Chronic NK-lymphocytosis (CNKL) is characterized by a chronic increase in the number of peripheral blood NK-cells without lymphadenopathy or organomegaly[14, 42, 228, 229]. Clinically, the disease presents with an indolent course, and no cytogenetic abnormalities are usually found. Although the disease itself has uncertain malignant potential, rare cases may develop into ANKL[230-232]. However, this may represent the presence of occult ANKL miscategorized as CNKL rather than transformation. Therefore, careful observation is needed for CNKL patients. Because EBV is not usually found in CNKL, testing for EBV may facilitate the differential diagnosis[233]. Seroreactivity to

HTLV-II has been reported in CNKL[234], but no evidence of viral DNA was found in the increased NK-cells[235]. CNKL is also associated with reactive conditions against viral infections or underlying solid tumors[14,228]. Careful whole-body examination is therefore recommended during the clinical management of patients with CNKL.

Therapy for localized extranodal NK-cell lymphoma

Radiotherapy alone has been used for the treatment of limited stage of ENKL[92,95,97], but the 5-year overall survival (OAS) is approximately 50%. In other subtypes of non-Hodgkin's lymphoma of similar clinical stage, 3 to 4 courses of chemotherapy followed by radiotherapy is now a standard therapy with 5-year overall survival rates of more than 80%[236,237]. However, this strategy is not effective for the treatment of NK-cell lymphoma. The 5-year overall survival rate is around 40%, which is comparable to or lower than the survival rate seen with radiotherapy alone[73,75,84,94,95,97].

Recently, several groups have treated patients with irradiation of more than 45 to 50 Gy followed by short courses of chemotherapy, and the reported 5-year OAS of this procedure reaches 70%[93,95-97]. However, the initial radiotherapy may miss underlying minimal lesions outside the radiation field. Therefore, a strategy of simultaneous chemoradiotherapy, as used for solid tumors, such as esophageal, laryngeal and lung cancers, may be beneficial for the treatment of ENKL[238-240]. Currently, the Japanese Clinical Oncology Study Group is performing a prospective evaluation for localized nasal NK/T-cell lymphoma.

Therapy for ANKL or advanced ENKL

Most patients with advanced disease tend to be treated with chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or third generation anthracycline-containing regimens, but most patients respond poorly and die within several months. Several reports demonstrated successful treatment using hematopoietic stem cell transplantation (HSCT) for these diseases[241-252]. Currently, HSCT is the only therapy expected to be curative in advanced cases. However, the results of transplant during relapse are poor, and this requires the development of more effective chemotherapeutic regimens for NK-cell neoplasms.

Aviles *et al*. described an active combination chemotherapy for advanced nasal NK/T-cell lymphoma, CMED (cyclophosphamide 2 g/m^2 and methotrexate 200 mg/m^2 on day 1, etoposide 300 mg/m^2 on day 1 and 2, and dexamethasone 20 mg/m^2 on day 1 to 4, supplemented by granulocyte colony stimulating factor on day 2 to 13)[253]. They treated 32 patients of stage III/IV disease with three courses of CMED therapy with an interval of two weeks, accompanied by 50 Gy irradiation of the nasal area and another three courses of CMED therapy. The complete remission rate and actuarial 5-year overall and disease free survival rates were 65%, but no other reports using this treatment regimen have been published. Yong *et al*. achieved good results with another novel chemoradiotherapy using L-asparaginase 6,000 IU/m^2 and dexamethasone 10 mg/body on days 1 to 7, and vincristine 1.4 mg/m^2 on day 1[254]. Although the treatment schedule was not uniform, 18 CHOP refractory patients were treated with this regimen from one to six courses with intervals of 21 to 28 days, followed by radiotherapy of 50 to 70 Gy (median : 56 Gy). In addition, several case reports claim an excellent efficacy of L-asparaginase in the treatment of refractory NK-cell malignancies[246,255,256].

Recently, the NK-cell Tumor Study Group started a phase I trial of a new combination chemotherapy named SMILE. The SMILE regimen consists of a steroid hormone, methotrexate, ifosfamide, L-asparaginase and etoposide, and is a dose-finding study for methotrexate and etoposide (Fig. 4). Methotrexate is administered on the first day, and etoposide and ifosfamide are given from the day after. This schedule is based on *in vitro* pharmacokinetic studies by Kano *et al*[257,258], including unpublished observations. They showed an additive effect of etoposide and ifosfamide when administered on simultaneous days and a synergistic effect of methotrexate when given before these two agents. When methotrexate and other drugs are used simultaneously, they are antagonistic. The toxicity and efficacy of SMILE therapy are now being prospectively evaluated.

Conclusion

Mature NK-cell tumors arise as two distinct entities, ANKL and ENKL. Clear differences exist between these conditions, but ANKL and stage IV ENKL can clinically be managed with the same therapeutic strategy. The mechanism of tumorgenesis remains unclear for both ANKL and ENKL,

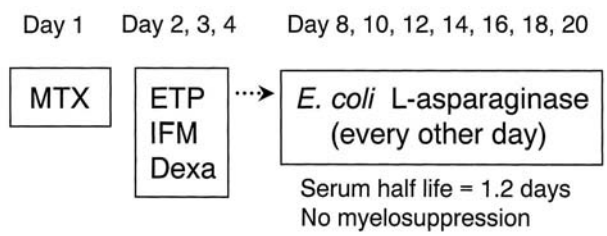

Fig. 4. Summary of SMILE chemotherapy
Methotrexate is given on the initial day of SMILE chemotherapy, accompanied by a 3-day course of etoposide, ifosfamide and dexamethasone (days 2-4). Because of the absence of myelosuppressive adverse reaction and a half-life of 1.3 days, L-asparaginase will be given on every other days from day 8 to day 20 (7 doses). The SMILE therapy will be repeated with an interval of 28 days. Doses of each agent will be determined in a prospective dose-escalation study.

and future studies are needed to clarify the molecular pathology of these diseases. Unfortunately, the prognoses of these malignancies are poor for both limited and advanced diseases, and new therapeutic modalities are needed to effectively treat patients. Appropriate therapeutic strategies should be explored in ongoing prospective studies.

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