Progress in Hematology

International Journal of
HEMATOLOGY

Leukemia and Lymphoma of Natural Killer Lineage Cells

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Received February 14, 2003; accepted March 7, 2003

Abstract

Natural killer (NK) cells are lymphocytes with a large granular lymphocyte morphology, a $CD3^{-}CD56^{+}$ phenotype, a non-major histocompatibility complex–restricted cytotoxicity, and germline configuration T-cell receptor genes. NK cell lineage tumors originate from either precursor NK cells or mature NK cells. Tumors originating conceivably from precursor NK cells include myeloid/NK cell precursor acute leukemia, precursor NK cell acute lymphoblastic leukemia, and blastic NK cell lymphoma. However, because the developmental pathway of normal NK cells and the characteristics of these NK precursors are not fully understood, the definition and characterization of the tumors are only provisional. Tumors of mature NK cell origin include aggressive NK cell leukemia/lymphoma, nasal-type NK cell lymphoma, and chronic NK lymphocytosis, but the last disorder seems to be reactive in most cases. Because NK cell tumors are rare and difficult to manage, vigorous studies are required for their understanding and management. *Int J Hematol.* 2003;78:18-23.

Key words: NK cell; Leukemia; Lymphoma

1. Introduction

Natural killer (NK) cells are lymphocytes with a large granular lymphocyte morphology, a $CD3^{-}CD56^{+}$ phenotype, a non-major histocompatibility complex–restricted cytotoxicity, and germline configuration T-cell receptor (TCR) genes [1-4]. NK cells develop in the bone marrow from hematopoietic stem cells via the intermediate developmental stages of lymphoid stem cells, bipotential T/NK progenitor cells, and committed NK progenitor cells [5-8]. The putative normal counterparts and the NK cell lineage tumors originating from these counterparts are shown in Figure 1. Provisionally, 6 types of NK cell lineage tumors have been proposed by our NK-Cell Tumor Study Group (NKSG) (Table 1) [9], 3 types of tumors originating from precursor NK cells and 3 types from mature NK cells. Myeloid/NK cell precursor acute leukemia originates conceivably from bipotential T/NK progenitor cells, and precursor NK cell acute lymphoblastic leukemia (ALL) and blastic NK cell lymphoma originate conceivably from committed NK progenitor cells. Aggressive NK cell leukemia/lymphoma, nasal-type NK cell lymphoma, and chronic NK lymphocytosis originate from mature NK cells. Based on the discussion at the Third NKSG Meeting in 1999, we proposed the definitions, the diagnostic criteria, and the clinical features of these tumors. They were summarized in Japanese in 2000 [9]. Here, I describe our currently used disease definitions, diagnostic criteria, and clinical features and discuss the pathogenesis and treatment of these diseases.

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2. Myeloid/NK Cell Precursor Acute Leukemia

This disease is a myeloid antigen–positive T/NK cell precursor acute leukemia conceivably originating from bipotential T/NK progenitor cells [10,11]. Diagnostic criteria include the presence of myeloperoxidase-negative and Sudan black B negatively staining blasts that are phenotypically $CD7^{+}CD56^{+}$, cytoplasmic $CD3^{\pm}$ ($cyCD3^{\pm}$; Leu $4^{\pm}$), surface $CD3^{-}$ ($sCD3^{-}$), and positive for myeloid antigens (CD13 or CD33). Their TCR-β and immunoglobulin H (IgH) genes should be in germline configuration, but the TCR-δ gene may be rearranged [8]. This disease is rare and manifests as leukemia or extramedullary lesions, mainly involving the lymph nodes and mediastinum with eventual leukemic change. Relapse is frequent, and the prognosis is poor.

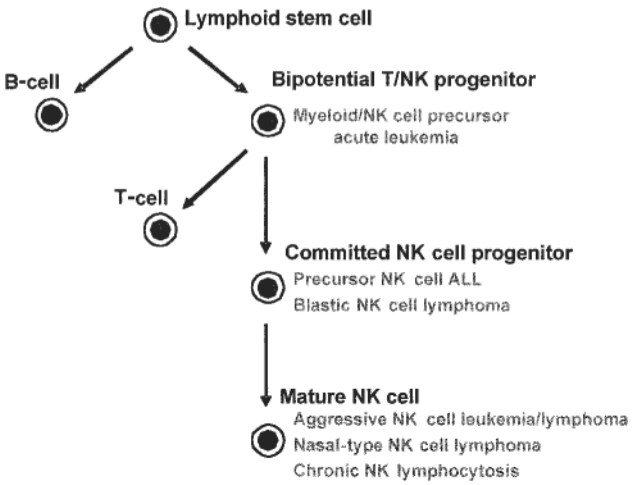

Figure 1. Natural killer (NK) cell tumors and their putative normal counterparts.

Suzuki et al originally described this disease in 1997 [10] and further characterized it in 1999 [11]. Because normal bipotential T/NK progenitor cells express CD13 and CD33 myeloid antigens [6], myeloid/NK cell precursor acute leukemia is difficult to differentiate from acute myeloid leukemia (AML) M0 (French-American-British classification), ie, AML expressing panmyeloid antigens and lacking B- and T-lymphoid–restricted antigens. However, the characteristics of $CD7^+CD56^+$ AML M0 are markedly different from those of other AML M0 cases and are consistent with those of myeloid/NK cell precursor acute leukemia. The presence of CD7 and CD56 clearly differentiates myeloid/NK cell precursor acute leukemia from other AML M0 [12].

3. Precursor NK Cell ALL

ALL developing from committed NK progenitor cells can be called precursor NK cell ALL [9,13]. Our original diagnostic criteria included the presence of 30% or more lymphoblasts in the bone marrow or peripheral blood, with the lymphoblasts having occasional azurophilic granules in the cytoplasm, $CD56^+$, $cyCD3^{\pm}$, $sCD3^-$, B-cell antigen–negative ($CD19^-$, $CD20^-$), and myeloid antigen–negative ($CD13^-$, $CD33^-$) phenotypes, and germline configuration TCR-β and IgH genes. Based on these criteria, we have documented 21 cases over a 5-year period, and they will be presented elsewhere. This disease is rare and develops both in children and in adults, with a median onset age of 55 years. Lymphadenopathy and hepatosplenomegaly are common. The prognosis is poor. The differentiation of this disease from blastic NK cell lymphoma is required, but because adequate information is lacking, it is unknown whether this disease is a leukemic form of blastic NK cell lymphoma or not. From our preliminary studies, the two diseases are indistinguishable in terms of their clinical features, except for the presence or absence of the tumor cells in the bone marrow or peripheral blood.

Table 1.
Provisional Classification of Natural Killer Cell Tumors*

1. Precursor NK cell tumors
   (1) Myeloid/NK cell precursor acute leukemia
   (2) Precursor NK cell acute lymphoblastic leukemia
   (3) Blastic NK cell lymphoma
2. Mature NK cell tumors
   (1) Aggressive NK cell leukemia/lymphoma
   (2) Nasal-type NK cell lymphoma
   (3) Chronic NK lymphocytosis

*Proposed at the Third NK-Cell Tumor Study Group Meeting [9]. NK indicates natural killer.

4. Blastic NK Cell Lymphoma

This lymphoma conceivably develops from committed NK progenitor cells [11]. Our diagnostic criteria include mass formation by a proliferation of lymphoblastoid cells with $CD56^+$, $cyCD3^{\pm}$, $sCD3^-$, $CD4^{\pm}$, B-cell antigen–negative ($CD19^-$, $CD20^-$), and myeloid antigen–negative ($CD13^-$, $CD33^-$) immunophenotypes and with the genotype of germline configuration TCR-β and IgH genes. This disease is rare and presents mainly with skin lesions and occasional leukemic change. The prognosis is poor. Differentiation from precursor NK cell ALL is required and will be made when adequate information becomes available.

Because recent reports from France [14-17] clearly indicate that $CD4^+CD56^+$ "blastic NK cell lymphoma" arises from the precursor of plasmacytoid dendritic cells, it must be determined whether the remaining cases of $CD4^-CD56^+$ blastic NK cell lymphoma really arise from NK precursor cells or from cells of another lineage. When purified tumor cells in culture develop NK lineage features in vitro, this finding will confirm the disease's NK cell origin.

5. Aggressive NK Cell Leukemia/Lymphoma

This disease is characterized by the presence of NK cells of a slightly immature-looking morphology, mainly in the peripheral blood, bone marrow, liver, and spleen, and by a rapidly progressive clinical course with a poor outcome [18]. Diagnostic criteria include the following: (1) cells with a slightly immature-looking morphology with broad, pale cytoplasm and azurophilic granules, a slightly fine nuclear chromatin, and the occasional presence of nucleoli; (2) $sCD3^-$, $CD56^+$, $CD16^{\pm}$, and $CD57^-$ immunophenotype; (3) genetically, germline configuration TCR-β and IgH genes; and (4) functionally, a high or sometimes absent non-major histocompatibility complex–restricted cytotoxicity. The NK cells appear slightly immature in morphology, but the presence of the CD94 antigen indicates its mature cell origin [19]. Younger patients are mainly affected, and fever, hepatosplenomegaly, and lymphadenopathy are common. The clinical course is rapidly progressive, and the prognosis is poor. Epstein-Barr virus (EBV) is frequently detectable. At presentation, this disease is sometimes indistinguishable from chronic NK lymphocytosis, but from our experience, the presence of conspicuous nucleoli in NK cells strongly supports the diagnosis of aggressive NK cell leukemia/lym-

phoma. In addition, an age less than 40 years, fever, lymph node swelling, and hepatosplenomegaly at presentation predict this diagnosis [20]. Nasal-type NK cell lymphoma may also present as this disease or eventually develop leukemic change, and the distinction between aggressive NK cell leukemia/lymphoma and nasal-type NK cell lymphoma is sometimes difficult unless a nasal lesion is found, and the distinction may be arbitrarily based on whether 30% or more of the cells present in the bone marrow or peripheral blood at presentation.

This disease was originally described by Imamura et al [18]. Because of its rare incidence, a treatment strategy is totally unknown. The disease is refractory to chemotherapy and exhibits a relentless progressive course and a poor outcome. As in nasal-type NK cell lymphoma, this poor outcome may be partially explained by the presence of P-glycoprotein (P-gp), a multidrug resistance gene 1–encoded protein on the NK cell membrane that extrudes various cytotoxic agents, such as vinca alkaloids and anthracyclines [21-23]. A recent report, however, indicates that NK cells express a 70 to 80 kD short-length P-gp but not the 170 kD full-length P-gp, and this mini–P-gp demonstrates a restricted substrate profile and is unable to extrude daunorubicin [24]. These findings may change the treatment strategy for advanced-stage NK cell tumors.

6. Nasal-Type NK Cell Lymphoma

This is an NK cell lymphoma arising in the nasal cavity or at extra-nasal sites such as the skin and intestinal tract.

6.1. Diagnostic Criteria

Our diagnostic criteria are as follows: (1) histology and morphology consisting of the diffuse, nonadhesive proliferation of lymphoid cells with a frequent association of tissue necrosis and coagulation, a perivascular (angiocentric) and angiodestructive infiltration of the tumor cells, and polymorphous and partly monomorphous tumor cells composed of large lymphoid cells, with imprint smears disclosing the presence of cytoplasmic azurophilic granules; (2) $CD45^+$ (leukocyte common antigen), $sCD3^-$, $CD56^+$, myeloid antigen–negative, and B-cell antigen–negative immunophenotype; (3) germline configuration TCR-β and IgH genes; and (4) EBV usually detectable in the tumor cells.

6.2. Clinical Features

Nasal-type NK cell lymphoma is characterized by extranodal presentation and an aggressive clinical course. The lymphoma is common in Asia and Latin America but is rare in North America and Europe. It develops in middle-aged persons, and men are more often affected than women. The nasal cavity is the main presenting site, and the skin, intestinal tract, and various other organs are less often involved at presentation. Because of the disease's predilection for vessels, a massive necrosis of the tissue is often one of the presenting features, and it is sometimes difficult to make a diagnosis, even with repeated biopsies.

NK cell lymphoma developing in extra-nasal sites such as the skin and intestinal tract also exhibits a relentless progressive course and does not show remission with chemotherapy.

6.3. Pathogenesis

Nasal NK cell lymphoma is almost always associated with EBV. In situ hybridization techniques reveal EBV-encoded small RNA (EBER) in the tumor cells, and Southern blot analysis detects the monoclonal proliferation of EBV. These findings indicate that EBV infection has been established at an early stage of tumorigenesis and strongly suggests EBV's etiologic role. Our recent experiments have clearly shown that EBV easily infects NK cells, and the expression of EBER in infected cells is confirmed by reverse transcriptase–polymerase chain reaction (unpublished data). Interestingly, this infection occurs in the absence of the CD21 antigen or the EBV receptor on the NK cell surface.

In addition to the conventional chromosomal analysis, various procedures, including comparative genomic hybridization, loss of heterozygosity analysis, and fluorescence in situ hybridization, have been applied to demonstrate genetic abnormalities. The results indicate that complex chromosomal abnormalities are often seen [25], and deletions at 6q and 13q are frequently found [26,27]. DNA gains are also frequent [27]. These abnormalities have recently been reviewed in the literature [28].

Various types of suppressor oncogenes are inactivated in NK cell lymphoma. These include *p53*, *p73*, *p16INK4A*, *p15INK4B*, and *p14ARF* [29,30]. Studies of oncogenes from our laboratory have shown normally expressed K-, H-, and N-*ras* genes, and c-*myc* and N-*myc* genes, but a strongly expressed *mdm2* gene [31]. The relationships between EBV infection, chromosomal abnormalities, and oncogene and suppressor oncogene abnormalities remain to be clarified.

6.4. Diagnostic Problems

Among patients with nasal lymphoma, three fourths have NK cell or T-cell lymphoma, and the rest have B-cell lymphoma. The incidence of T-cell lymphoma seems to be much lower than that of NK cell lymphoma, but its true incidence is not known. Distinguishing between the NK cell and T-cell lineages is sometimes difficult. As shown in Table 2, T-cells are positive for the sCD3 antigen, and NK cells are negative, but both T-cells and NK cells are positive for cyCD3. Because it is difficult to discriminate the sCD3 antigen from the cyCD3 antigen in paraffin-embedded specimens, distinguishing between NK cell and T-cell lineages is difficult when only paraffin-embedded specimens are available [32]. CD5 positivity, however, strongly suggests a T-cell lineage [33]. The demonstration of sCD3 by flow cytometry and monoclonal TCR gene bands by Southern blot analysis is helpful in the differentiation of these lineages, and these two procedures should be routinely employed. The large granular lymphocyte morphology demonstrated by Giemsa staining of imprint smears also suggests an NK cell lineage, but NK-like T-cells also have such a morphology. However, it is unknown

Table 2.
Distinction between T-Cells and Natural Killer Cells*

	T-Cell	NK Cell
Surface markers		
CD2	+	+
CD3	+	–
CD5	+	–
CD7	+	+
CD16	–	+/–
CD56	–/+	+
TCR	+	–
Cytoplasmic CD3	+	+
TCR gene rearrangement	+	–
LGL morphology	–/+	+
Non-MHC–restricted cytotoxicity	–/+	+
NK receptors	–/+	+

*TCR indicates T-cell receptor; LGL, large granular lymphocyte; MHC, major histocompatibility complex; NK, natural killer.

whether the vigorous effort to differentiate the NK cell lineage from T-cell lineage is clinically important in terms of treatment strategy or prognosis.

6.5. Treatment and Prognosis

Because of the rare incidence of this disease, no prospective treatment study has been reported, and no standard treatment protocol has been established. Seventy percent of the patients have stage I or stage II disease. In localized diffuse large B-cell lymphoma, 3 courses of CHOP (cyclophosphamide, doxorubicin, vincristine [Oncovin], and prednisone) followed by radiation therapy give excellent results. However, in localized nasal NK cell lymphoma, treatment with this protocol seems to be discouraging. The response of the primary tumors to such chemotherapy is minimal or transient if present, and early metastasis is common. Compared with combination chemotherapy, radiation therapy seems to be much more effective. To cure the disease, a dose of 50 Gy to the involved area is required [34-36]. Although bone marrow involvement at diagnosis is uncommon, radiotherapy alone is not sufficient, and long-term survival rates are 35% to 40%, possibly because of the presence of unidentified metastatic legions in some patients. The addition of chemotherapy, however, does not appear to modify significantly the survival outlook of patients, conceivably because of the early dissemination of the disease before the beginning of chemotherapy and the presence of P-gp in NK cells. In Japan, therefore, a prospective trial using concurrent radiation and chemotherapy will start soon. This trial is based on an observation made by Yamaguchi et al, who reported a good clinical outcome for combination chemotherapy with DeVIC (dexamethasone, etoposide [VP-16], ifosfamide, and carboplatin) and concurrent use of local radiotherapy [37]. This success may have been partly due to the choice of DeVIC combination chemotherapy, because the agents included in this regimen are unrelated to P-gp except for etoposide.

In advanced disease, the results with conventional chemotherapy regimens such as CHOP are discouraging, and the overall survival rate at 5 years is approximately 10% [38, 39]. L-asparaginase is a very effective agent for treating precursor B-cell or T-cell ALL, because these cells lack a sufficient amount of asparagine synthetase (AS). AS is an enzyme that synthesizes L-asparagine from L-aspartic acid and L-glutamine. Most nonmalignant normal cells have enough AS protein and activity to survive by compensating for extracellular asparagine depletion after L-asparaginase treatment. Kitoh et al established a semiquantitative system for detecting cellular AS protein expression by in situ immunostaining with a human AS-specific antibody [40] and showed that nasal-type NK cell lymphoma was almost always associated with low AS expression [41]. Abnormally expanded NK cells that do not have AS may be sensitive to L-asparaginase, and the integration of L-asparaginase into combination chemotherapy may be promising [42].

High-dose chemotherapy with autologous or allogeneic stem cell support is an alternative method of treatment. Liang et al [43] reported a successful outcome in 2 of 3 patients with autologous transplantation, and Takenaka et al [44] also reported a promising result with autologous and allogeneic transplantation.

7. Chronic NK Lymphocytosis

This disorder is characterized by chronic expansion of mature-looking NK cells in the peripheral blood [20,45]. Our diagnostic criteria include (1) a large granular lymphocyte morphology (large lymphocytes with 3 or more azurophilic granules in the cytoplasm), (2) $sCD3^{-}CD56^{\pm}$ and $CD16^{+}$ immunophenotype, and (3) germline configuration TCR-β and IgH genes. Cells fulfilling these 3 criteria can be called mature NK cells, and levels of 600/μL or greater of these cells must be present in the peripheral blood for at least 6 months. Clinically, most cases present with a chronic indolent course and are considered to have a reactive NK cell proliferation [46]. Rare cases present with a slowly progressive increase of peripheral blood NK cells and with organ involvement. These cases may be called 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/lymphoma.

8. Summary

Six types of NK cell tumors have arbitrarily been defined, and their clinical features have been presented. However, because of their rarity, we are still very far from an understanding of these diseases. It should be clarified whether precursor NK cell ALL and blastic NK cell lymphoma are two distinct diseases or just reflect two facets of a single disease, as are aggressive NK cell leukemia/lymphoma and nasal-type NK cell lymphoma. These issues will be resolved when the primary and secondary genetic events that give rise to the diseases or their progression have been clarified. DNA microarray technology is a good tool to analyze these issues.

Acknowledgments

This work was supported in part by grants from the Ministry of Health, Labor, and Welfare of the Japanese Government and by Kirin Brewery Co, Ltd. I thank Drs. Keisei

Kawa, Shigeo Nakamura, Ritsuro Suzuki, Junji Suzumiya, Shinichi Tagawa, Shizuo Kojya, Keisi Iwatsuki, Toshiyuki Kitoh, Nobutaka Imamura, Rieko Sato, and Hiroki Sugimori for their help and advice and the members of the NK-Cell Tumor Study Group.

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