

NK cell neoplasias

Clinics and Pathology

Disease	<p>Neoplasms of natural killer (NK) cells are rare, and have not been well characterized until the past decade. In the new WHO classification of hematolymphoid tumors, three categories of NK cell neoplasms are recognized:</p> <ul style="list-style-type: none">- extranodal NK/T cell lymphoma ,- aggressive NK cell leukemia, and- blastic NK cell lymphoma. <p>Blastic NK cell lymphoma is morphologically and immunologically different from the first two categories, lacks EBV association, and there is little compelling evidence that it truly represents an NK cell neoplasm. In fact, recent studies suggest that this may be a neoplasm of probable precursor dendritic cells related to plasmacytoid monocytes (plasmacytoid dendritic cells). Since its lineage is still uncertain, this entity will not be discussed.</p>
Phenotype / cell stem origin	<p>NK cell represents a distinctive lineage of lymphocyte that is closely related to T cell. It shows many immunophenotypic and functional similarities with cytotoxic T lymphocyte, but differs in the lack of expression of surface CD3 molecule and T-cell receptor, and the absence of rearranged T-cell receptor genes. It characteristically expresses CD56 (neuronal cell adhesion molecule, N-CAM), which is also expressed in some cytotoxic T lymphocytes. NK cells can lyse target cells without prior sensitization (spontaneous antibody-independent MHC-unrestricted cytotoxicity) via the NK receptors.</p>
Etiology	<p>The exact etiology is unknown, but a very strong association with Epstein Barr virus (EBV) has been demonstrated.</p>
Epidemiology	<p>NK cell neoplasms show a strong geographic differences in their prevalence. They are more common in Asia, Mexico, and South America, but are very rare in the Western populations.</p>
Clinics	<p>They occur predominantly in the nose/nasopharynx, but sometimes in extranasal sites (most commonly skin), in middle-aged to elderly patients. Systemic involvement is uncommon at diagnosis but rarely, they may present initially in a leukemic form. The most common presenting symptoms are nasal obstruction, nasal discharge and epistaxis. The full-blown midfacial destructive and ulcerative lesions (hence the name midline granuloma) are much less commonly seen nowadays. Patients with aggressive NK cell leukemia present with high swinging fever, systemic symptoms and hepatosplenomegaly; they are usually extremely ill, with deranged liver function and coagulation profile.</p>
Cytology	<p>The neoplastic NK cells are often heterogeneous in appearance but some (particularly the circulating leukemic cells) may resemble large-</p>

Pathology	<p>sized normal large granular lymphocytes with ample amount of pale or lightly blue cytoplasm that contains fine or coarse azurophilic granules. The malignant infiltrate is diffuse, often with a prominent angiocentric and angiodestructive component. Coagulative necrosis and apoptosis are common. The cytological spectrum is variable, ranging from small, medium-sized, large or anaplastic cells, to a mixture of these cells. The cells often have irregularly folded nuclei and granular chromatin. In Giemsa-stained cytologic preparations, azurophilic granules are often detected in the cytoplasm. Reactive histiocytes with haemophagocytosis are sometimes found in the bone marrow, particularly for the leukemic form. NK cell neoplasms are characterised by an immunophenotype of CD2+, surface CD3-, cytoplasmic CD3e+, CD56+ and T cell receptor (TCR)-, lack of TCR gene rearrangement, and strong association with EBV.</p>
Treatment	<p>The disease is often resistant to chemotherapy. For extranodal NK/T cell lymphoma, the best results are obtained by radiotherapy with or without aggressive chemotherapy/stem cell rescue. Plasma or serum EBV DNA and tissue p73 gene hypermethylation assay can be used for monitoring of disease status or detection of minimal residual disease. Aggressive NK cell leukemia is treated by chemotherapy, but response is typically poor.</p>
Evolution	<p>Although extranodal NK/T cell lymphoma is usually localized at presentation, systemic progression often occurs, usually early in the course of disease. Common distant sites of involvement are the skin, liver, lung, gastrointestinal tract, testis, and rarely bone marrow. Patients with aggressive NK cell leukemia typically exhibits a rapidly progressive clinical course, with multi-organ failure and bleeding tendency.</p>
Prognosis	<p>Clinical factors reported to have prognostic significance in extranodal NK/T cell lymphoma include stage and bulk of disease, B symptoms, age, performance status and International Prognostic Index. The overall survival for patients with extranodal NK/T cell lymphoma is 30-40%. Practically all patients with aggressive NK cell leukemia die from the disease within a few weeks or months of presentation.</p>

Genetics

In contrast to T cells, NK cells do not show rearrangements of the TCR genes. As expected from their proposed normal counterpart, NK cell neoplasms show a germline configuration of the TCR genes and do not express TCR proteins on the cell surface. The detection of single circularised episomal form of EBV in the neoplasm by Southern blot analysis provides indirect evidence to the clonal nature. Molecular demonstration of X chromosome inactivation in female patients with NK cell neoplasms also provides evidence for clonality. However, the most direct evidence for clonality of this group of tumors has been provided by the detection of clonal chromosomal abnormalities (see section below).

It has been shown that in over 90% of NK cell neoplasms, a specific pattern of promoter CpG methylation occurs, with p73 being consistently involved. It has been further suggested that p73 may be an important target in the oncogenesis of NK cell neoplasms, and the demonstration

of its methylation may serve as a useful molecular marker for disease monitoring.

Cytogenetics

Note A variety of genetic abnormalities has been described, but so far no specific and consistent chromosomal translocation has been identified by conventional cytogenetics. In most instances, the genetic changes involve loss or gain of genetic materials such as del(6q), and i(1q). Frequent genetic losses in 6q and 13q have been confirmed by both comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) analyses. Other non-random abnormalities include +X, i(1q), i(7q), +8, i(17q), and 11q23 rearrangement. Chromosomal deletion involving chromosome 6q at around q21-q25 is the commonest recurrent chromosomal abnormality, and fluorescence in situ hybridisation studies have shown that 6q22-q23 is the most frequently involved regions in the chromosome 6 deletions. A recent study using LOH and homozygosity mapping of deletion (HOMOD) analyses has, however, defined a distinct 3 Mb smallest region of overlapping on 6q25.

A possible involvement of 8p22-p23 in both NK cell neoplasms and NK cell line such as NK-92 has also been suggested. Translocation involving 8p23 has been reported in 3 cases of NK cell neoplasms, with the partner chromosomes being 8q13, 17q24 and 1q10. An add(8)(q23) abnormality has also been demonstrated in one case each of aggressive NK cell leukemia and extranodal NK/T cell lymphoma.

Bibliography

Neural cell adhesion molecule-positive peripheral T-cell lymphoma: a rare variant with a propensity for unusual sites of involvement.

Kern WF, Spier CM, Hanneman EH, Miller TP, Matzner M, Grogan TM.

Blood 1992; 79: 2432-2437.

Medline [1373974](#)

CD56 (NKH1)-positive hematolymphoid malignancies: an aggressive neoplasm featuring frequent cutaneous/mucosal involvement, cytoplasmic azurophilic granules and angiocentricity.

Wong KF, Chan JKC, Ng CS, Lee KC, Tsang WYW, Cheung MMC.

Hum Pathol 1992; 23: 798-804.

Medline [1377163](#)

Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm.

Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, Chan CH, Cheung MM, Lau WH.

Blood 1997; 89: 4501-4513.

Medline [9192774](#)

CD56+ NK lymphomas: clinicopathological features and prognosis.

Kwong YL, Chan AC, Liang R, Chiang AK, Chim CS, Chan TK, Todd D, Ho FC.

Br J Haematol 1997; 97: 821-829.

Medline [9217183](#)

Identification of del(6)(q21q25) as a recurring chromosomal abnormality of

putative NK cell lymphoma/leukemia.

Wong KF, Chan JKC, Kwong YL.
Br J Haematol 1997; 98: 922-926.
Medline [9326190](#)

Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients.

Cheung MM, Chan JK, Lau WH, Foo W, Chan PT, Ng CS, Ngan RK.
J Clin Oncol 1998; 16: 70-77.
Medline [9440725](#)

Comparative genomic hybridization analysis of natural killer cell lymphoma/leukaemia: recognition of consistent patterns of genetic alterations.

Siu LLP, Wong KF, Chan JKC, Kwong YL.
Am J Pathol 1999; 155: 1419-1425.
Medline [10550295](#)

Cytogenetic abnormalities in natural killer cell lymphoma/leukaemia. Is there a consistent pattern? (Review).

Wong KF, Zhang YM, Chan JKC.
Leuk Lymphoma 1999; 34: 241-250.
Medline [10439361](#)

Chromosome aberrations are restricted to the CD56+ CD3- tumour cell population in natural killer cell lymphomas: a combined immunophenotyping and FISH study.

Zhang Y, Wong KF, Siebert R, Matthiesen P, Harder S, Eimermacher H, Schlegelberger B.
Br J Haematol 1999; 105: 737-742.
Medline [10354139](#)

Consistent patterns of allelic loss in natural killer cell lymphoma.

Siu LLP, Chan V, Chan JKC, Wong KF, Liang R, Kwong YL.
Am J Pathol 2000; 157: 1803-1809.
Medline [11106552](#)

Aggressive NK-cell leukaemia.

Chan JKC, Wong KF, Jaffe ES, Ralfkiaer E.
In: Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours. Lyon: International Agency for Research on Cancer. 2001, pp. 198-200.

Extranodal NK/T -cell lymphoma, nasal type.

Chan JKC, Jaffe ES, Ralfkiaer E.
In: Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours. Lyon: International Agency for Research on Cancer. 2001, pp. 204-207.

Bone marrow involvement by nasal NK cell lymphoma at presentation is uncommon.

Wong KF, Chan JKC, Cheung MMC, So JCC.
Am J Clin Pathol 2001; 115: 266-270.
Medline [11211616](#)

Specific patterns of gene methylation in natural killer cell lymphomas: p73 is consistently involved.

Siu LLP, Chan JKC, Wong KF, Kwong YL
Am J Pathol 2002; 160: 59-66.
Medline [11786399](#)

Genetic changes in natural killer cell neoplasms (Editorial).

Wong KF.
Leuk Res 2002; 26: 977-978.
Medline [12363463](#)

Natural killer cell neoplasms: A distinctive group of highly aggressive lymphomas/leukemias. (Review).

Cheung MM, Chan JK, Wong KF.
Semin Hematol 2003; 40: 221-232.
Medline [12876671](#)

Aberrant promoter CpG methylation as a molecular marker for disease monitoring in natural killer cell lymphomas.

Siu LL, Chan JK, Wong KF, Choy C, Kwong YL.
Br J Haematol 2003; 122: 70-77.
Medline [12823347](#)

A 2.6 Mb interval on chromosome 6q25.2-q25.3 is commonly deleted in human nasal natural killer/T-cell lymphoma.

Sun HS, Su IJ, Lin YC, Chen JS, Fang SY.
Br J Haematol 2003; 122: 590-599.
Medline [12899714](#)

Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index.

Chim CS, Ma SY, Au WY, Choy C, Lie AK, Liang R, Yau CC, Kwong YL.
Blood 2004; 103: 216-221.
Medline [12933580](#)

A novel EBV-negative natural killer cell line (Editorial).

Wong KF.
Leuk Res 2004; 28: 225-227.
Medline [14687616](#)

Contributor(s)

Written 04-2004 K.F. Wong

Citation

This paper should be referenced as such :

Wong KF . NK cell neoplasias. Atlas Genet Cytogenet Oncol Haematol. April 2004 .
URL :
<http://www.infobiogen.fr/services/chromcancer/Anomalies/NKCellNeoplasiaID2125.html>

© *Atlas of Genetics and Cytogenetics in Oncology and Haematology*
