

## Leukaemia Section

### Short Communication

# Extranodal NK/T-cell lymphoma, nasal type (ENKL)

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## Abstract

Review on Extranodal NK/T-cell lymphoma and the genes involved.

### Keywords

Extranodal NK/T-cell lymphoma, nasal type; Angiocentric T-cell lymphoma; Malignant reticulosis

## Identity

### Other names

Angiocentric T-cell lymphoma  
Malignant reticulosis, NOS  
Malignant midline reticulosis  
T/NK-cell lymphoma  
Polymorphic reticulosis  
Extranodal NK/T-cell lymphoma, nasal type

## Clinics and pathology

### Disease

Peripheral T cell lymphomas (PTCL) are a heterogeneous group of aggressive neoplasm in adults. Among these are: peripheral T cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T cell lymphoma, extranodal NK/T cell lymphoma (nasal type), enteropathy associated T cell lymphoma, hepatosplenic T cell lymphoma. Extranodal natural killer/T-cell lymphoma, nasal type (ENKL), or nasal NK/T cell lymphoma (angiocentric lymphoma), is an

aggressive pathology, with predilection for Asian and South American populations (Barrionuevo C et al., 2007; Liang R et al., 2009). Neoplastic cells are surface CD3-, cytoplasmic CD3ε+, CD56+, cytotoxic-molecule positive, Epstein-Barr virus (EBV) positive, with germline T-cell receptor gene (Chan JK et al., 2008). This lymphoma is almost exclusively extranodal (Kwong YL et al., 2005). Occur commonly in the nasal and upper aerodigestive region. Occasional cases present in the skin, salivary gland, testis, and gastrointestinal tract. Quantification of circulating EBV DNA is an accurate biomarker of tumor load (Au WY et al., 2005). Concomitant sequential chemotherapy and radiotherapy is standard treatment.

### Etiology

Etiology is poorly understood, but is related in part to infection of the tumor cells with Epstein-Barr virus (EBV). Expression of EBV latent membrane protein-1 by immunohistochemistry has also been described (Kanavaros P et al., 1993).

### Epidemiology

NK/T-cell lymphomas occur worldwide, with a strong geographic predilection for Asian population (China, Japan, Korea and Southeast Asia) and for Central and South American population (Mexico, Peru, Argentina and Brazil) (Kwong YL et al., 2005).

Constituting 5-15% of lymphomas in these countries (Swerdlow SH et al., 2016).

The median age at presentation is 52 years (Au WY et al., 2009); however, rare cases have been reported

in childhood. There is a male predominance with an approximately 2:1 male to female ratio. (Chim SC et al., 2004; Li XY et al., 2009).

### Clinics

The large majority of patients present with localized disease resulting in symptoms of nasal obstruction, epistaxis, and/or a destructive mass involving the nose, sinuses, or palate (Liu QF et al., 2014). Other extranodal sites may be involved either primarily (extranasal NK/T cell lymphoma) or as a direct extension of the primary tumor. These sites include the upper airway, Waldeyer's ring, gastrointestinal tract, skin, testis, lung, eye, or soft tissue (Tse E et al., 2013). Lymph nodes may be involved secondarily, but are only rarely the primary site of involvement. Bone marrow involvement and B symptoms are seen in approximately 10 and 35 percent of patients, respectively (Li YX et al., 2009).

### Disease

**Diagnosis:** The diagnosis of ENKL is made based upon the evaluation of a biopsy specimen from the site of involvement, usually in the facial area. Because the morphology of the tumor cells is so variable, it is important to consider this diagnosis in all cases of aggressive extranodal lymphoma associated with vascular invasion and necrosis.

The key diagnostic features are the demonstration of NK/T cell markers and Epstein Barr virus (EBV). Although CD56 is typically expressed, tumors that do not express CD56 may still be classified as ENKL if both cytotoxic molecules and EBV are positive (Chan JK et al., 2008).

Immunophenotype in this case can be useful; these tumors express CD2, cytoplasmic CD3, CD56, and cytotoxic granule proteins (Chan JK et al., 2008).

### Cytology

Immunophenotype is similar to that of a NK cell. The atypical cells in most cases express CD2, CD56, and cytoplasmic CD3, but do not express surface CD3. Most cases express cytotoxic granule protein such as granzyme B, TIA-1, and perforin, and lack surface T cell receptor (TCR). Uncommon cases may express CD4, CD8, and/or CD7. (Lei KI et al., 2002).

### Pathology

The tumor cells can be of any size, but most commonly are either medium-sized or a mixture of small and large cells. They have a moderate amount of pale/clear cytoplasm with irregularly folded nuclei typically containing granular chromatin and inconspicuous or small nucleoli. Azurophilic granules may be seen on touch preps stained with giemsa (Swerdlow SH et al., 2008).

### Treatment

Therapy and prognosis are based upon the stage of the disease. In localized stages, combined modality

therapy is the frequent treatment option (i.e., radiotherapy with concurrent chemotherapy) (Tse E et al., 2012). Radiation dose of 50 Gy and concurrent therapy with reduced dose 2/3DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin) or VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase).

CHOP-based regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) is not recommended for NK/T-cell lymphoma (Kim SJ et al., 2010).

Other chemotherapy regimens like LVP (L-asparaginase, vincristine and prednisolone) or GELOX (gemcitabine, E. coli L-asparaginase, oxaplatin) are been used in this pathology with high rates of remissions.

In disseminated disease cases, SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase) achieves best results, but neutropenia occurred in most of the patients with high rates of serious infections (Kwong YL et al., 2012).

The use of hematopoietic stem cell transplantation (HSCT) has been explored in NK/T-cell lymphomas, however most studies contained small number of patients so the results are difficult to interpret.

### Prognosis

ENKL is an aggressive lymphoma. Without treatment survival is measured in months. The prognosis with treatment is largely related to the location and stage of disease at diagnosis.

Age over 60 years, stage III/IV disease, distant lymph node involvement, non-nasal type and detectable Epstein-Barr virus viral DNA titer are consider the most important patient information for the prognosis determination.

## Genetics

### Note

A high percentage of these tumors overexpress the p53 tumor suppressor protein, with about one-quarter showing evidence of p53 mutation (Quintanilla-Martinez L et al., 2001). In most other tumor types, p21 overexpression is linked to wild-type p53 expression, but in this tumor it has been found even with mutant p53 or low p53 expression. Other tumor suppressor genes that have been implicated in the pathogenesis of ENKL include PRDM1 and FOXO3 (Karube et al., 2011). The gene PRDM1 (alias BLIMP1) is particularly interesting because it regulates the maturation, homeostasis and proliferation of NK cells (Kallies A et al., 2011). Several oncogenic pathways are activated, including Notch-1, Wnt, JAK/STAT, AKT, and nuclear factor κB. Recently, whole-exome sequencing has identified somatic-activating mutations of the JAK3 gene in 35% of NK/T-cell lymphomas (Koo GC et al., 2012)

resulting in cytokine-independent constitutive JAK-STAT activation.

## Cytogenetics

### *Cytogenetics morphological*

The TCR and immunoglobulin (Ig) genes are usually germline, but a small fraction of cases demonstrate clonal rearrangement of TCR genes, suggesting derivation from a cytotoxic T lymphocyte (Lipford et al., 1988). Clonal EBV genomes are virtually always present. In situ hybridization for EBV encoded small nuclear RNAs is the preferred method of demonstrating the presence of EBV (Lei KL et al, 2002).

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