

## Anaplastic large cell lymphoma (ALCL)

### Identity

**Note** Anaplastic large cell lymphoma can be classified into :

- 1- primary systemic ALK+ ALCL
- 2- primary systemic ALK- ALCL
- 3- primary cutaneous ALCL. (see in paragraph Pathology)

NOTE The 2 first categories are defined according to the involvement (or not) of ALK in fusion proteins with various partners (see below); ALK+ ALCL cases are sometimes called ALK lymphomas, or ALKomas  
ALK+ ALCL can be further divided into t(2;5) cases, with NPM1-ALK fusion protein which localises both in the cytoplasm and in the nucleus, and t(2;Var), involving various partners and ALK, and a cytoplasmic localization of the fusion protein; the latter are called "cytoplasm only" ALK+ ALCL. ALCL may also arise from transformation of another lymphoma mycosis fungoides, peripheral T-cell lymphoma, ...); these ALCL are called secondary ALCL, and they bear a poor prognosis

### Clinics and Pathology

**Epidemiology** ALCL represent about 5% of non Hodgkin lymphomas (NHL) in adults, and 15 % of pediatric NHL (i.e. 20-30 % of large cell lymphomas in children). ALK+ ALCL represent 50 to 60 % of ALCL cases. ALK+ ALCL predominantly affect young male patients (most cases occur before the age of 40 yrs) , while ALK- ALCL is found in older patients (median age around 50 yrs) of both sex

**Clinics** ALK+ ALCL presents as an aggressive disease with systemic signs, and extranodal sites (bone marrow, skin, bone, soft tissues, and organs); less aggressive presentation in ALK- ALCL cases (but a worse prognosis, see below)  
Note: ALK+ ALCL without the t(2;5) (so called cytoplasmic only ALK cases) show clinical features similar to those of classical ALK+ ALCL. Were found in a recent series: mean age: 19 yrs, range 4 to 45 yrs; male/female ratio: 1.5, presentation with advanced disease (stage III-IV in 9 of 15 cases), systemic symptoms (11/15), and frequent involvement of extranodal sites.

**Pathology** 3 main histopathological types are found;  
the common type, characterized by large lymphoid cells with horseshoe shaped nuclei with many nucleoli, and large cytoplasm; may be ALK + or - ALCL  
the small cell type, together with the above described cells, show small and medium sized cells; almost exclusively ALK+ cases  
the lymphohistiocytic type also contains a number of reactive histiocytes, which, earlier, lead to the misdiagnosis of malignant histiocytosis; almost always ALK+ cases.  
All the 3 forms contain large cells, positive for CD30 (on the cell membrane and the golgi ); they are mostly epithelial membrane antigen

(EMA) positive.  
most cases are T-cell cases (often cytotoxic T-cells), or may be null cases, the null cases often involving the T-cell; B-cell cases may belong to a different category; ALK+/IgA+ immunoblastic large B-cell lymphomas could exist.

Aside are primary cutaneous anaplastic large cell lymphomas, a disease with indolent clinical course, negative for ALK, lacking the t(2;5) or variant translocations, close to the benign lymphomatoid papulosis

NOTE: there are cases where the differential diagnosis between [Hodgkin disease](#) (HD) -where CD30 is also strongly expressed- and ALCL is difficult (cases previously called ALCL-HD like).

Prognosis ALK+ ALCL have a favourable prognosis, whichever the ALK partner is: 70% to 80 % 5 yr survival, while ALK- ALCL cases have a much poorer prognosis (5 yr survival in only 30% -40 %). ALK+ cases without NPM1 involvement

## Genetics

The genetic background in ALK- cases remains unknown.

ALK+ cases are the result of the formation of a hybrid gene between ALK and either NPM1 (in 70-80% of the cases), or TPM3 (in 20% of the cases) or, rarely: MSN, ATIC, TFG, CLTC, ALO17, or MYH9 (these latter being "cytoplasm only" or cytoplasmic (TPM3, ATIC, TFG, CLTC, ALO17, MYH9) or membrane restricted (MSN) ALK+ ALCL).

## Cytogenetics

Cytogenetics [t\(2;5\)\(p23;q35\)](#) in the classical form with NPM1 involvement on chromosome 5, [t\(X;2\)\(q11;p23\)](#), [t\(1;2\)\(q25;p23\)](#), [inv\(2\)\(p23q35\)](#), [t\(2;3\)\(p23;q21\)](#), [t\(2;17\)\(p23;q23\)](#), [t\(2;17\)\(p23;q25\)](#) or [t\(2;22\)\(p23;q11.2\)](#) can also be found.

## Genes involved and Proteins

Note these translocations involve ALK in 2p23, and either MSN in Xq11, TPM3 in 1q25, ATIC in 1q35, TFG in 3q21, NPM1 in 5q35, CLTC in 17q23, ALO17 in 17q25, and MYH9 in 22q11.2.

**Gene Name** [ALK](#)

Location 2p23

Protein 1620 amino acids; 177 kDa; glycoprotein (200 kDa mature protein) ; membrane associated tyrosine kinase receptor

**Gene Name** [MSN](#)

Location Xq11

Protein 576 amino acids, 68 kDa; cytoskeleton protein; binds to the plasma membrane and interacts with actin.

**Gene Name** [TPM3](#)

Location 1q25

Protein 284 amino acids, 33 kDa; coiled coil structure; role in Calcium dependant actin-myosin interaction

**Gene Name** [ATIC](#)

Location 2q35

Protein 591 amino acids, 64 kDa; bifunctional purine biosynthesis:9th and 10th step of the de novo purine synthesis

**Gene Name** [TFG \(tropomyosin receptor kinase-fused gene\)](#)

Location 3q21  
Protein 406 amino acids, 44 kDa; widely expressed  
Somatic mutations apart from the TFG-ALK herein described, TFG is also known to be fused to NTRK1 in a subset of [thyroid papillary carcinomas](#)

**Gene Name** [NPM1](#)

Location 5q35  
Protein nuclear localisation; RNA binding nucleolar phosphoprotein involved in preribosomal assembly

**Gene Name** [CLTC](#)

Location 17q23  
Protein 1675 amino acids, 191 kDa; Component of the vesicles matrix originated from the plasma membrane or the golgi

**Gene Name** [ALO17](#)

Location 17q25  
Protein 1599 amino acids

**Gene Name** [MYH9](#)

Location 22q11  
Protein 1960 amino acids; 227 kDa; binds actin; protein of the cytoskeleton

**Result of the chromosomal anomaly**

**Hybrid gene**

Description 5' partner - 3' ALK

**Fusion Protein** N-term amino acids from the partner gene fused to the 562 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein.

**To be noted**

ALK and some of the above ALK partners, or closely related genes, are found implicated both in anaplastic large cell lymphoma and in [inflammatory myofibroblastic tumours](#); this is a new concept, that 2 different types of tumour may result from the same chromosomal/genes rearrangement.

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