

# Leukaemia Section

## Mini Review

## Anaplastic large cell lymphoma (ALCL)

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### 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).

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

### Note

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 80% of the cases), or, more rarely: MSN, TPM3, ATIC, TFG, or CLTCL1 (these latter being "cytoplasm only" or cytoplasmic and/or membrane restricted ALK+ ALCL).

## Cytogenetics

### Cytogenetics morphological

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), 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, or CLTCL1 in 22q11.

### ALK

#### Location

2p23

#### Protein

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

### MSN

#### Location

Xq11

#### Protein

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

### TPM3 (tropomyosin alpha chain)

#### Location

1q25

### Protein

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

### ATIC

#### Location

2q35

#### Protein

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

### 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.

### NPM1

#### Location

5q35

#### Protein

Nuclear localisation; RNA binding nucleolar phosphoprotein involved in preribosomal assembly.

### CLTCL1

#### Location

22q11.2

#### Protein

1640 amino acids, 187 kDa; component of the coat of vesicles originated from the plasma membrane or the golgi.

## Result of the chromosomal anomaly

### Hybrid gene

#### Description

5' partner - 3' ALK.

### Fusion protein

#### Description

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

### Note

ALK and some of the above ALK partners, or closely related genes, are found implicated 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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