Anaplastic large cell lymphoma (ALCL)

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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.

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 yrs survival, while ALK- ALCL cases have a much poorer prognosis (5 yrs 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 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 morphological**

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Description</th>
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<tr>
<td>t(2;5)(p23;q35)</td>
<td>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)(p23q23), t(2;17)(p23q25) or t(2;11)(p23q11.2).</td>
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**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.

**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**

| 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. |

**CLTC**

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

**ALO17**

| Location | 17q25 |
| Protein | 1599 amino acids. |

**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
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 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.

References


Lamant L, Dastugue N, Pulford K, Delsol G, Mariàmè B. A new fusion gene TPM3-ALK in anaplastic large cell lymphoma created by a (1;2)(q52;p23) translocation. Blood. 1999 May 1;93(9):3088-95

Rosenwald A, Ott G, Pulford K, Katzenberger T, Kühl J, Kalla J, Ott MM, Mason DY, Müller-Hermelink HK, t(1;2)(q52;p23) and t(2;3)(p23;q21): two novel variant translocations of the t(2;5)(p23;q35) in anaplastic large cell lymphoma. Blood. 1999 Jul 1;94(1):362-4


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