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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 agressive 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 involve-ment 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 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

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.

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; coilde coil structure; role in Calcium dependant actin-myosin interaction.

ATIC

Location
2q35

Protein
591 amino acids, 64 kDa; bifunctional purine biosythesis: 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 de 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.

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