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Anaplastic large cell lymphoma, ALK-positive and anaplastic large cell lymphoma ALK-negative

Introduction

In the 3rd edition of the WHO Classification of Hematopoietic Neoplasms, anaplastic lymphoma kinase-positive (ALK^+) and anaplastic lymphoma kinase-negative (ALK^-) anaplastic large cell lymphoma (ALCL) were considered as a single disease entity and defined as lymphomas consisting of lymphoid cells that were usually large with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei.[1] The cells are CD30-positive[2] and most cases express cytotoxic granule-associated proteins[3,4] and EMA.[5] It became clear that while ALCL expressing ALK constituted a relatively homogeneous entity, cases with similar morphology and phenotype but lacking ALK expression were much more heterogeneous. In the 4th WHO classification, ALCL, ALK^+ is a distinct entity and ALCL cases without ALK expression are a provisional entity.[6] ALK^+ ALCL are associated with a chromosomal abnormality, the t(2;5)(p23;q35), that fuses part of the nucleophosmin (NPM) gene on chromosome 5q35 to a portion of the ALK (anaplastic lymphoma kinase) receptor tyrosine kinase gene on chromosome 2p23, resulting in the expression of a unique chimeric NPM-ALK protein.[7,8] Besides the t(2;5), at least eleven variant translocations involving ALK gene at p23 have been recognized. All result in upregulation of ALK fusion protein. Primary systemic anaplastic large cell lymphoma, both ALK^+ and ALK^-, must be distinguished from ALCL of primary cutaneous type and from other subtypes of T or B-cell lymphoma with anaplastic features and/or CD30 expression (Jaffe 2001).

Anaplastic large cell lymphoma, anaplastic lymphoma kinase-positive

Clinical features

Anaplastic large cell lymphoma (ALCL) accounts for 5% of all non-Hodgkin's lymphoma and 10-30% of childhood lymphomas.[9] We have now collected more than 400 cases of ALK^+ ALCL. Majority of patients are under forty years of age, with a significant proportion between 10 and 19 years and a male predominance. ALCL positive for the ALK protein frequently involves both lymph nodes and extranodal sites. Extranodal sites commonly include skin (26%), bone (14%), soft tissues (15%), lung (11%) and liver (8%).[9-11] 75% of these patients present with stage IV disease. Several cases with a leukemic presentation have been

reported.[12] The incidence of bone marrow involvement is approximately 10% when analyzed with H&E, but increases significantly (30%) when immunohistochemical stains for CD30, EMA and/or ALK are used.[13] This is due to the fact that bone marrow involvement is often subtle with only scattered malignant cells that are difficult to detect by routine examination.

Morphologic features

ALCLs positive for the ALK protein show a broad morphologic spectrum.[6,14] However, all cases contain a variable proportion of large cells with eccentric horseshoe or kidney shaped nuclei often with an eosinophilic region near the nucleus, referred to as "hallmark" cells. Five morphologic patterns are recognised in the 4th edition of the WHO classification:[6] ALCL, common pattern (70%); ALCL, lymphohistiocytic pattern (10%);[15,16] ALCL, small cell pattern (10%);[17] ALCL, Hodgkin-like pattern (1-3%)[18] and ALCL with "composite pattern" (10-20% of cases) defined as having features of more than one pattern in a single lymph node biopsy. Other histologic patterns can be seen although they are not recognized as distinctive patterns in the WHO classification. They are often responsible for diagnostic difficulties (i.e. giant cell rich pattern, sarcomatoid pattern, "signet ring" cell pattern.).[6]

Immunophenotype

In most cases, virtually all neoplastic cells show strong CD30 staining on the cell membrane and in the Golgi region.[2,6] The majority of ALCLs are positive for EMA.[5] The great majority of ALCLs express one or more T-cell antigens and/or NK cell antigens.[9,14,19] However, due to loss of several pan T-cell antigens, some cases may have an apparent "null cell phenotype. CD3, the most widely used pan T-cell marker, is negative in more than 75% of cases.[14] This tendency for loss of CD3 is also seen in ALCL, ALK-negative. CD5 and CD7 are often negative as well. CD2 and CD4 are more useful and are positive in a significant proportion of cases. CD43 is expressed by more than two thirds of the cases, but this antigen lacks lineage specificity. Furthermore, most cases exhibit positivity for the cytotoxic associated antigens TIA-1, granzyme B, and/or perforin.[3,4] CD8 is usually negative, but rare $CD8^+$ cases exist. Occasional cases are positive for CD68/KP1 but not CD68/PGM1. CD15 expression is rarely observed and when present only a small proportion of the neoplastic cells are stained. ALCLs are consistently negative for EBV (i.e. EBER and LMP1).[6] Most ALK^+ ALCL are negative for Bcl-2. A number of other antigens are expressed in ALCL but they are not of diagnostic value. The ALK staining may be cytoplasmic, nuclear and nucleolar or may be restricted either to the cytoplasm or more rarely to the cell membrane.[6,20] ALK expression is virtually specific for ALCL since it is absent from all postnatal normal human tissues except rare cells in the brain.[20] It is also absent from human lymphoid neoplasms other than ALCL with the exception of ALK^+ large B-cell lymphomas,[21,22] and a novel form of histiocytosis seen in infancy that is ALK^+.[50]

Genetic/molecular findings

Approximately 90% of ALCLs show clonal rearrangement of the T-cell receptor (TCR) genes irrespective of whether they express T-cell antigens or not.[3] The majority of ALCL are associated with a reciprocal translocation, t(2;5)(p23;q35) which juxtaposes the gene at 5q35 encoding nucleophosmin (NPM), a nucleolar-associated phosphoprotein, with the gene coding for a receptor tyrosine kinase, the anaplastic lymphoma kinase (ALK), at 2p23.[7] Polyclonal and monoclonal antibodies recognizing the intracellular portion of ALK react with both NPM-ALK protein and with the full-

length ALK protein but no normal lymphoid cells express full-length ALK, and as a consequence immunostaining with anti-ALK has been used as a means of detecting ALCL cases carrying the t(2;5) translocation.[8,20] However, variant translocations involving ALK and other partner genes on chromosomes 1, 2, 3, 17, 19 and 22 also occur.[19,23-29] All result in upregulation of ALK, but the distribution of the staining varies depending on the translocation.[6] The classic t(2;5) leads to positive staining for ALK in both the nucleolus, nucleus and the cytoplasm.[30] In the variant translocations, often only cytoplasmic staining will be observed.[6] Besides the t(2;5), at least eleven variant translocations involving ALK gene at p23 have been recognized. In all these translocations the ALK gene is placed under the control of the promotor of genes which are constitutively expressed in lymphoid cells hence the ALK gene expression.[6] The most frequent ALK variant translocation is the t(1;2)(q25;p23) translocation in which the TPM3 gene on chromosome 1 (which encodes a non-muscular tropomyosin protein) is fused to the ALK catalytic domain.[23] However, in cases associated with the t(1;2) translocation which express the TPM3-ALK protein (104 kD), ALK staining is restricted to the cytoplasm of malignant cells and in virtually all cases one sees a stronger staining on the cell membrane . This staining pattern is found in 15-20% of ALK$^+$ ALCL. The genes fused with ALK in the t(2;3)(p23;q11) and the inv(2)(p23 q35) have also been identified.[24,25] Two different fusion proteins of 85 and 97 kD (TFG-ALKshort and TFG-ALKlong) are associated with the t(2;3)(p23;q11) which involves the TFG gene (TRK-fused gene). The inv(2)(p23 q35) involves ATIC gene (formerly known as pur-H) which encodes the 5-Aminomidazole-4-carboxamide-ribonucleotide transformylase-IMP cyclohydrolase (ATIC) which plays a key role in the *de novo* purine biosynthesis pathways.[24,27] In TFG-ALK and ATIC-ALK positive ALCLs, ALK staining is restricted to the cytoplasm in a diffuse pattern. Rare cases of ALCL show a unique granular ALK cytoplasmic staining pattern.[26] In these cases, the ALK gene is fused to CLTC gene which encodes the clathrin heavy polypeptide which is the main structural protein of coated vesicles. The sequence of the fusion gene suggests that these tumors might have reciprocal translocations involving breakpoints at 17q11-qter and 2p23. In a single report, moesin (MSN) gene at chromosome Xq11-12 was identified as a new ALK fused gene (MSN-ALK fusion protein) in a case of ALCL with a distinct ALK membrane restricted pattern.[31] The particular membrane staining pattern of ALK is probably due to the binding properties of the N-terminal domain of moesin to cell-membrane associated proteins. In the recently reported translocation of dicentric (dic) (2;4)(p23;q33) the ALK partner has not been identified.[32]

In a recent study, the supervised analysis by class comparison between ALK$^+$ and ALK$^-$ ALCL tumors provided distinct molecular signatures.[33] Among the 117 genes over-expressed in ALK$^+$ ALCL, BCL-6, PTPN12 (tyrosine phosphatase), serpinA1 and C/EBPβ were the four top genes, being over-expressed with the most significant p-value.

Clinical course and prognostic factors

The international prognostic index (IPI) appears to be of some value in predicting outcome, although less so than in other types of lymphoma.[34,35,37] Overall, in multivariate analysis three prognostic factors remain significant: mediastinal involvement, visceral involvement defined as lung, liver, or spleen involvement and skin lesions.[11] The most important prognostic indicator is ALK positivity, which has been associated with a favorable prognosis in series from North America, Europe, and Japan [8,34,35] No differences have been found between

NPM-ALK$^+$ tumors and tumors showing variant translocations involving ALK and fusion partners other than NPM.[34] The overall 5-year survival rate in ALK$^+$ ALCL is close to 80%, in contrast to only 48% in ALK$^-$ ALCL. In the recent study by Savage[38] and co-workers the overall 5-year survival of ALK$^+$ ALCL patients is only of 70% due to the exclusion of pediatric patients. Furthermore, the prognosis of PTCL-NOS with high CD30 expression, a group that can be difficult to differentiate histologically from ALK$^-$ ALCL, has a poor prognosis and a 5y OS of 19% compared to ALK$^-$ ALCL: 49%. Relapses are not uncommon (30% of cases), but often remain sensitive to chemotherapy.[39] Quantitative PCR for NPM-ALK in bone marrow and peripheral blood at diagnosis could allow identification of patients at risk of relapse.[40] In a recent study (unpublished results), we have found an ALK exon 28 deletion in 5/7 relapsing patients whereas it was never found in control patients. The presence of this deletion seems to be strongly associated with relapse.

Anaplastic large cell lymphoma anaplastic lymphoma kinase-negative

ALK$^-$ anaplastic large cell lymphoma (ALCL) is less well characterized and it is controversial whether tumors with morphologic and phenotypic features consistent with ALCL, but negative for ALK, should be considered a phenotypic variant of systemic ALCL or a different entity. We have no clear phenotypic or molecular markers to definitively answer this question. However, the clinical course of ALK$^+$ ALCLs compared to ALK$^-$ ones suggests that the latter represent a different, possibly heterogeneous, entity. However, there are also clinical data to suggest that ALK$^-$ ALCL have a better prognosis than PTCL, NOS.[39] Some experienced pathologists think that ALK$^-$ ALCLs, in the light of their poor prognosis and partially overlapping phenotype, should simply be considered an *anaplastic variant* of PTCL NOS.[37,42]

Definition of the disease

In the 4th edition of the WHO classification, ALK$^-$ ALCL is a provisional entity defined as "a neoplasm that is not reproducibly distinguishable on morphological grounds from ALK$^+$ ALCL".[43] Lymphoma cells are uniformly positive for CD30, express a T or null phenotype and a significant proportion of cases are positive for cytotoxic granule-associated proteins.

Clinical features

Unlike ALK$^+$ ALCL, the peak incidence of ALK$^-$ ALCL is in adults (40-65 years) without a clear male or female preponderance. Patients present with peripheral and/or abdominal lymphadenopathy and/or extranodal tumor, although extranodal involvement is less common than in ALK$^+$ ALCL.[9] Skin involvement must be distinguished from primary cutaneous ALCL, and in a case with only cutaneous involvement, the presumptive diagnosis is primary cutaneous ALCL.

Morphologic features

Like ALK$^+$ ALCL, ALK$^-$ ALCL shows a broad spectrum of morphologic features. On morphologic ground alone some cases are strictly similar to "ALCL common pattern" including "hallmark" cells that typically grow within sinuses. Some other cases consist of more pleomorphic cells with a high nuclear: cytoplasmic ratio.[8,34,38,44] Morphological features suggestive of aggressive classical Hodgkin lymphoma, either nodular sclerosis, grade 2, or lymphocyte depleted but not supported by immunophenotype may be observed. Of note, cases corresponding to "ALCL small

cell pattern" are not recognized in the WHO classification since there is today no phenotypic or molecular markers that allow to differentiate ALK⁻ ALCL from PTCL NOS expressing CD30.

Immunophenotype

In addition to homogeneous CD30 staining, more than half of all cases express one or more T-cell markers. Positive staining for CD3 is more common than in ALK⁺ ALCL. CD2 and CD4 are positive in significant proportion of cases, whereas CD8⁺ cases are rare. As in ALK⁺ ALCL loss of one or more T cell markers is frequently noted. In cases with a "null cell" phenotype, a diagnosis of Hodgkin lymphoma rich in neoplastic cells must be excluded. PAX5 is a very useful marker in this setting, as nearly all cases of Hodgkin lymphoma and "gray zone" lymphoma express PAX5. In contrast to ALK⁺ ALCL, expression of EMA is variable. Some pathologists have a tendency to make the diagnosis of ALK⁻ ALCL only in cases with typical morphologic features and coexpression of CD30 and EMA. The cytotoxic-associated markers TIA-1, granzyme B, and/or perforin are found in a significant proportion of cases. ALK⁻ ALCLs are consistently negative for EBV (i.e. EBER and LMP1).[43]

Genetic/molecular findings

T-cell receptor genes (TCR) are clonally rearranged in majority of cases, whether or not they express T-cell antigens. No recurrent primary cytogenetic abnormalities have been described. However, some studies indicate a tendency of ALK⁻ ALCL to differ in terms of chromosome losses or gains from both PTCL, NOS and ALK⁺ ALCL.[45, 46] In a recent study, ALK⁻ ALCL with complex chromosomal abnormalities were found to have a significantly shorter overall survival.[47] The molecular signature of ALK⁻ ALCL includes overexpression of CCR7, CNTFR, IL22 and IL21 genes but does not allow to identify the underlying oncogenic mechanism associated with these tumors.[47] In addition, these results do not provide definitive evidence as to whether ALK⁻ ALCL is more closely related to ALK⁺ ALCL or to peripheral T-cell lymphoma, NOS.[33,47]

Clinical course and prognostic factors

As mentioned above the clinical outcome of ALK⁻ ALCL with conventional therapy is clearly poorer than that of ALK⁺ ALCL.[49] In the recent study by Savage[39] and co-workers the overall 5-year survival of ALK⁻ ALCL patients is only of 49% (compared to 70% for ALK⁺ ALCL). Furthermore, PTCL-NOS with high CD30 expression, a group that can be difficult to differentiate histologically from ALK⁻ ALCL, has a poorer prognosis and a 5y OS of 19%.

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