Pathobiology of ALK-negative anaplastic large cell lymphoma

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Abstract

The authors revise the concept of ALK-negative anaplastic large cell lymphoma (ALCL) in the light of the recently updated WHO classification of Tumors of Hematopoietic and Lymphoid Tissues both on biological and clinical grounds. The main histological findings are illustrated as well as the phenotypic, molecular and clinical characteristics. Finally, the biological rationale for possible innovative targeted therapies is presented.

Introduction

Anaplastic large cell lymphoma (ALCL) is a peripheral T-cell lymphoma (PTCL), representing around 2.3% of all lymphoid neoplasms, according to the World Health Organization (WHO) estimates.1,2 Originally described by Stein et al. in 1985,3 it has undergone a series of revisions, which have led to a more restrictive definition of the process.1,2,4,5 In particular, two different entities are recognized as systemic forms, the ALK+ and ALK-ALCL.1,2,6 The former being characterized by the deregulated expression of chimeric proteins expressing the intracytoplasmic domain of the anaplastic lymphoma kinase (ALK) gene. Noteworthy, in the last edition of the WHO classification, ALK-ALCL was regarded as a provisional entity.1,2 However, emerging evidences suggest it represents a distinctive condition.7 On the other hand, differently from what initially reported by Stein et al.,3 the cutaneous variant was recognized as a different disease.8

Morphology

According to the WHO classification, ALK-ALCL, like the ALK+ form, includes morphologic variants: common, giant cell-rich, lympho-histiocytic, and Hodgkin-like.1,2,9,10 All morphological variants are characterized by a variable proportion of large hallmark cells with eccentric horse-shoe or kidney shaped nuclei). The giant cell-rich type is characterized by several multinucleated elements, often provided with Reed-Sternberg-like features and prominent intra-sinusoidal diffusion.1,2,9,11,12 The lymphohistiocytic variant displays a marked variability of the neoplastic cell size that ranges from small to large. These are almost obscured by abundant reactive histiocytes with eccentric nuclei, a finding that can lead to a misdiagnosis of hyper-immune reaction.1,2,9,12-15 Interestingly, transition from one histotype to the other is at times recorded within the same node (mixed variant) or in different nodes taken from the same patient at the time of diagnosis or in relapse: these modifications might correspond to intra-clonal modulation or different interaction between the tumor and micro-environment.5,16 Finally, the so-called ALCL of the Hodgkin-like type deserves special attention.17 It was originally described as a form of the tumor, presenting in young people with a bulky mediastinal mass and consisting of anaplastic cells arranged in nodules surrounded by sclerotic bands, as seen in nodular sclerosing Hodgkin’s lymphoma (NSHL).17 Following the introduction of the REAL Classification,5 which regarded it as a provisional entity, such diagnosis was by means also applied to cases of aggressive HL that could not be easily differentiated from ALCL, both on morphologic and phenotypic grounds.5 This led to a diffuse skepticism on the existence of such variant: it was considered a basket more than an entity. However, although rare, bona fide examples of ALK-ALCL of the Hodgkin-like type can be encountered. These are characterized by homogeneous CD30 positivity, lack of CD15 and B-cell activator protein (BSAP), variable expression of T-cell antigens, CD45 and epithelial membrane antigen (EMA), Epstein-Barr virus (EBV) negativity and clonal TCR gene rearrangement.

Phenotype

Neoplastic cells of ALK ALCL carry a distinctive phenotypic profile irrespectively of the histotype.1,2,9,13,14 They regularly express CD30,1,2,9,13,14 a glycoprotein of 120 kD carried by lymphoid elements following activation. At immunohistochemical analysis, the antibodies against CD30 produce different types of positivity: membrane-bound, dot-like in the Golgi area (corresponding to the accumulation of the 90 kD protein precursor), and diffuse.19 The first two patterns are exclusive of lymphoid elements with the exception of embryonic carci-

Molecular genetics

Recently, by using a comparative genomnic hybridization (CGH) platform, Salaverria et al.26 identified chromosomal imbalances in 65% of ALK cases, within a cohort of 31 tumors. In particular, gains of 1q and 6q21 were more frequently observed.25 Interestingly, few recurrent chromosomal imbalances were found in common with ALK-ALCL (gains of 7 and 6q and 13q losses), confirming that all ALCLs probably share common pathogenetic events (see below).

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As far as gene expression profiling (GEP) is concerned, Thompson et al.25 initially demonstrated the ability of GEP to correctly distinguish between ALK+ and ALK ALC L based on the analysis of their transcriptome and suggested that some pathogenetic mechanisms might be shared by these two entities, basing on the common expression of certain genes in both ALK+ and ALK cases.

Subsequently, Lamant et al.26 confirmed that the different morphological variants as well as ALK+ and ALK ALC L could be distinguished based on the expression of specific genes. Specifically, ALK ALC L were found to over-express CCR7, CNTFR, IL22 and IL21.

Our group then included some ALC L in a GEP study on PTCLs.29 Interestingly, we found that ALC L can be roughly distinguished from other PTCLs irrespectively of the ALK status, confirming the idea of common pathogenetic events. Finally, Piva et al.7 showed, that ALC L are molecularly distinct from PTCL/NOS. To this regard, grippingly, a predictive analysis allowed to identify 34 probe sets capable to distinguish ALC L from other PTCLs. Furthermore, it was possible to clearly differentiate ALK+ and ALK cases according to their GEPs, basing on the expression of selected genes, including GAS1, an ALK dependent molecule.7

More recently, Eckeler et al.23 studied isolated cells from ALC L cases. Interestingly, the analysis supported the derivation of ALC L from activated T cells, though it was not possible to identify a specific counterpart. Surprisingly, only few genes were differentially expressed between systemic and cutaneous ALC L despite their different clinical behavior, and between ALK ALC L and classical Hodgkin lymphoma, despite their different cellular origin.23

Clinical behavior

ALK ALC L is an aggressive lymphoma which frequently presents in advanced clinical stage (III-IV) with B-symptoms, and extra-nodal involvement, as other PTCLs do.11,30 Bone marrow involvement is detected in up to 30% of cases, being a relevant prognostic feature.31,33 Importantly, ALC L display quite different clinical features depending on the expression of ALK+ and ALK cases according to their GEPs, basing on the expression selected genes, including GAS1, an ALK dependent molecule.7

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Conclusions

Although ALK ALC L is still quoted as a provisional entity, increasing evidences, both biological and clinical, suggest that it actually represent a tumor with distinctive features.

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