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Short Communication

Anaplastic large cell lymphoma, ALK-negative

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Abstract

Review on Anaplastic large cell lymphoma, ALK-negative, with data on clinics, and the genes involved.

Keywords
Anaplastic large cell lymphoma, ALK-negative

Clinics and pathology

Disease

Anaplastic large cell lymphoma (ALCL), ALK-negative is a CD30-positive T-cell non-Hodgkin lymphoma that by definition resembles ALCL, ALK-positive but lacks ALK expression (Mason, Harris et al. 2008).
ALCL, ALK-negative was classified as a provisional entity distinct from ALCL, ALK-positive in the 2008 WHO classification, and is anticipated to be upgraded to a definite entity in the 2016 WHO update (Swerdlow, Campo et al. 2016).

Etiology

The etiology of ALCL, ALK negative is unknown.

Epidemiology

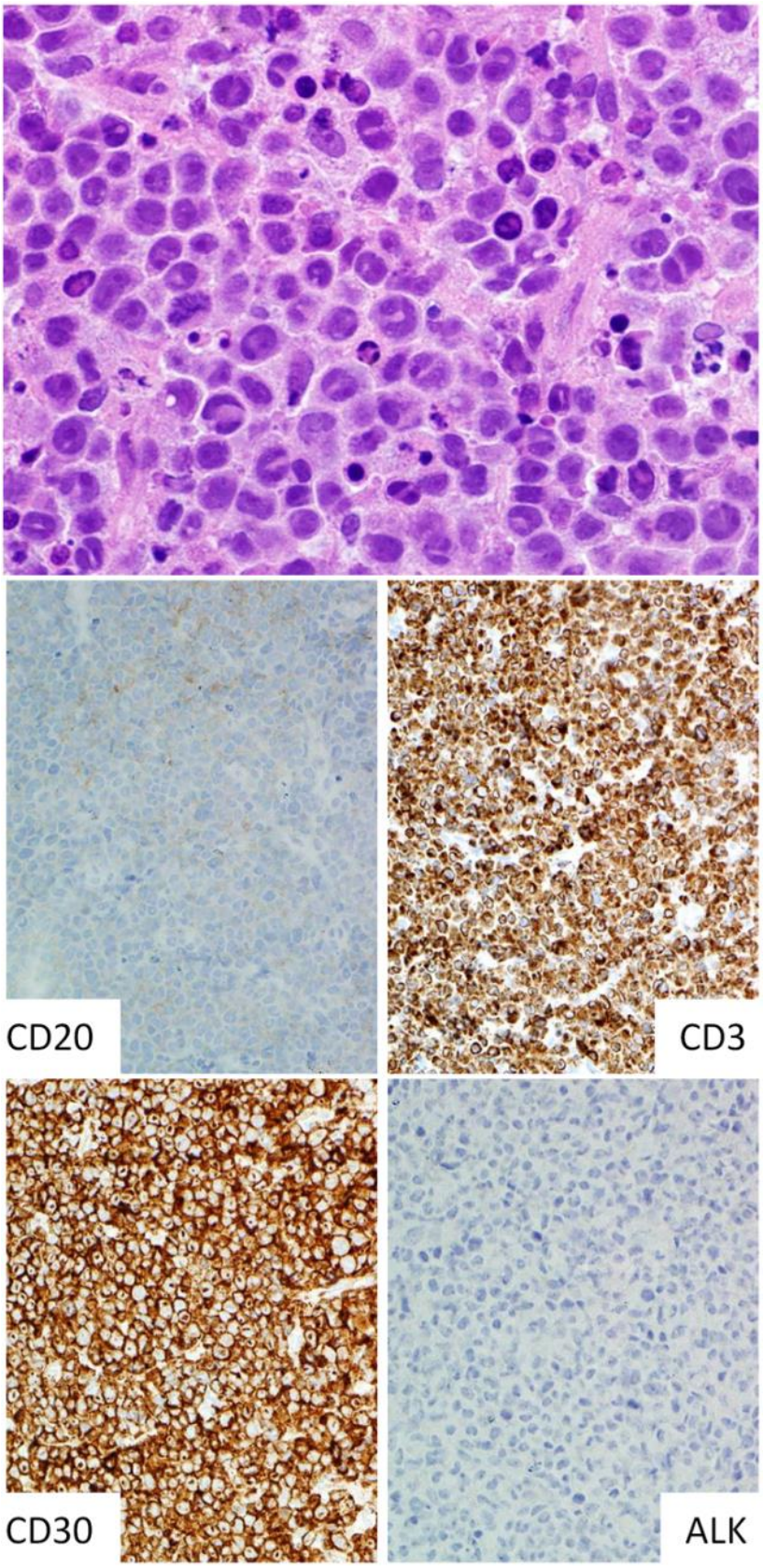
ALCL, ALK-negative makes up between 2.6% and 9.4% of T-/NK-cell non-Hodgkin lymphomas, with the lowest proportion occurring in Asia and the highest in Europe (Vose, Armitage et al. 2008). ALCL, ALK-negative generally occurs in older patients, with a median age of diagnosis of 55-60 years, compared to 25-35 years for ALK-positive ALCL (Ferreri, Govi et al. 2013).
Males are affected more commonly than females (M:F, ~1.5:1).

Clinics

Patients with ALCL, ALK-negative typically present with lymphadenopathy, often with stage III/IV disease, and B symptoms (ten Berge, de Bruin et al. 2003). Extranodal sites also may be involved, including skin, bone, and soft tissues. Secondary cutaneous involvement by ALCL, ALK-negative must be distinguished from primary cutaneous ALCL, which is a distinct entity (Bekkenk, Geelen et al. 2000).

Pathology

By definition, the morphologic appearance is similar to that seen in ALCL, ALK-positive (Mason, Harris et al. 2008). Specifically, most cases resemble the so-called "common" pattern of ALK, ALK-positive and show sheet-like growth of tumor cells, sometimes sparing residual lymphoid follicles (Delsol, Falini et al. 2008). Sinusoidal involvement is common, and cohesive clusters of intrasinusoidal tumor cells may mimic metastatic carcinoma. The tumor cells typically are large and may show significant pleomorphism. So-called "hallmark" cells, with horseshoe-shaped or reniform nuclei, always can be identified (Benharroch, Meguerian-Bedoyan et al. 1998). Immunophenotyping studies are essential to the diagnosis of ALCL, ALK-negative. All cases express CD30 by definition. Aberrant loss of pan-T-cell antigen expression is common, and about two-thirds of cases express cytotoxic proteins (TIA1, granzyme B, or perforin) (Savage, Harris et al. 2008). ALK protein is absent.



ALCL, ALK-negative. The tumor is composed of sheets of large pleomorphic cells, some with horseshoe-shaped nuclei ("hallmark" cells; H&E, top). By immunohistochemical stains the tumor cells are negative for the B-cell marker, CD20; positive for the T-cell marker, CD3; positive for CD30; and negative for ALK.

Treatment

ALCL, ALK-negative is typically treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy, often followed by autologous stem cell transplantation (Bennani-Baiti, Ansell et al. 2016). New targeted agents such as brentuximab vedotin and histone deacetylase inhibitors have demonstrated efficacy in relapsed and refractory disease.

Prognosis

The prognosis for ALCL, ALK-negative is poorer than for ALCL, ALK-positive, with a 5-year overall survival (OS) rate of 49% compared to 70% for the latter (Savage, Harris et al. 2008). However, prognosis is better than for most other types of T-cell non-Hodgkin lymphomas, including peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). Recent data have shown that ALCL, ALK-negative is a genetically heterogeneous disease, and that outcomes vary widely based on genetic subtype (Parrilla Castellar, Jaffe et al. 2014). Specifically, 5-year OS was very good (90%) in patients carrying DUSP22 rearrangements, poor (17%) in TP63/ -rearranged cases, and intermediate (42%) in patients lacking ALK/, DUSP22, and TP63 rearrangements.

Genetics

Recurrent somatic mutations in the JAK1/ and/or STAT3/ genes have been reported in 18% of ALCL, ALK-negative (Crescenzo, Abate et al. 2015). JAK1 mutations were most commonly G1097D/S, while STAT3 mutations included Y640F, N647I, D661Y, and A662V.

Cytogenetics

Cytogenetics morphological

Copy number losses involving PRDM1 (6q21) and/or TP53/ (17p13) are recurrent in ALCL, ALK-negative, and have been associated with poor survival (Boi, Rinaldi et al. 2013).

Recurrent chromosomal rearrangements involving the DUSP22 -IRF4/ locus on 6p25.3 are present in ~30% of ALCL, ALK-negative (Feldman, Law et al. 2009; Feldman, Dogan et al. 2011; Parrilla Castellar, Jaffe et al. 2014). The most common partner is a non-genic region on 7q32.3. DUSP22 rearrangements are associated with decreased expression of the dual-specificity phosphatase gene, DUSP22; lack of cytotoxic marker expression; favorable prognosis; and distinct morphologic features (King, Dao et al. 2016).

Rearrangements involving TP63, most often partnering with TBL1XR1/ occur in ~8% of ALCL, ALK-negative and have been associated with poor prognosis (Vasmatzis, Johnson et al. 2012; Parrilla Castellar, Jaffe et al. 2014).

Gene fusions involving tyrosine kinase genes other than ALK have been reported in ALCL, ALK-negative, including TYK2 (t(10;19)(q24;p13) (NFKB2/TYK2), t(1;19)(p34;p13) (PABPC4/TYK2) and ROS1 (t(6;10)(q22;q24) (NFKB2/ROS1), (NCOR2/ROS1)(Crescenzo, Abate et al. 2015).

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