Leukaemia Section
Short Communication

Aggressive natural killer leukemia (ANKL)

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Abstract

Review of the cytogenetics abnormalities and genes involved in aggressive natural killer leukemia (ANKL) which is a rare form of leukemia mostly reported in East Asia.

Keywords
Aggressive natural killer leukemia

Clinics and pathology

Disease

Aggressive natural killer leukemia (ANKL), previously known as "large granular lymphocyte (LGL) leukemia", is a rare neoplastic proliferation of mature natural killer (NK) cells described in the WHO classification of 2008 as a distinct entity separated it from T-cell LGL leukemia . The NK leukemic infiltration is predominantly systemic, involving the blood, bone marrow, liver, spleen, and less frequently, lymph nodes. ANKL has a rapidly fatal clinical course with a median survival of around 2 months (Suzuki et al, 2004).

Phenotype/cell stem origin

Morphologically, the leukemic NK cells are slightly larger than normal LGLs. There is an ample amount of pale or slightly basophilic cytoplasm containing fine or coarse azurophilic granules. Bone marrow shows massive or focal infiltration by NK leukemic cells that can be intermingled reactive histiocytes with hemophagocytosis. In tissue sections, NK cells show diffuse or patchy destructive infiltrate. Necrosis, apoptosis, angioinvasion, and angiodestruction are common findings.

It is believed that ANKL originates from mature NK cells. The neoplastic NK cells are typically $CD2^+$, surface $CD3^-$, cytoplasmic $CD3\varepsilon^+$, $CD56^+$, and EBV^+ with germline configuration of T-cell receptor (TCR) and immunoglobulin (Ig) genes. The exclusive expression of CD2 and CD56 and the absence of CD3 and TCRs in ANKL reflect its NK-cell origin.

A high expression rate of CD16 (75%) is also characteristic of ANKL (Li C et al 2014). CD16 is usually not expressed in other NK neoplasms, suggesting that CD16 is a specific marker for ANKL. Cases of ANKL are also positive for cytotoxic molecules and found to have high serum levels of CXCR1, CCR5 and soluble Fas ligand, suggesting that the chemokine system plays an important role in the systemic infiltration of NK leukemic cells and liver dysfunction (Makishima H et al, 2007).

Etiology

ANKL is almost always associated with Epstein-Barr virus (EBV) infection. EBV plays a role in the pathobiology of ANKL and is considered responsible for its aggressive clinical features.

Epidemiology

This rare leukemia has a distinct geographic distribution with the most prevalence among East Asian populations. A fewer than 200 cases have been described in the literature, as a small series or single case report.

The disease most commonly affects young to middle aged adults with a median age of 40 years. Both sexes are affected with a slight male predominance (Lima, M 2013; Zhang et al 2014).

Clinics

Patients usually present extremely ill with high fever, significant weight loss, cytopenia, jaundice and abnormal liver function. Hepatosplenomegaly is often massive accompanied by lymphadenopathy but less commonly skin lesions. Involvement of the gastrointestinal tract is present in many patients, and infiltration of leukemic NK cells into the cerebrospinal and peritoneal fluids, with clinical ascites, has been reported. The hemophagocytic syndrome is frequent at diagnosis or during the disease course, resulting from uncontrolled monocyte/macrophage activation in response to cytokines produced by the neoplastic NK-cells. Despite treatment, ANKL is rapidly progressive disease and most patients die within few weeks from disseminated intravascular coagulation and multi-organ failure (Liang and Graham 2008; Lima, 2013).

Treatment

ANKL is refractory to the available chemotherapies. L-asparaginase containing chemotherapy regimen followed by allogeneic stem cell transplantation appears to slightly prolong overall survival, but relapse is almost inevitable (Ishida F, 2012).

Prognosis

ANKL is a dismal disease with an almost uniform mortality. Survival is measured in days to weeks. The overall median survival is less than 2 months.

Cytogenetics

Cytogenetics morphological

Cytogenetic studies on ANKL are limited due to rarity of disease, and small samples marked with necrosis and mingled with inflammatory cells. Despite that, several studies have been reported some of them using comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) techniques (Siu L et al 1999; Ohshima et al 2002). Chromosome abnormalities are found in approximately 75% of cases including pseudodiploidy (57%), hyperdiploidy (30%), and hypodiploidy (13%). Although no disease-specific translocation(s) have not been identified, a complex karyotype with unbalanced rearrangements is found in most cases. Deletion of 6q appears to be the most frequent. Other recurrent abnormalities include +X, i(1q), dup(1q), i(7q), +8, del(13q), del(17p), i(17q), and 11q23 rearrangement (Wong K, 1999; Nazarullah et al 2015). Deletion of 17p/ TP53 was confirmed in at least one case with add(17p). Nakashima et al performed BAC-array CGH on 10 cases of ANKL to detect genomic imbalances across the whole genome; the recurrent regions characteristic of this leukemia, were gain of chromosome 1q23-q31 and loss of 7p15.-p22 and 17p13 (Nakashima et al, 2005). Further investigation by the same group using oligo-array CGH combined with gene-expression profiling of 32 clinical samples and 7 cell lines were used in an effort to delineate the molecular pathogenesis involved NK neoplasms (Karube K et al 2011). The gains of 1q31.2-44, 7q11.22-36.3, 16p13.3 and 11p15.5, and the losses of 6q16.1-27 and 7p15.3-22.2, were found in more than 8 cases (20%).

Genes involved and proteins

Note

Karube at al found that the 6q21 region encompassing POPDC3, PREP, PRDM1, ATG5, AIM1, LACE1, and FOXO3 was the most frequently deleted region of the whole genome. Both FOXO3 and PRDM1expression were down-regulated in most NK-cell neoplasms compared with normal NK normal cells. The seven candidate genes were transduced into NK cell lines and forced re-expression was induced. Re-expression of FOXO3 and PRDM1 in NK cell lines suppressed cellular proliferation, but this was not the case after re-expression of the other genes. Therefore, PRDM1 and FOXO3 are considered to be tumor suppressor genes play an important role in the pathogenesis of NK-cell neoplasms (Karube K et al 2011).

Yamanaka, et al study showed that dysregulation of microRNAs (miRNAs) has a significant role in the pathogenesis of NK-cell neoplasms. They demonstrated overexpression of two miRNA " MIR21and MIR155" in NK-cell lymphoma/leukemia primary specimens and cell lines. These two miRNAs act through PTEN and INPP5D (SHIP1), respectively, to regulate AKT1, a serine-threonine kinase involved in cell survival and proliferation. No translocations or genomic amplifications of the miR-2/17q23 or miR-155/12q21 locus have been identified in NK neoplasms. Recent reports suggest that EBV infection can lead directly to up-regulation of miR-21 and miR-155 which might be the first-hit genetic alterations in NK-cell pathogenesis. Finally, they proposed targeting miR-21 and/or miR-155 may represent a useful approach to treating NK-cell lymphoma/ leukemia (Yamanaka, et al, 2009).

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