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Leukaemia Section

Mini Review

NK cell neoplasias

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Clinics and pathology

Disease

Neoplasms of natural killer (NK) cells are rare, and have not been well characterized until the past decade. In the new WHO classification of hematolymphoid tumors, three categories of NK cell neoplasms are recognized:
- Extranodal NK/T cell lymphoma,
- Aggressive NK cell leukemia, and
- Blastic NK cell lymphoma.

Blastic NK cell lymphoma is morphologically and immunologically different from the first two categories, lacks EBV association, and there is little compelling evidence that it truly represents an NK cell neoplasm. In fact, recent studies suggest that this may be a neoplasm of probable precursor dendritic cells related to plasmacytoid monocytes (plasmacytoid dendritic cells). Since its lineage is still uncertain, this entity will not be discussed.

Phenotype/cell stem origin

NK cell represents a distinctive lineage of lymphocyte that is closely related to T cell. It shows many immunophenotypic and functional similarities with cytotoxic T lymphocyte, but differs in the lack of expression of surface CD3 molecule and T-cell receptor, and the absence of rearranged T-cell receptor genes. It characteris-tically expresses CD56 (neuronal cell adhesion molecule, N-CAM), which is also expressed in some cytotoxic T lymphocytes. NK cells can lyse target cells without prior sensitization (spontaneous antibody-independent MHC-unrestricted cytotoxi-city) via the NK receptors.

Etiology

The exact etiology is unknown, but a very strong association with Epstein Barr virus (EBV) has been demonstrated.

Epidemiology

NK cell neoplasms show strong geographic differences in their prevalence. They are more common in Asia, Mexico, and South America, but are very rare in the Western populations.

Clinics

They occur predominantly in the nose/nasopharynx, but sometimes in extranasal sites (most commonly skin), in middle-aged to elderly patients. Systemic involvement is uncommon at diagnosis but rarely, they may present initially in a leukemic form. The most common presenting symptoms are nasal obstruction, nasal discharge and epistaxis. The full-blown midfacial destructive and ulcerative lesions (hence the name midline granuloma) are much less commonly seen nowadays. Patients with aggressive NK cell leukemia present with high swinging fever, systemic symptoms and hepatosplenomegaly; they are usually extremely ill, with deranged liver function and coagulation profile.

Cytology

The neoplastic NK cells are often heterogeneous in appearance but some (particularly the circulating leukemic cells) may resemble large-sized normal large granular lymphocytes with ample amount of pale or lightly blue cytoplasm that contains fine or coarse azurophilic granules.

Pathology

The malignant infiltrate is diffuse, often with a prominent angiocentric and angiodestructive component. Coagulative necrosis and apoptosis are common. The cytological spectrum is variable, ranging from small, medium-sized, large or anaplastic cells, to a mixture of these cells. The cells often have irregularly folded nuclei and granular chromatin. In Giemsa-stained cytologic preparations, azurophilic granules are often detected in the cytoplasm. Reactive histiocytes with haemophagocytosis are sometimes found in the bone marrow, particularly for the leukemic form. NK cell neoplasms are characterised by an immunophenotype of CD2+, surface CD3-, cytoplasmic CD3e+, CD56+ and T cell receptor (TCR)-, lack of TCR gene rearrangement, and strong association with EBV.

Treatment

The disease is often resistant to chemotherapy. For extranodal NK/T cell lymphoma, the best results are obtained by radiotherapy with or without aggressive chemotherapy/stem cell rescue. Plasma or serum EBV DNA and tissue p73 gene hypermethylation assay can be used for monitoring of disease status or detection of minimal residual disease. Aggressive NK cell leukemia is treated by chemotherapy, but response is typically poor.

Evolution

Although extranodal NK/T cell lymphoma is usually localized at presentation, systemic progression often occurs, usually early in the course of disease. Common distant sites of involvement are the skin, liver, lung, gastrointestinal tract, testis, and rarely bone marrow. Patients with aggressive NK cell leukemia typically exhibit a rapidly progressive clinical course, with multi-organ failure and bleeding tendency.

Prognosis

Clinical factors reported to have prognostic significance in extranodal NK/T cell lymphoma include stage and hulk of disease, B symptoms, age, performance status and International Prognostic Index. The overall survival for patients with extranodal NK/T cell lymphoma is 30-40%. Practically all patients with aggressive NK cell leukemia die from the disease within a few weeks or months of presentation.

Genetics

Note

In contrast to T cells, NK cells do not show rearrangements of the TCR genes. As expected from their proposed normal counterpart, NK cell neoplasms show a germline configuration of the TCR genes and do not express TCR proteins on the cell surface. The detection of single circularised episomal form of EBV in the neoplasm by Southern blot analysis provides indirect evidence to the clonal nature. Molecular demonstration of X chromosome inactivation in female patients with NK cell neoplasms also provides evidence for clonality. However, the most direct evidence for clonallity of this group of tumors has been provided by the detection of clonal chromosomal abnormalities (see section below).

It has been shown that in over 90% of NK cell neoplasms, a specific pattern of promoter CpG methylation occurs, with p73 being consistently involved. It has been further suggested that p73 may be an important target in the oncogenesis of NK cell neoplasms, and the demonstration of its methylation may serve as a useful molecular marker for disease monitoring.

Cytogenetics

Note

A variety of genetic abnormalities has been described, but so far no specific and consistent chromosomal translocation has been identified by conventional cytogenetics. In most instances, the genetic changes involve loss or gain of genetic materials such as del(6q), and i(1q). Frequent genetic losses in 6q and 13q have been confirmed by both comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) analyses. Other non-random abnormalities include +X, i(1q), i(7q), +8, i(17q), and 11q23 rearrangement. Chromosomal deletion involving chromosome 6q at around q21-q25 is the commonest recurrent chromosomal abnormality, and fluorescence in situ hybridisation studies have shown that 6q22-q23 is the most frequently involved regions in the chromosome 6 deletions. A recent study using LOH and homozygoisty mapping of deletion (HOMOD) analyses has, however, defined a distinct 3 Mb smallest region of overlapping on 6q25.

A possible involvement of 8p22-p23 in both NK cell neoplasms and NK cell line such as NK-92 has also been suggested. Translocation involving 8p23 has been reported in 3 cases of NK cell neoplasms, with the partner chromosomes being 8q13, 17q24 and 1q10. An add(8)(q23) abnormality has also been demonstrated in one case each of aggressive NK cell leukemia and extranodal NK/T cell lymphoma.

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