Hodgkin lymphoma

Ralf Küppers

Institut of Cell Biology (Cancer Research) University of Duisburg-Essen, Medical School, Virchowstrasse 173, 45122 Essen, Germany (RK)

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Identity

Alias: Hodgkin's disease (HD)

Clinics and pathology

Disease

Hodgkin lymphoma (HL) involves a clonal expansion of neoplastic B lymphocytes. A very small subset of cases of classical HL may derive from T cells.

Epidemiology

A distinguishing feature with non-Hodgkin's lymphomas (NHLs) is its relative frequency in patients under 20 years.

Pathology

About 95% of HL belong to the subgroup of classical HL, the remaining 5% are lymphocyte predominant HL. Most classical HL can be classified as nodular sclerotic (NS) or mixed cellularity (MS) subtypes; two uncommon subtypes, lymphocyte-rich classical and lymphocyte depletion, present less typical pictures and examples of the former have sometimes been reclassified as low-grade B-cell NHLs. In classical HL, the tumor cells are called Hodgkin and Reed-Sternberg (HRS) cells, in lymphocyte predominant HL they are nowadays called LP cells (previously LH, lymphocytic and histiocytic, cells).

Prognosis

Unlike NHLs, the prognosis of HD has improved in recent decades with a five-year survival rate of over 80%.

Genetics

Note

Several recurrent genetic lesions have been identified in HRS cells of classical HL. The most frequently found lesions affect members of the NF-kappaB or JAK/STAT signaling pathways: inactivating mutation in NFKBIA (10-20% of cases), NFKBIE (ca. 10% of cases), TNFAIP3 (40%), SOCS1 (40%), genomic gains of REL (30%) and JAK2 (30%) and rare BCL3 translocations. TNFAIP3 mutations are mainly found in Epstein-Barr virus-negative cases of HL, suggesting that TNFAIP3 mutations and EBV infection are alternative pathogenetic mechanisms in HL. In very rare instances, mutations have been found in the tumor suppressor genes CD95 and TP53. Four or six cases analysed were found to harbor gains of MDM2. Further genomic imbalances have been identified by comparative genomic hybridization studies; these include gains of IKBKB, CD40 and MAP3K14, i.e. further regulators of NF-kappaB signalling.

Few genetic lesions are known for LP cells of lymphocyte predominant HL: mutations in SOCS1 and translocations involving the BCL6 protooncogene. Mutations in TNFAIP3 or NFKBIA seem to play no role in LP cells, although they also show strong NF-kappaB activity.

Both HRS and LP cells show aberrant somatic hypermutation of several proto-oncogenes (PIM1, Rho/ITF, MYC, PAX5) in a considerable fraction of cases. However, as most mutations are in the 5' untranslated regions of the genes, it is unclear whether or which fractions of these mutations have a pathogenetic relevance.
Cytogenetics

Cytogenetics morphological

The neoplastic cells in typical HL lymph nodes comprise mononuclear Hodgkin and multinucleate, binucleate or multinucleate Reed-Sternberg cells, and that these are clonal with modal chromosome numbers varying from case to case is indicated from direct chromosome analysis and DNA measurements and directly shown by the detection of clonal immunoglobulin V gene rearrangements in isolated HRS cells.

The modes are about twice as frequently in the triploid-tetraploid (particularly 65-80 chromosomes) as near diploid region; the clonal aneuploidy has been demonstrated by simultaneous fluorescence immunophenotyping and interphase chromosomal analysis to occur in the Hodgkin and Reed-Sternberg cells.

Unlike NHLs, where a number of chromosomal translocations specific for histopathological types of tumor have been discovered, similarly specific changes have unfortunately not been reported for HD; occasionally, translocations such as t(14;18) that are common in specific types of NHL have been found in about 20% of classical HL, but the partner genes are mostly still unknown; deletions and duplications, common in other types of tumor, including NHLs, have been described in HL, such as del(1p), dup(1q), del(6q) and del(7q); a nonrandom change involving chromosome 4, with breakpoints in the region 4q25-28, has been found on several occasions and merits further investigation.

In chromosome studies, both direct and after culturing, diploid as well as aneuploid metaphases are commonly found in HD, not unexpectedly since histopathological studies usually reveal a considerable excess of lymphocytes and other cells with normal morphology compared to the aneuploid Hodgkin and Reed-Sternberg cells; a recent intriguing finding using FISH, however, has been that 1-12% of "normal" nuclei in HD have abnormalities, most commonly trisomies for various chromosomes.

The multinucleated Reed-Sternberg cells most likely derive from mononucleated Hodgkin cells through a process similar to endomitosis, i.e. nuclear division without cell division.

References


This article should be referenced as such: