MLL amplification in leukemia

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Identity

Note
Recently, amplification of MLL/11q23 gene has been reported as another recurrent amplified gene in myeloid malignancy. It is mainly associated with elderly patients, often dysplastic bone marrow, and complex karyotypic abnormalities. It is suggested that MLL gain of function is the mechanism that contributes to the rapid progression and dismal outcome of this leukemia.

FISH using the LSI MLL breakapart probe (Vysis, Inc) showing MLL gene amplification in acute myeloid leukemia.

Clinics and pathology

Disease
De novo acute myeloid leukemia (AML), de novo myelodysplastic syndromes (MDS), therapy-related AML, therapy-related MDS, and AML transforming from MDS.

Phenotype/cell stem origin
Generally patients presented with anemia, low platelets, and often leukocytosis. AML are most often FAB subtypes M4 and M5 (particularly M5a), followed by M1, M2. MDS are mostly RAEB showing multilineage dysplasia. The leukemic cells are positive for CD45, CD13, CD15, CD33, CD34, HLA-DR.

Epidemiology
The exact incidence of MLL amplification in myeloid malignancies is difficult to establish. In large studies, MLL amplification has been found in < 1% of AML/MDS with abnormal karyotype. Amplification of MLL gene is the second most amplified gene in AML/MDS after CMYC oncogene. In one study, MLL amplification was found in 8/27 (29%) AML cases exhibiting homogenously staining region (hsr) and double minutes (dmin). AML/MDS with MLL amplification is associated with an elderly age, a median age at presentation of 72 years, ranged from 4 to 91 years, often prior history of therapy with alkylating agents or topoisomerase II, and slight female predominance. In therapy-related MDS/AML amplification of MLL gene was found in 12% patients.

Prognosis
Generally, leukemia with MLL amplification is associated with an aggressive clinical course with poor response to chemotherapy, and extremely short survival. The median survival of the patients with available data is 2-3 months.
Cytogenetics

Cytogenetics morphological
MLL amplification appears in variable cytogenetics manifestations including hsr, dmin, ring chromosome, derivative 11q, and marker chromosome.

Cytogenetics molecular
FISH has been useful in detecting MLL amplification. In many cases, the MLL amplification was suspected by conventional banded chromosomes, but was confirmed by FISH instead. Most cases are identified on the basis of multiple MLL signals by FISH. The number of copies of MLL is quit variable ranging from 5 to 90 copies per cell, and Southern blot analysis reveals a germline configuration of the amplified MLL gene in majority of cases. Simultaneous amplification of MLL and CMYC oncogenes on different chromosomal regions has been reported in at least two cases.

Additional anomalies
The majority of patients with MLL amplifications have complex aberrant karyotype, often hypodiploid; over 50% of them have five or more chromosomal abnormalities. No patient with normal karyotype was found. Recurrent chromosomal abnormalities seen in association with MLL/11q amplifications are -5/5q, -7/7q, -17/17p, -18/18q, and missing or structural abnormality of 11q. As determined by chromosome analysis, deletion of 5q5 and 17p17 are seen in approximately 80% and 50% respectively in AML/MDS cases exhibiting MLL amplification.

Genes involved and proteins

Note
Generally MLL amplification is not associated with rearrangement of this gene. RNA overexpression is the result of the increase copy number of MLL (gain of function). Moreover, the amplified region is not limited to the MLL/11q23.3 gene locus, and other genes in the MLL flanking region have been also amplified. FISH and other molecular techniques have identified genes at 11q such as DDX6, GAB2, ETS1, FLI1, SNX19 and/or NFRKB being co-amplified. The size and number of amplicons are variable and at least 9 regions have been identified at 11q23-24.

In addition, over 90% of AML/MDS cases with MLL amplification show an inactivation of TP53 by deletion or mutation indicating that functional TP53 loss is an important key alteration in this leukemia.

MLL (Mixed Lineage Leukemia)

Location
11q23.3

Protein
MLL is homologous to the transcriptional regulator Drosophila trithorax (trx) protein, which is involved in the regulation of HOX gene expression. MLL plays an essential role in embryonic development, also as regulator of growth of hematopoietic precursors.

To be noted
Case Report
Amplification of MLL gene in a new case of acute myeloid leukemia

References

Andersen MK, Christiansen DH, Kirchhoff M, Pedersen-Bjergaard J. Duplication or amplification of chromosome band 11q23, including the unrearranged MLL gene, is a recurrent abnormality in therapy-related MDS and AML, and is closely related to mutation of the TP53 gene and to previous therapy with alkylating agents. Genes Chromosomes Cancer. 2001 May;31(1):33-41


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