

Refractory anemia (RA)

Identity

Note This disorder is part of the heterogeneous category of [myelodysplastic syndrome](#) (MDS). According to the FAB classification of MDS, RA includes those patients with refractory cytopenia with multilineage dysplasia (RCMD), the latter category having been recognised as a distinct entity by the WHO classification (vide infra). Also, the [5q- syndrome](#) is part of the RA in the FAB classification. In this card, the FAB classification will be used, because the majority of available data on cytogenetic anomalies was derived from studies published before WHO classification.

Clinics and Pathology

Phenotype / cell stem origin RA is a clonal disorder originating from a totipotent stem cell or from a multipotent myeloid progenitor cell, characterized by ineffective hemopoiesis and diserythropoiesis.

Epidemiology There are few data on the epidemiology of RA, which may account for 30-40% of all MDS cases. MDS is predominantly diagnosed in the elderly population. The global incidence of all MDS was comprised between 3,5 and 12,6 new cases / year / per 100,000 in some studies. The incidence may rise from 0,5 MDS cases per year in the 40 years age-group to 89 cases per year in the >80 age-group.

Clinics RA usually presents with hypercellular bone marrow (BM) and anemia. There may be leukopenia and/or and thrombocytopenia, but these features do not represent a diagnostic requirement. In the WHO classification RA shows anemia, no or rare blasts in the peripheral blood, isolated erythroid dysplasia with <5% blasts and <15% ringed sideroblasts in the BM. RCMD shows cytopenias (bicytopenia or pancytopenia) in the peripheral blood plus dysplasia in more than 10% of the cells in 2 or more myeloid lineages.

Cytology Criteria for the recognition of dysplastic features of BM cells were published by the FAB group. Dyserythropoiesis includes megaloblastoid changes of erythroid precursors, multinuclearity, nuclear fragmentation, unstained area in the cytoplasm (dysemoglobinization).

Pathology The bone biopsy may be useful in some cases of MDS with BM fibrosis and allows for the demonstration of the so called "abnormal localization of immature precursors" (ALIP) which may represent a prognostic factor.

Treatment Treatment of this condition is largely supportive, including blood transfusion in patients with symptomatic anemia. Anemic patients with low serum erythropoietin (EPO) levels may benefit of the administration of rHu-EPO.

Evolution This is a preleukemic condition, carrying a 10-20% probability of evolving into leukemia. The probability of RA to transform into AML

may be lower when including the 5q- syndrome and excluding RCMD, but prospective studies are lacking. In a study 25% of the patient developed [acute myeloid leukemia](#) (AML) within 5 years.

Prognosis Median survival of RA may fall in the 27-50 month range. As noted above, heterogeneity of patient population may account for inter-study variability in median survival. The best outcome is usually observed in RA with isolated 5q- (5q- syndrome of the WHO classification) and in those patients without multilineage dysplasia, corresponding to the RA category in the WHO classification.

Chromosomal abnormalities have independent prognostic significance and are to be included in risk assessment at diagnosis. Favourable cytogenetic features are normal karyotype, 5q- or [20q-](#) isolated; unfavourable features are complex karyotype (i.e. 3 or more clonal anomalies) and abnormalities of chromosome 7q; other abnormalities identify patients in the intermediate cytogenetic-risk group.

Cytogenetics

Cytogenetics There is no specific chromosome marker for patients with RA, 70 to
 Morphological 80% of whom may show a normal karyotype. More sensitive techniques such as fluorescence in situ hybridization (FISH) failed to increase the percentage of abnormal cases in this category of MDS. The 5q- chromosome may be found in as many as 70% of RA with a clonal aberrations. Usually, but not invariably, the breakpoints involve the bands q13 and q33. When the 5q- is the sole change and it is associated with hypolobated megakaryocytes in the BM, with macrocytic anemia, with normal or increased platelet count then the patient should be diagnosed as having the "5q- syndrome". The 5q- can be present in other subsets of MDS.

A chromosome 20q deletion is found in 5% of all MDS and in 10-15% of RA with abnormal karyotype.

Other chromosome aberrations in RA include [trisomy 8](#) in 10% of cytogenetically abnormal cases [-7/7q-](#) or 11q- in < 5% of the abnormal cases.

A number of very rare chromosome aberrations were described in single reports.

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