

Refractory anemia with ringed sideroblasts (RARS)

Identity

Note This disorder is part of the heterogeneous category of [myelodysplastic syndrome](#) (MDS). According to the FAB classification of MDS, RARS includes those patients with refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS), the latter category having been recognised as a distinct entity by the WHO classification (vide infra).
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	RARS 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 RARS, which may account for 5-15% 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	RARS 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. According to the WHO classification RARS shows anemia, no blasts in the peripheral blood, isolated erythroid dysplasia with <5% blasts and >15% ringed sideroblasts in the BM. RCMD-RS shows cytopenias (bicytopenia or pancytopenia) in the peripheral blood plus dysplasia in more than 10% of the cells in 2 or more myeloid lineages and no Auer rods.
Cytology	Criteria for the recognition of dysplastic features of BM cells were published by the FAB group. Typically, more than 15% of the erythroid cells are ringed sideroblasts showing iron laden mitochondria around the nucleus. These cells appear as erythroblast with Prussian Blue-positive granules which form an arc extending around at least 30% of the nucleus. There is evidence that mutations occurring in the mitochondrial DNA may have a role in generating deranged mitochondrial iron metabolism with consequent accumulation of the of the ferric form (Fe ³⁺) in the matrix.
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 RARS to transform into AML may be lower when excluding RCMD, but prospective studies are lacking. In a study 25% of the patient developed acute myeloid leukemia (AML) in approximately 10 years.
Prognosis	Median survival of RARS may fall in the 40-50 month range. Chromosomal abnormalities have independent prognostic significance and are to be included in risk assessment at diagnosis. Favourable cytogenetic features are normal karyotype, 5q- syndrome or 20q- isolated; unfavourable features are complex karvotpe (i.e. 3 or more clonal anomalies) and abnormalities of chromosome 7q:

other abnormalities identify patients in the intermediate cytogenetic-risk group.

Cytogenetics

Cytogenetics Morphological There is no specific chromosome marker for patients with RARS, 70 to 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 20% of RARS with a clonal aberrations. A chromosome 11q deletion may be found in as many as 20% of the cases. A chromosome 20q deletion can be found in 5% of all MDS and in 10-15% of RARS with abnormal karyotype.

Other chromosome aberrations in RARS include [trisomy 8](#) in 20% of cytogenetically abnormal cases -7/7q- or 11q- in < 5% of the abnormal cases.

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

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