Review Article

Myelodysplastic syndromes: Classification

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ABSTRACT

The updated WHO classification system for myelodysplastic syndromes (MDS) includes some new entities, in particular "refractory cytopenias with unilineage dysplasia (RCUD)". The following review article presents a short overview regarding all subvariants of MDS but with special emphasis on the rare subtypes of MDS that can be exclusively recognized histomorphologically: (1) Hypoplastic MDS (MDS-hypo), (2) Fibrotic MDS (MDS-F) and MDS with associated systemic mastocytosis (SM-AHNMD).

Key words: Bone marrow, classification, dysplasia, histology, myelodysplastic syndromes

INTRODUCTION

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant clonal hematopoietic stem cell disorders characterized by cytomorphological atypia (dysplasia) and signs of progressive bone marrow failure.[1,2] Cytopenias are the lleading clinical feature of patients with MDS, transfusion-dependent anemia being here the most frequent problem. MDS is a disease of the older adult with a median age of 70 years and a male preponderance. Progression to secondary acute myeloid leukemia (sAML) occurs in a significant proportion of patients with MDS, but the risk for transformation strongly depends on the subtype of disease.[3] The updated World Health Organization (WHO) blue book contains major changes regarding classification and definition of MDS.[4,5] Cytopenia here is defined as <10 g/dL hemoglobin, <1.8 × 10^9/L neutrophils, and <100 × 10^9/L platelets.

CLASSIFICATION

The updated classification system includes the following subvariants of MDS:

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- Refractory cytopenia with unilineage dysplasia (RCUD)
  - Refractory anemia (RA)
  - Refractory neutropenia (RN)
  - Refractory thrombocytopenia (RT)
  - RA with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- RA with excess of blast cells 1 (RAEB-1)
- RA with excess of blast cells 2 (RAEB-2)
- MDS-unclassified (MDS-U)
- MDS associated with isolated del (5q).

RCUD

Amongst tshese three disorders, the subentities RN and RT have been newly defined as isolated dysplasia of the neutrophilic cells (RN) or megakaryocytes (RT), respectively. Like RA, all cases of RCUD have a good prognosis with prolonged survival obviously due to the very low amount of blast cells. The overall risk for transformation into sAML is only about 2%. In the very rare instances of marked cytological dysplasia without cytopenias, the term “idiopathic dysplasia of undetermined significance (IDUS)” seems appropriate. Some patients, however, show chronic cytopenias without dysplasia, which implies a descriptive diagnosis of “idiopathic cytopenia without dysplasia (ICUS)”.

RARS

RARS is a well-defined subgroup of MDS with an increase in ring sideroblasts (>15% of all erythroid cells), very low blast cell numbers, and lack of major atypia in nonerythroid cell lines. Only 1-2% of cases transform into sAML and the prognosis, therefore, is relatively good.

RCMD

RCMD is a type of MDS with dysplastic changes in at least two of the three myeloid lineages. Dysplastic changes must be present in <10% of all cells of the affected lineage. The blast cell count is low and the overall median survival of patients is about 30 months [Figures 1 and 2].

RAEB

RAEB is a prognostically unfavorable subtype of MDS with blast cell counts not exceeding 19% in blood and/or bone marrow. The subtype RAEB-1 is defined by 5-9% blast cells in the bone marrow and up to 4% blast cells in the peripheral blood, while RAEB-2 is defined by 10-19% blast cells in the bone marrow and up to 19% blast cells in circulation. Transformation into sAML is seen in about one-third of patients with RAEB-2 and the median survival, therefore, is only 9 months.

MDS-U

This entity lacks features appropriate for classification into any other MDS category, for example, patients exhibiting typical picture of RCUD or RCMD, but with 1% circulating blast cells would qualify for MDS-U.

MDS with Isolated Del (5q)

This entity has been included in the updated classification system of MDS due to its very characteristic clinicopathological features and an excellent prognosis (median survival is about 145 months). Definition includes an isolated anemia combined with thrombocytosis, low blast cell counts, and almost specific cytomorphology of megakaryocytes which are small and carry non- or hypolobated nuclei.

MORPHOLOGY

Cytomorphological evaluation of blood and bone marrow smears allows prompt detection of significant dysplasia in all three myeloid cell lines, while histological analysis is crucial for detection of microarchitectural alterations of the bone marrow, but cannot be recommended to reveal subtle dysplastic changes in neutrophilic and erythroid cells. Atypia of megakaryocytes, however, can easily be detected in both smear preparations and histological sections.

Cytomorphology

Dyserythropoiesis shows alterations of the nucleus (megaloblastoid changes, multinuclearity, budding, and internuclear bridging) and cytoplasm (vacuolization, periodic acid-Schiff positivity, and mitochondrial iron deposits = ring sideroblasts) of erythroblasts. Dysgranulopoiesis shows primarily nuclear hypolobation (pseudo Pelger anomaly), but nuclear hypersegmentation, cytoplasmic hypogranularity, Auer rods (as a very rare finding), and microcytosis can also be detected. Megakaryocytic dysplasia is characterized by both micro- and macrocytosis with often very prominent pleomorphism of the cells. The small, immature-appearing megakaryocytes contain non- or hypolobated nuclei. Small megakaryocytes with non-lobated hyperchromatic nuclei are termed micromegakaryocytes and are a prominent feature of chronic myeloid leukemia, but can also be seen in MDS.

Histomorphology

MDS subtypes RCUD including RA and RN, but also RARS cannot be diagnosed with certainty on the basis of a histological evaluation alone because subtle dysplastic changes of neutrophilic cells and/or erythroblasts cannot be recognized. Moreover, mitochondrial iron (in contrast to hemosiderin) as a feature of ring sideroblasts is destroyed during tissue processing. However, RCMD, RAEB, and MDS with isolated del (5q) show characteristic features that allow proper subtyping also in histological bone marrow sections. Evaluation must include immunohistochemical assessment of blast cell counts by using an antibody against the stem cell-associated antigen CD34. Small immature megakaryocytes and megakaryoblasts are visualized by anti-CD61, which detects a platelet-associated glycoprotein (GPIIIa). An increase in basophilic granulocytes is a feature of many cases of MDS and is not seen in reactive states. Since the metachromatic basophilic granules are destroyed during usual tissue processing with fixatives like formalin histological recognition of the basophils is only possible by using specific antibodies directed against basophil-related antigen like 2D7 and/or BB1. The likewise metachromatic granules of mast cells, however, are preserved. Mast cells and neoplastic basophils both can be visualized by an antibody against the protease tryptase. Tryptase-positive mast cells are round or spindle-shaped, medium-sized or large, while basophils are usually small, round tryptase-positive cells. A spindle-shaped cell expressing tryptase is always a mast cell. Finally, the number of monocytes which can be easily visualized by anti-CD14 is often slightly increased in MDS of various subtypes. A marked increase in CD14-positive cells, however, would more favor a diagnosis of chronic myelomonocytic leukemia. The following limited panel of antibodies is strongly recommended to be applied in each case of suspected MDS:[6-15]

- CD34: Progenitor/blast cells
- CD61: Megakaryocytes/megakaryoblasts
- CD14: Monocytes
- Tryptase: Mast cells, atypical basophilic granulocytes.

Since fibrosis and degree of cellularity can only be assessed histologically, the following rare "histological" subtypes of MDS should also be considered:

- Hypoplastic (hypocellular) MDS (MDS-hypo)
- MDS with fibrosis (MDS-F)
- MDS with an associated systemic mastocytosis (SM-AHNMD).

MDS-hypo

An extremely hypocellular bone marrow with marked increase in adipocytes is seen only in a small minority of MDS cases (<5%). Such findings usually are initially interpreted as toxic myelopathy or as aplastic anemia. It is therefore crucial in all cases with pronounced aplasia to perform at least two immunostains, namely CD34 and CD61. CD34 is essential to detect and enumerate even very small numbers of blast cells suggesting a diagnosis of MDS-hypo rather than (reactive) aplastic anemia. Considering the overall very low cellularity in MDS-hypo, diagnosis of RAEB-1 or RAEB-2 is more often considered than any other subtype of MDS. In

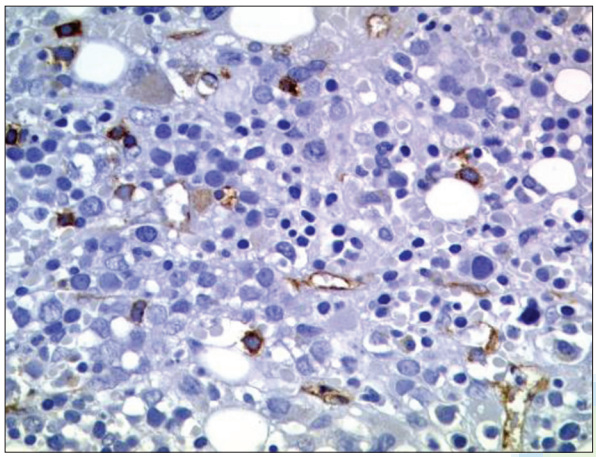

Figure 1: Refractory cytopenia with multilineage dysplasia (RCMD). Extremely hypercellular bone marrow with depletion of adipocytes. Atypical erythroblasts dominate the picture. Note the slight increase in CD34+ blast cells which are loosely scattered and do not form infiltrates (sinus lining endothelial cells also express CD34, which may serve as internal control in the absence of progenitor/blast cells). Easy quantitative assessment enables to state that the blast cell number is less than 5% of all nucleated cells, and thus, Refractory anemia with excess of blast cells 1 (RAEB-1) should not be diagnosed avidin biotin complex (ABC) method; anti-CD34)

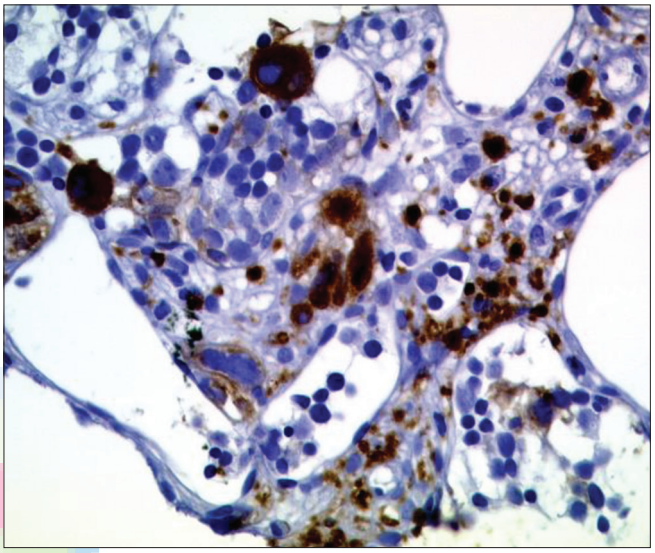

Figure 2: RCMD. Hypercellular bone marrow with focal increase in atypical immature megakaryocytes, which are easily recognized after application of an antibody against a platelet-associated antigen (CD61). Note that there are also some megakaryoblasts which cannot be identified without immunostaining (ABC method; anti-CD61)

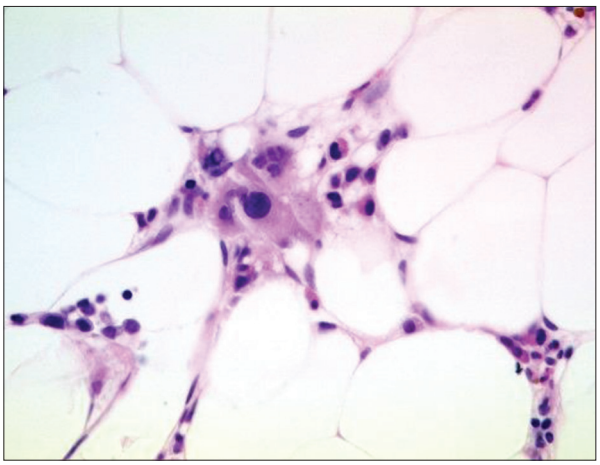

Figure 3: Hypoplastic (hypocellular) myelodysplastic syndromes (MDS-Hypo). Typical histomorphological features are shown: Hypocellularity of the bone marrow with marked increase in adipocytes and atypia of blood cell precursors. Note the group of highly dysmorphic small immature megakaryocytes, a finding which is never seen in reactive states of aplastic syndromes (hematoxylin and eosin (H and E))

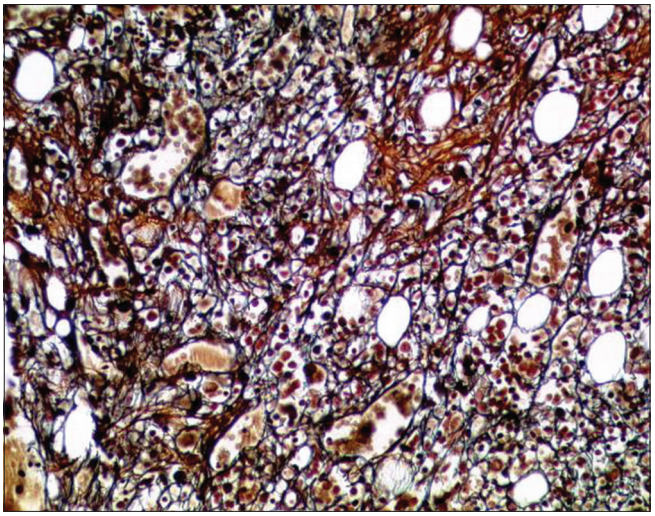

Figure 4: MDS with fibrosis (MDS-F). Hypercellular bone marrow with marked diffuse increase in reticulin fibers (Grade 2) qualifying this myeloid neoplasm to be subcategorized as fibrotic MDS (Gömöri's silver impregnation)

cases with higher blast cell numbers, clear distinction from hypoplastic AML may be extremely difficult. MDS-hypo can only be diagnosed on the basis of bone marrow histology. However, presence of atypical circulating neutrophils may be regarded as an important indication to analyze histological section thoroughly [Figure 3].

MDS-F

About 10% of MDS cases exhibit marked reticulin or even collagen fibrosis (at least Grade 2), and therefore, qualify to be included in the subcategory of fibrotic MDS. The term "MDS with myelofibrosis", although stated in the WHO blue book, should be avoided in order not to produce confusion with primary or secondary myelofibrosis, diseases which belong to the group of myeloproliferative neoplasms. In the majority of MDS-F cases there is an excess of blast cells leading to an overall very bad prognosis, which is also in part due to limited therapeutical options. Therefore, a diagnosis of MDS-F, subtype RAEB-F, can be established in most cases. Again, the separation of RAEB-F from hypoplastic AML may be extremely difficult or almost impossible [Figure 4].

SM-MDS

An association of MDS with systemic mastocytosis is rare, but has been repeatedly described. The disease should be adequately termed SM-AHNMD of SM-MDS subtype and can be diagnosed with certainty only on the basis of thorough histological evaluation of core biopsy specimens of the bone marrow. SM usually is an isolated bone marrow mastocytosis with minor degree of bone marrow infiltration and the MDS dominates the picture. In such cases, immunohistochemical investigation with antibodies against mast cell-related antigens like tryptase and CD117(KIT) is necessary to achieve the correct diagnosis. Demonstration of a few small, compact mast cell infiltrates expressing CD25 (abnormal immunophenotype of mast cells not seen in reactive states) and presence of the activating point mutation KIT-D816V can be of major help to finally confirm the diagnosis of SM-MDS. Almost all major subtypes of MDS have been seen in association with SM—RARS, RCMD, RAEB, and MDS with isolated del (5q). In a minority of cases SM shows a diffuse-compact infiltration of the bone marrow and the MDS is hard to detect. Since in smoldering and aggressive SM, which often show extensive infiltration of the bone marrow, a minor degree of dysplastic changes in blood cell precursors is included in the definition of the basic disease, diagnosis or exclusion of MDS here can be extremely challenging.

DIFFERENTIAL DIAGNOSIS

For diagnosis of MDS it is crucial to be sure that dysplastic cell changes are due to a clonal stem cell disorder and not related to a variety of nutritional or toxic effects. Most important here are vitamin B12 or folic acid deficiencies. Rarely, the application of hematopoietic growth factors may lead to a significant increase in progenitor cells almost indistinguishable from MDS RAEB-2 or even overt AML. In difficult case, repeated investigations of the bone marrow, including cytogenetic studies may be necessary to finally be able to establish a diagnosis of MDS. Cytogenetics and molecular findings may be of great importance to avoid misinterpreation of dysplastic changes since more than 50% of patients with MDS have such cytogenetic or molecular abnormalities, which clearly shows the clonal or neoplastic nature of the morphological changes. Another important issue is the separation of RAEB-2 from overt AML. The threshold has been defined as a maximum of 19% blast cells for RAEB-2 and at least 20% for diagnosis of sAML, but blast cell counts around this value can be very difficult to be determined with certainty. Histologic investigation of the bone marrow may be of help in such borderline cases. Demonstration of at least one compact blast cell infiltrate is sufficient for the diagnosis of AML. Finally, AML with myelodysplasia-related changes has to be considered. This is a special type of AML with at least 20% bone marrow blast and with or without a prior history of MDS. However, patients should not have a history of cytoreductive or radiation therapy, which would qualify the disease to be subcategorized as therapy-related myeloid neoplasm/AML.

SUMMARY

Combined investigation of smear preparation of blood and bone marrow together with histological/immunohistochemical evaluation of a core biopsy of the bone marrow are the optimum prerequisites to be able to establish a diagnosis of MDS. A limited panel of antibodies (CD14, CD34, CD61, and tryptase) has been shown to be sufficient in the daily work-up of the hematopathologist to be able to assess or exclude most subtypes of MDS histologically. Moreover, hypoplastic and fibrotic subvariants of MDS and SM-MDS are exclusive histological diagnoses.

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