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Chapter  

Diagnosis and Classification of Myelodysplastic Syndrome  

Gamal Abdul Hamid, Abdul Wahab Al-Nehmi and Safa Shukry  

Abstract  

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by morphological dysplastic changes in one or more of the major hematopoietic cell lines. MDS can present with varying degrees of single or multiple cytopenias including neutropenia, anemia and thrombocytopenia. Presentation of MDS can range from asymptomatic to life threatening. MDS diagnosis and classification present important challenges, particularly in the distinction from benign conditions. French-American-British (FAB) classification proposed a classification based on easily obtainable laboratory information and was recommended in early and as modified by guidelines of new classification of World Health Organization (WHO). The strategy of diagnostic laboratory in MDS depends on morphological changes and is based on existence of dysplastic changes in the peripheral blood and bone marrow including peripheral blood smear, bone marrow aspirate smear and bone marrow trephine biopsy. The correct morphological interpretation and the use of cytogenetics, immunophenotyping, immunohistochemistry and molecular analysis will give valuable information on diagnosis and prognosis.  

Keywords: myelodysplasia, cytopenia, diagnostic criteria, classification  

1. Introduction  

Myelodysplastic syndromes (MDS) are clonal stem cell disorders with a relatively heterogeneous spectrum, characterized by morphological dysplasia in hematopoietic cells and by bone marrow failure and varying degrees of peripheral blood cytopenias. MDS have been recognized for more than 70 years and named refractory anemia, oligoblastic leukemia and smoldering acute leukemia.  

The risks of MDS include infection, anemia, bleeding and transformation to acute myeloblastic leukemia (AML) in approximately 30% of cases. MDS incidence increased from less than 5/100,000 for patients less than 60 years to 36.2 per 100,000 in patients more than 80 year old and more common among men.  

In the last 20 years, different MDS classification and prognostic scoring systems have been proposed [1]. French-American-British (FAB) classification was recommended in early and as modified by the World Health Organization (WHO). The WHO classification system uses percentages of blasts in bone marrow, ring sideroblasts and dysplastic changes to differentiate MDS subtypes. The International Prognostic Scoring System (IPSS) is based on a multivariate to evaluate the prognosis. The updated and recent scoring system combine with WHO classification
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for identification transfusion need was modified by Malcovati and co-workers, the so-called WPSS (World Prognostic Scoring System). This score suggests that patients with unilineage erythroid dysplasia do not need transfusion [2].

2. Diagnosis

The risk of MDS increased with advancing age; approximately 86% of patients with newly diagnosed MDS predominate in the elderly, with a median age at diagnosis 65 years [3]. The age of MDS patients at diagnosis was different according to residency; the results of some studies on patients show that the median age of diagnosis in German, Japan, and Korea were 74, 60, and 57 years, respectively [4].

The chosen diagnostic criterion of MDS is the dysplasia in \( \geq 10\% \) of total count, this morphology features can point to underlying pathological cytogenetic changes which suggestive MDS diagnosis according to the World Health Organization (WHO) 2016 revision [5].

The minimal prerequisites diagnostic guidelines for MDS according to an International Working Group (IWG) are: (1) stable cytopenia for >6 months unless accompanied a specific chromosomal analysis (Karyotype) or bilineage dysplasia [6]; (2) the exclusion of other potential disorders as a primary reason for dysplasia or cytopenia or both.

3. Diagnostic workup

MDS diagnosis based on morphological characteristics of bone marrow dysplasia in patients with clinical manifestations evidence of hematopoiesis impairments by different combinations of anemia, leukopenia, neutropenia and thrombocytopenia. The National Comprehensive Cancer Network (NCCN) recommend specific guidelines for evaluation of MDS include physical examination; peripheral blood examination, bone marrow examination with iron stain and cytogenetic, RBC folate and vitamin B12 and serum ferritin [7]. The combination peripheral cytopenias despite of bone marrow hypercellularity is the hallmark of MDS, and is a consequence of bone marrow dysfunction with an increase apoptosis rate of bone marrow cells.

According to NCCN the diagnosis of MDS requires \( \geq 1 \) of MDS-related criteria: (1) dysplasia (\( \geq 10\% \) in \( \geq 1 \) of bone marrow cell line); (2) presence of 5–19% blast cells; and (3) presence of a specific MDS-linked chromosomal abnormalities like del(5q), del(20q), +8, or −7/del(7q) [8].

4. Differential diagnosis

Before treatment, the major role is to distinguish MDS from other causes of cytopenia and dysplastic changes and from other clonal stem cell disorders [9]. The investigations work-up is important to rule the possible differential diagnosis and pre-MDS conditions (Table 1).

4.1 Cytopenic causes

1. Chronic liver diseases

2. Drug induced cytopenia
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3. Excessive alcohol intake
4. Cytotoxic therapy
5. B12/folate deficiency
6. Autoimmune cytopenia
7. Anemia of chronic disorders
8. Parasitic manifestation (hypersplenism in malaria and leishmaniasis)
9. Human immunodeficiency virus infection (HIV)
10. Other stem cell disorder

4.2 Idiopathic cytopenia of uncertain significance (ICUS)

4.3 Idiopathic dysplasia of unknown significance (IDUS)

4.4 Clonal cytopenia of undetermined significance (CCUS)

4.5 Clonal hematopoiesis of indeterminate potential (CHIP)

5. Clinical presentation

Clinical presentation of MDS is nonspecific and varies considerably depending on subtypes and severity of cytopenias. This should include family history,
tobacco, alcohol intake, pesticides, heavy metals, prior chemotherapy, irradiation, radioiodine, radioimmunotherapy, concomitant medication including “alternative medication”, infection, tendency for bleeding/bruising, and a complete physical examination including spleen size. Symptoms can include general weakness, palor, shortness of breathing, bleeding manifestations; gum bleeding and petechiae.

6. Blood tests

Complete blood count (CBC) includes white blood cell count (WBC) with differential blood count including erythrocyte morphology, hemoglobin, platelet count, red blood cell indices, mean corpuscular volume (MCV), and reticulocyte count. Serum tests of erythropoietin, protein electrophoresis, folic acid, cobalamin, iron, total iron binding capacity (TIBC), ferritin, lactate dehydrogenase (LDH), bilirubin, Coombs test, alanine aminotransferase (ALT) test, aspartate aminotransferase (AST), alkaline phosphatase, albumin, uric acid, creatinine (S-immunoglobulins), B2 microglobulin and thyroid function tests.

Also some investigations are mandatory to exclude viral infection especially; anti-HIV, anti-Parvovirus B19 (hypoplastic MDS), hepatitis C antibody, hepatitis B surface antigen (HBsAg) and cytomegalovirus test (CMV) in transfusion dependent patients.

Cytogenetic study for BCR-ABL and JAK2 (Janus kinase 2) are important for differential diagnosis of myeloproliferative disorders.

6.1 Interpretation of peripheral blood

The WHO recommendations for the definition of cytopenia are the same reported in the International Prognostic Scoring System (IPSS), when the hemoglobin less than 10 g/dl, the leukocyte count 3000/mm$^3$, an absolute neutrophil less than 1800/mm$^3$ and platelets less than 100,000/mm$^3$. These thresholds have been a matter of debate, and as a result, any cytopenia should be differentiated from MDS in case of clear morphologic or the result of genetic features consistent with MDS [5, 6]. Anemia is represent in most patients, the mean corpuscular volume (MCV) is often increased and an increased erythrocyte distribution width (RDW) which the erythropoiesis disturbances. A dimorphic red blood cell (RBC) population (macrocytes and microcytes), anisocytosis, poikilocytosis, nucleated red blood cells, basophilic stippling and Howell-Jolly bodies are also indications that the erythrocyte has undergone abnormal development [10]. Peripheral blood may reveal very abnormal nuclei such as Pelger-Huet anomalies and hypo- or hypersegmentation and ring forms nuclei also occur in neutrophils are important morphological features in MDS/MPN peripheral blood when diagnosing and distinguishing MDS/MPN is important to understand the similarities and differences in pathologic mechanism from similar diseases (AML, infectious diseases and other causes of cytopenia). The platelet morphological changes include giant platelets and platelets hypogranulation or agranulation. Some platelets may possess large fused granules. Circulating micromegakaryocytes (dwarf cells), multiple small nuclei separated by strands of nuclear material, and large mononuclear cells with dysmorphic nuclear features have been described in peripheral blood from patients with MDS [11].

The diagnosis of MDS requires a careful light microscopic examination of optimally stained peripheral blood and bone marrow smear and trephine biopsy sections with presence of 1% blast in peripheral blood, with ≤5% BM blasts and uni- or multilineage dysplasia is defined as unclassifiable MDS. Monocytic hyperplasia accounting for >10% of the white blood cells is a common finding in chronic myelomonocytic leukemia (CMML) and is a common finding in dysplastic marrows and can be dominant manifestation of the hematopoietic abnormality in CMML for months and years.
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7. Bone marrow aspirate and biopsy

A diagnosis of MDS often requires repeated bone marrow aspiration/biopsy examinations a few weeks or months, or even years apart in order to firmly establish the diagnosis and to identify cases with rapid disease progression. Bone marrow morphology evaluation and dysplasia in blood and bone marrow follow guidelines in the WHO 2016 classification. A good quality diagnostic bone marrow analysis includes marrow aspirate May-Grunewald Giemsa (MGG)/equivalent and bone marrow iron stain and a bone marrow biopsy either decalcified/paraffin embedded or plastic embedded. Degree of fibrosis should be estimated. The cytochemistry staining should include iron staining, Peroxidase-Staining, in addition to hematoxylin-eosin/equivalent [12].

The highly specific dysplastic changes in granulocytes of patients with MDS are hypogranularity and nuclear abnormality of neutrophils in peripheral blood smear and positive on peroxidase reaction or Sudan black. The highly specific dysplastic changes in erythropoiesis are sideroblastic rings and megaloblastoid changes. The highly specific for dysmegakaryopoiesis are micromegakaryocytes.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Peripheral blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid</td>
<td>Dimorphic; macrocytic; anisocytosis; polychromatophilic; hypochromasia, tear drop cells; Pappenheimer bodies; basophilic stippling</td>
<td>Erythroid hyperplasia; megaloblastic changes; dyserthropoiesis; multinuclearity, nuclear bridges, nuclear budding, atypical mitosis, ring sideroblasts</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Hypersegmented neutrophils; hypogranular or agranular neutrophils; pseudo-Pelger cells</td>
<td>Shift to left, promyelocytes with absent or spares azurophilic granules; hypogranular myelocytes, metamyelocytes and neutrophils, Auer rods, pseudo-Pelger cells, nuclear anomalies</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Mature monocytes</td>
<td>Increase and morphological abnormalities of monocytes</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>Thrombocytosis; giant platelets</td>
<td>Increase or decrease; mononuclear megalakocytes, micromegakaryocytes, hypersegmented megakaryocytes</td>
</tr>
</tbody>
</table>

Table 2. MDS morphology abnormalities on peripheral blood and bone marrow [12, 13].

8. Dysplastic features

Dysplastic changes are the most important diagnostic features of myelodysplastic syndrome. A marrow cell lineage is considered picture of MDS if >10% of cells are affected.

8.1 Dyserthropoiesis

Dyserthropoiesis is the presence of oval macrocytes and erythroblast may resemble megaloblasts that have nuclear-cytoplasmic maturation asynchrony, nuclear fragmentation, or cytoplasmic nuclear remnants. This pattern is referred to as megaloblastoid erythropoiesis [14–16]. A dimorphic red blood cell population,
anisocytosis, poikilocytosis, nucleated red blood cells, Howell-Jolly bodies and basophilic stippling are indications that the erythrocyte has undergone abnormal development. The RBC with abnormally round nucleus may have lobes or buds, internuclear bridging, nuclear fragments and abnormal mitosis are occasionally present. Pathologic sideroblast may be identified when the marrow treated with Prussian blue stain (Figure 1) [14, 15].

8.2 Dysmyelopoiesis

The most striking abnormalities are hypogranulated neutrophils. The defect in granulation may be seen in myelocytes early in the course of disease. Very abnormal nuclei, such as Pelger-Huet anomalies and hypo- or hypergranulation, and ring shaped nuclei in neutrophils. Monocytic hyperplasia is a common finding in dysplastic marrows and can be the dominant manifestation of the hematopoietic abnormalities of CMML for months or years (Figure 1) [11]. Cytoplasmic changes may include uneven staining such as a dense ring of basophilia around the periphery with a clear unstained area around the nucleus [14, 15]. Occasionally there are Auer rods, either in circulating or BM blast cells, entails an unfavorable prognosis and this could lead to misclassification the disease in the AML. Myeloperoxidase and the study of specific immunophenotypic markers are helpful to differentiate between MDS and other types of AML [17].
8.3 Dysmegakaryopoiesis

The common changes include giant platelets and abnormal platelet granulation, either hypogranulation or agranulation. Some platelets may possess large fused granules. Circulating micromegakaryocytes, multiple small nuclei separated by stands of nuclear material and large mononuclear cell with dysmorphic nuclear features have been described in peripheral blood of patients with MDS (Figure 1) [13–15].

For significant dysplasia, dysplastic features should be present in at least 10% of the nucleated cells in the lineage in consideration.

9. Blast cells

9.1 Counting blasts

Myeloblast cell should be differentiated from promyelocyte. The promyelocyte is larger than myeloblast and characterized by clear Golgi zone and azurophilic granulations. Myeloblast was defined in terms of several nuclear characteristics, including a high nuclear/cytoplasmic ratio, easily visible nucleoli and usually contain fine nuclear chromatin and viable nuclear shape. The International Working Group (IWGM) recommended that myeloblast in MDS should be classified as agranular or granular [12]. Type II have scanty granules [18] and type III blast with more than 20 fine azurophilic granules as defined by Goasguen et al. [13]. The nuclear characteristic of promyelocytes included an eccentric or central nucleus and intermediate or fine chromatin and azurophilic granulation (Figure 2) [12].

10. Cytogenetic analysis

The cytogenetic study of bone marrow aspirate has a major role in determining clonality in patients with MDS. Karyotyping should be done in all patients, at least 25 metaphases, whenever possible, and described according to International System recommendations. Chromosomal abnormalities are reported in more
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than 50% of patients with MDS by counting 25 metaphase cytogenetic analysis, but not by fluorescence in situ hybridization (FISH) or sequencing technologies. The technique by using FISH method may be helpful to detect monosomy 7 and to clarify complex aberrations. Screening FISH (5q−, −7, +8) from peripheral blood may be performed in patients of dry tap bone marrow and this may influence management of the patient [19]. Different cytogenetic abnormalities are considered MDS-defining [20]. The presence monosomy 5, 7, or 13; 5q, 7q and 13q deletions; i(17p) and t(17p); 11q deletion; 9q or 12p deletion or t(12p), idic (X) (q13) allows for the diagnosis of MDS even in the absence of dysplastic changes. Cytogenetic is strongly correlated with not only the calculation prognosis but also selection of the most effective therapy; thus, a complete BM karyotype remains the standard work up evaluation procedure of the patient with MDS according to IPSS-R (Table 3) [21, 22].

11. Molecular genetic testing

The most important mutated genes for MDS prognostication involved in epigenetic regulation are acquired mutation have been detected in several genes: (ASXL1, EZH2, DNMT3A, TET2, IDH1/2, pre-mRNA splicing factors (SF3B1, SRSF2, U2AF1) transcription (RUNX1, TP53) and signaling transduction are seen in MDS and can demonstrate clonal disease [23]. According to the new 2016 World Health Organization (WHO) Classification of MDS, the analysis of the SF3B1 considered the only important diagnostic method for diagnosis of MDS-RS. The prognosis of MDS-RS is favorable in presence of SF3B1 mutations [24]. Mutations in the ASXL1, TP53, ETV6, RUNX1 and EZH2 are reported as independently associated with decreased overall survival in cases of MDS [25].

12. Immunophenotyping

By flow cytometry and immunohistochemistry, immunophenotyping of the blast population can be useful for emerging pathological CD34 and or CD117 and myeloperoxidase (MPO) positive populations are suggestive of transformation.
According to WHO classification 2016, the best method for diagnosis of MDS is the percentages of blast cells in bone marrow. The immunophenotyping can be useful to study the expression of maturation and anomalies as marker of dysplasia of a particular lineage [26].

Multiple aberrant features (>3) in maturation patterns of erythroid and myeloid lineage are highly specific for MDS, but single aberrancies are not diagnostic [27]. The role of flow cytometry can be useful in the diagnostic work-up of MDS, and to detect minimal residual disease after treatment according to the European Leukemia Net (ELN) work package for flow cytometry [28]. For prognostic follow-up, the increase expression of CD33, CD34, CD13, HLA-DR/human leukocyte antigen-DR and decreased reactivity for CD11b in the bone marrow have been associated with shorter survival and high risk of transformation to acute leukemia.

13. Classification

13.1 FAB classification

Several classifications have been developed to predict the transformation of MDS to acute myeloid leukemia (AML). In 1982, the FAB system, was introduced based on percentage of blasts and morphological features in blood and bone marrow, namely medullary and peripheral blast cell count, ringed sideroblasts, number of monocytes in peripheral blood, and Auer rods. According to this classification, patients are diagnosed with MDS when dysplastic changes in bone marrow are present and/or myeloblast cells are between 5 and 30% of all bone marrow cells. Five subgroups with significantly different prognoses were established: refractory anemia (RA) with blasts <5% in BM, refractory anemia with ringed sideroblasts (RARS) with blasts <5% and ring sideroblasts >15%, refractory anemia with excess of blasts between 5 and 20% (RAEB), RAEB in transformation to acute leukemia and blast cells ranged between 20 and 30% (RAEB-T) and chronic myelomonocytic leukemia (CMML) (Table 4) [20, 29]. For more than 20 years this classification served as the standard for the evaluation of MDS [30]. Hypercellular MDS, and MDS with bone marrow fibrosis were not recognized by the FAB classification [31].

<table>
<thead>
<tr>
<th>Type</th>
<th>Blasts in blood</th>
<th>Blasts in bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Refractory anemia (RA)</td>
<td>&lt;1%</td>
<td>Blasts &lt;5%, ring sideroblastic &lt;15%</td>
</tr>
<tr>
<td>2. Refractory anemia with ring sideroblastic (RARS)</td>
<td>&lt;1%</td>
<td>Blasts &lt;5%, ring sideroblasts &gt;15%</td>
</tr>
<tr>
<td>3. Refractory anemia with excess of blast (RAEB)</td>
<td>&lt;5%</td>
<td>Blasts 5–20%</td>
</tr>
<tr>
<td>4. Refractory anemia with excess blast in transformation (RAEB-t)</td>
<td>&lt;30%</td>
<td>Blasts 20–30%</td>
</tr>
<tr>
<td>5. Chronic myelomonocytic leukemia (CMMoL)</td>
<td>&lt;5% with increase monocytes</td>
<td>Blasts 0–20%</td>
</tr>
<tr>
<td>AML</td>
<td>&gt;30%</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>

Modified of Ref. [20].

CMML, chronic myelomonocytic leukemia blast cells <20% and monocytes ≥1000/μl; RA, refractory anemia <1% in PB and <5% blasts in BM; RAEB, RA with excess blasts in PB <5% and 5–20% blasts in BM; RAEB-T, RAEB with excess blasts in transformation between 20 and 30%; RARS, RA with ringed sideroblasts >15%.

Table 4. Myelodysplastic syndrome (MDS) according to FAB classification [20].
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13.2 WHO classification

The World Health Organization (WHO) classification of MDS revised in 1999 and redefine subtypes of MDS [32]. The definitions of refractory anemia (RA) and refractory anemia with ring sideroblastic (RARS) unchanged became more consistent and characterized by the presence of dysplastic morphology in the erythroid cell line. Refractory anemia with ring sideroblastic (RARS) is morphologically similar to RA with the presence of $\geq 15\%$ ring sideroblasts.

Refractory anemia with excess of blasts (RAEB) recognized by the World Health Organization (WHO) classification in all versions and remains unchanged but distinguishes between two categories of RAEB: RAEB-1 with 5–10% blast cells and RAEB-2 with 11–20% blasts in the bone marrow.

The other new subgroups of MDS were incorporated: (1) refractory cytopenia with multilineage dysplasia (RCUDys), is a frequent subtype of MDS, which is equivalent to RA or RARS in the FAB classification with the presence of dysplasia but lacking an increase in blast cells with no Auer rods or increase of monocytes; (2) del (5q) syndrome is a myelodysplastic disorder characterized by macrocytic anemia, dysplastic changes in the erythroid cell line only, thrombocytosis and increase of hypolobulated micromegakaryocyte; (3) MDS unclassifiable; myelodysplastic syndromes that do not meet criteria of a specific WHO entity.

RAEB-T and CMML subgroups were removed from the new MDS classification: RAEB-T, because of distinctive biologic features and similarities in treatment strategies with acute myeloid leukemia (AML), and CMML, because of having overlapping dysplastic and proliferative features and its close relation to myeloproliferative diseases [33].

<table>
<thead>
<tr>
<th>2008 WHO classification</th>
<th>2016 WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)</td>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)</td>
</tr>
<tr>
<td>encompassing refractory anemia (RA), refractory neutropenia</td>
<td>encompassing refractory anemia (RA), refractory neutropenia (RN) and refractory thrombocytopenia (RT)</td>
</tr>
<tr>
<td>(RN), and refractory thrombocytopenia (RT)</td>
<td>(RN), and refractory thrombocytopenia (RT)</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
</tr>
<tr>
<td></td>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
</tr>
<tr>
<td></td>
<td>MDS with ring sideroblasts (MDS-RS)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome associated with isolated del(5q)</td>
<td>Myelodysplastic syndrome associated with isolated del(5q)</td>
</tr>
<tr>
<td></td>
<td>MDS with isolated del(5q)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
</tr>
<tr>
<td></td>
<td>MDS with excess blasts (MDS-EB)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
</tr>
<tr>
<td></td>
<td>MDS-EB</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
</tr>
<tr>
<td></td>
<td>MDS, unclassifiable (MDS-U)</td>
</tr>
<tr>
<td></td>
<td>With 1% blood blasts</td>
</tr>
<tr>
<td></td>
<td>Based on defining cytogenetic abnormality</td>
</tr>
</tbody>
</table>

**Table 5.** World Health Organization (WHO) classifications of myelodysplastic syndromes [20, 22].
In 2001, the WHO proposed an alternative classification for MDS that was modified from the original French-American-British (FAB) definitions [18]. Since then, the WHO classification has been updated twice (2008 and 2016) (Table 5) [22, 33].

The last edition of WHO classification guidelines identify 6 types of MDS: MDS with single lineage dysplasia (MDS-SLD); MDS with ring sideroblasts (MDS-RS); MDS with multilineage dysplasia; MDS with excess blasts (MDS-EB); MDS with isolated del(5q); and MDS unclassifiable (MDS-U). There is an additional provisional entity termed “refractory cytopenia of childhood.” MDS-SLD includes refractory anemia (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), and refractory thrombocytopenia (unilineage dysmegakaryocytopenia). The latter 2 were previously classified as MDS-U in 2001 but were reclassified in the 2008 update [34].

According to 2016 WHO classification guidelines identify MDS subtypes based on results of blood and bone marrow test. The classification of 2016 WHO of MDS was according to factors that differ from those of the FAB system and defined by precise criteria including: (1) dysplastic changes (2) number of cytopenia in peripheral blood (3) percentage of sideroblastic rings (Table 6) [5].

### 13.2.1 MDS with single lineage dysplasia (MDS-SLD)

One dysplastic lineage with dysplasia in at least 10% of the early cells of 2 or 3 cell types (red blood cells, white blood cells, and/or megakaryocytes in the bone marrow. No Auer rods blast cells less than 5% in BM and <1% in PB. Sideroblastic ring less than 15% in BM and <5% in PB.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) MDS with single lineage dysplasia (MDS-SLD)</td>
<td>Single of bicytopenia</td>
<td>Dysplasia in ≥10 of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>(2) MDS with ring sideroblasts (MDS-RS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors w/ ring sideroblasts, or ≥5% of ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>(3) MDS with multilineage dysplasia (MDS-MLD)</td>
<td>Cytopenia(s) &lt;1 or 10↑/l monocytes</td>
<td>Dysplasia in ≥10 of cells in ≥2 hematopoietic lineages, ≥15% ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>(4.1) MDS with excess blasts-1 (MDS-EB-1)</td>
<td>Cytopenia(s), ≤2–4% blasts↑, &lt;1 × 10↑/l monocytes</td>
<td>Unilineage or multilineage dysplasia, 5–9% blasts, no Auer rods</td>
</tr>
<tr>
<td>(4.2) MDS with excess blasts-2 (MDS-EB-2)</td>
<td>Cytopenia(s), 5–19% blasts↑, &lt;1 × 10↑/l monocytes</td>
<td>Unilineage or multilineage dysplasia, 10–19% blasts, Auer rods</td>
</tr>
<tr>
<td>(5) MDS with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt;5% blasts</td>
</tr>
<tr>
<td>(6) MDS, unclassifiable (MDS-U)</td>
<td>Cytopenia(s), &lt;1% blasts on at least 2 occasions</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt;5% blasts</td>
</tr>
<tr>
<td>(7) Refractory cytopenia of childhood</td>
<td>Cytopenias, &lt;2% blasts</td>
<td>Dysplasia in 1–3 lineages, &lt;5% blasts</td>
</tr>
</tbody>
</table>

Cytopenias defined as: hemoglobin, 10 g/dl; absolute neutrophil count, 1800/mm³ and platelet count less than 100,000/mm³; S; bicytopenia may be observed in most cases of MDS.

Present of 5–9% myeloblast in BM and 2–4% myeloblasts in the blood, the diagnostic is MDS-EB-1 and 10–19% myeloblast in BM and 5–19% myeloblasts in the blood, the diagnostic is MDS-EB-2. Cases with pancytopenia with unilineage or absent dysplasia with 1% myeloblasts in the blood should be classified as MDS-U.

Table 6. Peripheral blood and bone marrow findings according to 2016 WHO classification of MDS [5, 20].
13.2.2 MDS with ring sideroblasts (MDS-RS)

MDS-RS previously named as refractory anemia with ring sideroblasts (RARS). In this type of MDS, there is increased sideroblastic rings of nucleated red blood and for diagnosis, ring sideroblasts seen in nucleated red blood cells or at least 5% if the cells also have high of SF3B1 mutations [35]. Mutations in SF3B1 are seen in $\geq 80\%$ of cases. MDS-RS include 2 subtypes based on dysplastic bone marrow:

- **MDS-RS with single lineage dysplasia (MDS-RS-SLD):** one dysplastic lineage, one or two PB cytopenia, sideroblastic rings $\geq 15\%$ in BM or $5\%$ in cases with SF3B1 mutation, blast cells $< 5\%$ in BM and $< 1\%$ in PB and no Auer rods.

- **MDS-RS with multilineage dysplasia (MDS-RS-MLD):** dysplasia in more than one lineage, one to three PB cytopenias, sideroblastic ring in BM $15\%$ and $5\%$ if SF3B1 mutation is present. Blast cells in BM $< 5\%$ and in PB $< 1\%$ without Auer rods.

This type of MDS is not common. It rarely turns into AML, and the outcome for people with this type is generally better than for some other types of MDS.

13.2.3 MDS with multilineage dysplasia (MDS-MLD)

Dysplastic changes in two or three lineages and PB cytopenia in one to three lineages, sideroblastic ring in $15\%$ in BM or $5\%$ in cases with SF3B1 mutation, blast cell without Auer rods $< 5\%$ in BM and $< 1\%$ in PB.

13.2.4 MDS with excess blasts (MDS-EB)

In this type of MDS, the blasts are present in the bone marrow and/or peripheral blood. Dysplastic changes present in one to three lineage and cytopenia in one to three lines. Sideroblastic ring not present.

There are 2 types, based on how many of the cells in the bone marrow or blood are blasts:

- **MDS with excess blasts-1 (MDS-EB1):** blast cells make up 5–9% in the bone marrow aspirate, or 2–4% of blast cells in peripheral blood and absent of Auer rods.

- **MDS with excess blasts-2 (MDS-EB2):** previously named refractory anemia with excess blasts (RAEB), characterized by excess blasts 10–19% of bone marrow aspirate cells, or 5–19% blast cells in peripheral blood and/or present of Auer rods.

13.2.5 MDS with isolated del(5q)

“5q– syndrome” is a specific type of myelodysplastic syndrome (MDS). Is not common and it occurs most often in older women. It is characterized by missing part of chromosome number 5. The patient also has cytopenia in one or two blood cell lines with common manifestations including severe anemia, typical dysmegakaryopoiesis, frequent thrombocytosis and favorable outcome [5]. The median survival of patients with isolated 5q– syndrome of 9 years and they have good prognosis and rarely transform to develop AML [35].
13.2.6 MDS, unclassifiable (MDS-U)

This type of MDS is uncommon. For MDS-U, the pathological findings in bone marrow more than in peripheral blood. We observe that, one or more cytopenias are a standard feature of MDS-U but other clinical features are variable. Dysplastic changes in bone marrow in less than 10% but typical cytogenetic abnormality was reported [5].

13.2.7 Refractory cytopenia of childhood

Usually hypocellular with similar picture of aplastic anemia. The mutations are less common than in adult MDS (24% of patients) and have a different profile NRAS/KRAS, SETBP1, ASXL1, RUNX1, BCOR/BCORL, PTPN.

14. Chronic myelomonocytic leukemia (CMML)

14.1 Definition

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder classified by the WHO as an overlapping feature of myelodysplastic syndromes and myeloproliferative neoplasms (MPN). It is characterized by peripheral blood monocytosis, dysplastic features in at least 1 hematopoietic cell line and increased risk of progression to AML [36].

The disease annual incidence became stable at around 0.4 per 100,000 population in Western countries [37]. CMML is occurring in elderly patients whose median age at diagnosis is 71–75 years. The incidence of CMML was higher in men than in women whose origin remains unclear [37].

14.2 Diagnosis of CMML

Diagnosis is based on the presence of sustained (>3 months) peripheral blood monocytosis ($\geq 1 \times 10^9/L$; monocytes $\geq$10%), along with bone marrow dysplastic changes. Bone marrow and BCR-ABL are recommended to exclude acute leukemia and a classic myeloproliferative neoplasms. Atypical monocytes differ from promonocytes and monoblasts. They contain no nucleolus, exhibit swelling, abnormally folded nuclei, aggregated chromatin, nucleus-cytoplasm asynchrony. Their presence is usually associated with increase of neutrophils and shift to left picture with increase of platelet count but the association of macrocytic anemia and thrombocytopenia are the most common [38]. The CMML classified into three groups/categories for precise prognostication include: CMML0; a group with <2% blasts in PB and <5% blast in BM, the second group CMML1 include patients with 2–5% blasts in PB and 5–9% blasts in BM and third group include patients with 5–9% blasts in PB and 10–19% blasts in BM (Table 7) [5, 39].

14.2.1 Immunophenotyping of CMML

An international nomenclature has been used to help diagnose CMML [40]. Human monocytes can be divided into three subsets; MO1, CD14+/CD16− (classical), MO2, CD14+/CD16+ (intermediate) and MO3, CD14−/CD16+ (nonclassical). CMML is characterized by the accumulation of classical monocytes with an MO1 threshold to 94% of total circulating monocytes and with different gene expression profiles, chemokine receptor expressions and phagocytic activities [41].
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14.2.2 Cytogenetic abnormalities of CMML

Clonal cytogenetic abnormalities identify non-specific chromosomal abnormalities in 30–40% of CMML patients. Peripheral blood/bone marrow for BCR-ABL rearrangement for all patients should be done to exclude any pathological disorder related to myeloproliferative disorders and PDGFRA, PDGFRB, FGFR1 rearrangements or PCM1-JAK2 (Table 7) [5, 42]. The most common alterations include; trisomy 8 (4–11%), —Y (5–20%), abnormalities of chromosome 7 (monosomy 7 and del7q) in 2–14%, trisomy 21, and complex karyotypes [43].

15. Conclusions

Myelodysplastic syndrome diagnosis based on data accumulated since the 2008 WHO classification of MDS, much of which relates to adequate medical information, cytomorphology and dysplastic assessment and new molecular genetic information about these neoplasms. The revised WHO classification is the more accurate classification introduces refinements in morphologic interpretation and cytopenia assessment and addresses the influence of genetic information in MDS diagnosis and classification of patients and will allow for better guidance of treatment. The evaluation of cytogenetic results is important for the classification and determination of the prognosis according to the revised International Prognostic Scoring System (IPSS-R). Immunophenotyping and molecular analysis will provide valuable information on diagnosis and prognosis.

Table 7.
Diagnostic criteria of CMML modified according to Daniel Arber of 2016 WHO classification Blood 2016 [5].

| Persistent monocytosis ≥1 × 10^9/l and monocytes ≥10% of WBC in peripheral blood |
| <20% blasts in peripheral blood and bone marrow aspiration* |
| No criteria and no previous history of CML, ET**, PV, and PMF |
| If eosinophilia, no PDGFRA, PDGFRB, FGFR1 rearrangement, no PMC1-JAK2 fusion gene |
| ≥1 following criteria: |
| 1. Acquired clonal cytogenetic or molecular abnormality in hematopoietic cells*** |
| 2. Dysplasia in ≥1 myeloid lineage |
| 3. Monocytosis persistent for at least 3 months, with other causes excluded |

CML, chronic myeloid leukemia; ET, essential thrombocythemia; PV, polycythemia vera; PMF, primary myelofibrosis; WBC, white blood cell. *Total blast cells include monoblast, promonoblasts and myeloblasts.
**Exclude of myeloproliferative neoplasms (MPN) associated with monocytosis by bone marrow cytology and/or of MPN-associated mutations (JAK2, calreticulin gene "CALR", or myeloproliferative leukemia mutation "MPL") tend to confirm the diagnosis of MPN with monocytosis rather than chronic myelomonocytic leukemia (CMML). ***The mutations associated with CMML which may support confirmation of diagnosis like ASXL1, SRSF2, SETBP1, TET2.

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