

# Leukaemia Section

## Review

## Myelodysplastic/myeloproliferative neoplasms

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### Abstract

Overview of myelodysplastic/myeloproliferative neoplasms detailing clinical, pathologic, cytogenetic, and molecular findings.

#### KEYWORDS

Myelodysplastic/myeloproliferative neoplasms; chronic myelomonocytic leukemia; atypical chronic myeloid leukemia; juvenile myelomonocytic leukemia; ring sideroblasts; genetics

### Identity

This category includes neoplasms which demonstrate overlapping clinical, morphologic, and genetic features with both myelodysplastic syndromes and myeloproliferative neoplasms. Well-defined entities within this category include chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, BCR /ABL1 negative (aCML), myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and juvenile myelomonocytic leukemia (JMML). This category also includes myelodysplastic/myeloproliferative neoplasms, unclassifiable, which is applied to neoplasms with both myelodysplastic and myeloproliferative features but which do not fit into any of the previously described entities. Cases are excluded from this category if WHO criteria are met for myelodysplastic syndromes, chronic myelogenous leukemia, primary myelofibrosis, polycythemia

vera, or essential thrombocythemia, and cases with PDGFRA, PDGFRB, FGFR1, or PCMI/JAK2.

### Clinics and pathology

#### Disease

**Chronic myelomonocytic leukemia (CMML)**

#### Phenotype/cell stem origin

Hematopoietic stem cell.

#### Epidemiology

CMML is the most common MDS/MPN, accounting for >90% of cases within this category. However, it is still relatively rare, with an incidence of 3-4/1,000,000 person-years (Guru Murthy et al. 2017; Srour et al., 2016). There is a slight male predominance of 3:1 (Guru Murthy et al. 2017; Maynadie et al., 2011). The disease predominantly affects patients in their 7<sup>th</sup> decade of life or later.

#### Clinics

CMML is characterized clinically by fever, infection, and hemorrhagic or thrombotic events. Patients demonstrate a variable clinical course. In some patients a myeloproliferative phenotype predominates, characterized by leukocytosis, whereas cytopenias are more common in other patients with a myelodysplastic phenotype. Hepatosplenomegaly is relatively common, especially in cases with a myeloproliferative phenotype.

## Pathology

Diagnosis of CMML requires the presence of a persistent peripheral blood monocytosis ( $>1 \times 10^9$  /L or  $>10\%$ ) and less than 20% blasts or blast equivalents in the peripheral blood and bone marrow. Monoblasts and promonocytes are included as blast equivalents. Dysplasia in one or more myeloid lineages is a criterion for diagnosis, but in its absence a diagnosis of CMML may still be rendered if an acquired clonal cytogenetic or molecular abnormality is present, the monocytosis has persisted for  $>3$  months, and all other causes of monocytosis have been excluded (Arber et al. 2016).

CMML is stratified into three prognostic categories in the 2016 WHO classification based on enumeration of peripheral blood and bone marrow blasts and blast equivalents (Table 1).

	Blast/Blast Equivalents(%)	
	Peripheral Blood	Bone Marrow
CMML-0	<2%	<5%
CMML-1	2-4%	5-9%
CMML-2	5-19%	10-19%

Note: The presence of Auer rods in the peripheral blood or bone marrow indicates CMML-

## Cytogenetics

No recurrent cytogenetic abnormalities are identified in CMML. 20-40% of cases demonstrate abnormal karyotypes, most commonly +8, -Y, and -7/del(7q) (Patnaik and Tefferi 2016).

## Genes

The majority ( $>90\%$ ) of cases of CMML demonstrate somatic mutations (Reinig et al., 2016), typically in genes encoding epigenetic regulators, signalling pathway components, and mRNA splicing and transcription machinery. Truncating ASXL1 mutations have been shown to confer a poor prognosis and are included in prognostic schema (Patnaik and Tefferi, 2016). The combination of concurrent TET2 and SRSF2 mutations has been shown to be highly specific for CMML (Malcovati et al. 2014; Patnaik and Tefferi 2016). RUNX1, NRAS, and CBL are also commonly mutated in CMML.

## Treatment

Allogeneic stem cell transplant is the only curative therapy available for CMML. Current therapies have

not been shown to modify disease course or risk of transformation to acute myeloid leukemia (AML). Treatment is based on symptom management and can include erythropoiesis-stimulating agents, hydroxyurea, and hypomethylating agents (Solary and Itzykson, 2017).

## Evolution

15-30% of patients transform to AML per year (Solary and Itzykson, 2017; Itzykson et al., 2013).

## Prognosis

Prognosis is highly variable, with median survival ranging from 13-31 months (Schuler et al., 2014). Several risk stratification schema incorporating clinical, pathologic, and genetic data have been proposed.

## Disease

**Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML)**

## Phenotype/cell stem origin

Hematopoietic stem cell

## Epidemiology

aCML is relatively rare, accounting for less than 10% of cases of MDS/MPN with an incidence rate of 0.1/1,000,000 person-years (Guru Murthy et al., 2017). There is a 2:1 male predominance.

## Clinics

Patients are typically in their 7<sup>th</sup> or 8<sup>th</sup> decades of life and present with hepatosplenomegaly, bleeding diatheses, or symptoms related to leucocytosis or anemia (Dao and Tyner, 2015)

## Pathology

Diagnosis of aCML requires peripheral blood leukocytosis  $>13 \times 10^9$  /L with  $>10\%$  immature granulocytes and dysgranulopoiesis. Absolute monocytosis and basophilia must be absent or minimal and a relative monocytosis cannot exist. The bone marrow should be hypercellular due to granulocytic proliferation with dysplastic features; erythroid and megakaryocytic dysplasia may be present. Blasts may be increased up to 19% in the peripheral blood or bone marrow (Arber et al., 2016).

## Cytogenetics

No recurrent cytogenetic abnormalities have been identified in aCML.

## Genes

aCML demonstrates a similar spectrum of mutated genes as CMML. Up to 30% of cases of aCML demonstrate SETBP1 mutations, a frequency much higher than in other MDS/MPNs (Meggendorfer et al., 2013). ASXL1, NRAS, KRAS, SRSF2, and TET2 mutations are common in aCML, whereas CSF3R and JAK2 mutations are relatively infrequent ( $<10\%$  of cases) (Meggendorfer et al., 2014).

### **Treatment**

Data to guide therapy is limited and no consensus guidelines are available. Allogeneic stem cell transplantation is the only curative therapy. Hydroxyurea, hypomethylating agents, and therapeutics targeted at specific genetic mutations may be considered (Gotlib J, 2017).

### **Evolution**

A formal subclassification of accelerated disease phases is not available. 8 to 40% of cases have been reported to transform to AML (Breccia et al., 2006; Patnaik et al., 2017).

### **Prognosis**

Median survival ranges from 11 to 25 months in reported series (Breccia et al., 2006; Patnaik et al., 2017).

### **Disease**

**Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)**

### **Phenotype/cell stem origin**

Hematopoietic stem cell.

### **Epidemiology**

Limited data on the incidence of MDS/MPN-RS-T exists, in part due to its recent transition from a provisional entity in the 2008 WHO classification to a full entity in the 2016 WHO classification (Arber et al., 2016). In general, MDS/MPN-RS-T is considered rare within MDS/MPNs.

### **Clinics**

Patients are typically in their 8<sup>th</sup> decade of life and present with symptoms related to anemia, haemorrhage, or thrombosis. Splenomegaly is present in a subset of patients (Broseus et al., 2012).

### **Pathology**

The diagnosis of MDS/MPN-RS-T requires persistent thrombocytosis ( $>450 \times 10^9 /L$ ) in combination with anemia with erythroid dysplasia and  $>15\%$  ring sideroblasts. Blasts are required to be less than 1% in the peripheral blood and less than 5% in the bone marrow. Bone marrow examination should demonstrate megakaryocytes with features similar to those in primary myelofibrosis or essential thrombocytosis; this feature is critical in distinguishing MDS/MPN-RS-T from MDS with ring sideroblasts. The presence of SF3B1 mutations is typical for MDS/MPN-RS-T but not required; in the absence of a mutation, the clinical history must be interrogated to exclude recent cytotoxic or growth factor therapy which may confound morphologic interpretation (Arber et al., 2016).

### **Cytogenetics**

No recurrent cytogenetic abnormalities have been identified in MDS/MPN-RS-T.

### **Genes**

Mutations in SF3B1 are frequent in MDS/MPN-RS-T ( $>80\%$ ). Mutations in JAK2 are also frequent (50% of cases) and co-occur with SF3B1 mutations (Broseus et al., 2013; Jeromin et al., 2013). MPL and CALR mutations are rare.

### **Treatment**

Data to guide therapy is limited and no consensus guidelines are available. Treatment is aimed at symptoms related to anemia and is generally similar to treatment for low risk MDS. Patnaik and Tefferi, 2015 PMID 25899435).

### **Evolution**

Transformation to AML is relatively rare ( $<2\%$ /year) (Broseus et al., 2012).

### **Prognosis**

Overall median survival has been reported as 6.2 years in one large series. Importantly, SF3B1 and JAK2 mutations has been identified as independent risk factors conferring a good prognosis (Broseus et al., 2013).

### **Disease**

**Juvenile myelomonocytic leukemia (JMML)**

### **Phenotype/cell stem origin**

Hematopoietic stem cell

### **Epidemiology**

JMML typically occurs in young children, with the majority of cases being diagnosed before 3 years of age. The incidence is 1.3/1,000,000 person-years in children under the age of 15 (Hasle H, 1994). There is a 2:1 male predominance (Emanuel PD, 2008).

### **Clinics**

Patients typically present with fevers and failure to thrive. Physical exam commonly demonstrates hepatosplenomegaly, lymphadenopathy, and/or rash. Patients with type 1 neurofibromatosis show typical findings of this syndrome.

### **Pathology**

Diagnosis of JMML requires the presence of peripheral monocytosis ( $>1 \times 10^9 /L$ ),  $<20\%$  blasts in blood or bone marrow, and splenomegaly. In addition, one of the following genetic findings is required: somatic mutations in PTPN11, KRAS, or NRAS; germline NF1 mutation or clinical diagnosis of type 1 neurofibromatosis; germline CBL mutation or loss of heterozygosity. In the absence of any of these genetic findings, the diagnosis may still be rendered if monosomy 7 or any other chromosomal abnormality is present and one the following four criteria are fulfilled: haemoglobin F increased for age; myeloid or erythroid precursors identified on the peripheral blood smear; GM-CSF hypersensitivity in colony assay; or

hyperphosphorylation of STAT5 (Arber et al., 2016).

### Cytogenetics

Partial or complete loss of chromosome 7 (Note: see also Familial monosomy 7 syndrome) occurs in 25% of cases (Emanuel PD, 2008; Luna-Fineman et al., 1995).

### Genes

Activating mutations in the RAS signalling pathway are present in 85-90% of cases. Specifically, in order of decreasing frequency, the following genes show somatic or germline mutations: PTPN11, NRAS, KRAS, CBL, and NF1 (Loh M et al., 2004; Tartaglia M et al., 2003).

### Treatment

Allogeneic stem cell transplantation is the primary treatment modality (Locatelli and Niemeyer, 2015). Optimal pre-transplant conditioning regimens are currently the subject of ongoing clinical trials.

### Evolution

Transformation to AML occurs in 10-15% of cases.

### Prognosis

The clinical course of JMML is variable and is partially dependent on the underlying molecular lesion. The majority of cases demonstrate a progressive clinical course. However, patients with germline CBL mutations show spontaneous remission (Locatelli and Niemeyer, 2015; Dvorak and Loh, 2014).

### Disease

#### Myelodysplastic/myeloproliferative neoplasm, unclassifiable

This entity is included under MDS/MPN to include rare cases which demonstrate both myelodysplastic and myeloproliferative clinicopathologic features, but which do not fulfil criteria for any other entities within the MDS/MPN category.

## Genes involved and proteins

#### Note

ASXL1, CALR, CBL, CSF3R, JAK2, KRAS, MPL, NF1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2.

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