Review Article

Chronic Myelomonocytic Leukemia: Hematopathology Perspective

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ABSTRACT

Our understanding of chronic myelomonocytic leukemia (CMML) has evolved tremendously over the past decade. Large-scale sequencing studies have led to increased insight into the genomic landscape of CMML and clinical implications of these changes. This in turn has resulted in refined and improved risk stratification models, which to date remain versatile and subject to remodeling, as new and evolving studies continue to refine our understanding of this disease. In this article, we present an up-to-date review of CMML from a hematopathology perspective, while providing a clinically practical summary that sheds light on the constant evolution of our understanding of this disease.

Keywords: chronic myelomonocytic leukemia, CMML, myelproliferative, myelodysplastic, MDS, MPN, *NRAS*, *ASXL1*, *SRSF2*, monocyte
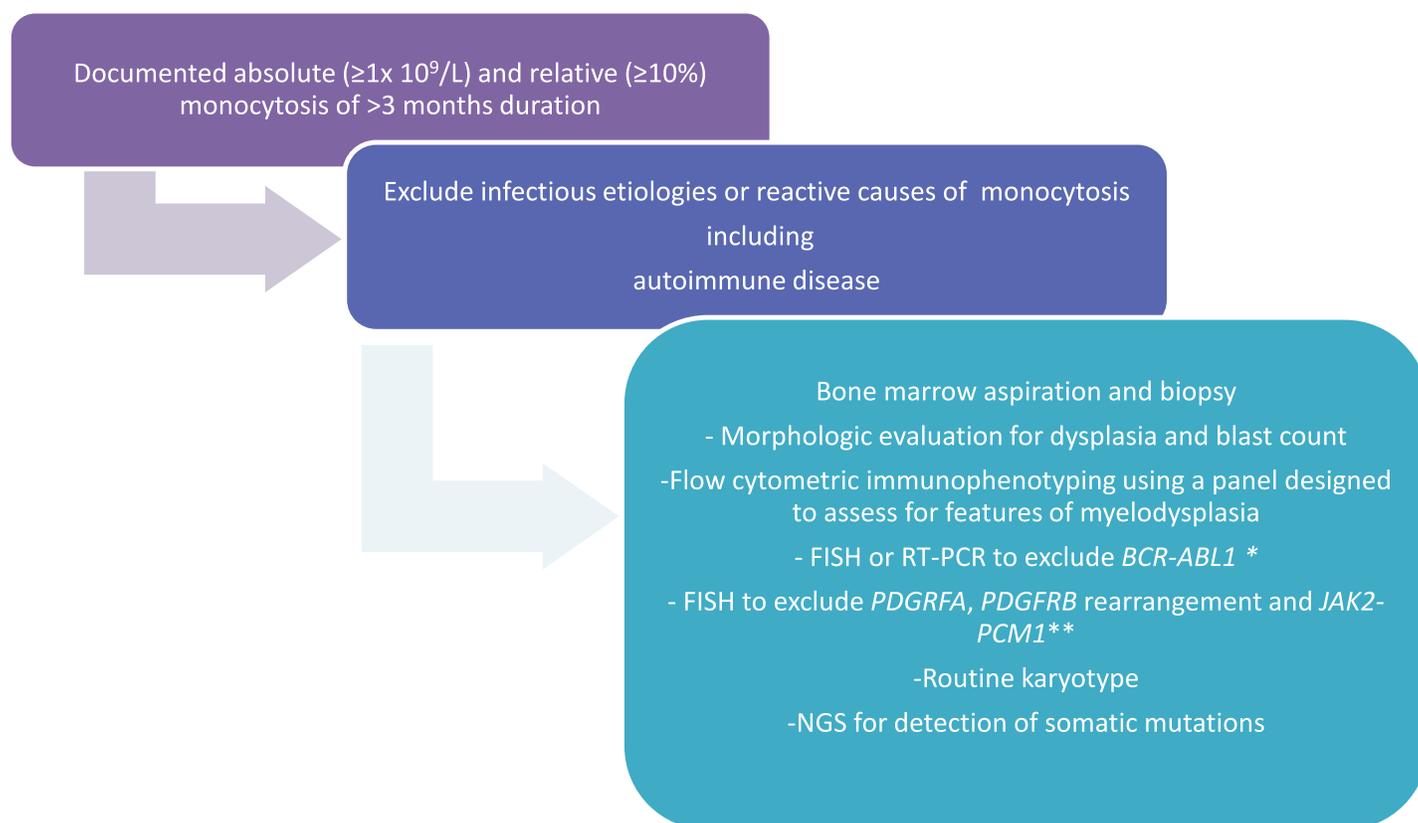
INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell neoplasm defined by relative ($\geq 10\%$) and absolute ($\geq 1 \times 10^9$/L) monocytosis, the presence of dysplasia in hematopoietic precursor cells, and an inherent risk for transformation to acute myeloid leukemia (AML).[1] The overall incidence of CMML is estimated to be around 4 cases per 100,000 persons/year; it usually affects elderly patients with a median age at diagnosis of 71–73 years, a male to female ratio of ~2.5:1, and a highly variable survival time ranging from 1 to more than 8 years.[1–4] CMML presents with a wide range of symptoms and signs, including constitutional symptoms, cytopenias manifesting as infection and/or bleeding, splenomegaly, cutaneous lesions, as well as inflammatory and autoimmune processes.[5] The diagnosis and risk stratification of CMML relies heavily on a thorough hematopathologic assessment of peripheral blood and bone marrow findings, as well as identifying the associated cytogenetic and molecular alterations. Figure 1 provides a schematic summary of our diagnostic approach to cases of suspected CMML, which we will review in detail throughout this paper to provide the reader with a practical guide to diagnosis, subclassification, and risk stratification of CMML.

HISTORICAL PERSPECTIVE ON DIAGNOSIS AND CLASSIFICATION

The French-American-British group subclassified CMML into two groups: myelodysplastic CMML (MD-CMML) (white blood cell [WBC] $< 13 \times 10^9$/L) and myeloproliferative CMML (MP-CMML) (WBC $\geq 13 \times 10^9$/L).[6]

In 2001[7] and 2008[8] the WHO (World Health Organization) classification scheme recognized CMML as a myelodysplastic/myeloproliferative neoplasm (MDS/MPN), and further subclassified it into two groups: CMML-1 (peripheral blood [PB] $< 5\%$; bone marrow [BM] $< 10\%$) and CMML-2 (PB 6–19%; BM 10–19%) with no significant emphasis on myelodysplastic or myeloproliferative subtypes. The 2016 iteration of the WHO incorporates two distinct subclassification updates: reincorporation of the MP-CMML and MD-CMML

Documented absolute (≥1x 10⁹/L) and relative (≥10%) monocytosis of >3 months duration

Exclude infectious etiologies or reactive causes of monocytosis including autoimmune disease

Bone marrow aspiration and biopsy
- Morphologic evaluation for dysplasia and blast count
-Flow cytometric immunophenotyping using a panel designed to assess for features of myelodysplasia
- FISH or RT-PCR to exclude *BCR-ABL1* *
- FISH to exclude *PDGRFA*, *PDGFRB* rearrangement and *JAK2-PCM1***
-Routine karyotype
-NGS for detection of somatic mutations

Figure 1. A systematic diagnostic approach to suspected chronic myelomonocytic leukemia (CMML) cases: After documentation of persistent monocytosis, the next step is to exclude nonneoplastic conditions including reactive, infectious, and autoimmune causes. A thorough morphologic-imunophenotypic evaluation of bone marrow specimens, integrating cytogenetic and molecular findings, is recommended to deliver the most accurate diagnosis. **Can also be performed on peripheral blood. **In cases with eosinophilia or abnormal mast cell aggregates. FISH: fluorescence in situ hybridization; NGS: next-generation sequencing; RT-PCR: real-time polymerase chain reaction.

subtypes and introduction of a novel three-tier classification system based on PB and BM blast counts. The 2016 WHO diagnostic criteria for CMML are summarized in Table 1.[9]

Table 1. WHO 2016 diagnostic criteria for chronic myelomonocytic leukemia[9]

Diagnostic Criteria
Persistent absolute ($\geq 1 \times 10^9$/L) and relative (> 10%) PB monocytosis
Not meeting WHO criteria for CML, PMF, PV, or ET
No evidence of *BCR-ABL1*, *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement, or *PCM1-JAK2****
< 20% blasts* in the BM and PB
BM dysplasia involving at least one cell lineage (megakaryocytic, erythroid, myeloid)**

BM: bone marrow; CML: chronic myeloid leukemia; ET: essential thrombocythemia; PB: peripheral blood; PMF: primary myelofibrosis; PV: polycythemia vera; WHO: World Health Organization.
*Blasts include myeloid blasts and monocytic blast equivalents including monoblasts and promonocytes.
**Morphologic dysplasia may be absent if all other criteria are met and there is evidence of an acquired clonal genetic (karyotypic or mutation) alteration or the duration of monocytosis has persisted ≥ 3 months and all reactive etiologies of monocytosis have been excluded.
***Particularly relevant in cases with associated eosinophilia.

HISTOPATHOLOGIC FEATURES

The morphologic features of CMML in the BM are not unique and overlap with other myelodysplastic syndromes/myeloproliferative neoplasms (Fig. 2a–c). Myelomonocytic hyperplasia is usually present (Fig. 2a). Morphologic dysplasia involving at least one bone marrow cellular lineage (myeloid, erythroid, or megakaryocytic) is one of the criteria used by the current WHO classification scheme for establishing a diagnosis of CMML. However, it is important to note that some cases show only mild or subtle morphologic changes, thus dysplasia may be omitted as a criterion in cases that have other evidence supporting clonality, such as chromosomal alterations or somatic gene mutations (Fig. 2b, c). An accurate blast count (including monocytic blast equivalents: monoblasts and promonocytes) is necessary for subclassification. The current WHO recommends a three-tier blast-based scheme,[9] including a novel CMML-0 category (PB < 2% and/or BM < 5%). However, from our study of a large cohort of CMMML patients ($n = 629$) at our institution and using the CMML-specific Prognostic Scoring System (CPSS),[10] as well as the MD Anderson Prognostic Scoring System for risk stratification (MDAPS),[11] we were unable to demonstrate a clear
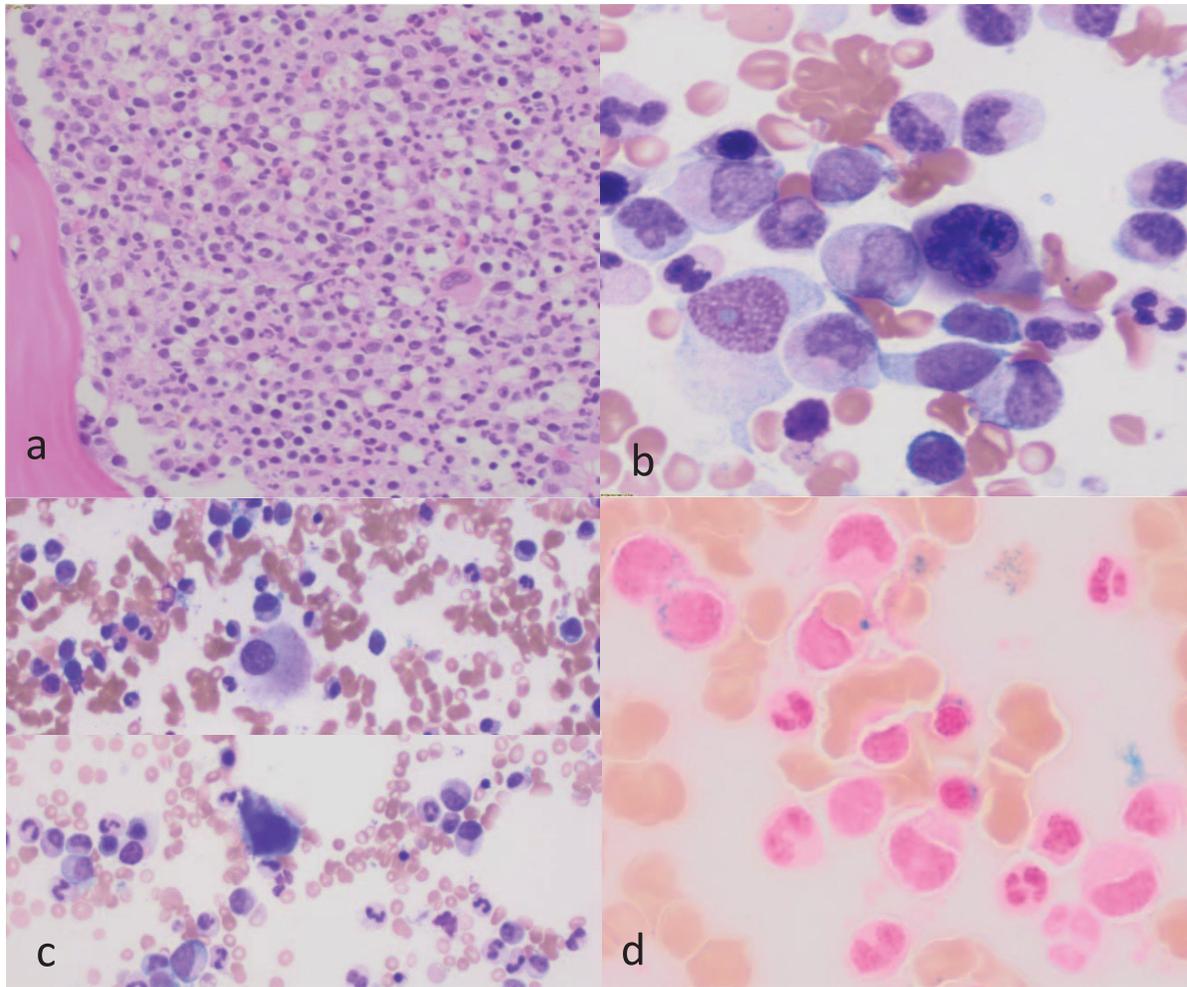
Figure 2. An example of chronic myelomonocytic leukemia demonstrating (a) hypercellular bone marrow with myemolonocytic hyperplasia; (b) granulocytic and erythroid dysplasia; (c) megakaryocytic dysplasia with increased monolobated megakaryocytes; (d) this case showed increased ring sideroblasts and harbored an *SF3B1* mutation.

improvement in risk stratification, using the proposed three-tier blast-based system.[12] We showed more than one-third of cases subclassified as CMML-0 were associated with higher-risk CPSS risk. The three-tier blast-based subclassification was not associated with leukemia-free survival and did not improve the prognostic power of CPPS.[12] Identification of monoblasts and promonocytes is highly subject to expertise with high interobserver variability, adding further complexity to this subclassification scheme.[13,14] Therefore, we suggest that perhaps further complicating the blast-based subclassification may not be clearly advantageous or reproducible.[15]

Increased mast cells (abnormal aggregates), plasmacytoid dendritic cells (mature or blastic), and eosinophils can be associated with specific genetic alterations and/or therapeutic relevance and should prompt additional evaluation. Nodular proliferations of mature plasmacytoid dendritic cells, observed in ~20–30% of bone marrow specimens of patients with CMML, must be distinguished from blastic plasmacytoid dendritic cell

neoplasms (BPDCNs), also known to be associated with CMML.[16] Immunohistochemical stains for CD123 (sensitive) and TCF4 (specific) help highlight both the mature plasmacytoid dendritic cell nodules and BPDCN cells[17]; however, they do not distinguish between the two. BPDCN tends to show blasts morphology, high Ki-67 proliferation index, and positive or negative TdT expression. A major differential diagnostic consideration of BPDCN is AML.[18] Aberrant expression of CD56 by plasmacytoid dendritic cells is a helpful clue to suspecting a neoplastic proliferation (mature or blastic); however, it is important to note that nonneoplastic plasmacytoid dendritic cells typically contain a small subset that shows CD56 expression but these cells do not exhibit other immunophenotypic aberrancies (see more details in the flow cytomtery discussion below). It is important to consider BPDCN in the differential diagnosis of any CD123+/CD4+ neoplasm, particularly in patients with underlying CMML, because accurate classification has direct therapeutic implications.[19–21]

Significant eosinophilia in the PB or BM should prompt evaluation for rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1*, and the *PCM1-JAK2*, as identification of any of these alterations would exclude a diagnosis of CMML. Among these, *PDGFRB* rearrangements are most likely to present with monocytosis,[22] and although typically identifiable on routine karyotyping studies (located on 5q32), rare cryptic cases, only identifiable by FISH (fluorescence in situ hybridization) exist.[23,24] *PDGFRA* fusions are almost nearly always cryptic and only identifiable by FISH, demonstrating *CHIC2* deletion.[1] In contrast, *PDGFRB* and *JAK2* rearrangements are typically identifiable on routine karyotype studies. Identification of these alterations has direct clinical and therapeutic implications because of the availability of targeted therapeutic agents. Imatinib has excellent efficacy in cases with *PDGFRA* and *PDGFRB* rearrangements.[25] Of note, evolving eosinophilia upon disease progression may be a clue to secondary acquisition of these genetic alterations and should prompt further investigation.[26]

Abnormally increased mast cells and mast cell aggregates can be a manifestation of systemic mastocytosis and is commonly associated with *KIT* p.D816 mutations.[27] Mast cells can be highlighted in the BM core biopsy by using immunohistochemical stains for CD117 or mast cell tryptase. When associated with CMML (or other well-defined myeloid neoplasms), systemic mastocytosis (SM) is classified as SM with an associated hematologic neoplasm (SM-AHN).[27] Compared with patients with CMML only, patients with SM and CMML are younger and more likely to have *CBL* (27 vs 13%) and *KIT* D816V (86 vs 1%) mutations.[28] The co-occurrence of CMML and mastocytosis does not influence prognosis.

A small subset (∼3%) of CMMLs is associated with substantial reticulin fibrosis at initial diagnosis. These cases are associated with unique clinicopathologic features including higher WBC count with more frequent MP-CMML phenotype, higher absolute monocytosis, higher BM blast percentage, higher serum lactate dehydrogenase levels, splenomegaly, and a significantly higher frequency of *JAK2* p.V617F mutations (up to 50%) and shorter overall survival.[29] Unlike cases of MDS with fibrosis in which the frequency of *TP53* mutations is high,[30] the frequency of *TP53* alterations is not increased relative to CMML without fibrosis.

Finally, it is noteworthy that the WHO classification scheme emphasizes the presence of absolute and relative monocytosis ($\geq 1 \times 10^9$/L and 10%, respectively) as an essential criterion for the diagnosis of CMML. Nevertheless, a subset of MDS/MPN cases with borderline monocytosis below the WHO recommended threshold ($\geq$ 10% PB monocytes with absolute monocyte count of 0.5–1 $\times$ 10^9/L), also referred to as oligomonocytic CMML, likely represent early evolving cases of MD-CMML, based on shared genetic and other clinicopathologic features.[31]

THE ROLE OF FLOW CYTOMETRY ANALYSIS IN THE SETTING OF CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

Flow cytometric immunophenotyping (FCI) of PB and BM is particularly helpful in establishing a diagnosis of CMML. Monocyte partitioning using PB, originally proposed by Selimoglu-Buet et al,[32] provides a valuable diagnostic tool for distinguishing CMML from reactive monocytosis and other myeloid neoplasms. Using antibodies directed toward CD14 and CD16, PB monocytes are divided into three distinct subsets: classical monocytes (CD14+/CD16–), intermediate monocytes (CD14+/CD16+), and nonclassical monocytes (CD14–/CD16+). In healthy individuals, the classical subtype represents most monocytes. This subset is typically expanded in the setting of CMML, which provides a diagnostic clue when other myeloid neoplasms or reactive conditions are in consideration, as the expansion of classical monocytes appears to be specific to CMML.[32] When using a $\geq$ 94% cutoff for classical monocytes, monocyte partitioning is able to distinguish CMML from other MDSs with a sensitivity of 72% and a specificity of 86%. Of note, cases of MDS with expansion of classical monocytes to extent seen in CMML have better prognosis and more commonly carry *SF3B1* mutations.[33] Monocyte partitioning is also useful for differentiating CMML from other MPNs with monocytosis. A 92% classical monocyte cutoff has a sensitivity of 93% and specificity of 100%, favoring CMML.[34]

FCI of BM aspirate is used to identify abnormal myeloid progenitors and aberrant monocytes, which is particularly helpful in excluding reactive cases of monocytosis. However, FCI features are not specific for CMML, as similar alterations can be detected in other myeloid stem cell neoplasms.[35] Similar to other myeloid stem cell neoplasms, CD34+ myeloblasts in the setting of CMML frequently exhibit an abnormal immunophenotype including increased intensity of CD13, CD34, CD117, CD123 and decreased intensify of CD38 and HLA-DR expression. Other immunophenotypic alterations include altered pattern of CD45 or side scatter; lineage infidelity as shown by aberrant expression of lymphoid markers including CD2, CD5, CD7, CD19, and CD56; and asynchronous expression of mature myelomonocytic markers such as CD15 and CD64. Maturing monocytes and granulocytes also frequently show immunophenotypic alterations (96 and 83%, respectively).[36]

Flow cytometry also provides a useful tool in detection of aberrant plasmacytoid dendritic cells, which may be encountered in patients in the setting of CMML.[37] Compared with normal plasmacytoid dendritic cells, neoplastic plasmacytoid dendritic cells (PDCs) show increased expression of CD56 and other immunophenotypic aberrancies. A recent study by Wang et al[37] summarized these features and showed decreased or negative CD38 (82%), expression of CD7 (64%), loss of

Epigenetic modifiers	Cell Signaling	mRNA splicing	DNA repair	Transcription factors
TET2 (60%) *ASXL1** (40%) *EZH2* (5%) *DNMT3A* * (5%) *IDH1* (1%) *IDH2* (10-50%)	• *CBL* (15%) • *NRAS** (15%) • *KRAS* (10%) • *PTPN11* (5%) • *JAK2* (3-10%) • *FLT3* (<5%)	• *SRSF2* (50%) • *SF3B1* (5-10%) • *U2AF1* (5-10%) • *ZRSR2* (5-10%)	*PHF6* (5%) *TP53* (1%)	• *RUNX1** (15%) • *SETBP1** (15%)

Figure 3. Recurrent mutations and their frequencies and respective functions in chronic myelomonocytic leukemia. *Associated with adverse prognosis in various studies. CMML: chronic myelomonocytic leukemia; mRNA: messenger RNA.

CD2 (81%), loss of CD303 (56%), and increased HLA-DR (69%) and decreased CD123 (78%) expression as features associated with BPDCN. Of note, they showed that reactive PDCs also consistently included a CD56+ subset, ranging from 1.3 to 20% (median 4.5%); however, these cells did not exhibit the other immunophenotypic aberrancies associated with BPDCN.[37]

IMPACT OF CHROMOSOMAL ALTERATIONS IN CMML

Clonal cytogenetic abnormalities are detected in ~20–30% of CMMLs,[38,39] the most common including trisomy 8, –Y, –7/del(7q), –21, and complex karyotype.[40–42] These abnormalities, although nonspecific for CMML and frequently detected in other hematopoietic neoplasms, help establish evidence for clonality. Identification of these alterations is particularly important because they can serve as a diagnostic criterion in cases that lack morphologic dysplasia; as such, if morphologic dysplasia is subtle or unidentifiable, genetic alterations can be used to confirm the neoplastic nature of the process.[1] Various CMML-specific risk stratification schemes rely heavily on the presence of cytogenetic abnormalities for predicting outcome in patients with CMML. In the schema proposed by Such et al,[38] a diploid karyotype and del Y are considered low risk, with a median overall survival (OS) of 33 months, whereas CMML with +8, –7/del(7q), and complex karyotype portend high risk with a median OS of 14 months. The remainder of patients belong to an intermediate-risk group with a median OS of 24 months.[38] Of note, Tang et al[39] have shown that patients with isolated trisomy 8 have a median OS of 22 months, similar to the intermediate-risk group, whereas patients with more than three chromosomal abnormalities have a significantly shorter OS of 8 months. The Mayo-French cytogenetic risk stratification demonstrated that all complex and monosomal karyotypes are high risk with a median OS of 3 months, whereas patients harboring der(3q) abnormality alone belong to a low-risk group, with a median OS of 41 months.[40]

IMPACT OF GENETIC MUTATIONS IN CMML

We advocate for the routine sequencing of any suspected case of CMML. At our institution, we use an 81-gene next-generation sequencing panel enriched for genes with recurrent mutations in myeloid neoplasms.[43] Somatic mutations have diagnostic and prognostic implications in the setting of CMML. The most commonly encountered mutations in CMML affect *TET2* (60%), *SRSF2* (50%),[44] *ASXL1* (40%), and genes of the RAS pathway (*KRAS, NRAS, PTPN11, NF1*) (30%)[45,46] Coexistence of *SRSF2* and *TET2* mutations in particular is highly suggestive of CMML.[47] Other recurrent mutations involve *SF3B1, U2AF1, IDH1/2, RUNX1, TP53*, and *SETBP1*. The spectrum of these lesions seem to alter with the CMML variant: for example, *SF3B1* and *U2AF1* mutations are more commonly seen in the MD-CMML variant[48]; mutations affecting the *RAS* pathway, *RUNX1* and *EZH2*, on the other hand are more common in the MP-CMML variant.[48,49] *SF3B1*-mutated CMML (Fig. 2d) is a unique subtype with predominant dysplastic features including increased ring sideroblasts, low frequency of *ASXL1* mutations, higher frequency of *JAK2* p.V617F, and other concurrent splicing factor mutations and in line with other MDS with *SF3B1* mutations, shows longer leukemia-free survival.[50] *TET2*-mutated CMML is associated with a survival advantage especially in the context of multiple *TET2* and truncating mutations.[51] Patients with *TET2*mut CMML are characteristically older, more likely to have MD-CMML, have a higher number of co-occurring mutations, and tend to fall in the lower-risk categories using the molecular-based risk stratification schemes.[51] *ASXL1* mutations are associated with adverse prognosis and a shorter overall survival[52,53]; however, the adverse prognostic impact of *ASXL1* mutation is partially mitigated by concurrent *TET2* mutation.[51] A summary of genes recurrently mutated in CMML and their respective frequencies and pathways involved is illustrated in Figure 3.
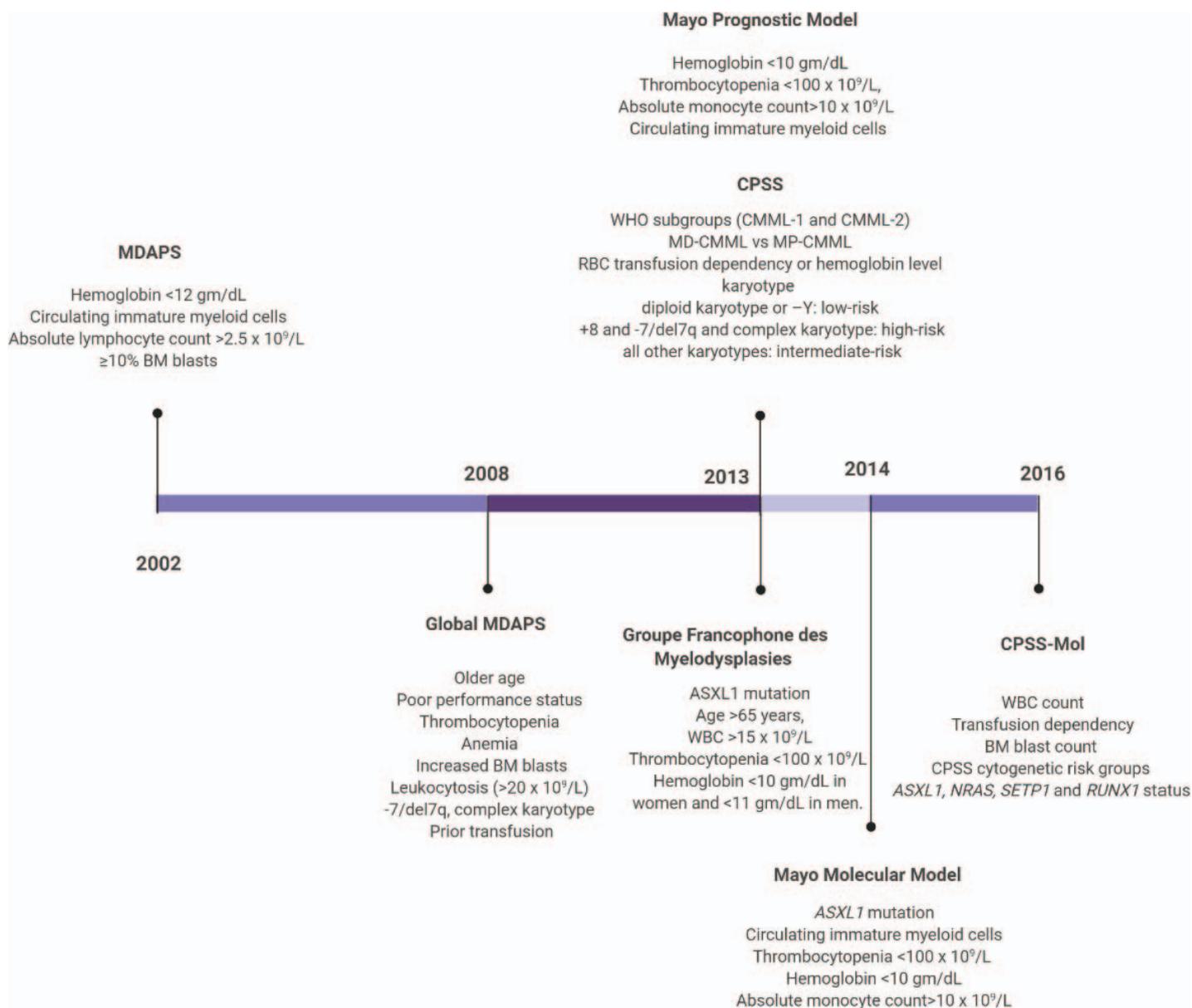
Figure 4. Evolution of prognostic models for chronic myelomonocytic leukemia (CMML) over time. Illustration created with BioRender.com. BM: bone marrow; CMML: chronic myelomonocytic leukemia; CPSS: CMML-specific prognostic scoring system; MD-CMML: myelodysplastic chronic myelomonocytic leukemia; MDAPS: MD Anderson Prognostic Scoring System; MP-CMML: myeloproliferative chronic myelomonocytic leukemia; WCB: white blood cell.

RISK STRATIFICATION MODELS

MDS-specific risk stratification models including the international prognostic scoring system (IPSS) and revised IPSS (IPSS-R) are of limited value in the setting of CMML. Therefore, several CMML-specific stratification models have been proposed to date.[10,11,53–56] A summary of these models and the criteria used for each is illustrated in Figure 4. The CPSS, the most commonly used prognostic model, incorporates four variables: WHO subgroups (CMML-1 and CMML-2), MDS versus MPN phenotypes, transfusion dependency, and karyotype.[38] Recent work to integrate clinicopathologic features, cytogenetic findings, and molecular findings

(*ASXL1*, *NRAS*, *SETBP1*, and *RUNX1* status) into the CPSS has led to the creation of the modified clinical-molecular CPSS (CPSS-Mol).[53] This prognostic system stratifies the genetic subgroups of CMML into four CPSS-Mol groups: low-risk (median OS not reached; 0% 48-month cumulative incidence of AML transformation); intermediate-1 risk (median OS, 68 months; 8% 48-month cumulative transformation incidence); intermediate-2 risk (median OS, 30 months; 24% 48-month cumulative transformation risk); and high-risk ($\geq$ 4 points; median OS, 17 months; 52% 48-month cumulative transformation incidence).[53]

The MDAPS has a predictive value similar to the CPSS[10,11,55,57,58]; in addition, it is a CMML-specific risk

stratification scheme.[11] The Global MDAPS, a modified risk stratification system, subgroups CMML cases into four categories: low-risk (median OS of 54 months), intermediate-1 risk (median OS of 25 months), intermediate-2 risk (median OS of 14 months), and high-risk (median OS of 6 months).[54]

The Mayo prognostic model for CMML utilizes anemia, thrombocytopenia, absolute monocytosis, and circulating immature myeloid cells to predict for inferior OS.[55] The Mayo Molecular Model is a revision to the original Mayo prognostic model with addition of *ASXL1* mutations as an independent factor predicting for inferior OS. Using these factors, the Mayo Molecular Model divides CMML patients into four risk groups: low, intermediate-1, intermediate-2, and high with median OS of 97, 58, 31, and 16 months, respectively.[59]

THERAPY AND MANAGEMENT

Detailed discussion of therapy and management for patients with CMML is beyond the scope of this review. Allogeneic hematopoietic stem cell transplant (HSCT) is the only curative option and remains the treatment of choice for younger patients with higher-risk disease. However, HSCT is not without complications and therefore the need for other less aggressive therapeutic options remains valid. Hypomethylating agents including azacitidine, decitabine, and oral decitabine/cedazuridine are currently approved by the US Food and Drug Administration for the management of CMML but are not considered curative options because although they restore hematopoiesis through epigenetic modulation in a subset of patients, they do not eliminate mutations and therefore eventual progression to acute myeloid leukemia occurs. A number of novel therapeutic options are becoming available. These agents and their mechanisms of action are discussed in detail in two recent reviews by Patnaik et al.[60,61] Targeted therapies exploiting specific genetic lesions and biologic pathways are attractive options that need to be further investigated in the setting of CMML.

CONCLUSION

The clinicopathologic presentation of CMML is heterogeneous, with variable combinations of proliferative and dysplastic features. A thorough hematopathology workup including morphologic evaluation, FCI, and assessment for chromosomal alterations and gene mutations in cases of suspected CMML is of essence for accurate diagnosis, subclassification, prognostication, and risk stratification that will ultimately lead to better patient management.

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