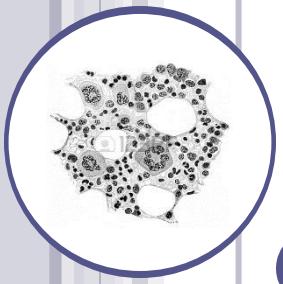
平成29年度 先駆的臨床検査技術研修会
第1回 日臨技骨髄像伝達研修会2017
2017.08.26(Sat)

今から使える、WHO2016
骨髄系腫瘍分類の変更点

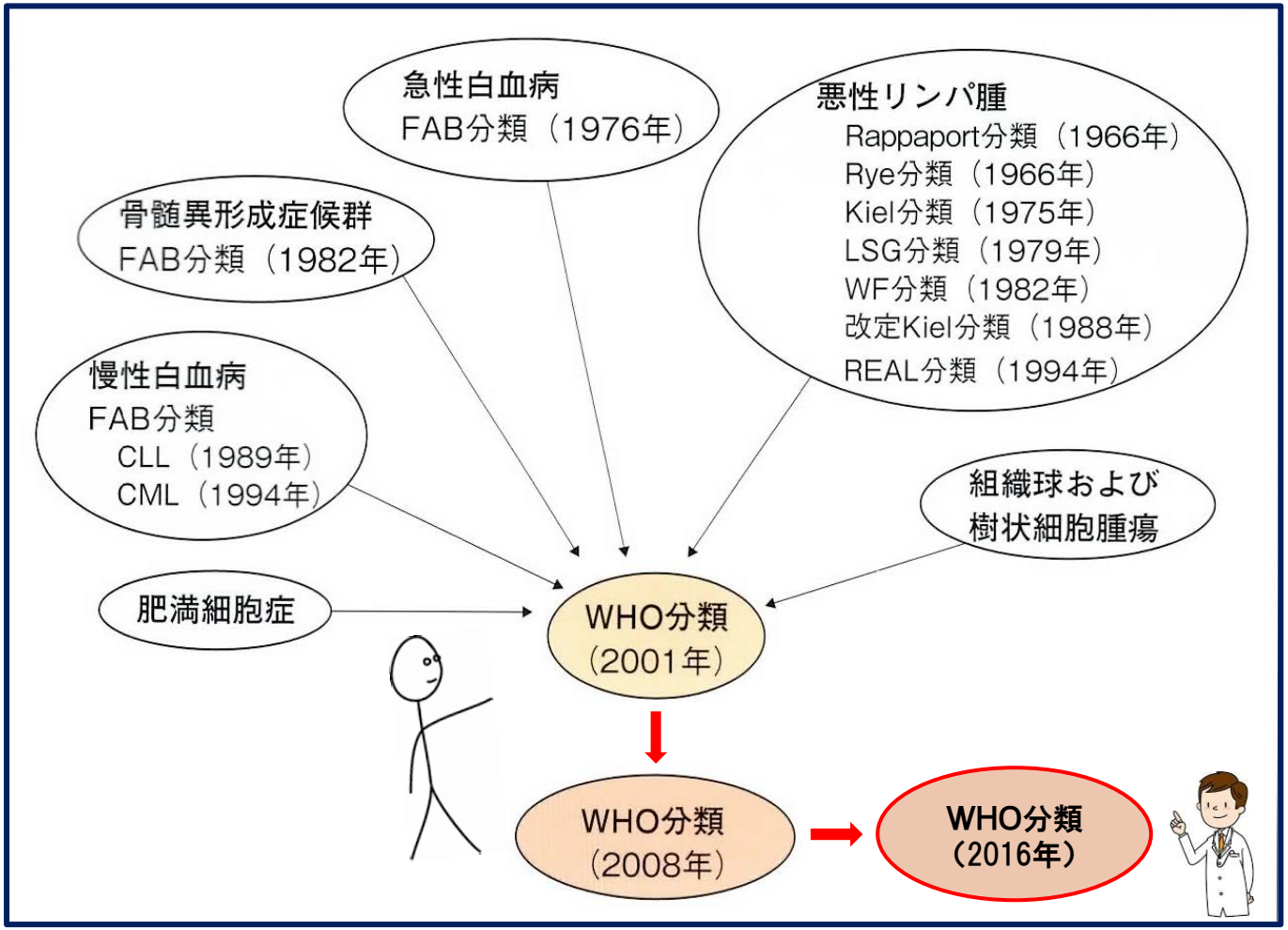


WHO 2016

NTT東日本関東病院 臨床検査部
後藤 文彦

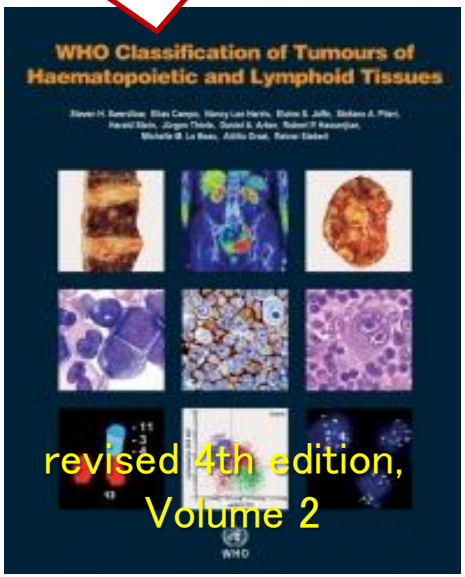
NTT MEDICAL CENTER Tokyo

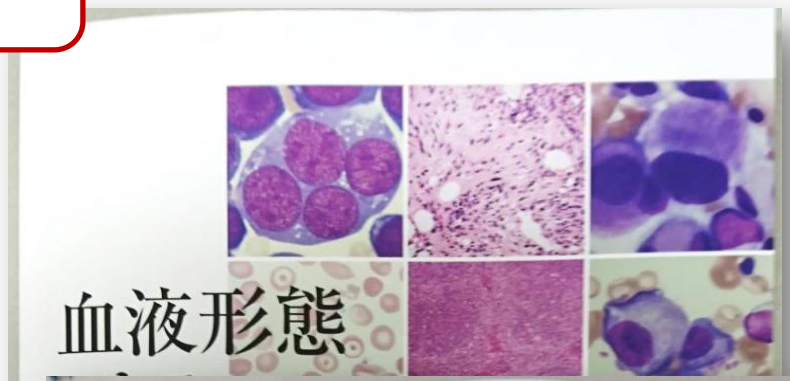
造血器腫瘍の分類

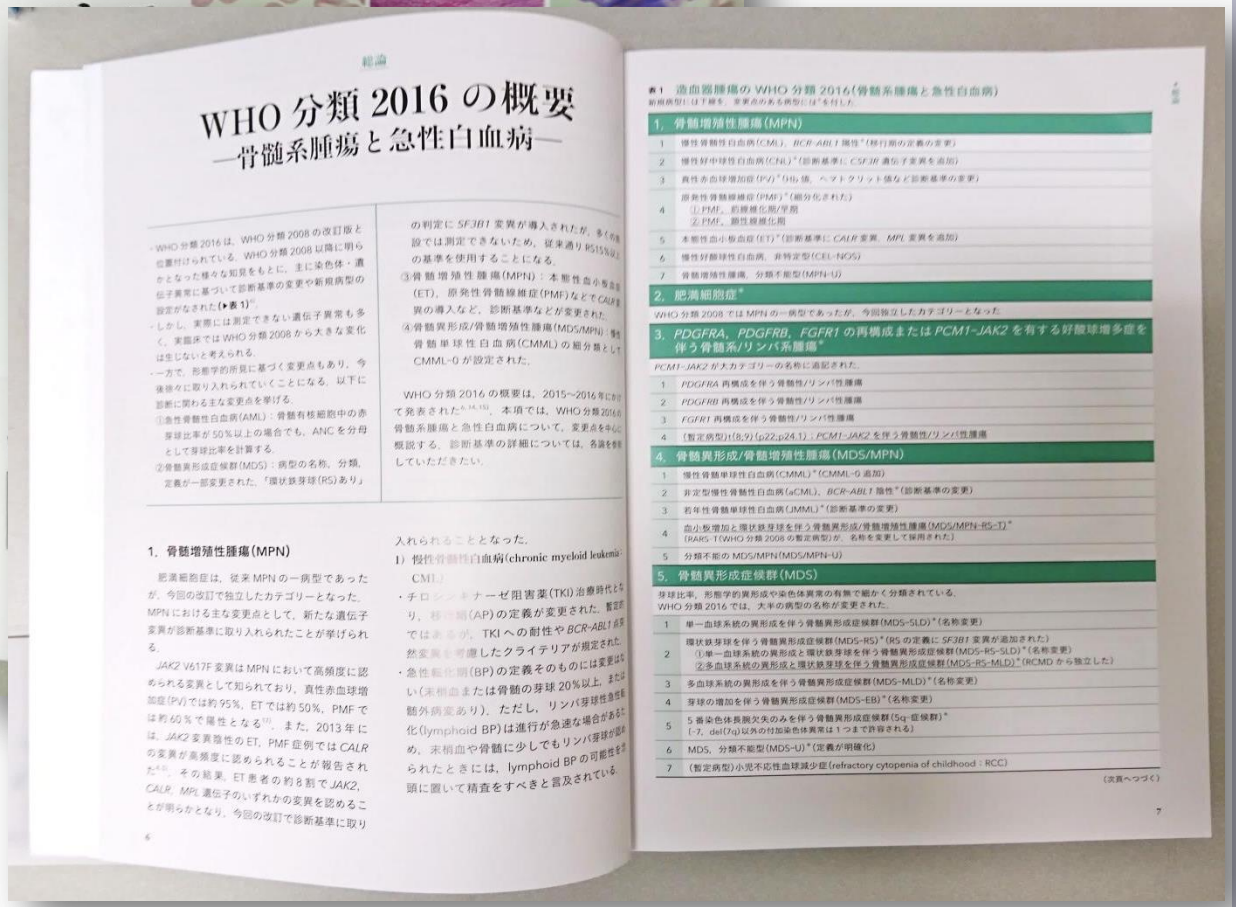


WHO分類第4版による白血病・リンパ系腫瘍の病態学　改変

comming soon







THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

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The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was last updated in 2008. Since then, there have been numerous advances in the identification of unique biomarkers associated with some myeloid neoplasms and acute leukemias, largely derived from gene expression analysis and next-generation sequencing that can significantly improve the diagnostic criteria as well as the prognostic relevance of entities currently included in the WHO classification and that also suggest new entities that should be added. Therefore, there is a clear need for a revision to the current classification. The revisions to the categories of myeloid neoplasms and acute leukemia will be published in a monograph in 2016 and reflect a consensus of opinion of hematopathologists, hematologists, oncologists, and geneticists. The 2016 edition represents a revision of the prior classification rather than an entirely new classification and attempts to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the last edition. The major changes in the classification and their rationale are presented here. (*Blood*. 2016; 127(20):2391-2405)

Introduction

In collaboration with the Society for Hematopathology and the European Association for Haematopathology, the World Health Organization (WHO) published the third and fourth editions of the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, in 2001 and 2008, respectively, as part of a series of *WHO Classification of Tumours* "blue book" monographs. In the spring of 2014, a clinical advisory committee (CAC) composed of ~100 pathologists, hematologists, oncologists, and geneticists from around the world convened to propose revisions to the fourth edition of the classification. The revision of the fourth edition follows the philosophy of the third and fourth editions to incorporate clinical features, morphology, immunophenotyping, cytogenetics, and molecular genetics to define disease entities of clinical significance. The fourth edition of the classification of hematopoietic and lymphoid tissues was the second volume of the WHO "blue book" tumor series, and the series publication is still in progress. A fifth edition series cannot begin until the fourth edition series is completed; but after 8 years of information and experience that have emerged from scientific and clinical studies, a revision of these criteria for hematopoietic and lymphoid neoplasms was felt to be necessary and timely. In relation to myeloid neoplasms and acute leukemia, this revision has been influenced by several factors including the following:

1. The discovery of recently identified molecular features has yielded new perspectives regarding diagnostic and prognostic markers that provide novel insights for the understanding of the pathobiology of these disorders.
2. Improved characterization and standardization of morphological features aiding in the differentiation of disease groups, particularly of the *BCR-ABL1*$^-$ myeloproliferative neoplasms (MPNs), has increased the reliability and reproducibility of di-agnoses.
3. A number of clinical-pathological studies have now validated the WHO postulate of an integrated approach that includes hematologic, morphologic, cytogenetic, and molecular genetic findings.

For these reasons, the fourth edition is being updated, but this 2016 classification is not a major overhaul of the disease categories. Rather, it is intended to incorporate new knowledge of these disorders obtained since the 2008 publication and is a revision of that classification. The purpose of this report is to summarize the major changes in the revised WHO classification of myeloid neoplasms and acute leukemia and to provide the rationale for those changes. Table 1 lists the major subtypes of myeloid neoplasms and acute leukemias according to the updated (2016) WHO classification.

Myeloproliferative neoplasms

The categories of MPNs have not significantly changed since the 2008 fourth edition of the classification, but discoveries of new mutations and improved understanding of the morphologic features of some entities have impacted the diagnostic criteria for the disease entities.

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Arbor DA, et al. BLOOD 127:2391–2405, 2016.

WHO分類2016概要

myeloid neoplasms and acute leukemia

Myeloproliferative neoplasms (MPN)
- Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
- Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
- *Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2*

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- *Provisional entity: Refractory cytopenia of childhood*

Myeloid neoplasms with germ line predisposition

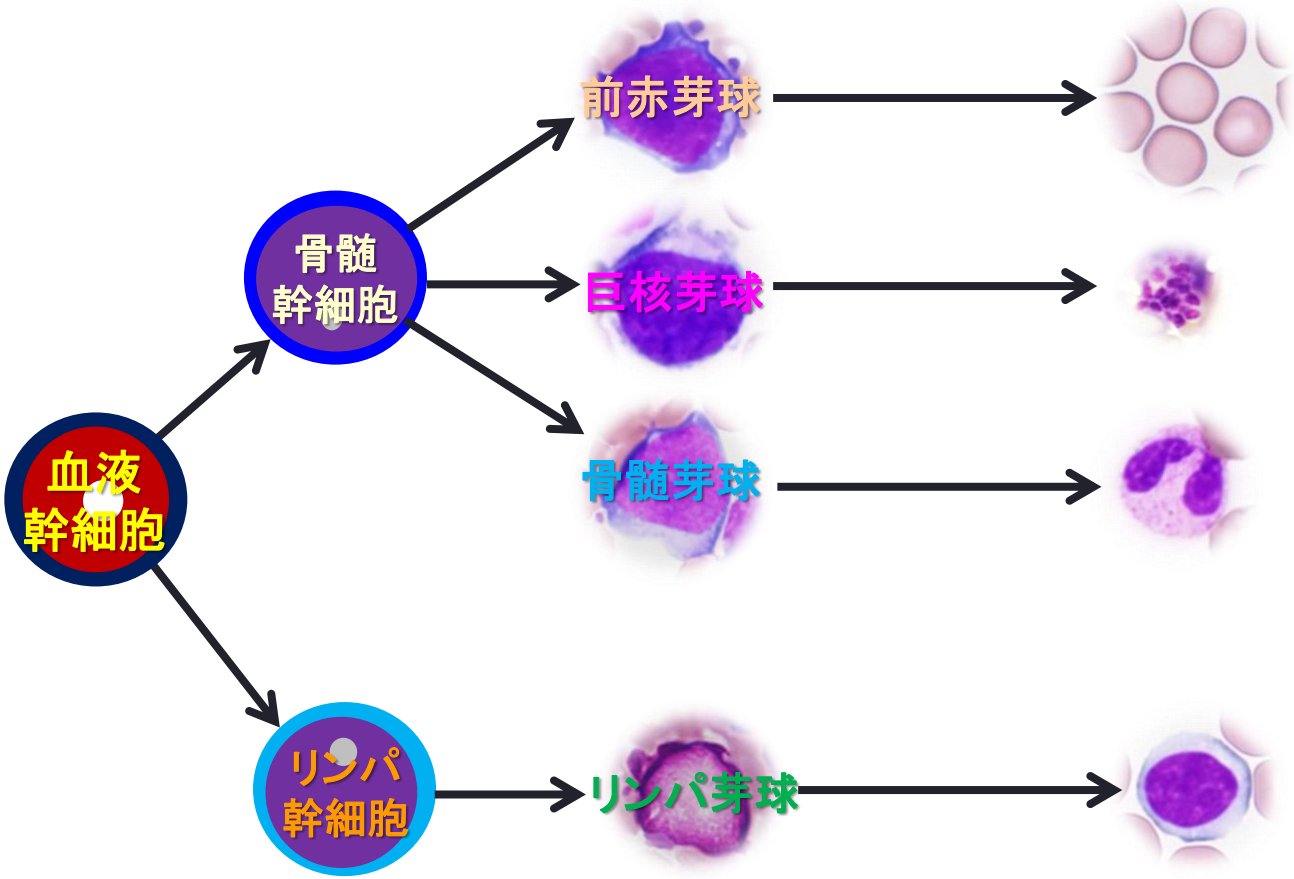
Acute myeloid leukemia (AML) and related neoplasms
- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis (TAM)
  - Myeloid leukemia associated with Down syndrome

WHO分類2016年改訂による骨髄系腫瘍

- 骨髄増殖性腫瘍
- 肥満細胞症
- *PDGFRA*、*PDGFRB* または*FGFR1* 遺伝子の再構成あるいは*PCM1–JAK2* を伴う骨髄/リンパ系腫瘍
- 骨髄異形成/骨髄増殖性腫瘍
- 骨髄異形成症候群
- 胚細胞系列の素因を伴う骨髄性腫瘍
- 急性骨髄性白血病と関連腫瘍
- 芽球形質細胞様樹状細胞腫瘍
- 系統が明らかでない急性白血病

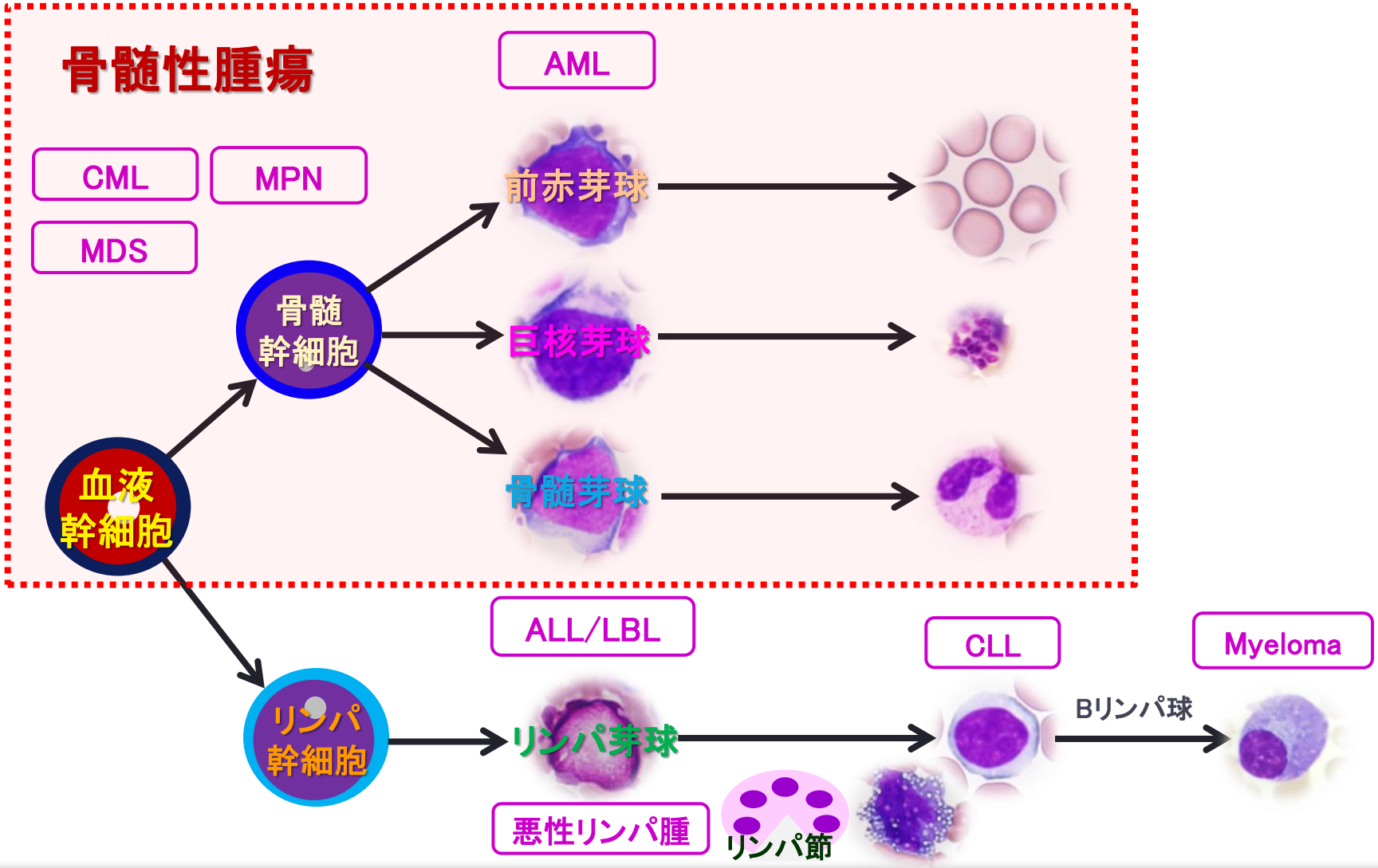
造血の模式図

■骨髄中の血液幹細胞が増殖して、様々な血液細胞に分化・成熟し、末梢血中で機能を営む。



造血の模式図

■造血器腫瘍の考え方



造血器腫瘍の診断

検査技術	結 果	客観性	汎用性	検査法
形態学的検査	評価	乏しい（主観的）	有	普通染色（Romanowsky染色）
細胞化学染色				POD染色、EST染色、PAS染色、FE染色 など
細胞免疫学的検査	解析	有	乏しい	細胞表面・内マーカーの解析（フローサイトメトリー）
細胞遺伝学的検査				G分染法、FISH　など
遺伝子検査				サザンブロット法、PCR法 DNAシーケンス法　など

急性骨髄性白血病の診断

≪WHO分類≫

≪FAB分類≫

顕微鏡 ： 形態／細胞化学検査

形態診断 ↓

造血器腫瘍の診断・病型分類

フロサイトメトリー
（FCM）

遺伝子/染色体検査

WHO分類　優れていること　劣ること

優	■コンセンサス分類であり、客観性がある。 ■疾患の発症背景、腫瘍細胞の形態、表面形質、染色体や遺伝子検査、治療反応性や予後を含む臨床像を総括して診断、病型が規定されている。
劣	■病型が多く、分類が複雑。 ■最終診断まで時間と費用を要する。 ・染色体/遺伝子検査の結果が重要視される。 ■遺伝子変異解析が困難。 ・研究機関でしかできない遺伝子変異がある。 ・わが国では、保険適用となっていない検査が多い。

今から使える、WHO分類2016骨髄系腫瘍の変更点

1. 骨髄増殖性腫瘍（MPN）

2. *PDGFRA*、*PDGFRB* または*FGFR1* 遺伝子の再構成

   あるいは*PCM1–JAK2* を伴う骨髄/リンパ系腫瘍

3. 骨髄異形成/骨髄増殖性腫瘍（MDS/MPN）

4. 骨髄異形成症候群（MDS）

5. 急性骨髄性白血病（AML）と関連腫瘍

骨髄増殖性腫瘍

■WHO2001においては「骨髄増殖性疾患（CMPD）」と呼ばれていたが、遺伝子解析の進歩で腫瘍性病変であることが確立した。

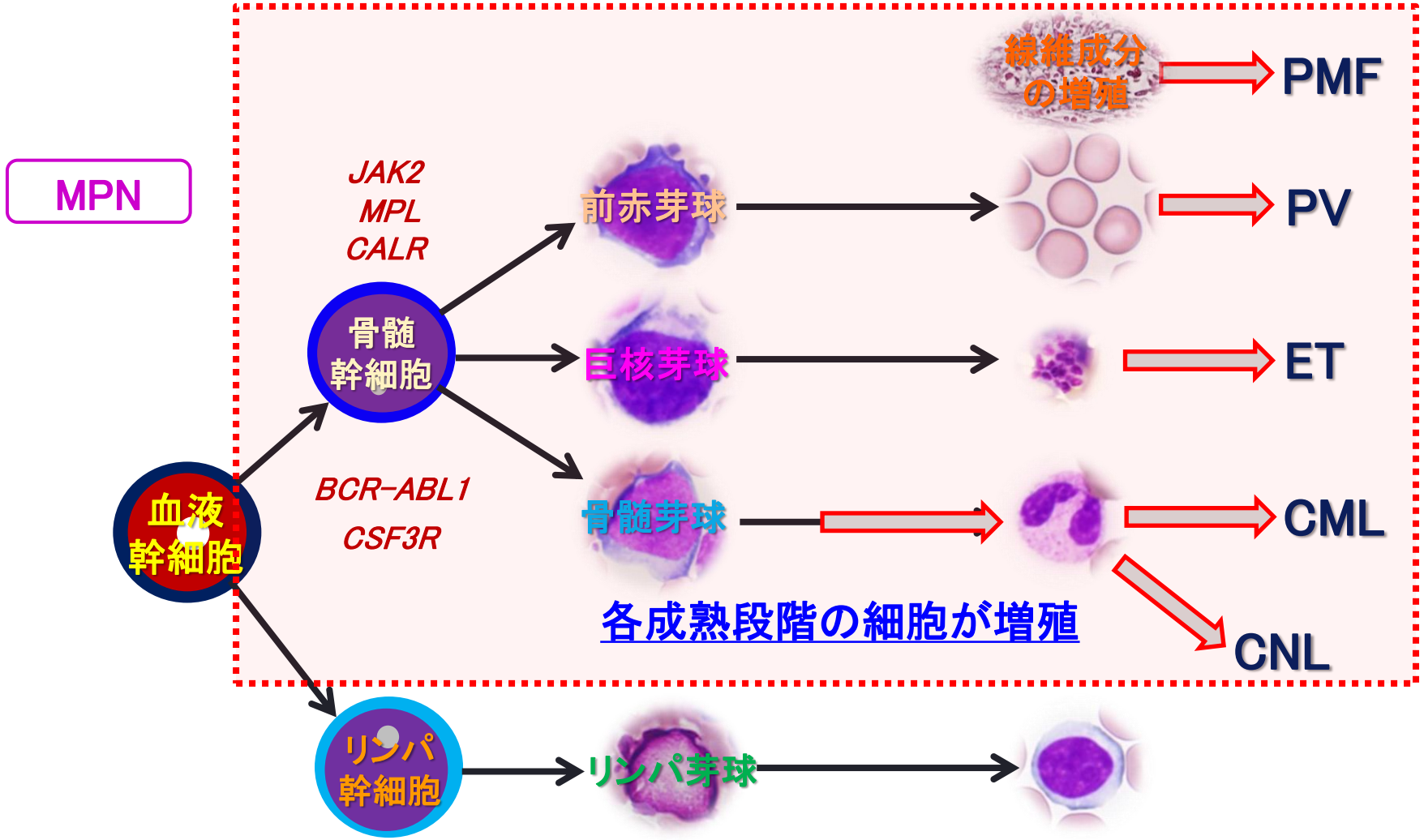
■WHO2008より「骨髄増殖性腫瘍（MPN）」となった.

※CMPD：Chronic myeloproliferative disorder

※MPN：Myeloproliferative neoplasms

造血の模式図

■骨髄増殖性腫瘍（MPN）　増殖と分化能は保持



WHO2016：骨髄増殖性腫瘍（MPN）の病型

■慢性骨髄性白血病（CML），*BCR-ABL1*

■慢性好中球性白血病（CNL）

■真性赤血球増加症（PV）

■原発性骨髄線維症（PMF）

・PMF，前線維化期/早期（pre PMF）

・PMF，線維化期

■本態性血小板血症（ET）

■他に特定されない慢性好酸球性白血病（CEL，NOS）

■分類不能型MPN（MPN-U）

MPNの変更点・ポイント

■PMF、ETに特徴的な遺伝子変異として、*JAK2*、*MPL* 変異に加え、*CALR* 変異が同定されたことにより、クローン性の証明、診断的価値、予後との関連性が明らかとなった。

■CNLと*CSF3R* 遺伝子変異との強い関連が明らかとなった。

■PV診断時（大基準）の ヘモグロビン基準が引き下げられた。また ヘマトクリット値も診断基準に採用された。

■PMFが「前線維化期（prePMF）」と「線維化期」に細分化された。特に「prePMF」と「ET」の鑑別が予後が異なるため重要とされた。そのため、骨髄生検が重要となった。

■ETでは「*JAK2*、*CALR* 、あるいは*MPL* 変異を認める」が大基準に追加された。

CML（移行期）の定義

Table 2. Criteria for CML, accelerated phase

CML, accelerated phase criteria	
Any 1 or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:	
• Persistent or increasing WBC (>10 × 10^9/L), unresponsive to therapy	**"Provisional" response-to-TKI criteria**
• Persistent or increasing splenomegaly, unresponsive to therapy	• Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response* to the first TKI) or
• Persistent thrombocytosis (>1000 × 10^9/L), unresponsive to therapy	• Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or
• Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy	• Occurrence of 2 or more mutations in *BCR-ABL1* during TKI therapy
• 20% or more basophils in the PB	
• 10%-19% blasts† in the PB and/or BM	
• Additional clonal chromosomal abnormalities in Ph^+ cells at diagnosis that include "major route" abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2	
• Any new clonal chromosomal abnormality in Ph^+ cells that occurs during therapy	

Large clusters or sheets of small, abnormal megakaryocytes, associated with marked reticulin or collagen fibrosis in biopsy specimens may be considered as presumptive evidence of AP, although these findings are usually associated with 1 or more of the criteria listed above.

*Complete hematologic response: WBC, <10 × 10^9/L; platelet count, <450 × 10^9/L, no immature granulocytes in the differential, and spleen nonpalpable.

†The finding of bona fide lymphoblasts in the blood or marrow, even if <10%, should prompt concern that lymphoblastic transformation may be imminent and warrants further clinical and genetic investigation; 20% or more blasts in blood or BM, or an infiltrative proliferation of blasts in an extramedullary site is CML, blast phase.

- provisonal（暫定）クライテリアとして、TKIへの反応性が追加された。
- lymphoid BPでは、進行が急速であるため、芽球20%以上や髄外腫瘤は必ずしも条件としなくてもよいかもしれない。

CNLの診断基準

Table 3. Diagnostic criteria for CNL

CNL diagnostic criteria
1. PB WBC ≥25 × 10^9/L
Segmented neutrophils plus band forms ≥80% of WBCs
Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) <10% of WBC
Myeloblasts rarely observed
Monocyte count <1 × 10^9/L
No dysgranulopoiesis
2. Hypercellular BM
Neutrophil granulocytes increased in percentage and number
Neutrophil maturation appears normal
Myeloblasts <5% of nucleated cells
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, ET, or PMF
4. No rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or *PCM1-JAK2*
5. Presence of *CSF3R* T618I or other activating *CSF3R* mutation
or
In the absence of a *CSFR3R* mutation, persistent neutrophilia (at least 3 mo), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies

■ *CSF3R* 遺伝子変異はCNLと強く関連していることが診断基準に追加されたが、必須項目ではない。

■ *CSF3R* 遺伝子のT618I変異は特に関連が強い。

■ 他にも*CSF3R* 遺伝子が活性化された変異が存在する。

CSF3R 遺伝子について

- CSF3R ： colony stimulating factor 3 receptor.
- *CSF3R* 遺伝子のT618I 変異は、慢性好中球性白血病（CNL)と関連が強いとされる。
- CNLの診断基準に組み込まれたが、必須項目ではない。
- この遺伝子変異は aCML、AML、CMMLでもみられるが、その頻度は低い。
- CSF3R蛋白が顆粒球コロニー刺激因子（G-CSF）の受容体であり、CNLでは*CSF3R* の活性型変異が存在していることから、G-CSFによる刺激が無くともそのシグナルが恒常的に活性化していると考えられる。

PVの診断基準

Table 4. WHO criteria for PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level　EPO低値　※PVで20%正常
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

【大基準】

1. Hbの診断基準の変更（2008の値）
   - 男性：＞16.5g/dL　（>18.5g/dL）
   - 女性：＞16.0g/dL　（>16.5g/dL）

■Htも診断基準に採用
   - 男性：＞49%、女性：＞48%

2. 骨髄生検　（2008では小基準だった）
   - 3血球系の増加、多彩な巨核球（様々な形態）の分化伴う。

3. *JAK2* V617Fまたはexon12 変異の存在。

※骨髄生検を欠くときは、以前のHb、Ht（男性：55.5%、女性：49.5%）レベルが必要である。

【小基準】

■内因性赤血球コロニー形成が除外された。

【参考】MPNにおける遺伝子異常（変異）

遺伝子変異	*JAK2*		*MPL* W515K/L	*CALR*
遺伝子名 / 疾患名	ヤヌスキナーゼ2		トロンボポエチン受容体	カルレティキュリン
	V617F変異	exon12変異		
PV 真性赤血球増加症（真性多血症）	95%以上	3%	0%	0%*
	ほぼ100%			
ET 本態性血小板血症	約60%		1～3%	25%*
PMF 原発性骨髄線維症	約50%		5～10%	35%*

*Klampfl らの報告（896 例）

※ET、PMFは、*JAK2*、*MPL*、*CALR* 何れかの遺伝子変異を有する症例が多い.

ETの診断基準

Table 5. WHO criteria for ET

WHO ET criteria
Major criteria【大基準】
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms ※線維化はあってもごく軽度
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion【小基準】
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

【大基準】（1～3は変更なし）

4. *JAK2*、*CALR* あるいは *MPL* 変異を認める。

【小基準】

- クローナルなマーカーを認めるか、反応性血小板増加症の所見を認めない。
- *JAK2*、*CALR*、*MPL* 遺伝子変異いずれも陰性の場合には、大基準の1～3および小基準を満たすことにより診断が可能。

PMFの変更点

■「前線維化期（prePMF）」と「線維化期」に細分化され、別々の診断基準が設けられた。

■「前線維化期」と「線維化期」は、線維化の程度（前線維化期：MF-0/1、線維化期は：MF-2/3）、白赤芽球症の有無で分ける。

■「prePMF」は「ET」との鑑別がしばしば困難だが、前者は急性白血病やMFへの移行率が高く、生存率が低いので鑑別が重要である。

【線維化の評価】 細網線維、膠原線維、骨硬細化の程度で評価

Table 8. Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

prePMFの診断基準

大基準

1. グレード1を超える細網繊維症を伴わない巨核球の増殖と異形成、年齢と比較した骨髄細胞数増加、顆粒球系細胞の増加としばしば赤芽球の減少。
2. CML、PV、ET、MDS、他の骨髄性腫瘍の診断基準を満たさない。
3. *JAK2*、*CALR* または *MPL*変異の存在、あるいはこれを欠くときもは何らかのクローン性の証明されるマーカーが存在すること、または反応性の細胞線維症が存在しないこと。

小基準

※少なくとも以下の一つの所見が2回連続して満たされること。

a. 合併症に起因しない貧血の存在
b. 白血球数の増加 ： ≧11,000/μL
c. 脾臓の触知
d. 基準値を超えるLD値

prePMFの診断基準

Table 6. WHO criteria for prePMF

WHO prePMF criteria
Major criteria【大基準】
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting the WHO criteria for *BCR-ABL1*$^{+}$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡
Minor criteria【小基準】
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^{9}/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

診断には大基準の3項目と小基準の少なくとも1項目を満たすことが必要。

PMF（線維化期）の診断基準

Table 7. WHO criteria for overt PMF

WHO overt PMF criteria
Major criteria【大基準】
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^{+}$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡
Minor criteria【小基準】
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^9/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
e. Leukoerythroblastosis 白赤芽球症
Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

診断には大基準の3項目と小基準の少なくとも1項目を満たすことが必要。

【参考】PV、ET、PMFの鑑別ポイント

	赤血球系	白血球系	血小板系	その他
PV 真性赤血球増加症 （真性多血症）	・著しい増加 （総血液量）	・増加	・50%の症例 で増加	・骨髄生検（大基準） ・EPO値低下（小基準） ・PMFへ移行しやすい （post PV MF：約20%）
	骨髄生検	・3血球系の増加：赤芽球、顆粒球、成熟巨核球（多彩な形態、異形成なし）		・JAK2 変異≒100% （V617F/exon12）
ET 本態性血小板血症	・増加している ことが多い	・増加している ことが多い	・血小板数増加 ≧45万/μL （≧100万のことが多い） （大型/巨大血小板）	・骨髄生検が必須 ・AMLやMFへの移行 はまれである
	骨髄生検	・好中球系（左方移動）または赤芽球造血の有意な増加は認めない。線維化はあっても軽度。 大型成熟巨核球の増生（stag-horn like、過分葉傾向）。PMFより異形成は軽度である。		・*JAK2* 変異：約60% ・*CALR* 変異：約25% ・*MPL* 変異：1～3%
PMF 原発性骨髄線維症	・貧血（合併症に 起因しない）	・増加（小基準） ≧11,000/μL	・巨大血小板の出現	・骨髄生検が必須 ・線維化の程度 ・AMLへ移行しやすい
	・白赤芽球症 ： 幼若顆粒球＋有核赤血球 ・涙滴赤血球の出現		・巨核球の増生と異形成（低分葉(Cloud like)や大型核裸核状巨核球が特徴	
	骨髄生検	・細網線維、膠原線維の増加の増生を伴う.		・*JAK2* 変異：約50% ・*CALR* 変異：約35% ・*MPL* 変異：5～10%

肥満細胞症の分類

Table 9. WHO classification of mastocytosis

WHO mastocytosis classification
1. Cutaneous mastocytosis (CM)
2. Systemic mastocytosis
a. Indolent systemic mastocytosis (ISM)*
b. Smoldering systemic mastocytosis (SSM)*
c. Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)†
d. Aggressive systemic mastocytosis (ASM)*
e. Mast cell leukemia (MCL)
3. Mast cell sarcoma (MCS)

*These subtypes require information regarding B and C findings for complete diagnosis,[20] all of which may not be available at the time of initial tissue diagnosis.

†This category is equivalent to the previously described "systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)." AHNMD and AHN can be used synonymously.

- WHO2008のMPN一病型より、「独立したカテゴリー」となった。
- 90%以上の症例に *KIT* 遺伝子変異（D816V）が検出される。
- 皮膚型、全身型、他の造血器腫瘍を伴う例も一つにまとめられた。

今から使える、WHO分類2016骨髄系腫瘍の変更点

1. 骨髄増殖性腫瘍（MPN）

2. *PDGFRA*、*PDGFRB* または*FGFR1* 遺伝子の再構成

   あるいは*PCM1–JAK2* を伴う骨髄/リンパ系腫瘍

3. 骨髄異形成/骨髄増殖性腫瘍（MDS/MPN）

4. 骨髄異形成症候群（MDS）

5. 急性骨髄性白血病（AML）と関連腫瘍

PDGFRA、*PDGFRB* または*FGFR1* 遺伝子の再構成あるいは*PCM1–JAK2* を伴う骨髄/リンパ系腫瘍の変更点・ポイント

Table 10. Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

Disease	Presentation	Genetics	Treatment
PDGFRA	Eosinophilia ↑Serum tryptase ↑Marrow mast cells	Cryptic deletion at 4q12 *FIP1L1-PDGFRA*, at least 66 other partners	Respond to TKI
PDGFRB	Eosinophilia Monocytosis mimicking CMML	t(5;12)(q32;p13.2) *ETV6-PDGFRB*, at least 25 other partners	Respond to TKI
FGFR1	Eosinophilia Often presents with T-ALL or AML	Translocations of 8p11.2 *FGFR1*-various partners	Poor prognosis; do not respond to TKI
PCM1-JAK2	Eosinophilia Rarely presents with T-LBL or B-ALL Bone marrow shows left-shifted erythroid predominance and lymphoid aggregates	t(8;9)(p22;p24.1) *PCM1-JAK2*	May respond to JAK2 inhibitors

↑, Increased.

■t(8;9)(p22;p24.1) *PCM1–JAK2* を伴う骨髄性/リンパ性腫瘍が(暫定病型)として追加された。

■JAK2阻害剤に反応する。

今から使える、WHO分類2016骨髄系腫瘍の変更点

1. 骨髄増殖性腫瘍（MPN）

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   あるいは*PCM1–JAK2* を伴う骨髄/リンパ系腫瘍

3. 骨髄異形成/骨髄増殖性腫瘍（MDS/MPN）

4. 骨髄異形成症候群（MDS）

5. 急性骨髄性白血病（AML）と関連腫瘍

WHO2016：MDS/MPNの変更点・ポイント

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable

■CMMLに「CMML-0（ゼロ）」が新設された。

■診断時に除外する遺伝子変異として*PCM1-JAK2*が追加された。

■WHO2008において暫定病型であった「RARS-T」が、「MDS/MPN-RS-T」と名称が変更され正式に採用された。

CMMLの診断基準

Table 11. Diagnostic criteria for CMML

CMML diagnostic criteria
• Persistent PB monocytosis ≥1 × 10^9/L, with monocytes accounting for ≥10% of the WBC count
• Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET*
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
• <20% blasts in the blood and BM†
• Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
• An acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells‡
or
• The monocytosis (as previously defined) has persisted for at least 3 mo and
• All other causes of monocytosis have been excluded

*Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

†Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes. Promonocytes are monocytic precursors with abundant light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count.

‡The presence of mutations in genes often associated with CMML (eg, *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in subclones. Therefore, caution would have to be used in the interpretation of these genetic results.

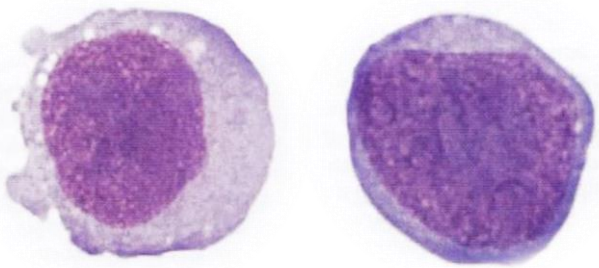
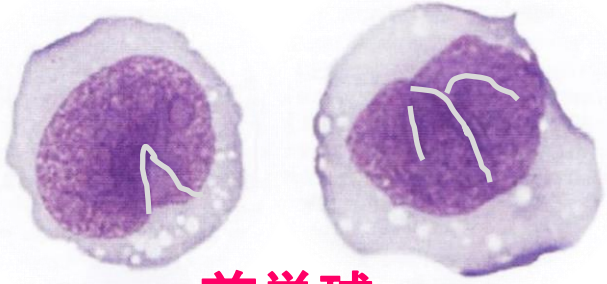
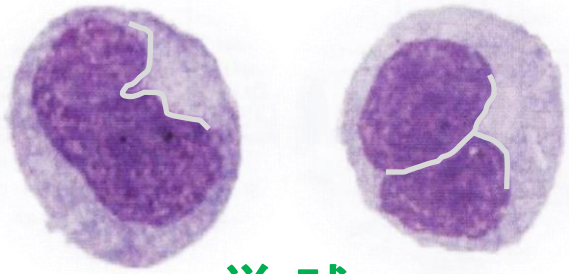
■CMMLで高頻度にみられる遺伝子変異（*TET2*、*ASXL1*、*SETBP1* など）が診断時の参考となる。

■形態学的に「前単球（芽球扱い）」と「成熟単球」の鑑別が重要。

CMMLの病型分類

芽球%	PB	BM
CMML-0	2%未満	5未満
CMML-1	2～4%	5～9%
CMML-2	5～19%	10～19%
	アウエル小体	

【参考】　単球系細胞

単球系細胞	形態学的な特徴	
 単芽球	大型細胞で、比較的広い細胞質を有する。	
	細胞質	中等度～強い好塩基性であり、偽足形成を認めることがある。散在する微小アズール顆粒と空胞を有することがある。
	核	円形、クロマチンはデリケートなレース状であり、明瞭な核小体を有する。
 前単球	細胞質	単芽球よりは好塩基性は弱く、しばしば微細で明瞭なアズール顆粒や空胞を有する。
	核	不整でデリケートな陥凹を認める。
 単 球	細胞質	灰青色、微細なアズール顆粒が散在する。
	核	不整で湾入や切れ込みを有する。
	・「単球」と「前単球」は、骨髄標本でいつも鑑別できるとは限らない。末梢血の方が明らかとなることが多い。	

aCMLの診断基準

Table 12. Diagnostic criteria for aCML, *BCR-ABL1*$^{-}$

aCML diagnostic criteria
• PB leukocytosis due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes, metamyelocytes) comprising ≥10% of leukocytes)
• Dysgranulopoiesis, which may include abnormal chromatin clumping
• No or minimal absolute basophilia; basophils usually <2% of leukocytes
• No or minimal absolute monocytosis; monocytes <10% of leukocytes
• Hypercellular BM with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
• <20% blasts in the blood and BM
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement, or *PCM1-JAK2*
• Not meeting WHO criteria for *BCR-ABL1*$^{+}$ CML, PMF, PV, or ET*

*Cases of MPN, particularly those in accelerated phase and/or in post-polycythemic or post-essential thrombocythemic myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the BM and/or MPN-associated mutations (in *JAK2*, *CALR*, or *MPL*) tend to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of *SETBP1* and/or *ETNK1* mutations. The presence of a *CSF3R* mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of CNL or other myeloid neoplasm.

- *CSF3R* 変異はCNLでは高率だが、aCMLでは稀である。
- *SETBP1* and /or *ETNK1* 変異は約1/3の症例にみられ、MPNに関連したドライバー変異（*JAK2*, *CALR*, *MPL*）は通常みられない。

MDS/MPN-RS-Tの診断基準

血小板増加を伴う不応性貧血

WHO2016で正式採用された病型。

Table 13. Diagnostic criteria for MDS/MPN with ring sideroblasts and thrombocytosis

MDS/MPN diagnostic criteria
• Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, ≥15% ring sideroblasts,* <1% blasts in PB and <5% blasts in the BM
• Persistent thrombocytosis with platelet count ≥450 × 10^9/L
• Presence of a *SF3B1* mutation or, in the absence of *SF3B1* mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†
• No *BCR-ABL1* fusion gene, no rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*; or *PCM1-JAK2*; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
• No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN

*At least 15% ring sideroblasts required even if *SF3B1* mutation is detected.
†A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of *SF3B1* mutation together with a mutation in *JAK2* V617F, *CALR*, or *MPL* genes.
‡In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del (5q)-no or minimal absolute basophilia; basophils usually <2% of leukocytes.

■ *SF3B1* 変異の有無にかかわらず，環状鉄芽球（RS）15%以上の場合のみにRSと診断する。

（MDS-RSとは異なるので注意）

■ *JAK2* V617F、*CALR*,、*MPL* 遺伝子変異も診断の参考となる。