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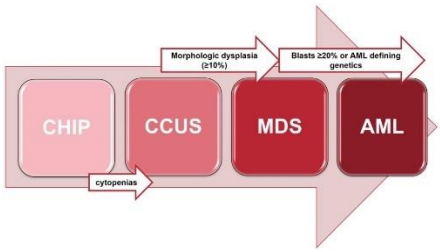
Myeloid proliferations and neoplasms

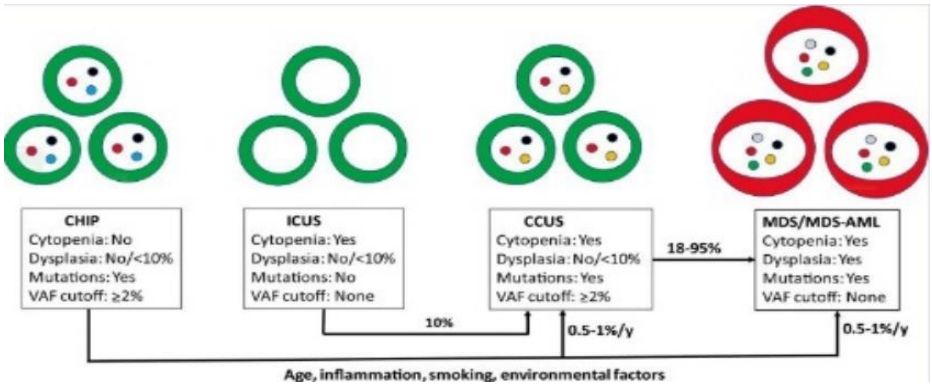
MYELOID PRECURSOR LESIONS

CLONAL HEMATOPOIESIS



- Clonal hematopoiesis (CH) in the context of ageing refers to the presence of a population of cells derived from a multipotent stem/progenitor cell harboring one or more driver gene mutations resulting in selective growth in individuals without hematological cancers, clonal disorders, or unexplained cytopenias.
- **Subtypes:** Clonal hematopoiesis of indeterminate potential (CHIP); VEXAS syndrome
- **VEXAS syndrome**: All patients have somatic mutations involving the X-linked gene *UBA1*, and they usually have autoinflammatory syndrome involving the skin, lungs, blood vessels, joints, and cartilage, and hematological conditions, including cytopenias
- **Histology:** Lack of features that define other hematologic malignancies; BM of patients with VEXAS syndrome shows cytoplasmic vacuoles in myeloid and erythroid precursors without dysplasia
- **Molecular:** Germline TERT mutation; somatic mutations in DNMT3A, TET2, ASXL1, SRSF2, U2AF1, IDH1 or IDH2, SF3B1, and other rare ones with a VAF of >2%

CLONAL CYTOPENIA OF UNDETERMINED SIGNIFICANCE



- Clonal cytopenia of undetermined significance (CCUS) refers to clonal hematopoiesis (CH) detected in the presence of one or more persistent cytopenias that are otherwise not explained by hematological or non-hematological conditions.
- Patients with clonal cytopenia of undetermined significance **will have at least one somatic mutation** in a myeloid malignancy gene in their blood or bone marrow cells and must not have another identifiable cause for their cytopenia, including benign conditions or myeloid neoplasms.
- A bone marrow biopsy is required to exclude myeloid neoplasms.
- Patients with clonal cytopenia of undetermined significance have an increased, variable risk of progression to a myeloid neoplasm, whereas patients with unexplained cytopenias and no myeloid gene mutations have a low risk of progression.
- **Essential:** detection of one or more somatic mutations involving CH driver genes (see below molecular section). one or more otherwise unexplained persistent cytopenias; absence of features diagnostic for defined myeloid neoplasms.
- **Molecular:** Germline TERT mutation; somatic mutations in (CH related mutations) including DNMT3A, TET2, ASXL1, SRSF2, U2AF1, IDH1 or IDH2, SF3B1, and other rare ones with a VAF of >2%

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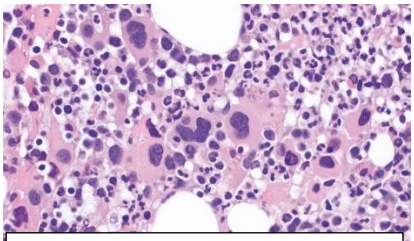
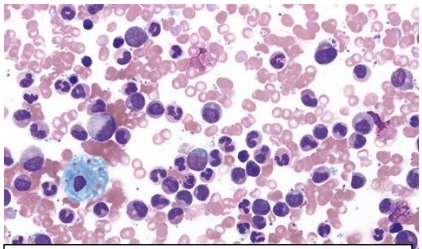
Myeloproliferative neoplasms

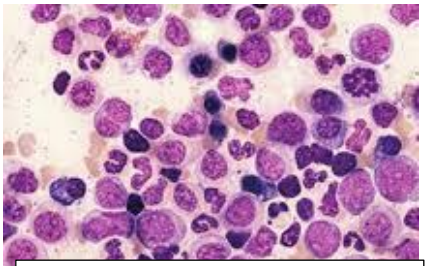
CHRONIC MYELOID LEUKEMIA



BMB: showing dwarf megas



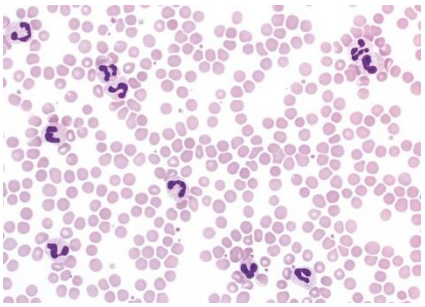
PBS: Showing sea blue histiocyte



BMA: Showing basophilia

- Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm defined by the *BCR*::*ABL1* fusion gene and characterized by neutrophilic granulocytosis.
- In the chronic phase (CP), the neoplastic cells are mostly confined to the blood, bone marrow, spleen, and liver.
- In the blast phase (BP), the blasts can infiltrate any extramedullary site, with a predilection for the spleen, liver, lymph nodes, skin, and soft tissues.
- **Histology:** Bone marrow core biopsy shows hypercellularity and notable granulocytic hyperplasia with left shift and increased eosinophils. Megakaryocytic hyperplasia is seen; the megakaryocytes are characteristically smaller than normal megakaryocytes (dwarf megakaryocytes).
- Bone marrow aspirate: Peripheral blood shows granulocytic left shift with a myelocyte bulge, basophilia, eosinophilia, and rare circulating blasts; additionally *Sea Blue histiocytes* (marker of increased cell turnover) are seen
- Chronic phase: leukocytosis (white blood cell count: 12–1000 × 10^9/L, median: ~80 × 10^9/L) due primarily to neutrophils in various stages of maturation without dysplasia. Eosinophilia or basophilia are common.
- Blast phase: Detection of ≥ 20% myeloid blasts in peripheral blood or bone marrow, or Presence of an extramedullary blast proliferation, or lymphoblasts in peripheral blood or bone marrow (even if < 10%) in a patient with CML.
- **Immunophenotype:** BP: Blasts express CD34 and MPO, and one or more of CD33, CD13, CD14, CD11b, CD11c, KIT (CD117), CD15, CD41, CD61, glycophorin
- **Molecular:** *BCR*::*ABL1* fusion, which exists in several different isoforms depending on the precise position of the t(9;22)(q34;q11.2)➔ *BCR* exon 13 and *BCR* exon 14, respectively and some cases express both which are targets for TKI therapy.

CHRONIC NEUTROPHILIC LEUKEMIA



- Chronic neutrophilic leukemia (CNL) is a myeloproliferative neoplasm characterized by sustained isolated peripheral blood neutrophilia and the presence of **activating *CSF3R* mutations** in most cases, without morphological dysplasia or detectable *BCR*::*ABL1*.
- **Histology:** Patients have sustained, mature peripheral blood neutrophilia with variable toxic granulation, which may be identified incidentally. Monocytosis, eosinophilia or basophilia are notably absent.
- The diagnosis of CNL requires careful exclusion of underlying causes of reactive neutrophilia and other neoplastic myeloid disorders such as myeloproliferative neoplasm (MPN) and MDS/MPN, particularly MDS/MPN-N (neutrophilia).
- **Molecular:** *CSF3R* mutation as a disease-associated genomic event. Other mutations including CHIP mutations such as ASXL1, TET2, DNMT3A, SRSF2, U2AF1/2 etc are also commonly seen.

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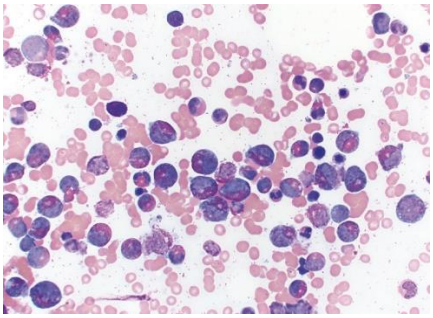
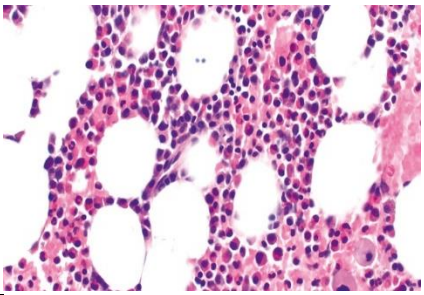
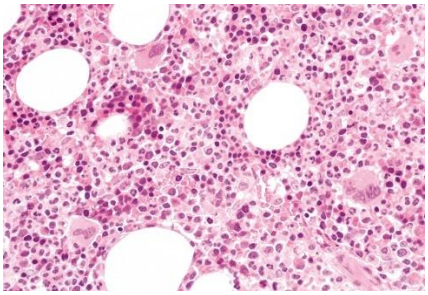
Chronic eosinophilic leukemia

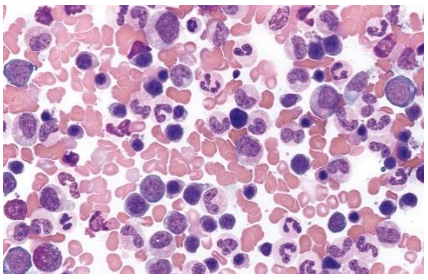




- Chronic eosinophilic leukemia (CEL) is a myeloproliferative neoplasm (MPN) characterized by an autonomous, clonal proliferation of eosinophil precursors, resulting in persistent eosinophilia in the blood and bone marrow.
- **Histology**: The bone marrow smear shows increased eosinophils with many immature forms.
- Essential: Hypereosinophilia (HE) is defined as peripheral blood eosinophilia > 1.5×10^9/L on at least two occasions over an interval of at least 4 weeks, but it is recognized that some cases with life-threatening organ damage may require urgent therapy without waiting for confirmation of sustained eosinophilia. Additionally, evidence of clonality; abnormal bone marrow morphology; not meeting diagnostic criteria for other myeloid or lymphoid neoplasms.
- **Molecular:** unclear, cases with JAK2 p.V617F and *KIT* p.D816V are seen in 3–4% of cases. Jack2 exon 13 has shown to affect IL-5R;
- Molecular testing should be performed to exclude other myeloid/lymphoid neoplasms with eosinophilia, including PDGFR testing, JACK2, CBFM::MYH11, ETV6::ABL1, KIT, IGH::IL3, etc to exclude AML with defined genetic aberrations.
- Main differentials include Hypereosinophilic Syndrome (HES) which presents with (organ damage) and Hypereosinophilia of uncertain significance (HE) with (no organ damage)→ both of which are reactive conditions.

Polycythemia vera





- Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by erythrocytosis, also accompanied by leukocytosis and/or thrombocytosis, and activating JAK2 mutations.
- **Histology**: core biopsy shows bone marrow characterized by hypercellularity and notable erythroid and megakaryocytic hyperplasia and PBS shows thrombocytosis. Postpolycythaemic myelofibrosis is usually associated with leucoerythroblastic findings, including poikilocytosis and teardrop-shaped red blood cells (dacrocytes).
- **DDX:** Reactive polycythemia, other MPNS (ET, MF)
- **Molecular:** *JAK2* p.V617F or exon 12 of *JAK2* mutations. Other genes commonly mutated in in PV include *TET2*, *ASXL1*, *IDH2*, and *SRSF2*.
- **Essential:** Major criteria: 1. Elevated Hgb (> 16.5 g/dL in men, > 16.0 g/dL in women) or elevated hematocrit (> 49% in men, > 48% in women) 2. Bone marrow biopsy showing hypercellularity with trilineage hematopoiesis, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes. Presence of JAK2 p.V617F or JAK2 exon 12 mutation
- Minor criterion: Subnormal serum erythropoietin (EPO) level
- Diagnosis requires all 3 major or the first 2 major plus minor criteria.

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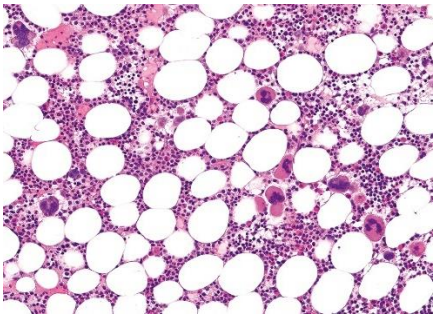
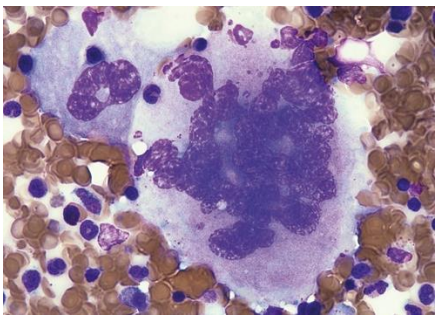
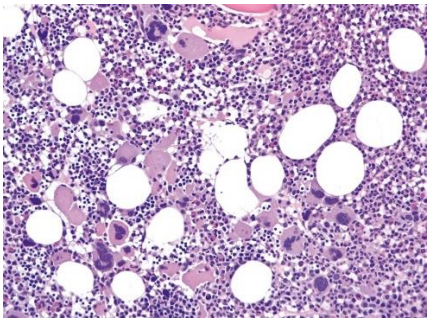
Essential thrombocythemia

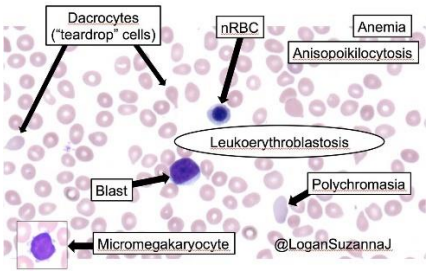


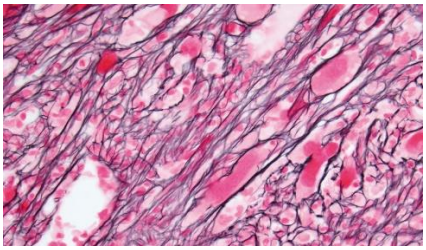


- Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by sustained thrombocytosis and increased numbers of large, mature megakaryocytes in a normocellular bone marrow.
- ET is usually diagnosed in the chronic phase. In a small number of cases, ET progresses to the accelerated phase (bone marrow blasts between 10-19%) and blast phase (blasts >20%).
- ET patients have lower MPN symptoms compared to PV or PMF patients
- **Histology:** Bone marrow biopsy shows normocellular bone marrow with an increased number of large to giant atypical megakaryocytes. Bone marrow aspirate shows presence of typical staghorn-like megakaryocytes. Myelofibrosis is usually 0-1.
- **IHC:** CD61, CD41, CD42b, Factor VIII to identify megas
- **Molecular:** JACK2 pV617F most common, followed by CALR, and MPL mutations
- **Essential:** Major criteria: Platelet count ≥ 450 × 10^9/L; Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage; *JAK2 (5-60%)*, *CALR(30%)*, or *MPL(3%)* mutation; criteria for other MPN, CML etc not met; Minor criteria: presence of clonality or exclusion of reactive thrombocytosis.

Primary myelofibrosis







- Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by abnormal proliferation of the megakaryocytic and granulocytic lineages associated with progressive marrow fibrosis, osteosclerosis, and extramedullary hematopoiesis.
- One third of patients are asymptomatic at diagnosis, blood tests may show anemia and thrombocytopenia. Splenomegaly and hepatomegaly are common and may be massive.
- **Histology:** BMB shows hypercellular marrow with increased megakaryocytes with an abnormal distribution and relatively normal erythroid and myeloid lineage. High magnification highlights increased numbers and clusters of megakaryocytes with marked variation in size and nuclear lobulation. Osteosclerosis can be seen.
- Reticulin stain: usually increased (1-3) with pattern 3 shown here: diffuse and dense increase in reticulin fibers with extensive intersections
- PBS shows leucoerythroblastosis: Myeloid and erythroid precursors in blood, with tear-drop cells and occasional blasts
- **Molecular:** *JAK2* V617F mutation (50 - 60%); *CALR* mutations (25 - 30%); *MPL* mutations (5 - 10%); Triple negative in (8 - 12%)
- **Diagnosis:** Profibrotic stage versus fibrotic stage.
- Essential criteria: Pre-fibrotic MF: Megakaryocytic proliferation and atypia, without reticulin fibrosis of grade higher than 1/3, accompanied by increased age-adjusted bone marrow cellularity
- Essential criteria fibrotic MF: Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grade 2 or 3
- **Other criteria:** Splenomegaly, anemia, leukocytosis, increased LDH

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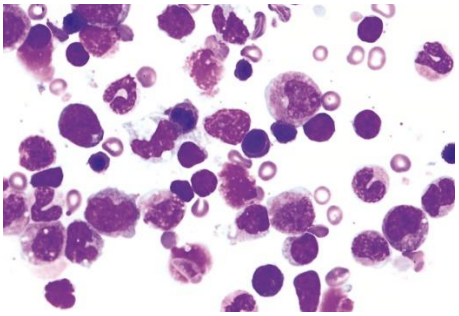
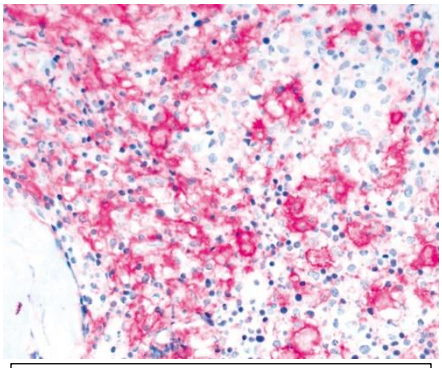
Juvenile myelomonocytic leukemia

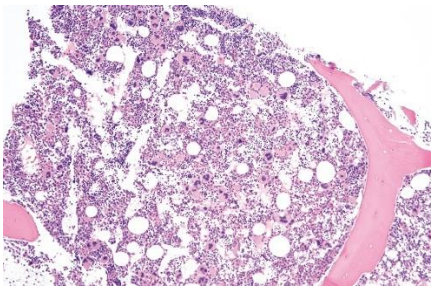




Bone marrow biopsy with increased CD14 (monocytes)

- Juvenile myelomonocytic leukemia (JMML) is a RAS pathway activation–driven myeloproliferative neoplasm of early childhood leading to peripheral granulocytosis and monocytosis, with frequent organ infiltration specially splenomegaly.
- **Subtypes:** PTPN11-mutated JMML; NRAS-mutated JMML; KRAS-mutated JMML; JMML in neurofibromatosis type 1; CBL syndrome, noonan syndrome. It has a male predominance; rarely involves the CNS.
- **Histology:** Peripheral blood smears typically show leukocytosis > 10×10^9/L, including monocytosis > 1×10^9/L. Monocytes often have atypical morphology. Neutrophilia is usually present and sometimes shows abnormal nuclear segmentation and pseudo–Pelger–Huët forms. Granulocytic precursors (e.g. promyelocytes, myelocytes, and metamyelocytes) are seen, and basophilia and eosinophilia may be occasionally present. Red blood cells are usually normocytic, but macrocytosis is observed in some patients, particularly those with **monosomy 7.** Megakaryocytes are usually reduced. Blasts, including blast-equivalent promonocytes, can be moderately elevated but lower than 20%.
- Immunophenotype: Blasts may express aberrant CD7; abnormal maturation pattern of grans with decreased CD13 and CD33; decreased HLA-DR on monocytes.
- Molecular: presence of **a RAS-activating genetic** lesion in the hematopoietic stem cell (usually somatic in syndromic cases such as CBL, noonan, etc).

Myeloproliferative neoplasm NOS (unclassifiable)



- Myeloproliferative neoplasm (MPN) not otherwise specified (NOS) is a diagnosis of exclusion for cases that have definite clinical, laboratory, morphological, and molecular features of an MPN but fail to meet the diagnostic criteria for any of the specific types in this disease category.
- **Histology:** Most cases that are diagnosed as MPN-NOS constitute very early stage disease, in which the differentiation between essential thrombocythemia, primary myelofibrosis (PMF), and polycythemia vera may be very difficult. Bone marrow trephine biopsy highlights hypercellular-for-age marrow with increased megakaryocytes with occasional tight clusters, and eosinophilia, panmyelosis (unusual in prefibrotic primary myelofibrosis), and minimal fibrosis
- **Molecular:** Like in specific MPN types, driver mutations involving *JAK2*, *CALR*, or *MPL* are often also present in MPN-NOS.
- **Essential:** Not meeting criteria for any other MPN, MDS, MDS/MPN, or myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

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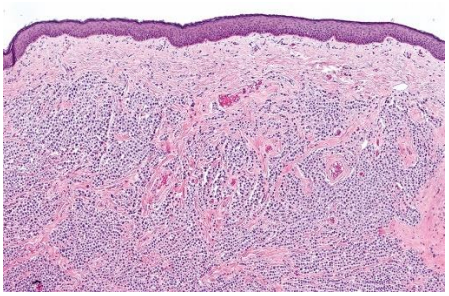
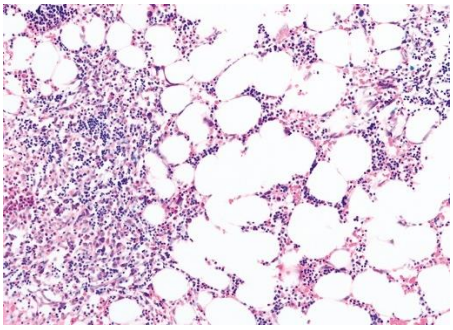
Mastocytosis

CUTANEOUS MASTOCYTOSIS



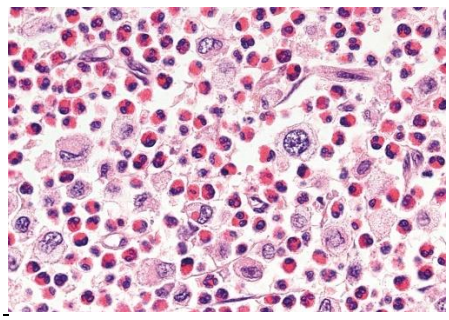
- Cutaneous mastocytosis (CM) is a form of mastocytosis primarily affecting the skin.
- **Subtypes:** Maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM), mastocytoma
- **Histology:** Dermal infiltrates. In MPCM, mast cells are often loosely scattered, with a tendency to aggregate around blood vessels and adnexa. Mast cells are usually markedly increased in DCM and form nodular infiltrates in mastocytomas. Mast cells often have pleomorphism
- **IHC:** Mast cells co-express tryptase and CD117. Neoplastic mast cells express CD2, CD25, and CD30.
- **Molecular:** detection of KIT mutations (exon 17 in adults and exon 18 in pediatric cases)

SYSTEMIC MASTOCYTOSIS



- Systemic mastocytosis (SM) is a myeloid neoplasm characterized by clonal proliferation of mast cells, typically harboring mutant *KIT*, and involving at least one extracutaneous organ system, with or without evidence of skin lesions.
- **Subtypes:** Indolent systemic mastocytosis (ISM); bone marrow mastocytosis (BMM); smoldering systemic mastocytosis (SSM); aggressive systemic mastocytosis (ASM); systemic mastocytosis with an associated hematological neoplasm (SM-AHN); mast cell leukemia (MCL)
- **Histology:** in BMM, bone marrow biopsy shows focal compact infiltrate of atypical and spindle-shaped mast cells accompanied by lymphocytes and eosinophils.
- **IHC:** All mast cells express CD117, and tryptase; neoplastic mast cells express CD2, CD25, and CD30.
- **Molecular**: Activating mutations in the tyrosine kinase 2 (TK2) domain (exon 17) of the *KIT* gene, especially *KIT* p.D816V

MAST CELL SARCOMA



- Mast cell sarcoma (MCS) is a rare and clinically aggressive form of mastocytosis characterized by the presence of a locally destructive solid tumor comprising highly atypical mast cells.
- MCS can present de novo (classic MCS), or as a transformation of a previous mast cell neoplasm.
- **Histology:** Highly polymorphic tumor cells, intermingled with numerous eosinophils; the neoplastic cells are polymorphic, sometimes with bilobated nuclei with cytoplasmic granules.
- **IHC:** Tryptase and CD117 expression with variable CD2, CD25, CD30; they can also express CD68, CD45, CD43 (potential pitfall)
- **Molecular:** MCS usually lacks the KIT D816V mutations

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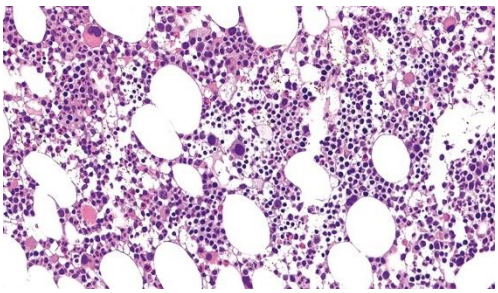
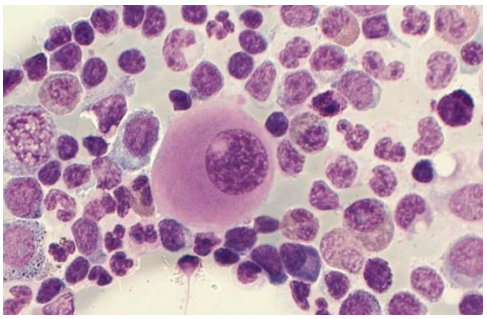
Myelodysplastic neoplasms

Myelodysplastic neoplasms with defining genetic abnormalities

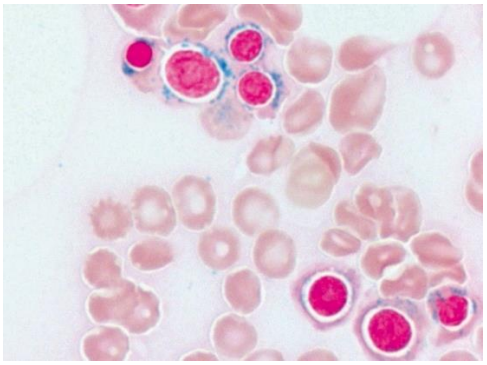
MYELODYSPLASTIC NEOPLASM WITH LOW BLASTS AND 5Q DELETION





- Myelodysplastic neoplasm (MDS) with low blasts and 5q deletion (MDS-5q) is a myeloid neoplasm with cytopenia and dysplasia, characterized by chromosome 5q deletion occurring in isolation or with one additional cytogenetic abnormality other than monosomy 7 or 7q deletion. Most common in elderly women.
- Anemia is often macrocytic and transfusion dependent
- **Histology:** the BM is usually normocellular or hypercellular, with erythroid hypoplasia. Megas are increased in size with small hypolobated forms. Blasts <5% in BM.
- Ring sideroblasts or SF3B1 maybe present, and do not exclude diagnosis of MDS-5q deletion.
- **Molecular/Ancillary**: presence of 5q deletion, presence of other abnormalities including SF3B1 except monosomy 7.
- Presence of strong p53 expression >1% is associated with worse prognosis→ Does not fulfil criteria for MDS- biallelic TP53 inactivation

MYELODYSPLASTIC NEOPLASM WITH LOW BLASTS AND SF3B1 MUTATION



Ring Sideroblasts: defined by having ≥ 5 iron granules encircling at least one third of the nucleus

- Myelodysplastic neoplasm (MDS) with low blasts and *SF3B1* mutation (MDS-*SF3B1*) is a myeloid neoplasm with cytopenia and dysplasia characterized by *SF3B1* mutation and often ring sideroblasts.
- Patients often present with macrocytic normochromic anemia
- **Histology:** Increased numbers of ring sideroblasts (as shown by iron staining) in hypercellular marrow and pronounced erythropoiesis often with dysplasia, myeloid may also show dysplasia; however, megakaryocytes are histologically normal.
- **Essential:** cytopenia involving one or more lineages, without thrombocytosis; blasts <5% of BM or <2% of blood.
- **Molecular:** Detection of *SF3B1* mutation or presence of ring sideroblasts constituting ≥ 15% of the erythroid precursors; absence of 5q deletion, monosomy 7 / 7q deletion, or complex karyotype; not fulfilling criteria for other MDS/MPN neoplasms.

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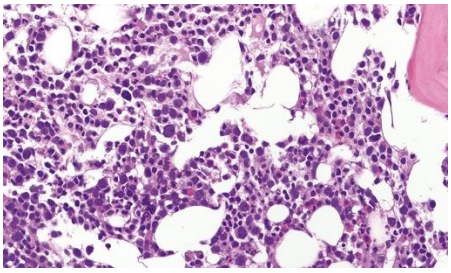
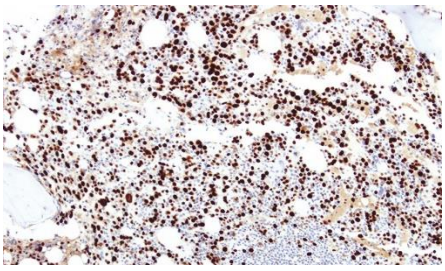
MYELODYSPLASTIC NEOPLASM WITH BIALLELIC TP53 INACTIVATION



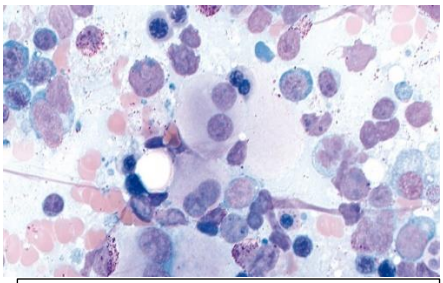


Mutant p53, overexpression

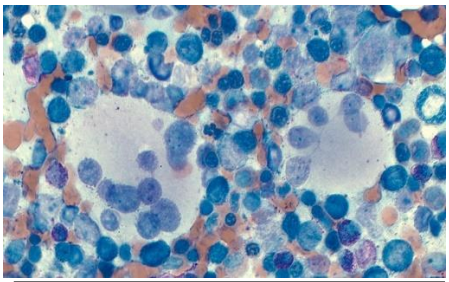
- Myelodysplastic neoplasm (MDS) with biallelic *TP53* inactivation (MDS-bi*TP53*) is a myeloid neoplasm with cytopenia, dysplasia, < 20% blasts, and < 30% proerythroblasts, characterized by two or more *TP53* mutations or one *TP53* mutation with copy-neutral loss of heterozygosity (LOH).
- MDS-bi*TP53* can occur spontaneously, after exposure to certain DNA-damaging agents or in inherited predisposition syndromes
- The majority of *TP53* alterations are missense mutations
- Histology: This type of MDS is associated with high-risk morphological findings, such as a higher blast count and fibrosis in the bone marrow as well as dysplasia in all 3 lineages.
- IHC: detection of mutant p53 by IHC can be a helpful screening tool; CD34 will show increased blasts (<20% in the marrow)
- *Essential:* cytopenia involving one or more lineages; dysplasia involving one or more lineages; blasts constitute < 20% of cells in the peripheral blood and bone marrow; detection of two or more *TP53* mutation; or one with copy-number LOH.

Myelodysplastic neoplasms defined morphologically

MYELODYSPLASTIC NEOPLASM WITH LOW BLASTS



MDS-LB-SLD: with dysplastic megas (single lineage)



MDS-LB-MLD: dysplasia in more than one lineage

- Myelodysplastic neoplasm (MDS) with low blasts (MDS-LB) is a myeloid neoplasm with cytopenia and dysplasia but without defining genetic abnormalities, defined by the presence of < 5% bone marrow blasts and < 2% peripheral blood blasts.
- **Subtypes include:** MDS-LB with single lineage dysplasia (MDS-LB-SLD) and MDS-LB-Multilineage dysplasia (MDS-LB-MLD)
- Cytopenia in at least one hematopoietic lineage is required for a diagnosis of MDS-LB.
- **Histology:** Bone marrow smears showing multilineage dysplasia with a micromegakaryocyte and hypogranulated white blood cell precursors, binucleated megakaryocytes, and megakaryocytes with multiple nuclei can be seen. Iron overload and increased erythropoiesis with megaloblastic changes are common.
- **Immunophenotype:** Flow cytometry shows aberrations in immature progenitor compartments and abnormal expression of neutrophils and monocytes; blast count should be on aspirates not CD34 flow or stain analysis for more accurate count
- **Molecular:** MDS-LB and usually involve *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, and *U2AF;* MDS-LB-MLD more frequently harboring RUNX1, ASXL1, SRSF2.

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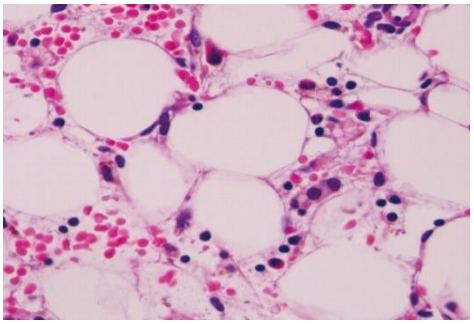
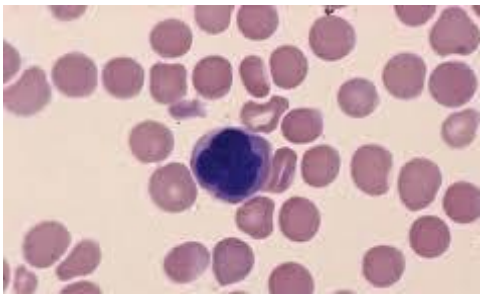
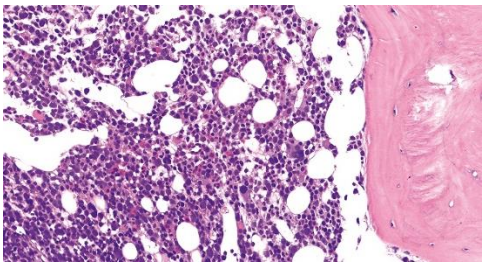
MYELODYSPLASTIC NEOPLASM, HYPOPLASTIC

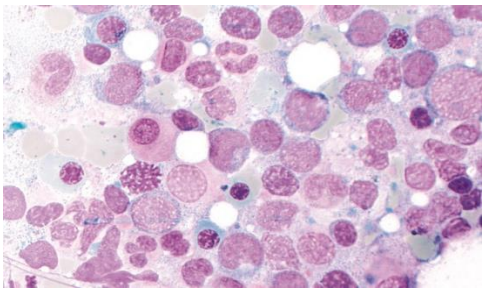


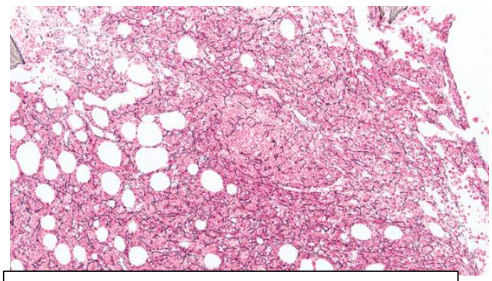


- Hypoplastic myelodysplastic neoplasm (hMDS) is a myeloid neoplasm with cytopenia and dysplasia, characterized by significantly decreased age-adjusted bone marrow cellularity as determined on a trephine biopsy. **DDX is Paroxysmal hemoglobinuria (PNH) and aplastic anemia.**
- hMDSs represent about 10–15% of all MDSs. Patients are usually younger than those with other MDS types but older than those with aplastic anemia
- **Histology:** Hypocellular marrow (by definition below 30% of normal cellularity in patients younger than 70 years and below 20% in patients older than 70 years).
- Hypocellularity is usually diffuse but may be patchy. Dysplastic features are identified in one or more hematopoietic lineages.
- **Molecular:** somatic mutation of the X-linked gene *PIGA* should be excluded. Additional mutations in GATA2, DDX41, and Fanconi anemia should be excluded especially in younger individuals.

MYELODYSPLASTIC NEOPLASM WITH INCREASED BLASTS







MDS with increased fibrosis (MDS-F)

- Myelodysplastic neoplasm (MDS) with increased blasts (MDS-IB) is a myeloid neoplasm with cytopenia and dysplasia but without defining genetic abnormalities, defined by increased blasts (≥ 5% and < 20% in bone marrow and/or ≥ 2% and < 20% in peripheral blood).
- **Subtypes:** MDS with increased blasts-1 (MDS-IB1; previously MDS-EB1); MDS with increased blasts-2 (MDS-IB2; previously MDS-EB2); MDS with increased blasts and fibrosis (MDS-F)
- **Histology:** Bone marrow histology shows hypercellular bone marrow. Erythroid precursors and micromegakaryocytes are abnormally located, approaching bone trabeculae. Multinucleated megakaryocytes are present. Immature blasts are typically abnormally located away from trabecula and sinuses. A significant degree of reticulin fibrosis may be present.
- **IHC:** CD34/CD117 can highlight blast population, which are also positive for CD38, HLA-DR, CD13 and CD33. Blasts may also show expression of CD7 or CD56. CD61, CD42b can be used for Megas.
- **Criteria:** *MDS with increased blasts-1 (MDS-IB1):* ≥ 5% and < 10% blasts in the bone marrow and/or ≥ 2% and < 5% blasts in the peripheral blood; without significant reticulin fibrosis.
- *MDS with increased blasts-2 (MDS-IB2):* ≥ 10% and < 20% blasts in the bone marrow and/or ≥ 5% and < 20% blasts in the peripheral blood; without significant reticulin fibrosis or presence of Auer rods.
- *MDS with increased blasts and fibrosis (MDS-F):* ≥ 5% and < 20% blasts in the bone marrow and/or ≥ 2% and < 20% blasts in the peripheral blood with significant bone marrow fibrosis (MF-2 or 3).

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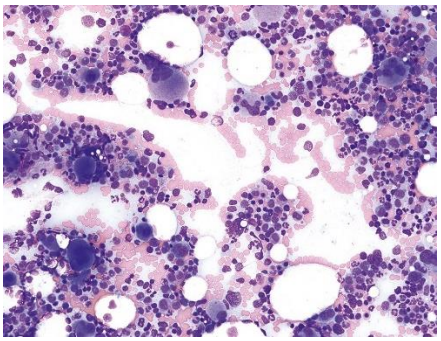
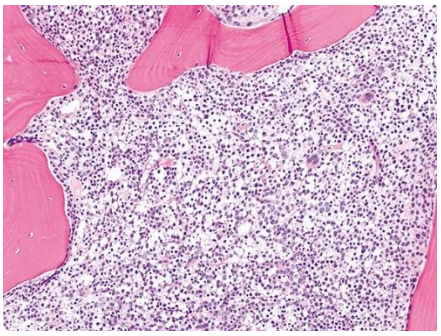
Myelodysplastic/myeloproliferative neoplasms

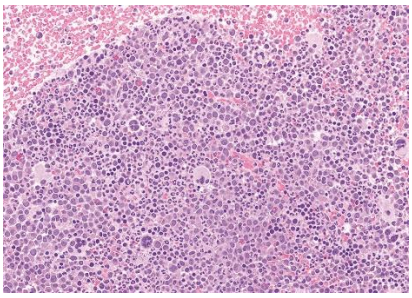
CHRONIC MYELOMONOCYTIC LEUKEMIA

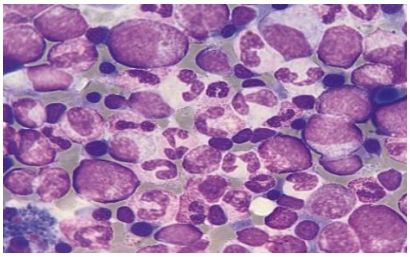




- Chronic myelomonocytic leukemia (CMML) is a myeloid neoplasm with myelodysplastic and myeloproliferative features, characterized by sustained peripheral blood monocytosis and various combinations of somatic mutations.
- Clinical presentation: MD-CMML→ cytopenia; MP-CMML→ more common constitutional symptoms.
- **Histology:** Bone marrow histology shows hypercellularity. Peripheral blood smear shows monocytes with characteristic folded nuclei and delicate chromatin in a dysplastic and granulocytic component. Occasional blasts can be seen.
- **Essential criteria:**
- Persistent absolute (≥ 0.5 × 109/ L) and relative (≥ 10%) peripheral blood monocytosis
- Blasts constitute < 20% of the cells in the peripheral blood and bone marrow
- Not meeting diagnostic criteria of chronic myeloid leukemia (CML) or other myeloproliferative neoplasms
- **IHC:** The monocyte population can be divided into CD14+/CD16− classic monocytes, CD14+/CD16+ intermediate monocytes, and CD14-low/CD16+ non-classic monocytes. Patients with CMML demonstrate a characteristic increase in CD14+/CD16− classic monocytes. Relative expansion of the classic monocytes subset (> 94%) is sensitive and specific in distinguishing CMML from reactive monocytosis and other hematological neoplasms.
- **Molecular:** most often associated with mutations: TET2, ASXL1, SRSF2, U2AF, DNMT3A etc

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM WITH NEUTROPHILIA





- Myelodysplastic/myeloproliferative neoplasm with neutrophilia (MDS/MPN-N), formerly known as atypical chronic myeloid leukemia, is a myeloid neoplasm with myelodysplastic and myeloproliferative features characterized by sustained peripheral blood neutrophilia and neutrophilic left shift.
- **Histology:** The bone marrow is typically hypercellular for age, with an elevated myeloid-to-erythroid ratio (> 10:1). Dysgranulopoiesis is a characteristic feature and is detected in ≥ 10% of granulocytes. Although the absolute monocyte count may be elevated, monocytes should not exceed 10% of the leukocytes.
- **Immunophenotype:** By flow cytometry, CD34-positive hematopoietic precursor cells usually have aberrancies consistent with a hematopoietic stem cell neoplasm but are <20% of the blood or BM cellularity.
- **Molecular:** *ETNK1 (early event)* and *SETBP1* (late event) mutations have been identified as key pathogenic events
- **Cytogenetics**: Karyotypic abnormalities are detected in 30–40% of cases, with chromosomes 8 and 20 being most commonly involved

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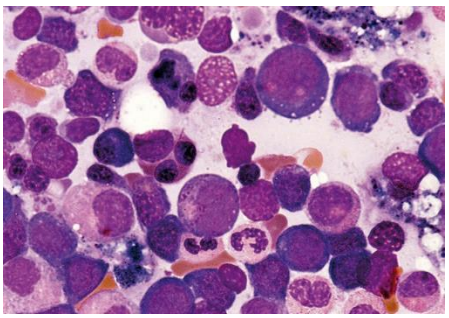
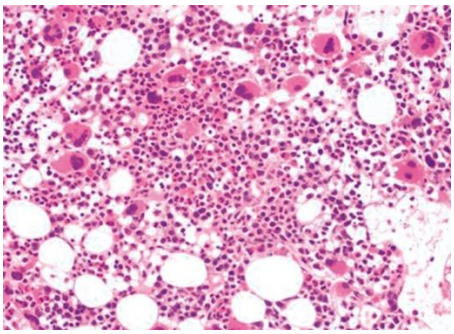
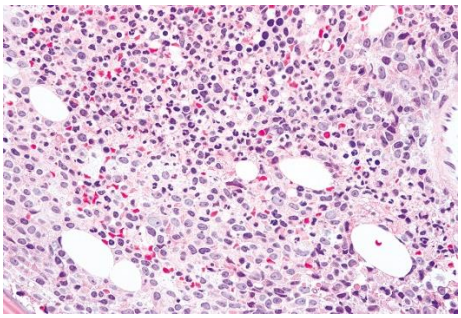
Myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis





- Myelodysplastic/myeloproliferative neoplasm (MDS/MPN) with *SF3B1* mutation and thrombocytosis (MDS/MPN-*SF3B1*-T) is a myeloid neoplasm with myelodysplastic and myeloproliferative features, characterized by *SF3B1* mutation, ring sideroblasts, and thrombocytosis.
- **Histology:** Bone marrow smears show florid erythroid hyperplasia with dyserythropoiesis in the form of multinucleation, bizarre nuclear shapes, and megaloblastic changes. Occasional hyposegmented and hypogranulated neutrophils are also seen. Ring sideroblasts are a manifestation of dyserythropoiesis.
- **Immunophenotype:** May see CD34-positive abnormalities.
- **Molecular:** In contrast to MDS with SF3B1, MDS/MPN with SF3B1 is characterized by concomitant mutations of JAK2 V617F, TET2, DNMT3A, ASXL1, SETBP1, SRSF2, and ZRSR2.
- ***Essential:*** anemia associated with dysplastic erythropoiesis and ≥ 15% ring sideroblasts, with or without dysplasia in the megakaryocytic and granulocytic lineages; persistent thrombocytosis, with a platelet count of ≥ 450 × 10^9/L; *SF3B1* mutations.

Myelodysplastic/myeloproliferative neoplasm NOS (unclassifiable)



- Myelodysplastic/myeloproliferative neoplasm (MDS/MPN) NOS is a myeloid neoplasm with dysplastic and proliferative features that does not meet the criteria for other defined MDS/MPN entities.
- **Histology:** Bone marrow biopsy and aspirates show a hypercellular marrow with dysplasia in erythroid, myeloid, and megas.
- **Immunophenotype:** May show CD34 abnormalities by flow/IHC
- **Molecular:** *TET2*, *NRAS*, *RUNX1*, *CBL*, *SETBP1*, and *ASXL1 mutations. If* Concomitant *SRSF2* or *SETBP1*→ poor outcome
- **Cytogenetics:** Complex karyotype with common abnormalities including trisomy 8, monosomy 7/7q deletion, and 20q deletion

Acute myeloid leukemia

Acute myeloid leukemia with defining genetic abnormalities

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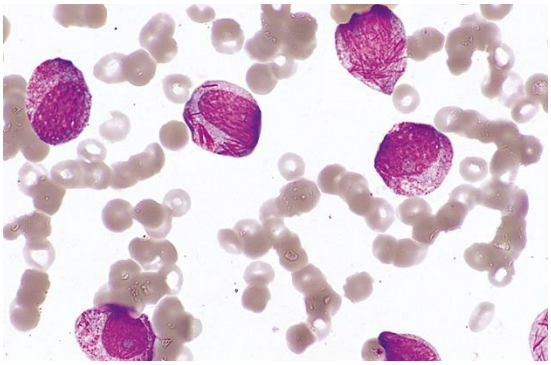
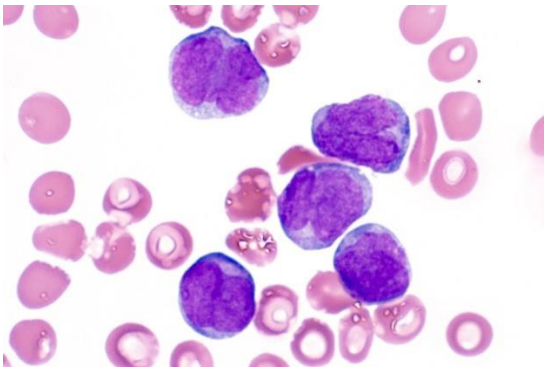
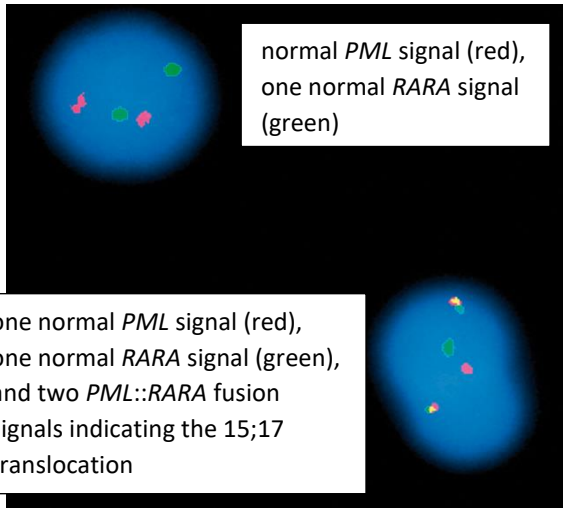
ACUTE PROMYELOCYTIC LEUKEMIA WITH PML::RARA FUSION







- Acute promyelocytic leukemia (APL) with *PML*::*RARA* is a type of acute myeloid leukemia (AML), characterized by a predominance of abnormal promyelocytes **and fusion of the promyelocytic leukemia gene (*PML*) with the retinoic acid receptor alpha gene (*RARA*) or variant RARA translocation.**
- APL is frequently associated with coagulopathy and a risk of disseminated intravascular coagulation, hyperfibrinolysis, often exacerbated on initiation of treatment, and early death.
- APL accounts for 5–8% of all AML cases in younger patients
- In **microgranular APL** , patients present with a very high white blood cell (WBC) count with a short doubling time.
- **Histology:** Subtypes include **Hypergranular (classic) and microgranular (hypogranular)**
- Hypergranular APL is characterized by abnormal promyelocytes whose cytoplasm contains densely packed large granules, staining bright pink, red, or purple. Atypical cells contain bundles of Auer rods randomly distributed within the cytoplasm (faggot cells). Myeloblasts with single Auer rods may also be observed. The Auer rods are usually larger than those in other types of AML. Nuclear size and shape in the abnormal promyelocytes can be highly variable, often including kidney-shaped or bilobed (Figure 8) nuclei.
- Microgranular APL is characterized by blasts with an apparent paucity or absence of granules and many bilobed nuclei. The hypogranular appearance of the cytoplasm is due to the submicroscopic size of the granules. The morphological features may overlap with those of acute myelomonocytic or acute monocytic leukemia.
- **Immunophenotype:** characterized by negative expression of CD34 and HLA-DR, with characteristically high side scatter and forward scatter. They are positive for CD13, CD33, and KIT (CD117). CD64 is frequently positive, but CD15, CD65, CD66b, and CD66c are often negative.
- CD56 is expressed in approximately 10% of APL cases, frequently with CD34 and CD2 (in microgranular variant)
- Monocytic and lymphoid markers are typically negative
- **Molecular:** The genetic hallmark of APL is a balanced chromosomal translocation, t(15;17)(q24;q21), leading to fusion of *PML* and *RARA*.
- CD2 expression (more common in microgranular variant) in APL has been associated with *FLT3* internal tandem duplication (ITD) mutation.

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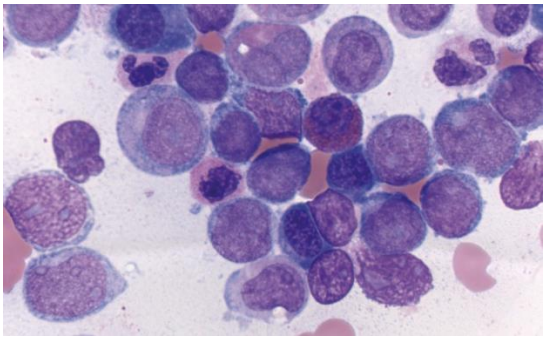
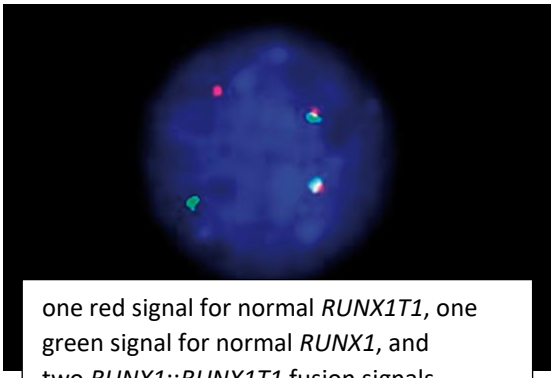
ACUTE MYELOID LEUKEMIA WITH RUNX1::RUNX1T1 FUSION

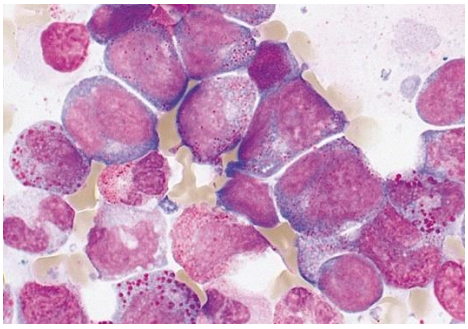


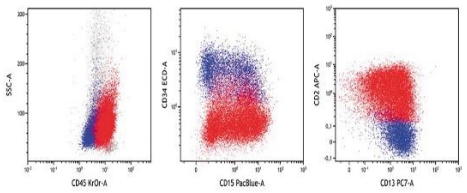


one red signal for normal *RUNX1T1*, one green signal for normal *RUNX1*, and two *RUNX1*::*RUNX1T1* fusion signals indicating a translocation

- Acute myeloid leukemia (AML) with RUNX1::RUNX1T1 is characterized by fusion of the RUNX family transcription factor 1 gene (RUNX1) and the RUNX1 partner transcriptional co-repressor 1 gene (RUNX1T1).
- The blood and bone marrow are always involved. Some patients may present with myeloid sarcoma.
- **Histology:** Bone marrow trephine biopsy or clot preparation usually shows extensive replacement by immature cells. Bone marrow smears show increased blasts and myeloid precursors at various stages of maturation with dysplasia in about 90% of cases. Approximately 10% of cases have features of AML without maturation.
- Blasts are large, with abundant basophilic cytoplasm, often containing numerous azurophilic granules and perinuclear clearing. Monocytes are few and eosinophils/precursors are increased without significant dysplasia.
- Auer rods are present, have a single long rod with tapered ends.
- **Immunophenotype:** high-intensity expression of CD34 and aberrant expression of the lymphoid markers CD19 and cCD79a. Other expressed markers include HLA-DR, CD13 and MPO. CD56 is positive in some cases. CD15 maybe expressed by blasts.
- **Molecular:** Detection of t(8;21)(q22;q22.1) and/or *RUNX1*::*RUNX1T1* can be achieved using chromosome banding analysis, FISH, and various molecular techniques.

ACUTE MYELOID LEUKEMIA WITH CBFB::MYH11 FUSION





Two blast cell populations are present: a more immature population with dim CD45 expression (blue), and a more mature and monocytic population with bright CD45 expression (red). Both populations express myeloid markers like CD13.

- Acute myeloid leukemia (AML) with *CBFB*::*MYH11* fusion is characterized by fusion of the core-binding factor beta subunit gene (*CBFB*) and the myosin heavy chain 11 gene (*MYH11*). Also known as acute myeloid leukemia with t(16;16)(p13.1;q22); acute myeloid leukemia with inv(16)(p13.1q22).
- AML with *CBFB*::*MYH11* fusion constitutes 5–8% of all AML cases in younger patients, and the incidence decreases in older patients.
- Histology: The bone marrow is hypercellular, with a myeloid predominance and increased immature cells. Bone marrow smears show increased blasts, usually with morphological features of myelomonocytic differentiation. Marrow eosinophilia and the presence of abnormal eosinophils is a feature of AML with *CBFB*::*MYH11*.
- Immunophenotype: Two aberrant blast populations are usually identified. One, a CD45-dim immature blast population, expresses CD34 and myeloid markers such as CD13, KIT (CD117), and myeloperoxidase. The second, a more mature monocytic CD45-bright population, expresses monocytic antigens such as CD14, CD64, and lysozyme, in addition to myeloid markers, but lacks CD34 expression. Blasts maybe<20%.
- Molecular: detection of *CBFB*::*MYH11*; not fulfilling diagnostic criteria for myeloid neoplasm post cytotoxic therapy.
- Cytogenetics*:* detection of inv(16)(p13.1q22) or t(16;16)(p13.1;q22).

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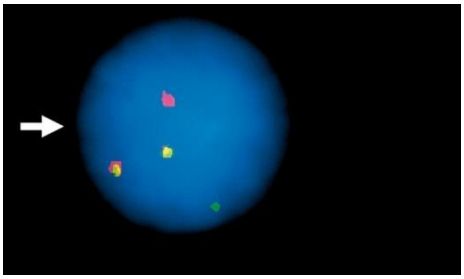
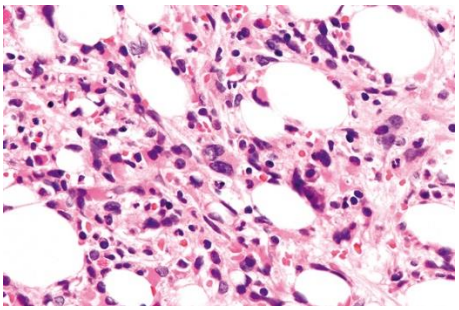
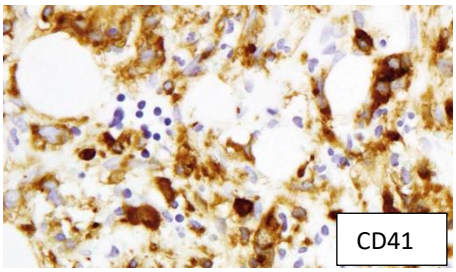
ACUTE MYELOID LEUKEMIA WITH DEK::NUP214 FUSION

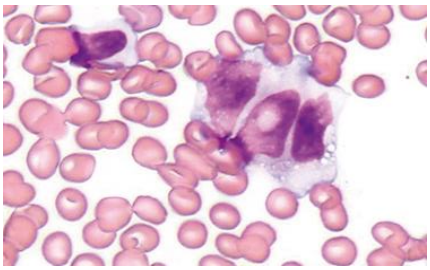


- Acute myeloid leukemia (AML) with *DEK*::*NUP214* fusion is characterized by fusion of the proto-oncogene *DEK* and the nucleoporin 214 gene (*NUP214*). Also known as acute myeloid leukemia with t(6;9)(p23;q34); *DEK-NUP214*
- **Histology:** The bone marrow is typically hypercellular. Bone marrow smears show increased blasts with maturation or with myelomonocytic differentiation. In some patients the morphological features are those of MDS with increased blasts. Multilineage dysplasia is common.
- **Immunophenotype:** Cells are typically positive for CD13, CD33, CD34 (maybe negative), CD38, CD117, CD123, HLA-DR, MPO; CD7, CD9, CD15, CD64, and TdT are variably expressed.
- **Molecular:** Detection of the DEK::NUP214 fusion may be achieved with FISH and/or molecular diagnostic techniques. Concurrent FLT3 internal tandem duplication (ITD) mutation occurs in 50–88% of patients, whereas FLT3 tyrosine kinase domain (TKD) mutations are generally rare. Mutations involving RAS pathway genes are common.
- **Cytogenetics**: The t(6;9) translocation is a driver alteration and often the sole karyotype finding.

ACUTE MYELOID LEUKEMIA WITH RBM15::MRTFA FUSION (MLK1)







- Acute myeloid leukemia (AML) with *RBM15*::*MRTFA* (*MKL1*) is a specific type of AML characterized by megakaryocytic differentiation.
- The peripheral blood, bone marrow, lymph nodes, and spleen are commonly involved. The disease can often arise in extramedullary sites as myeloid sarcoma.
- Most patients present with marked hepatosplenomegaly, anemia, thrombocytopenia. Infants present with fibrotic abdominal organs (liver)
- It occurs more frequently in infants (first 6 months of life) and young children (aged ≤ 3 years) without trisomy 21 (Down syndrome), with a female predominance.
- **Histology:** Blasts have megakaryocytic differentiation and may or may not exceed 20% of bone marrow cellularity. Megakaryoblasts are usually medium-sized to large, with a round, irregular, or convoluted nucleus containing several nucleoli and fine reticular chromatin. The cytoplasm is often agranular and basophilic, and it may have blebs. Dysplasia of granulocytic and erythroid lineages is usually absent.
- Megakaryoblasts may be mixed with more morphologically undifferentiated blasts with a high N:C ratio, resembling lymphoblasts.
- The bone marrow may be normocellular or hypercellular, usually with reticulin and collagenous fibrosis. Fibrosis often results in limited bone marrow aspirates and could lead to a falsely low blast count; therefore, a bone marrow trephine biopsy is required for full evaluation.
- **IHC:** Blasts express 2 or more megakaryocytic markers: CD41, CD61, and/or CD42b. Cytoplasmic CD41 or CD61 is more specific and sensitive. Blasts can be positive for CD13 and CD33, whereas CD34, CD45, HLA-DR, myeloperoxidase, TdT, and lymphoid markers are negative.
- **Molecular:** Detection of *RBM15*::*MRTFA* fusion by FISH and/or RT-PCR
- **Cytogenetics**: detection of t(1;22)(p13.3;q13.1) by karyotype analysis.

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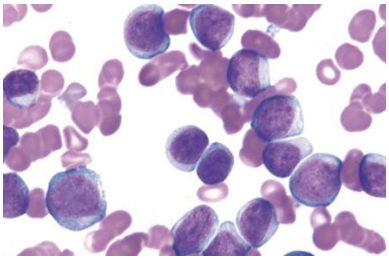
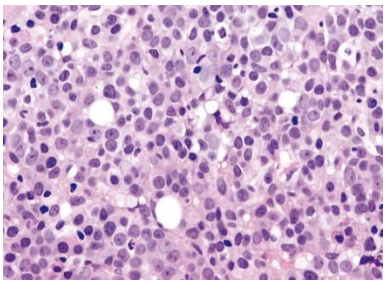
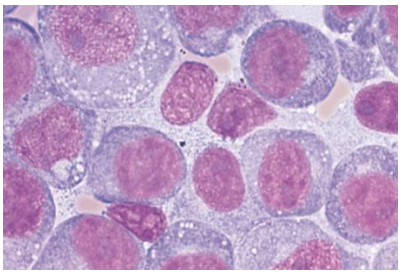
ACUTE MYELOID LEUKEMIA WITH BCR::ABL1 FUSION



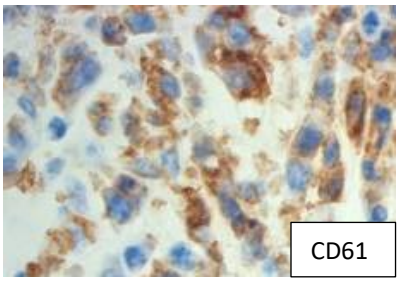


- Acute myeloid leukemia (AML) with BCR::ABL1 fusion is a de novo AML with >20% blasts and BCR::ABL1 detected at initial diagnosis and where no evidence of chronic myeloid leukemia (CML).
- Compared to patients with the myeloid blast phase of CML, patients with AML with *BCR*::*ABL1* tend to have a higher percentage of blasts, lower percentage of basophilia, and lower frequency of splenomegaly.
- **Histology:** Bone marrow biopsy shows sheets of blasts, often with prominent single or multiple nucleoli. There can be minimal differentiation or monocytic.
- **Immunophenotype**: most cases express CD34, HLA-DR, and myeloid antigens (CD13, CD33, CD117); there can be expression of CD7, CD19, and TdT.
- **Molecular**: detection of *BCR*::*ABL1* at initial diagnosis; with a p210 transcript (important for monitoring treatment response)
- **Cytogenetics:** presence of t(9;22)(q34;q11.2) on conventional karyotyping
- Lack of features of CML before or at diagnosis or after therapy; poor prognosis

ACUTE MYELOID LEUKEMIA WITH KMT2A REARRANGEMENT



various monoblasts with abundant cytoplasm, vacuoles, and azurophilic granules in this case of AML (monoblastic) with t(9;11)(p21.3;q23.3)/*KMT2A*::*MLLT3* rearrangement.



CD61

leukemic cells showing megakaryocytic maturation.

- Acute myeloid leukemia (AML) with *KMT2A* rearrangement (Blasts maybe <20%) is a myeloid neoplasm in which the *KMT2A* locus on chromosome 11q23.3 is fused with any of a number of partner genes. Also known as acute myeloid leukemia, 11q23 abnormalities; *KMT2A*::*MLLT3; or AML with t(9;11)(p21.3;q23.3).*
- In children KMT2A is the most common genetic abnormality; >50% of infants with AML.
- The blood and bone marrow are always involved. Extramedullary involvement is relatively frequent and identified in one third of adult patients.
- Rearrangement of *KMT2A* has been observed after treatment with **topoisomerase II inhibitors**, and such cases should be diagnosed as myeloid neoplasm post cytotoxic therapy. Specifically, the presence of the translocation **t(11;16)(q23;p13) leading to *KMT2A*::*CREBBP***.
- **Histology:** Morphology of blasts can be associated with a broad range of myeloid differentiation, with most cases having monocytic, monoblastic, or myelomonocytic features including large blasts, with abundant basophilic cytoplasm, and they may include many promonocytes.
- **Immunophenotype:** The immunophenotype varies depending on cell lineage. Most often, the leukemic cells are of the monocytic lineage and express CD33, CD65, CD4, CD15, HLA-DR, and lysozyme. Expression of CD34 and KIT (CD117) varies depending on subtype (most often negative in monocytic cases). A very common finding in *KMT2A* rearrangement is **expression of CSPG4 (NG2)**.
- In children especially, *KMT2A*::*MLLT3* and *KMT2A*::*MLLT10* can present as acute megakaryoblastic leukemia.
- **Molecular:** Presence of KMT2A rearrangement; fusion partners include: ABI1, AFDN, AFF1, MLLT1, and MLLT10 (high risk); ELL, MLLT3, MLLT11 (standard risk).

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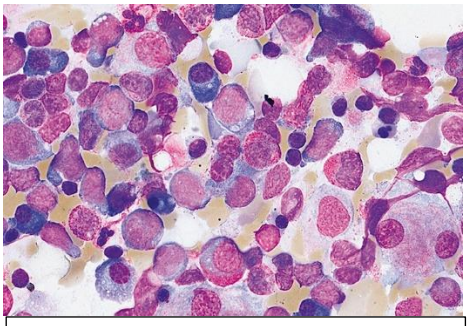
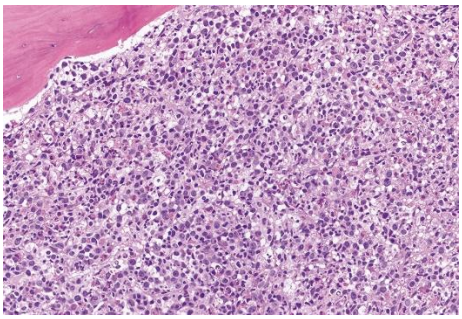
Acute myeloid leukemia with MECOM rearrangement

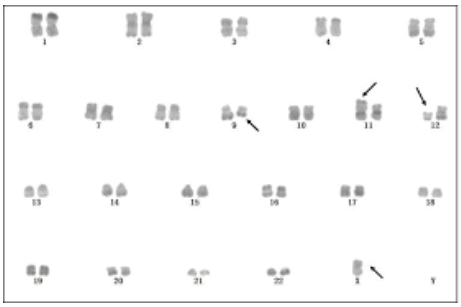


myeloid blasts, erythroid dysplasia, and (especially) several dysplastic megakaryocytes with non-lobed or bilobed nuclei



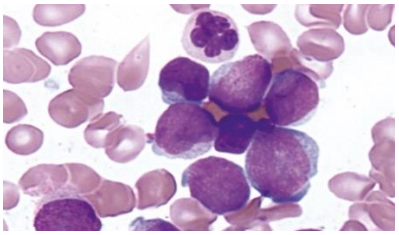
- Acute myeloid leukemia (AML; blasts maybe <20%) with *MECOM* rearrangement is a myeloid neoplasm characterized by rearrangements involving the *MDS1* and *EVI1* complex locus gene (*MECOM*). Also known as Acute myeloid leukemia with inv(3)(q21;q26.2) or t(3.3)(q21;q26.2).
- The incidence is highest among adults aged 18–40 years.
- **Histology:** Peripheral blood smears often show dysplastic neutrophils, with or without associated blasts. Blasts in the bone marrow have variable morphology, resembling acute myelomonocytic and acute megakaryoblastic leukemia. Multilineage dysplasia is common and most pronounced in megakaryocytes which are often small and non-lobated. Marrow eosinophils, basophils, and/or mast cells may be increased.
- **Immunoprofile:** Blasts are positive for CD34 (usually quite high in inv3), CD33, CD13, KIT (CD117), and HLA-DR; most are CD38-positive, with aberrant CD7 expression. Subset may express CD41 or CD61.
- **Molecular:** The most frequent rearrangement is *GATA2*::*MECOM*, which results from either inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), but > 30 partner genes have been described.
- **Cytogenetics:** The most common cytogenetic alterations involving *MECOM* include inv(3)(q21.3q26.2) and t(3;3)(q21.3;q26.2).

Acute myeloid leukemia with NUP98 rearrangement



- Acute myeloid leukemia (AML) with *NUP98* rearrangement is a poor prognosis type of AML, characterized by chromosomal translocations involving *NUP98* on chromosome 11p15.4 and various partner genes; typically in children.
- Patients present with anemia and thrombocytopenia and usually show leukocytosis. Those with *NUP98*::*KDM5A* tend to have lower white blood cell counts
- **Histology:** Varies but most cases show a high blast count with a myelomonocytic or monocytic. In children <3 tend to have megakaryoblastic features.
- **Immunophenotype:** CD34, CD117, CD13, CD33, HLA-DR, MPO; other markers may include, CD123, CD11b, CD11c, CD14, CD36, CD7.
- **Molecular:** More than 40 fusion partners of *NUP98* have been reported most commonly NSD1 (a non-HOX partner). If FLT3-ITD present→ worse

Acute myeloid leukemia with NPM1 mutation



- Acute myeloid leukemia (AML) with *NPM1* mutation is a myeloid neoplasm characterized by the presence of somatic mutations involving the nucleophosmin 1 gene (*NPM1*).
- The blood and bone marrow are nearly always involved. Some patients may present initially with myeloid sarcoma involving the skin, gingiva, lymph nodes, or other extramedullary sites

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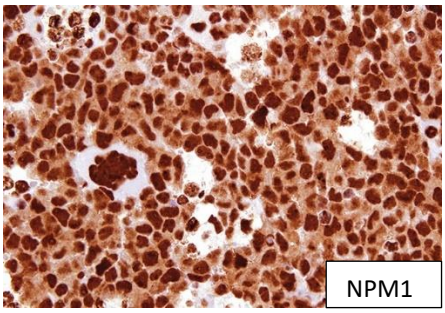
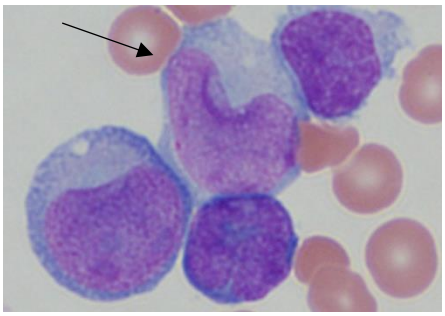
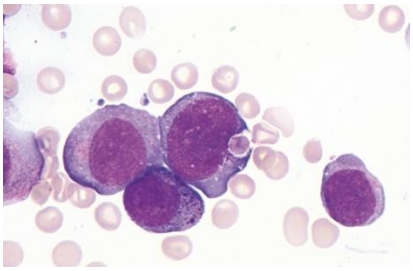




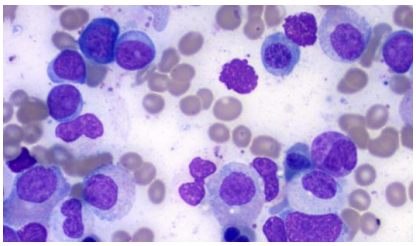
- Clinical features: Anemia and thrombocytopenia (however plt count is typically higher than other AMLs). More common in middle age females.
- Maybe associated with CHIP related mutations/entity
- **Histology:** Most cases are characterized by markedly hypercellular bone marrow. Myelomonocytic or monocytic differentiation is common, however, morphological features vary widely, and in some cases blasts may show less maturation. Multilineage dysplasia is observed in 20–25% of cases.
- **Blasts with cup-like nuclear morphology are strongly associated with the presence of *NPM1* and *FLT3* ITD mutations (shown by arrow)**
- **Immunophenotype**: Absence of CD34 and low CD13; CD33, KIT (CD117), and CD123 are commonly expressed. Other markers include HLA-DR, MPO, CD14, CD36, CD64 depending on the pattern of differentiation.
- Molecular: **The detection of cytoplasmic NPM1 by immunohistochemistry is a surrogate marker of *NPM1* mutation.**
- *NPM1* mutations are invariably heterozygous and primarily restricted to exon 12 (< 1% involving other exons). Often associated with FLT3-ITD.

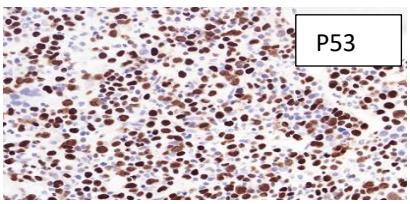
Acute myeloid leukemia with CEBPA mutation



- Acute myeloid leukemia (AML) with *CEBPA* mutation is characterized by *CEBPA* mutation that should be biallelic (bi*CEBPA*) or, if single, must be located in the bZIP region of the gene (smbZIP-*CEBPA*).
- Patients with bi*CEBPA* and smbZIP-*CEBPA* are younger and have higher white blood cell counts than those with a single mutation→ biCEBPA could be a result of germline mutation (Myeloid neoplasms with germline predisposition).
- Smear preparations show increased blasts with or without maturation. Dysplasia is common, especially dysgranulopoiesis and dysmegakaryopoiesis. Blasts may show phagocytosis (as shown by the image of erythrophagocytosis).
- **Immunophenotype:** cells are often positive for CD7, CD13, CD15, CD33, CD34, and HLA-DR, but they rarely express CD56 or CD14.
- **Molecular:** presence of biallelic mutations in *CEBPA*, or a single mutation located in the bZIP region of CEBPA gene.

Acute myeloid leukemia, myelodysplasia-related





- Myelodysplasia-related acute myeloid leukemia (AML-MR) is a myeloid neoplasm harboring specific cytogenetic and/or molecular abnormalities associated with myelodysplastic neoplasia, arising de novo or after a known diagnosis of MDS or MDS/MPN.
- **Histology:** Most cases have morphological evidence of multilineage dysplasia, with dysgranulopoiesis, dyserythropoiesis, and dysmegakaryopoiesis.
- **Immunophenotype:** Blasts often express CD34, KIT (CD117), and HLA-DR, as well as myeloid markers such as myeloperoxidase and CD13. Aberrant p53.
- **Molecular:** A list of somatic defining mutations for AML-MR include: ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2.
- A list of defining cytogenetic changes include: complex karyotype with at least three abnormalities: 5q deletion, monosomy7, 11q deletion, 12p deletion, monosomy 13, 17p deletion, isochromosome 17q.
- **Essential:** ≥ 20% blasts in blood or marrow; presence of at least one of the following two criteria: (1) a history of MDS or MDS/MPN, (2) one or more cytogenetic or molecular abnormalities listed above.

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Acute myeloid leukemia with other defined genetic alterations

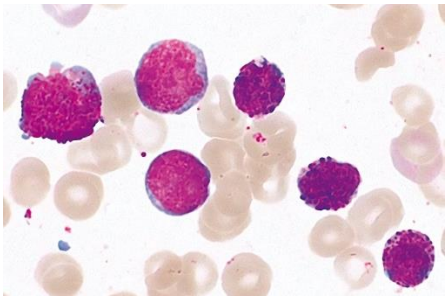
Acute myeloid leukemia (AML) with other defined genetic alterations includes emerging AML subtypes with distinct genetic features:

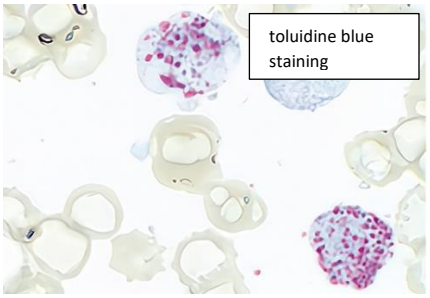
- Acute myeloid leukemia with *CBFA2T3*::*GLIS2* fusion
- Acute myeloid leukemia with *KAT6A*::*CREBBP* fusion
- Acute myeloid leukemia with *FUS*::*ERG* fusion
- Acute myeloid leukemia with *MNX1*::*ETV6* fusion
- Acute myeloid leukemia with *NPM1*::*MLF1* fusion

Essential: ≥ 20% blasts with myeloid immunophenotype in bone marrow and/or blood; detection of one or more of the cytogenetic or molecular aberrations listed above; not fulfilling diagnostic criteria for AML with defining genetic abnormalities, myelodysplasia-related AML, AML post cytotoxic therapy, or mixed-phenotype acute leukemia.

Acute myeloid leukemia defined by differentiation (lack defining genetic abnormalities)

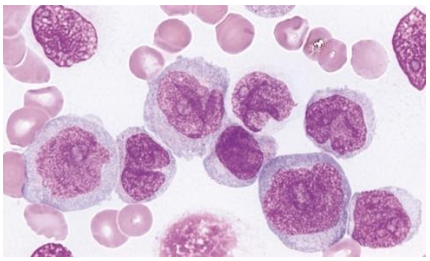
Acute basophilic leukemia





- Acute basophilic leukemia is an acute myeloid leukemia (AML) with basophilic differentiation that lacks defining genetic abnormalities.
- Bone marrow biopsy shows hypercellularity with diffuse replacement by blasts.
- Blasts are medium sized to large and characterized by a high N:C ratio; an oval, round, or irregular nucleus with dispersed chromatin; and one to several prominent nucleoli. The cytoplasm contains variable numbers of coarse basophilic granules. Immature basophils constitute 20-80% of cells
- **Immunophenotype:** Flow shows blast population and a population of cells with basophilic maturation. The blasts are usually positive for CD11b, CD13, CD33, CD34, CD38, CD123, and CD203c; Weak CD117 and CD9 and usually negative for HLA-DR. If CD117 is strong→ likely mast cells
- Differentials include CML blast phase, mast cell leukemia, and other AMLs with basophilic differentiation (eg DEK::NUP214)
- **Molecular:** Presence of MYB::GATA1 mutation and Recurrent translocation of t(X;6)(p11.2;q23) has been seen in some infant boys.

Acute myelomonocytic leukemia



- Acute myelomonocytic leukemia is an acute myeloid leukemia (AML) with evidence of granulocytic and monocytic maturation that lacks defining genetic abnormalities. Formerly AML M4.
- This leukemia predominantly involves the peripheral blood and bone marrow. There maybe peripheral blood leukocytosis with circulating blasts and promonocytes.
- **Histology**: Bone marrow aspirate shows a mix of blasts and promonocytes: promonocytes have more lobular and convoluted nuclear contours; blasts and promonocytes have fine, lacy chromatin with prominent nucleoli and abundant pale basophilic cytoplasm. Some blasts show cytoplasmic protrusions. Fine azurophilic granules can be present.
- The peripheral blood usually shows increased more mature monocytes
- **Immunophenothype:** blasts express CD13, CD15, CD33, CD65 and/or CD117 and monocytic markers such as CD4, CD11b, CD14, CD36, CD64, and CD163. CD7 and CD56 maybe expressed.
- **Molecular/cytogenetics:** trisomy 8 is common; frequently mutated genes include TET2, RUNX1, ASXL1; less commonly DNMT3A, STAG2, U2AF1.

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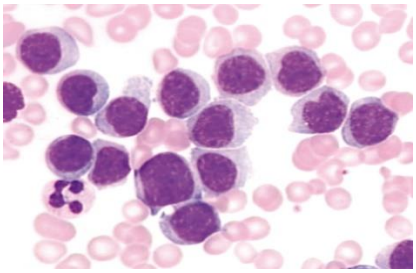
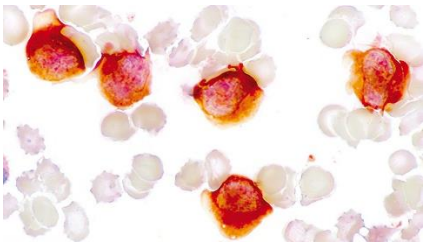
Acute monocytic leukemia



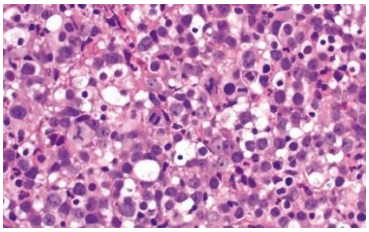


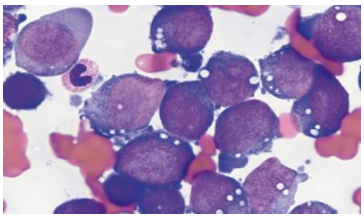
NSE:

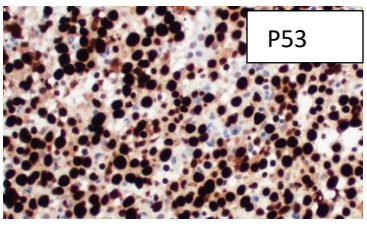
Nonspecific esterase

- Acute monocytic leukemia is an acute myeloid leukemia (AML) with monocytic differentiation that lacks defining genetic abnormalities, formerly AML M5.
- **Histology**: Bone marrow biopsy shows sheets of blasts, varying in size from intermediate to large, with fine chromatin, distinct nucleoli, and irregular lobular nuclear contours.
- Typical monoblasts are medium-sized or large, with abundant, moderately to intensely basophilic cytoplasm and round to oval nuclei. The nuclei have delicate, lace-like chromatin and one or more prominent nucleoli. Bone marrow aspirate shows a blast morphology with intermediate to large cells, with modest amounts of pale basophilic cytoplasm and oval to somewhat reniform/folded nuclear contours with fine chromatin.
- **Immunophenotype**: Blasts express myeloid markers including CD13, CD15, CD33 (bright), CD65, and CD117. Blasts may express CD34 and HLA-DR bright
- Monocytic markers are also expressed, including CD4 (dim), CD11b, CD11c, CD14, CD36 and CD64 (bright), and CD163. (Expression of 2 or more monocytic markers is required for monocytic differentiation.) CD7 and CD56 can be aberrantly expressed.
- **IHC** for CD68 and CD163 can be ordered on tissue biopsies
- **Molecular:** Not identified
- The main differential for this type of AML are microgranular APL, blast phase of CML, AML with NPM1 mutation
- *Essential:* ≥ 20% blasts and blast equivalents (promonocytes) in bone marrow and/or blood; ≥ 80% of the leukemic cells are monocytes or precursors

Acute erythroid leukemia







- Acute erythroid leukemia (AEL) is a neoplastic proliferation of erythroid cells with features of maturation arrest (increased proerythroblasts) and a high prevalence of biallelic *TP53* alterations.
- Patients may present with de novo AEL, but more often the disease arises after exposure to cytotoxic therapy or progression of a prior myeloid neoplasm, particularly myelodysplastic neoplasm
- **Histology:** On bone marrow smears, there is an overall erythroid predominance (usually ≥ 80% of marrow cellularity), which includes increased (≥ 30%) immature erythroid cells (proerythroblasts, or pronormoblasts) that are medium-sized to large with a round central nucleolus, dispersed to finely reticulated chromatin, one or several distinct nucleoli, and deeply basophilic and agranular cytoplasm. Cytoplasmic blebs and vacuoles are commonly seen
- **Immunophenotype**: CD71(highlights premature erythroids only); E-cadherin, and CD117 often highlight proerythroblasts at early maturation stages; however, these markers can not distinguish reactive from neoplastic erythroids. Detection of TP53 mutation by p53 staining can be helpful. **Molecular:** Biallelic (or multi-hit) *TP53* loss of function is characteristic, which often shows mutation in one allele and deletion in another allele, or two or more *TP53* mutations in cases without *TP53* deletion.

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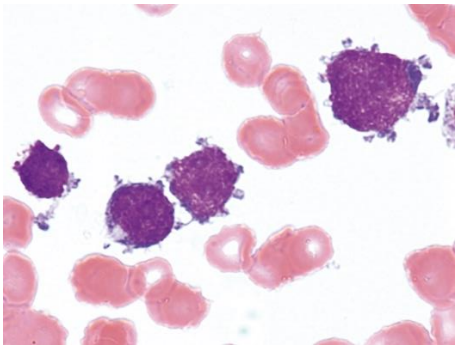
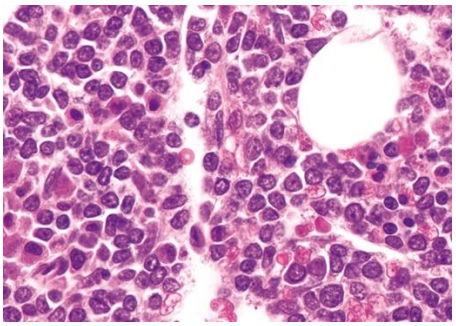
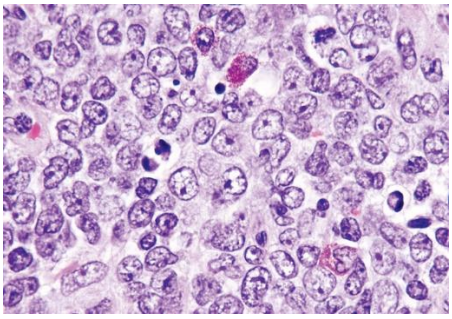
Acute megakaryoblastic leukemia

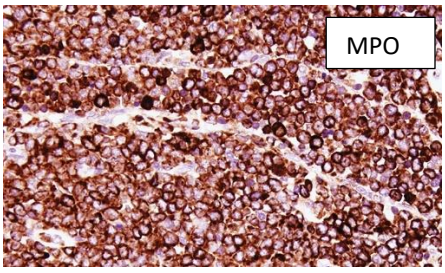




- Acute megakaryoblastic leukemia (AMKL) is characterized by ≥ 20% blasts with megakaryocytic differentiation.
- Patients with AMKL fall into 3 categories: Children with down syndrome, children without down syndrome, and adults.
- **Histology:** Bone marrow aspirate smear shows small to intermediate-sized blasts with high N:C ratios, pale basophilic cytoplasm with multiple cytoplasmic blebs or pseudopodal projections, fine chromatin, and small nucleoli.
- Bone marrow trephine biopsy usually shows sheets of undifferentiated blasts and sometimes a mixture of blasts, micro megakaryocytes, and dyspoietic megakaryocytes, typically with varying degrees of reticulin fibrosis.
- **Immunophenotype:** Blasts are positive for megakaryocytic markers by flow including CD36, CD41 (glycoprotein IIB), CD42b (glycoprotein Ib), and CD61 (glycoprotein IIa). Cytoplasmic expression is more specific for CD41/CD61.
- The blasts also express CD33; however, CD13 and CD117 expression is less. CD34 is expressed in half and HLA-DR is expressed in 1/3; MPO is negative. Aberrant expression of CD4, CD7, CD56 is common.
- **RAM phenotype**: a subset of cases with strong CD56 expression; variable CD34, variable CD117, and negative CD7, CD11b, CD13, CD45, HLA-DR and distinctly associated with ***CBFA2T3::GLIS2 → RAM has poor prognosis.***
- **IHC:** will be positive for CD61, CD41, von Willebrand factor, factor VIII
- **Molecular:** chromosomal translocations that produce fusion proteins, including *CBFA2T3*::*GLIS2*, *RBM15*::*MRTFA*, *NUP98*::*KDM5A*, and *KMT2A* rearrangements, Identified by cytogenetics and molecular.

Myeloid sarcoma





- Myeloid sarcoma is a tumor mass involving any anatomical site other than bone marrow (i.e. extramedullary) that effaces tissue architecture and is composed of myeloid blasts, with or without maturation.
- Myeloid sarcoma is a tumor mass involving any anatomical site other than bone marrow (i.e. extramedullary) that effaces tissue architecture and is composed of myeloid blasts, with or without maturation.
- It most often occurs concurrently with or as a relapse of AML, MDS, or MDS/MPN. Rarely, myeloid sarcoma can precede the onset of AML.
- Myeloid sarcoma shares cytogenetic and molecular abnormalities with bone marrow AML.
- **Histology:** Histology often shows a mass formation with effacement or architecture or diffuse proliferation by blasts which have folded nuclei and immature, blastic chromatin; some eosinophilic myelocytes are also present
- **Immunophenotype:** The blasts often express CD13, CD33, CD43, CD68, MPO; CD45, CD34, CD117 less frequent expression. In myelomonocytic cases there is expression of CD11b, CD11c, CD14, CD163, CD64, and lysozyme. **Aberrant expression of NPM1 is seen in CD34 negative cases.**
- **Molecular:** Chromosomal abnormalities assessed by conventional cytogenetics and/or FISH are detected in about 50% of cases. These abnormalities include t(8;21)/*RUNX1*::*RUNX1T1*, inv(16)/*CBFB*::*MYH11*, trisomy 4, trisomy 8, monosomy 7, and deletions of 5q and 20q.

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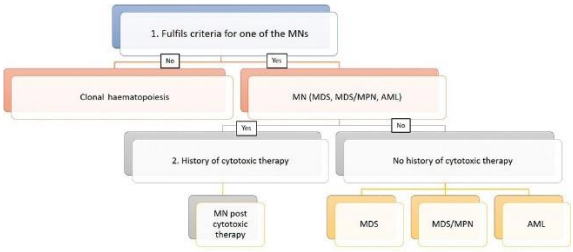
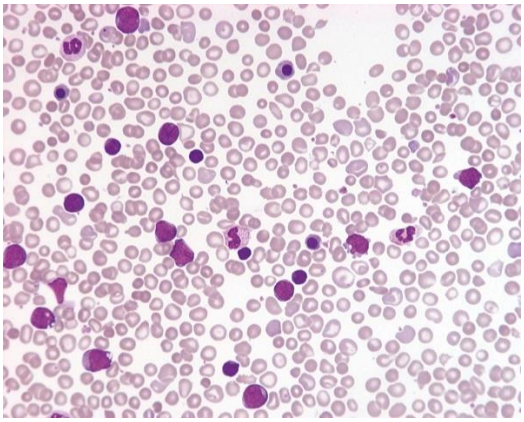
SECONDARY MYELOID NEOPLASMS

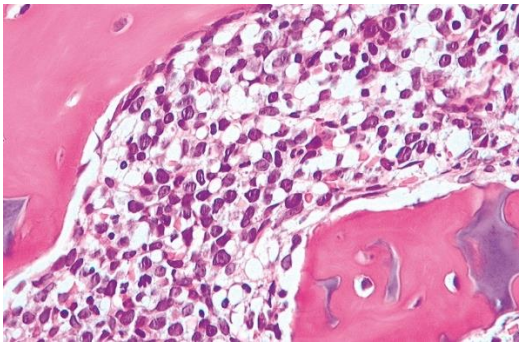
MYELOID NEOPLASM POST CYTOTOXIC THERAPY (MN-PCT)



- Myeloid neoplasms post cytotoxic therapy (MN-pCTs) include myelodysplastic neoplasms (MDSs), myelodysplastic/myeloproliferative neoplasms (MDS/MPNs), and acute myeloid leukemia (AML) that arise in a patient with a history of exposure to DNA-damaging cytotoxic chemotherapy and/or large-field radiation **therapy within the last 10 years.**
- Two clinical categories of MN-pCT have been recognized:
  - cases following exposure to alkylating agents and/or ionizing radiation (type 1)
  - cases following exposure to topoisomerase II inhibitors (type 2)
- **Immunophenotype:** heterogeneous and can span the full range of AML, MDS, and MDS/MPN types. Expression of lymphoid markers (CD19, cCD79, cCD3, CD5, CD7, CD25) is common.
- **Molecular:** patients with CHIP mutation in genes such as DNMT3A, ASXL1, TET2, TP53, and PPM1D have an increased risk of developing MN following Cytotoxic therapy.

MYELOID PROLIFERATIONS ASSOCIATED WITH DOWN SYNDROME





densely cellular bone marrow with a prominent blastic component

- Myeloid proliferations associated with Down syndrome encompass two clonal conditions that arise in children with trisomy 21:
  - transient abnormal myelopoiesis (TAM) and myeloid leukemia associated with Down syndrome (ML-DS).
- **Localization:** TAM manifests mainly in the peripheral blood; ML-DS affects the bone marrow, spleen, CNS.
- TAM: Most patients present within 7 days of birth. Severe disease manifests with hepatomegaly, skin rash, and pleural and/or pericardial effusion. Asymptomatic disease→ PBS shows blasts
- Manifestation: Leukocytosis with increased blasts is common and may be extreme (> 100 000 × 10^9/L).
- For ML-DS, the median age of onset is 1.6 years, and is typically preceded by a myelodysplastic neoplasm (MDS) and most patients have a history of TAM.
- **Histology:** TAM: Blast (>10%) with morphology varying from undifferentiated myeloblasts to typical small megakaryoblasts with cytoplasmic blebbing or large, partially differentiated megakaryoblasts.
- **Histology**: ML-DS: PBS shows increased blasts varying from undifferentiated to megakaryoblastic features (maybe <20% of the aspirate smears), and often accompanied by reticulin fibrosis.
- **Immunophenotype**: Blasts typically express CD117, with variable CD34, CD41/42b, CD235a (glycophorin A), CD7, or CD36
- **Molecular: TAM**: one or more hemizygous, prenatally acquired somatic mutations in exon 2 or 3 of *GATA1* lacking N-terminal
- **Molecular: ML-DS**: similar mutation as TAM (exon 2/3 of GATA1) plus additional secondary mutations in cohesion or tyrosine kinase such as JAK3.

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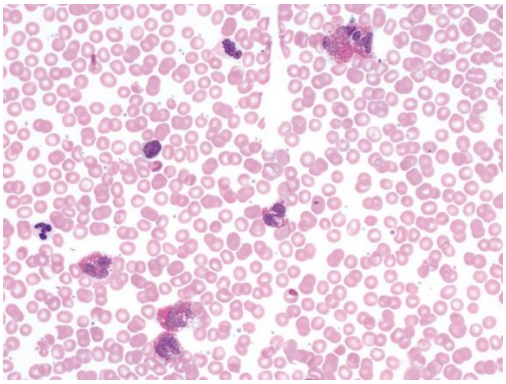
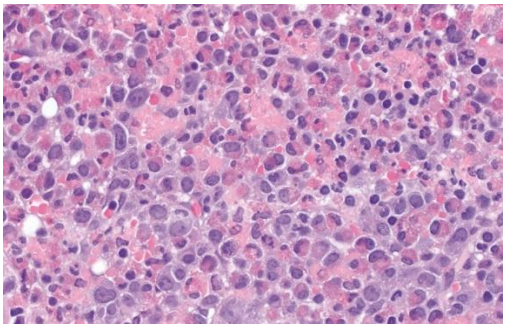
Myeloid/lymphoid neoplasms

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

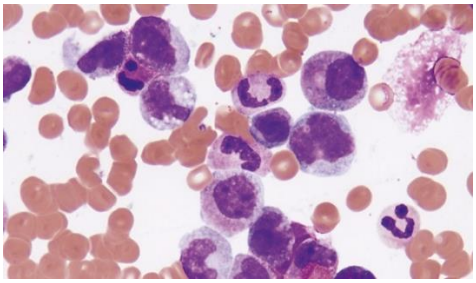
Myeloid/lymphoid neoplasm with PDGFRA rearrangement

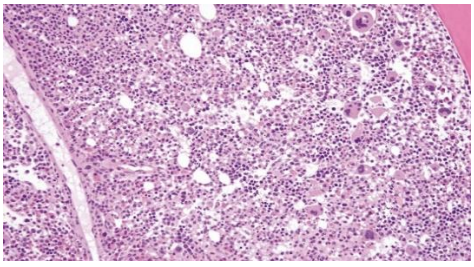




- Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement includes myeloid and lymphoid neoplasms and is frequently associated with eosinophilia.
- The most common symptoms include weakness and fatigue; pruritus; cough; dyspnea; and other respiratory, cardiac, and gastrointestinal symptoms.
- Serum tryptase is often elevated (≥ 12 ng/mL) and can be a useful surrogate marker for *FIP1L1*::*PDGFRA* fusion
- **Histology:** The bone marrow clot section is hypercellular (nearly 100%) and shows marked myeloid hyperplasia with a markedly increased myeloid-to-erythroid ratio and increased eosinophils.
- PBS/Aspirate smears show leukocytosis with relative and absolute eosinophilia. Eos are morphologically atypical with an abnormal distribution of cytoplasmic granules.
- **Immunophenotype**: Eos can show expression of activation markers such as CD23, CD25, and CD69. Increased mast cells maybe highlighted by CD117, tryptase, and CD25 stains (however unlike systemic mastocytosis CD2 expression is uncommon).
- **Molecular:** The majority of cases are characterized by cytogenetically cryptic deletion of 4q12, resulting in formation of the *FIP1L1*::*PDGFRA* fusion gene, although other partner genes have been described.

Myeloid/lymphoid neoplasm with PDGFRB rearrangement





- Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement includes myeloid and lymphoid neoplasms and is frequently associated with eosinophilia.
- Bone marrow is typically hypercellular, with an increased myeloid-to-erythroid ratio and variably increased dysplastic myeloid and megakaryocytic lineages. Atypical mast cells maybe increased.
- Bone marrow aspirates may show increased eosinophils and monocytosis. Myelofibrosis is common.
- **Immunophenotype:** Myeloid progenitors may show little to no alterations, and mast cells usually express aberrant CD2 and CD25.
- **Molecular**: The most common cytogenetic alteration is t(5;12)(q32;p13.2), resulting in *ETV6*::*PDGFRB* using RT-PCR, FISH with break-apart *PDGFRB* probes, or RNA sequencing.
- **Essential:** a myeloid or lymphoid neoplasm, often with prominent eosinophilia with varying degrees of neutrophilia or monocytosis; presence of a PDGFRB fusion gene; exclusion of BCR::ABL1-like B-ALL without evidence of an associated myeloid neoplasm.
- Sensitive to tyrosine kinase inhibitor (TKI) (e.g., imatinib)

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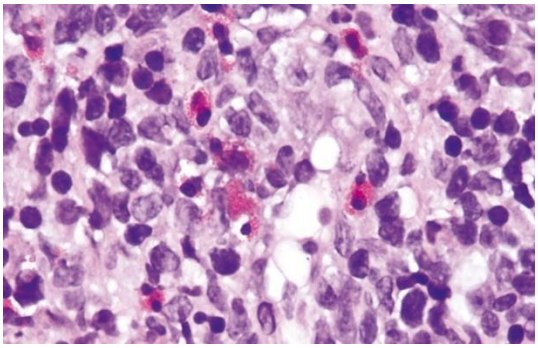
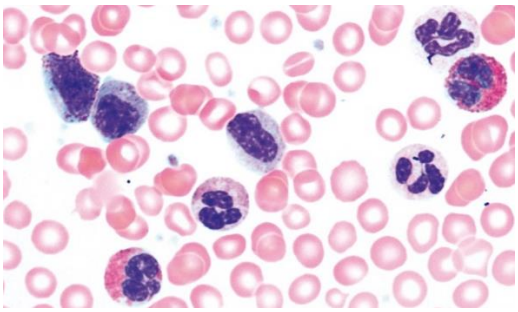
Myeloid/lymphoid neoplasm with FGFR1 rearrangement

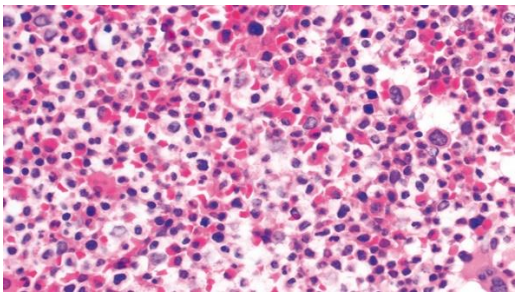


Lymph node core biopsy showing complete effacement of the architecture. Higher magnification shows a proliferation of a dual population of small lymphoid cells and larger, immature-appearing cells and admixed with scattered eosinophils.

- This is a heterogenous group of neoplasms (with ≥ 20% blasts) and *FGFR1* rearrangement, arising from a pluripotent hematopoietic stem cell that may manifest as chronic myeloid neoplasms or as blast-phase disease of B-cell, T-cell, myeloid, or mixed-phenotype origin, typically with associated eosinophilia. The phenotype may change throughout the disease course.
- **Histology:** Cases present as acute lymphoblastic (B- and T-), myeloid, or mixed-phenotype leukemias. Bone marrow may be normocellular or hypercellular with eosinophilia. Lymph nodes are typically involved by lymphoblastic leukemia/lymphoma, most often reported as being of T-cell lineage, but myeloid/T-cell neoplasms and (less often) myeloid sarcoma may be a manifestation.
- **Immunophenotype**: in the acute T-ALL phase, most cells express sCD3 and nuclear TDT; in the B-ALL phase the blasts show CD19 expression; and in the myeloid or mixed-phenotype MPO is typically expressed.
- **Molecular:** Presence of an *FGFR1* fusion gene by t(8;13)(p11.2;q12.1) or an alternative translocation partner. Trisomy 21 is most common secondary cytogenetic abnormality.

Myeloid/lymphoid neoplasm with JAK2 rearrangement





- This entity comprises myeloid and/or lymphoid neoplasms associated with a *JAK2* fusion. The most common fusion partner for this entity is *PCM1*, although many additional partner genes result in *JAK2* fusions driving myeloid and/or lymphoid neoplasms that fall into this diagnostic category.
- **Histology:** The bone marrow is typically hypercellular with eosinophilia. Myelofibrosis is common. Eosinophil morphology is variable, ranging from unremarkable to abnormal/dysplastic. Eosinophilic precursors may be increased. Megakaryocytes may be decreased with dysplastic features.
- **Immunophenotype:** detection of dysplastic megas (CD61/CD41); abnormal erythroids (CD71/E-cad), abnormal meyloids (MPO); and possibly B and T cell markers in increased blast population.
- **Molecular/cytogenetics:** cytogenetic identification of the translocation; molecular identification of the fusion gene, e.g. *PCM1*::*JAK2*. Concurrent somatic gene mutations involving *ASXL1*, *BCOR*, *ETV6*,*RUNX1*, *SRSF2*, *TET2*, and *TP53*.

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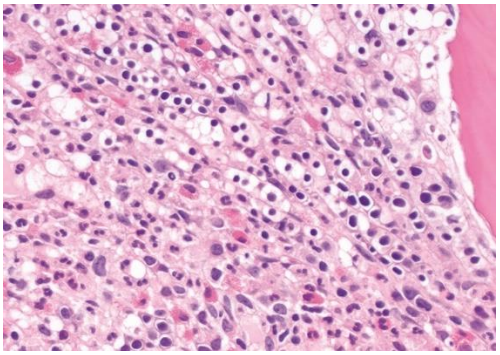
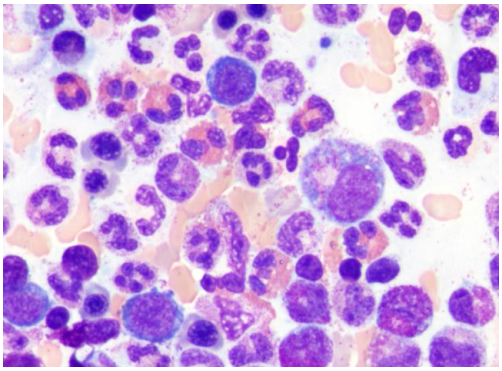
Myeloid/lymphoid neoplasm with FLT3 rearrangement

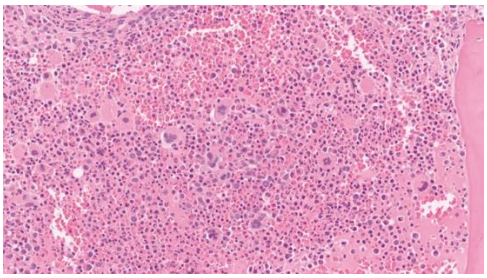




Myeloid hyperplasia and eosinophilia in a case of T lymphoblastic leukemia / lymphoma with eosinophilia and *TRIP11::FLT3* fusion

- Myeloid/lymphoid neoplasms with *FLT3* rearrangement are hematopoietic stem cell neoplasms associated with gene rearrangements forming a fusion gene involving the fms-related receptor tyrosine kinase 3 gene (*FLT3*), usually producing a myeloproliferative neoplasm and/or T-lymphoblastic leukemia/lymphoma with associated eosinophilia, although the phenotypic presentation may be variable and diverse.
- The bone marrow and peripheral blood are commonly involved but may be spared at initial presentation. Lymphadenopathy and splenomegaly may or may not be present. Lytic bone lesions may be seen on imaging studies
- **Histology:** Bone marrow involvement may manifest with features of myelodysplastic neoplasm (MDS), myeloproliferative neoplasms (including cases with features of chronic eosinophilic leukemia), myelodysplastic/myeloproliferative neoplasms (including cases with chronic myelomonocytic leukemia–like or juvenile myelomonocytic leukemia–like features, or with increased blasts of myeloid, T-cell, or B-cell lineage in the range of acute leukemia.
- Extramedullary involvement may manifest as T-lymphoblastic lymphoma or myeloid sarcoma, rarely mixed-phenotype type acute leukemia.
- **Cytogenetics:** Chromosomal rearrangements involving 13q12 are typically identifiable on routine karyotyping studies
- **Molecular:** Presence of *FLT3* fusion gene confirmed using additional methods (including break-apart FISH probes for *FLT3*, RT-PCR, or RNA sequencing).

Myeloid/lymphoid neoplasm with ETV6::ABL1 fusion



Bone marrow aspirate smear shows increased eosinophils, including eosinophilic myelocytes and degranulated eosinophils lacking overt dysplasia

- Myeloid/lymphoid neoplasm with ETV6::ABL1 fusion is a hematopoietic stem cell neoplasm associated with fusion of the **genes ETV6 and ABL1.**
- The peripheral blood and bone marrow are invariably involved. Extramedullary infiltration, including splenic involvement, is common.
- **Histology**: Myeloid/lymphoid neoplasms with *ETV6*::*ABL1* may show overlapping histopathological features with chronic myeloid leukemia (CML), including hypercellular bone marrow with an increased myeloid-to-erythroid ratio and prominent eosinophilia with or without basophilia.
- Megas can appear dysplastic, while eos, myeloids, erythroids usually lack dysplasia. There can be increased blasts in the range of acute leukemia.
- **Cytogenetics:** testing for t(9;12)(q34;p13) or complex aberrations involving other chromosomes.
- **Molecular:** FISH with a combination of *ETV6* and *ABL1* probes, RT-PCR, and RNA sequencing (more reliable than cytogenetics alone).

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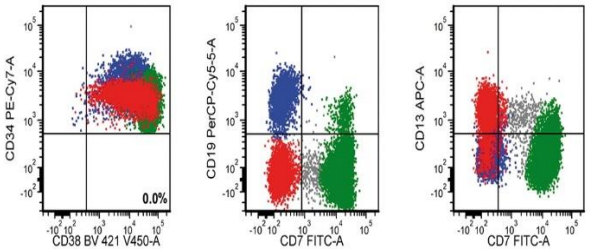
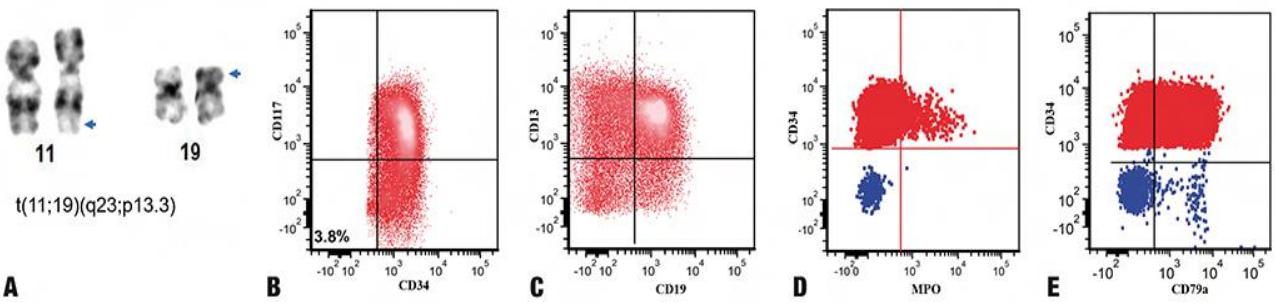
Acute leukemia of ambiguous lineage with <u>defining genetic abnormalities</u>

MIXED-PHENOTYPE ACUTE LEUKEMIA WITH BCR::ABL1 FUSION



- Mixed-phenotype acute leukemia (MPAL) with *BCR*::*ABL1* fusion is a de novo acute leukemia that fulfils the criteria for MPAL and harbors *BCR*::*ABL1* at initial diagnosis, without evidence of chronic myeloid leukemia.
- **Histology:** The peripheral blood or bone marrow typically shows 3 different population of blasts (B/T/myeloid). There are no unique morphological features that distinguish MPAL with *BCR*::*ABL1* from other types of MPAL. The blasts in MPAL with *BCR*::*ABL1* may resemble lymphoblasts or myeloblasts, and many cases show dimorphic blast populations.
- **Immunophenotype:** B/T/myeloid blasts are typically positive for CD34; B-lymphoblasts are positive for CD10(bright), CD19, CD20, CD22, CD33(variable), and TdT; T-lymphoblasts: CD2, cCD3, CD4, CD5, CD7, TdT; myeloblasts CD13, CD33, CD117, and MPO.
- **Molecular:** BCR::ABL1 and/or t(9;22)(q34;q11.2) detected at initial diagnosis; more commonly with a p190 but can be p210

MIXED-PHENOTYPE ACUTE LEUKEMIA WITH KMT2A REARRANGEMENT



- Mixed-phenotype acute leukemia (MPAL) with *KMT2A* rearrangement is an acute leukemia that fulfils the criteria for MPAL and in which the *KMT2A* locus on chromosome 11q23.3 is fused with any of a number of partner genes. Also known as Mixed-phenotype acute leukemia with t(v;11q23); *MLL*-rearranged.
- **Histology:** Peripheral blood smears and bone marrow aspirate smears often show extensive blast population (maybe <20% in some cases) with a dimorphic blast population, with some blasts resembling monoblasts/promonocytes and others resembling lymphoblasts.
- **Immunophenotype:** Typically has a B/myeloid immunophenotype. Less common, cases of T/myeloid have been described. Commonly expressed myeloid antigens include: CD11b, CD13, CD15, CD25, CD65, CD117, MPO, lysozyme; commonly expressed lymphoid antigens include CD2, CD7, CD19, CD22, cCD22, and cCD79a.
- CD10 is usually negative, CD56 is variable.
- **Cytogenetics:** Detection of *KMT2A* rearrangements via conventional karyotyping. However, some *KMT2A*rearrangements can be cytogenetically cryptic and require alternative techniques for detection, such as FISH or RNA sequencing particularly KMT2A::USP2
- **Molecular:** identification of the *KMT2A* fusion partner.

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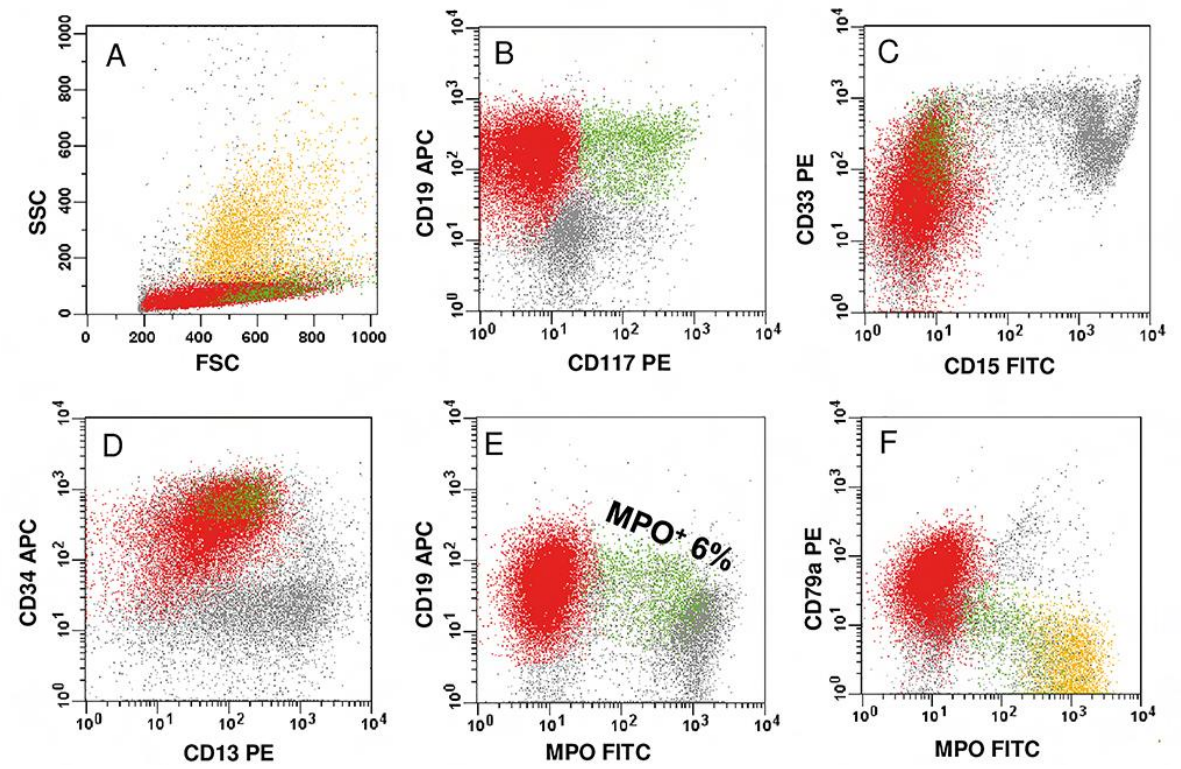
Acute leukemia of ambiguous lineage defined immunophenotypically

MIXED-PHENOTYPE ACUTE LEUKEMIA, B/MYELOID



- B/myeloid mixed-phenotype acute leukemia (MPAL-B/M) is an acute leukemia that expresses B-lineage and myeloid-lineage markers but does not meet criteria for mixed-phenotype acute leukemia (MPAL) with defined genetic alterations. ≥ 20% blasts in bone marrow and/or blood.
- **Histology:** Blasts do not have distinguishing features in most cases. They can resemble lymphoblasts, monoblasts, or myeloblasts, or they may consist of dimorphic populations.
- **Immunophenotype**: Blasts express both B-lineage and myeloid-lineage antigens eg: CD19, CD20, CD22, cCD79a, PAX5 and CD13, CD14, CD15, CD64, CD65, CD117.
- **Cytogenetics:** Most cases have complex karyotype. Cytogenetic analysis and molecular assessment are needed to exclude defining genetic abnormalities such as *KMT2A*rearrangements and *BCR*::*ABL1*. *Rearrangements of ZNF384* are common in childhood MPAL-B/M (reported in 48% of cases).
- **Molecular**: Mutations in genes encoding transcriptional regulators, particularly *PAX5* and *IKZF1*, are present in the majority of cases. Other common mutations include *NRAS* and *PTPN11*.

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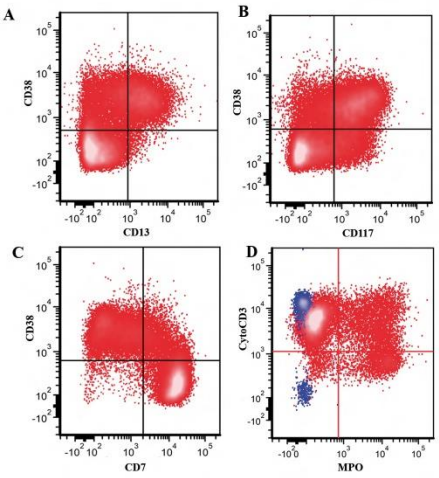
MIXED-PHENOTYPE ACUTE LEUKEMIA, T/MYELOID



- T/myeloid mixed-phenotype acute leukemia (MPAL-T/M) is an acute leukemia (≥ 20% blasts) that expresses T-lineage and myeloid-lineage markers but does not meet criteria for mixed-phenotype acute leukemia (MPAL) with defined genetic alterations.
- Bone marrow and peripheral blood are always involved. Lymph node involvement is common.
- **Histology:** Blasts do not have distinguishing features in most cases. They can resemble lymphoblasts or myeloblasts, or they may consist of dimorphic populations.
- **Immunophenotype:** Blasts express both myeloid and and T-lymphoid markers including cCD3(cytoplasmic), CD7, less commonly CD2, CD4, CD5, CD8; sCD3(surface) is less common; Myeloid markers include MPO, CD13, CD15, CD33, CD65, KIT
- Monocytic differentiation may occur CD11c, CD14, CD36, and CD64
- **Molecular:** *PICALM*::*MLLT10* rearrangement, resulting in a nuclear-localized fusion protein, is reported in 10–15% of MPAL-T/M cases; Other fusion genes such as ETV6, NUP214, BCL11A have been reported. DNMT3A and IDH2 mutations is described in adult cases.
- **Cytogenetics:** assessment are needed to exclude defining genetic abnormalities such as *KMT2A*rearrangements and *BCR*::*ABL1*.

Reference:

Alaggio, Rita et al. “The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms.” *Leukemia* vol. 36,7 (2022): 1720-1748. doi:10.1038/s41375-022-01620-2