
Primary Myelofibrosis

A clinicopathologic approach to marrow fibrosis and extramedullary hematopoiesis

Dr Abu Suraih Sakhri

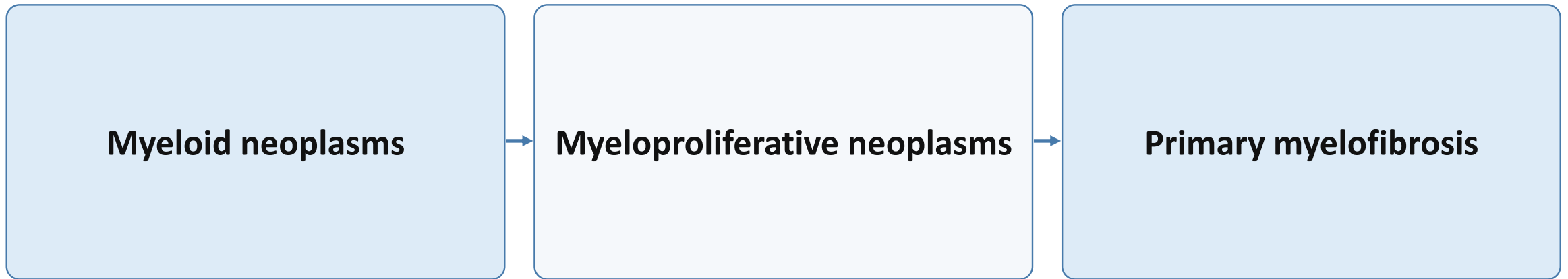
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how a clonal myeloproliferative neoplasm produces reactive marrow fibrosis.
- Recognize the marrow, spleen and peripheral blood morphology of PMF.
- Connect fibrosis to anemia, leukoerythroblastosis and splenomegaly.
- Distinguish primary disease from other causes of marrow fibrosis.

PMF within the spectrum of myeloid neoplasms



Myeloproliferation may ultimately coexist with marrow failure and extramedullary hematopoiesis.

Defining PMF

- A clonal myeloproliferative neoplasm with atypical megakaryocytic proliferation.
- Its defining late effect is progressive, obliterative marrow fibrosis.
- Secondary hematopoietic sites become prominent as marrow function declines.

Primary versus secondary myelofibrosis

Primary myelofibrosis

- The neoplasm is classified as PMF at presentation.
- Atypical megakaryocytes are part of the neoplastic process.
- Progressive fibrosis disrupts the marrow.

Post-PV / post-ET myelofibrosis

- Marrow fibrosis develops after established PV or ET.
- The fibrotic stage can be morphologically indistinguishable from PMF.
- Prior disease history is diagnostically decisive.

A central paradox: Fibrosis is reactive

- The neoplastic clone principally involves hematopoietic progenitors.
- Fibroblasts depositing collagen are described as nonneoplastic.
- Abnormal signals from neoplastic megakaryocytes promote stromal growth.

Three principal driver genes

JAK2

Constitutive kinase signaling amplifies hematopoietic growth responses.

CALR

Mutant calreticulin contributes to MPL-pathway activation.

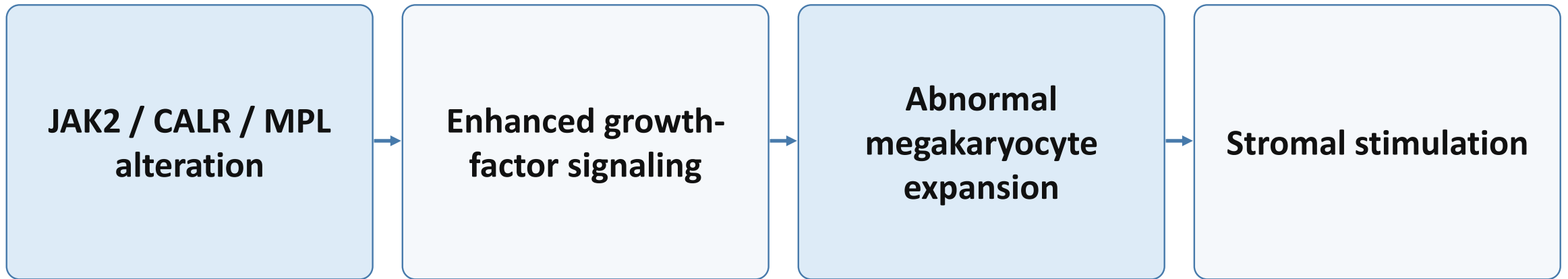
MPL

Altered thrombopoietin-receptor signaling promotes clonal expansion.

The molecular signature is shared, not exclusive

- JAK2, CALR or MPL mutations in approximately 90% of PMF cases.
- These driver alterations are also seen in essential thrombocythemia.
- Driver status supports clonality; It does not independently distinguish MPN subtypes.

Convergent signaling toward proliferation

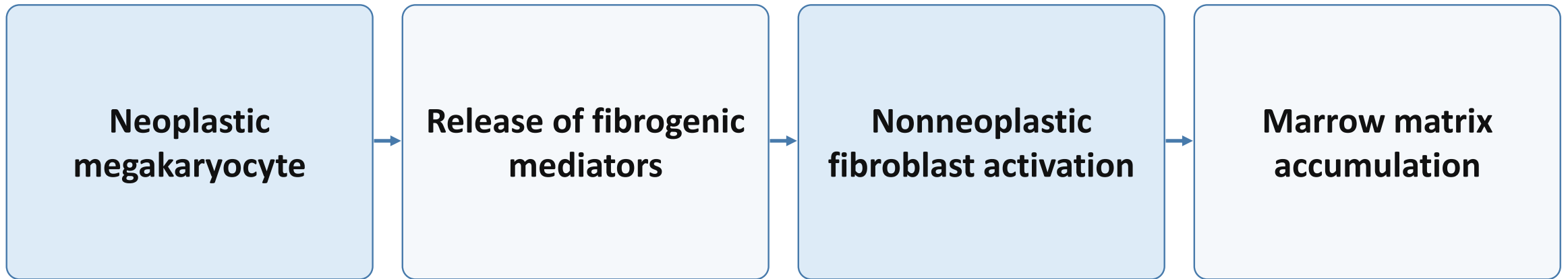


A shared molecular axis can generate different marrow phenotypes.

Why do abnormal megakaryocytes matter?

- They show conspicuous nuclear atypia and abnormal clustering in marrow.
- They are implicated as sources of fibrogenic growth factors.
- Their effects extend beyond the neoplastic cells into the marrow stroma.

Megakaryocyte–fibroblast interaction



Fibrosis is an indirect consequence of the neoplastic megakaryocyte compartment.

Two mediators highlighted by Robbins

Platelet-derived growth factor

- Acts as a fibroblast mitogen.
- Promotes stromal cell proliferation.
- Provides one candidate mechanism of fibroblast expansion.

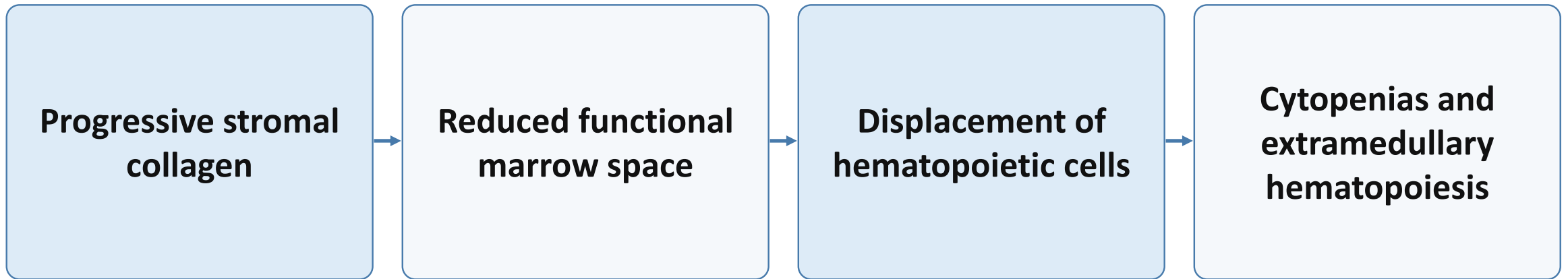
Transforming growth factor- β

- Has fibroblast-stimulatory activity.
- Promotes collagen deposition.
- Contributes to the angiogenic response.

TGF- β links fibrosis and vascular change

- The pathway favors increased collagen deposition by the stroma.
- Angiogenesis is another recognized component of PMF marrow remodeling.
- Vascular and stromal changes can amplify architectural distortion.

Why the marrow becomes dysfunctional

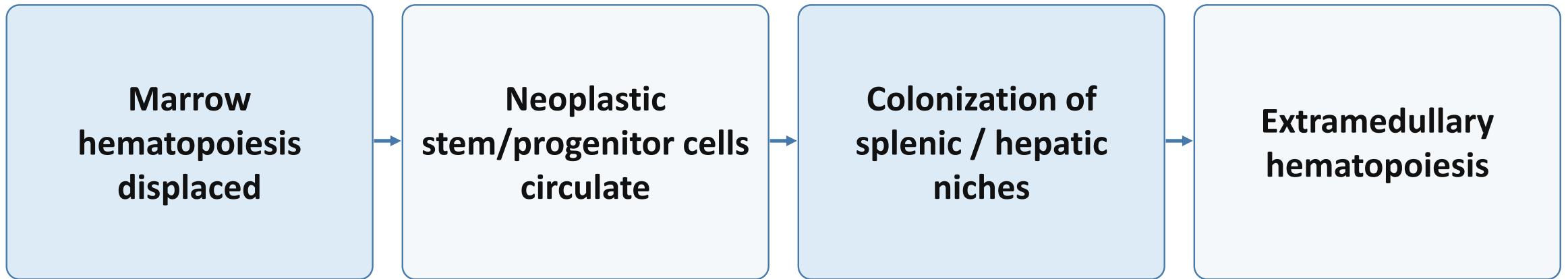


The primary clinical effect is loss of effective marrow hematopoiesis.

Fibrosis changes the marrow niche

- Normal spatial relationships between cells and sinusoids become distorted.
- Hematopoietic elements are displaced as the fibrous matrix expands.
- Even viable stem and progenitor cells may function in abnormal sites.

Migration into secondary hematopoietic organs

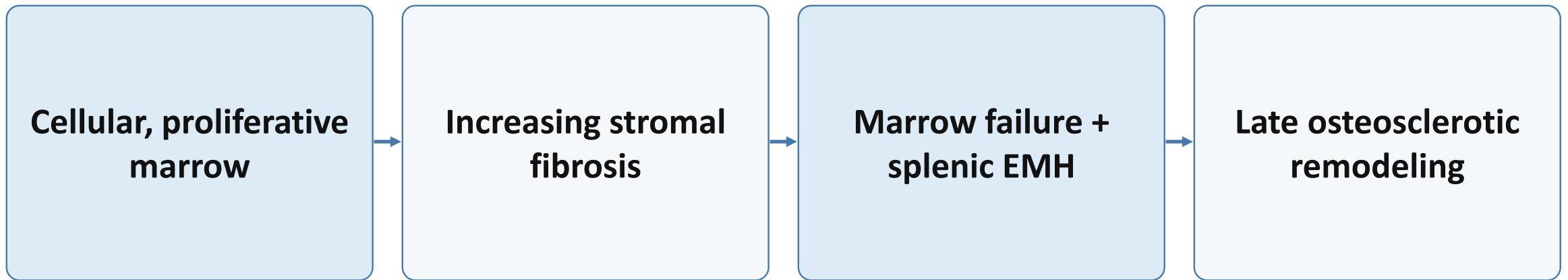


The spleen becomes a major site of blood cell production.

Why extramedullary hematopoiesis is insufficient

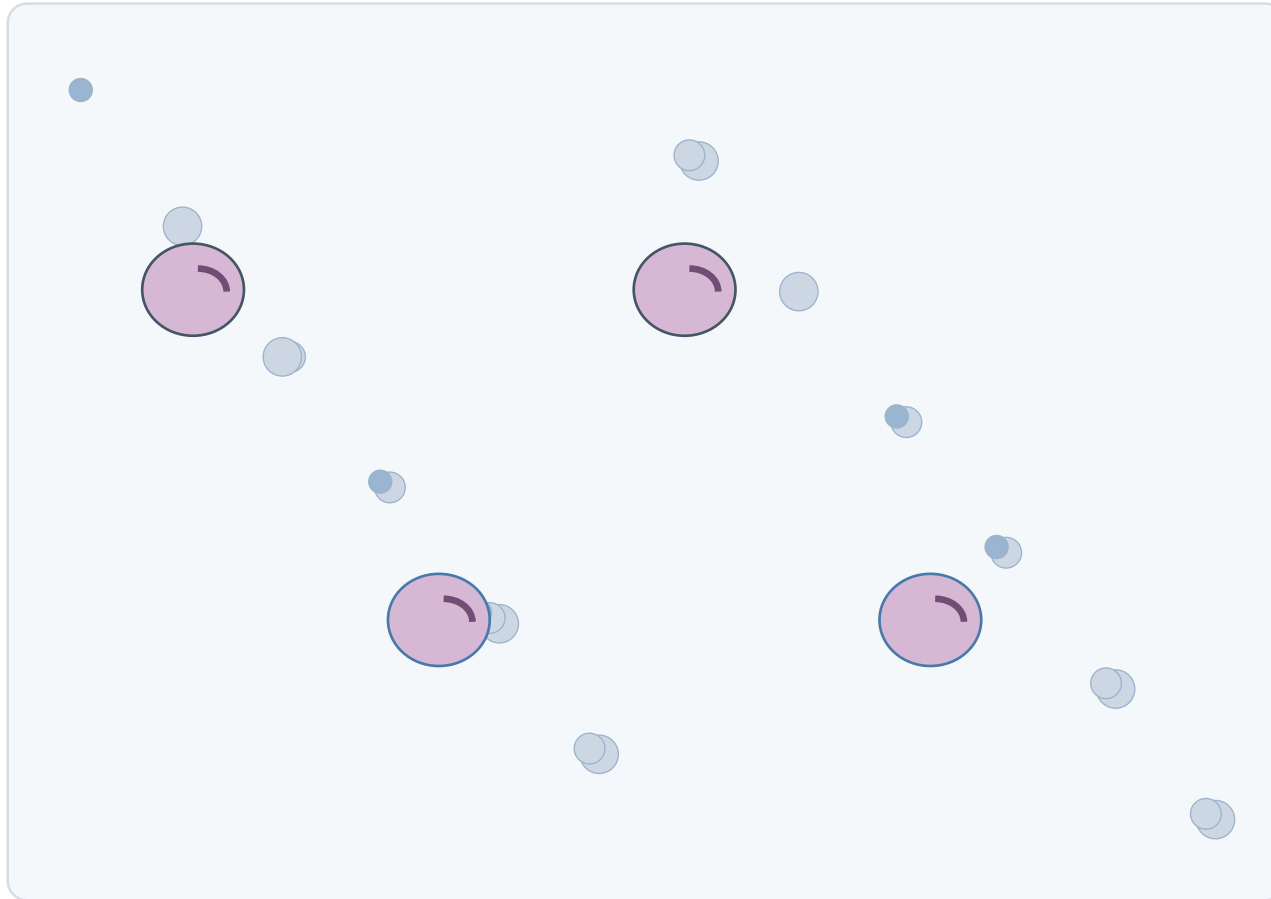
- Extramedullary red-cell production is disordered.
- It does not fully compensate for suppression of marrow erythropoiesis.
- The combined effects cause moderate to severe anemia.

Disease evolution: Functional consequences



The phenotype changes over time; Early blood counts may be elevated, later counts may fall.

Early PMF: A cellular marrow



Schematic marrow compartment

- Overall marrow cellularity may be increased.
- Maturing cells of multiple lineages are present.
- Megakaryocytic atypia is already evident.

Early erythroid and granulocytic precursors

- Apparently normal maturation morphology in early PMF.
- This contrasts with the striking atypia of the megakaryocytes.
- The dominant abnormality is not a general dysplasia of every lineage.

Atypical megakaryocytes: Morphology

Size

Large and sometimes conspicuous cells.

Nuclear features

Bulbous, hyperchromatic or cloud-like nuclei.

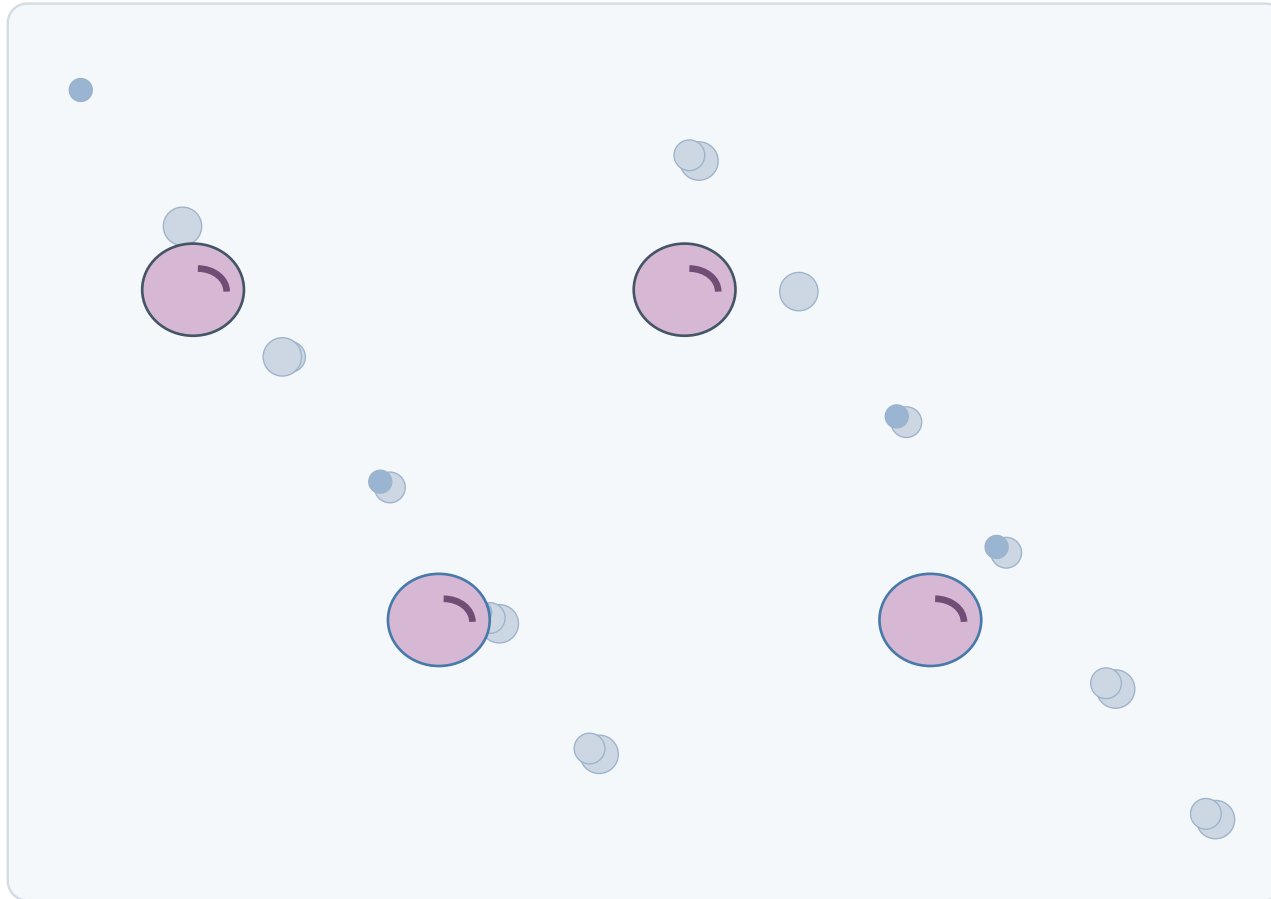
Distribution

Abnormally clustered within the marrow.

Megakaryocyte clustering is diagnostic context

- Tight groups of atypical megakaryocytes suggest abnormal growth architecture.
- Nuclear configuration is as important as megakaryocyte number.
- Assessment requires an adequately sampled marrow biopsy.

Prefibrotic / early stage: Matrix changes



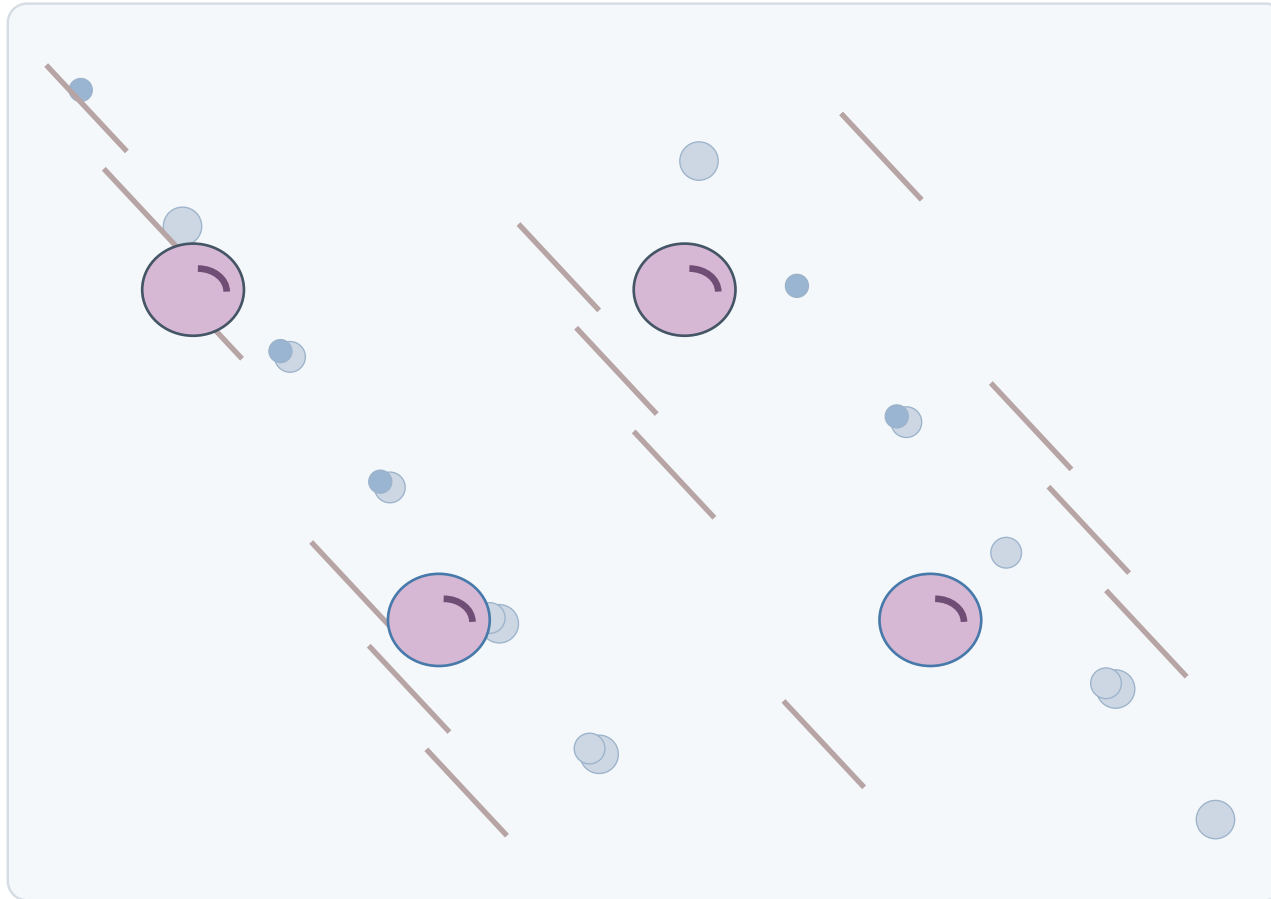
Schematic marrow compartment

- Fibrosis may be minimal at this stage.
- Leukocytosis or thrombocytosis can predominate.
- Morphology, not fibrosis alone, guides classification.

Why early PMF may resemble other MPNs

- Early marrow cellularity can resemble polycythemia vera.
- Platelets may be elevated, bringing essential thrombocythemia into the differential.
- Characteristic megakaryocyte atypia and the whole clinical picture are crucial.

Overt PMF: Progressive matrix deposition



Schematic marrow compartment

- Stromal fibrosis occupies increasing marrow space.
- Residual hematopoietic cells become disorganized.
- Atypical megakaryocyte clusters persist.

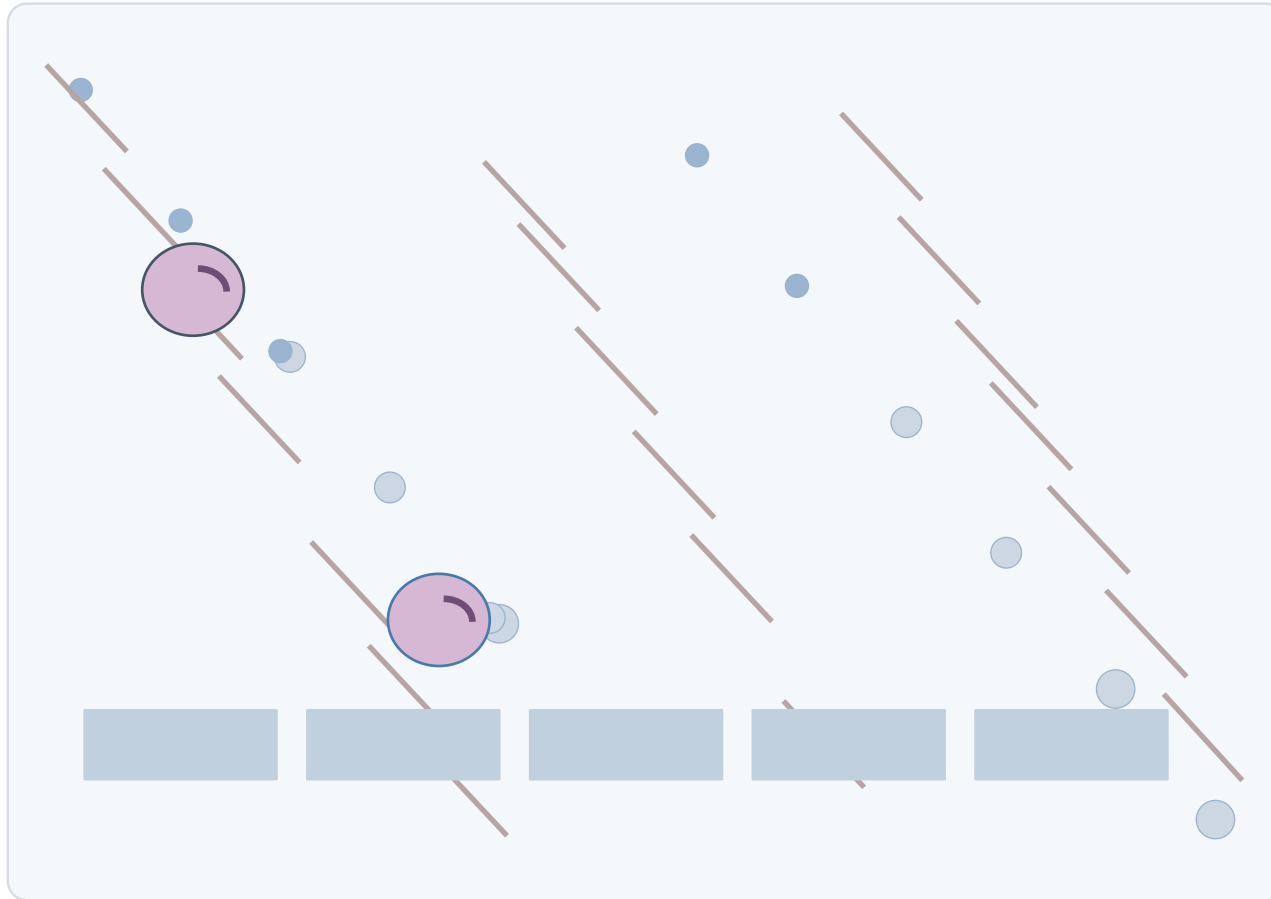
The late marrow is hypocellular and fibrotic

- With progression, hematopoietic elements are progressively depleted.
- Diffuse fibrosis replaces spaces previously occupied by blood-forming cells.
- Marrow failure results from both architectural loss and ineffective output.

Intrasinusoidal hematopoiesis signals distortion

- Hematopoietic cells can be found inside dilated marrow sinusoids.
- This is a manifestation of severely disrupted marrow architecture.
- It should be interpreted with megakaryocyte atypia and fibrosis.

Osteosclerosis in very late disease



Schematic marrow compartment

- The fibrotic marrow compartment may be replaced by bone.
- The change is termed osteosclerosis.
- It represents extreme marrow remodeling, not an early prerequisite.

Biopsy: Cellular features versus stromal features

Hematopoietic compartment

- Atypical megakaryocytes with unusual nuclei.
- Abnormal clustering and variable maturation patterns.
- Residual hematopoietic cellularity changes over time.

Stromal compartment

- Reticulin / collagen deposition.
- Distortion of vascular and marrow architecture.
- Potential late osteosclerosis.

Fibrosis is not pathognomonic for PMF

- Marrow fibrosis can accompany other myeloproliferative neoplasms.
- Granulomatous disorders and metastatic tumors may distort marrow.
- Diagnostic interpretation requires integration with history and clonality.

Organ distribution of extramedullary hematopoiesis

Spleen

Major extramedullary site;
Often markedly enlarged.

Liver

Often moderately enlarged
with sinusoidal
hematopoiesis.

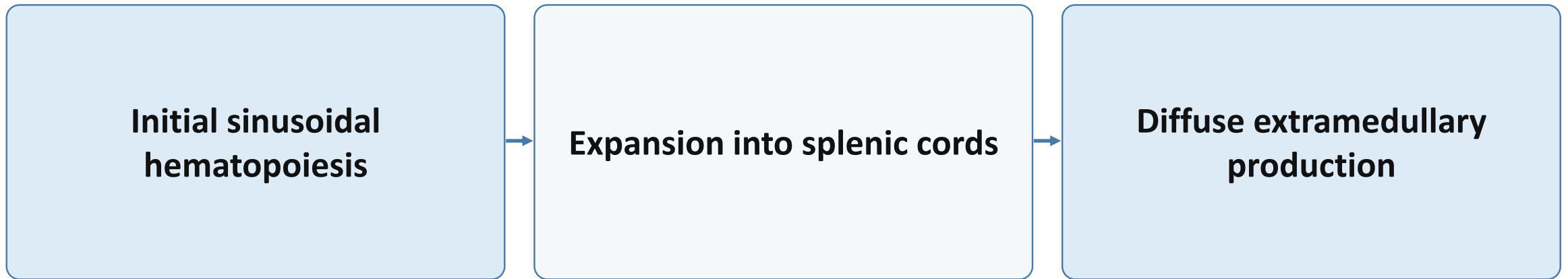
Lymph nodes

Foci may be present;
Substantial adenopathy is
uncommon.

Spleen: Striking gross enlargement

- The spleen is usually markedly enlarged in established PMF.
- Very large spleens, sometimes approaching 4000 g.
- Cut surfaces may appear firm and diffusely red to gray.

Splenic microscopic evolution



Progression changes the organization of red-pulp hematopoiesis.

Splenic infarction is a complication

- Subcapsular splenic infarcts are described in advanced disease.
- A very enlarged spleen may have compromised regional perfusion.
- A new focal pain syndrome warrants consideration of infarction.

Liver involvement is often more modest

- The liver may enlarge because of extramedullary hematopoietic foci.
- Sinusoidal localization is emphasized in the Robbins description.
- Hepatic enlargement is usually less prominent than splenomegaly.

Lymph nodes can harbor hematopoiesis

- Hematopoietic cells may seed lymph-node compartments.
- Clinically important lymphadenopathy is uncommon in PMF.
- Marked adenopathy should prompt evaluation for other explanations.

Origin of the leukoerythroblastic blood picture



Leukoerythroblastosis is a response to disordered hematopoietic architecture.

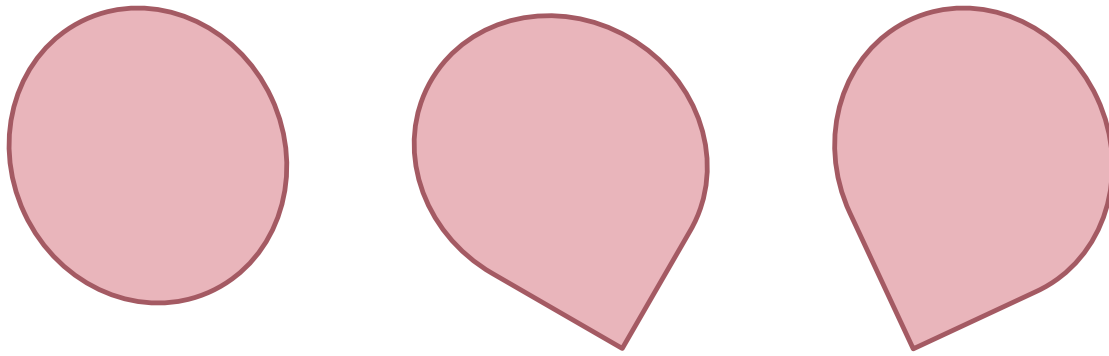
Nucleated erythroid cells in peripheral blood

- Nucleated red-cell precursors normally mature within hematopoietic tissue.
- In PMF, immature erythroid cells can appear in peripheral blood.
- Their presence contributes to the leukoerythroblastic picture.

Granulocytic left shift

- Immature myeloid precursors escape into the circulation.
- A left shift accompanies circulating nucleated erythroid cells.
- This pairing suggests marrow disruption or extramedullary hematopoiesis.

Dacryocytes: The teardrop-shaped erythrocytes



Schematic — not a blood film

Dacryocytes are associated with mechanical distortion during transit from a fibrotic marrow.

Mechanistic interpretation of dacryocytes

- Robbins suggests these cells may be damaged as they leave distorted marrow spaces.
- The blood film reflects physical as well as biological marrow abnormalities.
- The mechanism is plausible but not a disease-specific molecular signature.

Characteristic does not mean specific

Supports PMF

- Dacryocytes accompanied by leukoerythroblastosis.
- Anemia and substantial splenomegaly.
- Atypical megakaryocytes in fibrotic marrow.

Can occur elsewhere

- Other infiltrative marrow disorders.
- Granulomatous disease affecting the marrow.
- Metastatic tumor with marrow distortion.

Additional peripheral blood clues

- Platelets may be unusually large.
- Basophilia may be observed.
- These findings are supportive but not specific for PMF.

How counts change with disease stage

Hemoglobin

Progressive normocytic,
normochromic anemia.

Leukocytes

May be elevated early, then
normal or reduced.

Platelets

Often normal or increased at
diagnosis; May decline later.

Anemia: Predominant clinical laboratory problem

- Moderate to severe normochromic, normocytic anemia is typical.
- Loss of normal marrow erythropoiesis is a major mechanism.
- Disordered extramedullary red-cell production further limits compensation.

White cell counts are variable

- The total leukocyte count is often normal or mildly reduced.
- Marked leukocytosis may occur early in the course.
- Absolute counts alone cannot establish or exclude PMF.

Platelet counts change during progression

- Early thrombocytosis is compatible with a proliferative phase.
- At presentation, platelets may be normal or elevated.
- Late thrombocytopenia can develop as marrow failure progresses.

Early versus advanced clinical phenotype

Finding	Earlier / proliferative	More advanced / fibrotic
Marrow	Increased cellularity	Obliterative fibrosis
Blood counts	Leukocytosis, thrombocytosis possible	Anemia ± thrombocytopenia
Spleen	Variable expansion	Often markedly enlarged
Architecture	Atypical megakaryocytes	Fibrosis ± osteosclerosis

Typical presentation

- PMF usually comes to attention in older adults, often after age 60.
- Anemia develops gradually and may dominate the presenting symptoms.
- Splenomegaly is another principal clinical trigger for investigation.

Fatigue: A clinicopathologic correlation

- Reduced effective red-cell production causes impaired oxygen delivery.
- Patients may report exercise intolerance and decreased functional capacity.
- Constitutional inflammation and increased metabolic activity may contribute.

Splenomegaly and left upper quadrant fullness

- Substantial extramedullary hematopoiesis expands splenic tissue.
- Large splenic size produces fullness and abdominal discomfort.
- Infarction may add a focal acute pain component.

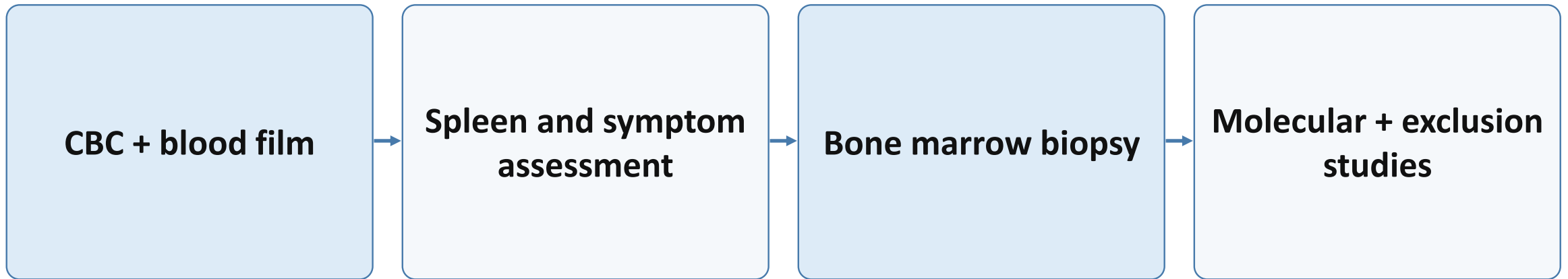
Constitutional symptoms

- Weight loss and night sweats may develop.
- The increasing hematopoietic cell mass is associated with altered metabolism.
- Symptoms are clinically important but nonspecific.

Hyperuricemia from cellular turnover

- A high rate of cell turnover may increase uric acid production.
- Secondary gout can complicate the clinical course.
- Biochemical consequences reflect proliferative activity despite anemia.

Initial investigation: An integrated pathway



No isolated smear or mutation result is sufficient for classification.

Why bone marrow biopsy is essential

- Peripheral blood abnormalities are not pathognomonic.
- Megakaryocyte morphology, distribution and fibrosis require tissue evaluation.
- A biopsy integrates cellular and stromal findings for diagnostic classification.

Two morphologic stages in WHO-5 / ICC

Prefibrotic PMF

- Megakaryocyte proliferation and atypia.
- Increased marrow cellularity / granulopoiesis.
- Fibrosis grade 0–1.

Overt fibrotic PMF

- Megakaryocyte proliferation and atypia.
- Reticulin and/or collagen fibrosis.
- Fibrosis grade 2–3.

WHO-5 / ICC: Diagnosis requires more than morphology

- Demonstrate a driver mutation or other credible evidence of clonality.
- Exclude other defined myeloid neoplasms and reactive fibrosis.
- Integrate compatible clinical and laboratory features with the biopsy.

Clinical–morphologic differential among classical MPNs

Feature	PMF	PV	ET
Defining feature	Atypical megakaryocytes; Fibrosis evolves	Increased red-cell mass	Platelet-predominant proliferation
Marrow	Megakaryocyte atypia; Variable fibrosis	Panmyelosis	Increased mature megakaryocytes
Blood pattern	Anemia / leukoerythroblastosis late	Erythrocytosis	Thrombocytosis
Later fibrosis	Intrinsic course	Possible spent phase	Possible spent phase

The critical ET versus early PMF distinction

- Both may carry JAK2, CALR or MPL driver mutations.
- Both can present with thrombocytosis and increased megakaryocytes.
- Megakaryocyte atypia, clustering and clinical context resolve the distinction.

Separate PMF from post-PV / post-ET fibrosis

- End-stage marrow appearances may be indistinguishable.
- Documented antecedent PV or ET changes the disease classification.
- Previous blood counts, treatment history and pathology are valuable.

Rule out CML in the MPN workup

- Chronic myeloid leukemia is a distinct myeloproliferative neoplasm.
- Its defining BCR::ABL1 fusion differentiates it from PMF.
- Molecular exclusion is integral to contemporary PMF classification.

Consider reactive and infiltrative marrow fibrosis

- Metastatic cancer and granulomatous disease can produce marrow distortion.
- Other inflammatory or hematologic disorders may cause reactive reticulin deposition.
- Biopsy morphology and appropriate clonality / exclusion testing matter.

Major disease complications

Marrow failure

Progressive anemia and other
cytopenias.

Thrombosis / bleeding

Events can arise with
qualitative platelet
abnormalities.

Acute leukemia

A minority of cases transform
to AML.

Infection and bleeding risks

- Cytopenias and marrow dysfunction increase vulnerability to infection.
- Bleeding may be related to quantitative and qualitative platelet abnormalities.
- Thrombotic events are another clinically important threat.

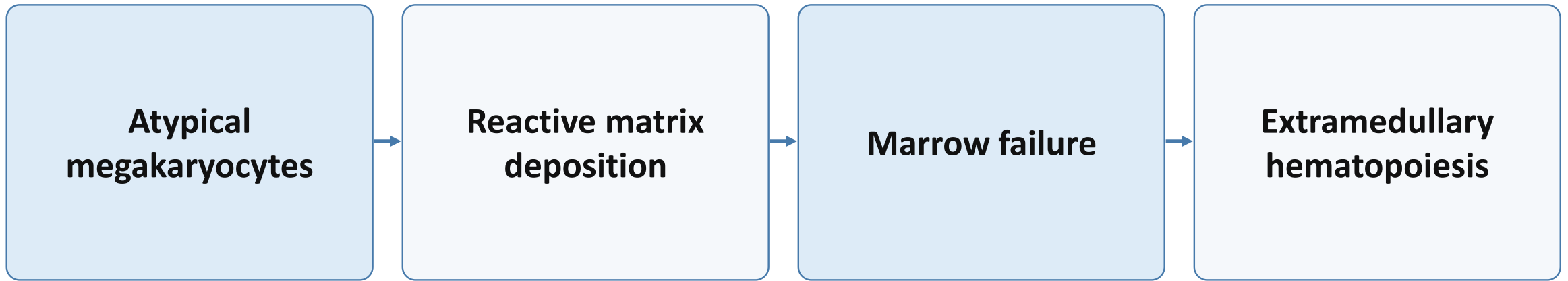
Transformation to acute myeloid leukemia

- PMF has an established risk of transformation to AML.
- Robbins gives a broad transformation frequency of 5%–20%.
- Leukemic evolution must be distinguished from fibrotic progression alone.

Prognosis is variable

- Robbins quotes a median survival range of 3–5 years discussion.
- This broad historical estimate is not an individual prognosis.
- Modern risk assessment must incorporate clinical, blood-count and molecular factors.

Clinical logic: Connecting the main findings



Produces anemia, leukoerythroblastosis and often massive splenomegaly.

Case 1 — progressive anemia and splenomegaly

A 68-year-old develops fatigue and left upper quadrant fullness. Peripheral blood shows anemia, nucleated erythroid cells, granulocytic left shift and dacryocytes.

What marrow abnormality would best connect these findings?

Case 1 — interpretation

- A leukoerythroblastic film indicates disruption of normal marrow output.
- Marrow fibrosis with atypical megakaryocytes would support PMF.
- A biopsy and exclusion of alternative infiltrative disorders are essential.

Case 2 — isolated thrombocytosis?

A patient with persistent thrombocytosis has a hypercellular marrow, dense atypical megakaryocyte clusters and minimal fibrosis. A JAK2 alteration is detected.

Why should essential thrombocythemia not be assumed?

Case 2 — reasoning

- JAK2 positivity does not discriminate ET from prefibrotic PMF.
- Megakaryocyte atypia and clustering are more informative than platelet count alone.
- Apply stage-specific WHO/ICC morphologic and exclusion criteria.

Case 3 — fibrosis with previous PV

An individual with well-documented polycythemia vera develops falling hemoglobin, a very large spleen and marked marrow fibrosis.

What distinction must the diagnosis preserve?

Case 3 — reasoning

- This presentation raises post-PV myelofibrosis rather than de novo PMF.
- Advanced fibrotic histology alone may not distinguish the two.
- Prior diagnostic records are part of the pathologic evidence.

Recognition summary: Connect finding to mechanism

Finding	Mechanistic explanation
Hypercellular early marrow	Increased production by the abnormal hematopoietic clone
Collagen-rich fibrosis	Fibroblastic response to abnormal megakaryocytic signals
Dacryocytes	Distortion during exit from affected marrow
Nucleated RBCs + myeloid precursors	Premature release / extramedullary contribution
Massive splenomegaly	Extensive extramedullary hematopoiesis

Final synthesis

- PMF is a clonal MPN whose fibrosis is largely a secondary stromal reaction.
- Megakaryocyte atypia and clustering are central morphologic clues.
- Marrow fibrosis produces anemia, leukoerythroblastosis and extramedullary hematopoiesis.
- Diagnosis requires biopsy, molecular context and exclusion of mimics.

References and classification context

Source	Use in lecture
Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Ch. 13, pp. 570–571	Core pathogenesis, morphology, presentation, course
Robbins, Ch. 13: PV, ET and Myeloid Neoplasms, pp. 560, 568–570	Differential and MPN parent context
Khoury et al. Leukemia. 2022;36:1703–1719. doi:10.1038/s41375-022-01613-1	WHO fifth-edition classification
Gianelli et al. Virchows Arch. 2023;482:53–68. doi:10.1007/s00428-022-03480-8	International Consensus Classification context