

Essential Thrombocythemia

Molecular pathogenesis · morphology · clinical consequences

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Learning objectives

- Explain how JAK2, MPL and mutant CALR converge on growth factor signaling.
- Recognize marrow and peripheral-blood morphological features of ET.
- Relate neoplastic platelet dysfunction to thrombosis and hemorrhage.
- Distinguish ET conceptually from reactive thrombocytosis, PV and PMF.

ET belongs to the myeloproliferative neoplasms

The essential lesion is autonomous myeloid proliferation

- Myeloproliferative neoplasms (MPNs) are clonal disorders with excessive mature-cell production.
- Acquired signaling changes reduce dependence on hematopoietic growth factors.
- Shared biologic features create clinical and morphological overlap.

Essential thrombocythemia: Working definition

- A clonal MPN characterized predominantly by increased platelet production.
- The key abnormality is dysregulated megakaryocytic proliferation.
- Elevated platelets may coexist with dysfunction and clinical vascular events.
- Unlike PV and PMF, erythrocytosis and overt marrow fibrosis are not defining.

The disease is not simply a high platelet count

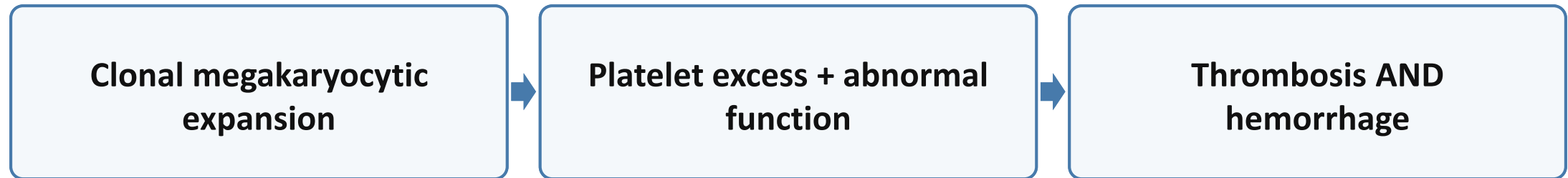
Observed feature

- Elevated peripheral platelet count
- Sometimes mild leukocytosis

Underlying disease

- Clonal progenitor growth
- Abnormal platelet function

One clone, two opposing vascular consequences

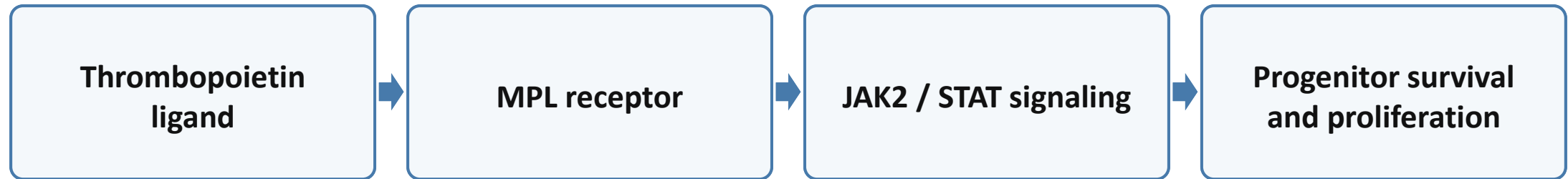


Clinical complications arise from both quantity and quality of platelets.

ET in the MPN differential

Entity	Dominant phenotype	Key differentiator
ET	Megakaryocytic / platelet excess	No defining erythrocytosis or overt fibrosis
Polycythemia vera	Red-cell mass increase with panmyelosis	Erythrocytosis dominates symptoms
Primary myelofibrosis	Obliterative marrow fibrosis	Marrow failure and extensive extramedullary hematopoiesis
Chronic myeloid leukemia	Marked granulocytic proliferation	BCR::ABL fusion

Normal thrombopoietin signaling: A reference



ET driver mutations converge on this normally ligand-controlled axis.

Three recurrent molecular drivers

Alteration	Approximate fraction of ET	Signaling consequence
JAK2 mutation	50–60%	Constitutive JAK2 kinase signaling
CALR mutation	25–35%	Mutant CALR acts as an alternative MPL ligand
MPL mutation	5–10%	Constitutive MPL pathway signaling

Most ET cases harbor one of these drivers

JAK2 · CALR · MPL

- JAK2, CALR or MPL alterations in over 90% of cases.
- These lesions are distinct molecular routes to increased JAK–STAT signaling.
- The absence of an identified driver does not by itself establish a reactive cause.

JAK2: Constitutive kinase activation



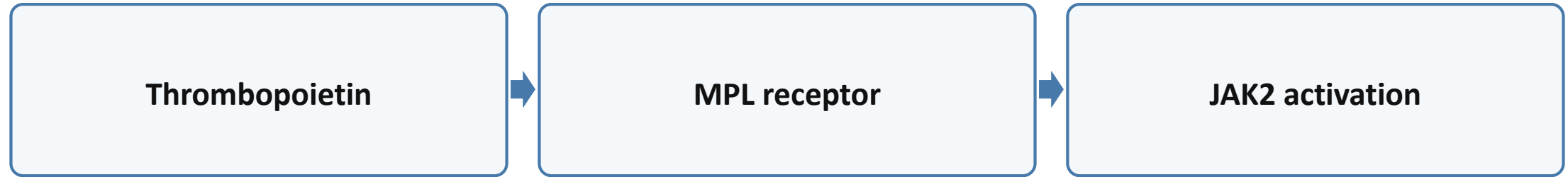
- JAK2 participates downstream of hematopoietic growth-factor receptors.
- A driver alteration bypasses part of normal ligand dependence.
- The consequence is excess production of mature blood elements.

The JAK2 mutation is not ET-specific

A shared mutation does not define the complete phenotype

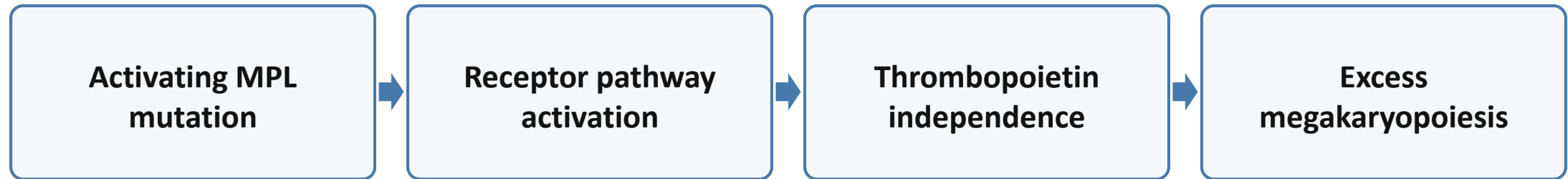
- The same JAK2 mutation is found in nearly all PV cases.
- Some individuals with a JAK2 mutation develop ET; Others develop PV.
- The basis for this phenotypic divergence remains uncertain.

MPL connects thrombopoietin to JAK2



- MPL is the receptor activated by thrombopoietin.
- Its downstream signal is transmitted through JAK2.
- Activating MPL mutations produce inappropriate pathway activity.

Mutant MPL creates ligand-independent signaling

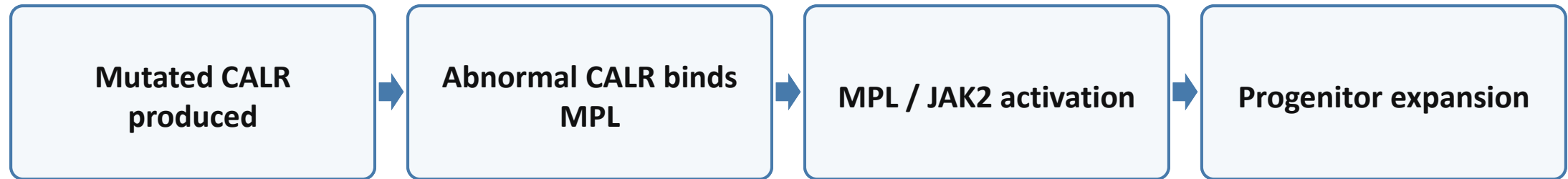


The biological endpoint resembles JAK2-driven ET despite a different molecular starting point.

Mutant CALR supplies an alternative MPL stimulus

- CALR encodes calreticulin; Mutation provides a mechanism distinct from direct kinase activation.
- Mutant CALR is secreted and able to bind the MPL receptor.
- This abnormal interaction activates thrombopoietin-receptor signaling.

Mutant CALR: Oncogenic autocrine feedback

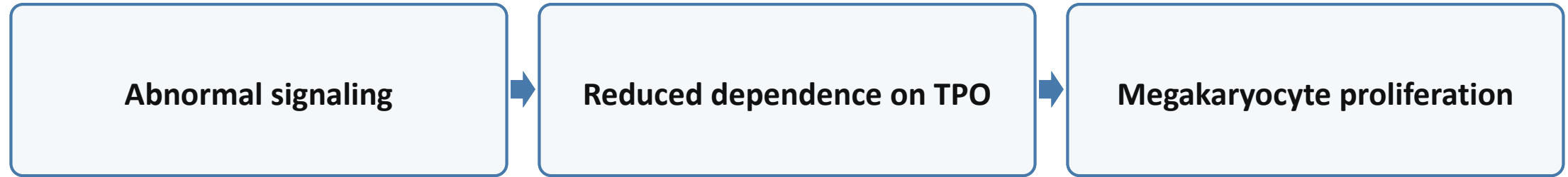


The ligand–receptor interaction as an oncogenic autocrine feedback loop.

Separate mutations converge on one signaling axis

Driver	Direct level of action	Common outcome
JAK2	Intracellular kinase	Increased JAK–STAT pathway activity
MPL	Thrombopoietin receptor	Increased JAK–STAT pathway activity
CALR	Alternative ligand for MPL	Increased JAK–STAT pathway activity

Thrombopoietin independence drives expansion



- Constitutive JAK2 or MPL signaling supports progenitor growth without normal input.
- Maturation is retained, so excess production appears as mature platelets.
- The marrow response underlies the elevated platelet count.

MPN proliferation generally preserves differentiation

Increased production without a primary differentiation block

- MPN signaling lesions with defects that block maturation.
- The major peripheral consequence is an increase in mature blood elements.
- ET particularly emphasizes the megakaryocytic lineage.

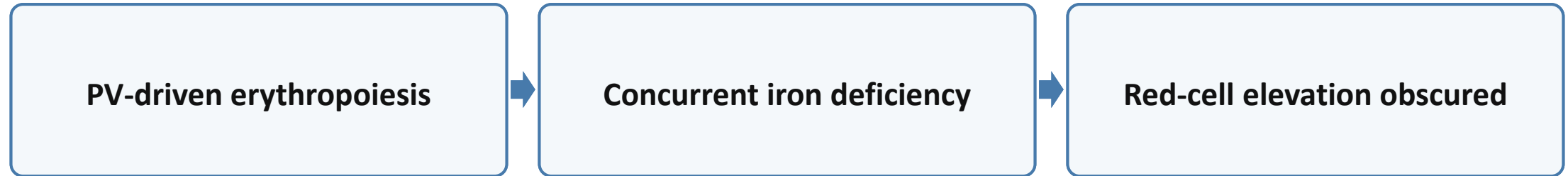
Clone behavior extends beyond the count

- A clonal megakaryocytic population gives rise to functionally abnormal platelets.
- Qualitative abnormalities are found in platelet-function testing.
- The count alone therefore cannot predict an individual's bleeding or thrombotic phenotype.

Interpreting a JAK2-positive thrombocytosis

- JAK2 positivity supports an MPN but cannot separate ET from PV on its own.
- Marrow morphology and red-cell findings must be interpreted together.
- Iron deficiency may complicate phenotypic recognition.

Iron deficiency may disguise polycythemia vera



- A small proportion of apparent ET may represent masked PV.
- Iron restriction can suppress the apparent red-cell phenotype.
- A thrombocytosis evaluation should not ignore the iron-status context.

Why identical drivers yield different MPNs

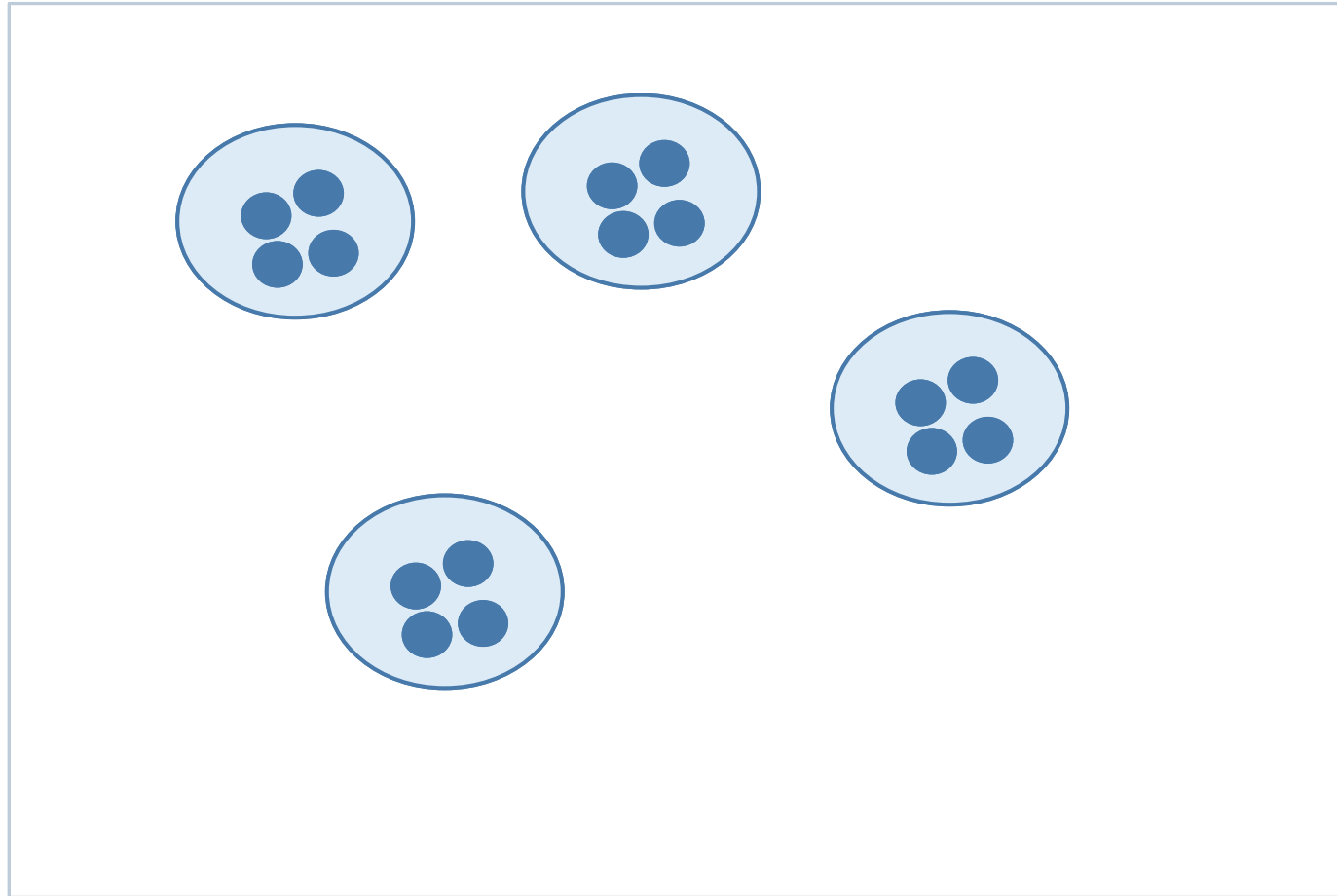
Genotype is informative; Phenotype still requires assessment

- JAK2-mutated ET and JAK2-mutated PV show different predominant cell-lineage outputs.
- Robbins does not establish a definitive mechanistic explanation.
- Avoid assigning a single molecular test a phenotype it cannot resolve.

Bone marrow cellularity is often only mildly elevated

- Total cellularity may be near normal or mildly increased.
- Megakaryocytes are disproportionally expanded relative to this modest change.
- A striking platelet phenotype does not require uniform panmarrow hypercellularity.

Megakaryocytes are markedly increased



Schematic — not a histologic specimen

Marrow interpretation

- Megakaryocytes disproportionately numerous
- Large cellular forms present
- Overall marrow cellularity may rise only mildly

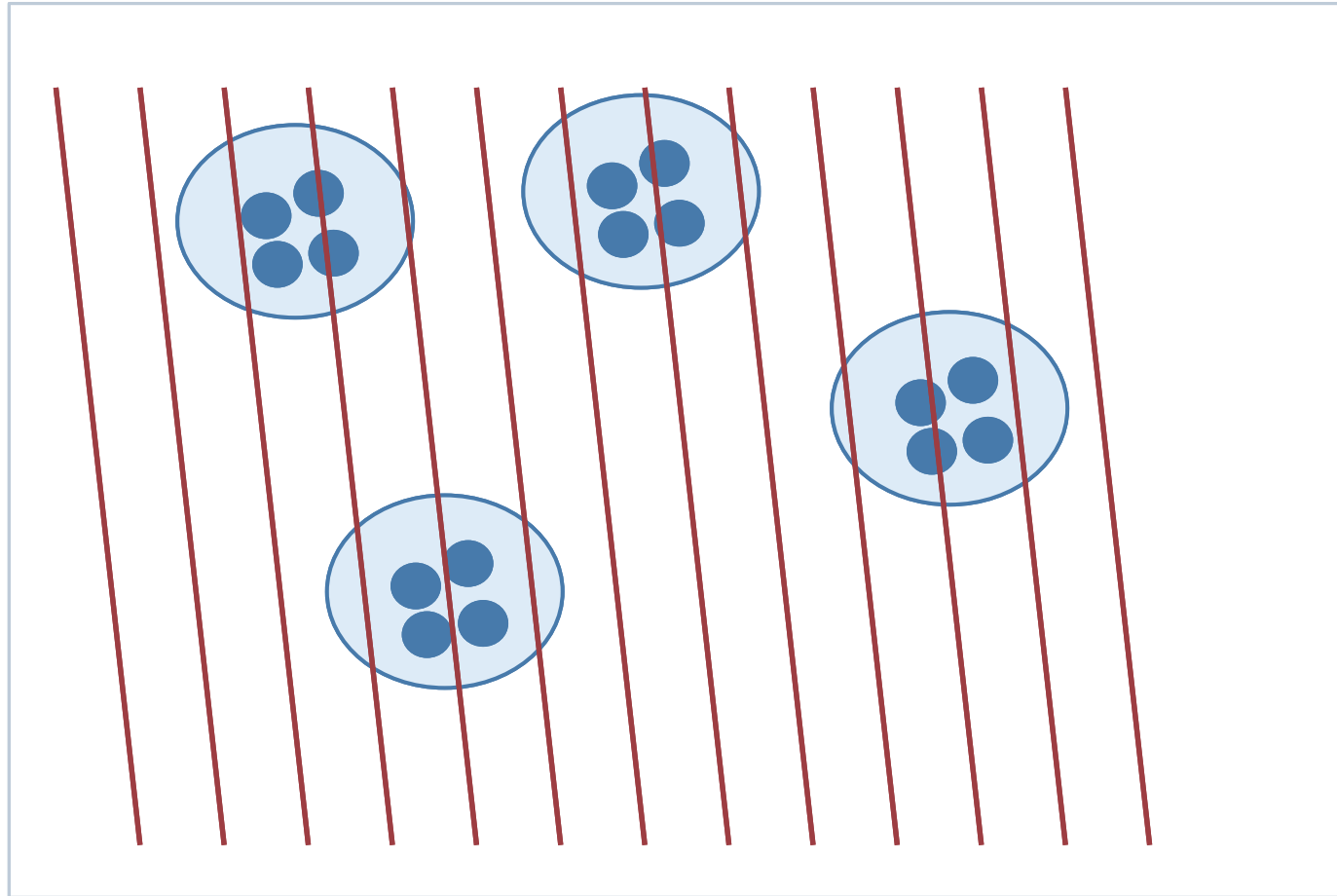
Megakaryocyte size is diagnostically informative

- Marrow megakaryocytes in ET include abnormally large forms.
- The expansion is both quantitative and morphologic.
- Recognition requires marrow assessment; The peripheral count is insufficient.

Reticulin is not equivalent to overt myelofibrosis

- Delicate reticulin fibrils may be seen in ET marrow.
- Overt replacement-type fibrosis characterizes primary myelofibrosis.
- The distinction is qualitative and architectural, not merely the presence of any fiber.

Overt fibrotic marrow suggests a different process



Schematic — not a histologic specimen

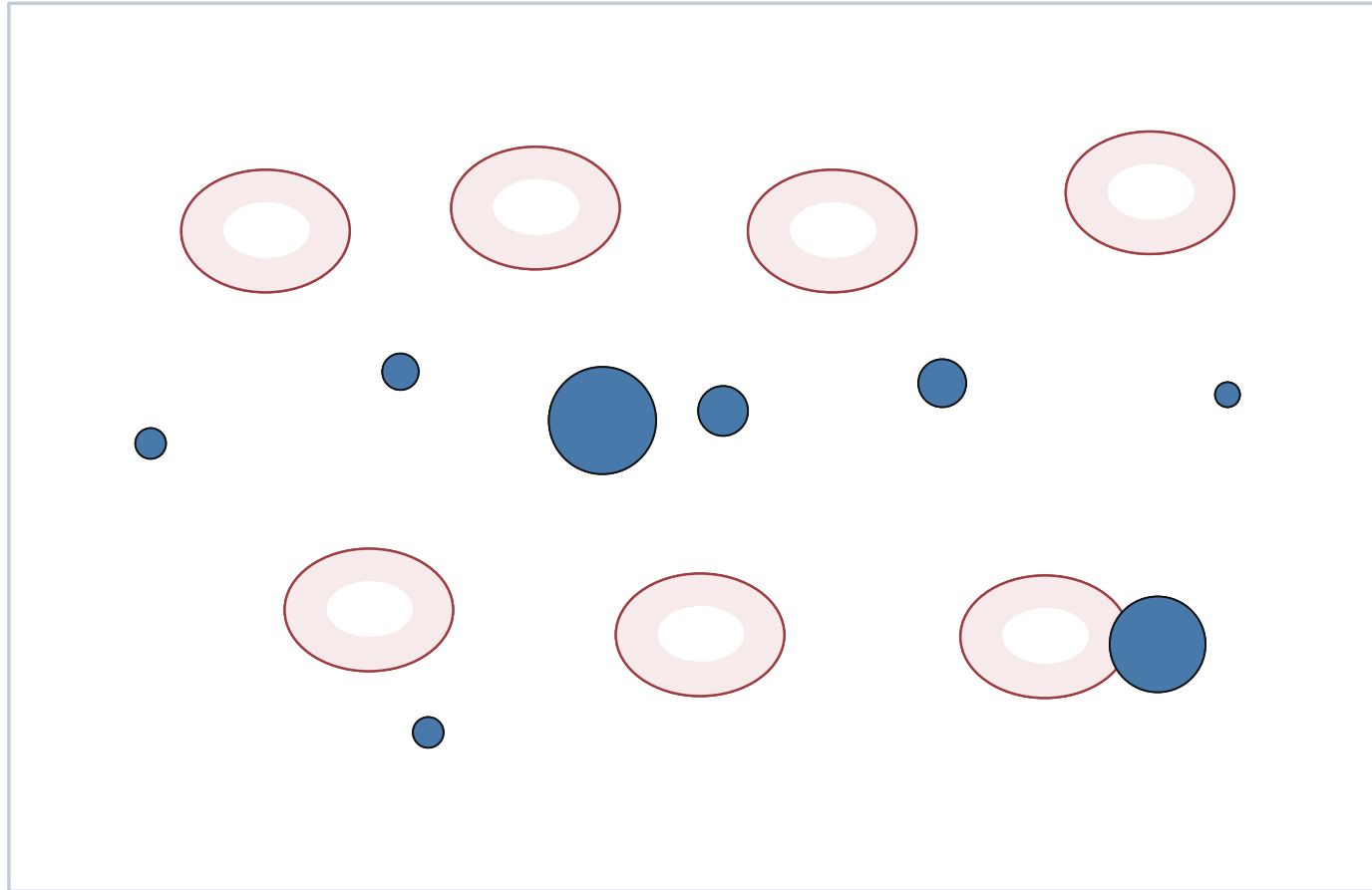
Marrow interpretation

- Dense replacement by fibrous tissue
- Suppression of normal marrow activity
- Contrasts with uncomplicated ET

The peripheral smear may show giant platelets

- Platelets may be abnormally large, even approaching erythrocyte dimensions.
- The textbook figure caption explicitly describes giant platelets in ET.
- Platelet size heterogeneity supports morphologic assessment but is not pathognomonic.

Platelet–erythrocyte scale: A schematic



Peripheral blood

- Increased platelet number
- Platelet size heterogeneity
- Some platelets approach erythrocyte size

Schematic (not a blood film)

Mild leukocytosis may accompany thrombocytosis

- The peripheral smear can show a modestly elevated leukocyte count.
- This is compatible with a myeloproliferative process involving mature lineages.
- The dominant feature remains the platelet / megakaryocytic abnormality.

Marrow and blood offer different evidence

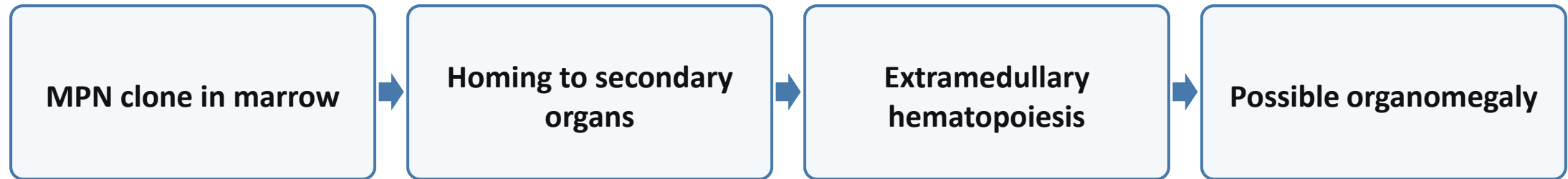
Bone marrow

- Megakaryocyte number and size
- Mild total-cellularity increase
- Reticulin versus overt fibrosis

Peripheral blood

- Elevated platelet count
- Large or giant platelets
- Sometimes mild leukocytosis

Extramedullary hematopoiesis can occur



In ET the extent is usually modest compared with overt primary myelofibrosis.

Mild organomegaly has a pathological basis

- Modest extramedullary hematopoiesis in ET.
- Mild organ enlargement is reported in approximately half of patients.
- Marked organ enlargement with marrow failure should prompt attention to the differential.

ET incidence and age distribution

- An annual U.S. Incidence of 1–3 per 100,000 people.
- Presentation is most common after the age of 60 years.
- Younger adults can also develop ET.

The disease may remain clinically silent

- Long asymptomatic intervals are characteristic.
- Diagnosis may precede any symptomatic vascular event.
- Clinical crises can interrupt an otherwise indolent course.

Platelet excess does not guarantee effective hemostasis

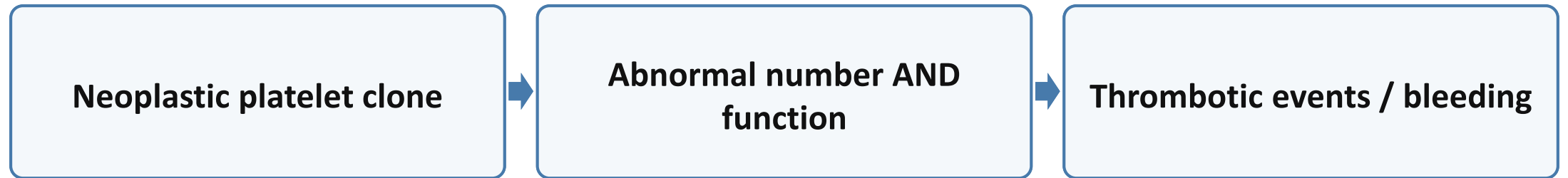
Quantitative excess

- High circulating platelet burden
- Greater opportunity for abnormal platelet interactions

Qualitative dysfunction

- Abnormal platelet-function tests
- Impaired hemostatic performance
- Potential bleeding despite high count

ET has a dual complication phenotype



Neither elevated count nor a single molecular variant replaces clinical assessment.

Thrombosis may involve deep veins

- Deep venous thrombosis is among the described manifestations.
- The abnormal clotting tendency overlaps that seen in polycythemia vera.
- A venous thrombotic presentation may bring previously silent ET to attention.

Portal and hepatic veins are important sites

- Portal and hepatic venous thrombosis.
- These events extend ET beyond ordinary peripheral-vein thrombosis.
- Unusual-site thrombosis should broaden consideration to myeloproliferative disease.

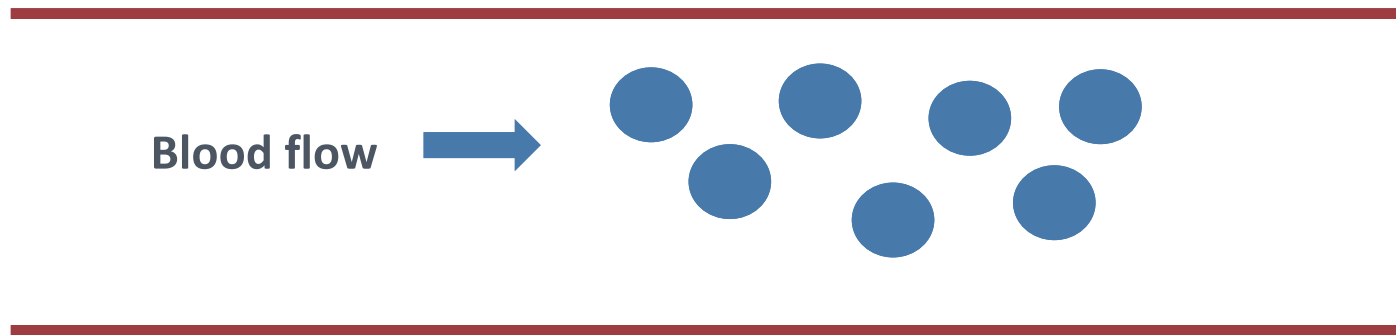
Arterial events include myocardial infarction

- Myocardial infarction among ET thrombotic manifestations.
- Both arterial and venous vascular beds may be involved.
- The clinical spectrum cannot be captured by platelet count alone.

Erythromelalgia is a characteristic symptom

- Patients may experience painful, throbbing burning of hands or feet.
- The symptom is due to small-arteriole occlusion by platelet aggregates.
- It is also recognized in polycythemia vera.

Erythromelalgia: Platelet aggregation in arterioles



Schematic platelet aggregation in a small arteriole

- Small-vessel obstruction
- Burning, throbbing pain of the hands or feet
- Shared manifestation with polycythemia vera

Hemorrhage is not paradoxical once function is considered

- Neoplastic platelets frequently display qualitative defects.
- Bleeding is a major ET manifestation despite thrombocytosis.
- Interpret hemostasis as the interaction of platelet number, function and other factors.

Acquired von Willebrand disease may coexist

- Acquired von Willebrand disease in up to one-third of ET patients.
- It may contribute to the hemorrhagic tendency.
- The excerpt characterizes its etiology as uncertain; Avoid inventing a mechanism here.

The thrombosis–bleeding paradox

Finding	Consequence	Reasoning
Elevated platelet count	Propensity to abnormal clotting	Increased and dysregulated platelet activity
Platelet qualitative abnormalities	Potential hemorrhage	Excess number does not ensure effective function
Acquired von Willebrand disease	Additional bleeding contribution	Reported association; mechanism uncertain in source

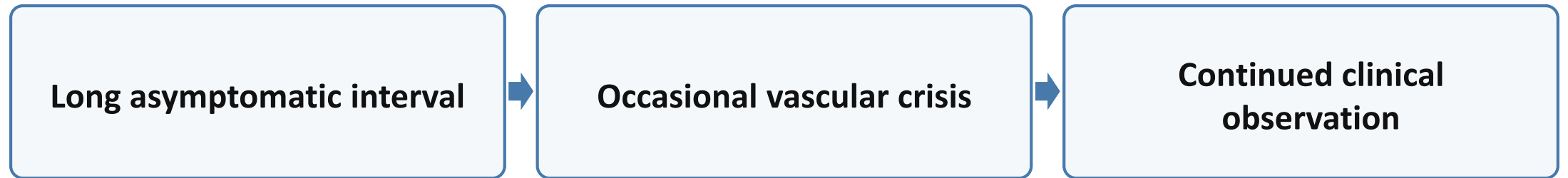
Very high platelet count modifies concern

- Thrombotic complications to very high platelet counts.
- The text also associates thrombotic events with homozygous JAK2 mutations.
- These are textbook associations, not a standalone contemporary risk-scoring scheme.

Bleeding history matters before antiplatelet treatment

- The source qualifies aspirin use to patients without evidence of bleeding.
- This reflects a central ET problem: Simultaneous hemorrhagic and thrombotic risks.
- Management reasoning starts with the actual clinical phenotype.

ET usually follows an indolent course

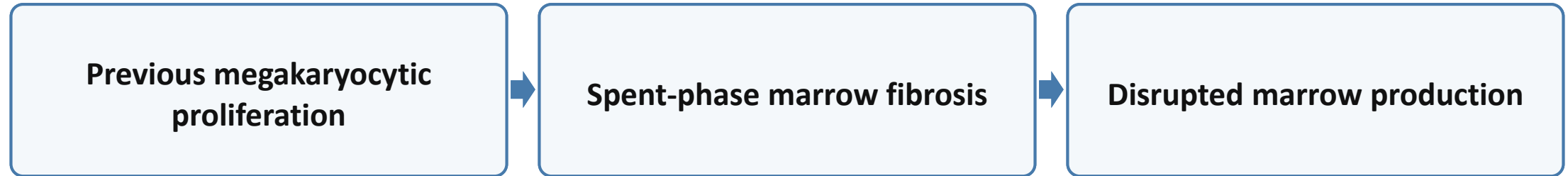


The course is punctuated by thrombosis or bleeding rather than uniform rapid progression.

A minority progress to marrow fibrosis

- An uncommon spent phase with marrow fibrosis.
- Fibrotic progression alters the primary production pattern.
- The evolution connects ET to the broader MPN biology of spent-phase disease.

Fibrotic progression changes hematopoiesis



- MPN fibrosis can accompany peripheral-blood cytopenias.
- Extramedullary hematopoiesis can become more important.
- Uncomplicated ET and advanced fibrotic evolution must not be conflated.

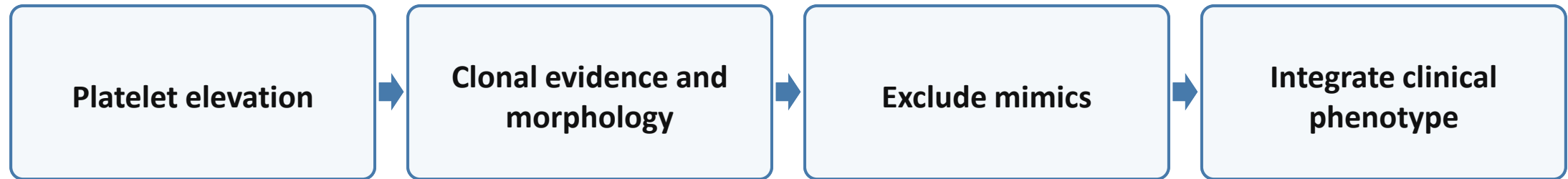
Transformation to acute myeloid leukemia is uncommon

- The Robbins ET section notes rare progression to AML.
- This represents a qualitative change in disease biology and prognosis.
- No ET-specific transformation rate is supplied in the excerpt; None is assumed.

Survival perspective

- Median survival of approximately 12–15 years for ET.
- The statement is a source-era summary, not an individualized survival prediction.
- Heterogeneous complications and evolution prevent a single course for every patient.

Diagnosis requires more than detecting thrombocytosis



This is a Robbins-grounded reasoning schematic, not a reproduction of formal WHO/ICC criteria.

Inflammatory thrombocytosis is a major mimic

- Reactive increases in platelets can occur in inflammatory disorders.
- A high platelet count therefore does not uniquely signal ET.
- Excluding reactive causes in driver-negative evaluations.

Iron deficiency produces two diagnostic pitfalls

Reactive alternative

- Iron deficiency may account for elevated platelets
- A nonclonal explanation must be assessed

Masked PV context

- Iron deficiency may obscure a PV red-cell phenotype
- Avoid labeling every apparent isolated thrombocytosis as ET

Marrow fibrosis is a high-value discriminator

- ET may have delicate reticulin without overt fibrotic replacement.
- Primary myelofibrosis is characterized by oblitative marrow fibrosis.
- The distinction is essential when platelet counts and driver mutations overlap.

ET versus polycythemia vera

Feature	Essential thrombocythemia	Polycythemia vera
Dominant lineage	Platelets / megakaryocytes	Red cells; panmyelosis
JAK2 status	Common, but not universal	Nearly all cases
Morphology	Many large megakaryocytes	Increased erythroid, granulocytic and platelet output
Key pitfall	Mistaking masked PV for ET	Iron deficiency can obscure hematocrit

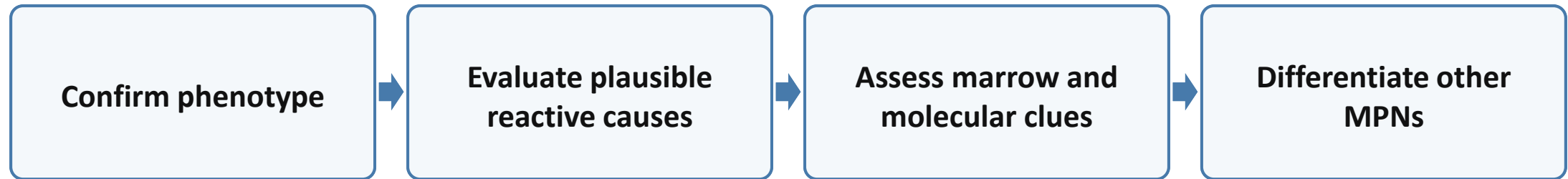
ET versus primary myelofibrosis

Feature	Essential thrombocythemia	Primary myelofibrosis
Typical marrow	Increased large megakaryocytes	Obliterative fibrosis
Fibers	Delicate reticulin may occur	Extensive collagen deposition
Extramedullary hematopoiesis	Usually modest	Often extensive
Clinical direction	Platelet excess / vascular events	Marrow failure, cytopenias

ET versus chronic myeloid leukemia

Feature	Essential thrombocythemia	Chronic myeloid leukemia
Characteristic output	Megakaryocytes / platelets	Maturing granulocytes
Key genetic lesion	JAK2 / CALR / MPL	BCR::ABL fusion
Blood clues	Thrombocytosis, sometimes mild leukocytosis	Marked leukocytosis with immature forms
Diagnostic logic	Integrate clonality and phenotype	Define BCR::ABL status

A coherent diagnostic assessment



Formal numerical diagnostic criteria were not reproduced from the provided source.

Therapy aims to reduce platelet-driven complications

- Mild cytoreductive treatment to suppress thrombopoiesis.
- The rationale is to reduce the neoplastic platelet burden.
- Treatment choice is beyond the excerpt's detailed scope; Drug regimens are not invented.

Aspirin use is qualified by bleeding status

- Low-dose aspirin in patients without evidence of bleeding.
- Antiplatelet therapy addresses the thrombotic side of ET biology.
- The possibility of hemorrhage and acquired von Willebrand disease requires clinical judgment.

Case: Isolated thrombocytosis with iron deficiency

An adult is referred for persistently elevated platelets and evidence of iron deficiency.
No marrow study or driver test is yet available.

What diagnostic assumptions would be premature?

- What non-neoplastic explanation needs consideration?
- Why does iron deficiency also complicate the ET–PV distinction?

Case analysis: Test the phenotype, not a label

- Iron deficiency is a recognized cause of reactive thrombocytosis.
- In a separate scenario, iron deficiency can suppress an otherwise apparent PV erythrocytosis.
- A single elevated platelet result cannot resolve these alternatives.

Case: Thrombocytosis associated with bleeding

A patient with a known clonal MPN has very high platelets but develops mucosal bleeding.

How can bleeding coexist with a high platelet count?

- Consider neoplastic platelet qualitative dysfunction.
- Acquired von Willebrand disease is a reported ET association.
- The case illustrates why the count alone cannot justify an aspirin decision.

Case: Burning pain in the fingers and toes

A patient with thrombocytosis reports repeated episodes of throbbing, burning pain in the distal extremities.

What clinical manifestation links the symptom to platelet behavior?

- Identify erythromelalgia as the characteristic symptom.
- Explain its proposed mechanism: Platelet aggregates in small arterioles.
- Recognize that a similar manifestation can occur in PV.

Integrative reasoning: Four diagnostic questions

- Is thrombocytosis persistent and clinically consequential?
- Is there evidence of an MPN-associated driver or clonal megakaryocytic morphology?
- Could inflammation or iron deficiency explain the platelet increase?
- Are features of PV, PMF or CML more compelling?

Essential thrombocythemia: Five propositions

- JAK2, CALR and MPL lesions converge on excessive signaling.
- Marrow megakaryocytes increase; Large forms and giant platelets are characteristic.
- Reticulin may be delicate, but overt primary fibrotic disease is different.
- Thrombosis and bleeding both arise in the setting of neoplastic platelets.
- Molecular, morphologic and clinical context prevents diagnostic oversimplification.

Source references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 13: Myeloproliferative Neoplasms and Essential Thrombocythemia.
- Adjacent Robbins sections: Chronic Myeloid Leukemia, Polycythemia Vera, and Primary Myelofibrosis.
- Mechanistic and morphologic schematics in this lecture are original editable teaching diagrams, not patient specimens.
- Formal WHO/ICC diagnostic thresholds and therapeutic algorithms were not added because they are not present in the supplied excerpt.