

Other Forms of Marrow Failure

Mechanisms, morphology and clinicopathologic interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

Distinguish marrow replacement from diminished erythropoietin signaling.

Explain leukoerythroblastosis and teardrop erythrocytes mechanistically.

Relate renal, hepatic and endocrine disease to characteristic anemia patterns.

Use cause-specific clues to interpret complex underproduction anemia.

The lesion may involve marrow architecture, systemic support, or several mechanisms simultaneously.

Four routes to inadequate erythropoiesis

Marrow replacement

**Renal erythropoietin
loss**

Hepatocellular disease

Endocrine dysfunction

Distinct causal categories — not sequential stages

Different initiating lesions converge on diminished circulating red cells.

Only marrow replacement intrinsically requires space-occupying lesions.

Schematic

Locate the dominant disturbance

Condition	Principal disturbance	Additional contribution
Myelophthisic anemia	Marrow space + architecture lost	Disordered cellular release
Chronic renal failure	Inadequate erythropoietin	Reduced RBC survival; bleeding
Hepatocellular disease	Impaired marrow function	Folate / iron deficits; membrane lipid change
Endocrine disease	Underproduction association	Often mild, normal RBC size and color

Underproduction does not imply one mechanism

Stem-cell loss, restricted erythroid production and marrow displacement differ biologically.

Systemic disease can reduce erythropoiesis without a primary marrow infiltrate.

RBC survival, bleeding and nutritional deficiency may coexist with underproduction.

Do not infer the cause of low red-cell counts from “marrow failure” alone.

Myelophthisic anemia: Defining lesion

Space-occupying processes replace normal marrow hematopoietic elements.

Replacement distorts the remaining hematopoietic environment.

Fibrosis and abnormal marrow egress help explain the blood-film phenotype.

The defining mechanism is structural displacement, not simply reduced erythropoietin.

Malignancies associated with marrow replacement

Source	Pathologic role	Interpretive point
Breast carcinoma	Metastatic infiltration of marrow	A common metastatic primary
Lung carcinoma	Metastatic infiltration of marrow	Consider an epithelial malignancy
Prostate carcinoma	Metastatic infiltration of marrow	May replace hematopoietic space

Marrow infiltration need not be malignant

Metastatic cancer

Most common myelophthisic cause

Often carcinomas of breast, lung or prostate

Infiltrating cells displace native hematopoiesis

Granulomatous disease

Non-neoplastic space-occupying process

Can distort marrow like a malignancy

Can produce the same downstream blood changes

A leukoerythroblastic pattern does not identify the precise infiltrating disease.

Myeloproliferative neoplasms can end in marrow failure

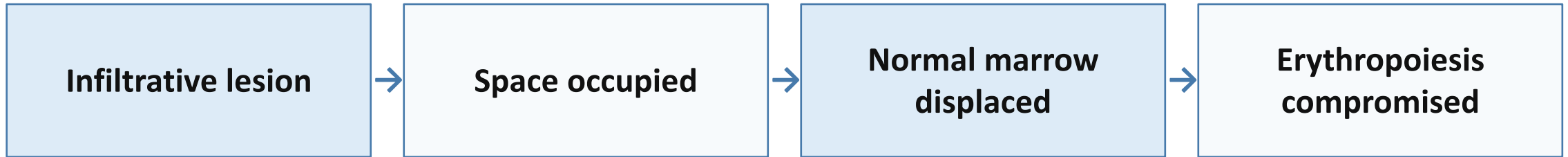
The “spent phase” of a myeloproliferative neoplasm may produce myelophthisic anemia.

Progressive marrow fibrosis progressively displaces hematopoietic elements.

A late fibrotic state can resemble other causes of architectural replacement.

Consider a clonal marrow disorder even when no metastatic carcinoma is present.

How infiltrative lesions produce anemia



Fibrosis can amplify the structural disturbance.

Both production capacity and marrow-to-blood release may be affected.

Schematic

Two consequences of architectural distortion

Hematopoietic capacity

Normal marrow elements are displaced

Available space for red-cell production falls

Anemia reflects reduced effective output

Cellular traffic

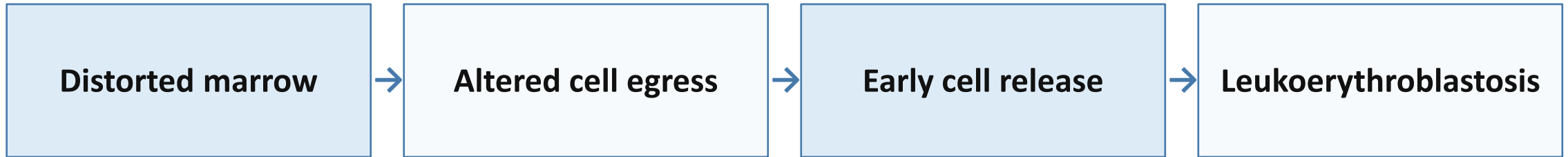
Normal cellular egress is disturbed

Immature erythroid and myeloid forms escape

Abnormal red-cell shapes may appear

The blood film can provide evidence of marrow disturbance, not only RBC deficit.

Fibrosis disrupts the marrow–blood interface



Fibrosis accompanies several myelophthisic processes.

The mechanism links a tissue-level lesion to a recognizable circulating-cell pattern.

Schematic

Leukoerythroblastosis: A paired blood finding

Nucleated erythroid precursors circulate before normal maturation.

Immature granulocytic forms also enter the peripheral blood.

The coexistence of these populations signals disturbed marrow release.

The two immature cell lines together are more informative than anemia alone.

Why nucleated erythroid cells appear

Normally organized marrow

Erythroid precursors mature within marrow compartments

Cell-release mechanisms preserve appropriate timing

Architecturally distorted marrow

Normal egress control is disturbed

Nucleated erythroid precursors enter circulation prematurely

Circulating nucleated erythroid cells are a consequence of altered release in this context.

Why immature granulocytes appear

Normal marrow organization

Granulocytic maturation occurs before usual release

The marrow provides a regulated exit environment

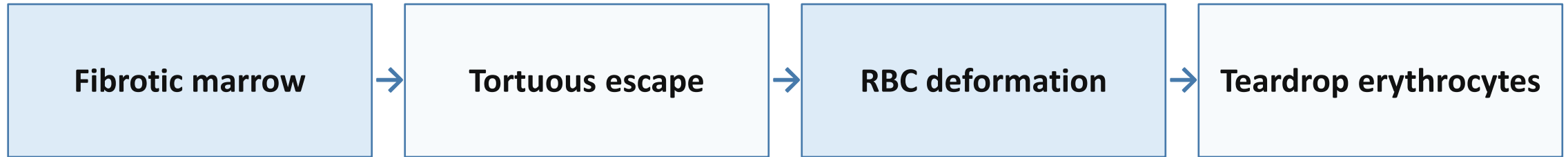
Myelophthisic marrow

Infiltration and fibrosis disturb release

Immature granulocytic forms enter the blood

The same disordered architectural environment affects more than erythroid cells.

Teardrop cells: Proposed deformation pathway



Mechanical deformation during tortuous escape is the proposed explanation.

This finding is compatible with marrow distortion, but not specific to one cause.

Schematic

Read the myelophthisic blood pattern as a whole

Finding	Direct observation	Interpretation
Anemia	Reduced circulating RBC compartment	Inadequate effective red-cell production
Nucleated erythroid cells	Early erythroid forms in blood	Disordered release
Immature granulocytes	Early myeloid forms in blood	Disordered release
Teardrop RBCs	Altered red-cell contours	Compatible with fibrotic distortion

Conceptual map: Cells escaping a fibrotic marrow

MARROW: Distorted release

Nucleated erythroid precursors

Immature granulocytic forms

Teardrop erythrocytes



PERIPHERAL BLOOD: Findings

Nucleated erythroid precursors

Immature granulocytic forms

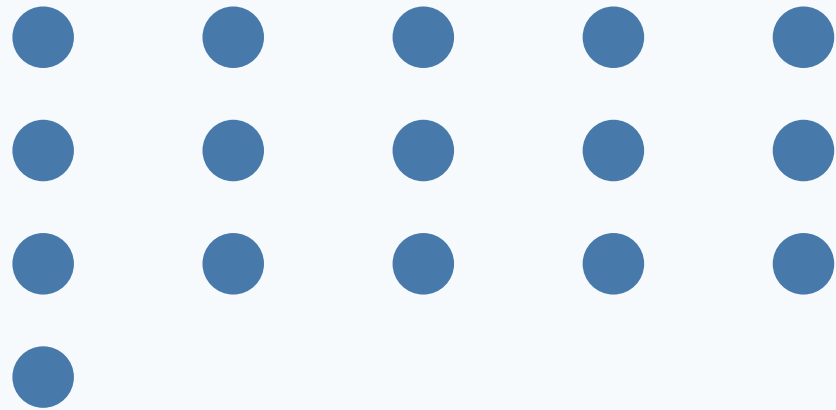
Teardrop erythrocytes



Schematic correspondence, not a blood-film image or a diagnostic cell drawing.

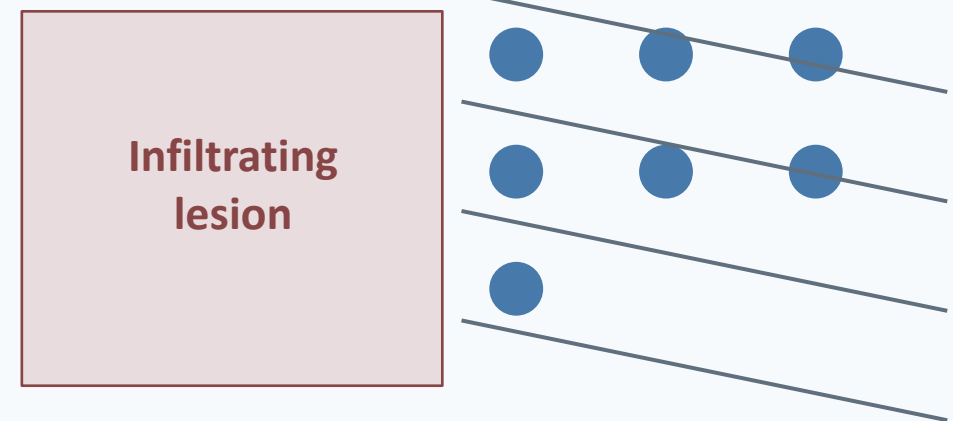
Conceptual architecture: Preserved versus replaced marrow

Preserved hematopoietic space



Schematic

Space-occupying / fibrotic marrow



Schematic

Replacement and fibrosis reduce space and disturb regulated escape of immature cells.

Architectural replacement is not classic aplasia

Myelophthistic process

Infiltration or fibrosis displaces marrow

Distorted cellular egress is characteristic

Leukoerythroblastic blood picture may occur

Aplastic anemia

Markedly hypocellular marrow with fat predominance

Stem-cell/progenitor failure is central

Reticulocytopenia and pancytopenia characterize disease

Both impair blood-cell production, but the underlying marrow lesion differs.

Compare myelophthisis with pure red cell aplasia

Myelophthisic anemia

Space-occupying marrow disturbance

Immature erythroid and granulocytic cells may circulate

Broader architectural problem

Pure red cell aplasia

Selective suppression of erythroid progenitors

Severe cases show absent erythroid precursors

Other marrow lineages not intrinsically targeted

The lineage selectivity and marrow architecture help localize the lesion.

What a suggestive smear can and cannot establish

Leukoerythroblastosis with teardrop forms supports marrow distortion.

Metastatic cancer, granulomatous infiltration and fibrotic myeloid disease remain possibilities.

The circulating pattern alone does not specify the underlying lesion.

Distinguish a mechanistic clue from a definitive etiologic diagnosis.

Case: Anemia in a patient with carcinoma

A patient with a known solid-organ carcinoma develops anemia. The blood film contains nucleated erythroid precursors, immature granulocytic cells and teardrop erythrocytes.

Clinical information

Anemia in the setting of carcinoma

Leukoerythroblastic pattern

Teardrop-shaped erythrocytes

Which marrow process best unifies these findings?

Case interpretation: Metastatic myelophthisis

The pattern is most consistent with architectural marrow distortion.

Metastatic carcinoma can occupy marrow space.

Secondary fibrosis and distorted egress permit premature cell release.

Teardrop erythrocytes support a fibrotic/distorted environment.

Myelophthisic anemia is the mechanistic diagnosis; The underlying lesion still requires confirmation.

Case: Same smear, no known carcinoma

An anemic patient without a recognized malignancy has nucleated erythroid cells, immature granulocytes and teardrop red cells.

Clinical information

No established metastatic neoplasm

Marrow-distortion phenotype

Alternative infiltrative processes are plausible

What competing causal categories should remain open?

Case interpretation: An etiologic differential

Do not equate a myelophthisic smear with metastatic cancer.

Metastatic carcinoma is common but not exclusive.

Granulomatous marrow involvement can produce identical downstream findings.

Advanced fibrotic myeloproliferative disease is another mechanism.

The smear identifies an architectural disturbance; Its cause must be established.

Chronic renal failure: Anemia is expected

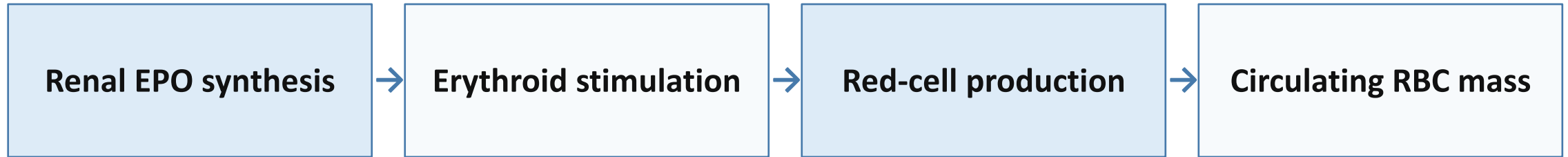
Anemia accompanies chronic renal failure across etiologies.

Severity tends to track the degree of uremia approximately.

Impaired erythropoietin synthesis is the dominant mechanistic driver.

Renal anemia is primarily failure of systemic erythroid support.

Kidney-to-marrow erythropoietin axis

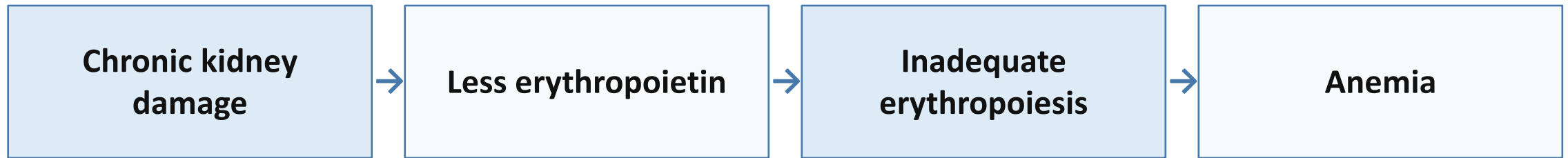


Damage to the kidney weakens this stimulatory axis.

Erythropoietin acts on committed erythroid progenitors in marrow.

Schematic

The main lesion in renal anemia



This remains the dominant mechanism across causes of chronic renal failure.

Reduced production is distinct from physical replacement of marrow.

Renal impairment and anemia severity

More pronounced uremia is generally associated with more severe anemia.

The relationship is approximate, not a diagnostic conversion formula.

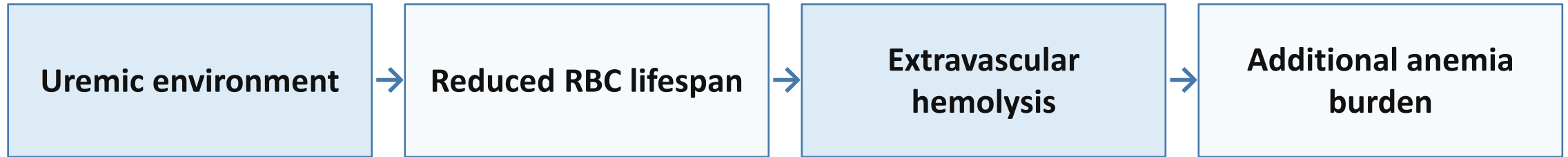
Other contributions can change the observed severity in an individual.

Avoid treating renal function alone as a complete explanation of the hemoglobin level.

Renal anemia is multifactorial

Component	Mechanistic change	Consequence
Dominant	Reduced renal erythropoietin synthesis	Insufficient red-cell production
Additional	Uremia shortens RBC lifespan	More rapid red-cell loss
Additional	Uremic platelet dysfunction	Bleeding can exacerbate anemia
Downstream	Blood loss and iron depletion	Reduced available iron for erythropoiesis

Uremia can shorten red-cell survival

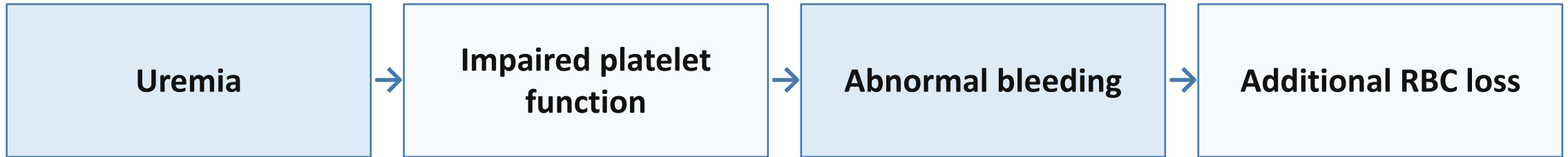


The detailed mechanism of shortened survival remains uncertain.

The effect compounds the inadequate red-cell production caused by low EPO.

Schematic

Uremic platelet dysfunction exacerbates anemia

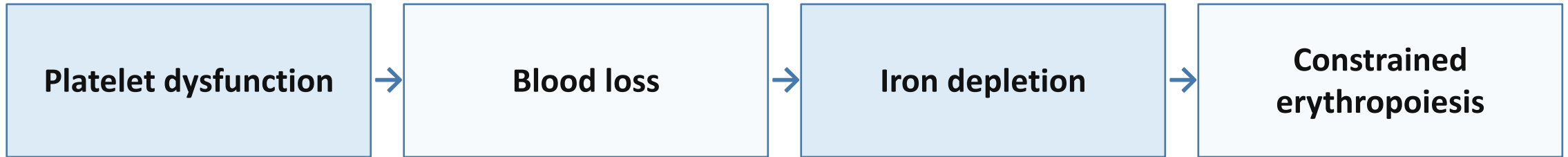


The source does not specify a single molecular cause of platelet dysfunction.

Bleeding provides a route from renal disease to further anemia.

Schematic

Bleeding can secondarily restrict iron supply



Iron deficiency can emerge as a downstream effect of chronic bleeding.

A correct explanation of renal anemia may therefore require more than EPO loss.

Renal anemia: Converging mechanisms

Deficient production

Kidney injury



↓ Erythropoietin



↓ Erythropoiesis

Shortened survival

Uremic milieu



↓ RBC lifespan



Extravascular hemolysis

Loss + iron restriction

Platelet dysfunction



Bleeding



Iron depletion

The dominant EPO pathway coexists with renal anemia modifiers.

Separate low production from excess loss

Insufficient erythropoiesis

Damaged kidney synthesizes less erythropoietin

Erythroid progenitors receive inadequate support

Central mechanism

Additional red-cell deficit

Shorter circulating RBC survival

Uremic bleeding may occur

Possible subsequent iron deficiency

These components are complementary rather than mutually exclusive.

Why recombinant erythropoietin helps

The missing kidney-derived growth signal is replaced pharmacologically.

Erythroid progenitors can receive renewed stimulatory input.

Recombinant erythropoietin can substantially improve renal anemia.

Treatment response is mechanistically consistent with erythropoietin deficiency.

Why iron replacement also matters

Bleeding-associated iron deficiency may coexist with low erythropoietin.

Erythroid output requires an adequate substrate for hemoglobin synthesis.

Iron replacement can improve renal anemia when iron supply is insufficient.

Restoring a growth signal does not remove a concurrent iron deficit.

Match an intervention to a causal defect

Observed pathway	Rationale	Mechanistic approach
Inadequate erythropoietin	Restore erythroid stimulus	Recombinant erythropoietin
Iron depletion from bleeding	Restore substrate for Hb synthesis	Iron replacement
Shortened RBC lifespan	Additional loss persists	Recognize as contributor
Uremic platelet dysfunction	Bleeding can continue	Recognize as contributor

Marrow replacement versus renal underproduction

Myelophthisic anemia

Primary lesion occupies/distorts marrow

Leukoerythroblastosis and teardrops can appear

Egress architecture altered

Renal anemia

Primary lesion reduces EPO production

Shorter RBC lifespan and bleeding add to deficit

Marrow infiltration not required

Similar anemia may arise from very different anatomic and physiologic lesions.

Case: Anemia with progressive uremia

A patient with chronic renal insufficiency develops worsening anemia and intermittent abnormal bleeding. There is no evidence supplied for an infiltrative marrow lesion.

Clinical information

Chronic kidney failure

Worsening uremia

Bleeding may be contributing

Which mechanism is dominant, and which additional pathway matters?

Case interpretation: More than one renal mechanism

Start with inadequate erythropoietin production.

Renal damage suppresses the principal erythroid stimulus.

Uremia may shorten RBC survival.

Platelet dysfunction, bleeding and possible iron loss can compound the anemia.

Dominant EPO deficiency and secondary contributors should both appear in the explanation.

Hepatocellular disease: Diverse causes, common anemia

Toxic, infectious and cirrhotic liver disease can be associated with anemia.

Reduced marrow function is a principal component of hepatic anemia.

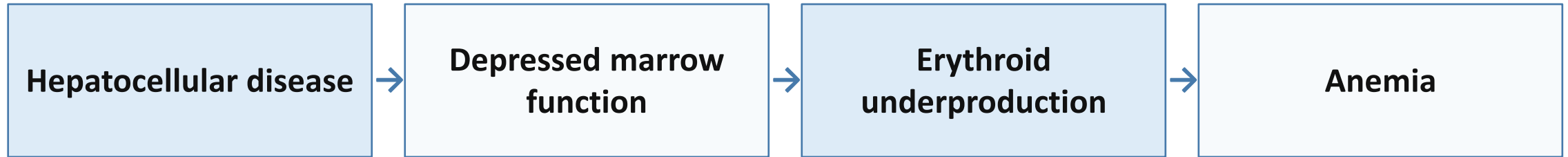
Nutritional deficits, blood loss and altered RBC membranes may coexist.

A hepatic anemia often combines production and peripheral red-cell abnormalities.

Different liver insults converge on anemia

Hepatic context	Shared consequence	Exacerbating mechanisms
Toxic hepatocellular disease	Depressed marrow function	Nutritional / bleeding factors
Infectious hepatocellular disease	Depressed marrow function	Nutritional / bleeding factors
Cirrhotic hepatocellular disease	Depressed marrow function	Nutritional / bleeding factors

Hepatocellular injury and erythroid output



No single universal molecular mechanism explains the association.

Concurrent iron and folate deficiencies can exacerbate the result.

Schematic

Lineage involvement in hepatic marrow suppression

Erythroid lineage

Preferentially affected

Anemia is the characteristic hematologic outcome

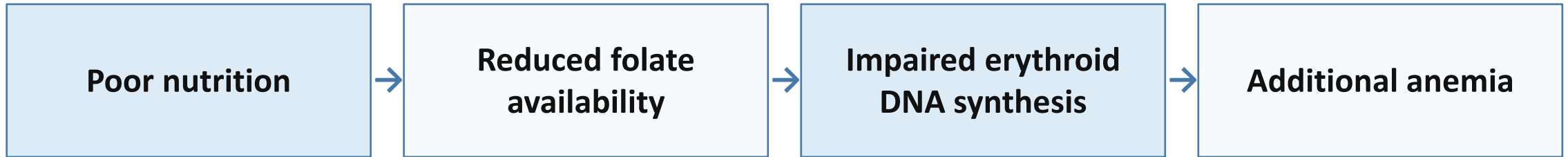
Leukocytes and platelets

Counts can also be depressed

These changes occur less often than the erythroid effect

Do not assume a uniform degree of pancytopenia in hepatic disease.

Folate deficiency can intensify hepatic anemia

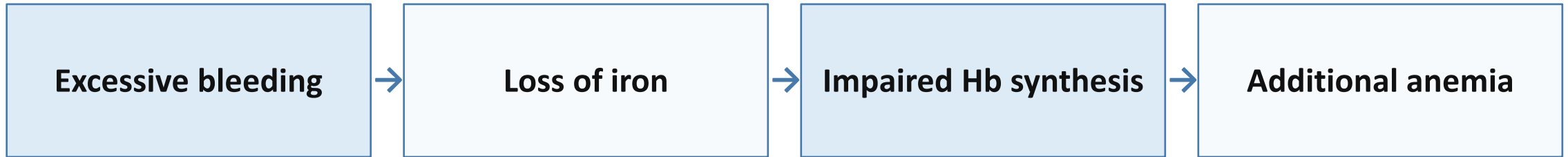


Folate deficiency is an important exacerbating factor.

The defective DNA-synthesis pathway is established elsewhere in this chapter.

Schematic

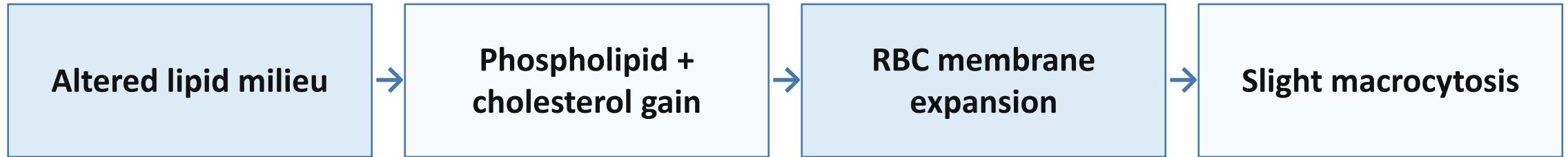
Bleeding and iron deficiency in liver disease



Poor nutritional status may independently restrict iron supply.

Iron deficiency is an aggravating factor rather than the only hepatic mechanism.

Hepatic lipid changes can enlarge red cells



The change develops as RBCs circulate in peripheral blood.

This mechanism differs from folate/B12-related defective DNA replication.

Two pathways to increased RBC size

Liver-associated macrocytosis

RBCs acquire membrane lipid while circulating

Increased membrane area can enlarge cells

Often slight macrocytosis

Megaloblastic macrocytosis

Folate/B12 deficiency impairs DNA replication

Abnormal enlarged erythroid precursors develop

Ineffective hematopoiesis may follow

A shared MCV pattern does not imply an identical cellular mechanism.

Why the blood picture can be heterogeneous

Decreased erythroid production provides one component of anemia.

Nutritional folate and iron deficits may be superimposed.

Membrane-lipid changes can shift measured RBC size upward.

Leukocyte or platelet reductions may occur but are less frequent.

Avoid forcing hepatic anemia into a single uniform morphology.

Renal versus hepatic anemia

Chronic renal failure

Dominant EPO deficiency

Uremic shortened RBC survival / bleeding

Iron deficiency may develop

Hepatocellular disease

Depressed marrow function with multifactorial additions

Folate and iron deficiency common aggravators

Membrane lipid effects cause slight macrocytosis

The causal priorities differ even when systemic organ failure is present.

Case: Macrocytosis in hepatocellular disease

A patient with longstanding cirrhotic liver disease develops mild macrocytosis and anemia. The history also suggests poor nutrition and recurrent bleeding.

Clinical information

Cirrhosis

Slight macrocytosis

Possible folate and iron deficits

Name the distinct pathways that can coexist without assuming one mechanism.

Case interpretation: Layered hepatic mechanisms

Separate the red-cell size change from additional production deficits.

Lipid-related membrane acquisition may cause slight macrocytosis.

Reduced marrow function contributes to anemia.

Folate deficiency and iron loss can exacerbate impaired production.

A single morphological descriptor does not resolve the full etiology.

Endocrine disorders: A separate underproduction group

Endocrine dysfunction can contribute to diminished erythropoiesis.

Hypothyroidism is specifically highlighted.

The associated anemia is typically mild, normocytic and normochromic.

This presentation is a pattern association, not a disease-specific hematologic test.

Why normal cell size does not exclude anemia

Cell quantity

Red-cell production can be reduced

The circulating red-cell compartment may decline

Cell morphology

RBC size may remain normal

Hemoglobin coloration may remain normal

A mild normocytic, normochromic anemia can still reflect systemic endocrine dysfunction.

Diagnostic specificity of the RBC-size pattern

Pattern	Representative setting	Interpretive limit
Normocytic / normochromic	Hypothyroidism-associated anemia	Not disease-specific
Slightly macrocytic	Hepatocellular disease	Membrane lipid change may contribute
Leukoerythroblastic / teardrops	Myelophthisic marrow	Suggests distorted egress
Low red-cell production	Renal EPO deficiency	Requires clinical renal context

Four causes: Mechanism and distinguishing context

Cause	Dominant issue	Helpful clue
Marrow infiltration	Displacement + fibrosis	Leukoerythroblastosis, teardrops
Chronic renal failure	Reduced erythropoietin	Uremia; possible bleeding/iron loss
Hepatocellular disease	Reduced marrow function + other effects	Slight macrocytosis; nutritional overlap
Hypothyroidism	Endocrine-associated underproduction	Usually mild normocytic/normochromic anemia

Which marrow lineage is emphasized?

Mechanism	Erythroid effect	Other blood-cell effects
Marrow replacement	Hematopoietic space displaced	Immature erythroid and granulocytic release
Pure red cell aplasia	Selective erythroid progenitor suppression	Other lineages relatively spared
Aplastic anemia	General marrow production failure	Pancytopenia
Hepatocellular disease	Preferential erythroid depression	WBC / platelets less often depressed

Peripheral morphology must be interpreted causally

Teardrop red cells plus immature forms point toward marrow distortion.

Slight macrocytosis in hepatic failure may arise from altered membrane lipids.

Normocytic morphology does not exclude an endocrine contribution.

Red-cell morphology cannot alone settle all four etiologies.

Link a blood finding to its mechanism, then evaluate the clinical context.

Mechanism-first interpretation of underproduction anemia

Underproduction anemia: Interpret the mechanism

Marrow architecture

Immature forms + teardrops

Renal endocrine support

Kidney failure / low EPO mechanism

Hepatic pathways

Membrane lipid + nutrition

Endocrine setting

Hypothyroidism; Mild normocytic

Look for more than one pathway in systemic disease

Interpretive teaching algorithm, not a validated diagnostic rule.

Avoid three common reasoning errors

Do not identify every leukoerythroblastic smear as metastatic carcinoma.

Do not explain renal anemia solely by erythropoietin loss when bleeding may coexist.

Do not call all macrocytosis “megaloblastic” in patients with liver disease.

The distinguishing feature is mechanism, not a single surface finding.

Integrated case: Renal and hepatic disease coexist

A patient with chronic kidney disease and cirrhotic hepatocellular disease develops anemia, slight macrocytosis and recurrent bleeding.

Clinical information

Potential deficiency of EPO

Hepatic lipid and marrow effects

Bleeding-associated iron depletion

Would a single-pathway explanation be defensible?

Integrated case: Construct a causal explanation

A combined explanation is more coherent than exclusive attribution.

Renal disease reduces EPO-driven red-cell production.

Hepatic disease may depress marrow function and enlarge RBC membranes.

Bleeding and possible iron deficiency add another mechanism.

Do not equate a plausible dominant cause with the only cause.

Clinical pattern recognition: Four short prompts

Presentation	Mechanism most directly suggested
Anemia, teardrops and nucleated erythroid cells	Myelophthistic marrow distortion
Uremia with inadequate erythropoiesis	Reduced renal erythropoietin
Hepatocellular disease and slight macrocytosis	Lipid-associated membrane enlargement
Hypothyroidism and mild normocytic anemia	Endocrine-associated underproduction

Final synthesis: Local lesion or systemic support?

Marrow architecture

EPO support

Hepatic milieu

Endocrine milieu

Distinct causal categories — not sequential stages

All four categories can culminate in inadequate effective red-cell production.

Search for concurrent RBC survival, bleeding or nutritional contributors.

Schematic

Principal conclusions

Myelophthisis: Marrow infiltration/fibrosis produces displacement and disturbed cell release.

Renal failure: Decreased EPO dominates; Uremia, bleeding and iron loss add effects.

Hepatic disease: Preferential erythroid impairment plus nutritional and membrane-lipid effects.

Endocrine disease: Hypothyroidism can cause mild normocytic, normochromic anemia.

Mechanism + morphology + organ context produces a stronger interpretation than MCV alone.

Principal reference

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026)

Chapter 14: Red Blood Cell and Bleeding Disorders

Related marrow fibrosis context: Chapter 13

Primary section: “Other Forms of Marrow Failure”