

Multiple Myeloma

Pathogenesis · Morphology · Clinical correlations · Diagnosis

A plasma cell neoplasm with skeletal and systemic consequences

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Learning objectives

- Link clonal plasma cells to bone destruction and systemic injury.
- Recognize marrow, bone, and peripheral blood morphology.
- Interpret monoclonal immunoglobulin and free light-chain tests.
- Apply CRAB findings and distinguish related plasma cell disorders.
- Explain major prognostic markers and treatment mechanisms.

The disease in one definition

- Malignant proliferation of terminally differentiated B-lineage plasma cells.
- Usually disseminated within bone marrow and associated with destructive skeletal lesions.
- Frequently produces a monoclonal immunoglobulin or free light chain.
- Organ injury arises from tumor infiltration, bone remodeling, and abnormal secreted proteins.

Three pathologic axes: Cell mass · bone injury · paraprotein

Three mechanisms account for major manifestations

Marrow infiltration

- Replacement of hematopoietic marrow
- Anemia and skeletal tumor deposits

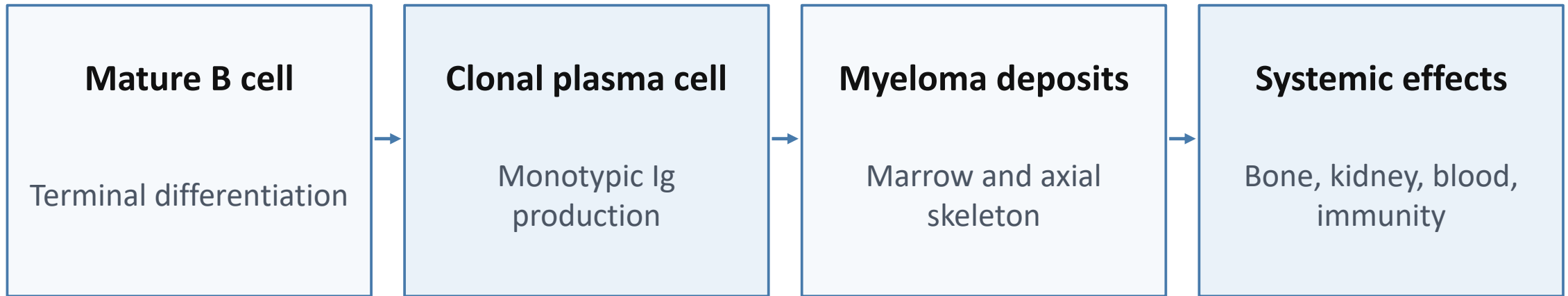
Paraprotein production

- Monoclonal intact Ig and/or free light chains
- Renal toxicity, hyperviscosity, amyloid

Immune dysregulation

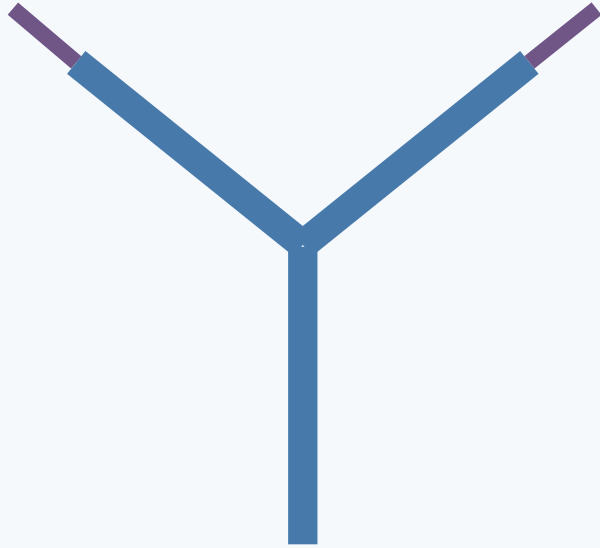
- Reduced normal immunoglobulins
- Recurrent bacterial infection

Plasma cell neoplasm: Biological context



Myeloma retains the secretory phenotype of plasma cells.

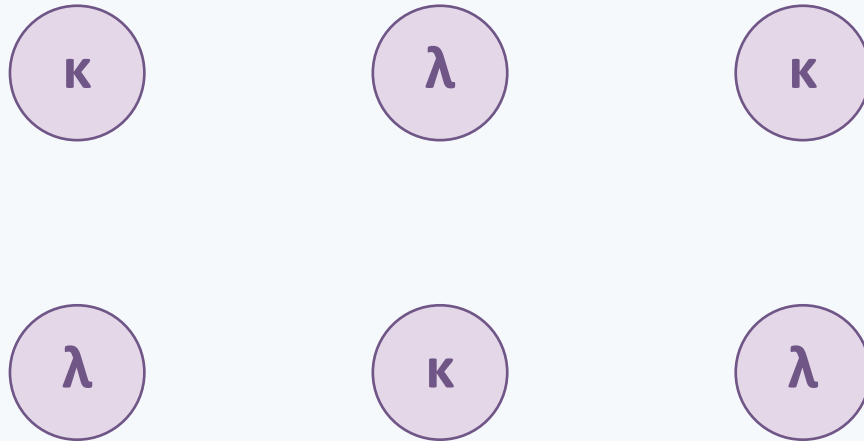
Intact immunoglobulin versus monoclonal M protein



Conceptual immunoglobulin (intact molecule)

- An M component denotes a monoclonal immunoglobulin in blood.
- The tumor population produces immunoglobulin with a shared molecular identity.
- Its measurement can assist detection and longitudinal assessment.

Free light chains and Bence Jones protein



Free light chains: Low-molecular-weight proteins

- Plasma cells may secrete excess κ or λ light chain.
- Small free light chains pass through the glomerular filter.
- Urinary monoclonal light chains are termed Bence Jones proteins.

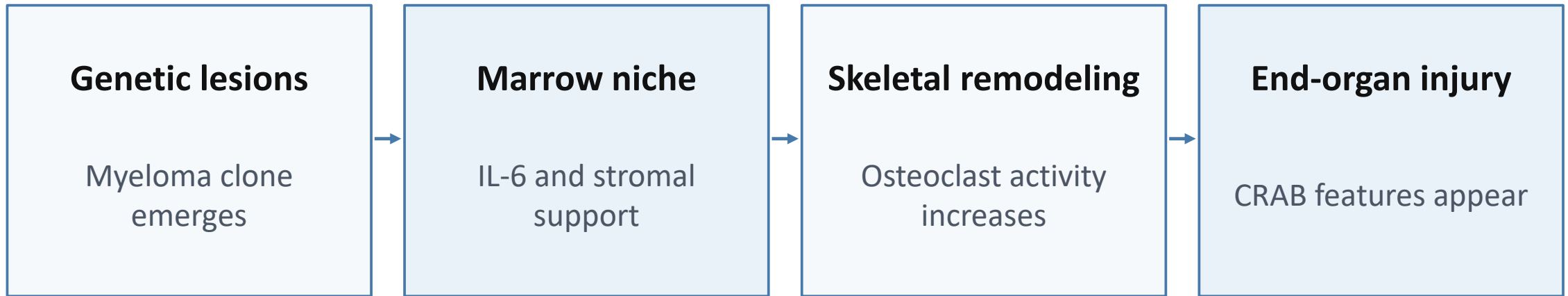
One clone, several secretory phenotypes

Production pattern	Diagnostic implication
Intact monoclonal immunoglobulin	Detectable serum M component
Intact Ig plus free light chains	Serum M protein with urinary or serum FLC
Free light chain only	Routine serum electrophoresis can be less informative
Rare nonsecretory disease	No measurable monoclonal protein does not rule out myeloma

Clinical epidemiology

- Predominantly affects older adults; Peak age of incidence is 65–70 years.
- Incidence is higher in males than in females.
- Incidence is higher in people of African descent.
- The clinical disease frequently presents through skeletal symptoms or organ dysfunction.

From clonal expansion to clinical disease

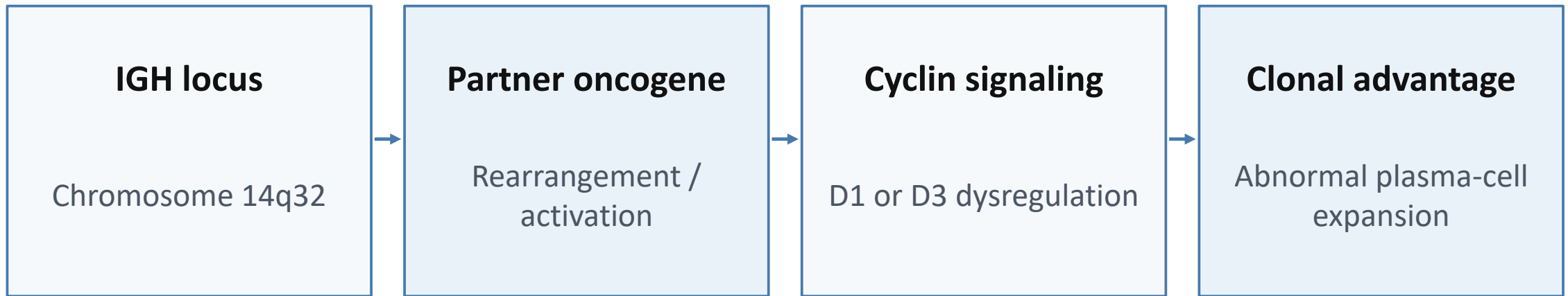


The genotype and microenvironment jointly shape the phenotype.

Genetic heterogeneity is a defining feature

- Frequent structural rearrangements involve IGH at chromosome 14q32.
- Multiple different proto-oncogenes become dysregulated.
- Myeloma is not defined by one universal fusion gene.
- Additional genomic abnormalities are associated with aggressive disease.

IGH rearrangements and cell-cycle dysregulation



Illustrative pathway: Specific partners and consequences vary by tumor.

Cyclin D1 and cyclin D3 in myeloma

- CCND1 and CCND3 encode regulators of progression through G1.
- Their deregulation can favor cell-cycle entry in clonal plasma cells.
- Cyclin D1–associated rearrangements are described in a prognostically favorable subset.
- Cyclin dysregulation is a recurrent molecular theme, not a unique diagnostic marker.

Genetic abnormalities and biologic implications

IGH rearrangements

- Dysregulate partner oncogenes
- Heterogeneous initiating landscape

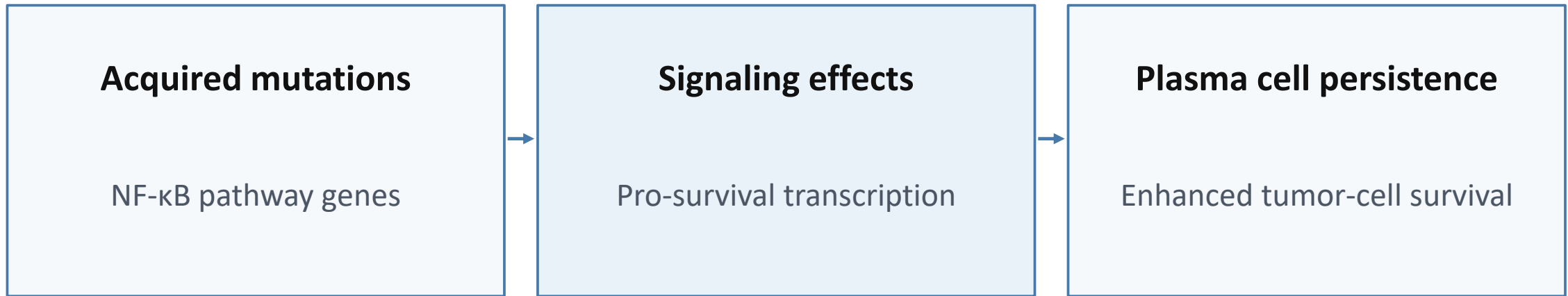
17p deletion / TP53

- Loss involving a tumor suppressor locus
- Poor-outcome association

MYC rearrangements

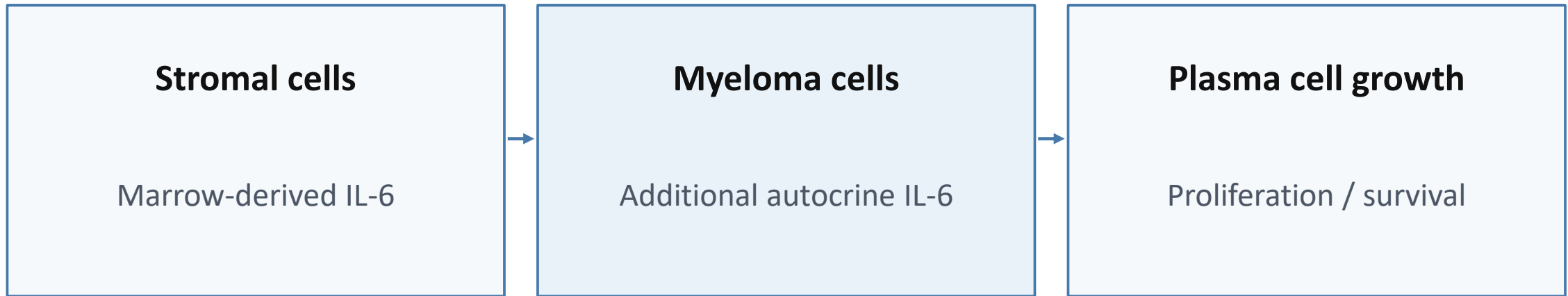
- Noted in highly aggressive forms
- Associated with plasma cell leukemia

NF- κ B signaling and myeloma survival



Recurrent lesions in this survival pathway.

Interleukin-6 supports tumor growth



Higher serum IL-6 in active disease is associated with adverse prognosis.

The bone marrow microenvironment

Soluble signals

- IL-6 is a major plasma-cell growth factor
- Both stromal and tumor production

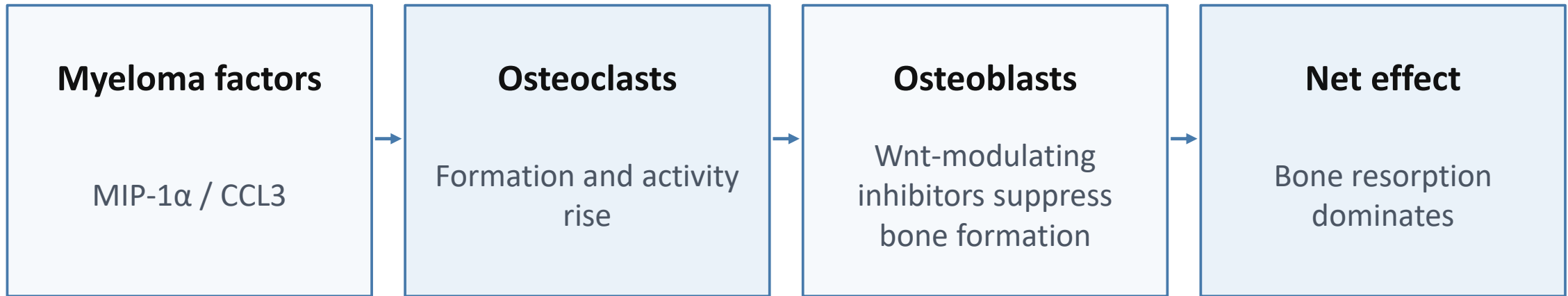
Cell contact

- Direct interactions with marrow stromal cells
- Additional survival advantage

Clinical result

- Persistence within a supportive marrow niche
- Potential therapeutic vulnerability

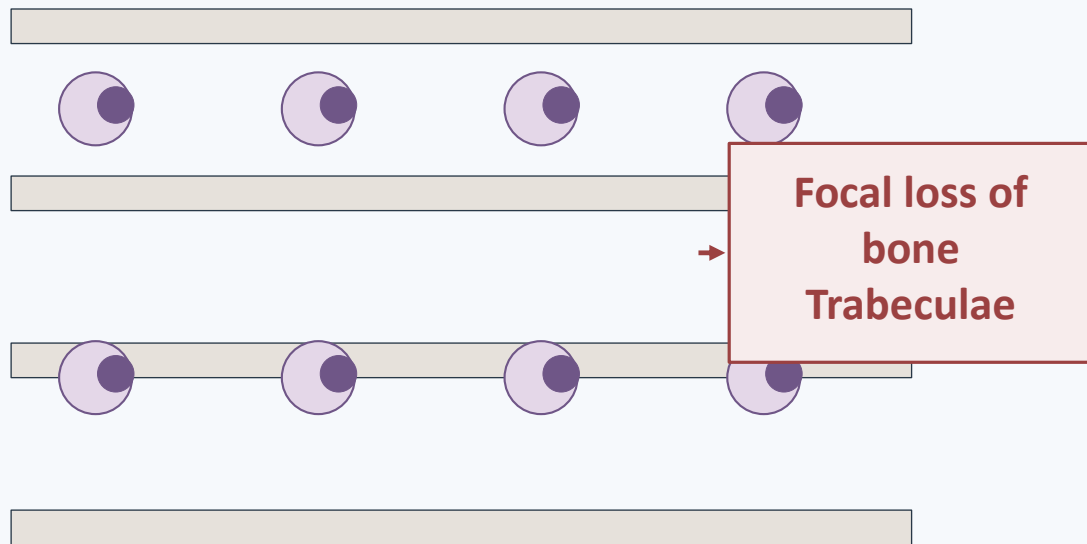
Why do osteolytic lesions form?



Bone destruction is not merely passive displacement by tumor.

Coupled skeletal injury: Bone loss exceeds repair

Schematic: Cancellous bone and marrow



- Osteoclast recruitment accelerates resorption.
- Osteoblast suppression limits replacement of lost bone.
- The imbalance produces lytic lesions and fragility.
- Calcium released from bone contributes to hypercalcemia.

Local signaling and the resulting skeletal phenotype

Tumor-associated signal	Pathologic consequence
MIP-1 α (CCL3)	Facilitates osteoclast formation
Wnt-pathway modulators	Suppress osteoblast function
Increased resorption	Lytic defects and pathologic fracture
Excess skeletal calcium release	Hypercalcemia

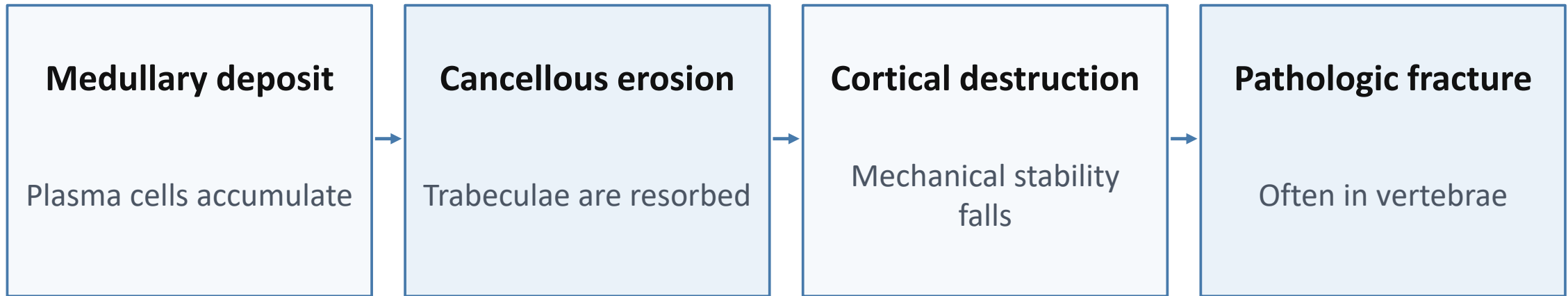
Integrated pathogenesis: Why multiple organs fail

- Marrow plasmacytosis interferes with normal blood-cell production.
- Osteoclast activation and osteoblast inhibition weaken bone.
- Light chains injure renal tubules and sometimes form AL amyloid.
- Suppression of polyclonal Ig compromises antibacterial defense.

Skeletal distribution is typically axial

- The vertebral column, ribs, skull, and pelvis are preferential sites.
- Femur, clavicle, and scapula may also be involved.
- Tumor deposits begin within medullary spaces.
- Advanced lesions can erode cortex and produce fractures.

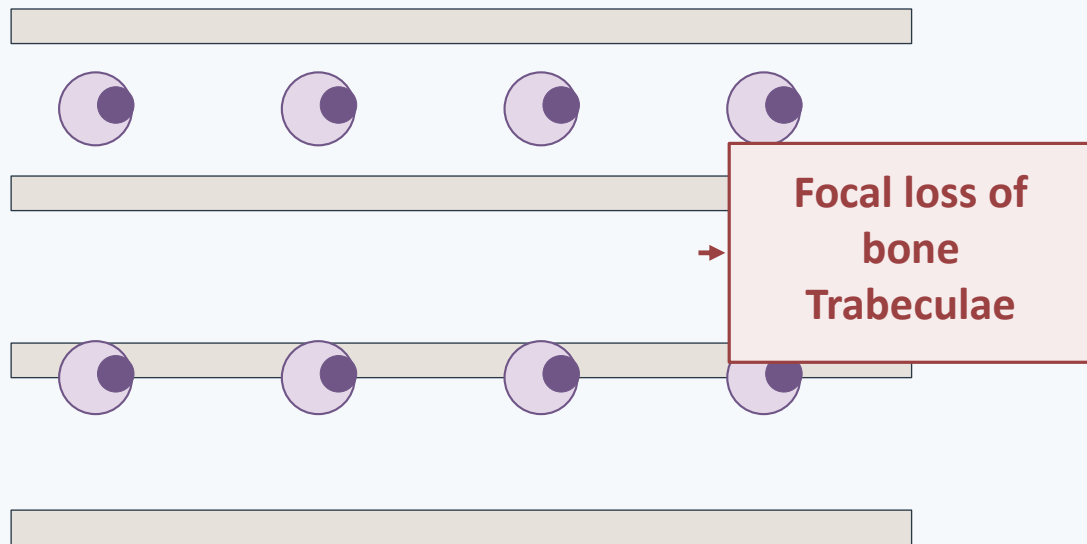
Anatomy of a developing lytic lesion



Morphologic sequence of bone injury, not a measure of time.

Punched-out skeletal defects

Schematic: Cancellous bone and marrow



- Focal sharply circumscribed lytic lesions are characteristic.
- Radiographic defects typically 1–4 cm.
- Vertebrae and calvaria are common sites of involvement.
- Diffuse osteopenia can replace discrete lesions in some patients.

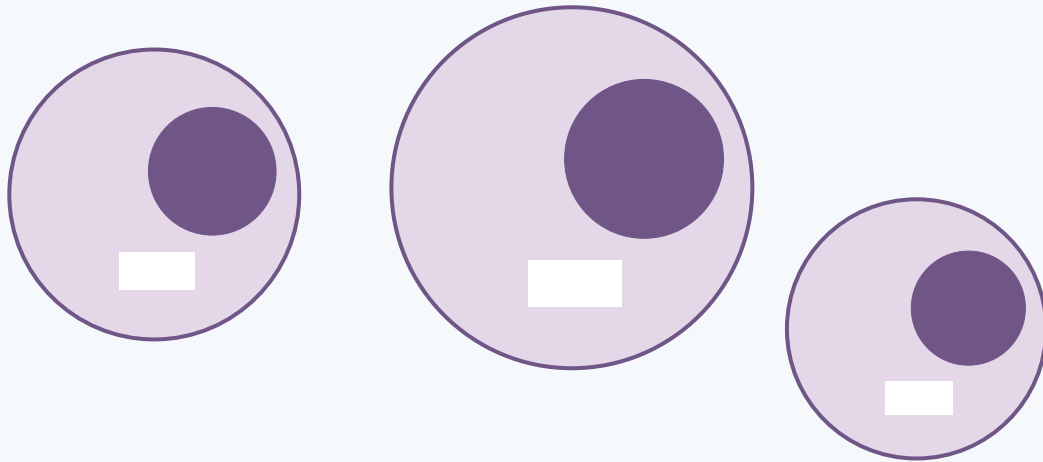
Two major patterns of myelomatous bone disease

Focal osteolysis	Diffuse skeletal loss
Discrete punched-out radiolucencies	Generalized demineralization / osteopenia
Local tumor deposits plus resorption	Widespread remodeling imbalance
May cause localized structural failure	Associated with generalized skeletal fragility

Gross appearance of skeletal tumor deposits

- Myeloma lesions are soft, red, and often gelatinous.
- They occupy marrow cavities as expanding plasmacytomas.
- Progressive bone erosion may penetrate the cortex.
- Lesions at multiple sites support disseminated skeletal disease.

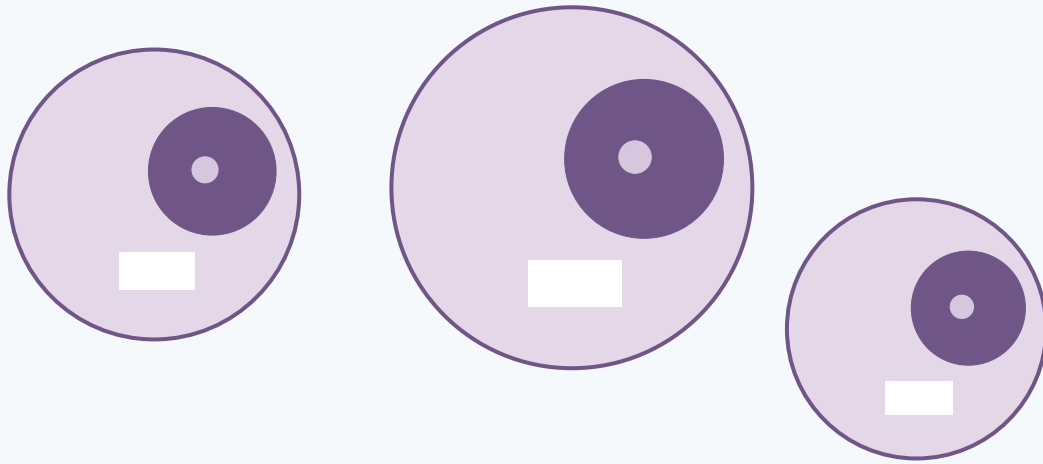
Typical plasma cell: Morphologic landmarks



Stylized plasma cell morphology — schematic, not a micrograph

- Eccentrically positioned nucleus.
- Abundant basophilic cytoplasm.
- Pale perinuclear Golgi zone (hof).
- These features are preserved in many myeloma cells.

Marrow myeloma: Cytologic variability



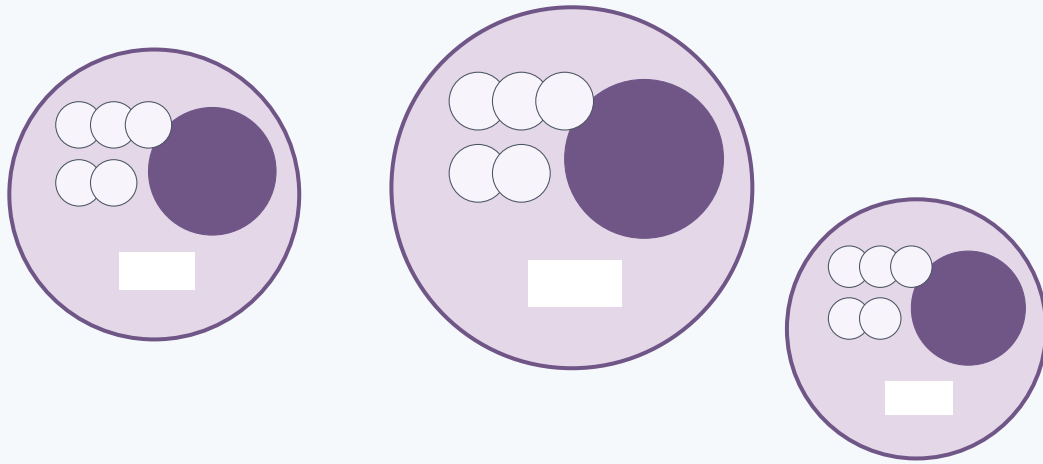
Stylized plasma cell morphology — schematic, not a micrograph

- Relatively mature plasma cells may predominate.
- Plasmablasts show vesicular chromatin and prominent nucleoli.
- Bizarre or multinucleated cells also occur.
- Morphology alone must be integrated with clonality and clinical findings.

Mature-appearing versus plasmablastic cells

Relatively mature plasma cell	Plasmablastic morphology
Eccentric condensed nucleus	More open / vesicular nuclear chromatin
Perinuclear Golgi clearing	Conspicuous nucleolus
Usually recognizable plasma-cell outline	Greater cytologic atypia
Not benign merely because mature-looking	Requires full diagnostic correlation

Mott cells and cytoplasmic immunoglobulin



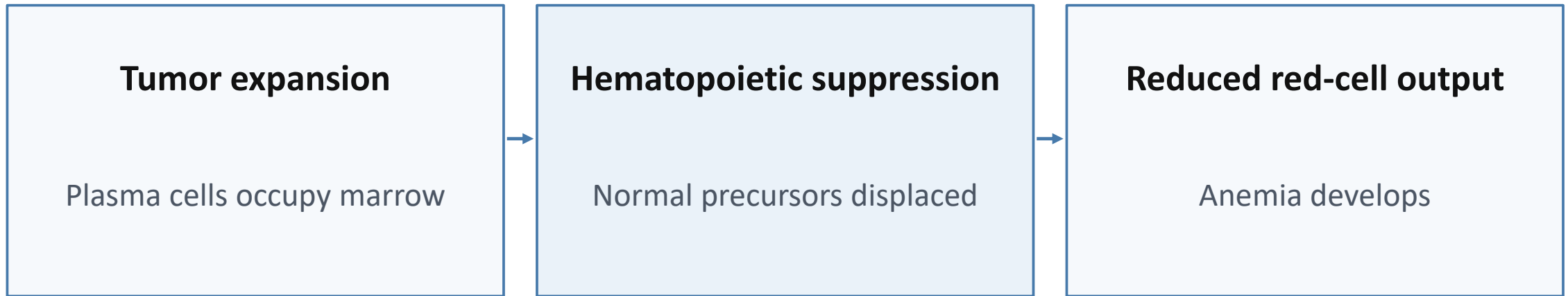
Stylized plasma cell morphology — schematic, not a micrograph

- Disordered secretory handling can accumulate Ig inside the cell.
- Mott cells contain multiple droplet-like cytoplasmic inclusions.
- Cytoplasmic Ig globules are called Russell bodies.
- Recognize them as secretory abnormalities, not pathogen inclusions.

Other plasma cell inclusion patterns

- Flame cells show brightly eosinophilic, red-tinged cytoplasm.
- Dutcher bodies appear as intranuclear immunoglobulin inclusions.
- Crystal-like rods, fibrils, and globules may also be observed.
- Such inclusions reflect dysregulated protein synthesis and handling.

Marrow replacement produces cytopenia



The marrow infiltration pattern may range from subtle to extensive.

Marrow infiltration: Extent and pattern

- Plasma cells often exceed 30% of marrow cellularity in overt myeloma.
- Both interstitial infiltrates and near-complete replacement occur.
- Sampling must be interpreted together with clinical and protein studies.

Bone marrow versus extramedullary spread

Bone marrow disease	Advanced extramedullary involvement
Primary dominant compartment	Secondary dissemination late in course
Lytic skeletal lesions and cytopenias	Possible soft-tissue organ infiltrates
Axial skeleton commonly involved	Spleen, liver, kidney, lung and nodes can be affected

Rouleaux: A peripheral blood clue

- High concentrations of monoclonal protein promote linear red-cell stacking.
- The appearance is called rouleaux formation.
- It is supportive, not specific, for multiple myeloma.
- Other high-protein states can produce the same smear pattern.

Diagnostic morphology: What each specimen answers

Bone marrow aspirate

- Plasma-cell cytology
- Maturation, atypia, inclusions

Core biopsy

- Infiltration architecture
- Distribution and marrow replacement

Peripheral blood smear

- Rouleaux / rare circulating plasma cells
- Systemic hematologic effect

Plasma cell immunophenotype

CD138

Syndecan-1: Supports plasma-cell identification

CD56

Frequently expressed in neoplastic plasma cells; Not universal

κ or λ

Cytoplasmic light-chain restriction supports clonality

No single immunostain independently establishes symptomatic myeloma.

Clonality versus lineage: Distinguish the questions

Lineage evidence	Clonal evidence
CD138 establishes plasma-cell differentiation	κ or λ restriction supports a single clone
CD56 may aid tumor recognition	Correlate with marrow morphology and protein studies
Plasma-cell phenotype is not disease-stage proof	Myeloma requires clinical or biomarker-defining evidence

CRAB: Four categories of myeloma injury

C

Hypercalcemia from
bone resorption

R

Renal impairment;
Often light-chain
mediated

A

Anemia from marrow
disease

B

Bone lesions:
Osteolysis and
fractures

CRAB injury must be attributable to the plasma-cell disorder.

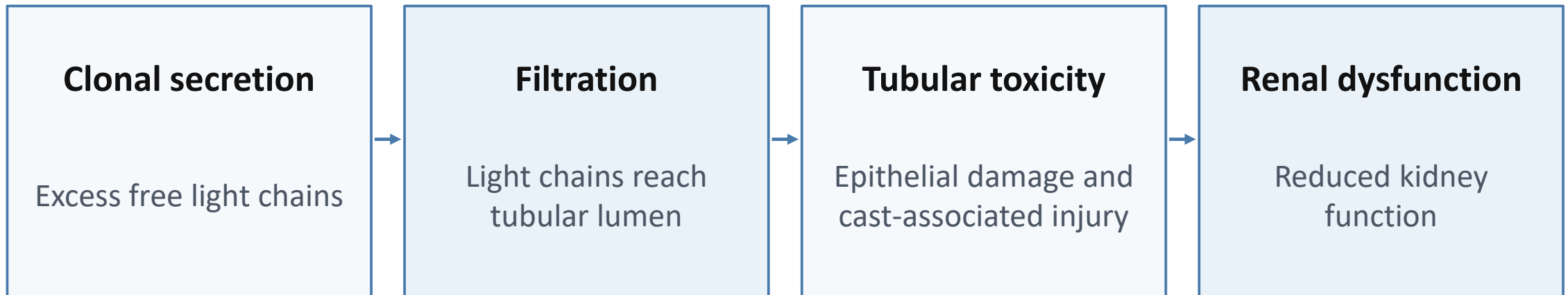
Why skeletal pain and fracture occur

- Osteolysis weakens structural support of the bone.
- Weight-bearing and vertebral lesions can become painful.
- Compression fractures commonly involve the vertebral column.
- Fractures are a major cause of disability and morbidity.

Hypercalcemia: Biochemical injury from bone

- Osteoclast-mediated resorption releases mineral into circulation.
- Clinical effects can include constipation, polyuria, weakness, and lethargy.
- More severe hypercalcemia may cause confusion.
- Hypercalcemia also contributes to renal dysfunction.

Light chains injure the renal tubule

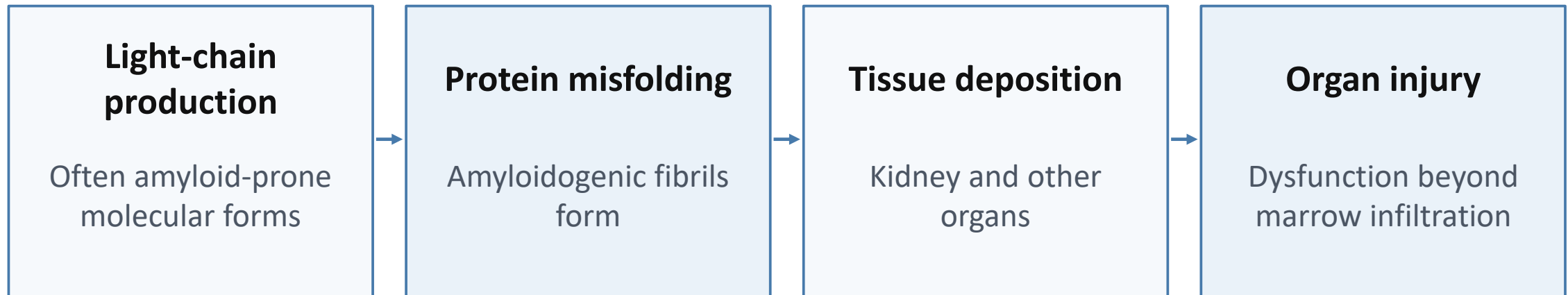


This is the major renal mechanism emphasized by Robbins.

Renal impairment is multifactorial

- Light-chain tubular toxicity is a major contributor.
- Hypercalcemia can worsen kidney dysfunction.
- Dehydration and other insults may compound damage.
- AL amyloid deposition can contribute in affected patients.

Monoclonal light chain can become AL amyloid

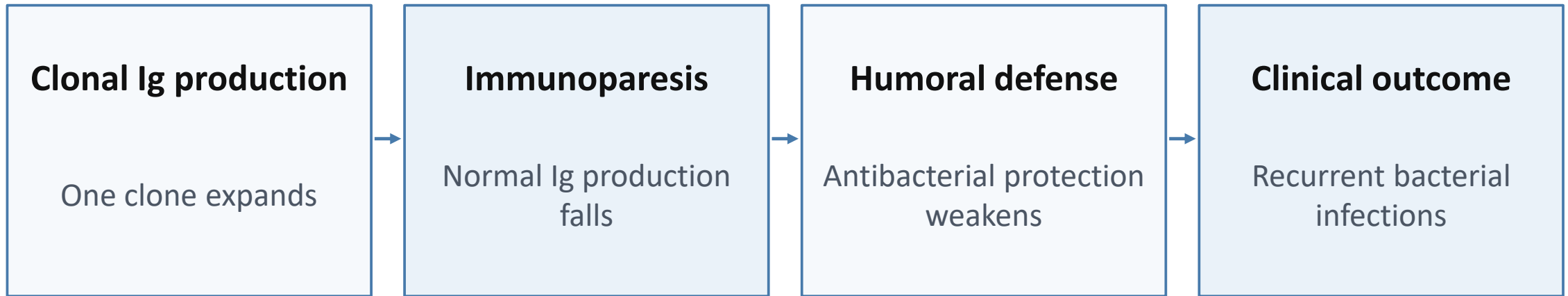


AL amyloidosis may occur with overt myeloma or smaller clones.

Anemia in multiple myeloma

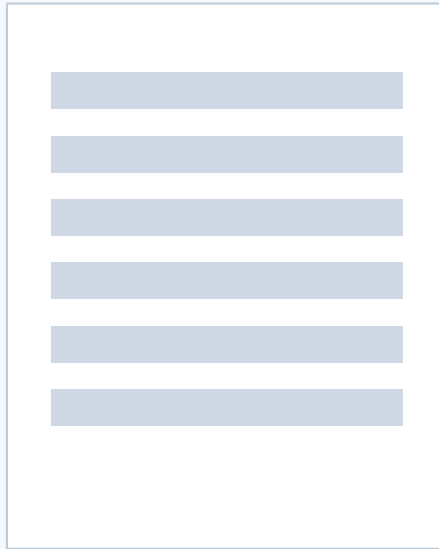
- Marrow infiltration reduces effective erythropoiesis.
- Renal dysfunction may also contribute to anemia.
- The resulting fatigue can dominate early clinical presentation.
- Anemia should be evaluated together with marrow and renal findings.

Suppressed normal Ig drives recurrent infection

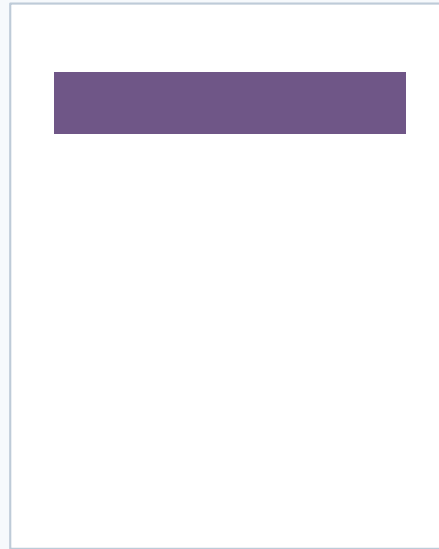


Cell-mediated immunity is described as relatively preserved.

Serum protein electrophoresis: Pattern recognition



Normal polyclonal



Monoclonal

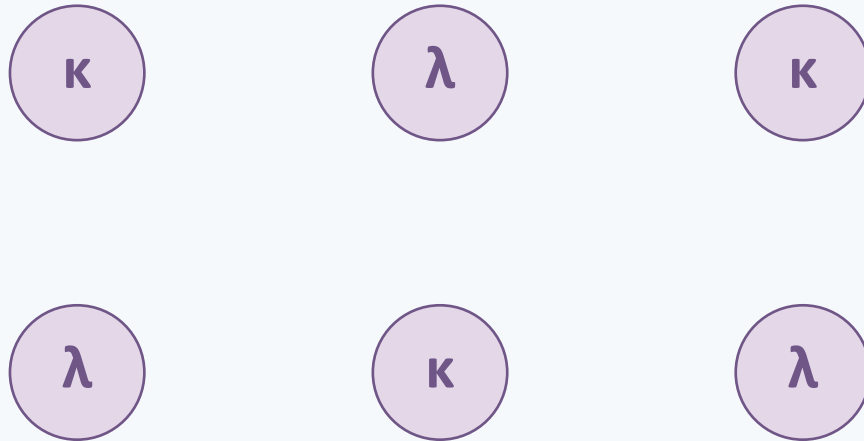
Band-width concept only; Not patient electrophoresis data

- Normal polyclonal immunoglobulin gives a distributed pattern.
- A narrow monoclonal band raises suspicion for an M component.
- Immunofixation is needed to determine heavy- and light-chain identity.

Immunofixation identifies the monoclonal protein

- Type the immunoglobulin heavy chain, such as IgG or IgA.
- Identify κ versus λ light chain pairing.
- Confirm that the abnormal electrophoretic band is monoclonal.
- Protein typing and disease activity are distinct diagnostic questions.

Serum free light-chain evaluation



Free light chains: Low-molecular-weight proteins

- Measure κ and λ free light chains in serum.
- An imbalanced κ : λ relationship supports monoclonal secretion.
- Interpret the ratio with involved-chain concentration and clinical context.
- Free light-chain detection matters in light-chain-only myeloma.

Urine testing adds complementary information

- Urinary monoclonal free light chains are Bence Jones proteins.
- Urine electrophoresis and immunofixation can characterize excreted proteins.
- The renal effect of monoclonal light chains can be disproportionate to serum M-spike size.
- Serum and urine testing should be integrated, not viewed in isolation.

Major immunoglobulin classes in myeloma

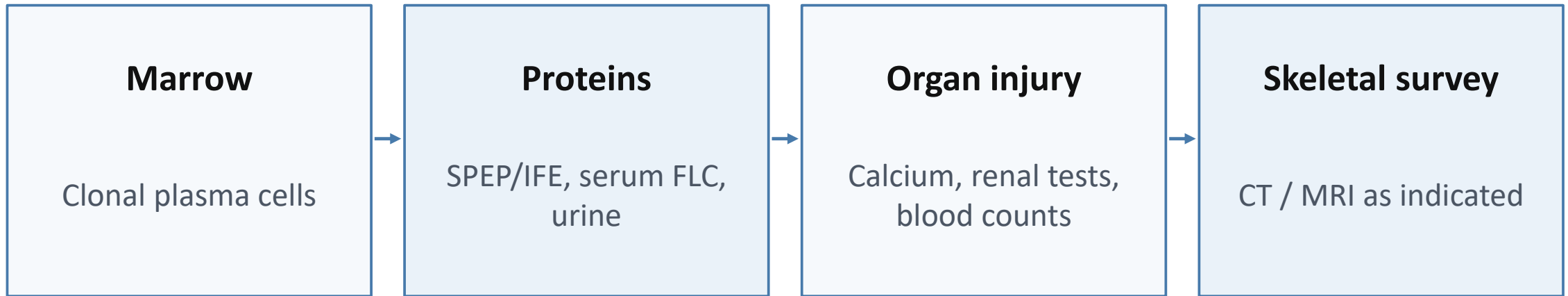
IgG	IgA	Less frequent patterns
• Most frequent heavy-chain class • Approximately 55% of cases	• Second most frequent class • Approximately 25%	• IgM, IgD, IgE rare • Light-chain-only and nonsecretory variants also occur

Percentages are textbook estimates, not current surveillance data.

When an M spike is absent

- Some tumors produce free light chains without intact immunoglobulin.
- Rare tumors are nonsecretory.
- A normal-looking serum electrophoretic trace therefore does not exclude myeloma.
- Proceed with serum FLC, urine studies, marrow evaluation, and appropriate imaging when suspicion persists.

Core diagnostic workup: Complementary domains



An integrated diagnosis cannot be made from a paraprotein alone.

Bone marrow examination: Specific tasks

- Quantify clonal plasma cells and examine infiltration architecture.
- Document plasma-cell differentiation and light-chain restriction.
- Assess morphology for plasmablastic or other atypical forms.
- Obtain clinically indicated cytogenetic and molecular risk information.

IMWG diagnostic framework: Two requirements

Clonal substrate

≥10% clonal marrow plasma cells, OR biopsy-proven plasmacytoma

Myeloma-defining event

At least one attributable CRAB feature OR validated SLiM biomarker

IMWG (2014; Clinical criteria), supplementary to the Robbins narrative.

IMWG: Attributable CRAB thresholds

Calcium

>11 mg/dL or >1 mg/dL above upper limit of normal

Renal

Creatinine clearance <40 mL/min or serum creatinine >2 mg/dL

Anemia

Hemoglobin <10 g/dL or >2 g/dL below lower normal limit

Bone

≥1 osteolytic lesion on appropriate imaging*

*With <10% clonal marrow cells, >1 lesion is required to distinguish solitary plasmacytoma.

IMWG: SLiM biomarkers of active myeloma

S

≥60% clonal plasma cells in
bone marrow

Li

Involved:uninvolved serum
FLC ratio ≥100 AND involved
FLC ≥100 mg/L

M

More than one MRI focal
lesion, each ≥5 mm

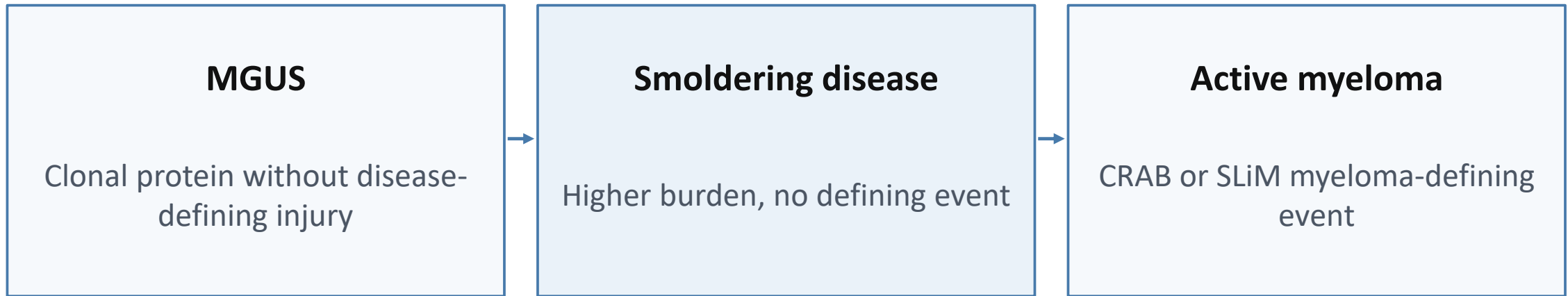
These biomarkers may define active disease without symptomatic CRAB injury.

Myeloma-defining lesion versus incidental finding

Supported disease attribution	Potential diagnostic pitfall
Osteolysis attributable to the plasma-cell disorder	Other causes of lytic bone disease require assessment
Renal damage related to monoclonal protein	Coexisting kidney disease may have other etiologies
Anemia from marrow / systemic disease	Do not automatically attribute any anemia to myeloma
Clonal plasma cells plus defining event	M component alone does not prove active disease

The diagnostic criterion is disease-attributable end-organ damage.

From precursor states to symptomatic myeloma



A biological continuum; Progression is not inevitable in an individual patient.

MGUS, smoldering myeloma, and active myeloma

Disease state	Core discriminator
MGUS	Asymptomatic clone without defining events
Smoldering myeloma	Higher clonal burden without defining events
Active multiple myeloma	Clonal substrate plus attributable CRAB or SLiM finding

Formal clinical classification depends on contemporary diagnostic criteria, not M protein alone.

Multiple myeloma versus solitary plasmacytoma

Systemic myeloma	Solitary plasmacytoma
Multiple marrow / skeletal sites	Single localized tumor mass
Myeloma-defining systemic pattern	No qualifying systemic myeloma-defining disease
May show multiple M-protein patterns	M protein may be absent or limited
Systemic treatment framework	Local management often central

Multiple myeloma versus Waldenström syndrome

Multiple myeloma	Lymphoplasmacytic lymphoma
Plasma-cell neoplasm	B-cell neoplasm with plasmacytic differentiation
Commonly IgG or IgA	Usually monoclonal IgM
Lytic bone destruction prominent	Bone destruction is not characteristic
Light-chain kidney injury clinically important	Hyperviscosity from IgM dominates selected cases

Multiple myeloma prognosis is heterogeneous

- Disease burden and end-organ injury substantially influence outcome.
- Genomic features contribute to risk stratification.
- Approximately 60% 5-year survival as a historical summary.
- Advances in therapy have steadily improved outcomes; Do not interpret older estimates as an individualized forecast.

Selected prognostic genomic correlates

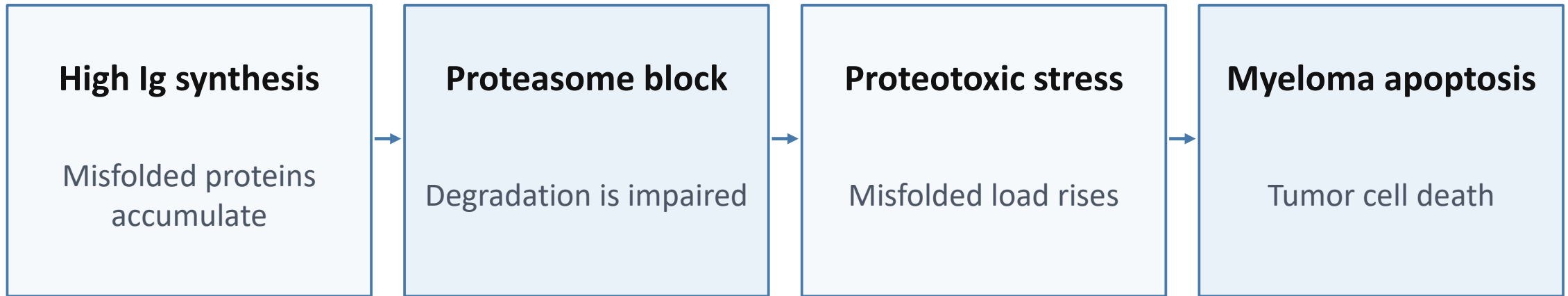
Favorable association	Adverse associations	Additional risk signal
• Cyclin D1 translocation • An association, not an absolute prediction	• Deletion of 17p / TP53 • Deletion of 13q	• T(4;14) • Aggressive biology in relevant contexts

Risk assignment requires an integrated, validated clinical framework.

A biomarker may have different roles

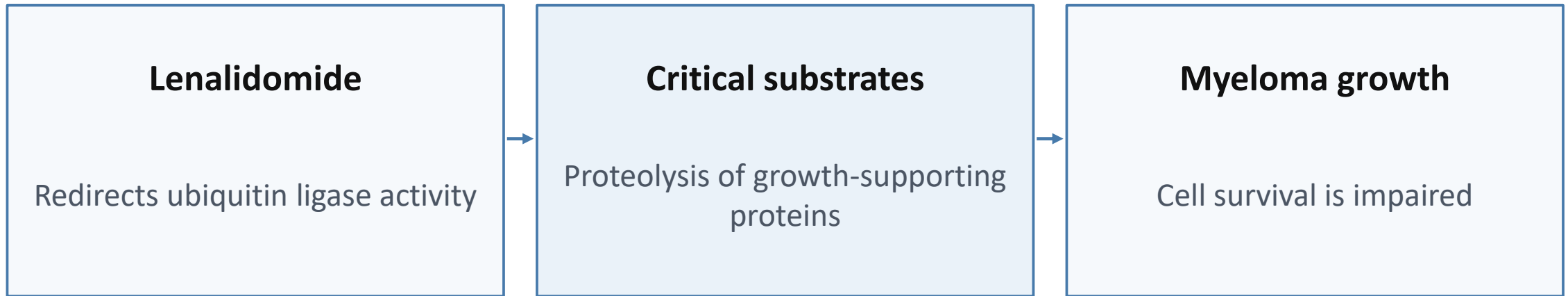
Question	Example from myeloma
Diagnostic: Is the clone present?	Monotypic cytoplasmic κ or λ restriction
Prognostic: What is its likely course?	Del(17p), t(4;14), other risk markers
Predictive: Does a specific therapy work?	Treatment selection needs regimen-specific evidence; Do not infer prediction from prognosis

Proteasome inhibition exploits protein stress



A mechanism-based therapeutic vulnerability highlighted by the textbook.

Immunomodulatory drugs alter protein disposal



The mechanism differs from simple proteasome blockade.

Treatment strategies: Pathology-based rationale

Skeletal support

- Bisphosphonates inhibit bone resorption
- Reduce fracture risk and hypercalcemia

Cellular therapy

- Hematopoietic stem-cell transplantation
- Extends survival; Not reliably curative

Antigen targeting

- BCMA-directed CAR-T cells
- Deep remissions with substantial toxicity risks

Toxicity matters in BCMA-directed cell therapy

- Cytokine-release syndrome as an important adverse effect.
- Neurotoxicity may accompany immune-effector therapy.
- Hypogammaglobulinemia can contribute to infection risk.
- Treatment choices require specialized assessment beyond morphologic diagnosis.

Clinical case: Evaluate the pattern

An older adult presents with persistent axial back pain, normocytic anemia, renal dysfunction and multiple punched-out calvarial lesions. Serum testing reveals a monoclonal immunoglobulin.

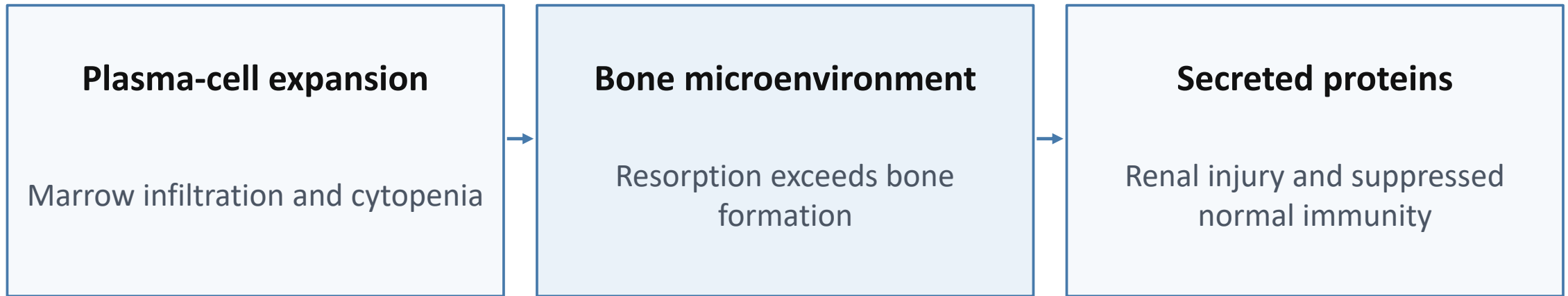
- Which tissue lesion unifies bone pain and marrow-related anemia?
- Which additional studies establish clonality and myeloma-defining injury?
- Which component of the paraprotein may be directly nephrotoxic?

Case resolution: Pathologic reasoning

The constellation raises strong suspicion for active plasma-cell myeloma; No single finding is sufficient on its own.

- Confirm marrow plasma-cell clonality and burden.
- Correlate imaging and CRAB results with the plasma-cell disorder.
- Characterize serum and urinary immunoglobulins and free light chains.
- Complete risk assessment and organ-function evaluation.

Synthesis: One clone, three mechanisms of disease



Integrate molecular pathology, morphology, and clinical findings.

References and scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. (2026), Chapter 13, pp. 552–555.
- Rajkumar SV et al. International Myeloma Working Group updated diagnostic criteria. Lancet Oncol. 2014;15:e538–e548.
- Current diagnostic biomarkers and thresholds are presented as an IMWG supplement; all other content derives principally from the supplied Robbins text.
- Clinical diagnostic criteria and management are subject to subsequent guideline revisions.