

SYSTEMIC SCLEROSIS

(Scleroderma)

Autoimmunity, microvascular injury, and progressive fibrosis

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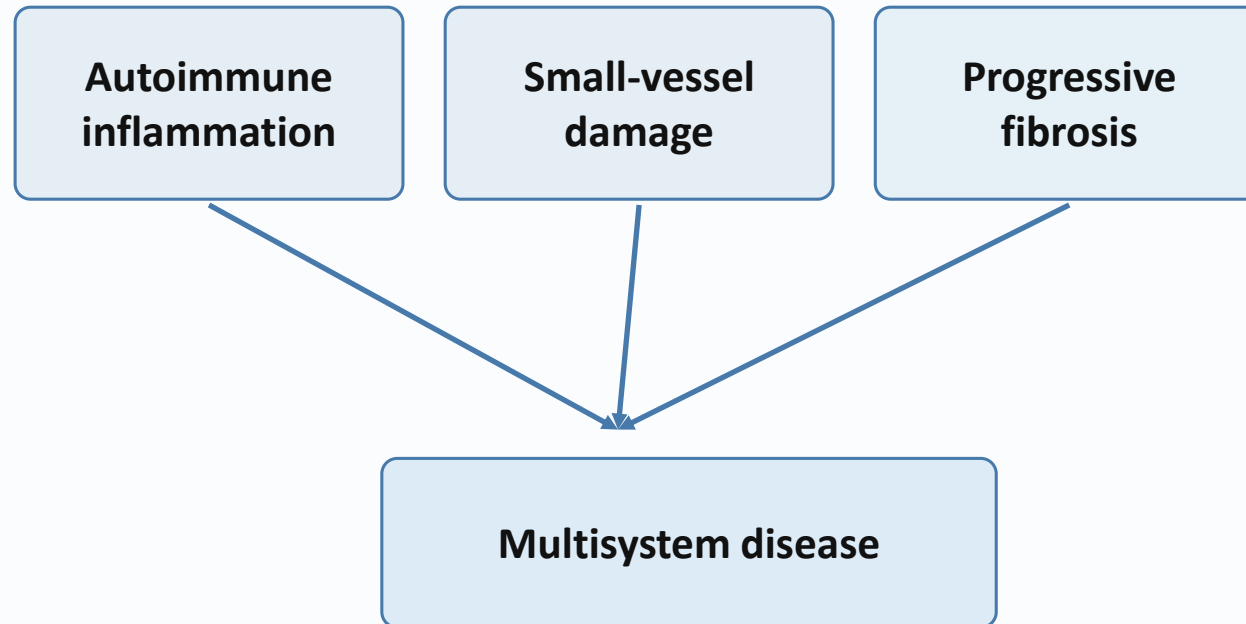
What this lecture explains

- Recognize the three defining pathologic processes.
- Distinguish diffuse and limited cutaneous phenotypes.
- Trace vascular and immune injury to organ fibrosis.
- Connect tissue morphology with clinical consequences.

Central question

How do small-vessel injury and persistent fibrogenic signaling produce multisystem disease?

The defining triad

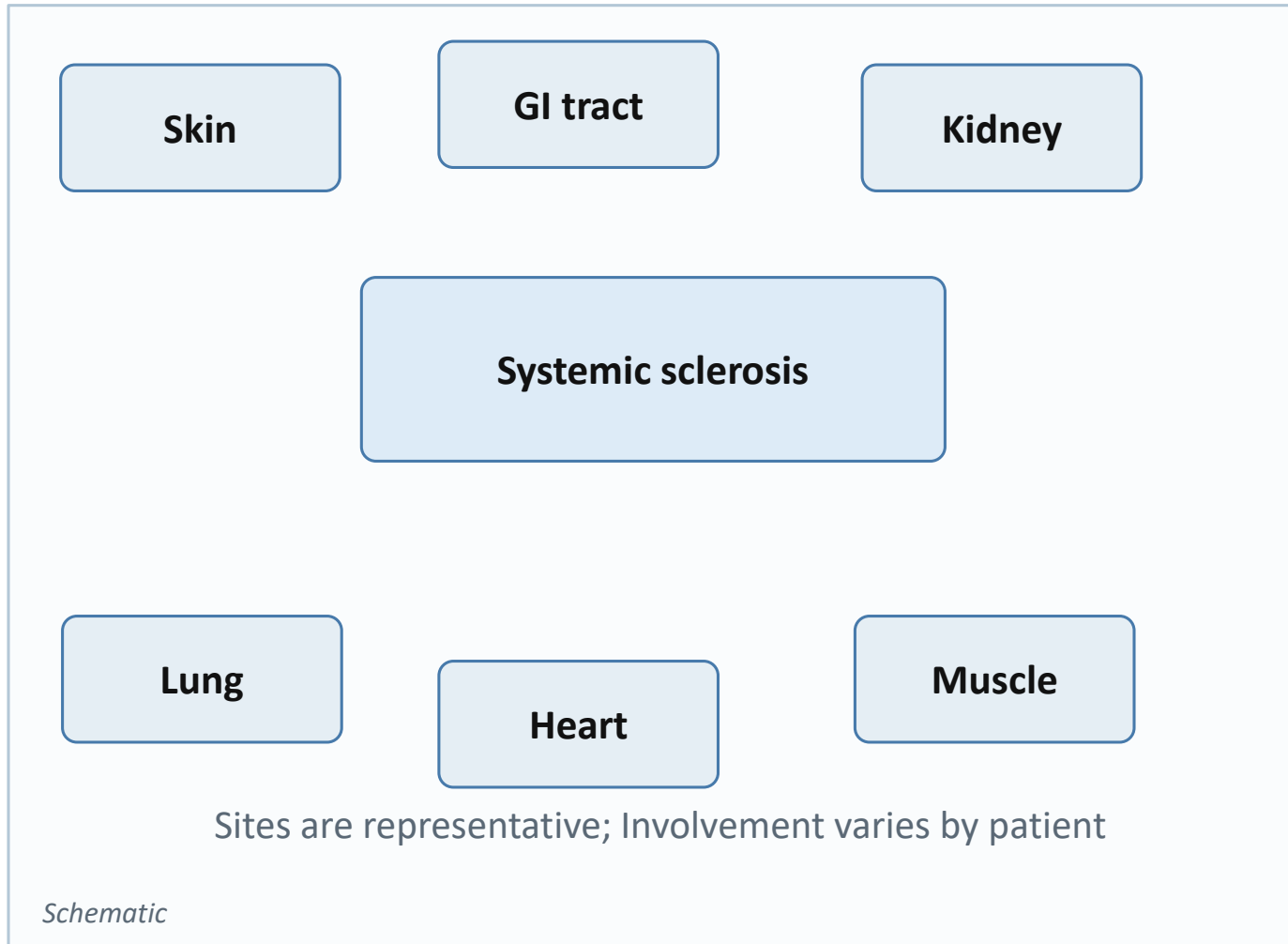


Interacting processes, not a single proven linear cause

Schematic

- Chronic inflammation is thought to reflect autoimmunity.
- Widespread damage involves the microvasculature.
- Progressive interstitial and perivascular fibrosis affects skin and viscera.

“Systemic” is more than skin sclerosis



- Skin involvement is conspicuous but is not the entire disease.
- Gastrointestinal tract, kidney, lung, heart, and muscle may be affected.
- Visceral fibrosis and vasculopathy determine many serious complications.

Two principal cutaneous phenotypes

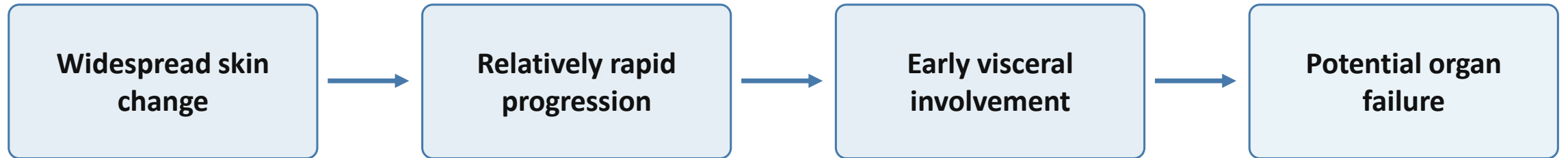
Diffuse cutaneous disease

- Widespread skin involvement near onset
- Often rapidly progressive
- Visceral involvement commonly early

Limited cutaneous disease

- Skin often restricted to fingers, forearms, face
- Organ involvement may emerge late
- Generally slower and less severe course

Diffuse disease: Timing matters



- The cutaneous extent provides a clinical clue to systemic risk.
- Extent is not equivalent to a quantitative organ-damage score.

Limited disease: Late does not mean absent

- Skin involvement may remain confined distally for years.
- Esophageal and pulmonary vascular disease may develop later.
- The source describes a comparatively favorable average course.
- Late visceral complications still warrant clinical attention.

Key distinction

Limited cutaneous involvement is not the same as organ-limited disease.

Diffuse versus limited: Pattern recognition

Feature	Diffuse	Limited
Cutaneous distribution	Widespread early	Fingers, forearms, face
Tempo	Often rapid	Often slower
Visceral involvement	Earlier	Can occur later
CREST phenotype	Not defining	Characteristic association

CREST: A five-feature clinical pattern

C

Calcinosis

R

Raynaud phenomenon

E

Esophageal dysmotility

S

Sclerodactyly

T

Telangiectasia

Schematic

- CREST is a recognized constellation in some patients with limited disease.
- The abbreviation denotes manifestations—not five obligatory diagnostic tests.
- Cutaneous, vascular, and gastrointestinal processes coexist.

Calcinosis and telangiectasia

Calcinosis

- Subcutaneous calcific deposits
- Can be focal or diffuse
- Particularly noted with CREST

Telangiectasia

- Dilated superficial small vessels
- Belongs to CREST constellation
- Reflects a vascular component of the phenotype

Raynaud phenomenon: A vascular clue

Baseline digital artery



Maintained flow

Episodic vasoconstriction



Reduced flow

Diagram illustrates functional constriction, not a clinical angiogram

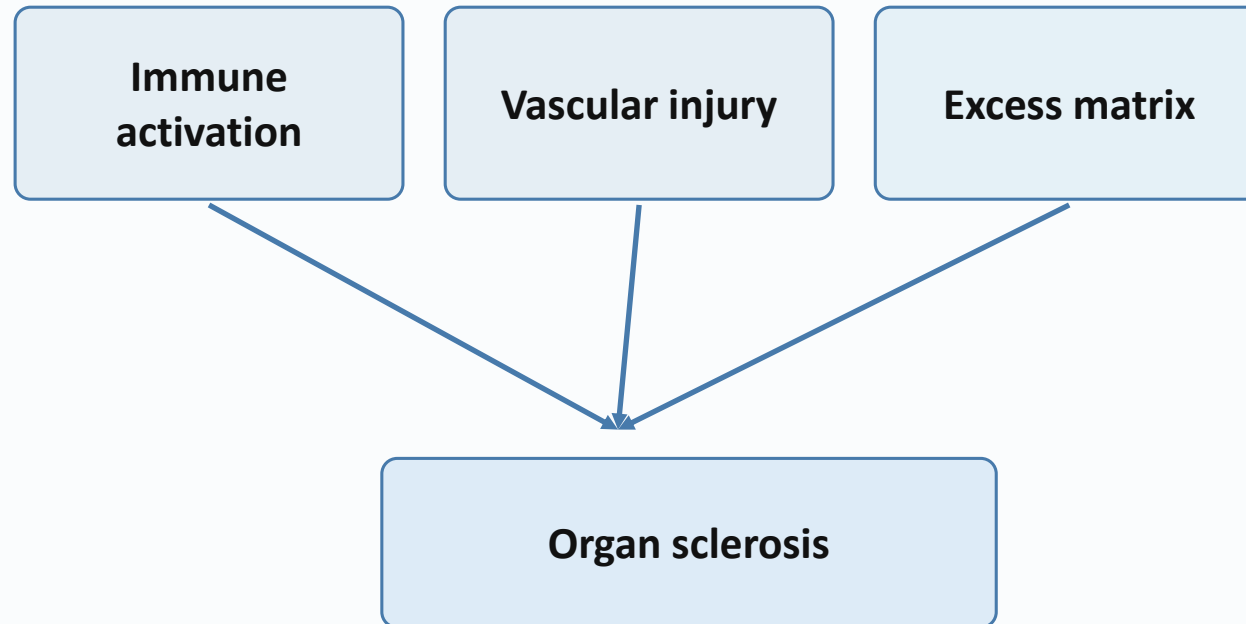
Schematic

- Episodes result from constriction of digital arteries and arterioles.
- Numbness and tingling may precede prominent sclerosis.
- Vasospasm and structural microangiopathy are related but distinct processes.

Organ distribution is uneven

Tissue	Principal pathologic process	Clinical consequence
Skin	Dermal sclerosis; vessel loss	Tight skin; limited movement
Esophagus	Muscular atrophy; fibrosis	Hypomotility; reflux
Kidney	Small-artery intimal lesions	Ischemia; hypertension
Lung	Fibrosis; vascular lesions	Respiratory dysfunction
Heart	Fibrosis; arteriolar change	Arrhythmia or failure

Three interrelated pathogenetic processes



Interacting processes, not a single proven linear cause

Schematic

- Autoreactive immune responses supply inflammatory mediators.
- Endothelial injury generates an obliterative vasculopathy.
- Fibroblast activation drives persistent extracellular-matrix deposition.

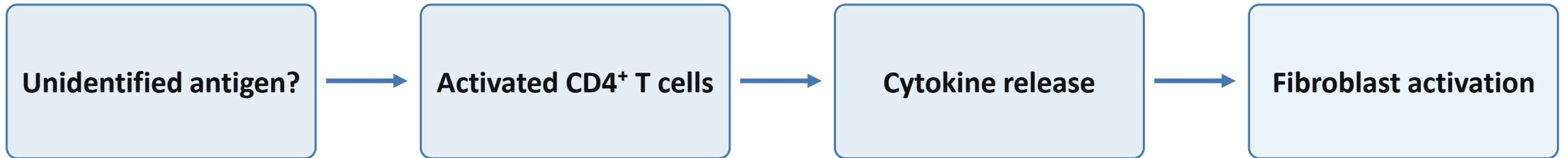
The initiating stimulus remains unknown

- The cause of systemic sclerosis has not been established.
- Unknown external stimuli are proposed in susceptible individuals.
- Immune activation and vascular injury may interact from early disease.
- The source does not establish a single obligatory causal order.

Interpretive caution

A working model is not proof of the initiating event.

CD4⁺ T cells in cutaneous lesions



- Activated T cells can be present despite relatively sparse skin inflammation.
- The putative inciting antigen has not been established.

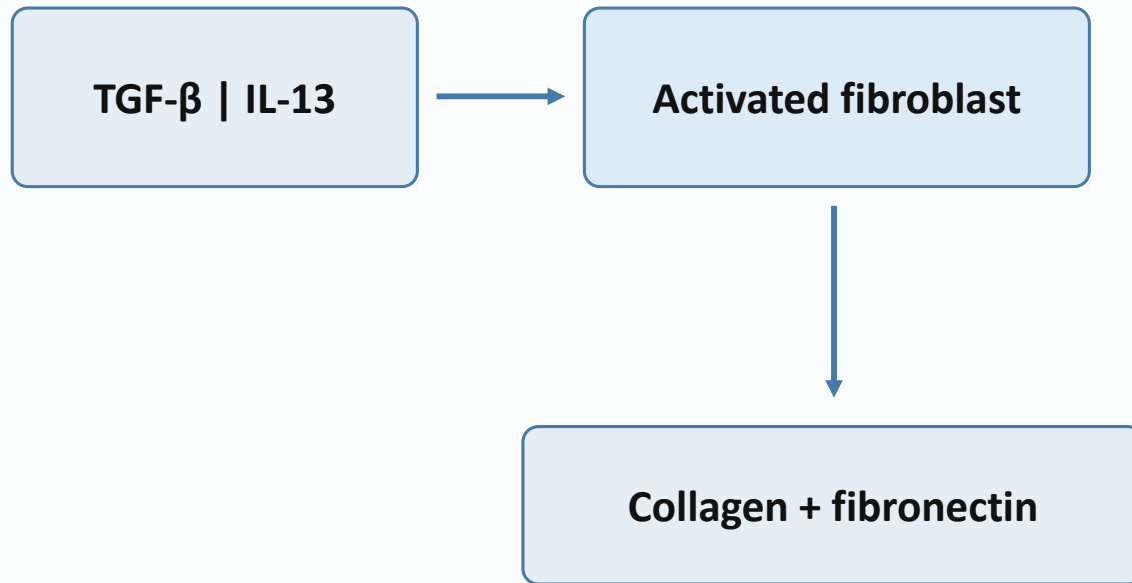
Th2-associated profibrotic signals

- Th2 cells have been isolated from affected skin.
- Transforming growth factor- β (TGF- β) is profibrotic.
- Interleukin-13 (IL-13) can promote matrix-gene expression.
- These signals act on fibroblasts rather than directly constituting collagen.

Mechanism

Cytokine signaling changes the transcriptional program of matrix-producing cells.

How cytokines expand the extracellular matrix



Cytokines promote extracellular-matrix gene expression

Schematic

- TGF- β and IL-13 promote collagen-gene transcription.
- Fibronectin and other matrix proteins can also increase.
- Accumulated matrix changes tissue architecture and organ compliance.

Inflammation persists without dense infiltrates

- Skin inflammatory infiltrates may be sparse.
- Cytokines still recruit and activate leukocytes.
- Persistent soluble signals may amplify fibroblast responses.
- Absence of florid inflammation does not exclude fibrotic disease.

Histology–biology link

The density of inflammatory cells does not measure prior or ongoing matrix signaling.

Autoantibodies: Association versus causation

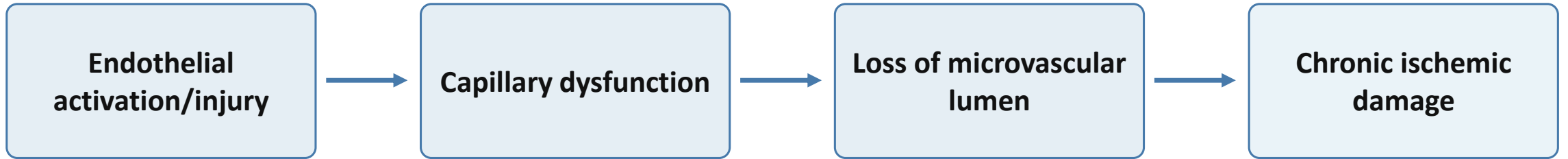
Supported by the source

- Antinuclear antibodies are common
- Antibody specificity can aid disease recognition
- Some profiles correlate with phenotype

Not established

- ANAs as the primary fibrotic driver
- A proven fibrosis-inducing mechanism for these ANAs
- A single antibody sufficient to explain every lesion

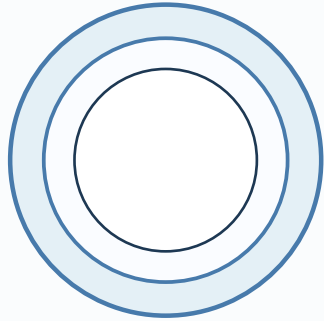
Microangiopathy may be very early



- The vascular lesion can precede prominent fibrosis.
- Whether vascular damage is initiating or secondary remains unresolved.

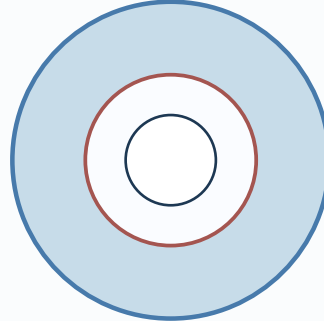
Digital arterial intimal proliferation

Relatively preserved vessel



Wide lumen

Intimal thickening



Reduced lumen

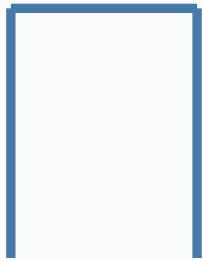
Original vessel cross-sections — not histology

Schematic

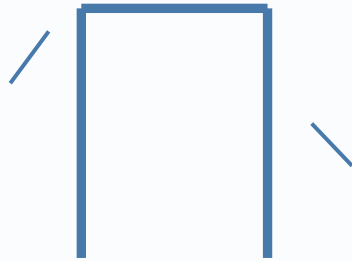
- Small arteries develop intimal thickening.
- Luminal narrowing restricts blood flow to distal tissues.
- This structural change complements episodic vasoconstriction.

Capillaries: Dilation, leak, and loss

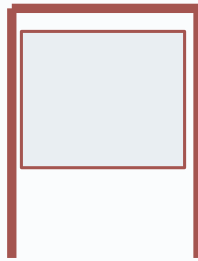
Preserved



Dilated / leaky



Lost / occluded



Conceptual capillary loop changes — no measured patient data

Schematic

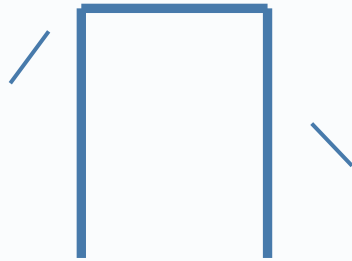
- Microvessels may be dilated and abnormally permeable.
- Endothelial destruction reduces capillary density.
- Progressive vessel loss contributes to chronic tissue hypoperfusion.

Nailfold capillaries evolve with disease

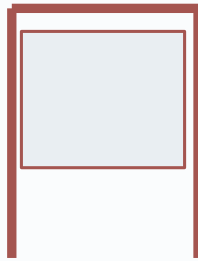
Loop preserved



Loop distorted



Loop obliterated



Conceptual capillary loop changes — no measured patient data

Schematic

- Capillary loops may be distorted early.
- Advanced stages may show capillary obliteration.
- Morphology makes otherwise hidden microvascular disease clinically visible.

Biologic evidence of endothelial and platelet activation

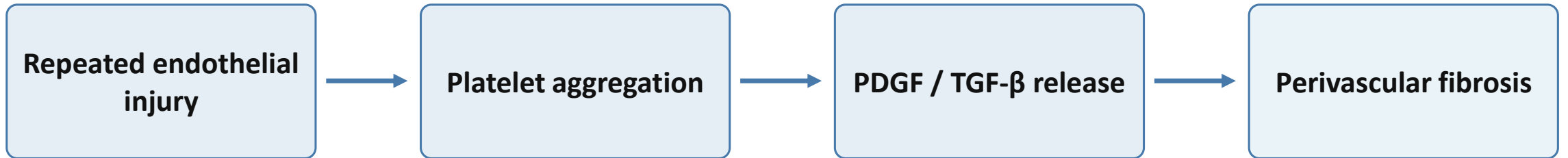
Endothelium

- Evidence of activation and injury
- Increased von Willebrand factor reported
- Early capillary and small-artery lesions

Platelets

- Increased circulating platelet aggregates
- Recruited to endothelial damage
- Provide fibrogenic mediators

Injury and repair amplify perivascular fibrosis



- PDGF = platelet-derived growth factor.
- The cycle may continue despite an unidentified primary injury.

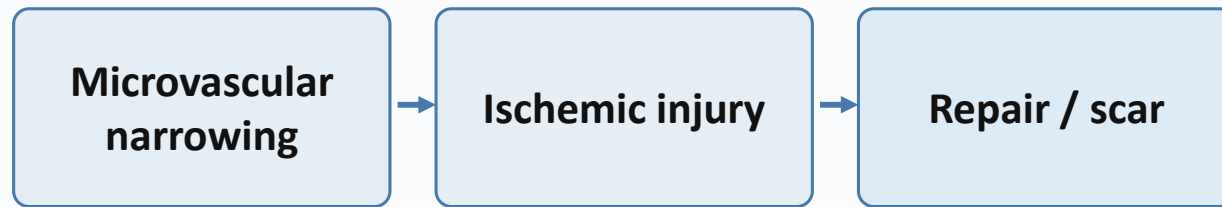
Vascular smooth-muscle abnormalities

- Small-vessel smooth muscle shows abnormal responses.
- Increased adrenergic receptor expression is described.
- Vasoconstriction adds to fixed structural narrowing.
- Prolonged perfusion impairment supports tissue injury and repair.

Two contributors

Functional vasospasm +
anatomic luminal loss →
ischemic burden.

The final common vascular consequence



Interacting mechanisms and consequences

Schematic

- Microvascular lumen progressively narrows.
- Reduced flow causes repeated or sustained ischemia.
- Repair of damaged tissues can leave permanent scarring.

Fibrosis has multiple converging drivers



Interacting mechanisms and consequences

Schematic

- Inflammatory cytokines stimulate matrix deposition.
- Alternatively activated macrophages may contribute.
- Fibroblast hyperresponsiveness and ischemic scarring reinforce deposition.

Fibroblast hyperresponsiveness

- Fibroblasts may react excessively to fibrogenic signals.
- Their persistent activation favors matrix over normal architecture.
- Clinical sclerosis emerges from net matrix accumulation.
- This describes abnormal cell behavior, not a confirmed initiating mutation.

Interpretation

A normal stimulus can yield an abnormal response if the effector cell is hypersensitive.

Intrinsic fibroblast abnormality: Unresolved

Observation

- Cultured patient fibroblasts can make excess collagen
- Suggests a cell-intrinsic component

Uncertainty

- Causal relationship in vivo remains unclear
- Cannot isolate this observation as the sole mechanism

Immune and vascular pathways converge



Interacting mechanisms and consequences

Schematic

- Cytokine-driven fibroblasts increase matrix synthesis.
- Vascular ischemia leads to injury followed by repair.
- Both pathways support progressive interstitial and perivascular fibrosis.

Sclerosis is an architectural lesion

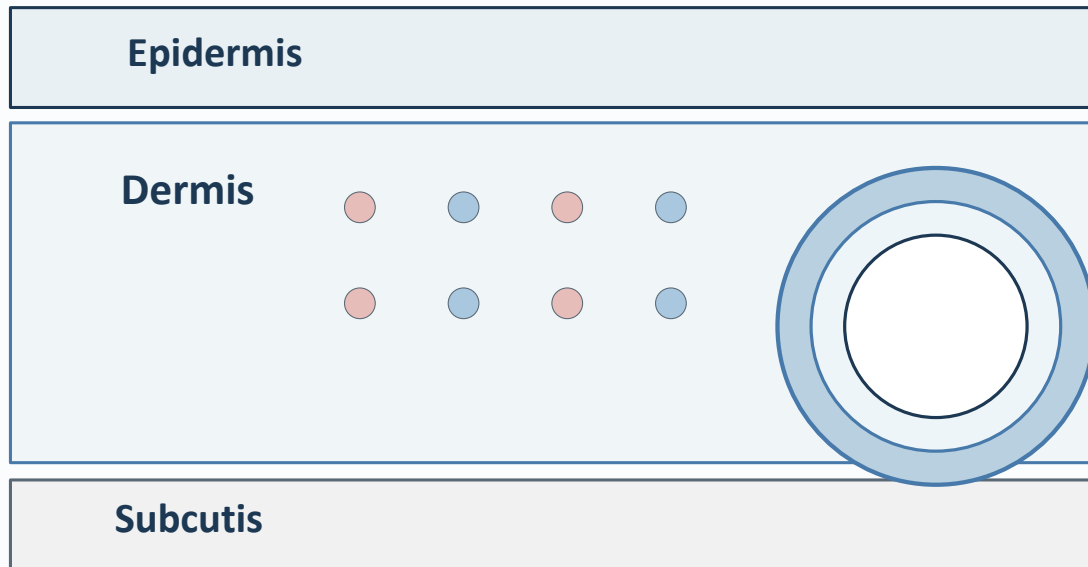
- Normal tissue is replaced or compressed by excess collagen.
- Vascular wall thickening accompanies parenchymal matrix deposition.
- Loss of elasticity and tissue-specific function follows.
- Morphology must be read together with organ physiology.

Tissue logic

Fibrosis is not merely a visible surface change; It alters the organ substrate.

Skin: Early inflammatory and vascular changes

Early affected skin



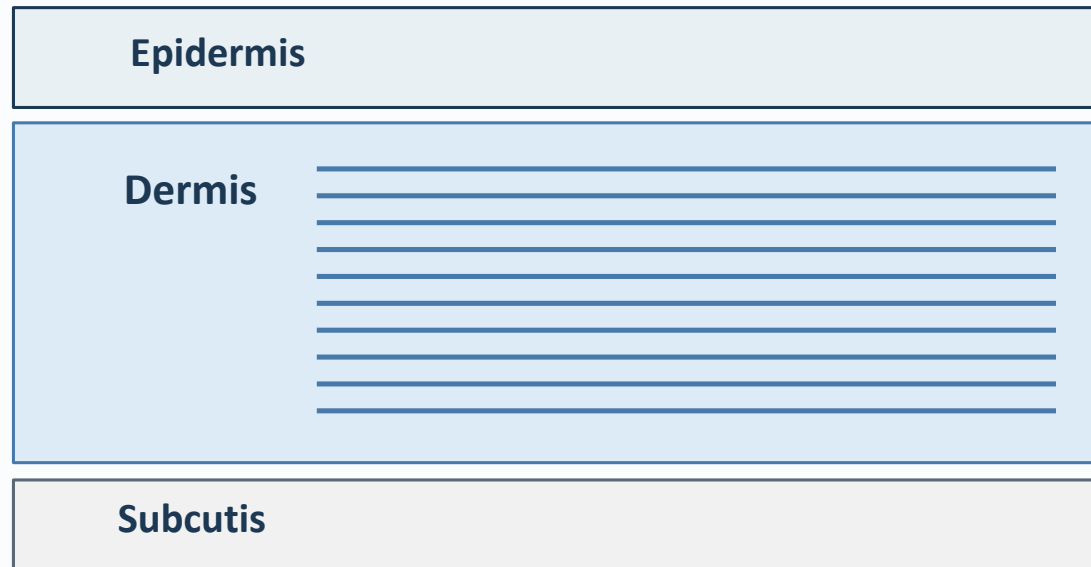
Perivascular immune cells and early vascular injury

Schematic

- Early lesions may contain perivascular CD4⁺ lymphocytes and edema.
- Collagen can become conspicuously eosinophilic.
- Small vessels show endothelial damage and basal-lamina thickening.

Skin: Progressive dermal sclerosis

Established sclerosis



Compacted dermal collagen with architectural attenuation

Schematic

- Dense compact collagen progressively fills the dermis.
- Fibrotic dermis becomes adherent to deeper subcutaneous tissue.
- Skin stiffness and retraction follow loss of normal architecture.

Epidermis and appendages change secondarily

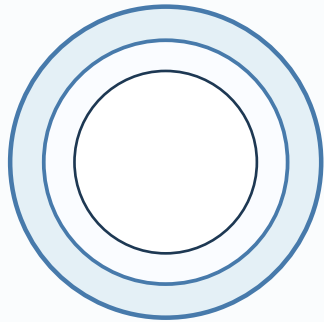
- Epidermal thinning and rete-peg loss may be present.
- Dermal appendages undergo atrophy.
- Compact collagen dominates the dermal compartment.
- These changes together explain tight, atrophic skin.

Histologic combination

Sclerosis + appendage loss + epidermal thinning, not simply increased collagen alone.

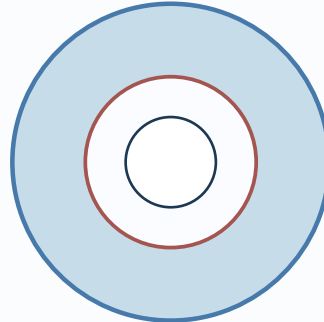
Dermal arterioles and capillaries

Relatively preserved vessel



Wide lumen

Intimal thickening



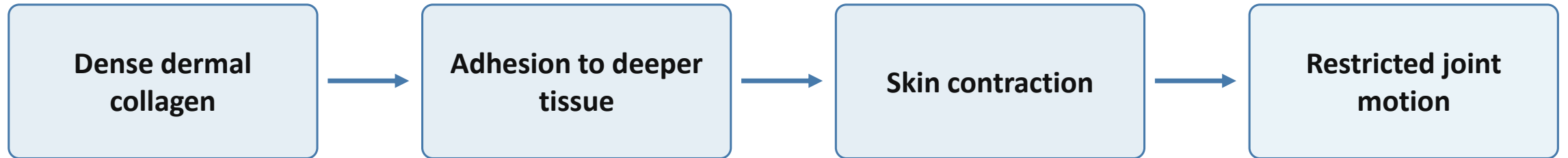
Reduced lumen

Original vessel cross-sections — not histology

Schematic

- Hyaline thickening of dermal vascular walls is described.
- Endothelial damage coexists with narrowing or partial occlusion.
- Dermal microangiopathy helps explain ischemic cutaneous changes.

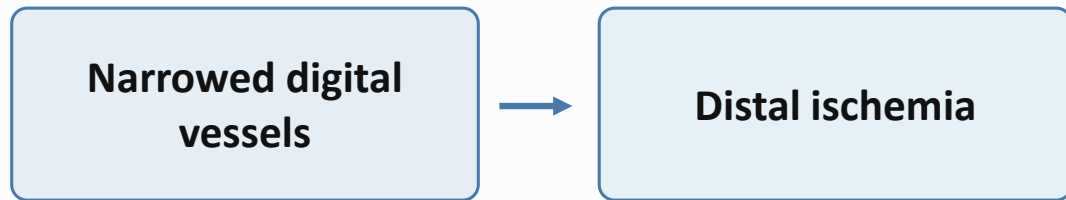
Advanced skin disease: Clinical consequence



- Finger tapering and a clawlike posture can occur.
- Facial tightening may produce a masklike appearance.

Digital ischemia causes tissue loss

Convergent digital injuries



Ulceration • terminal atrophy • tissue loss

Schematic

- Impaired blood supply can lead to digital ulcers.
- Terminal phalanges may undergo atrophy.
- Severe distal damage can culminate in autoamputation.

Cutaneous progression: Early to advanced

Stage	Microscopic emphasis	Clinical expression
Early	Perivascular inflammation; edema	Raynaud / evolving swelling
Established	Increasing compact dermal collagen	Skin tightening; reduced mobility
Advanced	Appendage loss; vascular obliteration	Atrophy; ulcers; contracture

The gastrointestinal tract is frequently involved

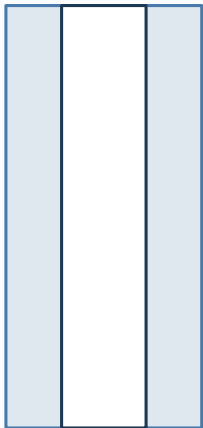
- Gastrointestinal involvement in ~90% of patients.
- Progressive muscular atrophy and fibrosis may occur at several levels.
- Esophageal disease is especially conspicuous.
- Dysphagia, reflux, and malabsorption reflect organ-specific lesions.

Mechanism

Muscular replacement by collagen impairs propulsion and sphincter function.

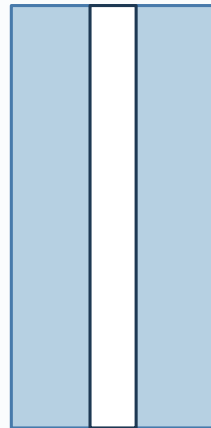
Esophagus: Atrophic muscularis and fibrosis

Normal wall



Motility preserved

Fibrotic muscularis



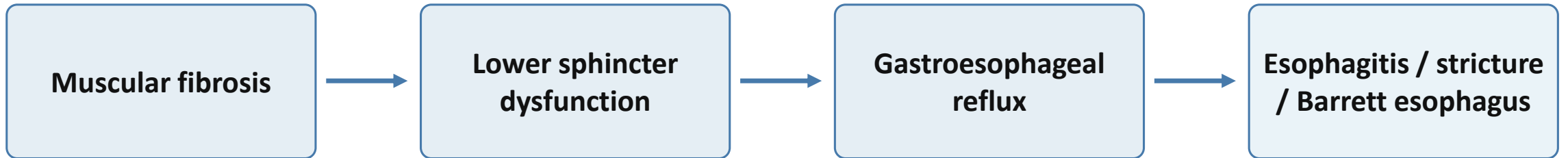
Hypomotility

Muscle replacement is schematic; Lumen size is illustrative only

Schematic

- Lower esophageal segments are particularly vulnerable.
- The muscularis is replaced by collagenous fibrosis.
- Reduced compliance and dysmotility impair bolus movement.

Esophageal dysfunction creates reflux injury



- The resulting mucosal pathology is a consequence of motility failure.
- This is a causal teaching chain, not a universal sequence in every patient.

Mucosal and submucosal changes

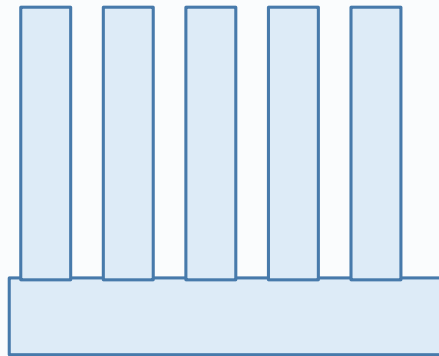
- Esophageal mucosa may be thinned or ulcerated.
- Lamina propria and submucosa can show excessive collagen.
- Mucosal injury combines with abnormal propulsion and reflux.
- Lower-esophageal dilatation may develop with atony.

Pathology correlation

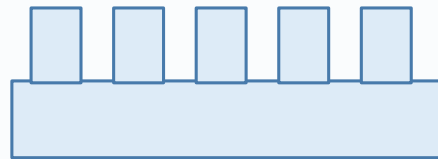
Muscle disease and mucosal lesions coexist through different mechanisms.

Small-bowel disease: Malabsorption

Preserved villi



Villus loss / flattening



Simplified villus architecture, not tissue microscopy

Schematic

- Small-intestinal involvement can impair absorptive function.
- Loss of villi and microvilli is described in the source.
- Malabsorption may produce weight loss and nutritional anemia.

Early joints: Inflammatory synovitis

- Inflammation can produce synovial hypertrophy and hyperplasia.
- Early joint changes may resemble rheumatoid arthritis.
- That destructive arthritis is uncommon.
- Later fibrosis alters mobility and soft-tissue function.

Differential teaching point

Similar synovitis does not imply the same degree of joint destruction.

Musculoskeletal disease changes with stage

Earlier

- Synovial inflammation
- Hypertrophy and hyperplasia
- Inflammatory changes occur before later fibrosis

Later

- Fibrous change is more conspicuous
- Restricted mobility and contracture
- Erosive joint destruction is not a hallmark

Inflammatory myositis is a recognized subset

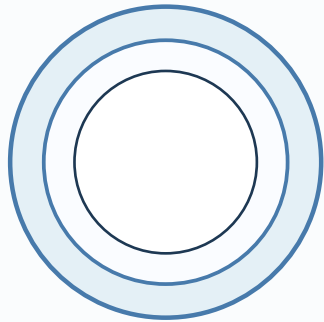
- Inflammatory myositis in a minority of patients (~10%).
- Muscle weakness need not be explained entirely by skin contracture.
- This demonstrates an additional immune-mediated tissue target.
- Inflammatory myopathy as a separate disease family lies outside this unit.

Scope

Recognize overlap without substituting a full lecture on inflammatory myopathies.

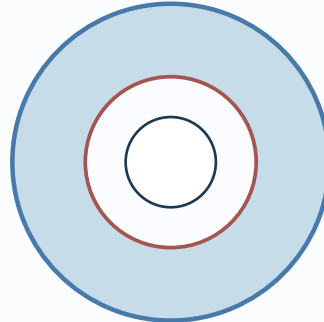
Renal injury predominantly affects vessels

Relatively preserved vessel



Wide lumen

Intimal thickening



Reduced lumen

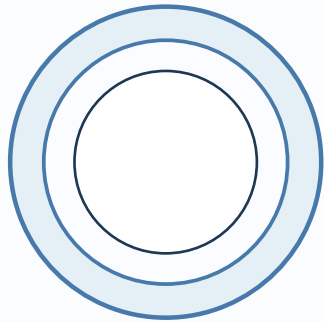
Original vessel cross-sections — not histology

Schematic

- Renal vascular lesions are more characteristic than a specific glomerular pattern.
- Interlobular arteries develop thickened intima and reduced lumen.
- Ischemic vascular injury underlies dangerous renal presentations.

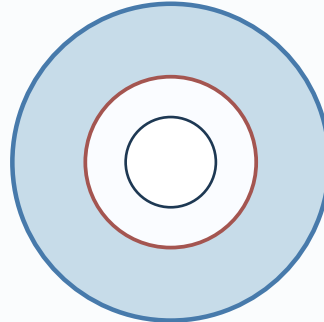
Concentric renal intimal change

Relatively preserved vessel



Wide lumen

Intimal thickening



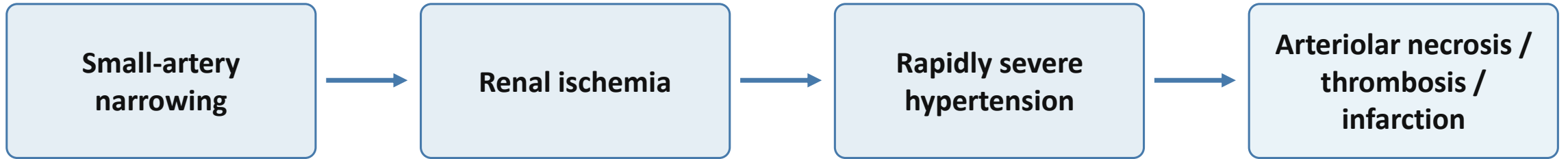
Reduced lumen

Original vessel cross-sections — not histology

Schematic

- Intimal accumulation includes mucinous or collagenous material.
- Concentric intimal-cell proliferation can narrow the lumen.
- The changes may resemble lesions associated with severe hypertension.

Hypertension can accelerate renal vascular injury



- The source describes a severe, rapidly progressive hypertensive subset.
- Not every patient with renal vascular lesions is hypertensive.

Scleroderma renal disease: What to recognize

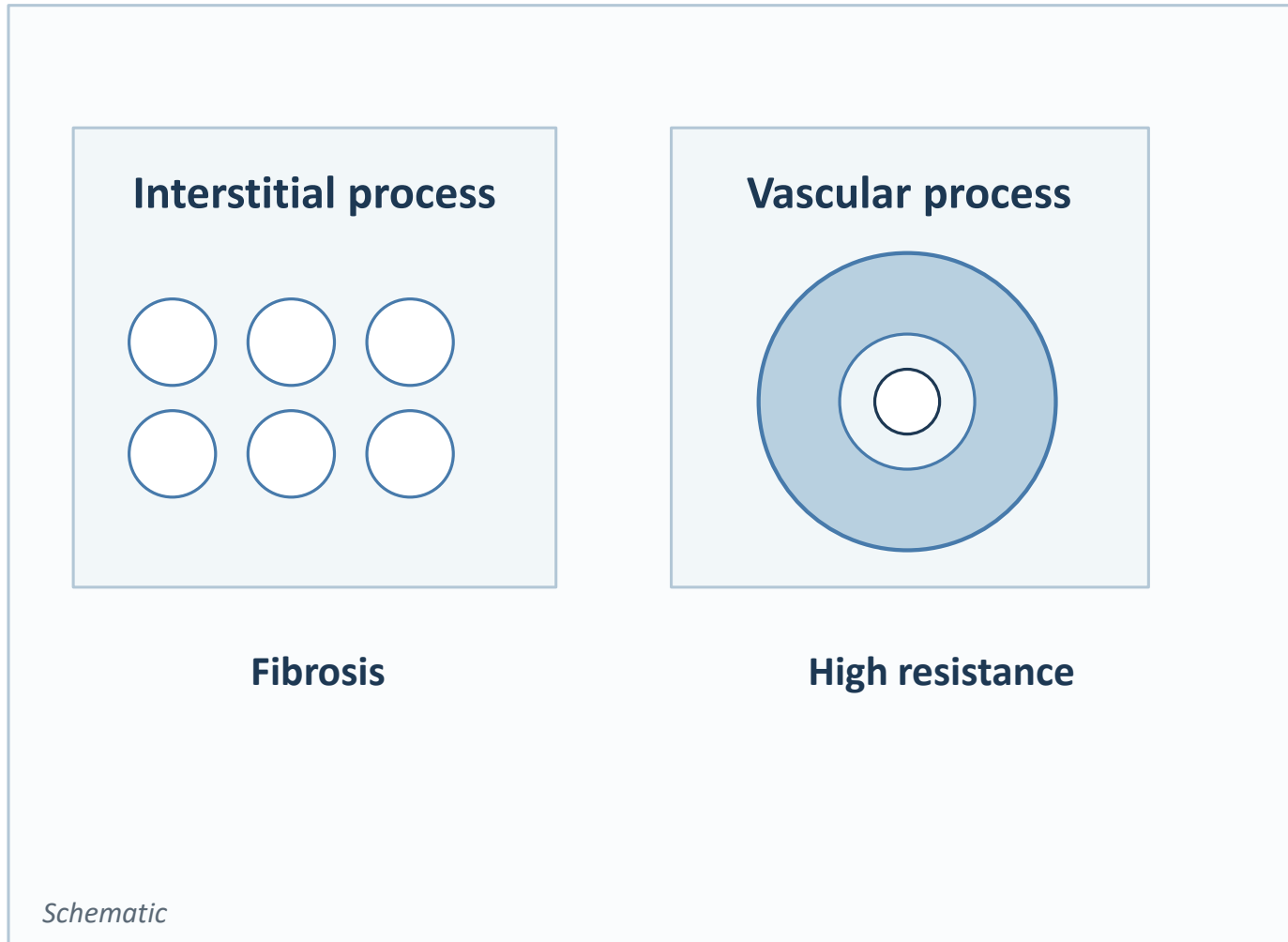
Primary lesion

- Vascular intimal thickening
- Luminal compromise and ischemia
- No specific glomerular lesion

Dangerous progression

- Severe hypertension
- Fibrinoid arteriolar necrosis
- Thrombosis and renal failure

Lungs: Two major pathologic pathways



- Pulmonary interstitial fibrosis impairs lung function.
- Pulmonary vascular dysfunction can produce hypertension.
- Parenchymal and vascular injury may coexist but are distinct lesions.

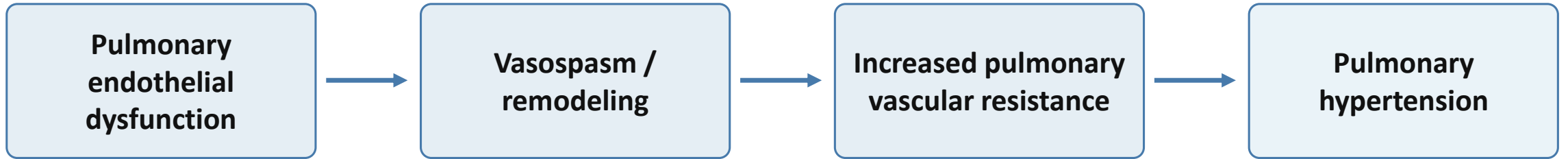
Pulmonary interstitial fibrosis

- The source reports pulmonary involvement in more than half of patients.
- Interstitial scarring alters the alveolar support framework.
- Fibrotic morphology may resemble idiopathic pulmonary fibrosis.
- Respiratory insufficiency is a major clinical consequence.

Morphologic limitation

Histology alone may not identify systemic sclerosis as the cause of fibrosis.

Pulmonary hypertension: Vascular mechanism



- This is a vascular pathway, not simply a synonym for interstitial fibrosis.
- Cardiac effects can develop from the increased pulmonary pressure.

Pulmonary fibrosis and hypertension are not interchangeable

Question	Interstitial fibrosis	Pulmonary vascular disease
Primary compartment	Interstitium / parenchyma	Pulmonary microvasculature
Mechanism	Matrix accumulation	Endothelial injury; vasospasm
Functional result	Restricted gas exchange	Raised vascular resistance
Clinical overlap	May coexist with vascular disease	May coexist with parenchymal fibrosis

Heart: Three types of reported lesions

Pericarditis + effusion

Myocardial fibrosis

Arteriolar thickening

- Pericarditis may be accompanied by effusion.
- Myocardial fibrosis alters the cardiac muscle substrate.
- Small intramyocardial arteries can develop wall thickening.

Schematic

Myocardial pathology explains functional impairment

- Myocardial fibrosis can contribute to arrhythmia.
- Diffuse or focal dysfunction may culminate in cardiac failure.
- Pulmonary disease may impose an additional right-heart burden.
- Morphologic myocardial involvement may exceed symptomatic involvement.

Clinicopathologic distinction

Direct myocardial injury and secondary right-heart stress have different causes.

A multisystem lesion-to-symptom map

Structural lesion	Physiologic effect	Clinical clue
Dermal collagen increase	Skin contraction	Sclerodactyly
Digital arterial disease	Distal ischemia	Raynaud; ulcer
Esophageal muscle fibrosis	Poor motility	Dysphagia; reflux
Renal arterial disease	Renal ischemia	Hypertension / renal failure
Pulmonary scarring	Reduced respiratory function	Dyspnea

Clinical presentation: Demographic pattern

- A female-to-male ratio of approximately 3:1.
- Peak incidence is described in the 50- to 60-year age group.
- Clinical recognition rests on the syndrome and its organ pattern.
- Population figures are descriptive, not diagnostic criteria.

Use appropriately

Demographics change pretest expectation; They cannot establish or exclude disease.

Antinuclear antibodies: Role in evaluation

- Antinuclear antibodies are frequent in systemic sclerosis.
- Their antigen specificity provides phenotypic information.
- Antibody status should be integrated with skin and organ findings.
- The pathogenic role of common ANAs remains incompletely resolved.

Three uses to separate

Diagnostic association ≠
prognostic correlation ≠
proven pathogenic
mechanism.

Anti-topoisomerase I (anti-Scl-70)

Recognition

- Targets DNA topoisomerase I
- Described as highly specific
- Associated with diffuse disease

Clinicopathologic correlation

- Pulmonary fibrosis more likely
- Peripheral vascular disease association
- Frequency varies with population and assay

Anticentromere antibodies

Recognition

- Associated with limited phenotype
- Often seen with CREST pattern
- Correlates with a different clinical course

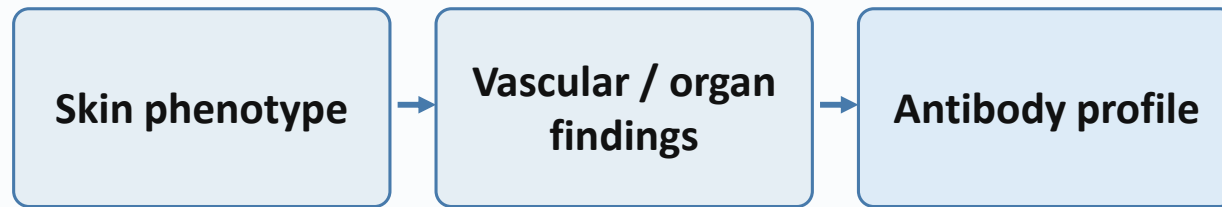
Clinical significance

- Visceral involvement may occur later
- Late pulmonary hypertension remains possible
- Does not imply complete absence of internal disease

Two antibodies: Do not overinterpret

Characteristic	Anti-topoisomerase I	Anticentromere
Typical phenotype	Diffuse more often	Limited / CREST more often
Important association	Interstitial lung / vascular disease	Limited skin; late organ disease
Interpretive role	Phenotypic / prognostic marker	Phenotypic / prognostic marker
Not proof of	Antibody-driven fibrosis	No future visceral disease

The clinical diagnosis is an integrated pattern



Integrated clinicopathologic assessment

Schematic

- Skin distribution establishes a major phenotypic clue.
- Raynaud and microvascular features reveal early vascular disease.
- Visceral manifestations and antibody profiles refine the picture.

Overlap disorders: Avoid a single-feature diagnosis

- Some features overlap with systemic lupus erythematosus.
- Synovial inflammation overlaps clinically with rheumatoid arthritis.
- Inflammatory muscle disease can overlap with myositis.
- The combination of sclerosis and microangiopathy is more distinctive.

Boundary

This lecture does not replace disease-specific classification criteria.

Case: Progressive skin tightness

Hypothetical vignette: A patient develops rapid extension of skin tightening beyond the hands, followed by dysphagia and respiratory symptoms.

Which phenotypic pattern is most consistent?

Reasoning

- Diffuse cutaneous disease is favored by proximal early spread.
- Early visceral symptoms reinforce a higher-risk pattern.
- Skin distribution alone does not prove a particular visceral lesion.

Case: Distal skin disease with CREST features

Hypothetical vignette: Long-standing Raynaud episodes are followed by distal skin tightening, calcific deposits, and esophageal dysmotility.

Which clinical constellation does this illustrate?

Reasoning

- A limited cutaneous / CREST-associated pattern is plausible.
- Raynaud illustrates vascular dysfunction; Dysmotility reflects tissue disease.
- A limited skin phenotype does not exclude later organ involvement.

Case: Abrupt renal deterioration

Hypothetical vignette: In a patient with established skin sclerosis, blood pressure increases rapidly as renal function declines.

Which tissue lesion is the major mechanistic concern?

Reasoning

- Renal small-artery intimal and arteriolar vascular injury.
- Luminal compromise may intensify ischemia and severe hypertension.
- The source does not define a specific primary glomerular lesion.

Case: Two mechanisms of dyspnea

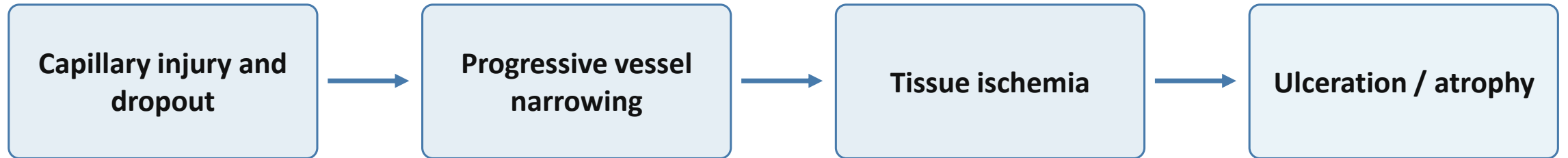
Hypothetical vignette: A person with systemic sclerosis develops progressive dyspnea; The lecture identifies both parenchymal and vascular pulmonary lesions.

Which two distinct processes should be considered?

Reasoning

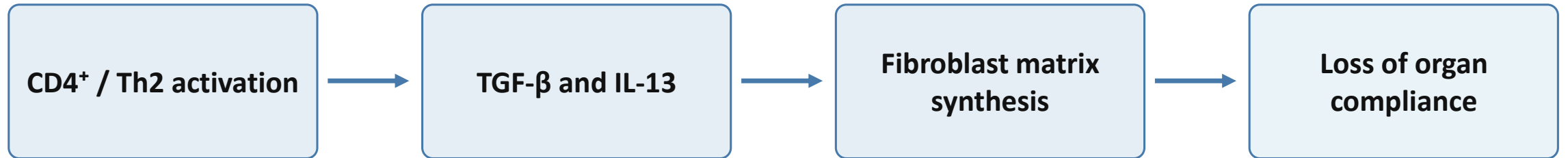
- Interstitial lung fibrosis affecting parenchymal structure.
- Pulmonary vasculopathy contributing to pulmonary hypertension.
- The two processes are mechanistically distinct and may coexist.

Sequence: Microvascular disease to tissue loss



- This explains digital injury without attributing every lesion to inflammation.
- Episodic Raynaud is an early, functional component of vascular disease.

Sequence: Cytokines to sclerotic organ failure

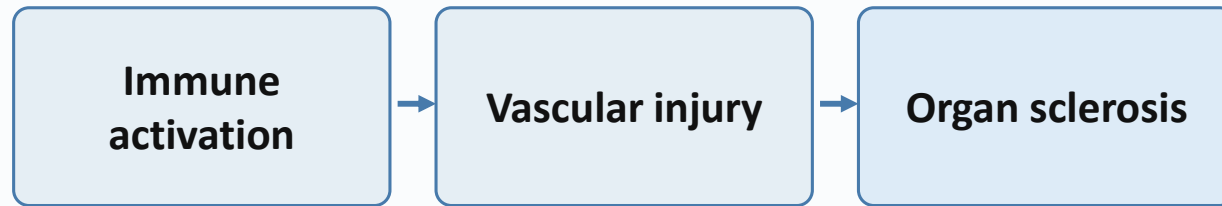


- Cytokine activation and chronic repair reinforce one another.
- The same general lesion has organ-specific physiologic consequences.

The essential diagnostic distinctions

Do not confuse	With	Why the difference matters
Limited skin disease	Absence of systemic disease	Viscera can be affected late
Raynaud vasospasm	Only vascular mechanism	Fixed obliterative lesions also occur
Positive ANA	Proven cause of fibrosis	Causation not established
Pulmonary fibrosis	Pulmonary hypertension	Distinct primary compartments
Renal disease	Primary glomerulonephritis	Vascular lesions dominate

Mechanism-to-morphology synthesis



Interacting mechanisms and consequences

Schematic

- Early endothelial injury narrows and depletes small vessels.
- Immune-derived cytokines promote fibroblast matrix production.
- Progressive sclerosis and ischemia disrupt organ-specific function.

Five lasting clinicopathologic principles

- Systemic sclerosis combines autoimmunity, vasculopathy, and fibrosis.
- Diffuse versus limited phenotypes chiefly differ in distribution and timing.
- Organ manifestations follow the compartment injured in each tissue.
- Antibody associations aid interpretation but do not prove causality.

Synthesis

Recognize the vascular and fibrotic processes together—not as competing explanations.

Source and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 6, Diseases of the Immune System: Systemic Sclerosis (Scleroderma), pp. 204–206.
- Diagrams are original editable teaching schematics, not diagnostic microscopy.
- Clinical vignettes are hypothetical and illustrate the textbook mechanisms.