

# Necrotizing lesions of the nose and upper airways

Invasive fungal infection · Granulomatosis with polyangiitis · Extranodal NK/T-cell lymphoma

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Mechanisms · Morphology · Clinicopathologic differential

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## Learning objectives

- Recognize the three major etiologic categories of destructive nasal lesions.
- Explain how fungal invasion, vasculitis, and neoplastic angioinvasion cause tissue necrosis.
- Distinguish the characteristic morphology and relevant associated findings.
- Apply a tissue- and context-based differential to selected clinical patterns.

# A destructive nasal lesion is a pattern, not a diagnosis

Ulceration and necrosis may arise through fundamentally different processes.

## **Infection**

Invasive hyphae damage vessels and adjacent tissue.

## **Inflammation**

Necrotizing granulomatous vasculitis disrupts vascular integrity.

## **Neoplasia**

Angioinvasive lymphoid tumor produces ischemic necrosis.

## Three major causes named

### **Acute invasive fungi**

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Mucormycosis and invasive aspergillosis

Particularly with diabetes or immunosuppression

### **GPA**

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Necrotizing granulomas and vasculitis

May involve upper airway, lungs, and kidneys

### **Extranodal NK/T lymphoma**

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EBV-associated malignant lymphoid proliferation

Destructive nasal/nasopharyngeal mass

# The local anatomical field

## **Nasal cavity**

Ulceration and destructive mucosal lesions

## **Paranasal sinuses**

Entry and extension of invasive disease

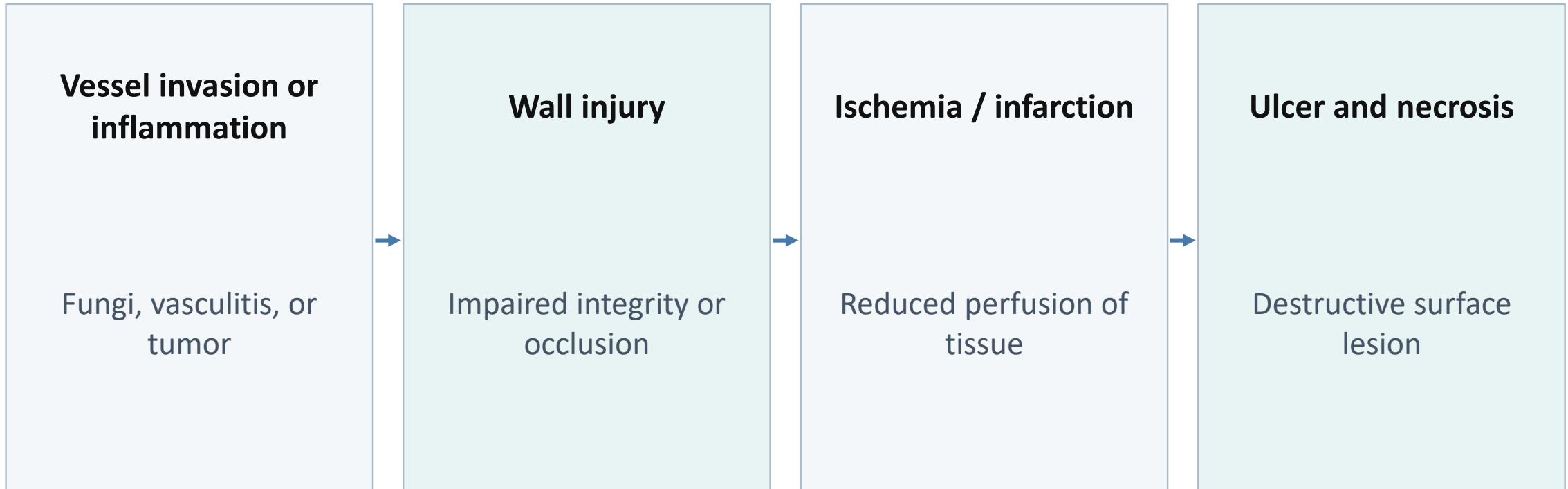
## **Nasopharynx / upper airway**

Malignant and inflammatory injury

## **Orbit / cranial vault**

Potential sites of serious spread

# Why the vessels matter



Different etiologies converge on loss of tissue viability.

# The competing mechanisms of necrosis

## Fungi

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Hyphae enter tissues and  
arterial walls

Thrombosis, infarction,  
extension

## GPA

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Granulomatous inflammation  
plus necrotizing vasculitis

Ulceration and local  
destruction

## NK/T lymphoma

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Neoplastic cells surround and  
invade vessels

Ischemic necrosis within mass

## Context: Ordinary rhinitis is different

### **Common rhinitis**

Edematous, red mucosa

Catarrhal discharge; Usually transient

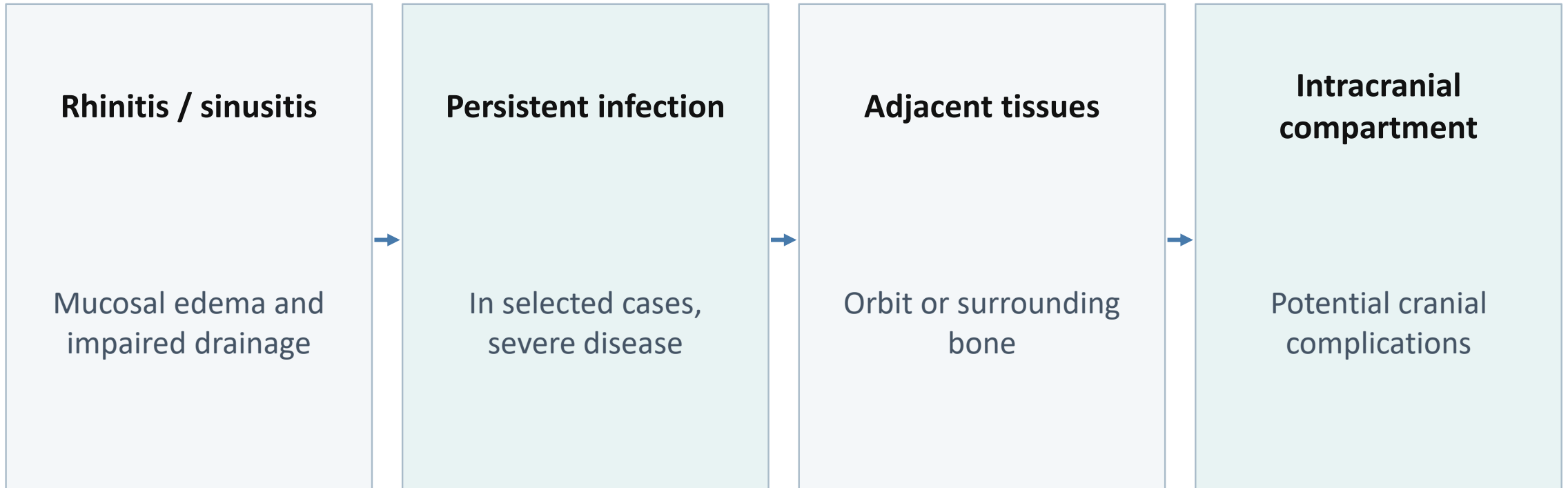
### **Destructive pathology**

Ulceration with deep necrosis

Requires explanation beyond routine rhinitis

Superinfection can coexist with a primary destructive process.

## Sinusitis can become a pathway for extension



Spread beyond the sinuses is uncommon but consequential.

## Shared necrosis, distinct clinical contexts

| Pattern                                           | Clues in provided Robbins sections        |
|---------------------------------------------------|-------------------------------------------|
| <b>Predisposing immune/metabolic defect</b>       | Prioritize invasive fungal infection      |
| <b>Sinus disease with lung and renal findings</b> | Consider granulomatosis with polyangiitis |
| <b>Destructive mass with EBV-associated tumor</b> | Consider extranodal NK/T-cell lymphoma    |

## Do not diagnose by necrosis alone

- Necrotic debris can conceal the process responsible for injury.
- The key tissue features differ: Fungal hyphae, granulomatous vasculitis, or neoplastic lymphoid cells.
- Clinical associations and lesions at distant sites provide vital context.
- A concurrent bacterial infection may complicate, rather than explain, an underlying neoplasm.

# Interpretation begins with three questions

## Necrotizing ulceration / mass

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graph TD; A[Necrotizing ulceration / mass] --> B[Are fungal elements invading tissue?]; A --> C[Is there granulomatous vasculitis?]; A --> D[Is there angioinvasive atypical lymphoid proliferation?];
```

**Are fungal elements invading tissue?**

Invasive fungal infection

**Is there granulomatous vasculitis?**

GPA in suitable clinical context

**Is there angioinvasive atypical lymphoid proliferation?**

Extranodal NK/T lymphoma

## Invasive fungal infection: Fundamental lesion

- Acute invasive fungal infection is a key cause of necrotizing nasal lesions.
- Mucormycosis is specifically emphasized for diabetic and immunosuppressed patients.
- Invasion of vascular structures distinguishes dangerous tissue-destructive disease.
- Invasive aspergillosis can also produce comparable rhinocerebral lesions.

# Causative fungi in mucormycosis

Environmental members of Mucormycotina.

## **Mucor species**

Opportunistic infection after spore exposure

## **Rhizopus species**

An important cause of invasive disease

## **Rhizomucor / Cunninghamella**

Additional implicated genera

# Who is vulnerable to mucormycosis?

Host defense and metabolic factors shape invasion risk.

## **Defective leukocyte defense**

Neutropenia or corticosteroid exposure

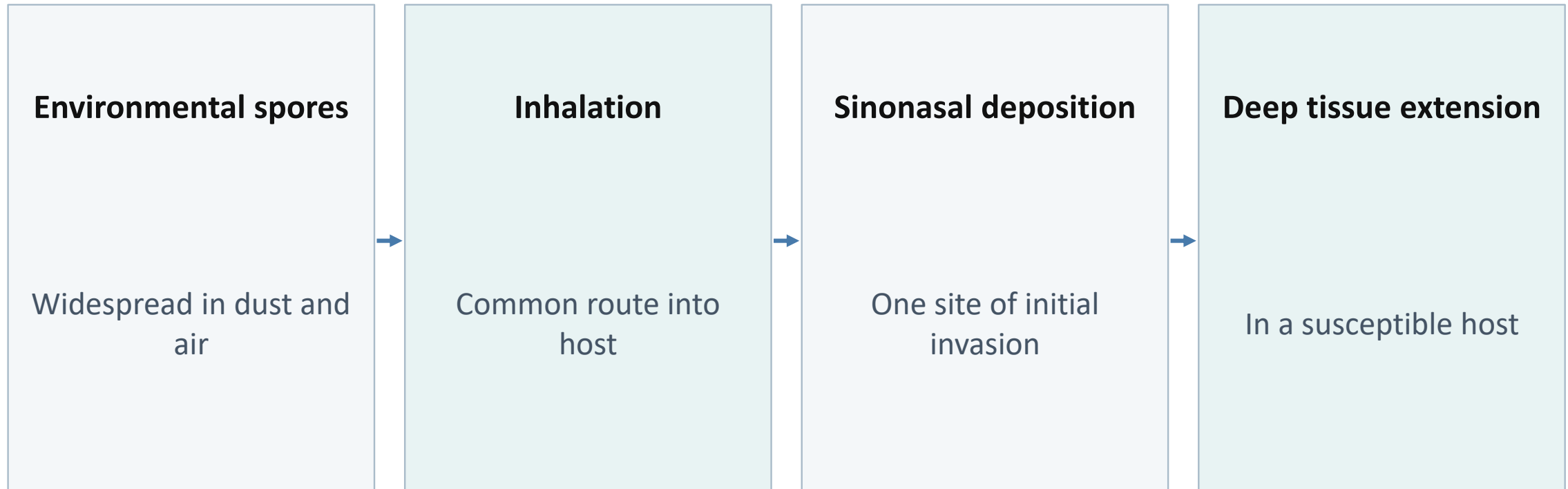
## **Metabolic environment**

Diabetes mellitus; Especially ketoacidosis

## **Increased available iron**

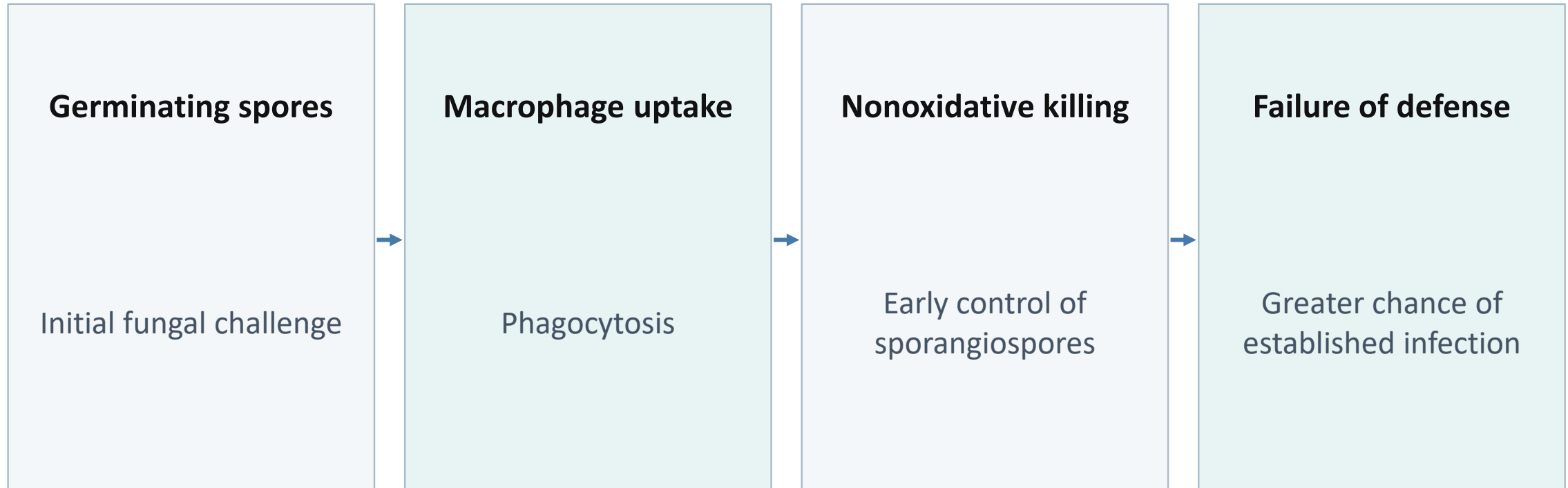
Iron overload; Deferoxamine treatment

# Airborne spores establish the route of entry



Percutaneous and gastrointestinal routes occur but are less relevant to nasal disease.

# Macrophages provide the early barrier



Protection depends on functional innate immune cells.

# Neutrophils confront established hyphae

## Effective defense

Neutrophils directly damage hyphal walls

Growth constrained after germination

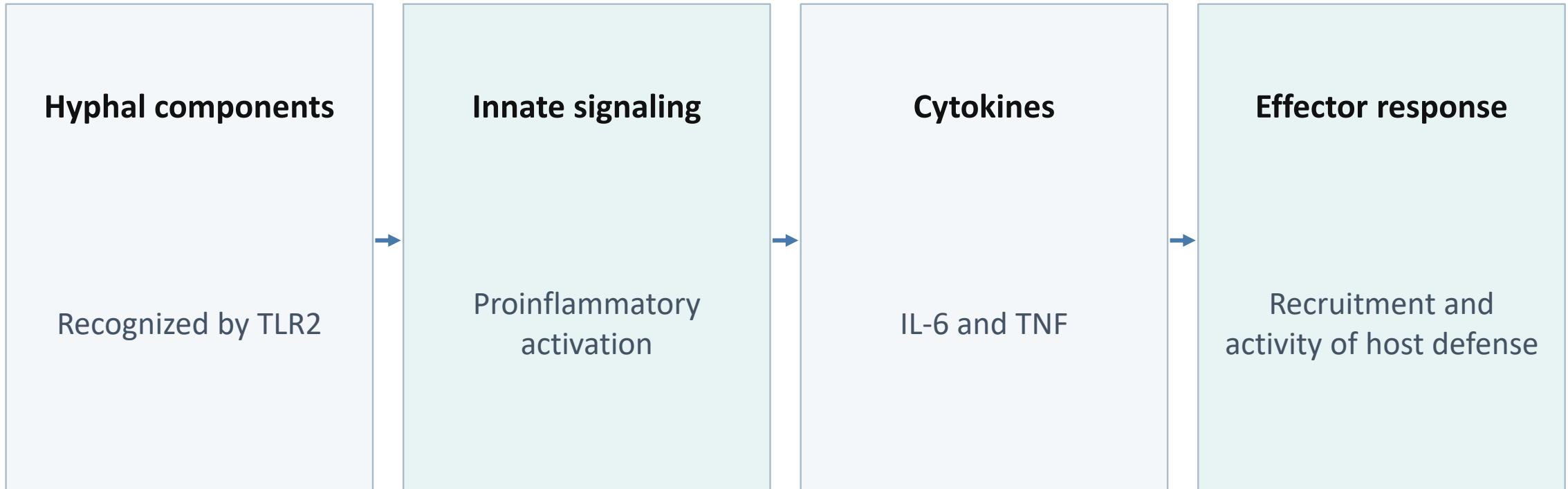
## Compromised defense

Fewer or dysfunctional neutrophils

Invasion becomes more likely

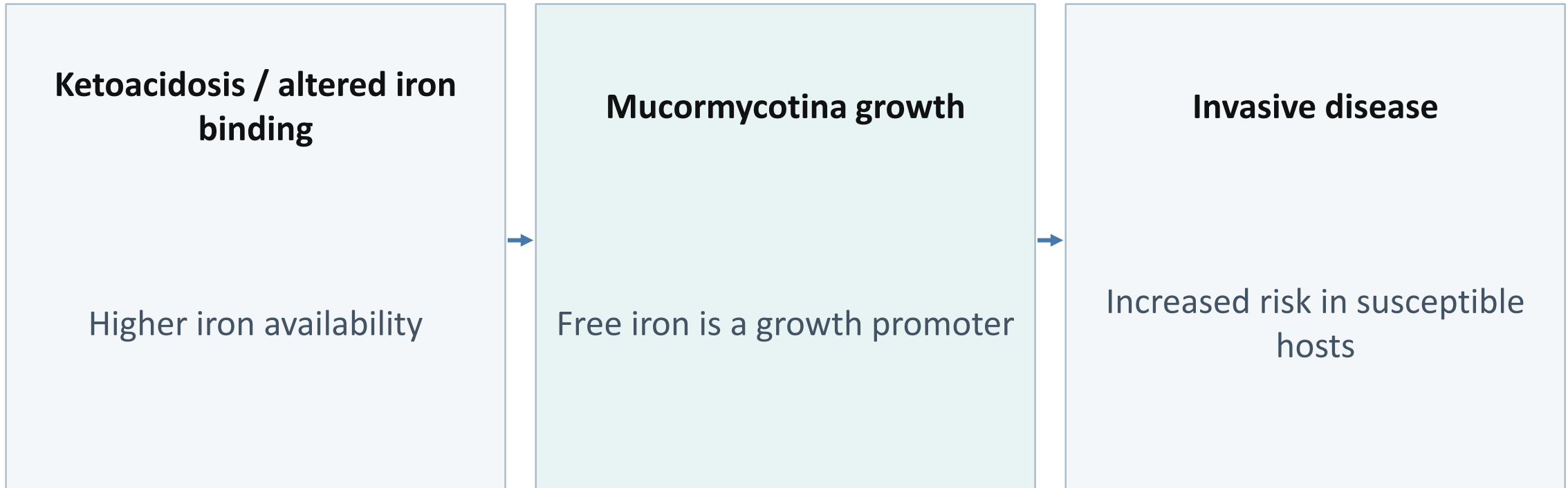
The fungal challenge changes from spores to invasive hyphae.

# The innate inflammatory response



Inflammation alone does not compensate for severe phagocyte dysfunction.

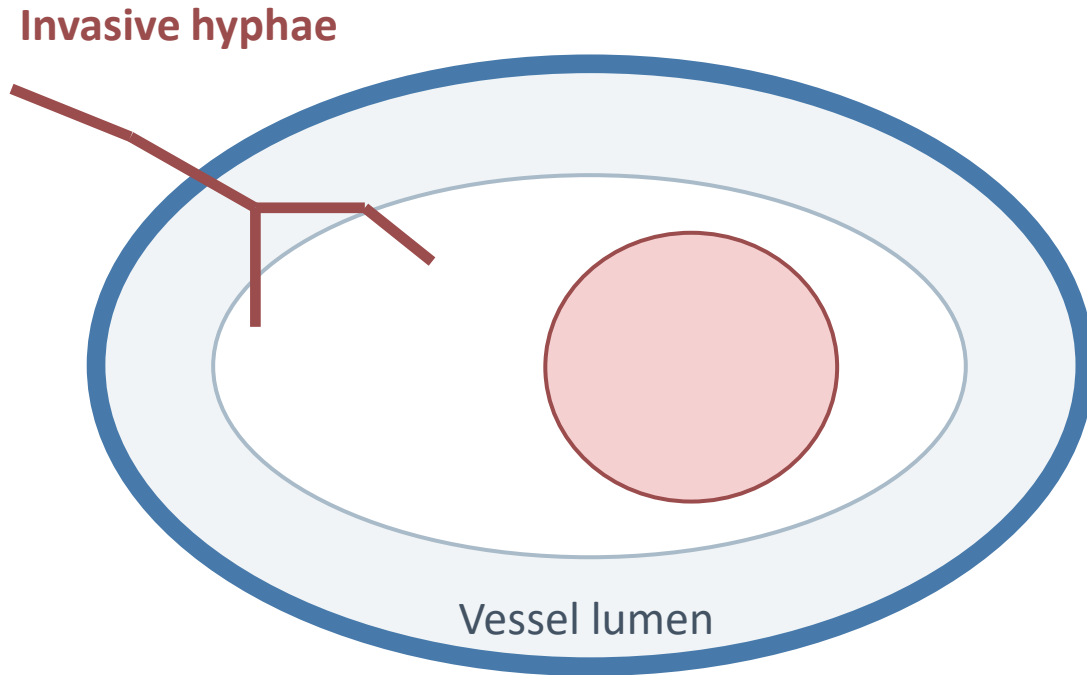
# Free iron favors fungal growth



Deferoxamine may also function as a siderophore for these fungi.

# Angioinvasion is the destructive turning point

*Schematic – not a histologic image*



- Hyphae invade arterial walls.
- Thrombi compromise distal perfusion.
- Necrosis develops in surrounding tissue.

# Mucormycosis: Defining tissue morphology

- Broad hyphae of variable width are characteristically pauciseptate or nonseptate.
- Frequent approximately right-angle branching is described.
- Fungal elements may be demonstrable on H&E and special fungal stains.
- Arterial wall invasion and adjacent necrosis provide the destructive context.

# Mucorales versus Aspergillus: Hyphal pattern

## Mucormycotina

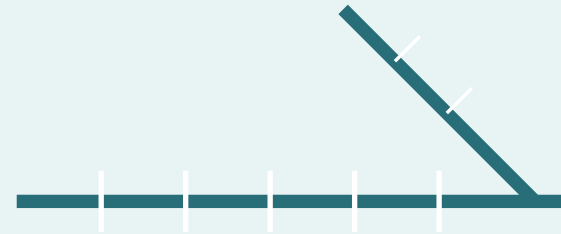


Broad, irregular

Pauciseptate / nonseptate

Often near-right-angle branching

## Aspergillus



Narrower, more uniform

Septate hyphae

Typically acute-angle branching

Schematic morphology, not a photomicrograph

## Aspergillus can also invade vessels

- Vascular invasion in invasive aspergillosis.
- Hemorrhagic infarction may accompany necrotizing inflammation.
- Rhinocerebral aspergillosis in immunosuppressed patients can resemble mucormycosis.
- Morphology and clinical setting together guide interpretation of fungal lesions.

# The major rhinocerebral route

## **Paranasal sinuses**

Frequent initial disease location

## **Periorbital tissues**

Contiguous spread

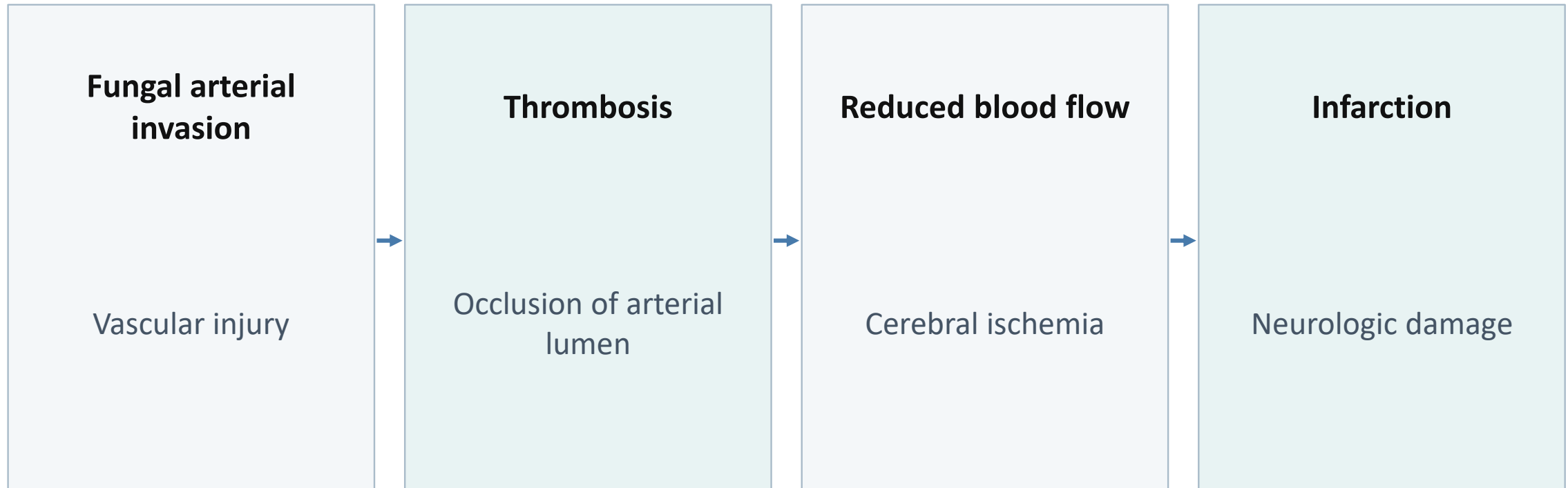
## **Cranial vault**

Further penetration

## **Brain / arteries**

Meningoencephalitis or infarction

## Arterial invasion explains cerebral infarcts



Rhinocerebral infection can also be complicated by meningoencephalitis.

# The sinus lesion can be only the beginning

## **At the primary site**

Mucosal and deep tissue necrosis

Local angioinvasion

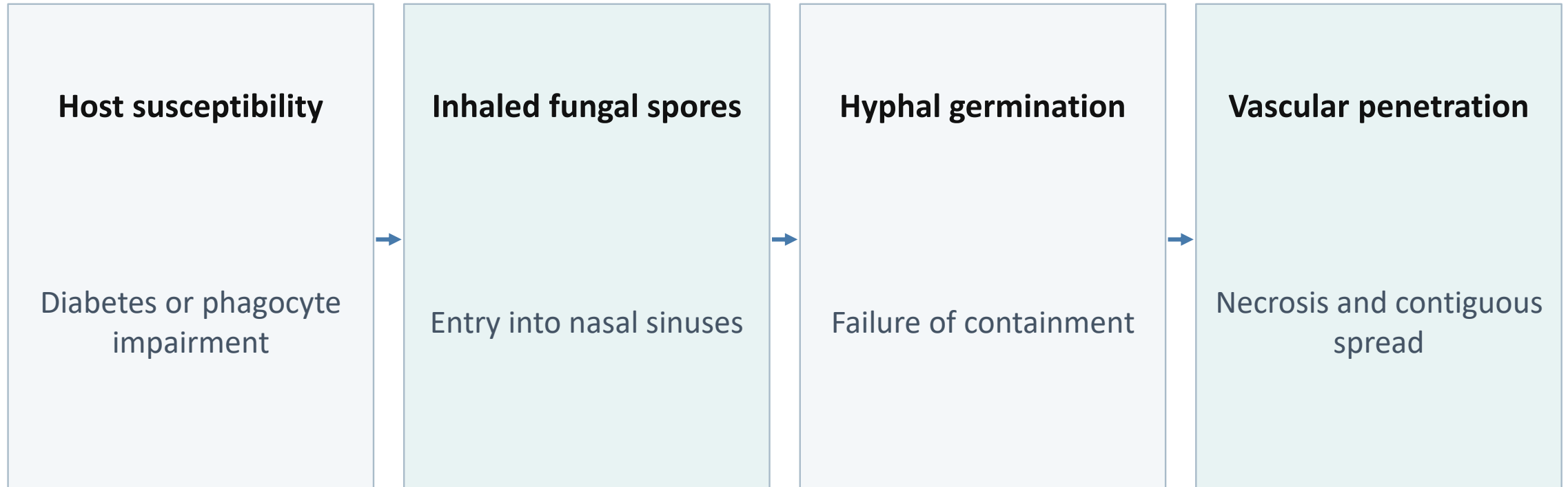
## **With extension**

Orbital or cranial involvement

Meningoencephalitis / cerebral infarction

The relevant biological behavior is invasion, not mere fungal presence.

# A conceptual sequence of invasive fungal damage



Each arrow represents a mechanistically plausible transition.

## Case A: Rapid destructive sinonasal disease

A patient with diabetes and ketoacidosis develops extensive necrotizing sinonasal disease with possible orbital extension.

- Predisposing metabolic condition
- Anatomical spread from sinuses
- Tissue destruction rather than ordinary rhinitis

**Which etiologic category should move to the top of the differential?**

## Case A: Explanation

### **Acute invasive fungal infection — particularly mucormycosis**

- Diabetes with ketoacidosis is a major setting for rhinocerebral disease.
- Angioinvasive fungi can progress from the nasal sinuses toward the orbit and brain.
- Histologic identification of invasive hyphae differentiates infection from GPA and lymphoma.

## Fungal injury: Reasoning checkpoints

### **Predisposition**

Neutropenia, corticosteroids, diabetes, abnormal iron availability

### **Organism pattern**

Broad pauciseptate hyphae versus narrower septate acute-branching hyphae

### **Destructive mechanism**

Vascular invasion, thrombosis, tissue infarction

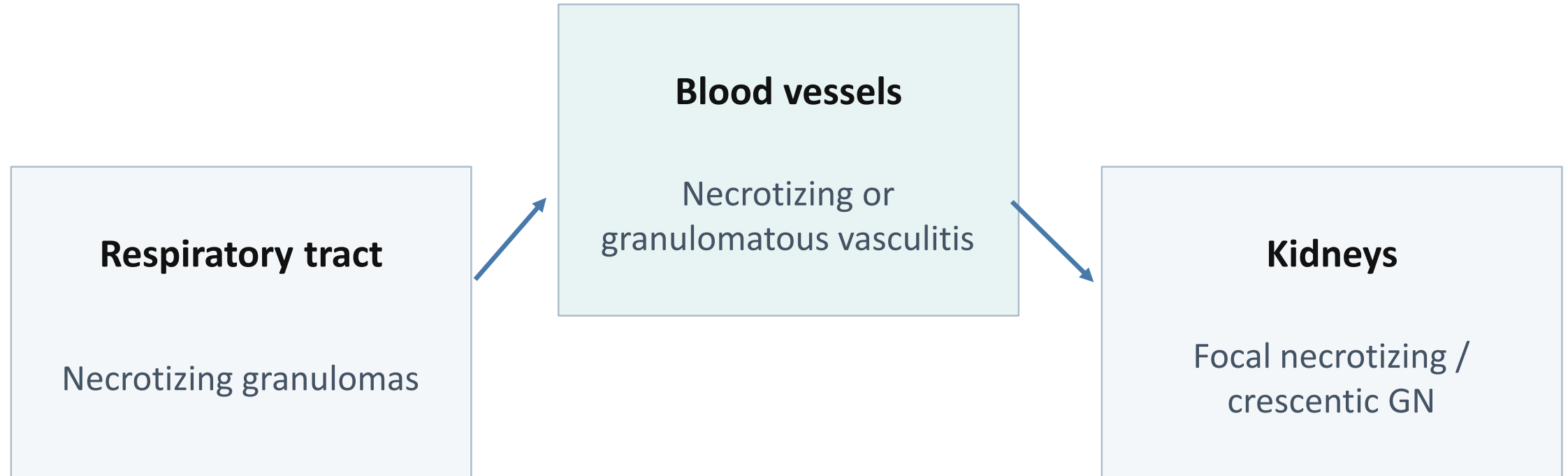
### **Potential extension**

Orbit, cranial vault and brain

## GPA is an ANCA-associated necrotizing vasculitis

- Granulomatosis with polyangiitis is the current name; Wegener granulomatosis is historical.
- Necrotizing granulomatous inflammation affects respiratory tissue.
- Vasculitis involves small and medium-sized vessels.
- Necrotizing glomerulonephritis is a major systemic component.

# The classic GPA triad



Three linked manifestations of one systemic inflammatory disease

# GPA: Upper and lower respiratory involvement

## Upper respiratory tract

Ear, nose, sinuses and throat

Ulceration and granulomatous sinusitis

## Lower respiratory tract

Lung nodules and infiltrates

Necrosis, cavitation or hemorrhage

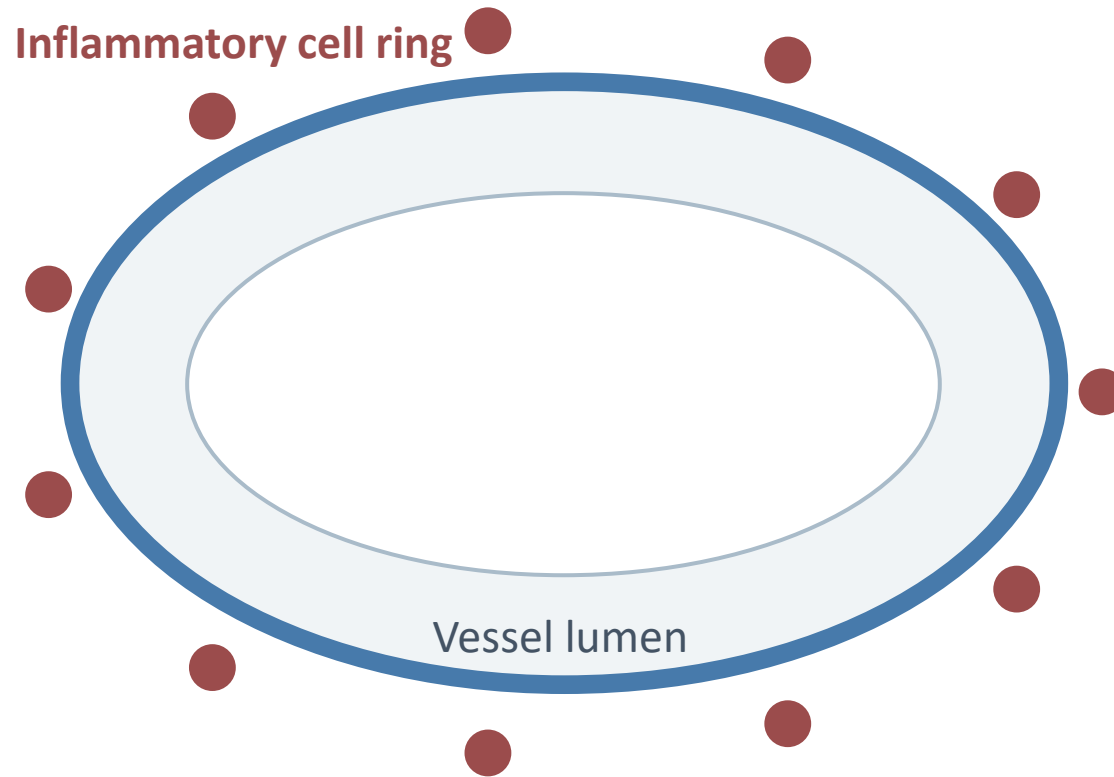
Limited disease may remain confined to the respiratory tract.

## Upper-airway GPA causes destructive ulceration

- Nasal, palatal and pharyngeal ulcerative lesions can occur.
- Granulomatous sinusitis reflects inflammatory tissue injury.
- Small- or medium-vessel involvement contributes to necrosis.
- The same process can occur alongside lung or renal disease.

# Vascular pathology in GPA

*Schematic – not a histologic image*



- Small- to medium-sized vessels are injured by necrotizing inflammation.
- Granulomatous inflammation may accompany vasculitis.
- The respiratory tract is a prominent site of disease.

# Granulomatous destruction is more than vasculitis

Complementary manifestations of immune injury — not a fixed chronological sequence.

## **Immune response**

A T-cell–mediated reaction to inhaled agents.

## **Granulomatous injury**

Necrotizing granulomas can affect mucosa and lung.

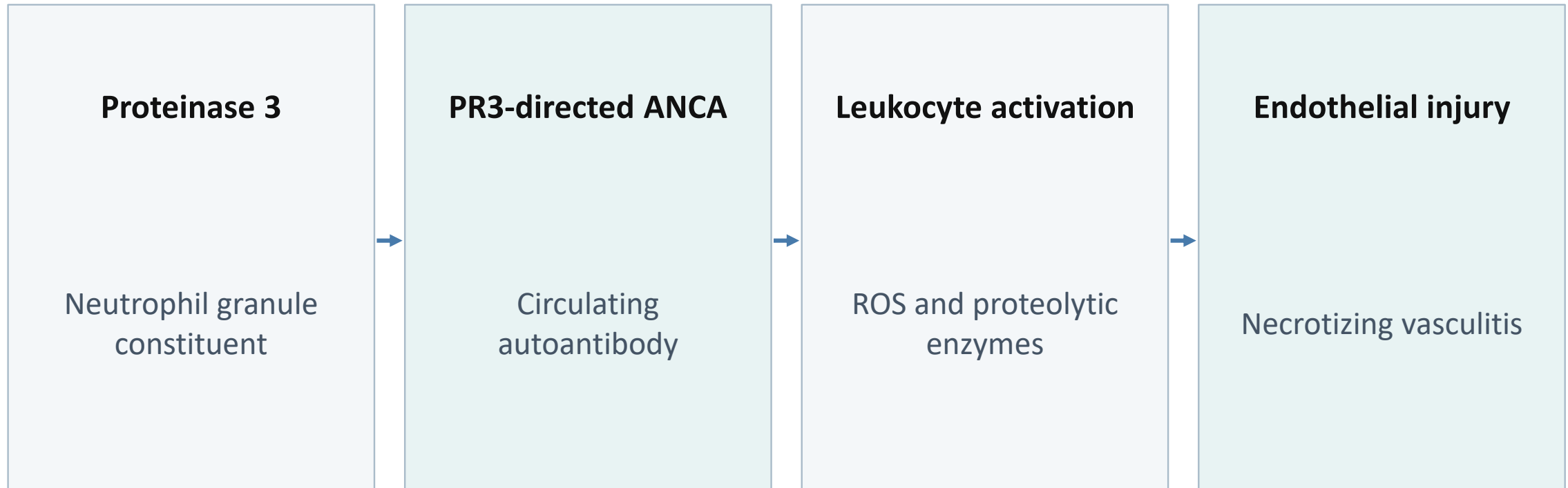
## **Vascular injury**

Small- and medium-vessel inflammation contributes to destruction.

## GPA: Proposed immunopathogenesis

- An abnormal immune response to usually innocuous inhaled agents.
- T-cell-mediated hypersensitivity is considered likely.
- PR3-ANCA is strongly associated with the disease.
- Both immune effector activity and vascular injury contribute to disease expression.

## PR3-ANCA identifies the main antibody target



A general ANCA-associated vasculitis mechanism; Not a complete model for every GPA lesion.

# Why ANCA-associated lesions are pauci-immune

## **Autoantibody target**

Neutrophil constituents

No requirement for deposited circulating immune complexes

## **Vascular injury**

Activated leukocytes release toxic mediators

Little detectable antibody/complement in vessel lesions

Pauci-immune describes the immunopathologic pattern, not absence of immune activity.

## PR3-ANCA: Association is not morphology

- PR3-ANCA in up to 95% of GPA cases.
- PR3-ANCA can assist assessment of response and early relapse.
- The characteristic clinicopathologic pattern remains important.
- The upper-airway differential still includes fungal infection and malignant lymphoma.

# Lung involvement contributes diagnostic context

Several lung manifestations.

## **Nodular disease**

Granulomata may coalesce into radiologically evident lesions.

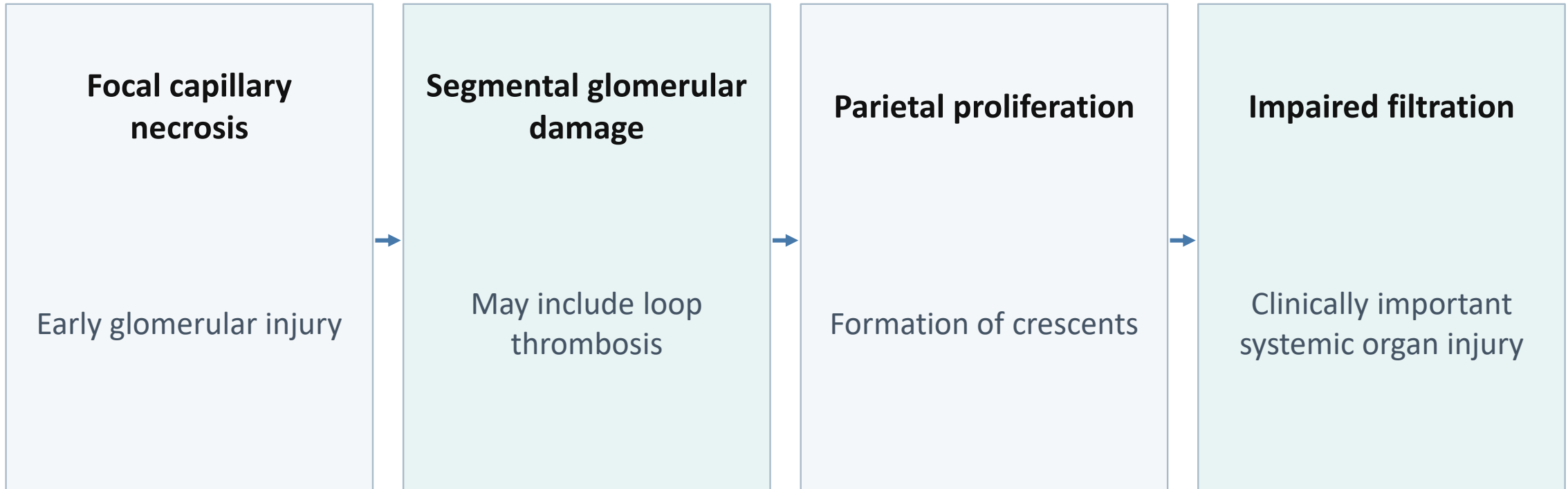
## **Cavitation**

Necrotizing pulmonary nodules may cavitate.

## **Alveolar hemorrhage**

Prominent in some cases of pulmonary vasculitis.

## Renal GPA: Focal to crescentic injury



A spectrum from focal necrosis to diffuse crescentic lesions.

## What changes when GPA becomes systemic?

| Site                    | Documented expression                                  |
|-------------------------|--------------------------------------------------------|
| Nose / palate / pharynx | Ulceration and granulomatous sinusitis                 |
| Lungs                   | Nodules, cavitation, infiltrates, hemorrhage           |
| Kidneys                 | Necrotizing glomerulonephritis; crescents              |
| Other organs            | Eyes, skin, heart and additional sites may be affected |

## GPA compared with two related vasculitides

| Vasculitis                                           | Discriminating textbook pattern                              |
|------------------------------------------------------|--------------------------------------------------------------|
| <b>GPA</b>                                           | Necrotizing granulomas; upper airways; often PR3-ANCA        |
| <b>Microscopic polyangiitis</b>                      | Necrotizing small-vessel injury; granulomas absent           |
| <b>Eosinophilic granulomatosis with polyangiitis</b> | Asthma, eosinophils and necrotizing granulomatous vasculitis |

## Case B: Sinonasal lesions with other organ clues

Persistent necrotizing sinonasal lesions occur with pulmonary nodules and glomerular injury.

- Respiratory tract lesions above and below the larynx
- Renal necrotizing pathology
- Systemic rather than isolated local process

**Which of the three Robbins causes best accounts for the complete pattern?**

## Case B: Explanation

### **Granulomatosis with polyangiitis**

- The classical triad links respiratory granulomas, necrotizing vasculitis and glomerulonephritis.
- PR3-ANCA is an informative associated marker.
- Fungal invasion and an EBV-associated destructive lymphoma require different tissue evidence.

## GPA: Treatment principle and disease course

- The disease was often fatal before effective immunosuppression.
- Corticosteroids and other immunosuppressive agents changed prognosis markedly.
- The resulting course as chronic, relapsing and remitting.
- Clinical response and serologic follow-up require interpretation together.

# GPA: Diagnostic synthesis

## Local injury

Necrotizing granulomas and small-/medium-vessel vasculitis

## Upper airway

Granulomatous sinusitis; Nasal, palatal or pharyngeal ulceration

## Systemic clues

Pulmonary nodules/cavities, glomerulonephritis

## Immune context

Strong association with PR3-ANCA; Pauci-immune vasculitis

## Extranodal NK/T-cell lymphoma: Destructive neoplasm

- A malignant NK-/T-lineage proliferation can present as a destructive nasopharyngeal mass.
- The tumor infiltrate surrounds and enters small vessels.
- Vascular destruction leads to extensive ischemic necrosis.
- The malignancy is strongly associated with Epstein–Barr virus.

# Nasal lymphoma: Epidemiologic context

These are associations reported by Robbins, not diagnostic criteria.

## **Demographic tendency**

More often men in their fifth or sixth decade.

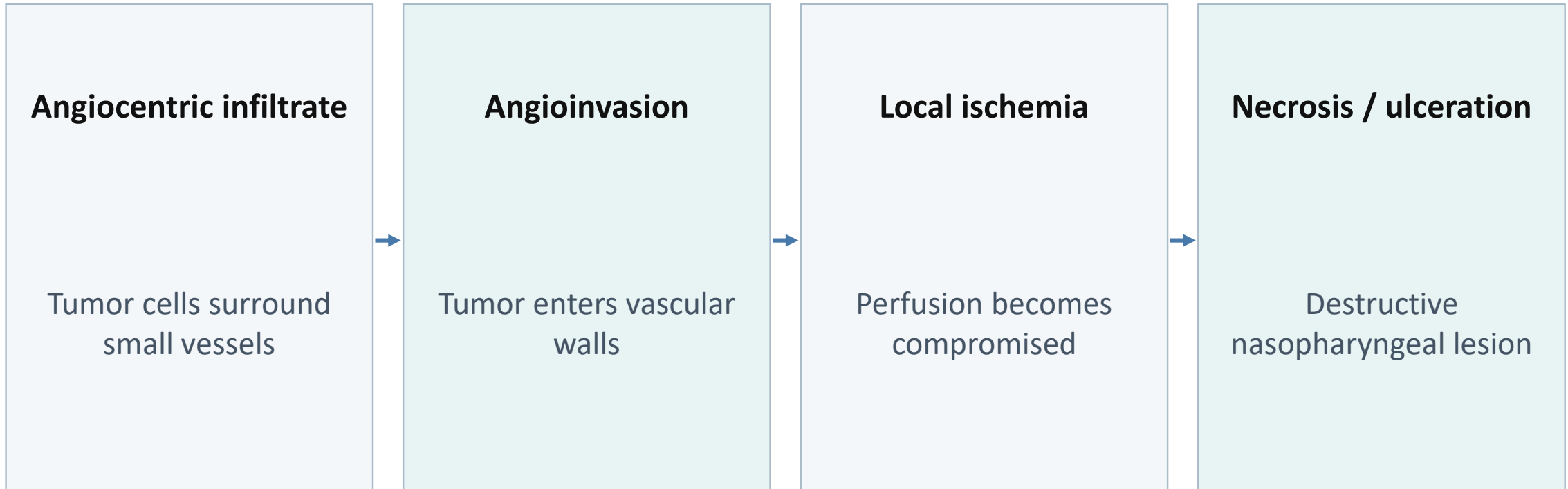
## **Population distribution**

More common in Asian and Latin American populations.

## **Geographic pattern**

Rare in the United States/Europe; More common in Asia.

# Why does the lymphoma ulcerate?

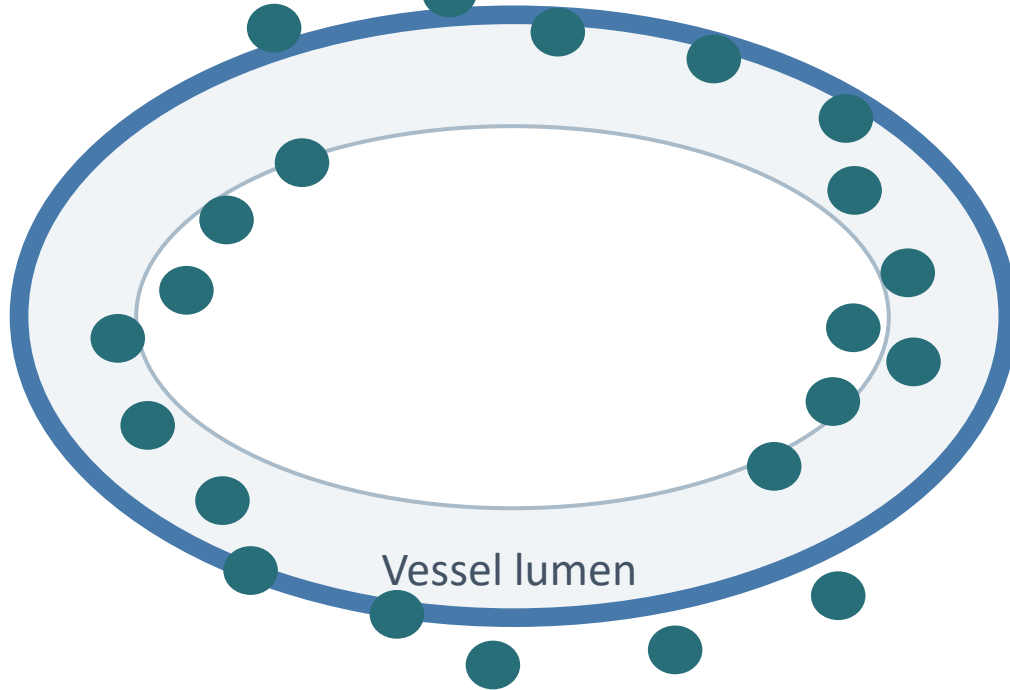


Vascular invasion is a direct link between tumor biology and the clinical lesion.

# Tumor-associated vascular injury

*Schematic – not a histologic image*

**Angioinvasive tumor cells**

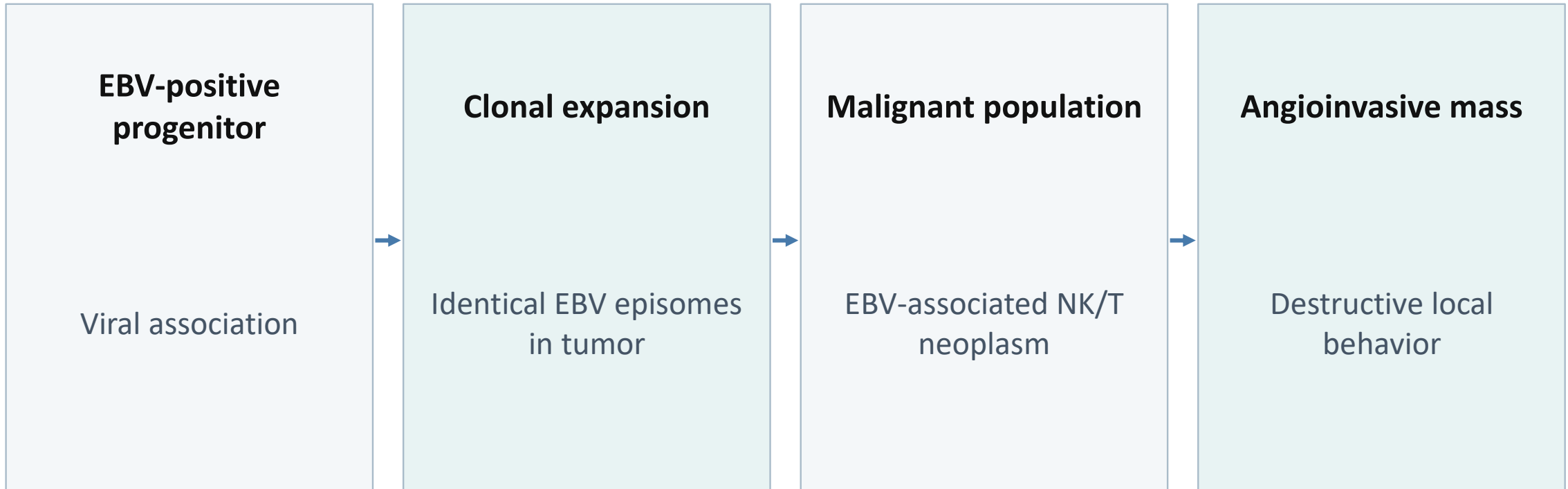


- Neoplastic lymphoid cells cluster around vessels.
- Cells invade vessel walls and produce ischemia.
- The resulting necrosis may obscure the tumor.

## The lymphoma phenotype has NK-cell features

- Most described tumors have an NK-cell phenotype.
- Lack of T-cell receptor gene rearrangement supports NK rather than conventional T-cell origin.
- Cytoplasmic large azurophilic granules resemble those of normal NK cells.
- No single phenotype element should substitute for identifying the neoplastic process.

# EBV is central to this neoplasm



The mechanism of EBV entry into these cells is uncertain.

# The EBV evidence is clonality, not coincidence

## Association

Strong link of neoplasm to EBV

Malignant cells harbor the virus

## Clonality

Identical viral episomes within a patient

Supports origin from one infected precursor

Uncertainty about how EBV enters cells lacking the usual B-cell receptor CD21.

# Molecular abnormalities are heterogeneous

Recurrent changes without a unique defining chromosomal aberration.

## **JAK/STAT pathway**

Recurrent pathway gene alterations

## **Epigenetic regulators**

Altered chromatin-related control

## **TP53**

Reported recurrent mutations

# What makes the clinical course severe?

Aggressive local invasion and infectious complications both matter.

## **Local spread**

Destruction of surrounding tissues

## **Cranial penetration**

Extension toward the cranial vault

## **Secondary infection**

Bacterial infection and potential septic dissemination

# Bacterial infection may conceal the primary lesion

## Visible complication

Ulceration and secondary infection

Inflammation can dominate sampled necrotic tissue

## Underlying disease

EBV-associated lymphoid malignancy

Angiodestruction explains primary tissue injury

Do not equate a superimposed infection with the full cause of a destructive mass.

## Local control does not eliminate recurrence risk

- Localized cases may respond to radiotherapy.
- Relapse and recurrence remain important problems.
- Advanced disease has a generally poor prognosis.
- The chapter describes resistance to conventional chemotherapy in many cases.

## Aggressive disease may require other modalities

- The hematopathology chapter discusses allogeneic transplantation in advanced disease.
- Immune checkpoint inhibitors may produce responses in this virus-associated neoplasm.
- These approaches carry important risks and are not universal recommendations.
- For a pathology lecture, the central requirement is correct tissue classification.

## Case C: Destructive nasopharyngeal mass

An adult presents with a destructive nasopharyngeal mass, ulceration and a superimposed bacterial infection. Biopsy suggests angioinvasive lymphoid malignancy.

- A true mass-forming lymphoid proliferation
- Vascular invasion causing ischemic necrosis
- The relevant tumor category is strongly EBV-associated

**Identify the major diagnostic category and explain the necrosis.**

## Case C: Explanation

### **Extranodal NK/T-cell lymphoma, nasal type**

- Tumor cells center on and invade small vessels.
- Vessel injury leads to ischemia and extensive local necrosis.
- EBV association is strong; Bacterial infection may be superimposed.

# Lymphoma: Essential discriminating features

## Local lesion

Destructive nasal or nasopharyngeal mass

## Microscopic behavior

Perivascular and angioinvasive tumor cells

## Pathogenesis

Ischemic necrosis from vascular injury

## Biologic association

EBV-positive malignant population

## The three patterns: One-page differential

| Feature          | Invasive fungal disease   | GPA                    | NK/T lymphoma           |
|------------------|---------------------------|------------------------|-------------------------|
| Predisposition   | Diabetes / immune deficit | Autoimmune context     | EBV-associated tumor    |
| Tissue mechanism | Hyphal vascular invasion  | Necrotizing vasculitis | Tumor angioinvasion     |
| Tissue clue      | Fungal hyphae             | Granulomas + vessels   | Atypical lymphoid cells |
| Other sites      | Orbit / brain extension   | Lungs / kidneys        | Local / cranial spread  |

# Three vascular routes to the same tissue endpoint

## **Fungal angioinvasion**

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Organism breaches artery

Thrombus and infarction

## **Immune-mediated vasculitis**

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Inflammation targets vessel  
wall

Necrosis with granulomas

## **Neoplastic angioinvasion**

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Tumor clusters invade vessels

Ischemic tumor-associated  
necrosis

## Comparison: What confirms the lesion category?

| Cause                                | Distinctive positive evidence                                                      |
|--------------------------------------|------------------------------------------------------------------------------------|
| <b>Mucormycosis / invasive fungi</b> | Tissue-invasive hyphae with compatible fungal morphology                           |
| <b>GPA</b>                           | Respiratory granulomatous vasculitis; renal/pulmonary context and PR3-ANCA support |
| <b>NK/T lymphoma</b>                 | Angioinvasive neoplastic lymphoid infiltrate with EBV association                  |

# A tissue-section interpretation framework

## **Destructive sinonasal lesion**

```
graph TD; A[Destructive sinonasal lesion] --> B[Invasive fungal profiles<br/>Seek vessel-invading hyphae]; A --> C[Granulomatous vascular injury<br/>Integrate airway, lung and kidney]; A --> D[Atypical lymphoid angioinvasion<br/>Integrate NK phenotype and EBV];
```

### **Invasive fungal profiles**

Seek vessel-invading hyphae

### **Granulomatous vascular injury**

Integrate airway, lung and kidney

### **Atypical lymphoid angioinvasion**

Integrate NK phenotype and EBV

## Diagnostic pitfall: A necrotic sample

- Necrosis is a shared consequence and is not etiology-specific.
- Fungal elements, vasculitic structures, or viable tumor cells are the distinguishing findings.
- A destructive mass with surface infection can still be lymphoma.
- A systemic respiratory–renal pattern should not be reduced to local sinusitis.

# Diagnostic pitfall: Anatomic overlap

## **Both fungi and lymphoma**

May show extensive local necrosis

May extend toward the cranial compartment

## **GPA and infection**

Both may involve sinuses and lung

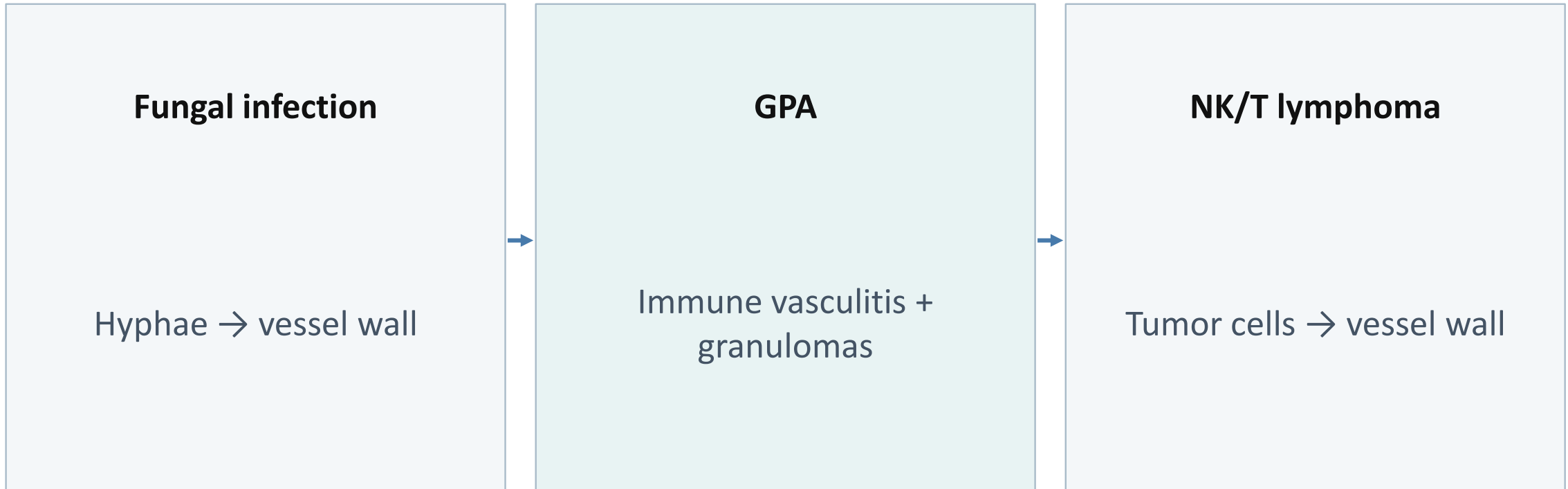
Mechanisms differ: Immune injury vs invasive organism

Site alone cannot resolve the etiologic differential.

## Integrated application: Choose the defining clue

| Observed constellation                            | Highest-yield interpretation |
|---------------------------------------------------|------------------------------|
| <b>Ketoacidosis + arterial fungal invasion</b>    | Rhinocerebral mucormycosis   |
| <b>Necrotizing granulomas + crescentic GN</b>     | GPA                          |
| <b>EBV-associated angioinvasive lymphoid mass</b> | Extranodal NK/T lymphoma     |

## Rapid recall: Explain the necrosis



Shared endpoint: Tissue destruction; Distinct etiologies require distinct evidence.

# Three exam-level take-home principles

Interpretation rests on cause and mechanism, not ulcer appearance alone.

## **Identify the invasive agent**

Hyphae in tissue support infection.

## **Search for the systemic signature**

Respiratory granulomas plus vasculitis and renal injury suggest GPA.

## **Recognize EBV-linked malignancy**

Angioinvasive lymphoid cells indicate NK/T lymphoma.

## Primary reference and expansion sources

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Ch. 16, “Necrotizing Lesions of the Nose and Upper Airways,” p. 673.

Same textbook, Ch. 8, “Mucormycosis” and “Aspergillosis,” pp. 352–353.

Same textbook, Ch. 11, “ANCA-Associated Vasculitis” and “Granulomatosis With Polyangiitis,” pp. 469–470.

Same textbook, Ch. 13, “Extranodal NK-/T-Cell Lymphoma,” pp. 552–553.