

# **IgG4-Related Disease**

Mechanisms, morphology and clinicopathologic patterns

**Dr Abu Suraih Sakhri**

MBBS, MD (Pathology)

[www.abusuraihsakhri.com](http://www.abusuraihsakhri.com)

# Learning outcomes

## **Recognize**

Identify the characteristic tissue pattern.

## **Explain**

Separate immune observations from uncertain causation.

## **Apply**

Interpret common organ presentations and mimics.

## Opening diagnostic problem

An older adult has a firm pancreatic mass and a fibrosing lesion at another site.

One tissue sample contains abundant lymphocytes and plasma cells.

**Question: How could a single systemic process explain both lesions?**

A systemic fibroinflammatory disease

**IgG4-related disease links lymphoplasmacytic inflammation, fibrosis and characteristic venous involvement across organs.**

It is a disease spectrum rather than a single organ diagnosis.

# Four recurring diagnostic observations

## Cells

Lymphocytes and numerous IgG4-producing plasma cells

## Stroma

Prominent fibrosis; Often storiform

## Vessels

Obliterative phlebitis

## Serum

IgG4 usually increased, not invariably

## The name does not establish the cause

### Observed

- IgG4-producing plasma cells are prominent in lesions.
- Serum IgG4 is usually increased.

### Not established

- IgG4 antibodies directly cause tissue fibrosis.
- A causative autoantigen has been identified.

# Organ involvement is widely distributed

## Glandular

Salivary glands

Lacrimal/periorbital tissues

Thyroid

Pancreas

## Abdominal

Biliary tree

Retroperitoneal tissues

Kidneys

Prostate

## Other systems

Lungs and lymph nodes

Aorta and pericardium

Meninges

Breast and skin

## Disease labels that joined one spectrum

### **Mikulicz syndrome**

Some salivary gland cases

### **Riedel thyroiditis**

A fibrosing thyroid lesion

### **Retroperitoneal fibrosis**

Some previously idiopathic cases

### **Autoimmune pancreatitis**

Type 1 form

### **Sclerosing cholangitis**

Some fibroinflammatory biliary lesions

## Demographic pattern

- IgG4-RD most often affects middle-aged or older individuals.
- A male predominance is.
- Age and sex support clinical suspicion; Neither establishes a diagnosis.

## A common mechanism, distinct organ effects



A tissue response may be shared while the clinical consequence depends on anatomical location.

# The fundamental tissue pattern

## Inflammation

Lymphoplasmacytic  
inflammation

## Fibrosis

Storiform fibrosis

## Vascular injury

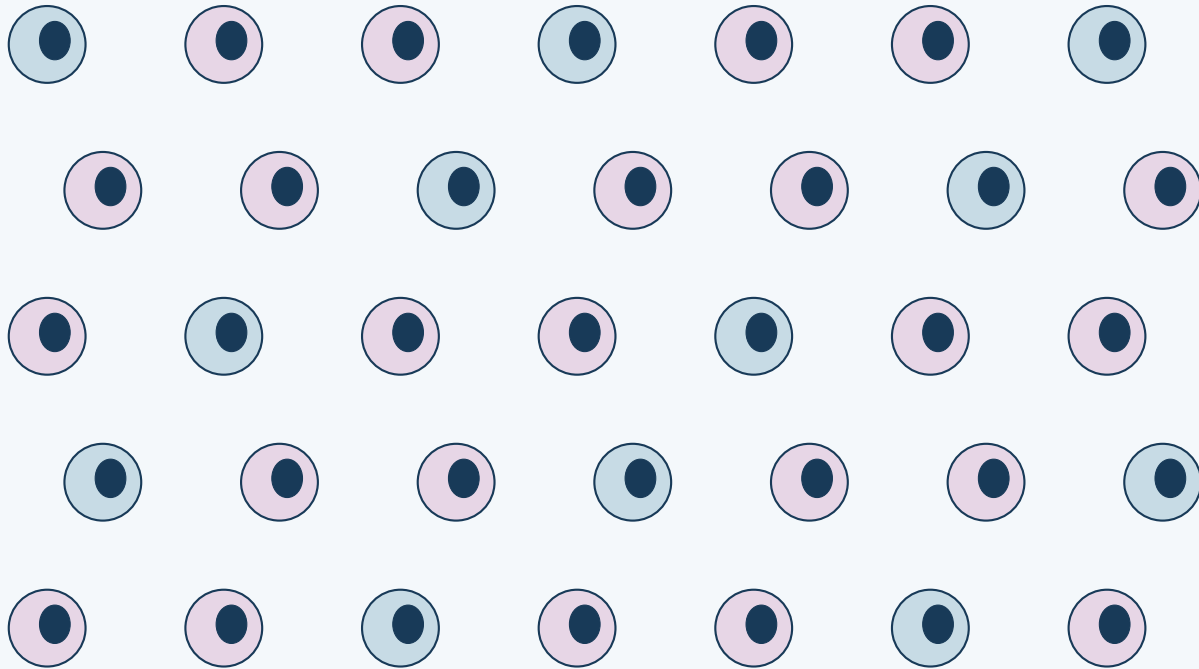
Obliterative phlebitis

The three findings describe different tissue compartments of one fibroinflammatory process.

## Lymphocytes are a major infiltrating population

- The source emphasizes lymphocytes, particularly T cells, in affected tissues.
- Lymphoid inflammation accompanies plasma cells and the fibrotic reaction.
- Presence of T cells does not by itself reveal the initiating antigen.

# Plasma cells give the lesion its name



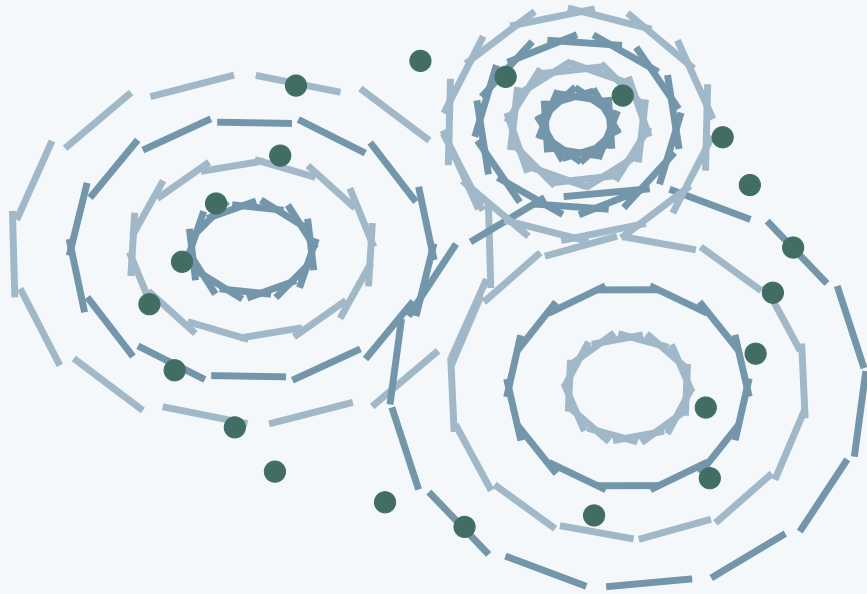
Schematic: Dense cellular infiltrate (not a specimen)

**Lymphocytes and plasma cells**

**IgG4 staining identifies a  
plasma-cell subset**

**Cells alone do not prove causal  
antibody activity**

# Storiform fibrosis: A pattern of organization



Schematic: Interweaving collagen whorls + inflammatory cells

**Whorled collagen**

**Nearby lymphocytes and  
plasma cells**

**Interpret alongside vascular  
findings**

# Why storiform is more informative than “fibrosis”

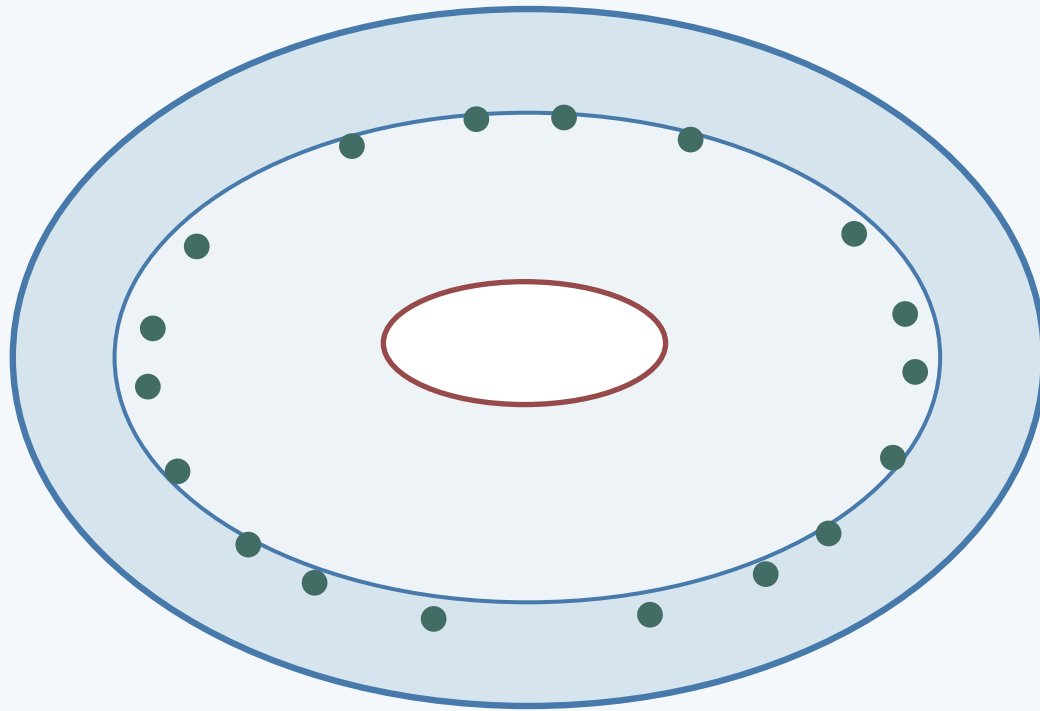
## Generic description

- An organ contains increased collagen or scar-like tissue.
- Does not specify its arrangement.

## Pattern-level description

- Collagen is arranged in a characteristic swirling/storiform pattern.
- Can be considered alongside cells and venous lesions.

# Obliterative phlebitis: Vein involvement



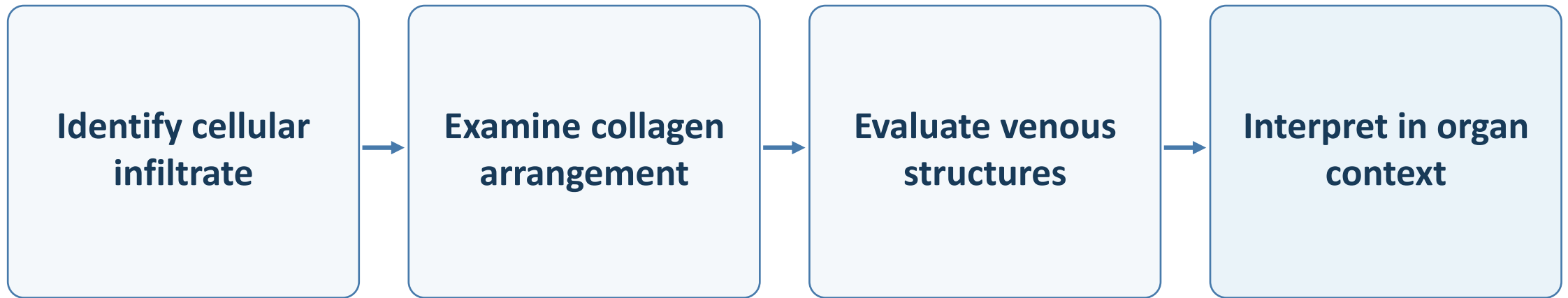
Schematic: Fibrosing venous inflammation and reduced lumen

**Vein with inflammatory wall**

**Fibrosis and inflammatory cells**

**Lumen markedly narrowed**

## The triad provides a structured reading order



Educational review sequence—not a published diagnostic scoring system.

## Interpret the biopsy as a whole

- IgG4-positive cells, fibrosis and venous change represent different elements of the process.
- One isolated feature provides less contextual information than the combined tissue pattern.
- Organ-specific architecture and competing diagnoses must remain in view.

## The figures show four evidence types

### **Bile duct gross**

A sclerotic, gray-white cross section

### **Bile duct tissue**

Storiform fibrosis

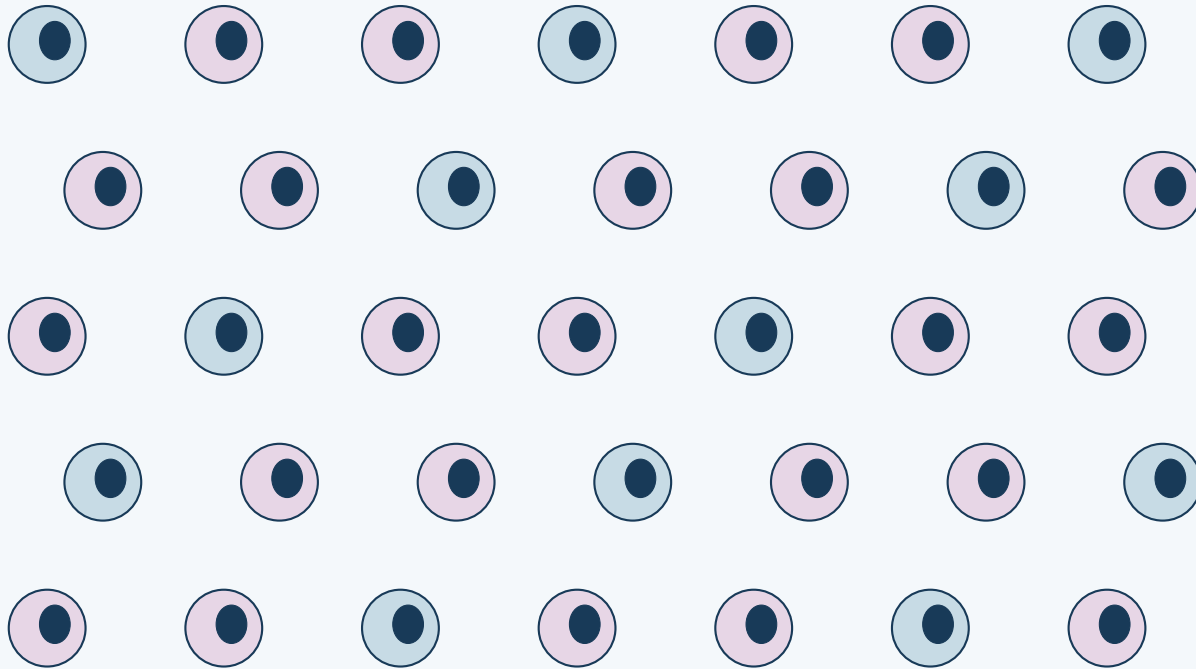
### **Submandibular tissue**

Lymphoplasmacytic infiltrate with whorled fibrosis

### **Lacrimal IgG4 stain**

Numerous IgG4-producing plasma cells

# IgG4 immunostain: What is visualized



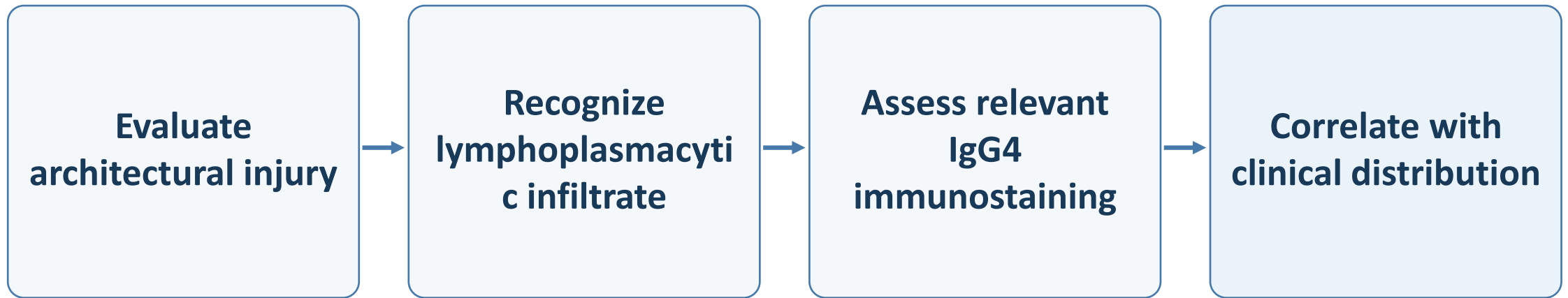
Schematic: Dense cellular infiltrate (not a specimen)

**Lymphocytes and plasma cells**

**IgG4 staining identifies a  
plasma-cell subset**

**Cells alone do not prove causal  
antibody activity**

# Morphology first; Immunophenotype in context



Reasoning aid, not a formal case definition or sensitivity/specificity claim.

## The central pathogenic uncertainty

**The source states that the pathogenesis of IgG4-RD is not understood.**

Autoimmune mechanisms are suspected, but causative autoantigens have not been identified.

# IgG4 has unusual effector characteristics

## Complement

IgG4 does not activate complement efficiently.

## Fc receptors

IgG4 does not bind leukocyte Fc receptors.

## Fibrosis

How IgG4 might induce fibrosis is unknown.

# Antibody abundance is not causal evidence

## Association

- IgG4 is abundant in lesions and often elevated in serum.
- A reliable tissue association can be diagnostically valuable.

## Causation

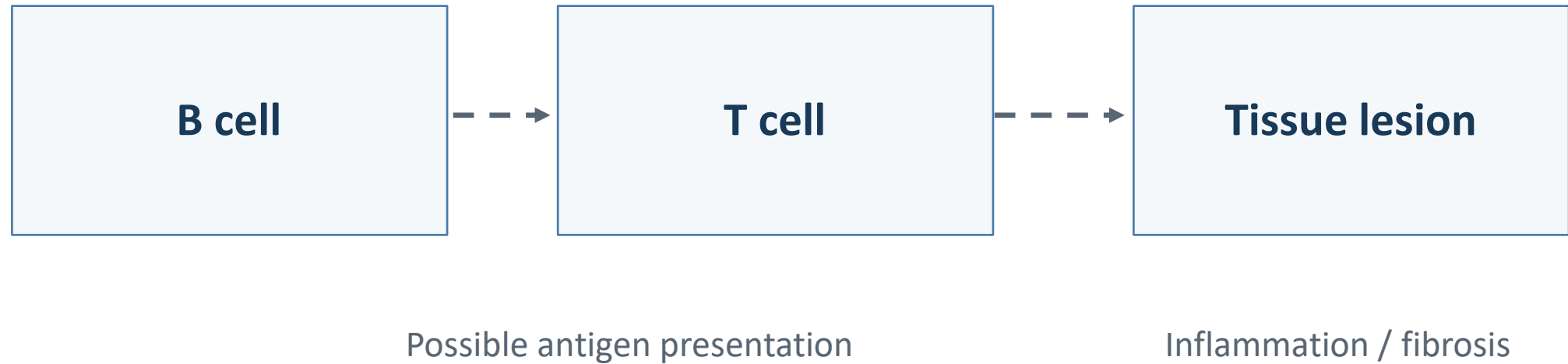
- The antibody must be demonstrated to drive the lesion.
- Robbins does not establish this mechanism.

## B cells have a supported functional role



The treatment response supports biological relevance but does not specify every step of causation.

# B-cell antigen presentation remains a proposal



Proposed model; Causal links remain incompletely resolved.

## Autoimmunity: Suspected, not fully identified

### Supported interpretation

- An autoimmune process is suspected.
- B-cell depletion can improve disease.

### Missing evidence

- No causative autoantigen is identified.
- IgG4 itself is not proven to induce fibrosis.

# Separate three evidence levels

## Observation

IgG4-rich infiltrates, fibrosis,  
phlebitis

## Clinical intervention

Benefit from anti-B-cell  
antibodies

## Hypothesis

Autoantigen-driven B–T-cell  
interactions

## Type 1 autoimmune pancreatitis belongs to IgG4-RD

- Type 1 autoimmune pancreatitis exhibits abundant IgG4-secreting plasma cells.
- It is a pancreatic manifestation of IgG4-related disease.
- Robbins separates it from type 2 and checkpoint-inhibitor–related type 3.

# Type 1 pancreatitis has the archetypal triad

## Inflammation

Storiform pancreatic fibrosis

## Fibrosis

Obliterative inflammatory  
phlebitis

## Vascular injury

Dense IgG4-rich  
lymphoplasmacytic  
inflammation

The three findings describe different tissue compartments of one fibroinflammatory process.

## Type 1 vs type 2 autoimmune pancreatitis

| Feature                    | Type 1 AIP                    | Type 2 AIP                                       |
|----------------------------|-------------------------------|--------------------------------------------------|
| IgG4-rich infiltrate       | Characteristic                | Not abundant                                     |
| Characteristic duct lesion | Not the defining feature here | Granulocytic epithelial lesion                   |
| Systemic association       | IgG4-RD manifestation         | Usually pancreatic; UC in a subset               |
| Inflammation               | Lymphoplasmacytic             | Lymphoplasmacytic plus neutrophilic duct lesions |

# Type 3 pancreatitis is a different setting

## Trigger

Immune checkpoint inhibitor treatment

## Pathology

Histology incompletely characterized

## Context

Often diagnosed through imaging and enzyme abnormalities

## Distinction

Should not be conflated with IgG4-related type 1 AIP

# Pancreatic mass: Distinguish inflammation from tumor

## Presentation

- Autoimmune pancreatitis can resemble carcinoma.
- A pancreatic head mass is specifically noted.

## Implication

- Fibroinflammation cannot be assumed benign without evaluation.
- Histopathology and clinical assessment matter.

## Therapeutic response provides a clinical clue

- Autoimmune pancreatitis as steroid responsive.
- Treatment response increases the clinical relevance of separating autoimmune pancreatitis from neoplasia.
- Response is contextual information—not a substitute for exclusion of malignancy.

## IgG4-related biliary disease may appear sclerotic

- The spectrum includes some forms of sclerosing cholangitis.
- A grayish-white, sclerosed bile duct.
- Associated histology shows a storiform fibrotic pattern.

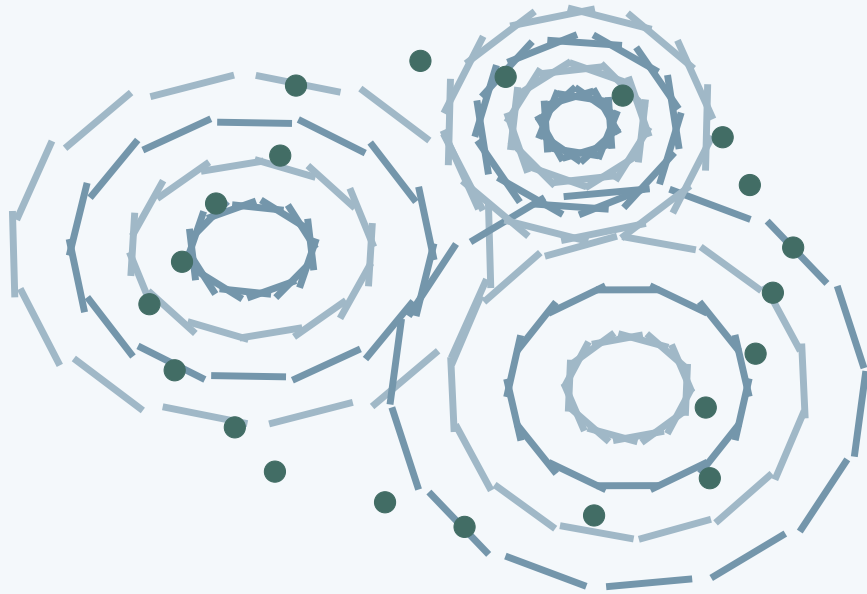
## Sclerosing cholangitis: Macro-to-micro



## Gallbladder disease can enter the spectrum

- IgG4-related sclerosing cholecystitis as a rare form of chronic cholecystitis.
- This extends the fibroinflammatory phenotype to the gallbladder.
- It is not equivalent to labeling all chronic cholecystitis IgG4-related.

# Submandibular gland: Cellular and fibrotic change



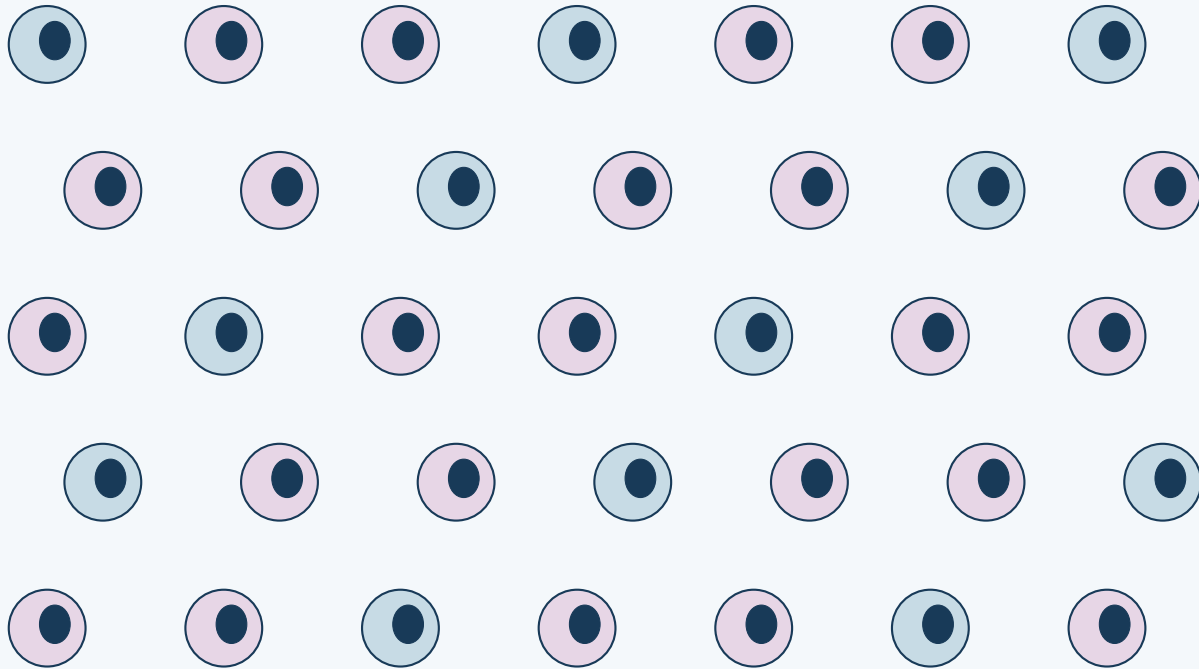
Schematic: Interweaving collagen whorls + inflammatory cells

**Whorled collagen**

**Nearby lymphocytes and  
plasma cells**

**Interpret alongside vascular  
findings**

# Lacrimal gland: Immunohistochemical clue



Schematic: Dense cellular infiltrate (not a specimen)

**Lymphocytes and plasma cells**

**IgG4 staining identifies a  
plasma-cell subset**

**Cells alone do not prove causal  
antibody activity**

## Riedel thyroiditis: A fibrosing thyroid phenotype

- Riedel thyroiditis is a rare thyroid disorder with extensive fibrosis.
- Fibrosis can extend into contiguous neck structures.
- This entity to the IgG4-RD spectrum.

# A hard thyroid mass can simulate carcinoma

## What is observed

- A hard, fixed thyroid mass with marked fibrosis.
- Adjacent neck tissues may be involved.

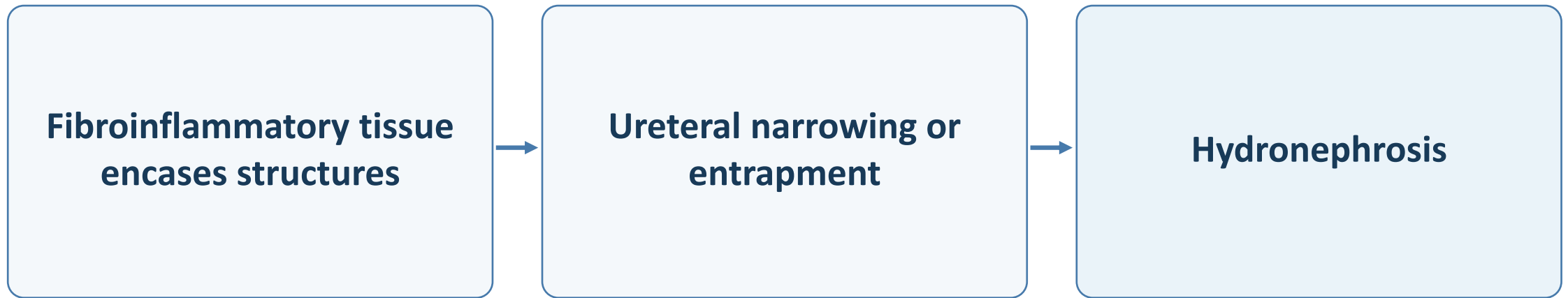
## Diagnostic risk

- Clinical findings can resemble thyroid carcinoma.
- The presence of fibrosis does not remove the need to evaluate malignancy.

## Retroperitoneal fibrosis: Systemic disease in context

- Sclerosing retroperitonitis is also called idiopathic retroperitoneal fibrosis or Ormond disease.
- Many cases are considered part of IgG4-related sclerosing disease.
- The fibrotic tissue may extend toward mesenteric or other retroperitoneal structures.

# Retroperitoneal fibrosis can obstruct ureters



Anatomical mechanism of obstructive injury.

## Retroperitoneal fibrosis: Microscopic clues

- Storiform fibrosis can surround lymphocytes and plasma cells.
- Germinal centers and eosinophils may be present.
- IgG4-positive plasma cells are frequent in this setting.

## Not all retroperitoneal fibrosis is IgG4-RD

| Category               | Alternatives in Robbins                         |
|------------------------|-------------------------------------------------|
| Drugs                  | Ergot derivatives; $\beta$ -adrenergic blockers |
| Inflammatory disorders | Vasculitis; diverticulitis; Crohn disease       |
| Malignancy             | Lymphoma; urinary tract carcinoma               |
| Unexplained            | Some cases remain idiopathic                    |

## Orbital inflammation: Assess systemic causes

- Orbital fibroinflammation can involve the lacrimal gland, extraocular muscles or other compartments.
- IgG4-RD should be considered before labeling such inflammation idiopathic.
- Systemic involvement may coexist in retroperitoneum, mediastinum or thyroid.

# The orbit has important look-alikes

## Inflammatory

- Idiopathic orbital inflammation is lymphoplasmacytic and sometimes fibrosing.
- Vasculitis or necrosis suggests other systemic inflammatory processes.

## Neoplastic

- Lymphomas can also occupy orbital compartments.
- Tumors may resemble inflammatory masses.

## Other potential target organs

### Thorax

Lung

Aorta

Pericardium

### Excretory/reproductive

Kidney

Prostate

### Other sites

Meninges

Lymph nodes

Breast

Skin

## Anatomy determines the presenting problem

| Site                 | Typical structural problem supported by Robbins |
|----------------------|-------------------------------------------------|
| Pancreas             | A mass-like lesion; chronic inflammatory injury |
| Thyroid              | A hard fixed fibrous mass                       |
| Retroperitoneum      | Ureteral encasement and hydronephrosis          |
| Orbit/lacrimal gland | Inflammatory mass or gland involvement          |
| Biliary tract        | Sclerosing lesion of bile duct                  |

## Serum IgG4: Supportive, not universally elevated

### Key Pathologic Findings

- Serum IgG4 is usually increased.

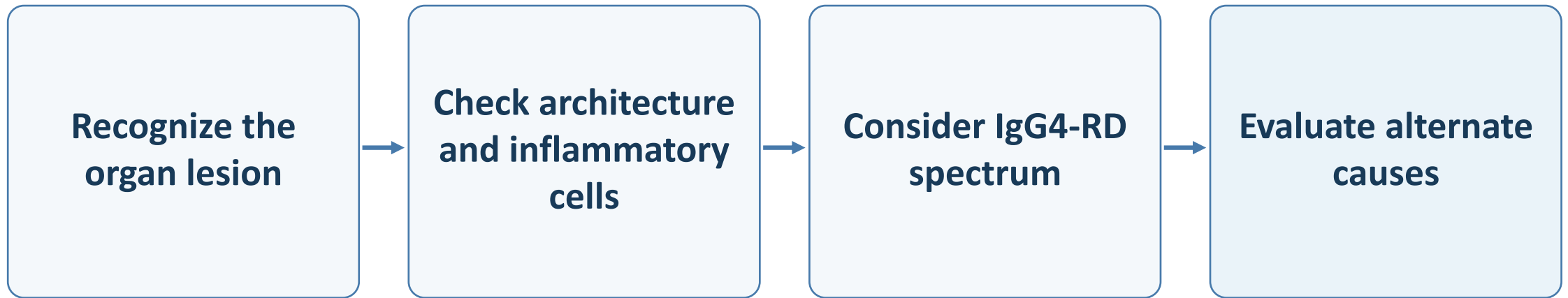
### What follows logically

- “Usually” does not mean “always.”
- A serum result should not be isolated from tissue and organ findings.

## Avoid the isolated-immunostain shortcut

- IgG4-positive plasma cells identify an immunophenotype in a tissue sample.
- The source also emphasizes fibrosis, phlebitis and lymphocytes.
- A coherent interpretation therefore integrates morphology with organ distribution.

## A practical, non-criteria reasoning pathway



Educational logic only—no formal diagnostic thresholds or classification criteria implied.

## The differential depends on the organ

| Setting                       | Competing explanation highlighted in Robbins           |
|-------------------------------|--------------------------------------------------------|
| Pancreatic mass               | Pancreatic carcinoma; type 2 or type 3 AIP             |
| Hard thyroid lesion           | Thyroid carcinoma                                      |
| Retroperitoneal mass/fibrosis | Drug injury, inflammatory disease, lymphoma, carcinoma |
| Orbital mass                  | Lymphoma and other orbital tumors                      |

## Case 1: Pancreatic head mass

An older patient has a pancreatic head mass.

Tissue sections show whorled fibrosis, abundant IgG4-positive plasma cells and inflamed obliterated veins.

**Question: Which AIP subtype is most consistent with this pattern?**

## Case 1: Interpret the tissue pattern

**Most consistent pattern** Type 1 autoimmune pancreatitis.

**Why** Storiform fibrosis + obliterative phlebitis + IgG4-rich inflammation.

**Essential caution** A pancreatic mass requires appropriate evaluation for carcinoma.

## Case 2: Retroperitoneal obstruction

A patient develops hydronephrosis and imaging shows fibrous tissue encasing the ureter.

Biopsy contains lymphocytes, plasma cells and storiform fibrosis.

**Question: What systemic disease spectrum merits consideration?**

## Case 2: Avoid etiologic anchoring

**Working possibility** IgG4-related retroperitoneal fibrosis.

**Mechanism** Fibrous encasement can obstruct the ureter.

**Competing causes** Drugs, inflammatory disease and malignancy are also recognized.

## Case 3: Orbital fibroinflammation

A lacrimal/orbital lesion contains lymphocytes and plasma cells with fibrosis.

A separate fibrosing lesion is present in the thyroid or retroperitoneum.

**Question: Why is “idiopathic orbital inflammation” an incomplete initial conclusion?**

## Case 3: Interpret the distribution

### **Pattern**

Orbital inflammation plus fibrosis elsewhere.

### **Implication**

An IgG4-related systemic process should be considered.

### **Differential**

Other inflammatory diseases and orbital lymphoma remain important.

# Five observations to retain

## Scope

Multiorgan fibroinflammatory disorder

## Cells

Lymphocytes and IgG4-rich plasma cells

## Stroma

Storiform fibrosis

## Vessels

Obliterative phlebitis

## Causation

IgG4 pathogenicity unproven

# Three places to avoid overinterpretation

## **Serum**

Usually increased  $\neq$  always increased

## **Tissue stain**

IgG4 positivity  $\neq$  isolated proof of causation

## **Mechanism**

Benefit from B-cell depletion  $\neq$  identified autoantigen

## References and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 6, “IgG4-Related Disease” and Fig. 6.31.
- Robbins cross-references: autoimmune pancreatitis (Chapter 19); sclerosing retroperitonitis (Chapters 16, 21); Riedel thyroiditis; biliary and orbital inflammation.
- No external diagnostic classification scheme or numerical IgG4 threshold has been introduced.