IgG4-Related Disease

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Introduction

- Increasingly recognized syndrome of unknown etiology comprised of a collection of disorders that share specific pathologic, serologic, and clinical features

- Two major presentations of IgG4-RD:
  - Type 1 Autoimmune Pancreatitis
  - Salivary gland disease
    - May present as salivary gland enlargement (Mikulicz disease) or sclerosing sialadenitis (Küttner's tumor)

Introduction

- **Multiple Names:**
  - IgG4-related disease
  - IgG4-related systemic disease
  - IgG4-syndrome
  - IgG4-associated disease
  - IgG4-related sclerosing disease
  - IgG4-related systemic sclerosing disease
  - IgG4-related autoimmune disease
  - IgG4-positive multiorgan lymphoproliferative syndrome
  - Hyper-IgG4 disease
  - Systemic IgG4-related plasmacytic syndrome
  - Systemic IgG4-related sclerosing syndrome
  - Multifocal fibrosclerosis
  - Multifocal idiopathic fibrosclerosis

IgG4-RD Associated Disorders

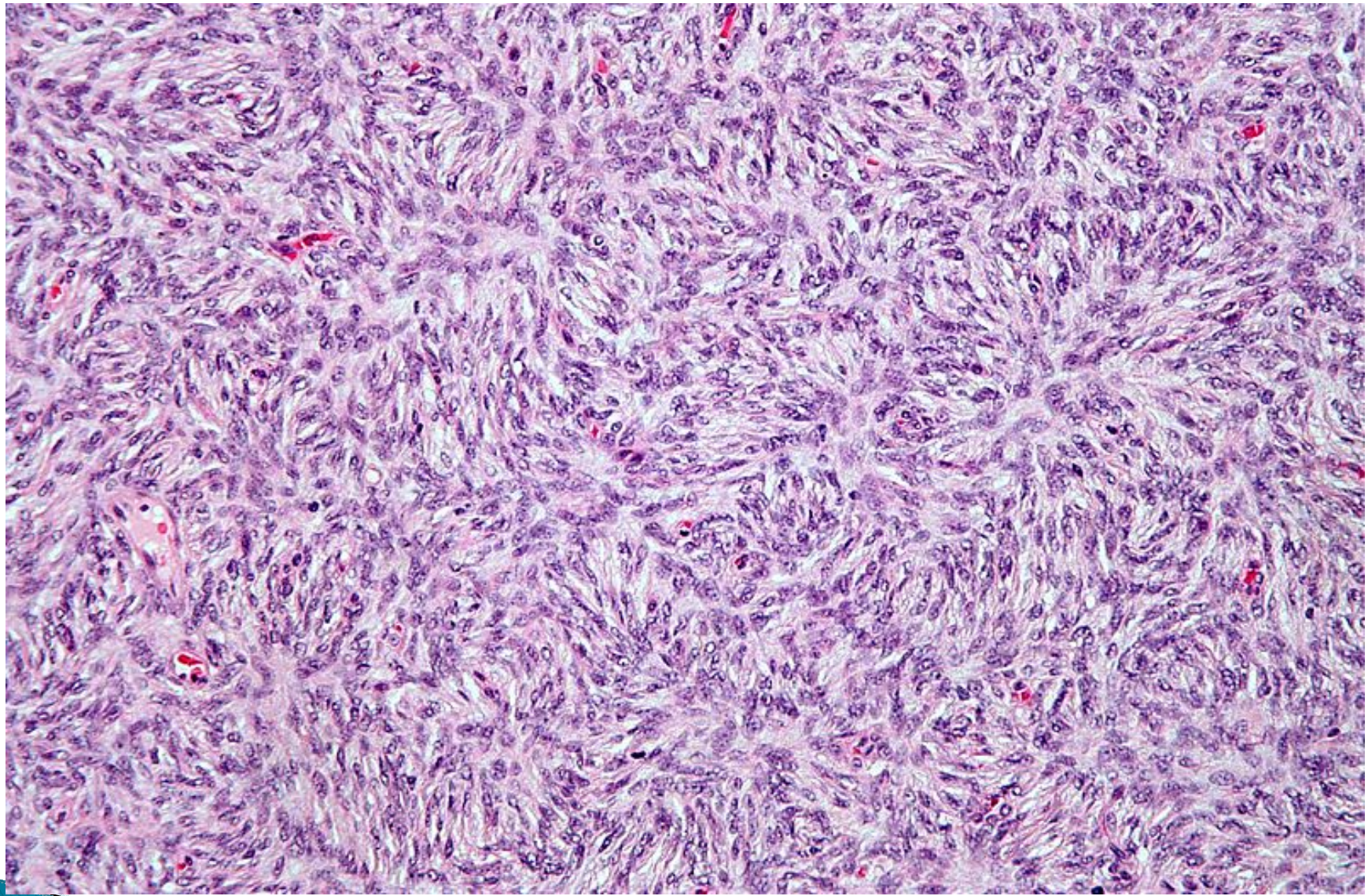
- Type I autoimmune pancreatitis (IgG4-related pancreatis)
- IgG4-related sclerosing cholangitis
- Mikulicz disease (IgG4-related dacryoadenitis and sialadenitis)
- Sclerosing sialadenitis (Küttner's tumor)
- Inflammatory orbital pseudotumor
- Chronic sclerosing dacryoadenitis
- "Idiopathic" retroperitoneal fibrosis (Ormond's disease)

IgG4-RD Associated Disorders

- Chronic sclerosing aortitis and periaortitis
- Riedel's thyroiditis
- IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors
- IgG4-related kidney disease (tubulointerstitial nephritis and MGN)
- IgG4-related hypophysitis
- IgG4-related pachymeningitis

Definition and Histology

- Hallmarks of IgG4-Related Disease (IgG4-RD)
  - Lymphoplasmacytic tissue infiltration with a predominance of IgG4 + plasma cells and T-lymphocytes
  - Fibrosis
  - Obliterative phlebitis
  - Elevated serum levels of IgG4
    - Sizeable minority (<40%) have normal serum IgG4 despite classic histopathological changes in tissue
  - Good initial response to glucocorticoids is characteristic
- Histology
  - Fibrosis has a characteristic “storiform” pattern, typified by a cartwheel appearance of the arranged fibroblasts and inflammatory cells
  - Modest tissue eosinophilia



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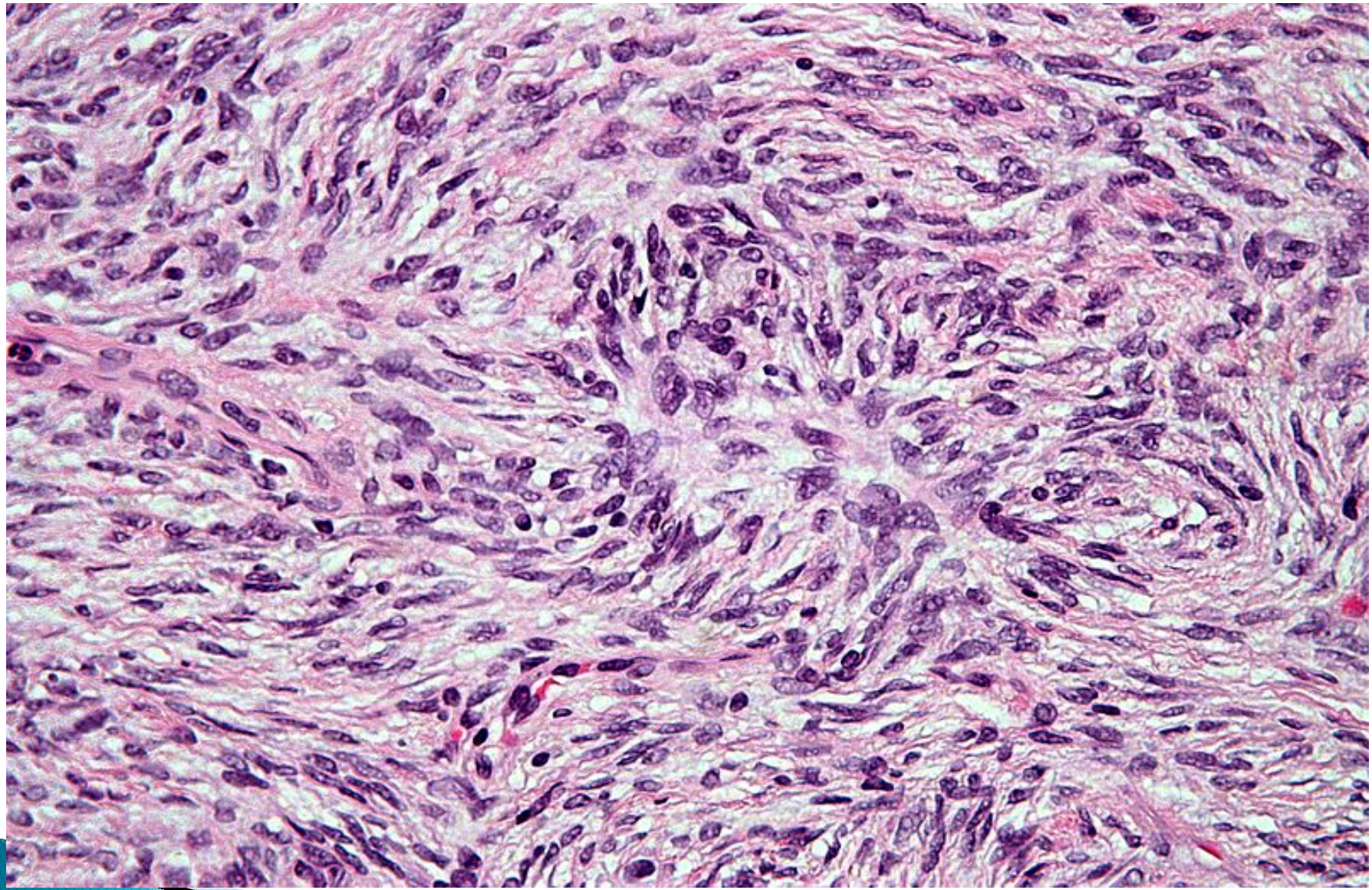

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Epidemiology

- Remains largely undefined
- Most often described as occurring in middle-aged and older men
- Type I Autoimmune Pancreatitis more often in older men (best-studied group)
- Definitive assessments of the incidence and prevalence of IgG4-RD in the general population or among different geographic or ethnic populations are lacking

Pathogenesis

- Poorly understood
- Findings consistent with both an autoimmune and an allergic disorder
- IgG4 has been postulated to have a role in tolerance to allergens and in responses to certain infectious agents but physiologic role is poorly understood

Pathogenesis

- **Autoimmune**
  - Particularly evident in type I autoimmune pancreatitis
  - Association with a specific class II histocompatibility antigen genotype
  - ANA sometimes present
  - Autoantibodies have been described against lactoferrin and carbonic anhydrase II

Pathogenesis

- **Autoimmune**
  - Some studies have suggested possible role for molecular mimicry involving H.pylori
  - Immune complex deposition in the pancreas, kidneys, and other affected tissues have been reported
  - Autoantibody studies have been inconsistent
  - No definitive evidence for a role of autoimmunity in this disease

Pathogenesis

- **Allergic**
  - Elevated levels of Th2 cytokines in affected tissues
  - Increased amounts of serum IgE
  - Patients with IgG4-RD have an increased prevalence of allergic rhinitis and bronchial asthma
  - Increased numbers of T regulatory cells (Tregs) in peripheral blood
  - Increased cytokine levels produced by Tregs (IL-10 and TGF-β)
  - Up to 40% of patients with IgG-RD have a peripheral eosinophila

Clinical Manifestations

- Can involve one or multiple organs
- Often present with subacute development of a mass in the affected organ (eg, an orbital pseudotumor, renal mass resembling RCC, or nodular lesions in the lungs) or diffuse enlargement of an organ (eg, the pancreas)
- Multiple organs are affected in 60–90%
- Share specific pathologic, serologic, and clinical features regardless of the organ involved

Clinical Manifestations

- Lymphadenopathy is common
- Symptoms of asthma or allergy are present in approximately 40%
- Patients often feel well at time of diagnosis and constitutional symptoms
- Often recognized incidentally

Lymphadenopathy

- Common
- 80% of patients with autoimmune pancreatitis
- Usually observed together with other clinical or laboratory manifestations but may be the initial or only manifestation
- Symptoms occasionally occur due to mass effect
- Typically no more than 2cm but can be up to 5cm
- Multiple groups of lymph nodes are usually involved

Lymphadenopathy

- **Five histologic patterns may be seen**
  - **Type I**–Multicentric Castleman disease–like
  - **Type II**–Follicular hyperplasia
  - **Type III**–Interfollicular expansion
  - **Type IV**–Progressive transformation of germinal center–like
  - **Type V**–Nodal inflammatory pseudotumor–like

- May exhibit elevated serum IgG4, serum IgG and IgE, polyclonal hypergammaglobulinemia, and elevated ESR

Autoimmune Pancreatitis

- Chronic inflammation and sclerosing disease of the pancreas
- Dense infiltration of the pancreas with lymphocytes and plasma cells
- Recently a protein expressed in the pancreatic acinar cells, **UBR2** (ubiquitin-protein ligase E_3 component n-recognin 2) has been proposed to be the target of the antibody
- Antibodies also react to a protein of H.pylori, **PBP** (plasminogen-binding protein), suggesting a role for H.pylori infection in AIP

Autoimmune Pancreatitis

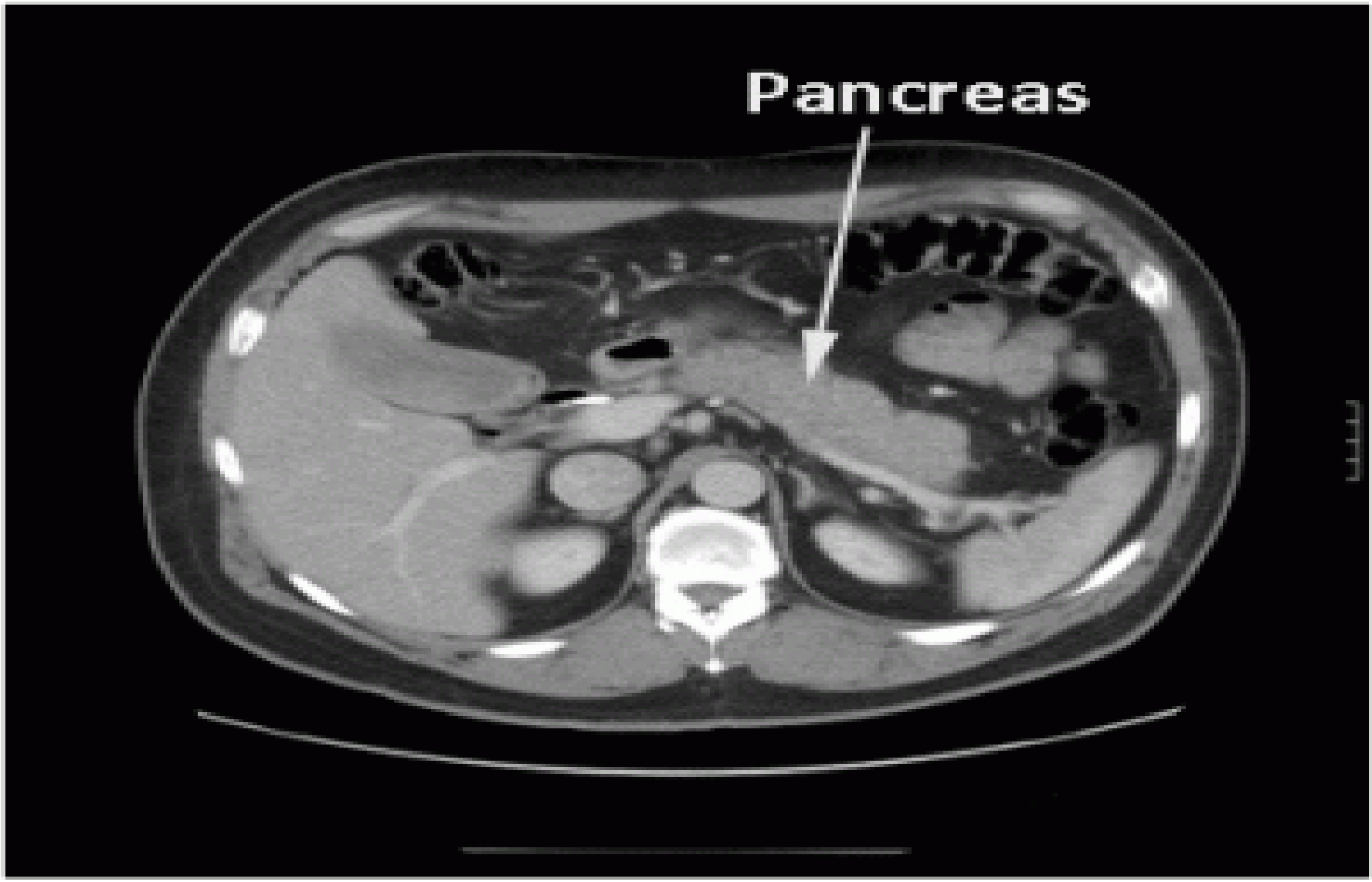
- Isolated form
- May be associated with extrapancreatic manifestations:
  - Biliary strictures
  - Hilar lymphadenopathy
  - Sclerosing sialadenitis
  - Retroperitoneal fibrosis
  - Tubulointerstitial nephritis
- **Epidemiology**
  - Men 2:1
  - Usually manifests in middle age; >85% present after age 50

Autoimmune Pancreatitis

- **Clinical Presentation**
  - Most common presentation is obstructive jaundice
  - Jaundice may occur from compression of the bile duct by the enlarged pancreas or by infiltration of the biliary tree by chronic inflammatory process
  - Weight loss
  - Vomiting
  - Glucose intolerance
  - Pain is not frequently present
  - These features coupled with imaging often raise suspicion of adenocarcinoma

Autoimmune Pancreatitis

- Imaging
  - Abdominal U/S and EUS
    - Diffusely enlarged and hypoechoic pancreas
  - CT/MRI
    - Diffusely enlarged sausage-shaped pancreas in which enhancement with IV contrast agent is delayed and prolonged
    - Some patients may have a capsule-like low-density rim around the pancreas in delayed images
  - MRCP
    - Very helpful in identifying the biliary strictures and in visualizing the PD
  - ERCP
    - Better able to visualize the PD if it is thread-like and diffusely affected than MRCP



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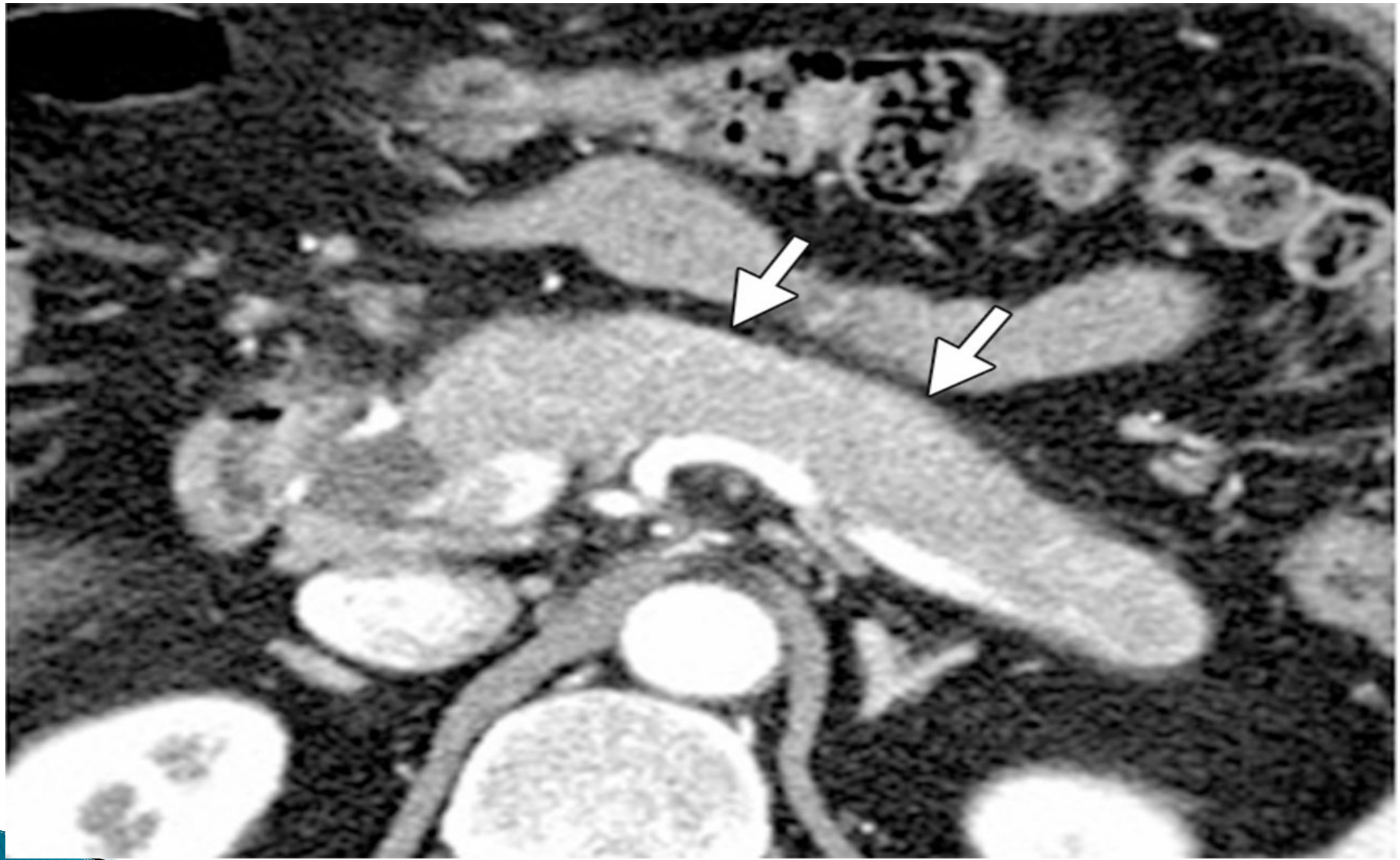

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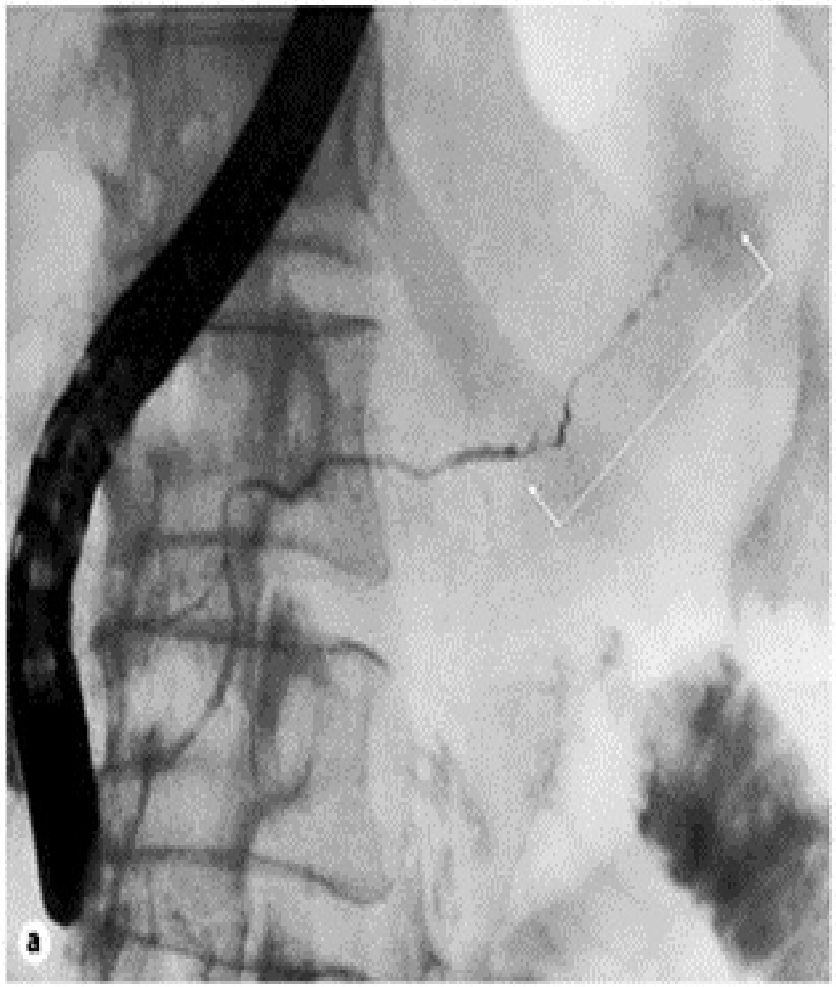

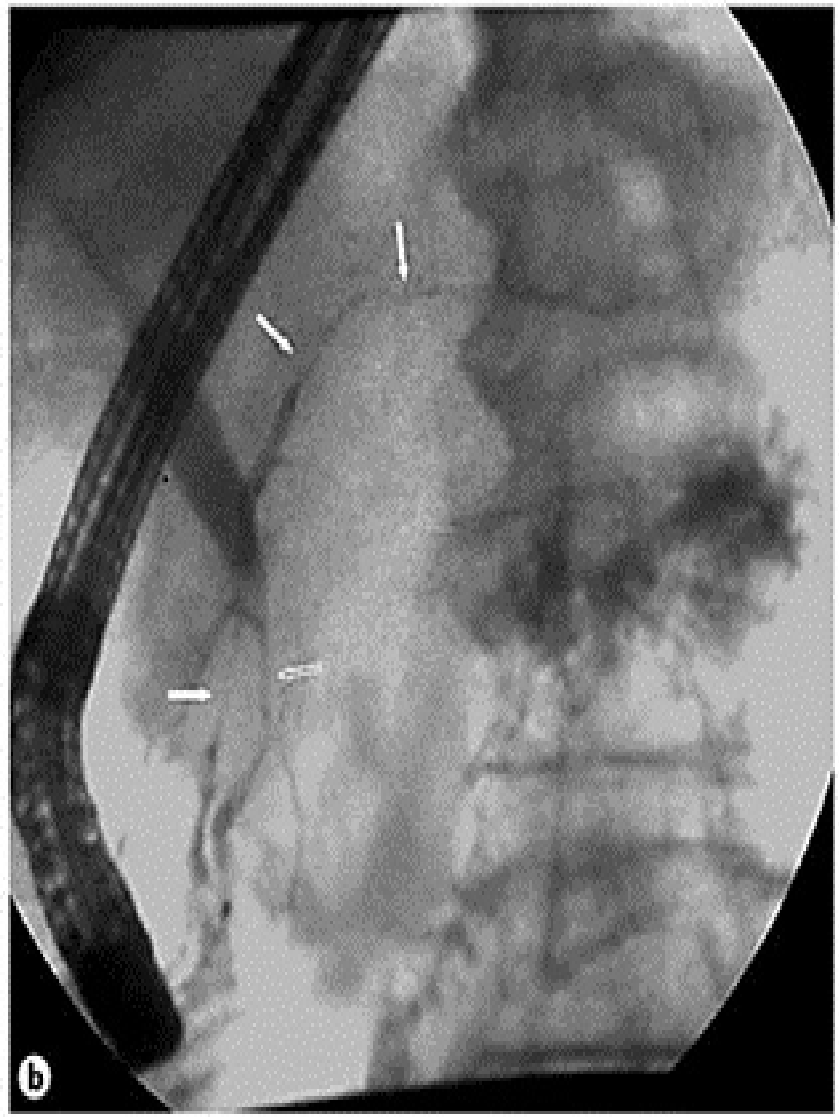

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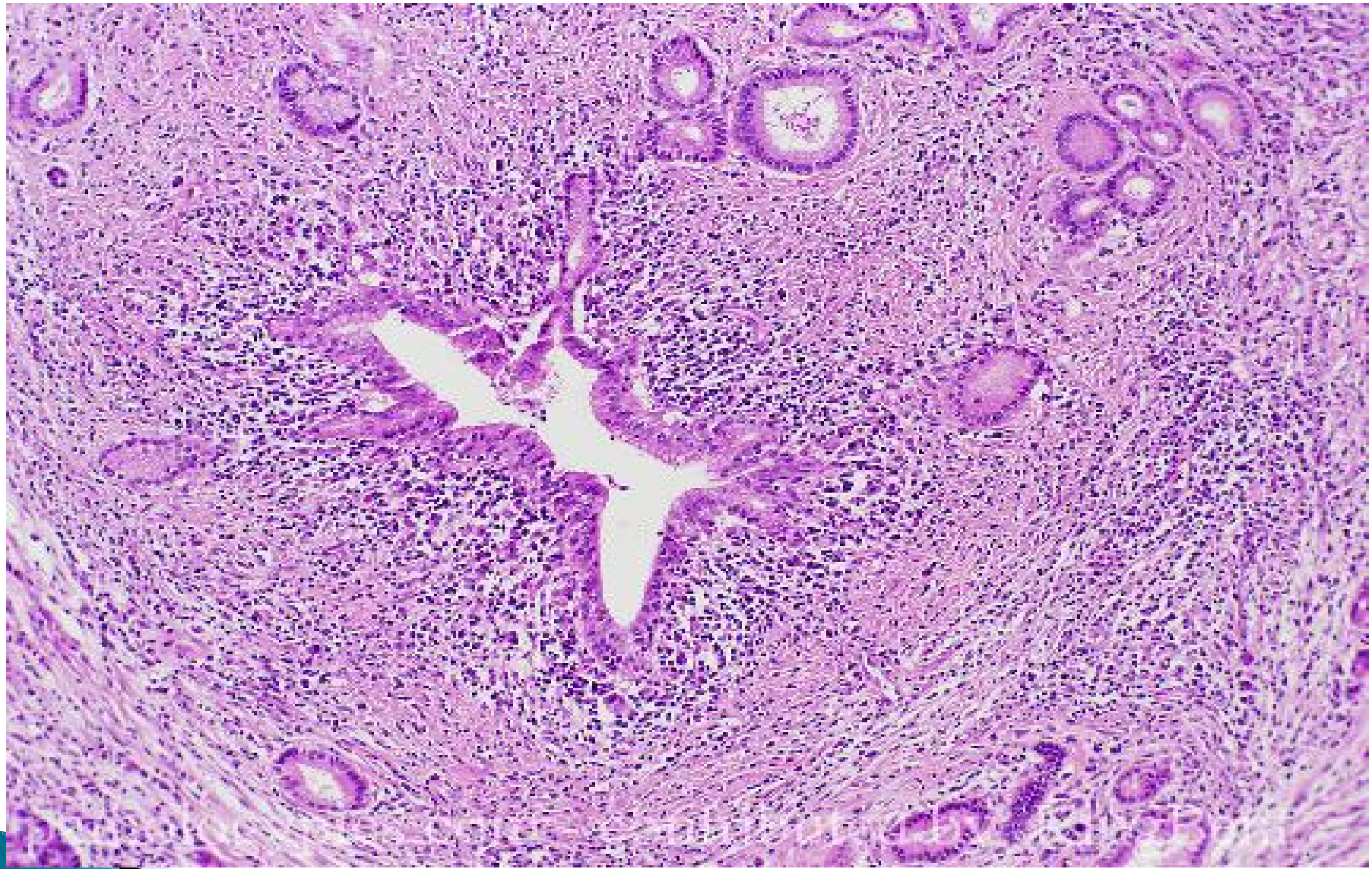
Autoimmune Pancreatitis

- Pathology
  - Two histologic variants
    1. Lymphoplasmacytic Sclerosing Pancreatitis (LPSP)
       - Infiltration of inflammatory cells (T-lymphocytes and plasma cells) and fibrosis around medium-sized interlobular ducts
       - Obliterative phlebitis of medium and small veins and a whirling or storiform fibrosis of the pancreas, is characteristic
       - Interstitial fibrosis with acinar cell atrophy is another common finding
    2. Idiopathic Duct Centric Chronic Pancreatitis (IDCP)
       - Less common
       - Neutrophilic infiltrate with microabscesses and obliterative phlebitis is rare



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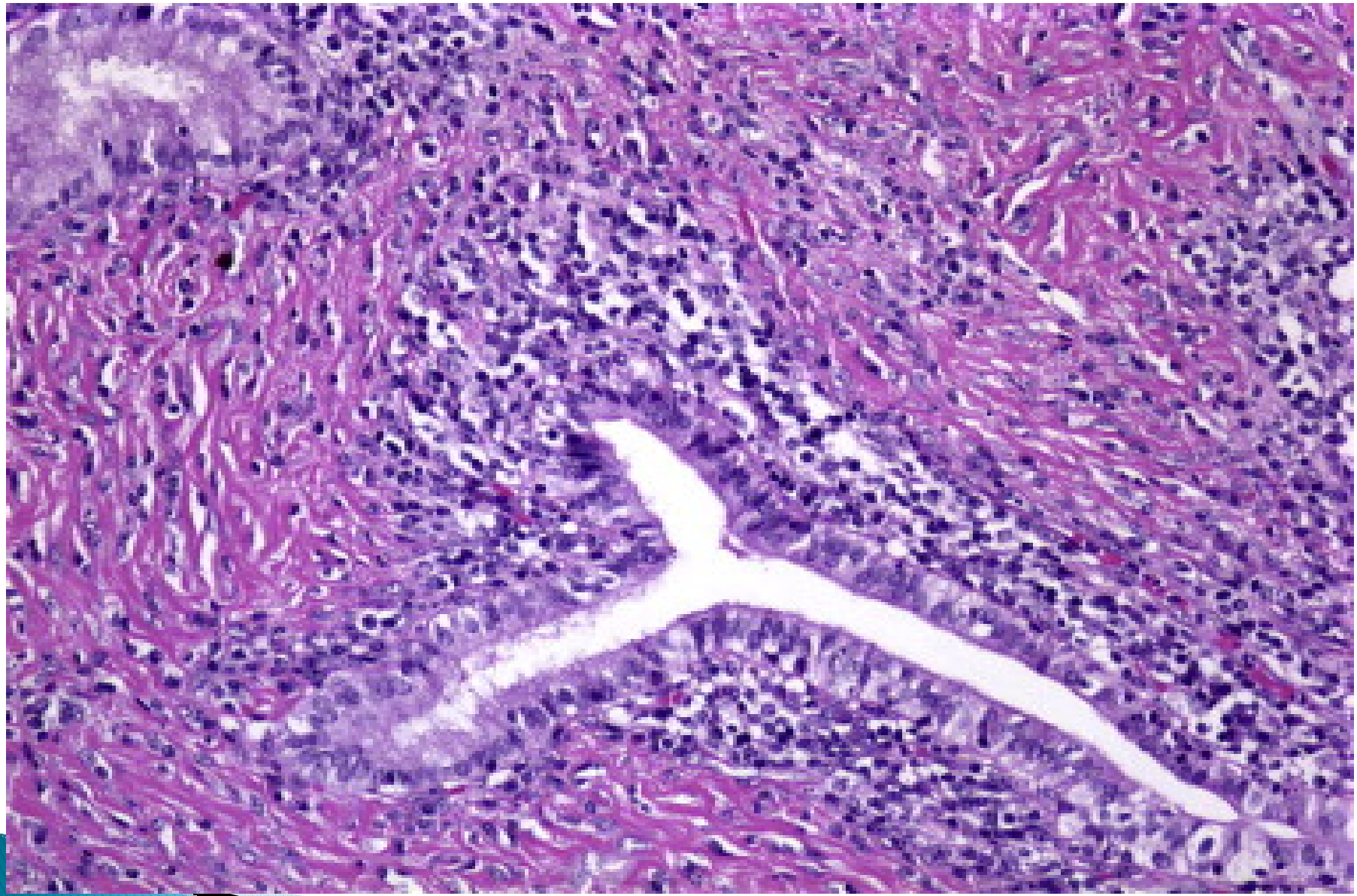

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Autoimmune Pancreatitis

- Variety of autoantibodies have been reported:
  - ANA
  - Antilactoferrin antibodies
  - Anticarbonic anhydrase II antibodies
  - Antismooth muscle antibodies
  - Rhuematoid factor
  - Antimitochondrial antibody
  - Do not have the sensitivity of IgG4 and are inferior for diagnostic purposes

Autoimmune Pancreatitis

- Diagnostic Criteria-(See Sleisenger and Fordtran pg 993)
  - Mayo Clinic HISORt Criteria
    - *H*istology, *I*maging, *S*erology, *O*ther organ involvement, and *R*esponse to *t*herapy
  - Japan-Korea Consensus Criteria

Autoimmune Pancreatitis

- **Treatment**
  - May progress rapidly from initial onset of symptoms to end-stage within months
  - Glucocorticoid therapy usually produces rather dramatic improvement with rapid resolution of both symptoms and radiographic abnormalities
  - No clear recommendation for steroid dose
  - Important to exclude malignancy but some cases may not be possible
  - May improve not only structural abnormalities but also exocrine and endocrine function
  - Clinical relapses after resection are rare (eg, pancreaticoduodenotomy)

Autoimmune Pancreatitis

- Treatment Option
  - Prednisone 30-40mg/day for 4-8 weeks
  - Repeat pancreatic imaging at 4 weeks is prudent to assess for clinical response
  - Once response is clear cut then tapering 5mg/week
  - Complete serologic response (normal IgG4) may not be apparent for several months
  - 30-40% experience relapse; repeat dosing with maintenance of Prednisone 5-10mg/day
  - Azathioprine has been used in a few steroid-dependent patients with success

IgG4-Related Sclerosing Cholangitis

- Most frequent extrapancreatic manifestation of type I AIP (>70%)
- Rarely occurs in absence of pancreatitis
- Shares cholangiographic and clinical features of PSC but differs in response to glucocorticoid therapy
- High numbers of IgG4 + lymphocytes (>20 per HPF) are identified in pinch biopsies obtained from the major papilla or bile duct may be diagnostic
- Persons without IBD who present with symptoms and imaging consistent with PSC should undergo measurement of serum IgG4 levels as well as endoscopy and biopsy of major papilla

Salivary and Lacrimal Gland Involvement

- Salivary gland involvement is a common feature
- **Mikulicz Disease (or Syndrome)**
  - Enlargement of lacrimal and salivary glands (parotid and/or submandibular)
- **Küttner Tumor**
  - Chronic sclerosing sialadenitis and unilateral or bilateral submandibular gland enlargement
- Found in nearly 40% of patients with IgG4-related pancreatitis, while AIP may be seen in only 17% of patients presenting with sialadenitis

Salivary and Lacrimal Gland Involvement

- **Features that distinguish it from Sjögren's Syndrome**
  - Fewer patients with dry mouth, dry eyes, or arthralgia (38, 33, and 16 percent vs 87, 94, and 48 percent)
  - Higher frequency of allergic rhinitis and bronchial asthma (41 and 14 percent vs 7 and 3 percent)
  - Higher frequency of AIP and interstitial nephritis (17 and 17 percent vs 0 and 7 percent)
  - Low frequencies of autoantibodies, including RF, ANA, anti-SSA, and anti-SSB (27, 23, 2, and 0 percent vs 87, 90, 100, and 100 percent)

Retroperitoneal Fibrosis

- Rare condition characterized by the presence of inflammatory and fibrous retroperitoneal tissue; may cause obstructive uropathy
- Disorder initially called Ormond's disease
- **Clinical Features**
  - Nonspecific and diagnosis is often not considered until there is significant organ involvement
  - Most patients have ureteral obstruction and renal impairment by the time they come to medical attention

Retroperitoneal Fibrosis

- **Clinical Manifestations**
  - Pain in the lower back, abdomen or flank is the most common
    - Dull and poorly localized and not affected by activity or posture
    - Bilateral or unilateral
    - May be acute like renal colic
    - Better relieved with NSAIDs than opiates
  - Malaise
  - Anorexia
  - Weight loss
  - Fever
  - Nausea/Vomiting
  - Testicular pain
  - Upper leg claudication
  - Urgency, frequency, and dysuria

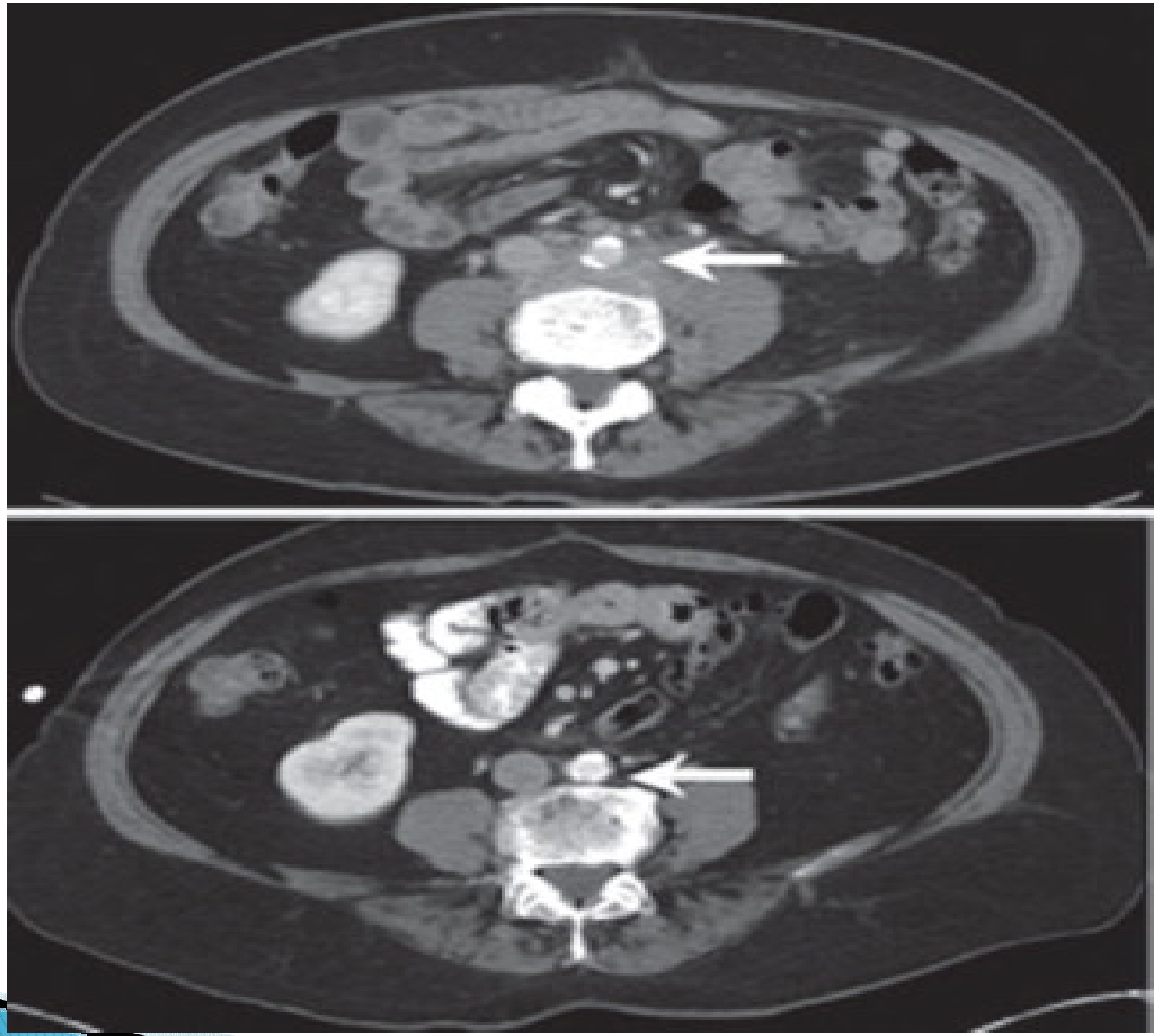
Retroperitoneal Fibrosis

- **Clinical Manifestations (continued)**
  - Lower extremity edema
  - Thrombophlebitis
  - DVT
  - Hydrocele

- **Laboratory Findings**
  - No hematologic or biochemical abnormalities
  - Urinary sediment most often normal
  - Elevation of ESR and CRP

Retroperitoneal Fibrosis

- Imaging
  - Ultrasonography
    - Poorly marginated, perioaortic mass that is typically echo-free or hypoechoic
    - Hydronephrosis
    - Limitations (body habitus, bowel gas, adjacent bony structures, etc)
    - Not the optimal imaging of choice
  - CT Scan
    - Imaging of choice
    - Visualizes the extent of fibrosis; assess the presence of lymphadenopathy
  - MRI
    - Produces findings comparable to those with CT scanning



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- Aortitis and Periaortitis
  - Recognized as one of the causes of noninfectious aortitis
  - Series of patients with thoracic lymphoplasmacytic aortitis or with inflammatory AAA and abdominal periaortitis has been identified in retrospective pathologic studies

- **Thyroid Disease**
  - Reidel's Thyroiditis
  - Fibrous variant of Hashimoto's thyroiditis

- **Lung and Pleural Disease**
  - May be asymptomatic or present with cough, hemoptysis, dyspnea, pleurisy, or chest pain
  - Visceral or parietal pleural thickening may occur
  - Obliterative arteritis is more common in the lung than in other organs affected by IgG4-RD
  - May mimic sarcoidosis
  - **Four Patterns of Lung Involvement:**
    - Solid nodular
    - Bronchovascular
    - Alveolar interstitial (with honeycombing, bronchiectasis, and diffuse ground-glass)
    - Round-shaped ground-glass opacities

- **Tubulointerstitial Nephritis**
  - Primarily middle-aged and older men
  - Nodular lesions mimicking renal carcinoma may be seen
- **Other Involved Organs and Tissues**
  - Skin disease, including a subset of cutaneous pseudolymphoma
  - IgG4-hepatopathy, resembling AIH, and hepatic inflammatory pseudotumor
  - Lymphoplasmacytic gastritis associated with AIP
  - Sclerosing mastitis and inflammatory pseudotumors of the breast
  - Hypopituitarism with IgG4-related hypophysitis
  - Prostatitis
  - Constrictive pericarditis

- **Indications for Diagnostic Evaluation**
  - Patients at high risk for having IgG4-RD are those with any of the following:
    1. Pancreatitis of unknown origin
    2. Sclerosing cholangitis
    3. Bilateral salivary and/or lacrimal gland enlargement

- **Prognosis**
  - Natural history has not been well-defined
  - Some patients improve spontaneously without treatment but many relapse
  - Significant morbidity and mortality in untreated patients include cirrhosis and portal HTN; retroperitoneal fibrosis; complications from aortic aneurysms; biliary obstruction; and DM
  - Additional studies of long term prognosis are needed

- Risk of Malignancy
  - Several types of lymphoma have been reported but further studies needed
  - A study in N. America, which involved 111 pt with IgG4-RD, 3 cases of NHL were found 3-5 years after diagnosis; standardized incidence ratio was 16.0 (95% CI 3.3-45.5), suggesting an increased risk of NHL
  - Several cases of pancreatic cancer, salivary duct carcinoma, pulmonary adenocarcinoma, SCLC, and GI clear cell sarcoma have also been reported

Summary

1. Increasingly recognized syndrome of unknown etiology that can affect practically any organ

2. Lymphoplasmacytic tissue infiltration of mainly IgG4 + plasma cells and small lymphocytes on histopathology

3. Elevated serum levels of IgG4

4. Responds to glucocorticosteroids fairly quickly