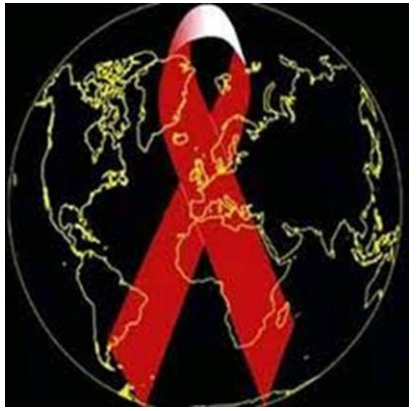
IgG4 related disease misdiagnosis in a patient with HIV

Elahe Nasri
Infectious Diseases in Immunocompromised Host & Transplantation

Case presentation



A 50-year-old female patient presented to our hospital's emergency department with weakness, lethargy, loss of appetite, and weight loss that had progressively started four months ago.

CBC : WBC : 2130 HB: 10.7 ESR : 110

On examination, there was axillary lymphadenopathy and the patient complained of retrosternal pain.

CT scan of chest , abdomen and pelvic

- There are some axillary chain lymph nodes with maximum SAD : 12mm bilaterally.
- Aortocaval LAP with central hypo enhancement and rounded morphology in size 24 . 15 .15 mm is seen.
- There are some iliac chain lymph nodes with maximum SAD : 7mm bilaterally.

The patient was evaluated during her previous hospitalization for weight loss and lymphadenopathy, and a biopsy of the axillary lymph node showed fibrosis and plasma cells infiltration. With suspicion of lymphoma, a hematologist performed a bone marrow biopsy, which resulted in:

Mild hypercellular marrow with mild increased T cell lymphocyte.

Flow cytometry immunophenotyping

- No flow cytometry evidence of B cell lymphoma or acute leukemia in this specimen
- Increase CD8 T cell lymphocytes with partial loss of CD7

Rheumatology consultation

- Due to the rejection of lymphoma, a rheumatology consultation is requested.

Immunological tests (RF, HLAB27, ANA, ANCA were all negative, with the exception of elevated IgG4 (160 mg/mL).

- considering the aortocaval lymph node and the total IgG4, started pulse methylprednisolone for the patient with a diagnosis of possible IgG4 RD and discharged the patient with oral prednisolone.

In the current hospitalization, the patient underwent endoscopy with worsening weakness and lethargy, odynophagia, and dysphagia, and the biopsy results are as follows:

Diffuse whitish were seen in lower third of esophagus (probable candidiasis)

Finally, an infectious disease consultation was requested due to oesophageal candidiasis.

In addition to starting fluconazole, the patient was asked to take an HIV test, which was positive with CD4: 15.

Due to the positive HIV result, combination ART was immediately initiated with a once-daily regimen of dolutegravir/ tenofovir / emtricitabine.

The Great Mimicker: Unmasking IgG4-Related Disease

Unmasking the complex fibro-inflammatory condition often confused with malignancy, requiring a multi-domain approach for accurate diagnosis.

THE DIAGNOSTIC CHALLENGE

Frequently Misdiagnosed as Cancer

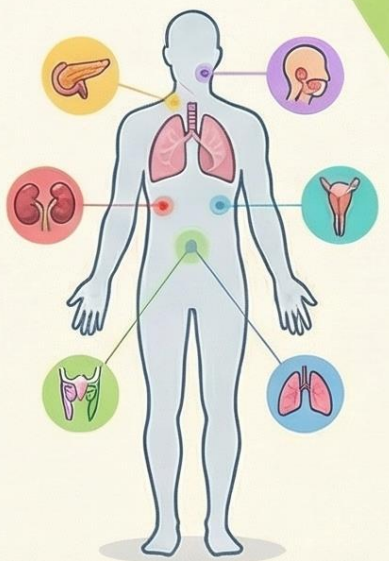
Mass-like lesions and organ swelling can lead to unnecessary surgeries and cancer treatments.

Elevated Serum IgG4 is Not Definitive

Only 22.4% of patients with an elevated serum IgG4 level actually meet the diagnostic criteria for IgG4-RD.

Affects Nearly Any Organ System

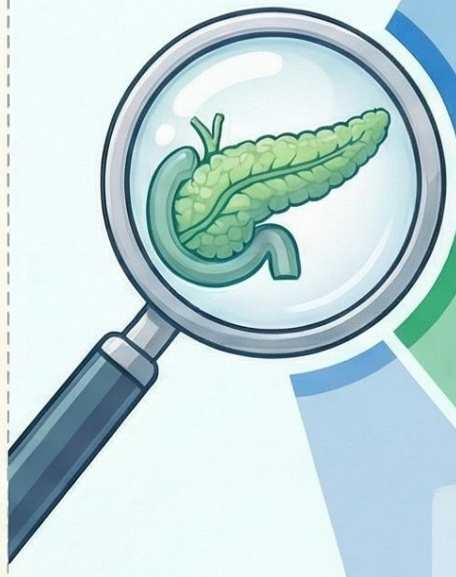
The disease can present with diverse symptoms depending on the organ(s) involved.



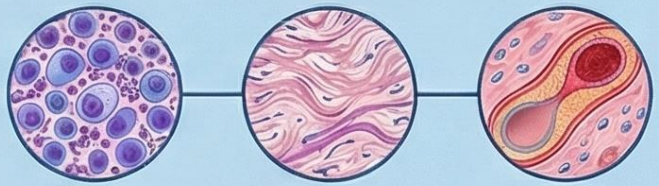
COMMON MANIFESTATIONS

Organ System	Description
Pancreas / Biliary	Autoimmune Pancreatitis (AIP), Sclerosing Cholangitis
Head & Neck	Swelling of Salivary & Lacrimal Glands (Mikulicz's disease)
Kidney & Retroperitoneum	Tubulointerstitial Nephritis, Retroperitoneal Fibrosis / Periortitis
Lungs	Nodules, Thickening of Bronchial Walls & Septa

THE PATH TO DIAGNOSIS



Crucial Histopathological Hallmarks

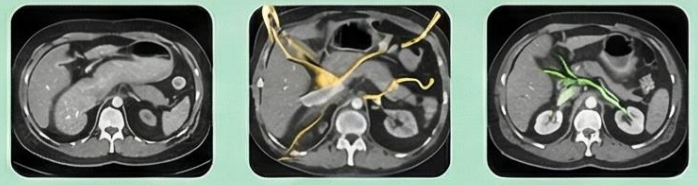


Dense Lymphopiasmacytic Inhitrate

Storiform Fibrosis

Obliterative Phlebitis

Characteristic Radiological Patterns



Sausage-like Pancreas

Perineural Disease

Symmetric Duct Wall Thickening

Diagnosis Requires Integration and Exclusion

Clinical Findings

Serological

Radiological

Pathological Findings

Clue #1: The Patient Presentation.

Pancreatic Cancer (PC)	Type 1 AIP / IgG4-RD
• **Age/Gender:** Mean age ~71 years; M:F ratio 1:1.	• **Age/Gender:** Mean age 60-70 years; strong male predominance (3:1).
• **Presentation:** Insidious onset, leading to late diagnosis.	• **Presentation:** Subacute or chronic, often found incidentally. Acute pancreatitis is uncommon.
• **Abdominal Pain:** Common (80%), often moderate to severe and progressive.	• **Abdominal Pain:** Less common (35%) and generally mild.
• **Jaundice:** Frequent (50%), especially with tumors in the pancreatic head.	• **Jaundice:** Very common (40-80%), often painless.
• **Weight Loss:** Significant and rapid (60%+), often progressing to cachexia.	• **Weight Loss:** Milder (35%), rarely progressing to wasting syndrome.
• **Extrapancreatic Signs:** Metastases, local invasion, paraneoplastic syndromes.	• **Extrapancreatic Signs: Crucial Clue.** Common involvement of other organs (sclerosing cholangitis, sialadenitis, retroperitoneal fibrosis). History of atopy in up to 40% of cases.

Clue #2: The Serological Evidence

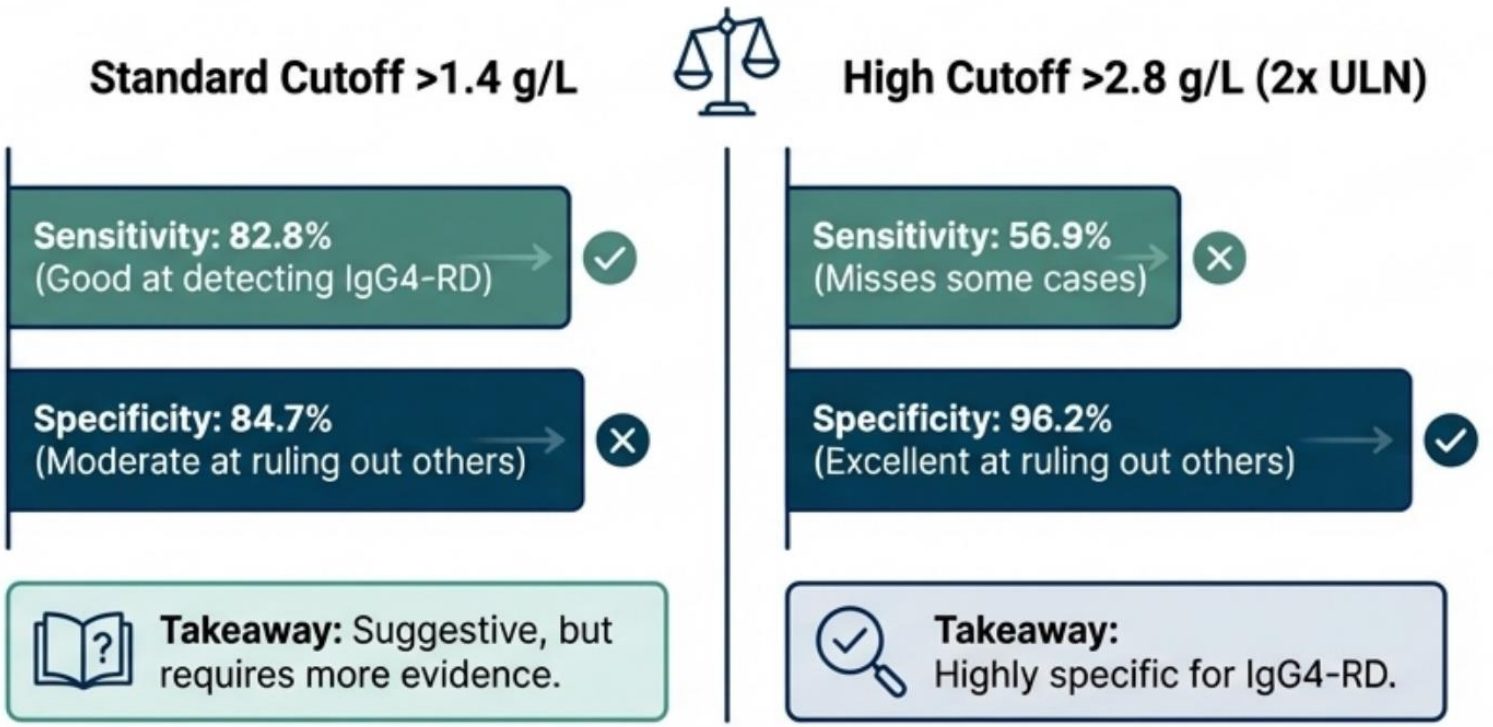
Serum IgG4 Concentration

While not a perfect marker, serum IgG4 is a powerful clue when interpreted correctly.

Up to 30% of patients with biopsy-proven IgG4-RD have normal serum IgG4 levels.

Conversely, elevated levels can be seen in other conditions, including PC (~10% of cases).

The Specificity vs. Sensitivity Trade-off



Supporting Evidence

- **CA 19-9**: Often elevated in PC, but also elevated in 27% of AIP patients. Not a reliable differentiator.
- **Autoantibodies (ANA, RF)**: Can be present in AIP, but lack specificity and sensitivity.

Clue #3: The Imaging Evidence

Autoimmune Pancreatitis (AIP)

CT Findings

- **Diffuse Pattern** (most common): **"Sausage-shaped"** pancreas—diffusely enlarged with loss of normal lobulated contours.
- **Hypodense "Capsule-like Rim"**: A characteristic low-density halo on delayed phase, representing peripancreatic inflammation/fibrosis.
- **Focal Pattern**: Can present as a focal mass, making differentiation difficult.

MRCP/ERCP Findings

- Diffuse or segmental ***irregular*** narrowing of the main pancreatic duct.
- Absence of significant upstream ductal dilation.
- **"Duct penetrating sign"**: Pancreatic duct is seen running through the mass.
- Often associated with IgG4-related sclerosing cholangitis (IgG4-SC) findings.

Pancreatic Cancer (PC)

CT Findings

- Focal, poorly defined, hypodense mass with spiculated margins.
- Disorganized infiltration of adjacent vessels and organs.
- Distal parenchymal atrophy.

MRCP/ERCP Findings

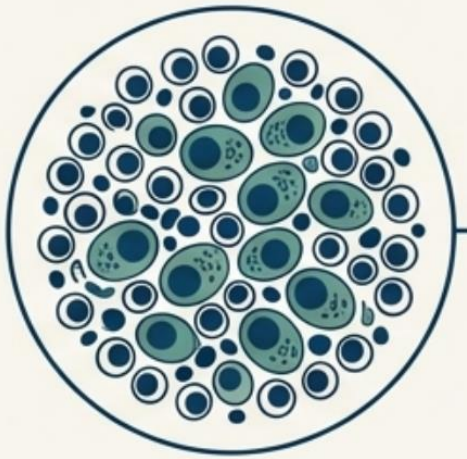
- Focal, ***abrupt*** stricturing or **"amputation"** of the pancreatic duct at the tumor site.
- Significant pre-obstruction ductal dilation is common.
- **"Double-duct sign"** (dilation of both pancreatic and bile ducts) present in 70% of head of pancreas cancers.

Clue #4: The Pathological 'Smoking Gun'

Histology is often required to definitively distinguish AIP from PC. A core needle biopsy is preferred over fine-needle aspiration (FNA) to preserve tissue architecture.

The Histologic Triad of IgG4-RD

1. Dense Lymphoplasmacytic Infiltrate



2. Storiform Fibrosis

3. Obliterative Phlebitis

1. Dense Lymphoplasmacytic Infiltrate

A rich infiltration of lymphocytes and plasma cells. IHC reveals >10 IgG4+ plasma cells/HPF and an IgG4+/IgG+ ratio >40%.

2. Storiform Fibrosis

A characteristic swirling pattern of fibrosis. Highly specific for IgG4-RD.

3. Obliterative Phlebitis

Fibrous obliteration of small veins by an inflammatory infiltrate. Also highly specific.

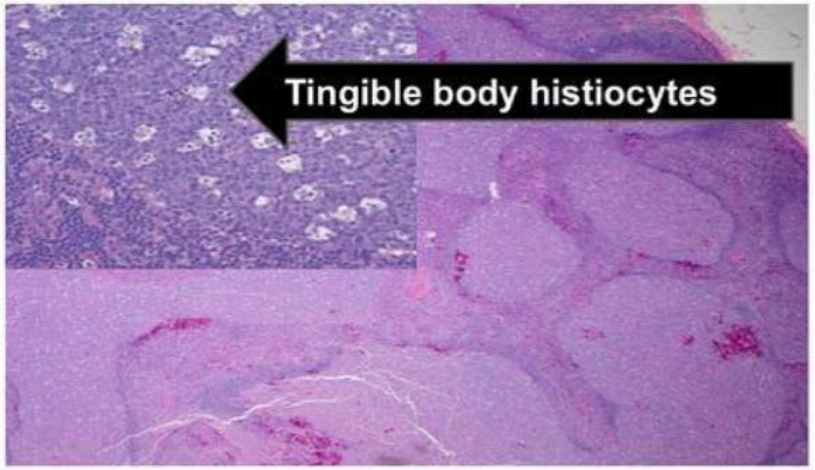
Contrast with Pancreatic Cancer

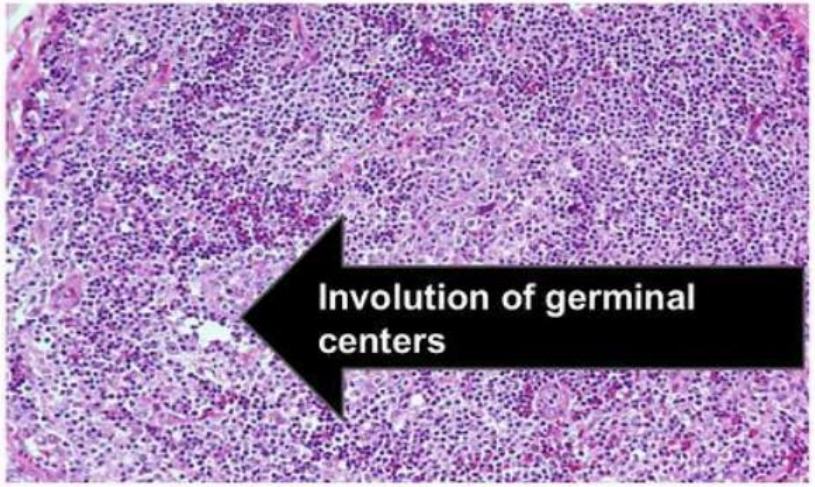
Histology: Ductal adenocarcinoma. Malignant glands infiltrate a dense desmoplastic stroma. Cellular atypia is present.

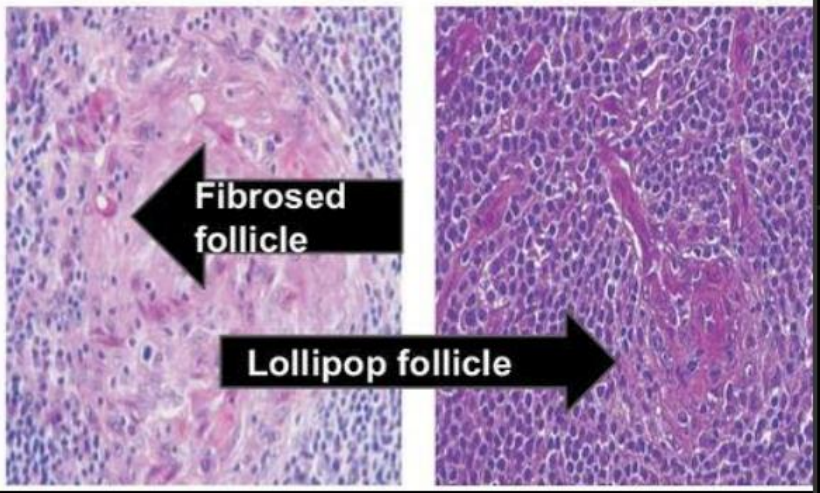
Note: IgG4+ plasma cells can be found in the inflammatory reaction around a PC, but the characteristic fibrosis and phlebitis are absent.

Patterns of HIV associated lymphadenitis

Pattern A (Active)	Pattern B (Chronic)	Pattern C (Burn-out)
■ Enlarged lymph node ■ Hyperplastic, serpiginous follicles ■ Reactive germinal centers ■ Apoptosis, folliculolysis ■ Tingible-body macrophages ■ Disruption of dendritic network ■ Mitoses ■ Hemorrhages, polynuclear cells ■ Monocytoid aggregates ■ Warthin-Finkeldey giant cells	■ Effacement of follicles ■ Involution of germinal centers ■ Depletion of lymphocytes ■ Plasma cells ■ Vascular hyperplasia	■ Small or absent follicles ■ Hyalinized germinal centers ■ Transfixing, collagen-ensheathed arterioles ("lollipop" follicle) ■ Lymphocyte depletion ■ Plasma cells ■ Deposits that stain with periodic acid–Schiff ■ Extensive angiogenesis







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The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD

Table 2. The 2020 Revised comprehensive diagnostic (RCD) criteria for IgG4-RD.

[Item 1] clinical and radiological features
One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.
[Item 2] serological diagnosis
Serum IgG4 levels greater than 135 mg/dl.
[Item 3] pathological diagnosis
Positivity for two of the following three criteria:
① Dense lymphocyte and plasma cell infiltration with fibrosis.
② Ratio of IgG4-positive plasma cells /IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field
③Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis
Diagnosis:
Definite: 1) +2) +3)
Probable: 1) +3):
Possible: 1) +2)


thankful
full of gratitude