IgG4-Related Disease

Adam Mahomed
Gastroenterologist & Hepatologist
University of Witwatersrand
Charlotte Maxeke Johannesburg Academic hospital
Wits Donald Gordon Medical Centre
Wits Transplant Unit

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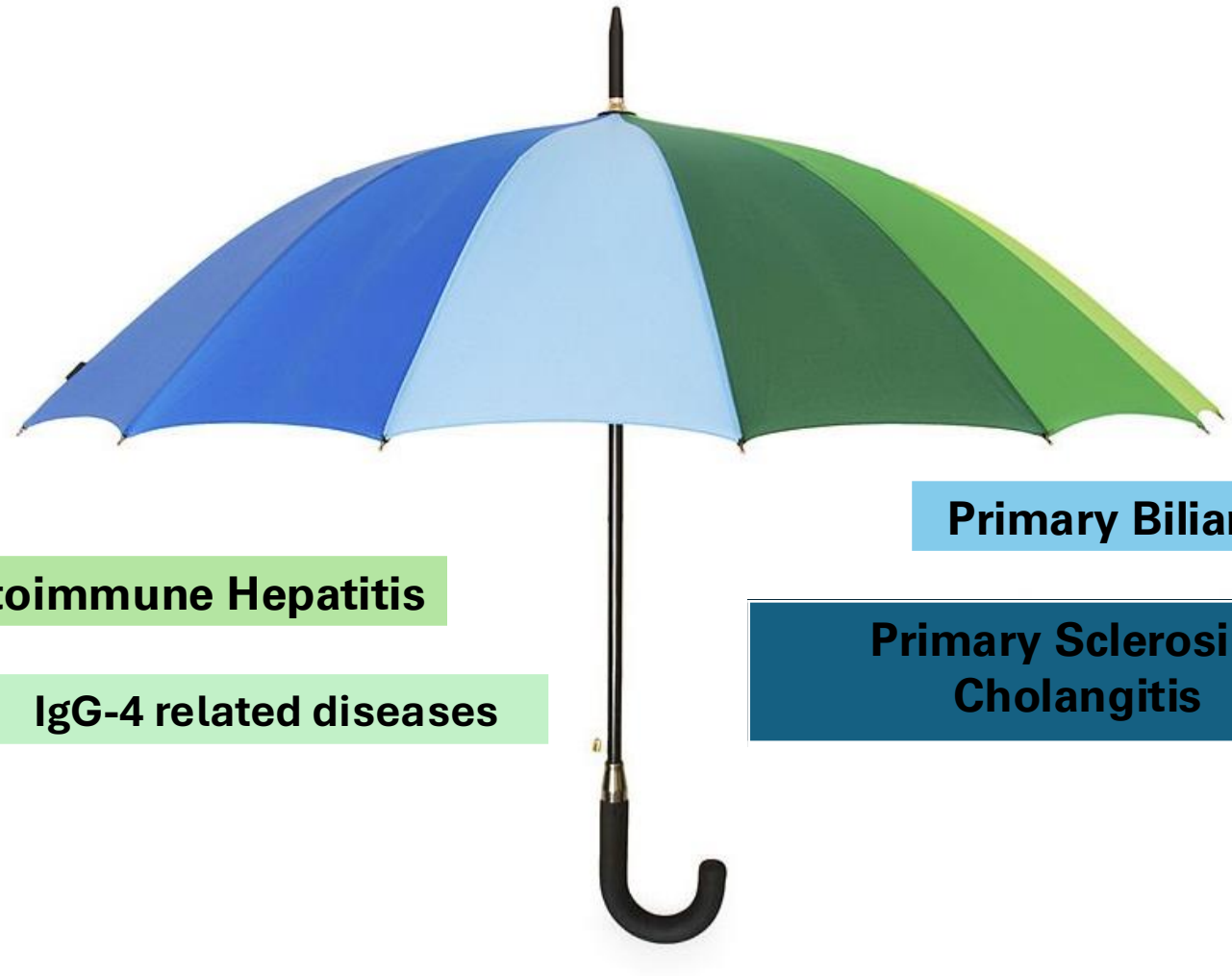


Primary Biliary Cholangitis

Autoimmune Hepatitis

Primary Sclerosing Cholangitis

IgG-4 related diseases

Introduction

- IgG4-related disease is progressive, immune-mediated and fibrotic
- Tumour-like mass formation in affected organs
- High serum IgG4 concentrations or high $IgG4^+$ plasma cells in tissue
- M2 macrophages, activated B cells, $CD4^+$ CTLs and fibroblasts
- Decline after B cell-targeted therapy suggests the culprit role B cells

Epidemiology

- Older men
- 6th decade
- True prevalence remains unknown

Aetiology

- Genetic
- Bacterial
- Molecular mimicry
- Autoimmune disease

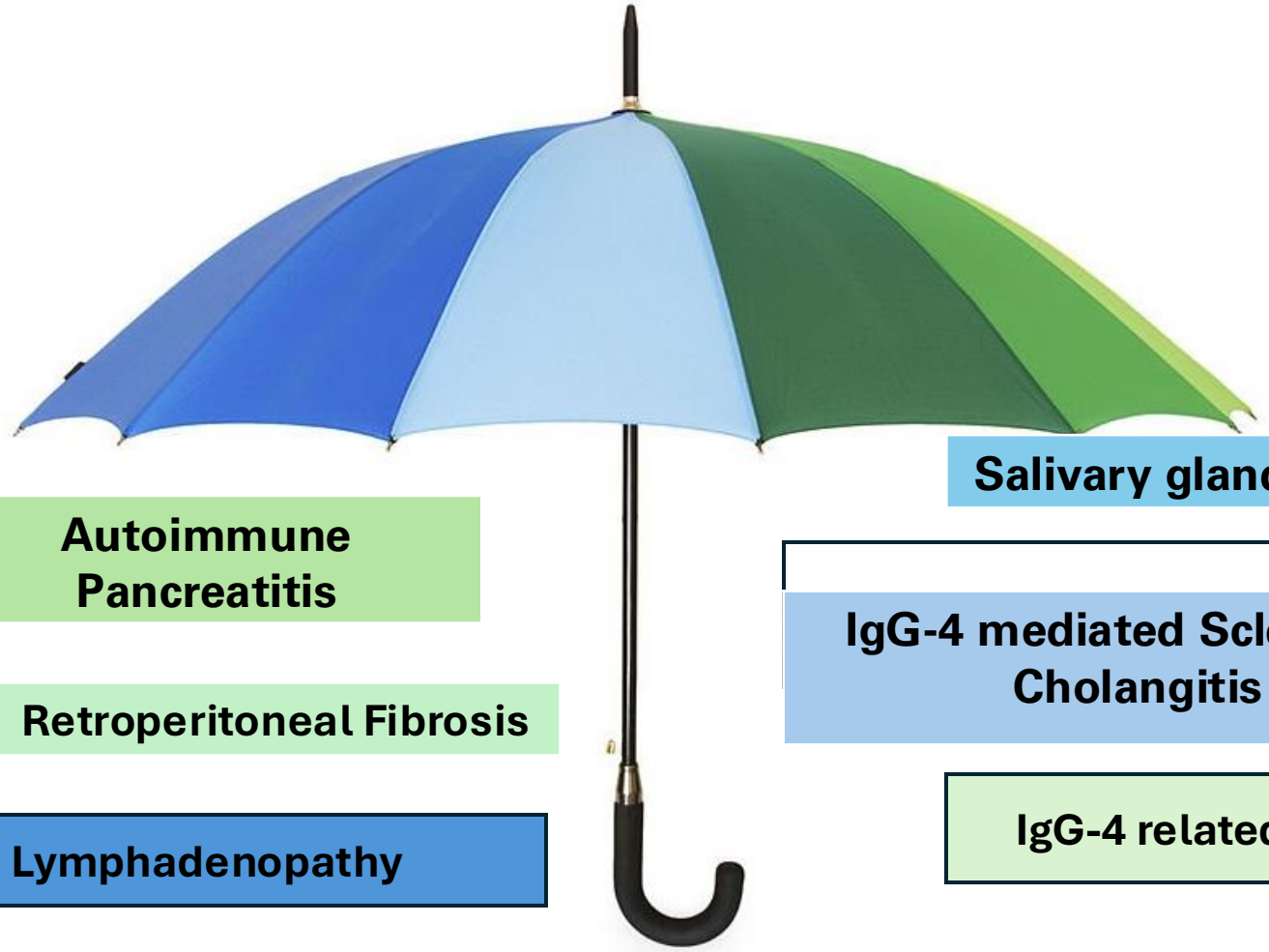
Clinical Presentation

- Multiorgan involvement
- Subacute presentation
- Mass like lesions
- Forty percent of patients will give a history of allergy

Japanese Clinical Diagnostic Criteria

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Histopathological examination shows:
(1) Marked lymphocyte and plasmacyte infiltration and fibrosis
(2) Infiltration of IgG4+plasma cells: ration of IgG4+/IgG +cells > 40 % and > 10 IgG4+plasma cells/HPF
Definite: 1) + 2) + 3)
Probable: 1) + 3)
Possible: 1) + 2)

Spectrum of IgG-4 Related Disease



Autoimmune Pancreatitis

Retroperitoneal Fibrosis

Lymphadenopathy

Salivary gland involvement

IgG-4 mediated Sclerosing Cholangitis

IgG-4 related renal disease

IgG-4 related Autoimmune Pancreatitis Type 1

- Older males
- Obstructive jaundice
- Hyperglobulinemia, and elevated serum IgG4
- Histologic features but !
- Extra-pancreatic involvement

IgG-4 related Autoimmune Pancreatitis Type 1

- Sausage-like pattern
- Focal or multifocal swelling of the pancreas, with delayed enhancement in the venous phase
- Capsule-like rim is seen as a bandlike low-intensity area on T2-weighed images.
- Narrowing or invisibleness of the main pancreatic duct

HISORt Criteria for AIP type 1

Criterion H-Histology (at least one of the following)	1. Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis 2. Lymphoplasmacytic infiltrate, storiform fibrosis, abundant IgG4+ cells (≥10 HPF)
Criterion I-Imaging of pancreas	1. Typical-diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct 2. Others-Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; pancreatitis
Criterion S-Serology	Elevated serum IgG4 (normal: 8-140 mg/dL)
Criterion O-Other organ involvement (can be confirmed by biopsy or resolution/ improvement with steroid therapy)	Hilar/intrahepatic biliary strictures; persistent distal biliary stricture; parotid/lacrimal gland involvement; mediastinal lymphadenopathy; retroperitoneal fibrosis
Criterion R-Response to steroid therapy	Resolution or marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled	1. Criterion H 2. Criterion I+S 3. Strong clinical suspicion of autoimmune pancreatitis (idiopathic pancreatic disease+Criterion S and/or O)+Criterion R

IgG4-related Sclerosing Cholangitis

- Present in > 70% of patients with AIP type 1
- Asymptomatic at time of presentation (as opposed to PSC)
- Extra biliary manifestations
- Combination of biliary tract and pancreatic disease is nearly diagnostic
- Serum IgG4/IgG ratio
- Red flag-CA199
- Wall of bile duct becomes thicker

IgG4-related Sclerosing Cholangitis

- Type 1: lower part of the CBD
- Type 2: strictures throughout intrahepatic bile ducts: segmental strictures with prestenotic dilation (type 2a) and diffuse strictures without prestenotic dilation (type 2b)
- Type 3: stenosis in the hilar hepatic lesions and the lower part of the common bile duct
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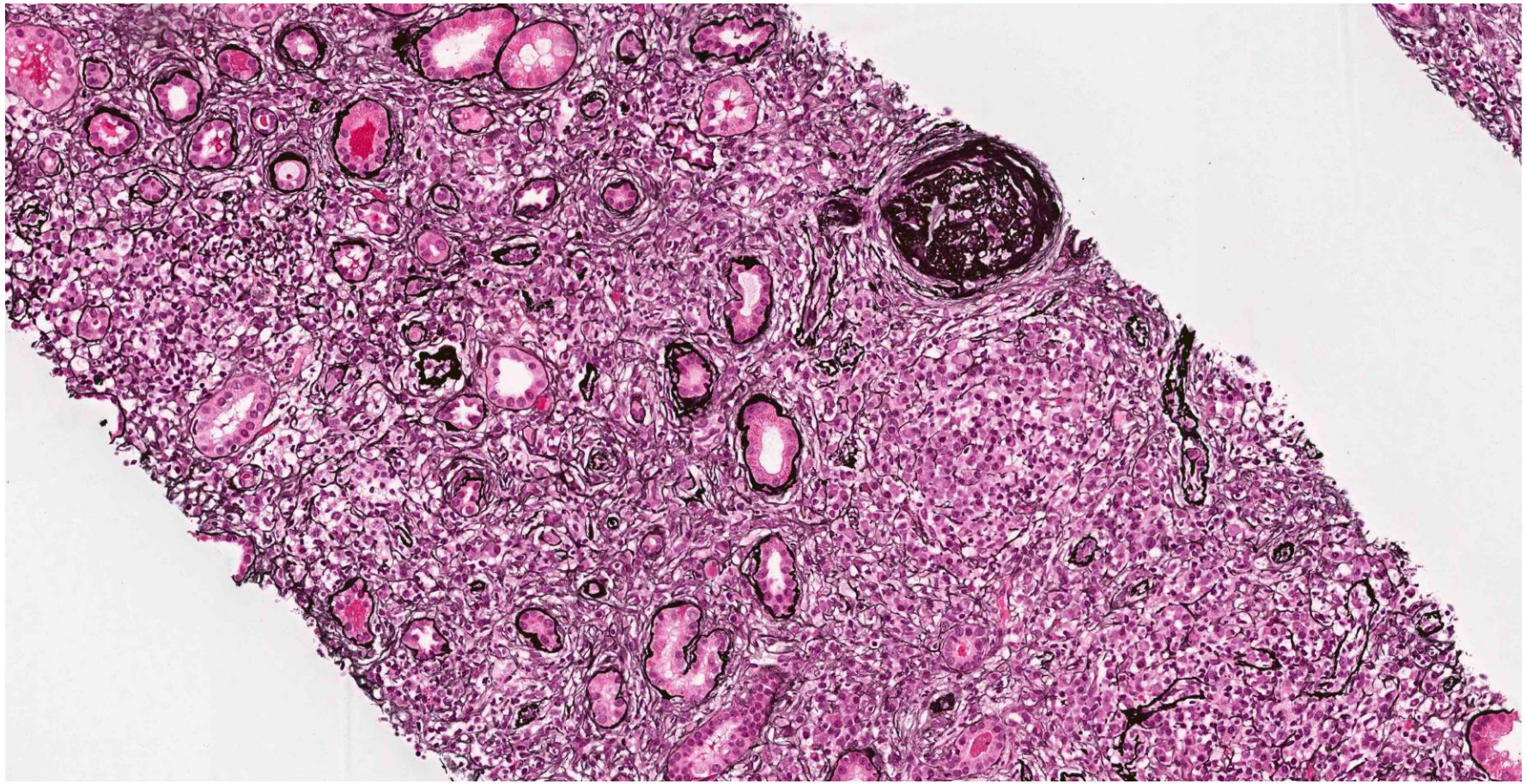
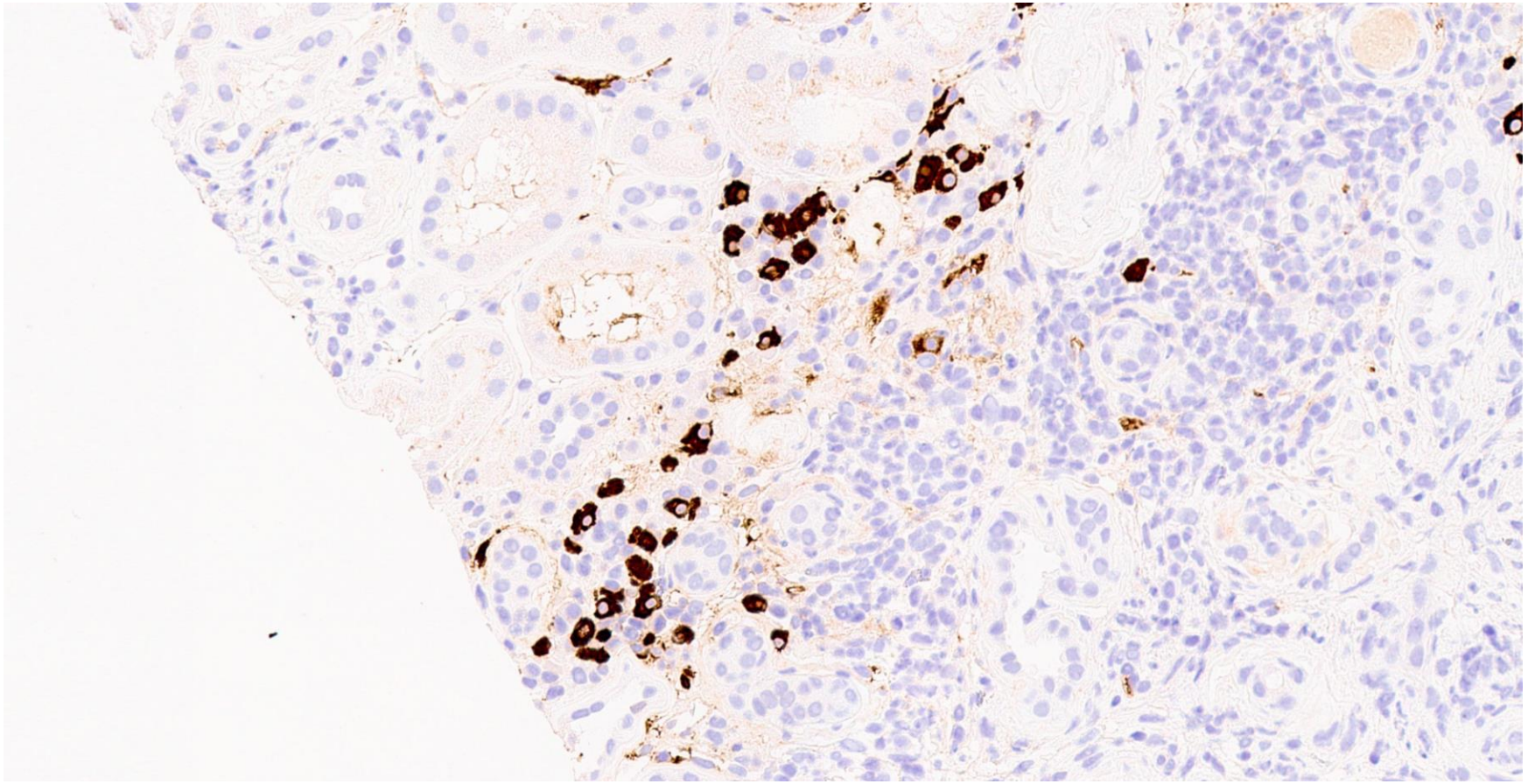
Histopathology

- Lymphoplasmacytic infiltrate
- Storiform fibrosis
- Obliterative phlebitis
- IgG4 positive plasma cell

Histopathology



Histopathology



Laboratory Diagnosis

- High serum IgG4 not diagnostic
- Normal serum IgG4 does not rule out
- Total IgG and IgG subclasses
- IgE
- ESR & CRP
- SPEP
- ANA & RF
- Hypocomplementemia

Radiological Diagnosis

- **CT & MRI**
  -Diffusely enlarged pancreas with delayed enhancement and borders
  -No features in the presence/absence of a capsule-like rim on contrasted CT & MRI with more than twice the upper limit of IgG4

- **EUS & ERCP**
  - Tissue samples

Treatment

- **Japan**
  - Prednisone 0.6 mg/kg per day for 2 to 4 weeks
  - Tapered 3 to 6 months to a dose of 5 mg per day
  - Continued at a dose between 2.5 to 5 mg per day for up to 3 years
- **Mayo**
  - Prednisone 40 mg per day
  - Maintain this dose for 4 weeks
  - Follow with a 7-week prednisone taper
  - Reduce the dose of prednisone by 5 mg per week and stop
  - Total duration 11 weeks

Treatment

- **Biliary Stenting**
  - In addition to steroids
  - Early symptomatic improvement

- **Recurrent or refractory disease**
  - Azathioprine (2 mg/kg per day)
  - Mycophenolate mofetil (up to 2.5 g/day as tolerated)
  - Methotrexate

- **B Cell depletion**
  - Rituximab

Treatment

- Bortezomib
- Abatacept (targeting CD80/86)
- Prezalumab (targeting inducible costimulatory ligand)
- Anakinra (targeting IL-1/IL-1R)
- Infliximab
- JAK 1 and 2 inhibitors

Treatment

Surgical Options

- Compression
- Symptoms relieve
- Severe fibrosis
- Irreversible organ fibrosis

Differential Diagnosis

Autoimmune

- Sjogren syndrome
- Primary sclerosing cholangitis
- Secondary retroperitoneal fibrosis
- Wegener granulomatosis
- Churg-Strauss syndrome

Differential Diagnosis

Malignancy & Other

- Cancer
- Lymphoma
- Plasma cell neoplasm
- Polyclonal hypergammaglobulinemia
- Hypereosinophilic syndromes
- Sarcoidosis

Predictors of Relapse

- Male
- Younger age of onset
- Longer disease duration
- IgG4 level (2 x ULN)
- Lower steroid dose
- Faster tapering of steroids
- No maintenance therapy
- Delayed treatment
- History of recurrence
- Proximal bile duct involvement
- Multi-organ involvement

Emerging Biomarkers

- IgG2
- Soluble IL-2 receptor
- Chemokine C-C motif ligand 18
- Eotaxin-3
- Laminin-511-E8
- Galectin-3
- Annexin-A11
- Antiproliferative protein (Prohibitin)
- Follicular regulatory T cells
- Peripheral helper T cells

Conclusion

- Complex
- Interprofessional team
- Lack of randomized clinical trials
- Relapses are common
- High index of suspicion

References

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THANK YOU!