Update in Rheumatology 2014

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What’s New in Rheumatology 2014
• Chapter I: Newly recognized diseases
• Chapter II: Newly renamed disease
• Chapter III: New disease treatments

Chapter I: Clinical Case #1
• 65 year old male with a history of cholangitis six months earlier presents with chronic worsening or vague abd pain and pruritis. PE exam is normal except for mild scleral icterus. Labs are normal except for modestly elevated alkaline phosphatase, and MRCP followed by ERCP clearly suggest a diagnosis of sclerosing cholangitis.

ERCP

Stricture
Question

• The American Association for the Study of Liver Diseases (AASLD) recommends which of the following next steps:
  • A. Check a serum IgG4 level
  • B. Perform a liver biopsy
  • C. Initiate treatment with corticosteroids
  • D. Antibiotic prophylaxis for all PSC patients to prevent bacterial cholangitis

IgG4-Related Systemic Disease (IgG4-RSD)

• Increasingly recognized syndrome of unknown etiology
• Collection of organ-specific disorders that share common clinical, serologic, and pathologic features
• Unifying concepts:
  – Sclerosing/fibrotic disease with typical “storiform” pattern
  – Tumefactive lesions (can mimic malignancy clinically and even pathologically)
  – Lymphoplasmocytic cell infiltrate enriched in IgG4+ plasma cells
  – Elevated serum IgG4 levels in majority but not all patients
  – Allergic/atopic diathesis (eczema, atopy, asthma)
IgG4 Related Systemic Disease: Is it a new disease or a newly recognized disease?

- 1995: Autoimmune pancreatitis (AIP) first described in Japan

- 2001: Some AIP patients found to have elevated serum levels of IgG4
  - Led to recognition of two distinct types of AIP
    - Type I “classical” AIP patients had elevated IgG4

- 2003: Extra-pancreatic manifestations demonstrated in patients with Type I AIP
  - Similar histopathology

IgG4 Related Systemic Disease: Is it really a new disease?

- Many diseases once thought of as distinct illnesses are increasingly recognized as organ-specific manifestations of IgG4-RSD (partial list)

- Some of these diseases have been recognized as distinct clinical entities for over 100 years
  - Autoimmune Pancreatitis (1995)
  - Sclerosing cholangitis
  - Fibrosing subset of Hashimoto’s thyroiditis and Riedel’s thyroiditis
  - Retroperitoneal fibrosis
  - Chronic sclerosing Aortitis and Chormic Inflammatory Aortitis
  - Sjogren’s syndrome like sialadenitis (Mikulicz’s disease)

Overall Clinical Features

- 2-3 times more prevalent in men than women
- Majority over age of 50
- Subacute onset and course in majority
  - Patients usually without constitutional symptoms
  - Modest if any elevations in CRP
  - Frequently diagnosed incidentally on imaging or pathology specimen

Clinical Features

- Focal presentation in affected organ
  - Tumor like masses mimicking malignancy
    - Pancreatic, renal, orbital, salivary gland, hepatic masses
  - Diffuse enlargement of an organ
  - Inflammation and sclerosis/fibrosis of an organ, duct, or retroperitoneal tissue

- Multi-organ involvement (60-90%)
  - Is often subclinical but can progress insidiously
  - Involvement of multiple organs occur concomitantly or sequentially
IgG4-RSD: Organ Specific Manifestations

Organ Specific Manifestations: Autoimmune Pancreatitis

- 6% of ALL cases of chronic pancreatitis in Japan are thought to be related to AIP
- 11% of 245 patients at Mayo clinic who underwent pancreatic resection for benign reasons had AIP
- Type I AIP associated with IgG4-RSD – “Classical AIP” and is most prevalent form

Autoimmune Pancreatitis Type I

Can present as focal mass or localized inflammation, or as diffuse swelling, inflammation, and fibrosis

AIP: Histopathology

Periductal lymphoplasmatic/cytic inflammation with “cartwheeling” fibrosis

Vlachou P A et al. Radiographics 2011;31:1379-1402

Diffuse swelling and infiltration of pancreas
Disease specific Antibody??

Frulloni et al. NEJM 2009

• Antibody crossreacts with H. pylori peptide and antigen in pancreatic acini
• 95% of AIP patients had antibody vs. 10% of patients with pancreatic cancer
• 54% of patients had elevated levels of IgG4
• Article is fuzzy about who had type I vs Type II AIP
• Remains controversial

Sclerosing Cholangitis Variant

• 79% of patients with AIP had IgG4-RSD associated sclerosing cholangitis in Japanese cohort
• Male predominant
• Older age (two decades older than PSC patients)
• Not associated with ulcerative colitis and IBD
• Unlike PSC, IgG4-RSD SC is generally steroid responsive
  — Reasoning behind AASLD’s recommendations to check serum IgG4 level (despite its shortcomings)

IgG4-RSD Sclerosing Cholangitis

ERCP appearance can look like PSC but it tends to involve lower common bile duct more often

Histopathology with lymphoplasmacytic inflammation and transmural fibrosis

IgG4 staining plasma cells

Chronic Sialadenitis

• Originally described as separate diseases > 100 years ago
  — Present in 24% of patients with AIP in Japanese cohort
• Two forms:
  — Bilateral painless symmetrical swelling of lacrimal/salivary glands: Mikulicz's disease
    • Frequently misdiagnosed as Sjogren’s Syndrome (SS) variant
  — Chronic sclerosing sialadenitis with unilateral or bilateral submandibular gland enlargement (Kuttner tumor)
    ■ Frequently misdiagnosed as a salivary gland tumor
• Clues to distinguish IgG4-RSD from SS
  Male predominance
  Older age onset
  Seronegative (SSA/SSB)
  Steroid responsiveness
Retroperitoneal Fibrosis

- Generally presents non-specifically with constitutional symptoms or sequelae of obstruction (eg. ureteral or aortic)
- Thick retroperitoneal fibrotic mass
  - Earlier cases may be more cellular/ later cases may be more fibrotic
- Lymphoplasmacytic infiltrate enriched with IgG4 plasma cells and phlebitis (venulitis)

Other organ involvement
(Not complete list)

- Riedel's thyroiditis
  - Chronic inflammatory and fibrosing disease often associated with AIP I, sclerosing cholangitis, retroperitoneal fibrosis
- Sclerosing variant of Hashimoto's thyroiditis
- Aortitis and periarteritis
- Tubulointerstitial nephritis
- Prostatitis

Misdiagnosis

- Failure to recognize and diagnose can lead to:
  - Disease progression, irreversible fibrosis, and organ damage
  - Unnecessary surgical procedures
    - Whipple for suspected pancreatic cancer
    - Surgery for cholangiocarcinoma
    - Removal of orbital pseudotumors
    - Thoracotomies

Diagnosis: Utility of Serum IgG4 Levels

- Elevated serum IgG4 present in majority but not all patients
  - Approximately 70% have elevated IgG4
  - Higher serum IgG4 titers may have more specificity for diagnosis
  - Elevated IgG4 neither necessary nor sufficient to make diagnosis
  - Helpful in suggesting the diagnosis (AASLD guidelines for sclerosing cholangitis)
Identification of IgG4 Plasma Cells in Path Specimens

- Presence of IgG4 positive plasma cells in tissue is necessary but neither specific nor sufficient to confirm diagnosis
- The larger the ratio of IgG4 staining plasma cells to other plasma cells in a specimen may be more suggestive of IgG4-RSD

Clinical Course

- Some patients can have spontaneous remissions (but many of those relapse)
- Others progress to major tissue damage and organ failure
  - Most often subacute-chronic course
  - Progressive fibrosis and organ distortion/destruction
    - Cirrhosis and portal hypertension
    - Retoripitoneal fibrosis
    - Aortic aneurisms
  - Cholangitis can lead to hepatic failure more quickly
  - Tumefactive lesions can lead to obstruction
  - Possible increased malignancy risk
    - Lymphoma, GI clear cell carcinoma, lung cancer, salivary gland cancer

Characteristic Pathology is Diagnostic

1. Lymphoplasmacytic infiltration of tissue fibrosis with “cartwheeling fibroblasts”
2. Elevated numbers of IgG4 plasma cells
3. Obliterative Phlebitis

Treatment

- Not all patients need to be treated (painless lymphadenopathy)
- Most symptomatic cases of organ involvement should be treated to prevent progression to tissue destruction
- Most manifestations are responsive to corticosteroids
IgG4-RSD/Sclerosing Cholangitis: Treatment with Corticosteroids

Corticosteroids and Other Therapies

- Failure to treat in many patients can lead to irreversible fibro-sclerosis and organ damage
- Patients can usually be tapered over the course of several months
- Some patients will relapse
- Experimental therapy with anti-B lymphocyte therapy Rituximab has shown some promise
- Symptom-specific therapy (e.g. stenting biliary strictures)

Case II

- 57 year old female develops significant proximal muscle weakness and mild myalgias 9 months after starting therapy with a statin. The statin is discontinued but her symptoms continue to worsen more than 12 months after discontinuing therapy. On exam, she has 4/5 proximal muscle weakness in her bilateral deltoids and quadiceps muscles, her TSH is normal, and her CK level is 3200. She is on no other medications.

Case II

Which of the following statements is true?

A. Statin associated myopathy always improves within a year of stopping the statin
B. Statin associated myopathy causes pain but not weakness
C. Statin associated myopathy is not a prevalent complication of therapy
D. Statin associated myopathy can be associated with autoantibodies
Case: II

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Statin Myopathy

- Muscle symptoms are prevalent in statin users
  - Painless elevations of CK
  - Myalgias without CK elevations
  - Both of the above +/- weakness
  - Frank rhabdomyolysis (can be fatal)

Statin Myopathy

- Thought that statins interfere with mitochondrial energy metabolism
- Potentiation of effect by concomitant use of fibrates and some medications that inhibit cytochrome p450 3A4
- Most symptoms resolve within weeks to months after d/c statin (supportive therapy)

Sera from some patients with a particular type of necrotizing myopathy can immunoprecipitate 100KD and 200 KD antigens from HeLa cell extract.
Anti-HMGCoAR Antibodies

- Anti-100KD antibodies recognize HMG CoA Reductase (57KD)
- Statins induce increased levels of HMGCoAR in regenerating muscle cells
- 92% of patients at Johns Hopkins with anti-HMGCoAR antibodies had statin exposure
- Self-perpetuating autoimmunity

Autoimmune Necrotizing Myopathy

- Small subsegment of patients with statin myopathy actually develop autoimmune syndrome
  - Antibodies to HMG CoA Reductase
  - Relatively pauci-immune necrotizing myopathy
  - Severe polymyositis like syndrome difficult to treat (can be poorly responsive to therapy) with high CK
  - Doesn’t resolve with d/c statin therapy
  - More to follow......

Chapter II: Case

- 36 year old female is admitted to the hospital with hemoptysis, respiratory distress, and acute kidney injury. She is taking no medications, is married, and has no children.

- Her exam is significant for hypoxemia, and hypertension and her workup includes CXR with bilateral pulmonary nodules and infiltrates and an elevated creatinine with hematuria and dysmorphic RBC’s. Her urine tox screen is negative and C-ANCA and Proteinase-3 antibodies are positive. Kidney biopsy reveals a pauci-immune necrotizing glomerulonephritis.
Question

• This patient’s diagnosis is most consistent with:

A. Wegener’s Granulomatosis
B. Microscopic polyangiitis
C. Systemic Lupus Erythematosus
D. None of the Above

Apologies!!!

Chapter II: A Renamed Disease!

• This patient’s diagnosis is most consistent with:

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B. Microscopic polyangiitis
C. Systemic Lupus Erythematosus
D. None of the Above

Granulomatosis with Polyangiitis (GPA)

• Friedrich Wegener: German pathologist credited with describing the disease (died in 1990)
• Wegener’s past ties to nazi party (1932) and work near Jewish Ghetto of Lodz have become more clearly understood in recent years
• 2011: Led to renaming of WG as GPA by major medical organizations including the ACR
• This patient does have this disease!!

Case continued

• The patient is initially treated with high dose pulses of IV corticosteroids and begins to improve. However when cytotoxic therapy with oral cyclophosphamide is recommended, she expresses concern over her risks of becoming infertile, and she strongly desires to have a child in the next few years.
Question

• Which of the following statements is not correct?

A. Risk of premature menopause resulting from cytoxan is dose and age-dependent
B. Corticosteroids alone are not sufficient therapy to treat this disease
C. Cytotoxic therapy should not be delayed for several months while the patient undergoes egg harvesting and cryopreservation
D. Oral Cyclophosphamide is the only therapy approved to treat GPA

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

Rituximab, B-cells, and ANCA

• Antineutrophil cytoplasmic antibodies are possibly implicated in pathogenesis or propagation/potentiation of ANCA-vasculitis
• Rituximab is a selective B-cell depleting antibody (anti-CD20)
• Possibility to remove ANCA by eliminating B-cells that would replace short-lived ANCA producing plasma cells
• Other possible mechanisms by which B-cells might be implicated in ANCA vasculitis
RAVE Study

• Multicenter, randomized, double dummy, double blinded placebo controlled non-inferiority trial
• Oral Cytoxan (Gold standard) vs. Rituximab
• Both regimens given with corticosteroids
• Included patients with both GPA and MPO (microscopic polyangiitis) as well as patients with relapsing disease
• Primary outcome: remission at 6 months free of glucocorticoid use (won’t get into specifics of how remission defined).

RAVE: Summary

• 197 patients enrolled
• 64% patients in rituximab arm reached endpoint vs. 53% in cytoxan arm (p<0.001)
  – Comparable non-inferiority for GPA and MPA
  – Comparable non-inferiority for alveolar hemorrhage or major renal disease
• Ritux more effective for relapsing patients to achieve primary endpoint (67%) vs. cytoxan (42%) (P=0.01)
• No difference in Adverse Events (surprising)
  – Our patient was concerned about fertility, not infections!
• FDA approval for rituximab to treat both GPA and MPA in 4/2011