RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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THE ZEBRA: IgG4-RD

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OBJECTIVES

- Understand the cause and pathogenesis of IgG4-RD.
- Describe the common presentation of a patient with IgG4-RD.
- Describe diagnostic features of IgG4-RD.
- Describe testing that is useful in the initial diagnostic evaluation.
- Understand why early treatment is important for IgG4-RD.
- Describe surgical and medication management of IgG4-RD.

IgG4-RD

- Immunoglobulin G4-related disease (IgG4-RD) is an uncommon immune mediated fibroinflammatory condition that is capable of affecting multiple organs. Frequently in a metachronous fashion-i.e., first one organ, then another, and another. It can lead to organ failure and death if left untreated.
- The pathology seems to be primarily affected by Bcells.
- The pathophysiology is unknown, thought to be a genetic predisposition and environmental triggers.
- Often mimics cancer with mass forming lesions, infections, & rheumatologic conditions such as Wegner’s polyangiitis and Sjogren's Syndrome.

IgG4-RD

- Typically an acute onset.
- Associated with allegy symptoms(e.g.,asthma, allergic rhinitis, eczema, etc).
- Organ damage often occurs when patients are asymptomatic years before diagnosis.
- Fevers are rare.
- Most common symptom is FATIGUE!
- Usually present for an evaluation d/t weight loss of 10-15 lbs d/t pancreatic dysfunction. Damaged pancreas no longer produces appropriate amount of digestive enzymes.

Common Presentations:

- Type 1(IgG4-RD) autoimmune pancreatitis.
- Sclerosing cholangitis.
- Salivary gland disease(Mikulicz disease-lacrimal, parotid, and submandibular gland enlargement).
- Orbital disease-proptosis(orbital pseudotumor).
- Retroperitoneal fibrosis(RFP)-chronic periaortitis can often affect the ureters, leading to hydronephrosis and renal injury.

Diagnostic testing

- Labs:
- IgG subclasses
- Blood plasmablast concentrations.
- Immunoglobulin profile
- Serum complements
- Biopsy of affected tissue.
- X-ray, CT, PET scan.

Diagnosis

- Diagnosis-based on a combination of the following:
- 1. Clinical findings.
- 2. Serological data: elevated serum concentrations of IgG4 in 60-70% of patients. Hypocomplementemia-C3 & C4.
- 3. Radiology studies(PET CT scan)
- 4. Pathology: lymphoplasmacytic infiltrate enriched in IgG4 positive plasma cells and a degree of fibrosis- “storiform” pattern.

Pretreatment Evaluation

- After the diagnosis of IgG4-RD has been established, disease extent should be evaluated before initiating treatment.
- **Baseline testing:**
- CBC with diff including eosinophil count.
- Serum chemistry panel including renal and liver function test, amylase & lipase.
- IgG4 subclass levels.
- IgG4 concentrations.
- Serum C3 & C4 concentrations. Typically low, especially if they have TIN. **Can monitor levels as a gauge to therapy response.**
- Hgb A1C.
- **Stool testing-** fecal elastase in patients with known suspected pancreatic involvement.
- **Urinalysis- tubulointerstitial nephritis (TIN).**
- **Imaging**-CT(with contrast) of the chest, abdomen, pelvis and orbits**.** Patients may have subclinical disease.
- **PET scan**-can help determine extent of disease.

Treatment

- **Urgent treatment needed if pancreatobiliary or renal disease to prevent organ dysfunction and failure.**
- First line of treatment-monotherapy Glucocorticoids 0.6mg/kg QD(typically 30-40mg). Majority of patients respond(2-4 weeks), but flare after taper is complete(gradual taper over 6 months). 40% of patients fail to achieve complete remission or relapse in 1 year.
- B cell depletion with Rituximab(preferred over AZA and MMF-greater evidence of efficacy). Can prescribe with glucocorticoids.

TREATMENT

- Surgical & other interventional procedures-stenting to relieve mechanical obstruction.

1. Hydronephrosis-RPF & periaortitis that is associated with ureteral obstruction requires stenting or nephrostomies.

2. Vascular & organ compression from mesenteritis require surgical debulking.

3. Obstructive jaundice-biliary tract obstruction requires stenting and drainage.

4. Aortic aneurysm & aortitis-may require arterial graft replacement, stent grafting, or endovascular repair.

5. Compressive symptoms of Riedel; thyroiditis, such as hoarseness, dyspnea, and dysphagia may require surgical intervention because response to treatment is inadequate.

Prognosis

- The natural history of IgG4-RD has not been defined.
- A small amount of patients improve without treatment, but temporarily.
- Majority will relapse, most have chronic disease.
- Mortality and morbidity is seen in untreated patients with cirrhosis, portal hypertension, retroperitoneal fibrosis, complications from aortic aneurysms, biliary obstruction, and diabetes mellitus.
- Risk of malignancy-studies suggest the risk maybe increased in the year after diagnosis. Further studies required to determine this risk.

Table 2: Previously Recognized Conditions That Comprise or May Comprise Parts of the IgG4-RD Spectrum.[19]

IgG4-RD accounts for some or all of the cases known previously by the following names:

- Mikulicz's disease
- Küttner's tumor
- Riedel's thyroiditis
- Eosinophilic angiocentric fibrosis
- Multifocal fibrosclerosis
- Lymphoplasmacytic sclerosing pancreatitis/ autoimmune pancreatitis
- Inflammatory pseudotumor
- Fibrosing mediastinitis
- Sclerosing mesenteritis
- Retroperitoneal fibrosis (Ormond's disease)
- Periaortitis /periarteritis
- Inflammatory aortic aneurysm
- Cutaneous pseudolymphoma
- Idiopathic hypertrophic pachymeningitis
- Idiopathic tubulointerstitial nephritis
- Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Membranous glomerulonephritis
- Idiopathic cervical (paravertebral) fibrosis

CASE PRESENTATION

- 75 yo Caucasian male. PMH: Gout, BPH, OSA, diverticulosis, hyperlipidemia.
- Married, accompanied by his wife of Retired technical writer for Xerox, writing manuals. Plays bass in a band.
- Referred to Rheumatology on 11/20/2020 by General surgery, post op small bowel resection for a terminal ileum mass. He initially reported abdominal pain, underwent an MRI of the abdomen; was treated for colitis with antibiotics. Imaging revealed a terminal ileum mass. Underwent colonoscopy, mass biopsied. Biopsy was initially nondiagnostic and was referred to general surgery.
- Surgical pathology: Immunohistochemical analysis shows numerous IgG4-positive plasma cells in these foci (sometimes greater than 90 per high power field), and serum IgG4 analysis shows an elevated level of 703.0 mg/dL (normal 2.4 to 121.0 mg/dL). These results are most consistent with IgG4-related sclerosing mesenteritis. Negative for neuroendocrine tumor and carcinoma.
- CT chest: small cavitary subpleural lesions LL lobe, new small solid nodule 10x9 mm LL lobe.

CASE PRESENTATION

- ROS:
- Negative for fevers, & night sweats.
- Endorsed moderate to severe daily fatigue.
- No appetite changes, occasional diarrhea. Weight loss of ~10-15 lbs.
- No sicca symptoms
- No rashes.
- Denied chest pain, dyspnea, cough, or sputum production.
- + hematuria-hx of BPH. Negative work up by Urologist
- + joint pain-hx of non-crystal proven Gout for the past 20 years.

PHYSICAL EXAM

- In general, the patient is well-appearing and in no acute distress, pleasant.
- HEENT: Sclera non-icteric and non-erythematous. Mouth is moist without any ulcers or thrush. No malar rash. Male pattern balding. Hearing aids in place.
- Neck: Supple with no palpable lymphadenopathy in the anterior or posterior chains.
- Cardiovascular: NRRR, no murmurs or rubs.
- Pulmonary: Clear to auscultation, no wheezes or crackles.
- Abdomen: Soft and non-tender, protuberant. Mostly healed lower midline surgical incision.
- Extremities: No clubbing, cyanosis, or edema.
- Joints: No signs of synovitis or arthritis in the joints of the hands, wrists, elbows, shoulders, hips, knees, ankles, and feet except for crepitus in knees. Bunion at b/l 1st MTP
- Skin: No significant rashes noted on exposed areas of face, upper, and lower. extremities. Scattered seborrheic keratoses. 3 hyperpigmented melanocytic papules on back. Hyperkeratotic thickening of toenails
- Neuro: Strength is 5/5 in all extremities; sensation is grossly intact to light touch in upper and lower extremities.
- Psych: Affect is within normal limits.

PLAN

- PET/CT to evaluate for any evidence of active inflammatory foci possibly related to IgG4 related disease that would require additional work-up or treatments. Malignancy can also still be a mimicker of IgG4 related disease. If lab work and PET scan is otherwise reassuring, clinical monitoring would be reasonable given his lack of symptoms. Ways to monitor his clinical response would include symptoms, serial imaging, serum IgG4 levels and potentially inflammatory markers and complement levels if these are abnormal at baseline. If however there is evidence of other active inflammatory disease, then we will need to consider initiating treatment with prednisone and possibly rituximab.

PLAN

- Labs:

Complete Blood Count (CBC) with Differential
- Comprehensive Metabolic Panel (CMP)
- Quantiferon TB Gold PLUS
- Urinalysis Complete
- Protein/Creatinine Ratio, Random Urine
- Protein Electrophoresis, Serum
- Immunoglobulin Free Lt Chains Blood
- Protein Electrophoresis, Urine
- Immunoglobulin Profile
- Lipase
- 25 OH Vitamin D
- Uric Acid

PLAN

- Labs:
- -Antinuclear Antibody Screen
- • Neutrophil Cytoplasmic Ab Scrn
- • Antibodies-Sm,RNP,Ro,La
- • C3 Complement
- • C4 Complement
- IgG Subclasses, Serum
- • Sedimentation Rate-Automated
- • C-Reactive Protein (CRP), Inflammatory
- • Hepatitis B Core Antibody, Total
- • Hepatitis B Surface Antibody
- • Hepatitis B Surface Antigen
- Hepatitis C Antibody with reflex to PCR

PLAN

- Radiology: PET CT skull base to midthigh.
- **IMPRESSION**
- 1. Mild avidity of bilateral hilar lymph nodes and right axillary lymph
- node, favored inflammatory.
- 2. Innumerable pulmonary nodules are without appreciable metabolic
- activity, though the majority are below PET resolution. Attention on
- follow-up.
- 3. Increased metabolic activity in the pancreatic tail, as may be seen in
- the setting of IgG4 disease.
- 4. Small focus of FDG avidity in the central liver near the hilum is of
- uncertain significance. Recommend attention on follow-up.
- 5. Redemonstrated metabolic activity in soft tissue stranding about the rectum, again suggestive of proctocolitis.

TESTING RESULTS

- **IgG** 588-1,573 mg/dL **2,040 High**
- **IgM** 57 - 237 mg/dL 65
- **IgA** 46 - 287 mg/dL 123
- **IgE** 4 - 269 IU/mL **297 High**

- **Immunoglobulin G, Total** 767 - 1590 mg/dL **1900 High**
- **Immunoglobulin G, Subclass 1** 341 - 894 mg/dL **931 High**
- **Immunoglobulin G, Subclass 2** 171 - 632 mg/dL **86 Low**
- **Immunoglobulin G, Subclass 3** 18.4 - 106.0 mg/dL 44.8

- **Immunoglobulin G, Subclass 4** 2.4 - 121.0 mg/dL **1060.0 High**

TESTING RESULTS

- Extensive lab testing confirmed persistently elevated IgG4 levels and immunoglobulins.
- Mildly positive ANA test, which is nonspecific and false positive based on your symptoms and exam.
- All antibody tests for other autoimmune diseases were negative.

- Tuberculosis and hepatitis labs were negative.

- **Diagnosis consistent with IgG4 disease.**

TREATMENT

- Based on symptoms, I do not see a clear indication for treatment, but based on PET scan, I do think prednisone would be appropriate to control active inflammation with goal of preventing irreversible damage. We can monitor his response based on serum IgG4 levels and follow-up PET scan in the future.

- Prednisone 10mg tablets. Take 4 tablets by mouth daily for 14 days, then take 3 tablets by mouth daily for 14 days, then take 2 tablets by mouth daily for 14 days, then take 1 tablets by mouth daily for 14 days, then take 0.5 tablets by mouth daily x 14 days then stop.
- Repeat serum IgG4 levels in 4 weeks.

TREATMENT

- **Repeat IgG4 results after completion of prednisone taper:**

- **Immunoglobulin G, Total (**767 - 1590 mg/dL)1050

Immunoglobulin G, Subclass 1 **(**341 - 894 mg/dL) 486

- **Immunoglobulin G, Subclass 2** **(**171 - 632 mg/dL) **81 Low**
- **Immunoglobulin G, Subclass 3** **(**18.4 - 106.0 mg/dL 31.1
- **Immunoglobulin G, Subclass 4** **(**2.4 - 121.0 mg/dL) **565.0 High**

- **4/28/2021 recheck IgG4 subclasses:**
- Immunoglobulin G, total (767-1590 mg/dl) **1490**
- Immunoglobulin G, subclass 1 (341-894 mg/dl) **713 High**
- Immunoglobulin G, subclass 2 (171-632 mg/dl) **101**
- Immunoglobulin G, subclass 3 (18.4-106.0 mg/dl) **48.7**
- Immunoglobulin G, subclass 4 (2.4-121.0 mg/dl) **737.0 High**l

Immunoglobulin profile(IgG, IgM, IgA, IgE)-normal.

TREATMENT & PLAN

- **4/28/2021:**
- Based on elevated IgG4 serum levels Rituximab was started at 1000 mg IV 2 doses separated by 2 weeks. Patient continue c/o chronic cough, GI symptoms.
- **8/12/2021:** follow up visit.
- Completed 1 round of Rituximab, off prednisone. Cough and GI symptoms resolved, so most likely were IgG4-RD.
- Plans: recheck IgG4 serum levels today and a PET scan at the end of the year. IF signs of active disease will redose with Rituximab.
- Immunoglobulin G, total (767-1590 mg/dl) **731**
- Immunoglobulin G, subclass 1 (341-894 mg/dl) **437**
- Immunoglobulin G, subclass 2 (171-632 mg/dl) **93**
- Immunoglobulin G, subclass 3 (18.4-106.0 mg/dl) **31.1**
- Immunoglobulin G, subclass 4 (2.4-121.0 mg/dl) **215-High**
- **PLAN-IgG4 lower from previous of 737.0, decision was mage to continue to monitor and hold on repeating Rituximab and/or steroids. Patient asymptomatic.**

TREATMENT & PLAN

- **11/30/2021-Follow up visit.**
- Patient reports no return of cough, noted increased loose stools.
- Serum IgG4 subclasses obtained.
- PET CT scan skullbase to midthigh ordered.

- **RESULTS:normal IgG4.**
- Immunoglobulin G, total (767-1590 mg/dl) **735**
- Immunoglobulin G, subclass 1 (341-894 mg/dl) **401**
- Immunoglobulin G, subclass 2 (171-632 mg/dl) **100**
- Immunoglobulin G, subclass 3 (18.4-106.0 mg/dl) **32.7**
- Immunoglobulin G, subclass 4 (2.4-121.0 mg/dl) **96.2**

PET CT-No evidence of hypermetabolic disease

TREATMENT & PLAN

- **3/10/2022:Follow up visit.**

- Continues with loose stool, no other complaints or symptoms.
- Fortunately, his serum IgG4 levels does appear to correlate reasonably well with his disease as most recent IgG4 as well as PET scan was normal. We will recheck his labs including IgG4 levels today and continue to monitor clinically. If there is evidence of increase in his IgG4 level, we can consider the need for repeat PET scan and/or redosing of rituximab at that time. We will continue to monitor closely every 6 months or sooner if needed.
- Serum IgG4 subclasses obtained.
- **Results: normal levels.**
- Immunoglobulin G, total (767-1590 mg/dl) 864
- Immunoglobulin G, subclass 1 (341-894 mg/dl) 456
- Immunoglobulin G, subclass 2 (171-632 mg/dl) 120
- Immunoglobulin G, subclass 3 (18.4-106.0 mg/dl) 35.6
- Immunoglobulin G, subclass 4 (2.4-121.0 mg/dl) 93.0

- **Next follow up visit-9/13/2022.**

WRAP UP

- IgG4-RD:
- Is an immune mediated disease, it is the result of a dysregulated immune system.
- Classic patient is middle aged to elderly, males greater than females. In rare cases can affect children.
- Capable of affecting multiple organs, **commonly** the pancreas(autoimmune pancreatitis), salivary glands(salivary gland enlargement or sclerosing cholangitis), orbital disease(proptosis), & Retroperitoneal fibrosis(RFP).
- Development of a mass in any of the following organs: pancreas, biliary tree, orbits, lungs, kidneys, major salivary gland, or lacrimal gland.
- Diagnosis based on a combination of clinical presentation, serologic & radiologic findings, and characteristic histopathlogic-lymphoplasmatic infiltrate enriched IgG4 positive plasma cells and a variable degree of fibrosis in a “storiform” pattern.
- Treatment consist of glucocorticoid steroids as first line. 0.6 mg/kg QdD for 2-4 weeks, the slow taper over 6 months. In patients refractory to glucocorticoids, B-cell depletion with Rituximab 1000 mg IV 2 doses 2 weeks apart.

IgG4-RD

- Questions?

Thank You!