Inflammatory Orbital Disease: IgG4-Related Orbitopathy: Clinical, Histopathologic, & Immunopathologic Features

I. IgG4-Related Orbitopathy: Clinical & Radiographic Findings
   A. Previous diagnoses for this entity
      1. Sclerosing inflammatory pseudotumor
      2. Multifocal fibrosclerosis (Ormond’s disease)
   B. Demographics & associations
      1. 4th to 7th decade of life, peak in 6th decade
      2. Male preponderance
      3. Frequent history of asthma or drug allergy
   C. Ophthalmic manifestations
      1. Proptosis
      2. Bilateral involvement
      3. Predilection for superolateral orbit
      4. Imaging: often reveals lacrimal gland mass
   D. Imaging characteristics
      1. MRI: T1 & T2 images - homogeneous signal intensity isodense to muscle
         a. contrast enhancement
         b. early or rapidly progressive disease - high T2 signal due to edema and cellularity
      2. CT: Solid homogeneous masses indistinguishable from muscle; no bone destruction

II. IgG4-Related Orbitopathy: Histopathological & Serological Findings
   A. Fibrosis
   B. Lymphoplasmacytic infiltrates (includes T-cells)
   C. Follicular hyperplasia
   D. Eosinophils
   E. Obstructive phlebitis/eosinophilic angiocentric fibrosis
   F. IgG4+ plasma cells: IgG4/IgG >40%; absolute number of IgG4+ plasma cells >10-40/hpf
   G. Serum IgG4: >135mg/dl

III. IgG4-Related Disease: Criteria
   A. Diagnostic of disease
      1. Diagnostic: 1) Serum IgG4 >135 mg/dL and 2) Tissue infiltration with IgG4+ plasma cells (>10-40/hpf) or IgG4*/IgG+ (x100) > 40%
      2. Suspected disease: Either 1 or 2 of the above criteria
      3. Patients with other distinct disorder and criteria 1 & 2: Distinct disorder + suspected association with IgG4-related disease
      4. Patients meeting definition but unresponsive to corticosteroids: Should be re-diagnosed
   B. Suspicious for disease
      1. Presence of one:
         a. Symmetrical swelling of lacrimal or salivary glands
         b. Autoimmune pancreatitis
         c. Inflammatory pseudotumor
         d. Retroperitoneal fibrosis
         e. Lymphadenopathy/lymphoplasmacytosis/Castleman’s disease
      2. Presence of at least two:
         a. Unilateral swelling of lacrimal or salivary glands
         b. Orbital pseudotumor
         c. Autoimmune hepatitis or sclerosing cholangitis
         d. Prostatitis or interstitial nephritis
         e. Interstitial pneumonitis or mediastinal fibrosis
         f. Patchy meningitis, hypophysitis, or inflammatory aneurysm
         g. Thyroiditis or hypothyroidism
      3. Common findings in IgG4-related disease: IgG & IgE gammopathy, eosinophilia, hypocomplementemia, serum immune complexes, lymphadenopathy or tumorous lesion accumulating ⁶⁷Ga or ¹⁸FDG-PET isotope
IV. IgG4-Related Systemic Disease
A. Head & neck
   1. Chronic rhinosinusitis
   2. Submandibular & parotid fibrosis
   3. Sjogren’s syndrome
   4. Hashimoto’s thyroiditis & Graves’ disease
   5. Other ophthalmic involvement: conjunctiva, uvea, retinal macula
B. Other associated systemic manifestations (diseases)
   1. Multifocal fibrosclerosis
   2. Systemic fibrosis (Ormand’s disease)
   3. Autoimmune pancreatitis
   4. Inflammatory pseudotumor
   5. Retroperitoneal fibrosis
   6. Mediastinal fibrosis
   7. Sclerosing cholangitis
   8. Mikulicz’s disease
   9. Kuttner’s tumor
   10. Xanthofibrogranulomatosis/xanthogranuloma
   11. Inflammatory myofibroblastic tumor
   12. Eosinophilic angiocentric fibrosis
C. 67Gallium scan uptake: commonly involve tissues
   a. pulmonary hila - 77%
   b. pancreas – 77%
   c. salivary gland – 54%
   d. lacrimal gland – 54%
   e. periaortic tissue – 23%
D. Chronic inflammatory conditions mimicking IgG4-related disease
   1. Sialadenitis
   2. Oral cavity: numerous lesions (including cysts)
   3. Lower GI tract: numerous lesions (including Crohn’s, UC, diverticulitis)
   4. Synovium: numerous lesions (including RA)
   5. Numerous carcinomas (including SCCA, adenoCA)
   6. Skin: numerous chronic inflammatory lesions

V. Immunopathophysiology of IgG4-related disease
A. Fibrosis is a hallmark of the disease
   1. Th2 inflammation - fibroblast proliferation, extracellular matrix secretion, B-cell maturation
   2. Th2 cytokines (IL-4, IL-5, IL-10, & IL-13) dominate in IgG4-related diseases & upregulate TGF-β & CTGF, major pro-fibrotic growth factors
   3. TGF-β properties include:
      a. Myofibroblast differentiation in collagen secretion
      b. Promotion of contraction of extracellular matrix by myofibroblasts
      c. Induction of collagen, metalloproteinase, and secondary growth factor (CTGF) genes
      d. Signaling is reactive oxygen species- & glutathione (GSH) pathways-dependent
      e. Regulated by non-lipid raft or lipid raft (degradative) uptake pathways
B. Cellular interactions: leukocytes & resident tissue cells interact to promote fibrosis
   1. CD4+ helper T-cells are prominent in IgG4-related diseases & interact with B-cells, resulting in chronic B-cell activation, autoantibody production, & elaboration of pro-fibrotic cytokines
   2. Potential autoantigens include an unknown 13 kDa protein in all IgG4-related diseases
   3. Th2 inflammation, which also occurs in allergic and parasitic disease, may be suppressed by TReg cells, promoting non-inflammatory IgG4 synthesis
   4. In IgG4-related disease, self antigens presented by dendritic cells induce Th1, then Th2 responses
      a. TGF-β and IL-10 regulate fibrosis
      b. TReg cells compensate - inhibit Th2 responses & promote non-reactive IgG4 synthesis
C. IgG4 elaboration is a compensatory mechanism in IgG4-related disease, in contrast to other IgG: IgG4 does not bind Fc receptors on cells, induce antibody-dependent cell toxicity, or activate complement

VI. Key hallmark of IgG4-related disease: Universal response to corticosteroids
A. 100% response
B. Initial moderate dose of corticosteroids followed by gradual taper
C. Azathioprine & mycophenolate mofetil often used as corticosteroid-sparing agents
D. Role of radiotherapy not established