The Big Picture of Uveitis Notes

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October 8th, 2016

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Objectives

- Immunology review
- Ocular anatomy review
- Review of the SUN clinical data
- Uveitis classifications and types
- Laboratory evaluation
- To review uveitis treatment goals

PART 1: BASIC PRINCIPLES

Uvea – from the Latin *uva*, meaning "grape"

- What is uveitis?
  - Why does it occur?
  - What is the general course?
  - What are we to do, what is our role?

Basic Concepts in Immunology

- An "immune response" is a sequence of molecular and cellular events intended to rid the host of a threat.
- "Inflammatory response" = an immune response that becomes clinically evident

Basic Concepts in Immunology

Manifestations due to cellular recruitment and altered vascular permeability include:

1. Pain
2. Hyperemia
3. Edema
4. Heat
5. Loss of function

Ocular Anatomy

Review anatomy of the Uvea

- Uvea consists of the middle, pigmented, vascular layer of the eye and includes the iris, ciliary body, and choroid
- Derived from the neuroectoderm, neural crest cells, and vascular channels
- Prone to inflammation due to the vascularity of the uveal tract

Iris Anatomy

- Measures 12 mm in diameter and has a circumference of 38 mm.
- The "root" attaches to the ciliary body
- Functions to regulate entry of light into eye
- Four layers:
  1. Anterior border layer
  2. Stroma and sphincter muscle
  3. Anterior epithelium and dilator muscle
  4. Posterior pigment epithelium

Ciliary Body Anatomy

- 6 mm wide triangular band, divided into the anterior "pars plicata" and the posterior "pars plana"
- Functions to secrete the aqueous humor and to facilitate accommodation
- Consists of:
  1. Ciliary epithelium
  2. Ciliary stroma
  3. Ciliary muscle
  4. Supraciliary layer

Choroid Anatomy

- Primary function is to provide blood nourishment to the outer layers of the retina
  - Also helps in heat exchange, regulation of IOP, and light absorption
- Consists of:
  1. Lamina fusca
  2. Choroidal stroma
  3. Choriocapillaris

Signs of Uveitis

Anterior Segment

- Keratic Precipitates
- Inflammatory Cells
- Flare
- Fibrin
- Hypopyon
- Pigment Dispersion
- Pupillary Miosis
- Iris Nodules
- Anterior and Posterior Synechiae
- Band Keratopathy
- IOP changes

Signs of Uveitis

Intermediate

- Vitreal inflammatory cells
- Snowball opacities
- Snowbanks = exudates of the pars plan
- Vitreal strands

Signs of Uveitis

Posterior Segment

- Retinal or choroidal inflammatory infiltrates
- Inflammatory sheathing of arteries or veins
- Structural complications
  - Retinal detachments
  - Retinal pigment epithelial (RPE) hypertrophy or atrophy
  - Atrophy or swelling of the retina, choroid, or optic nerve head
  - Preretinal or subretinal fibrosis
  - Retinal or choroidal neovascularization

PART 2: CLASSIFICATION OF UVEITIS

Classification of Uveitis

- Anatomy (portion of uvea involved)
- Clinical course (acute, chronic, or recurrent)
- Etiology (Infectious vs. noninfectious)
- Histology (granulomatous vs nongranulomatous)

SUN Working Group

Standardization of Uveitis Nomenclature (SUN)

- Working Group for reporting of clinical data
- Results of the First International Workshop
  - November 8-9, 2004, results reported in 2005

- Worked to develop:
  - Anatomic classification of uveitis
  - Descriptors of uveitis (onset, duration and course)
  - Standardized grading system
  - Develop standards for uveitis clinical studies

Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. Sep 2005;140(3):509-16.

SUN Anatomical Classification

Type	Primary Inflammation Site	Includes
Anterior Uveitis	Anterior Chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate Uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior Uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

SUN Descriptors in Uveitis

Category	Descriptor	Comment
Onset	Sudden Insidious	
Duration	Limited Persistent	≤3 months' duration >3 months' duration
Course	Acute Recurrent Chronic	Episode characterized by sudden onset and limited duration Repeated episodes separated by periods of inactivity without treatment ≥3 months' duration Persistent uveitis with relapse in <3 months after discontinuing treatment

SUN Activity of Uveitis

Term	Definition
Inactive	Grade 0 cells (anterior chamber)
Worsening activity	2-step increase in level of inflammation (ex. Anterior chamber cells) or increase from grade 3+ to 4+
Improved activity	2-step decrease in level of inflammation (ex. Anterior chamber cells) or decrease to grade 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

SUN Anterior Chamber Cells

Grade	Number of Cells in 1x1mm SL Beam	Ex. of old Grading System
0	<1 cell	Rare
½+ Cells (X)	X = 1 to 5 Cells [ex. ½+ Cells (3)]	Occasional
1+ Cells	6-15 Cells	
2+ Cells	16-25 Cells	
3+ Cells	26-50 Cells	
4+ Cells	>50 Cells	4+ = Hypopyon present

Note: Hypopyon recorded separately

SUN Anterior Chamber Flare

Grade	Description
0 Cells	None
1+ Cells	Faint
2+ Cells	Moderate (iris and lens details clear)
3+ Cells	Marked (iris and lens detail hazy)
4+ Cells	Intense (fibrin or plasmoid aqueous)

Intermediate Cells

Grade	Number of Cells
0 Cells	0
½+ Cells	1-5
1+ Cells	6-10
2+ Cells	11-20
3+ Cells	21-50
4+ Cells	>50

Note: The SUN Group did not achieve consensus regarding a grading system for vitreous cells. Above is a standard scale currently used in trials.

PART 2: UVEITIS SYNDROMES

Classification of uveitis:

- Infectious vs. Non-infectious
- Anatomical
  1. Anterior
  2. Intermediate
  3. Posterior
  4. Panuveitis

Infectious Ocular Inflammatory Diseases

Type	Organism
Viral Uveitis	Herpes simplex and varicella zoster, cytomegalovirus, Epstein-Barr, Rubella, measles, West Nile, and others
Fungal	Ocular histoplasmosis syndrome (OHS)
Protozoal	Toxoplasmosis
Helminthic	Toxocariasis, cysticercosis, onchocerciasis
Bacterial	Syphilis, Lyme, Leptospirosis, Nocardiosis, Tuberculosis, Bartonellosis, Whipple disease

Non-Infectious Inflammatory Diseases

Further divided into masquerade syndromes, drug-induced, traumatic, and autoimmune.

Anatomical Classification	Condition
Anterior Uveitis	Acute, chronic, idiopathic, HLA-B27, Tubulointerstitial nephritis and uveitis syndrome, glaucomatocyclitic crisis, lens-associated , IOL-associated, drug-induced, juvenile, and Fuchs heterochromic uveitis
Intermediate Uveitis	Sarcoidosis and multiple sclerosis
Posterior Uveitis	Lupus, polyarteritis nodosa, granulomatosis with polyangiitis (Wegener), Susac syndrome, white dot syndromes, birdshot, APMPPE, serpiginous choroiditis, multifocal choroiditis and panuveitis, punctate inner choroiditis, MEWDS, acute retinal pigment epitheliitis, and AZOOR
Pan Uveitis	Sarcoidosis, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome, and Behcet disease

Non-Infectious Inflammatory Diseases

Further divided into masquerade syndromes, drug-induced, traumatic, and autoimmune.

Masquerade Syndrome	Condition
Neoplastic	Primary central nervous system lymphoma, leukemia, melanoma, retinoblastoma, juvenile xanthogranuloma, and metastatic tumors
Nonneoplastic	Retinitis pigmentosa, ocular ischemic syndrome, chronic rhegmatogenous retinal detachment, foreign bodies, and pigment dispersion syndrome

Diagnostic evaluation

- Usual suspects:
  - HLA-B27
  - Angiotensin-converting enzyme (ACE)
  - Lysozyme
  - Antinuclear antibody (ANA)
  - Fluorescent treponemal antibody-absorption (FTA-ABS)
  - Chest X-Ray

Part 3: MANAGEMENT OF UVEITIS

Goal is to control the inflammation and minimize complications such as:

- Band keratopathy
- Cataracts
- Glaucoma
- Hypotony
- Cystoid macular edema
- Rhegmatogenous retinal detachment
- Retinal and choroidal neovascularization

Management of Uveitis

Therapy

- Mydriatic and cycloplegic agents
- Nonsteroidal anti-inflammatories
- Corticosteroids
- Immunomodulatory medications

Mydriatic and Cycloplegic Agents

- Goals:
  - To relieve pain by immobilizing the iris
  - To prevent adhesion of the iris to the anterior lens capsule, which can lead to iris bombe and elevated IOP
  - To stabilize the blood-aqueous barrier and help prevent further protein leakage
- In general, the stronger the inflammation, the stronger the cycloplegic agent
- Caution: do not over-prescribe cycloplegics

Nonsteroidal anti-inflammatories

- Goals:
  - Reduction in inflammation, especially useful when used with corticosteroid
  - Treatment in cystoid macular edema (CME)
- Mechanism:
  - Inhibit cyclooxygenase (COX) isoforms 1 and 2, or 2 alone
  - Reduce prostaglandin synthesis
- Caution: can cause keratitis and corneal perforations

Corticosteroids

- Goals: primary uveitis treatment
- Topical, periocular, intravitreal, or systemic
- Dose and duration is dependent on the amount in inflammation
  - Preferable to begin with high dose and taper once inflammation is controlled
  - Must use gradual taper if on steroids longer than a week
- Use great caution due to systemic and ocular side effects

Immunomodulatory medications

- Goals: Reduction in ocular inflammation that is either uncontrolled or in patients that also have systemic inflammation
- Types:
  - Antimetabolites
  - T-cell signaling inhibitors
  - Alkylating agents
  - Biologic response inhibitors

Uveitis Treatment Goals

1. Promptly reduce ocular inflammation
2. Prevent scarring to ocular structures
3. Minimize damage to uveal vasculature
4. Manage intraocular pressure and cataract development

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