Learning Objectives

- Understand etiology of GVHD
- Identify ocular complications of cGVHD
- Review management options for this condition
- Demonstrate role of eye care providers in management of patients with this condition

Definition of Terms

- Hematopoietic: having to do with formation of blood
- Allogeneic: being genetically different although belonging to the same species
  - Syngeneic
  - Related
  - Unrelated

Background

- 30,000 allogeneic hematopoietic cell transplants (HCT) performed annually worldwide
  - Ferrara JL et al, Lancet 373:1550-61
- Indications include both non-malignant and malignant disorders
  - Gratwohl et al, JAMA 303(16):1617-1624
- Outcomes vary by condition and relationship of donor to recipient
Stem cell sources

- Bone marrow
- Peripheral blood
- Cord blood


What is GVHD?

- Complication of allogeneic hematopoietic cell transplantation
- GvL: Graft vs. Leukemia
  - Transplanted T lymphocytes attack target cells (leukemia, malignancies)
- GvHD: Graft vs. Host Disease
  - Develops when donor T-cells respond to recipient tissue antigens in addition to target tumor cells

Incidence

- Acute GVHD:
  - 26%-32% of recipients of sibling donor grafts
  - 42%-52% of recipients of unrelated donor grafts
  - Responsible for up to 60% non-relapse related deaths

- Chronic GVHD
  - 30% of recipients of sibling donor grafts
  - 60%-70% of recipients of unrelated donor grafts
  - Responsible for up to 50% non-relapse related deaths

Risk Factors

- Source of donor tissue
- Degree of histocompatibility
- Age
- Underlying condition
- Intensity of conditioning
- Female donor to male recipient
- Female donor with prior pregnancies or transfusion

Classification of Disease

- Original classification: time of onset
- Current classification: clinical manifestations

- Acute GVHD
  - Classic acute GVHD
  - Persistent, recurrent or late GVHD

- Chronic GVHD
  - Classic chronic GVHD
  - Overlap syndrome
Acute GVHD
- Primarily involves skin, liver, GI tract
- Diagnosis based on clinical presentation, confirmed by biopsy of affected tissue
- Primarily treated with systemic corticosteroids

The eye in aGVHD
- Conjunctival hyperemia
- Conjunctival chemosis
- Serosanguinous discharge
- Pseudomembranous conjunctivitis
- Corneal epithelial sloughing

Chronic GVHD
- Affects a variety of organs/organ systems (skin, nails, scalp/hair, eyes, mouth, genitalia, GI tract, lungs, muscles/joints)
- Less clearly understood than acute GVHD
- No definitive consensus on “best treatment”

Diagnostic Signs
- Sider Phagocytes: Birefringence, short forms, achromatic, septate end forms, elongate form, end forms, other areas of hypopigmentation, hyperpigmentation, or hypopigmentation
- Nails: Nails dystrophy, or loss
- Hair: Alopecia, scaling
- Mouth: Xerostomia, restriction of mouth opening, denture soreness, mucosal atrophy, palatal membranes and ulcers
- Muscle, fascia, joints: Fasciitis, myositis, or joint contractures
- Gastrointestinal: Ulcer, Anemia, weight loss, malabsorption with or without, Elevation of total bilirubin and liver enzymes
- Lungs: Restrictive or obstructive defects due to pulmonary fibrosis, bronchiolitis obliterans, pleural effusions
- Kidneys: Nephrotic syndrome
- Heart: Pericarditis
- Bone Marrow: Thrombocytopenia, anemia, neutropenia


Distinctive Manifestations
- New onset dry gritty or painful eyes
- Cicatricial conjunctivitis
- Keratoconjunctivitis sicca
- Confluent areas of punctate keratopathy
- Other features:
  - Photophobia
  - Periorbital hyperpigmentation
  - Blepharitis

Prevalence of Ocular Involvement

- 60%-90% of patients with cGVHD
  - Kim, Curr Opin Ophthalmol 2006;17:344-348
- Severe ocular surface disease is noted in 40-76% of cases

Posterior Segment Manifestations

- Vitritis
- Microvascular retinopathy
- Scleritis
  - Kim, Am J Ophthalmol 2002;133:843-845
- Central serous chorioretinopathy

Anterior Segment Involvement

SEVERE OCULAR SURFACE DISEASE

- Inflammatory Conjunctival Disease
  - Kim, Current Opin Ophthalmol 2006 Aug;17(4):344-8
- Meibomian Gland Dysfunction
- Lacrimal Gland Stasis

Meibomian Gland Dysfunction

http://www.optometric.com/archive

Lacrimal Gland Stasis

Note the skin isotop dehydratis from stage IV skin (GVHD). The posttransplantation Biokeratopathy scores of 23mm 6-0, decreased to 3mm in the setting of stage II acute ocular GVHD.

Kim, Current Opin Ophthalmol 2006 Aug;17(4):344-8
Decreased TBUT

Persistent Epithelial Defects

Neovascularization

Corneal Perforation

Etiology of OSD
- Inflammatory response causing cell injury and death
- Lacrimal gland dysfunction
- Lid abnormalities
- Medication side effects

Clinical Evaluation
- Symptom assessment (OSDI)
- Vital staining
- Tear break-up time
- Slit lamp evaluation
- Schirmer test
- Corneal sensitivity
- Tear evaporimetry
- Corneal/conjunctival impression cytology
Classification of Conjunctivitis

0: None
1: Hyperemia
2: Palpebral conjunctival fibrovascular changes
3: Palpebral conjunctival fibrovascular changes affecting 25-75% of surface
4: Palpebral conjunctival fibrovascular changes affecting >75% of surface, possible cicatricial entropion

NIH-Recommended Staging

0: No dry eye symptoms
1: Dry eye symptoms not affecting ADL or asymptomatic KCS
2: Dry eye symptoms partially affecting ADL without vision impairment
3: Dry eye symptoms significantly affecting ADL, unable to work, vision loss

Treatment of OSD in cGVHD

“Stepped approach”
Supportive, not curative, intervention

Ocular therapeutic goals
- Lubrication and tear preservation
- Reduction of inflammation
- Prevention of tear evaporation
- Epithelial support

Step 1:

Step 2:

Call your doctor today to see if Restasis is right for you.

Step 2:
Step 2:

- Oral therapy (in combination with methotrexate)
  - Ram et al, Bone Marrow Transplant 2009;43:943-53

- Tacrolimus
  - Protopic
  - Topical therapy
    - Tam et al, Bone Marrow Transplant 2010;45:957-8.
    - Zhai et al, BioDrugs 2011;25(2):89-103

- Ram et al, Bone Marrow Transplant 2009;43:943-53

Step 3:

- Autologous serum tears
  - Contain molecules that support epithelial health
  - Early studies encouraging
  - Cost and availability are potential impediments

- Protopic
  - Topical therapy
    - Tam et al, Bone Marrow Transplant 2010;45:957-8.
    - Zhai et al, BioDrugs 2011;25(2):89-103
Step 3:
- Topical retinoic acid
  - Murphy et al, Bone Marrow Transplant 1996 Sep;18(3):641-2
- Systemic secretagogues (i.e. cevimeline or pilocarpine)

Step 4:
- Scleral lenses/ocular surface prosthetics
  - Provide continuous corneal hydration
  - Protect conjunctival tissue
  - Non-invasive, reversible
  - Can be used in conjunction with other therapy
    - Takahide et al, Biol Blood Marrow Transplant 2007 Sep;13(9):1016-21

Scleral Lenses or Prosthetic Devices

Step 5:
- Partial or full tarsorrhaphy
- Amniotic membrane graft
- Conjunctival flap (Gunderson flap)

Case #1
- Caucasian male
- Diagnosed with acute lymphoblastic lymphoma in February 2003 (age 31)
- Chemotherapy allowed for several cycles of remission, followed by relapses
- Fully matched unrelated donor identified (peripheral blood stem cells)

Case #1
- 4/2005: Allogeneic peripheral blood stem cell transplant performed
- GVHD prophylaxis initiated immediately
  - Cyclosporine
  - Methotrexate
- Day 25: diagnosed with graft vs. host disease
- Days 25-400: "stormy" course, but in remission
Case #1

- Day 398: ocular irritation noted
- Days 400-420: rapid deterioration of ocular comfort.
  - Plugs placed
  - Topical cyclosporine prescribed
  - Lubrication regimen initiated

Case #1

- March 2007
  - Filamentary keratitis despite maximal medical management
  - Referred for scleral lens evaluation
  - Patient reported immediate improvement in comfort with diagnostic lenses
  - Fit with custom Jupiter lenses (19.6 mm OAD)
  - Also recommended moisture chamber glasses

Case #1

- Ongoing care:
  - Cataract surgery in December 2007 and February 2008
  - After surgery, discovered that he could achieve sufficient comfort with moisture chamber glasses alone
  - Currently wears scleral lenses only when in challenging environments

Case #2

- DG: 61 year old Caucasian male
- Diagnosed with Renal Cell Carcinoma Feb. 1998
- Stem Cell Transplant January 2005
- s/p PCIOL December 2006 OS, January 2007 OD
- GvHD March 2007
- Severe dry eye with filamentary keratitis OU

Case #2

- Symptoms include burning, foreign body sensation, photophobia, sensitivity to wind
- Unresponsive to lubricants, Restasis™, steroids
Case #2

• Experienced relief with ocular prosthetic device immediately
• Filaments and staining resolved after 3 hours of wear

Multidisciplinary Approach

- Hematology
- GI/Hepatology
- Dermatology
- Optometry/ophthalmology
- Dentistry
- Gynecology
- Neurology
- Immunology
- Musculoskeletal evaluation
- Psychology/psychiatry

Long-Term Ocular Prognosis

- Stable visual acuity
- Stable tear production
- Possible improvement in dry eye symptoms

Bibliography
