46b - Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Selected Syndromes in Stem Cell Transplant Recipients

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7/17/2022

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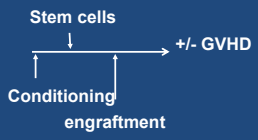
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Cidara Therapeutics
- Employment: Sfunga Therapeutics
- Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics

PEARLS

- Fundamentals – risks (temporality)
  - Early – mucositis, neutropenia
  - Late – GVHD (steroids, asplenia, T cell dysfunction)
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: Alveolar hemorrhage, IPS
  - Late pulmonary syndromes
    - CMV, respiratory viruses, IFI
    - Non-infectious: BOOP
- Hemorrhagic cystitis
  - BK
  - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
  - Herpes viruses
  - Non-infectious: GVHD
- Neurologic syndromes
  - Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis, PML (JCV)
  - Non-infectious: PRES, antibiotics

Fundamentals of BMT



- Immune risks for infection are temporal
  - Neutropenia (early, w/in 30 days)
    - Bacterial infections
    - Fungal infections
  - Impaired cellular and humoral immunity (later, post-engraftment)
    - Bacterial infections
    - Fungal infections
    - Viral infections

Fundamentals of BMT

- Autologous (self) vs. allogeneic (other)
- Types of allogeneic donors
  - Related, HLA – matched (MR)
  - Related, HLA - mismatched (haploidentical)
  - Unrelated, HLA – matched (MUD) or Unrelated, HLA – mismatched (MM-URD)
- Types of stem cells
  - Bone marrow
  - Peripheral blood
  - Cord blood
- Types of conditioning regimens
  - Myeloablative
  - Nonmyeloablative

Approach for the boards

- Know common infections and non-infectious mimics
- Approach stems in context
  - Patient's age, disease, history impact risks after BMT
  - What kind of BMT did the patient have?
  - Is the patient early vs. late after BMT?

Type of BMT and timeline impacts immunity, drugs and exposures

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Case #1

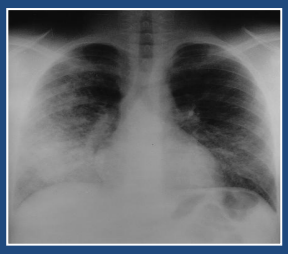
42 year old M AML 20 days after a matched unrelated donor BMT (nonmyeloablative) develops fever, cough, pulmonary infiltrates.

Pre-transplant: HSV+, VZV+, CMV D+/R-

Exam– 98% sat on 2L nc, T 38.3, crackles RLL

Labs- Cr 2.2, WBC 1200 cells/mL, plt 122

He's currently receiving acyclovir and fluconazole for prophylaxis.



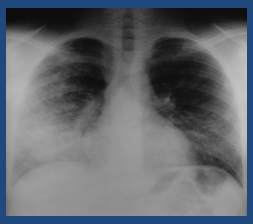
Case #1

What is the most likely cause of his current process?

A. *Candida albicans*
B. *Klebsiella pneumoniae*
C. CMV
D. Parainfluenza virus
E. Hemorrhage

Pulmonary Complications

- Bacterial pathogens
  - *P. aeruginosa, Streptococci*, Legionella, *S. aureus*
  - Aspiration events with severe mucositis early after BMT
  - Encapsulated sinopulmonary pathogens late after BMT
- Filamentous fungi early and late (*A. fumigatus)*



Pulmonary Complications (Con't)

- Respiratory virus infection follows seasonal epidemiology
  - Increased risk for lower tract involvement
  - Influenza, RSV, Parainfluenza 3, Human metapneumovirus
  - Adenovirus: reactivation and acute infection (particular issue with kids)
- Herpes viruses
  - CMV with prolonged impairment in cellular immunity
  - HSV classically described with prior airway manipulation

Early non-infectious lung injury

- Diffuse alveolar hemorrhage
  - Bleeding in alveolar space, heterogeneous etiology
    - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
  - Within 1st 120 days of BMT, non-infectious
  - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

Case #2

A 46 year old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids. One month s/p Parainfluenza 3 URI, with chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

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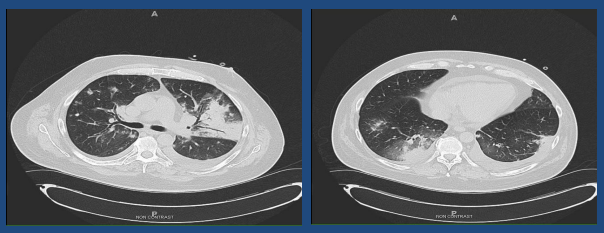
Case # 2 (con't.)



Case # 2 (con't.)

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative. What is the most likely cause of his current process?

A. *Cryptococcus neoformans*
B. *E. coli*
C. MRSA
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

DDx of Late pulmonary syndromes

- Infectious
  - CMV disease
  - Respiratory virus infections
  - PJP
- Non-infectious
  - Bronchiolitis obliterans syndromes

CMV Infection after BMT

- Reactivation occurs in seropositive patients (R+).
  - Reactivation alone triggers cytokine storm, GVHD, disease
  - Risk for *disease* dependent on immunity
    - Highest risk group for disease after BMT: D- / R+
      - No transferred immunity to CMV
      - This is different than SOT, where highest risk group is D+ / R-
- Primary infection in seronegative patients (R-) from community, positive graft (D+) or blood products (rare)

CMV Disease

- Pneumonitis
  - Indolent cough, fever, SOB, interstitial infiltrates
- Gastrointestinal disease
  - Esophagitis, colitis, hepatitis (rare)
- Encephalitis, retinitis less frequent

CMV Disease after BMT (con't.)

- Treatment concepts
  - Pre-emption with ganciclovir driven by PCR
    - Not prophylaxis (SOT) with ganciclovir (toxicities)
    - Prophylaxis of R+ patients with letermovir
  - Induction therapy with maintenance GCV
  - Resistance to GCV is *rare* (as opposed to SOT)
    - Most failures are due to steroids, T cell depletion
    - Recipe for GCV – resistance: long exposure to suboptimal doses of GCV in a patient with poor cellular immunity
    - Refractory disease can be due to Res and intolerance (neutropenia)
      - Miribavir (inhibits UL-97 kinase) approved for refractory treatment

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Pneumocystis Pneumonia

- Common late after BMT
  - Steroid receipt, T-cell depletion
- Prophylaxis at least 6 months
  - Bactrim
  - Toxicities
    - Dapsone, atovaquone, aerosolized pentamidine
      - Less effective, other infections occur**
- Late diagnoses occur
  - BAL DFA less sensitive

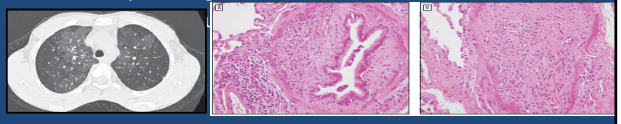
Toxoplasmosis

- Clusters of disease reported in BMT patients
  - T-depleted BMT
  - Some early. Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease with pre-emptive therapy
- Pneumonia, encephalitis, fever

Isa et al, ID Week 2014
Meers et al. Clin Infect Dis, 2010 Apr 15;50(8):1127-34

Bronchiolitis Obliterans

- Chronic GVHD of lung
  - Allorecognition of lung antigens
- Circumferential fibrosis of terminal airways ultimately leading to airflow obstruction



Williams JAMA 2009

A. Obliteration of bronchiolar lumen
B. Inflammation between the epithelium and the smooth muscle

Case #3

35 yr old F, 80 days after allogeneic BMT with 5 days of anorexia, nausea, epigastric pain, and diarrhea. CMV D-/R+, HSV+, VZV+.
Exam: faint maculopapular rash on upper body. Afebrile.
Meds: acyclovir, TMP-SMX and fluconazole.
ANC 1000, ALC 250. LFTs normal.

What is the most appropriate initial work-up and management?

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send C. diff toxin and start oral vancomycin
D. CMV PCR, stool C. diff, bacterial culture
E. #D *and* upper, lower endoscopy

Graft vs. Host Disease (GVHD)

- Acute (early after HSCT)
  - Fever
  - Rash
  - GI: hepatic, colon
- Chronic (later after HSCT)
  - Skin changes (lichen planus, sceroderma)
  - Hepatic (cholestatic)
  - Ocular (keratoconjunctivitis)
  - GI (oral, dysphagia)
  - Pulmonary syndromes

DDx of GI Disease in BMT

HEPATITIS

- GVHD
- Herpes viruses (CMV, VZV)
- Hepatitis B virus
  - Increased viral replication and liver damage
  - Hepatitis not common during neutropenia

DIARRHEA

- GVHD
- CMV
- C. difficile
- Norovirus (chronic diarrhea mimicking GVHD)
- Adenovirus

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Adenovirus Infection after BMT

- More common in children, high risk BMT
  - Severe GVHD and steroids
- Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis
- No controlled treatment studies
  - Taper immunosuppression
  - Cidofovir most active in vitro
  - Ribavirin not effective in larger studies

Case #4

53 year old F 7 yrs s/P allo BMT presents with fever, chills, rigors. H/O severe chronic GVHD skin. PE – T 39.2. tachycardia, tachypnea, hypotension. Skin thick, cracked (Sjogren-like). Social- dog and two cats, no recent exposures. Labs- WBC 8200 / mm3, platelet 43,000/mm3. CT of her chest, abdomen, pelvis - splenic atrophy. Blood cultures positive for gram-negative rods after 5 days.

Most likely cause of her current condition:

A. *Fusobacterium nucleatum*
B. *Eikenella corrodens*
C. *Capnocytophaga canimorsus*
D. *Acinetobacter baumannii*

Case #5

40 year old M day 60 after allogeneic BMT from unrelated donor, with bloody urine for 6 days. Has skin GVHD, receiving a prednisone taper (1 mg/kg/day). Exam, faint diffuse erythematous rash. Cr 1. LFTs normal. CMV pcr negative.

The most likely etiology is:

A. Cyclophosphamide
B. CMV
C. EBV
D. BK
E. JC virus

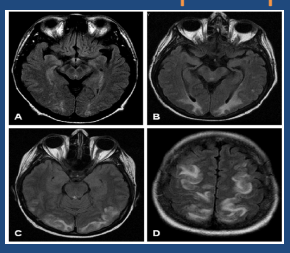
DDx of Hemorrhagic Cystitis

- Conditioning related (early)
  - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)

DDx of Neurologic Syndromes

- Infection
  - Herpes viruses: HSV, CMV, HHV6*
  - West nile virus
  - JCV – PML (especially with T-depleting Abs)
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - Nocardia
    - Toxoplasmosis
- Drugs: carbapenems, cefepime, PRES*

Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

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HHV-6 after BMT

- HHV-6 seroprevalence > 95% after age 2
  - Early reactivation common after BMT 38-60% SCT (type B)
  - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis**
  - Nonspecific presentation (confusion, memory loss, EEG / MRI: temporal)
  - Early - within 60 days of BMT
  - RFs: MM/URD or UCB SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- ACV-resistant. Treat with ganciclovir, foscarnet, cidofovir

VZV Infection after BMT

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
  - Classic: abd pain, transaminitis late
  - Can occur without skin lesions
- VZV seropositive
- Severe GVHD, acyclovir prophylaxis effective long term
- Recent study: 1% rate of infection, high rate after 1 yr

Baumrin et al. Biol Blood and Marrow Trans 2019 (in press)

PEARLS

- **Fundamentals – Risks (temporality)**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis**
  - **PML**
  - **Non-infectious: PRES, antibiotics**

Thank you

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