Infection in the (non-HIV) Immunocompromised Host

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Lecture outline

• Background/why is this topic important?
• Solid organ transplantation
• Heme malignancy/stem cell transplantation
• Biologics
Lecture outline

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  - Solid organ transplantation
  - Heme malignancy/stem cell transplantation
  - Biologics

Most to least?

- Heme malign/stem cell transplant
- Organ transplantation
- Treatment for autoimmune diseases
- Treatment for solid tumors
- Acquired/genetic immune deficiencies
- Hyposplenism
A challenge: diagnosis and treatment of infection in the non-HIV IS host?

1. Infectious DDx is broad
2. Clinical manifestations often atypical
3. Diagnostic tests are insensitive and slow
4. Treatments = toxicity & drug interactions
How is this different from HIV immunosuppressed patients?

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune defect</td>
<td>Death of CD4+ T-cells</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>OI risk stratification</td>
<td>CD4+ count</td>
<td>No reliable tests available</td>
</tr>
</tbody>
</table>

Lecture outline

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- Solid organ transplantation
- Heme malignancy/stem cell transplantation
- Biologics
Solid organ transplants in U.S. 1988-2012

http://optn.transplant.hrsa.gov/data/

Immunosuppression in SOT

Depleting antibodies: Thymoglobulin, Campath
IL-2 receptor blockers: Basiliximab
Antimetabolites (Mycophenolate)
Calcineurin inhibitors (Tacrolimus, Cyclosporine)
Corticosteroids
T-cell costimulation blocker (Belatacept)
Acquisition of infection to organ transplant recipients

**Prophylaxis**

- Reactivation of latent infections
  - Herpesviruses
  - TB
  - Strongyloides
  - Hepatitis B

- Surgery-related infection
  - Obstruction/leaks

**Environmental exposures**

- Community vs. Nosocomial
- Opportunistic

**Donor-derived infections**

- Bacteria
- Viruses
- Fungi
- Parasites

**Screening and treatment of latent infections**

**Treatment of rejection**

- Opportunistic
  - CMV
  - Aspergillus
  - PCP
  - Cryptococcus
  - Endemic mycoses
  - Tuberculosis

- Community Acquired
  - Nocardia
  - Listeria
  - Toxoplasmosis

- NOSOCOMIAL, TECHNICAL

- Degree of immunosuppression

- Months post-transplant
Case 1

• 65 y/o woman 10 months post liver transplant presents w/ ear fullness and pain

• Diagnosed with mastoiditis by MRI

• Mastoid biopsy:
  – Bacterial cultures: negative
  – Path: lymphocytic inflammation, no granulomas/organisms
Case 1: continued

- Patient was discharged with IV cefepime
- Readmitted with continued ear pain, fatigue
- ID team evaluated the patient and ordered retesting of prior pathology specimens

What is your diagnosis?

A. Aspergillus fumigatus
B. Candida albicans
C. Cefepime-resistant Pseudomonas
D. Mucormycosis
E. Mycobacterium tuberculosis
Dx: Disseminated TB w/ mastoiditis

Why was the Dx missed on pathology?

• Pathologists did not stain for mycobacteria because there were no granulomas present
Tuberculosis in SOT recipients

- Active TB Risk: >25x risk vs. gen population
- At Dx- 30-50% will have extrapulmonary disease
- Treatment complicated by drug interactions
- Attributable mortality 9.5-20%

Singh N. CID. 1998, Torre-Cisneros J. CID. 2009
When do SOT recipients present with TB post-transplant?

- Renal
- Liver
- Heart
- Lung

% of TB cases post-transplant

Time post-transplant at diagnosis

Case 1: Summary

- Pathological (and clinical) manifestations of infection may be atypical in SOT recipients
- Risk of reactivation is >25 fold in SOT
- Treatment for LTBI pre-transplant or early post-transplant decreases risk of active TB
Case 2

• 38 y/o F s/p renal transplant 8 mo ago presents with fever and cough progressive over 1 week
• No improvement on levofloxacin x 7 days
• Exam: 39.4, 98, 122/87, 28, 94% on 4L NC
• General: Increased work of breathing
• Lungs: scattered crackles

Case 2

Medications
• Tacrolimus
• Mycophenolate
• Prednisone 5 mg
• TMP-SMX DS 3x/wk

PMH
• Trisomy 21
• Congenital heart dz
• IgA nephropathy
Case 2: Labs

- WBC: 2.5
- Hematocrit: 25
- Platelets: 75
- Cr: 1.7
- LFTs: WNL
DDx of bilateral ground glass opacities

- Infection
  - PCP
  - Viral infection
- Edema
- Hemorrhage
- Interstitial lung diseases

DDx of ground glass opacities (GGO) on CT scan

- Infection
  - PCP
  - Viral infection
- Edema
- Hemorrhage
- Interstitial lung diseases
## Our Infectious DDx

<table>
<thead>
<tr>
<th></th>
<th>PCP</th>
<th>Resp virus (flu, RSV, etc.)</th>
<th>CMV</th>
</tr>
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<tbody>
<tr>
<td>Risk?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pancytopenia?</td>
<td>No</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>On prophylaxis?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>Serum β,D-glucan: negative</td>
<td>Season? yes</td>
<td>Donor CMV IgG+; recipient IgG-</td>
</tr>
<tr>
<td>Empiric Rx?</td>
<td>No</td>
<td>Oseltamivir</td>
<td>Ganciclovir</td>
</tr>
</tbody>
</table>

### Case 2: Results

- **Results:**
  - Resp virus PCR panel (nasal swab): negative
  - CMV PCR blood: 930,000 copies/ml
- **Rx:** Ganciclovir IV for CMV pneumonitis
- **Course**
  - WBC and platelets slowly normalized
  - ICU for 2 weeks
Spectrum of CMV disease in SOT

Asymptomatic viremia

“CMV syndrome”
- Fever/malaise
- Pancytopenia

End-organ disease
- GI disease (colitis)
- Hepatitis
- Pneumonitis
- Rare (CNS, retinitis)

Diagnosis and treatment of CMV

• Diagnosis:
  – CMV PCR serum (if low consider other Dx)
  – Biopsy of infected organ

• Treatment:
  – IV Ganciclovir or PO Valganciclovir
  – Rx until PCR undetectable and 2-3 weeks
  – Secondary prophylaxis in select cases
Case 2: take home points

• “Ground-glass” on CT: PCP, CMV, resp virus
• CMV common post SOT, often “late-onset”
• Fever, pancytopenia +/- end-organ disease
• Dx: Serum CMV PCR (antigen) +/- tissue biopsy
• Rx: Ganciclovir (IV) or valganciclovir (PO)

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• Biologics
Risk of infection in patients with hematological malignancies

- Underlying disease:
  - Hypogammaglobulinemia (MM and CLL)
  - Neutropenia due to BM infiltration

- Treatment:
  - Chemotherapy
  - Stem cell transplant
Chemotherapy induced neutropenia

Neutropenia + Mucositis + Central venous catheters + Prior antibiotic exposure

Neutropenia-associated infections

- Bacterial pathogens
  - Bacteremias (oral and GI flora)
  - Typhlitis
  - Pneumonia and CRBSI
- Fungal infections
  - Candidemia
  - Aspergillus (if prolonged)
- Viral infections
  - HSV
Management of high-risk, febrile neutropenic patient?

- Empiric therapy 1st (medical emergency):
  - Cefepime, carbapenem*, or pip-tazo
  - Add Vancomycin if CRBSI, SSTI, PNA, or critically ill

- Diagnostics: Pan-culture and image

- No response to empiric therapy?
  - Continue work-up for source
  - Consider escalate antibiotics → add antifungal

*anti-pseudomonal carbapenem (aka not ertapenem)

Freifeld AG. Clin Infect Dis. 2011

Initial management of febrile stem cell transplant recipient?

- Empiric therapy:
  - Empiric antibiotics based on likely source

- Diagnostics:
  - How far post-transplant?
  - GVHD?
  - Specific signs/symptoms?

Freifeld AG. Clin Infect Dis. 2011
Cell recovery and infection risk post stem cell transplant

Case 3

- 21 year-old with refractory AML has been neutropenic for over 8 weeks and has been on prophylactic levofloxacin, fluconazole, and acyclovir

- He presents to clinic with 3 days of fatigue, mild cough, and pleuritic chest pain

- LABS: 0.9>33<31, ANC = 0.2
Chest X-ray: 3 months ago

Chest X-ray: Today

Chest CT
DDx of cavitary lung lesions?

- **Fungal:**
  - Molds: Aspergillus >>> mucormycosis
  - Endemic mycoses: cocci, histo, etc.

- **Bacterial:**
  - Septic pulmonary emboli
  - *S. aureus*, Gram negatives, Nocardia

- **Mycobacteria:** TB and NTM
Case 3: micro results

- Galactomannan serum: 0.3 (normal <0.5)
- β-D-glucan serum: < 40 (normal < 40)
- Bronchoscopy
  - Bacterial culture: negative
  - Mycobacterial: negative
  - Fungal culture: negative
  - **Galactomannan: 10.1** (normal < 0.5)

Aspergillus diagnostics (sensitivity)

- Biopsy: gold standard
- Fungal cultures BAL: 25-50%
- Galactomannan (aspergillus specific)
  - Serum: 60%
  - BAL: 70-95%
- Beta-D glucan (asperg, candida, PCP)
  - Serum: 55-95%

False positives

Galactomannan
- Piperacillin-tazobactam
- Amoxicillin-clav acid
- Fungal cross-reactivity

B-D glucan
- IV Ig
- Albumin
- Select HD filters
- Gauze packing

Kędzierska A. Eur J Clin Microbiol Infect Dis. 2007

Treatment of invasive aspergillosis: Voriconazole vs. Ampho B

Voriconazole group
Ampho B group

P=0.02

Herbrecht R. NEJM. 2002
Vori vs. Vori plus anidulafungin for invasive aspergillosis

Marr KA. Ann Intern Med. 2015

Isavuconazole vs. Voriconazole for invasive aspergillosis
(Primary outcome: all cause mortality at 6 weeks)

Maertens J. Lancet. 2015
Case 3: take home points

• DDx for cavitary nodules: mold>bacteria> AFB
• Fungal testing limited sensitivity and specificity
• BAL GM has increased sensitivity for aspergillus
• Biopsy is the gold standard for diagnosis
• Voriconazole is 1st-line treatment of aspergillus

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• Heme malignancy/stem cell transplantation
• Biologics (focus on TNF blockers)
TNF inhibition in the treatment of septic shock

Fischer CJ. NEJM. 1996

TNF inhibition

• Clinical scenarios
  – Rheumatoid arthritis
  – Inflammatory bowel disease
  – Psoriasis/psoriatic arthritis
TNF inhib: tuberculosis

- Post-marketing survey of TB cases following release of infliximab (1998-2001)
- 70 cases of TB
- Median time to diagnosis: 12 wks (range 1-52)
- TB characteristics
  - Extrapulmonary disease: 40/70 (57%)
  - Disseminated disease: 17/70 (24%)

Keane J. NEJM. 2001

TNF inhib: fungal infections

- Survey of serious infection on TNF inhib in U.S.
  - Non-tuberculous mycobacteria: 32
  - Tuberculosis: 17
  - Histoplasmosis: 56
- FDA Alert 2008: 256 cases of histoplasmosis in patients on TNF inhibitors

Case 4

• 43 y/o female with Crohn’s disease on infliximab (Remicade®) presents with 3 weeks of cough and fever. Works as a CPA in Bakersfield, CA. No pets.

• She received 1 week of moxifloxacin without improvement.
Which infections are in the DDx?

- Bacterial, mycobacterial, and endemic mycoses
- Cocci IgM/IgG sent
  - Negative
- Now what?

Coccidioides risk regions

KOH stain from BAL fluid

Coccidioides immitis

Serological testing can be insensitive in immunocompromised patients!

Blair J. Mycopathologia. 2006
Sensitivity of cocci serologies in Immunocompromised

<table>
<thead>
<tr>
<th></th>
<th>EIA (IgM/IgG)</th>
<th>ID (IgM/IgG)</th>
<th>CF (IgG)</th>
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<tbody>
<tr>
<td>Heme malig</td>
<td>33</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>Cancer chemo</td>
<td>72</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>SOT</td>
<td>71</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Rheum</td>
<td>82</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Other</td>
<td>90</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>87</td>
<td>73</td>
<td>75</td>
</tr>
</tbody>
</table>

Blair JE. Mycopathologia 2006

Biologics and viral infections

- Hepatitis B reactivation
  - Reactivation with TNF inhibitors reported
  - Rituximab (Rituxan®) - common

- JC virus (PML)
  - Natalizumab (Tysabri): must check JCV IgG
  - Rituximab (Rituxan®): very rare
Evaluation prior to TNF inhibitor use?

- Evaluate for LTBI
  - Check PPD or IGRA, CXR, take TB history
- Evaluate for recent endemic mycoses infection
  - Take travel history, symptom check
- Evaluate for HBV
  - Check hepatitis B surface antigen and core antibody


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*Many images were obtained from the UCSF Microbiology Teaching Pictures Collection*