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

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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>
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</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>
Does CD4 help in non-HIV populations?

Kowalski R. Clin Transplantation. 2003

Will you be seeing any of these non-HIV immunosuppressed patients?

Solid organ transplants in U.S. 1988-2012

Stem cell transplants in the US: 1988-2010

Biologics are increasingly used for many autoimmune diseases

- Rheumatoid arthritis: 1.5 million
- Inflammatory bowel disease: 1.4 million
- Psoriasis: 7.5 million
- New ones developed annually!

Some biologics used to treat autoimmune diseases

- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Adalimumab (Humira®)
- Golimumab (Simponi®)
- Certolizumab (Cimzia®)

TNF blockers

Some biologics used to treat autoimmune diseases

- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Adalimumab (Humira®/
  Simpatic®)
- Golimumab (Simponi®)
- Certolizumab (Cimzia®)

IL-1 receptor blocker

- Anakira (Kineret®)

Anti-CD20 antibody

- Rituximab (Rituxan®)

Some biologics used to treat autoimmune diseases

- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Abatacept (Orencia®)
- Golimumab (Simponi®)
- Certolizumab (Cimzia®)

T-cell costimulation blocker

IL-6 receptor blocker

- Tocilizumab (Actemra®)

Some biologics used to treat autoimmune diseases

- Tofacitinib (Xeljanz®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Adalimumab (Humira®/
  Simpatic®)
- Abatacept (Orencia®)
- Tocilizumab (Actemra®)
- Certolizumab (Cimzia®)

JAK3 inhibitor

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**Indication for hospitalization post-transplantation**

- Infection
- Rejection

Dharnidharka VR. AJT. 04

**Immunosuppression in SOT**

- **Depleting antibodies:** Thymoglobulin, Campath
- **IL-2 receptor blockers:** Basiliximab
- **Antimetabolites (Mycophenolate)**
- **Calcineurin inhibitors** (Tacrolimus, Cyclosporine)
- **Corticosteroids**
- **T-cell costimulation blocker** (Belatacept)

**Impact of OI prophylaxis on the post-transplant “timeline”**

- PCP prophylaxis: all; 6 months-life
- CMV prophylaxis: most; 3 months-1 year
- Mold prophylaxis: lung, 3 months
Case 1
- 65 year-old Chinese woman 10 months post liver transplant presents w/ ear fullness and pain
- Diagnosed with mastoiditis by MRI
- Mastoid biopsy:
  - Bacterial and fungal cultures: negative
  - Path: lymphocytic inflammation with no granulomas, bacteria or fungi

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%

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>
</thead>
<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 pneumonia
- 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 viral load consider other Dx)
  – Biopsy of infected organ

• Treatment:
  – IV Ganciclovir or PO Valganciclovir
  – Treat until PCR undetectable and at least 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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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

Image: The Perfect Storm
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)

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?

Cell recovery and infection risk post stem cell transplant

Prevention of infection in patients with heme malignancy

- Bacterial infections:
  - G-CSF
  - Antibacterial prophylaxis (levofloxacin in high-risk)
- Fungal infections:
  - Antifungal prophylaxis (candida, molds, PCP)
- Viral infections:
  - Anti-viral prophylaxis (Acyclovir for HSV/VZV)
  - Preemptive monitoring (CMV)

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

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
- IVIg
- Albumin
- Select HD filters
- Gauze packing

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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Granuloma

Granuloma post TNF inhibitor
TNF inhibition in the treatment of septic shock

![Graph showing survival rates](Fischer_CJ_NEJM_1996)

TNF inhibition
- Clinical scenarios
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Psoriasis/psoriatic arthritis

TNF inhibitors used in clinical practice
- TNF-alpha receptor fusion protein
  - Etanercept (Enbrel)
- Anti-TNF-alpha antibody
  - Infliximab (Remicade)
  - Adalimumab (Humira)
  - Certolizumab (Cemzia)
  - Golimumab (Simponi)

TNF inhibitors and infection
- Overall infection risk?
- Mycobacterial infections (TB)
- Fungal infections
- Viral infections

TNF inhib: hospitalization for serious infection
- Retrospective, 1998-2007, rheum, derm, IBD
- Matched on disease score
- TNF inhib: etanercept, infliximab, adalimumab

<table>
<thead>
<tr>
<th>Hospitalizations for serious infx/100 per yrs</th>
<th>Adjusted Hazard Ratio</th>
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<tbody>
<tr>
<td>TNF</td>
<td>Other IS</td>
</tr>
<tr>
<td>All 8.16</td>
<td>7.78</td>
</tr>
<tr>
<td></td>
<td>1.05 [95% CI, 0.91-1.21]</td>
</tr>
</tbody>
</table>

Grijalva CG. JAMA. 2011

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?

Biologics and viral infections

- Hepatitis B reactivation
  - Reactivation with TNF inhibitors reported (rare)
  - Rituximab (Rituxan®) - common
- JC virus (progressive multifocal leukoencephalopathy)
  - Natalizumab (Tysabri) – must check JCV IgG
  - Rituximab (Rituxan®) – reports, less common

KOH stain from BAL fluid

*Coccidioides immitis*

Serological testing can be insensitive in immunocompromised patients!

Blair J. Mycopathologia. 2006

http://updates.cltopics.org/
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


Many images were obtained from the UCSF Microbiology Teaching Pictures Collection