Pneumocystis jirovecii and Toxoplasma gondii: A Tale of Two Parasites or Opportunistic Infections In Immuno-deficient Hosts
Charles Knirsch, MD, MPH

Protozoan Parasites

1. Toxoplasma gondii

2. The Malarias
   - Plasmodium falciparum
   - Plasmodium vivax
   - Plasmodium ovale
   - Plasmodium malariae

3. Diarrheal disease-causing protozoa:
   - Giardia lamblia
   - Entameba histolytica
   - Cryptosporidium parvum
   - Cyclospora cayetanensis
Protozoa:

Toxoplasma gondii

and

Pneumocystis jirovecii*

formerly P. carinii

*actually an unusual fungus
And the Band Played On

- Politics, people and the AIDS epidemic
- CDC April 1981: “This guy should go back to medical school if he can’t find some simple neoplasm”
- June 1981 MMWR: Pneumocystis pneumonia in young men
- GRID
Opportunistic Infections Associated with Progressive Immunodeficiency

![Graph showing CD4+ T-lymphocytes per cubic millimeter over time after HIV infection.]

**Pneumocystis jirovecii (PCP)**

- Commensal organism and opportunistic pathogen
- Morphologically resembles protozoan
- Difficult to grow in vitro
- Life cycle???
  - Cyst stage: 5 um in diameter with 4-8 sporozoites
  - Trophozoite: 2-5 um in diameter – attach to cell surfaces
Folic Acid Inhibitors are Drugs of Choice for PCP

Pteridine + PABA (Para-aminobenzoic Acid)

Dihydropteroate Synthetase → Sulfonamides / Dapsone

Folic acid → Dihydrofolate reductase

Dihydrofolate reductase → Pyrimethamine, Proguanil

Tetrahydrofolate acid
Is P. carinii a Fungus or Protozoon?

**Protozoon**
- Morphology
- Inability to culture in vitro
- Response to anti/protozoal drugs

**Fungus**
- Ribosomal rRNA sequence homology
- ELF3
Protozoa:

*Toxoplasma gondii*

The Apicomplexa

*Toxoplasma gondii*
The Plasmodia (malaria)
*Cryptosporidium hominis*
Toxoplasma gondii infects all mammals and all tissues in each of them.
Felines are the definitive hosts for *Toxoplasma gondii*
Oocysts of *Toxoplasma gondii*

- **Sporulated**
- **Unsporulated**

Rack of lamb is usually served rare
Macrophage Infected With *Toxoplasma gondii*

* The hunter becomes the hunted
*Toxoplasma gondii* in culture

Trophozoites (T) prevent fusion of lysosomal membranes to the parasitophorous vacuole, thereby escaping digestion.

Heat-killed organisms cannot prevent fusion of lysosomal membranes with the parasitophorous vacuole.
Clinical Disease:

Congenital

Adult-acquired

AIDS-related

Congenital Toxoplasmosis
Calcified Lesions Due To Congenital Toxoplasmosis

Congenital Toxoplasmosis

Photo courtesy: Gary Baumbach, M.D., Department of Pathology, University of Iowa College of Medicine
Congenital Toxoplasmosis:

- Still Birth
- Chorioretinitis
- Mental Retardation

Congenital Toxoplasmosis Following Maternal Infection During First and Second Trimester*

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Infected</td>
<td>73%</td>
</tr>
<tr>
<td>Subclinical Infection</td>
<td>13%</td>
</tr>
<tr>
<td>Mild Infection</td>
<td>7%</td>
</tr>
<tr>
<td>Severe Infection</td>
<td>6%</td>
</tr>
</tbody>
</table>

* From Desmonts and Couvier, NEJM 290: 1110, 1974
Toxoplasma Ocular Disease

- Usually from congenital infection manifesting in adults
  - Episodic flares may destroy retinal tissue
  - Specific treatment necessary
Adult-Acquired Toxoplasmosis

Infection by Blood or Organ Transplant

- Parasitemia (WBC’s) for up to 1 year post infection
- Heart, bone marrow, liver, kidney donors
  - Dangerous when recipient toxo (-)
- Myocarditis, diffuse lymphadenopathy
Adult-Acquired Toxoplasmosis

Signs and symptoms:
- Lymphadenopathy
- Fever
- Headache
- Chronic Malaise
### Differential Diagnosis of Lymphadenopathy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Toxoplasmosis</th>
<th>Inf. Mono</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy Without Other Symptoms</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Monocytosis, Eosinophilia</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Atypical Lymphocytes</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Positive Heterophil</td>
<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Altered Liver Function</td>
<td>0</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hilar Lymphadenopathy</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Lymph Node Pathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulum Cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germinal Cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bizarre Cells</td>
<td></td>
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</table>

Pseudocyst of *Toxoplasma gondii* in Liver
AIDS-related Disease

Pseudocysts of *Toxoplasma gondii* in a microglial nodule with a variety of inflammatory cell types in an HIV/AIDS patient
AIDS-related Disease:
1. CD4 < 200 and reactivation of latent infection

2. Encephalitis
   1. Diffuse inflammation and swelling
   2. Localized ring enhancing lesions on CT scan
   3. Herniation
   4. Death if untreated

Toxoplasma abscess in the brain would appear as a ring-enhancing lesion with CT scan.
Diagnosis

Serological correlates in acute and chronic infection
Indirect Fluorescent Antibody (IFA) Test

**PABA (Para-aminobenzoic Acid)**

**Pteridine**

**Sulfonamides / Dapsone**

**Dihydropteroate Synthetase**

**Folic Acid Inhibitors are Drugs of Choice**

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Prevention:

1. Prevent pregnant women from handling cat litter
2. Avoid eating raw or under-cooked meats

Host status

- **Pneumocystis carinii**
  - No Life cycle!
  - Lung disease in AIDS
  - Malnourished children
  - Organ Transplants

- **Toxoplasma gondii**
  - Cat definitive host
  - Disease: Host status
  - CNS Disease in AIDS
  - Congenital Infections
  - Organ Transplants
Some Good News Regarding Extinction:

- Smallpox - eliminated (probably)
- Polio - nearly gone
- Yaws - almost eliminated
- Onchocerciasis - on its way out

### The Most Common Neglected Infections of Poor People

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Cases</th>
<th>Population at-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascariasis</td>
<td>807 million</td>
<td>4.2 billion</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>604 million</td>
<td>3.2 billion</td>
</tr>
<tr>
<td>Hookworm</td>
<td>576 million</td>
<td>3.2 billion</td>
</tr>
<tr>
<td>Amebiasis</td>
<td>500 million</td>
<td>ND</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>200 million</td>
<td>0.6 billion</td>
</tr>
<tr>
<td><strong>Lymphatic Filariasis</strong></td>
<td><strong>120 million</strong></td>
<td><strong>1.0 billion</strong></td>
</tr>
<tr>
<td>Trachoma</td>
<td>84 million</td>
<td>0.5 billion</td>
</tr>
<tr>
<td><strong>Onchocerciasis</strong></td>
<td><strong>18 million</strong></td>
<td><strong>0.1 billion</strong></td>
</tr>
<tr>
<td>Chagas Disease</td>
<td>16 million</td>
<td>0.1 billion</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>12 million</td>
<td>0.4 billion</td>
</tr>
<tr>
<td>Leprosy</td>
<td>0.4 million</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Dracunculiasis</strong></td>
<td><strong>0.01 million</strong></td>
<td>ND</td>
</tr>
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Global Network for Neglected Tropical Diseases
http://www.GNNTDC.org

- Schistosomiasis Control Initiative
- International Trachoma Initiative
- Helen Keller International
- Liverpool School - GAELF
- Human Hookworm Vaccine Initiative
- Earth Institute at Columbia Univ.
- Task Force for Child Survival
  - Mectizan Donation Program
  - Albendazole Donation Program
  - Mebendazole Donation Program

More Bad News:
Most vector-borne diseases are on the rise