Parasitic Infections in Immunocompromised Hosts
(Clinical cases)

Professor PL Chiodini
Case 1
“Brian”

- Middle-aged male farmer
- Resident in Ireland
- Severe haemolytic anaemia
Diagnosis: *Babesia divergens*

- Previously splenectomised
- Infected from the bite of *Ixodes ricinus*
Babesia divergens

- Pyriform pairs, up to 180 degrees
- Periphery of red cell
- 0.4 x 1.5 um
- Pleomorphic; pear-shaped, oval or round
- Human cases: rings, loops, clubs, rods and amoeboid shapes. Occasional divergent forms. Up to 70% parasitaemia recorded
**Babesia microti**

- Ring, rod-shaped, pyriform, amoeboid and “Maltese Cross” forms
- Heavy infections show different stages in same red cell
- 2 x 1.5 μm
- May be extracellular in heavy infections
- Parasitaemia 1 to 10%
- Up to 85% if splenectomised
Babesia Serology

- *Babesia microti* only
- IFAT
- Screening dilution 1 in 64
- Acute infection: titres $\geq 1$ in 1024
- Fall to 1 in 64 over approximately 1 year
Babesia PCR

• Target is DNA coding for small sub-unit ribosomal RNA
• Consider in blood film negative, antibody positive individuals
**B. divergens** - treatment

- Fatal if untreated
- Exchange transfusion (2-3 blood volumes)
- IV clindamycin plus IV quinine
- Atovaquone active *in vitro*
**B. microti - treatment**

- Most recover spontaneously
- Several months of fatigue and malaise
- Atovaquone plus azithromycin
  
  **OR**
  
- Quinine plus clindamycin
- Exchange transfusion if very ill with high parasitaemia
Case 2
“Carlos”

- 27 year old male
- Previously well
- Six week history of headache and convulsions
- Mass lesion in the frontal lobe
- HIV negative
Differential Diagnosis?

???
“Carlos”

- Brain biopsy
  - Numerous amoebae

- PCR
  - *Balamuthia mandrillaris*
  - *Acanthamoeba spp.* NOT detected
  - *Naegleria fowleri* NOT detected
**Balamuthia mandrillaris**

Cases reported from

- Europe
- North and South America
- Australia
- India
- Far East
Balamuthia mandrillaris

- Encephalitis
- May have preceding skin lesion
- CSF:
  - Raised protein
  - Pleocytosis (predominantly lymphocytes)
  - Normal or low glucose
  - Abnormal neuroimaging
Balamuthia mandrillaris

- Diagnosis:
  - Histopathology
  - Serology (IFAT)
  - Fluorescent labelling on paraffin sections
  - PCR on brain tissue or CSF
Balamuthia mandrillaris trophozoite in skin
Balamuthia mandrillaris

- Misdiagnoses:
  - Tuberculosis
  - Viral meningoencephalitis
  - Neurocysticercosis
  - Acute disseminated encephalomyelitis
Balamuthia mandrillaris

Treatment

- No controlled trials!
- pentamidine
- plus albendazole
- plus fluconazole or itraconazole
- plus miltefosine
Case 3
“Sheila”

- 45 year old female
- HIV positive
  - CD4 count 280; viral load 20
- Pain in left eye; queried foreign body
- Oedematous cornea with a small ulcer
- No previous ophthalmic history
Differential Diagnosis?
Cysts present in corneal biopsy
Clinical features

• Delayed diagnosis common
• May be misdiagnosed as HSV keratitis; fungal infection
• May wax and wane
• Typically pain out of proportion to corneal findings
• Often see a ring opacity
• Usually unilateral
Investigations

• Culture
  Non-nutrient *Escherichia coli* agar
  Grow in 1 to 10 days
• Histology
• PCR
  18s rRNA gene
Acanthamoeba treatment

CNS Infection
• pentamidine
plus
• fluconazole
plus
• miltefosine
Acanthamoeba treatment

Keratitis

• Topical biguanide-chlorhexidine or topical polyhexamethylene biguanide

Plus

• Topical propamidine or topical hexamidine
Case 4
"Richard"

- 36 year old man
- Advanced HIV infection (AIDS)
- Diarrhoea
- “Spores” seen in faeces
- Diarrhoea settled without treatment
- 9 months later sinusitis, dysuria, frequency, urethral discharge
Diagnosis

- *Encephalitozoon intestinalis*

- Treated successfully with albendazole 400 mg po BD for 28 days
Diagnosis of microsporidiosis

- Hot trichrome stain on smear
- Histology of biopsy specimens
- Electron microscopy of biopsy specimens
- Real time PCR
Microsporidial PCR


Melt curve analysis
- E. bieneusi
- E. hellem
- E. intestinalis
- E. cuniculi

Cycle time (CT) analysis
Treatment

- Ocular
  - Topical fumagillin plus oral albendazole

- Intestinal or disseminated
  - Albendazole
    - For *E. intestinalis*
    - (plus itraconazole if *Trachipleistophora* or *Anncaiia*)
  - Clindamycin has some activity vs *E. intestinalis*
  - Fumagillin for *E. bieneusi*
Case 5
“Joan”

- 60 year old woman
- Acute myeloid leukaemia
  - Induction chemotherapy
  - Allogeneic stem cell transplant
- Day 400
  - Headache
  - Convulsion
  - Mass lesion in the frontal lobe
Differential Diagnosis?
Smear from brain biopsy
Toxoplasma Life Cycle
Differential Diagnosis of Toxoplasma Encephalitis

- CNS Lymphoma
- PML
- CMV
- Cryptococcosis
- Aspergillus infection
- TB
Diagnosis of Toxoplasma Encephalitis

- Neuroimaging
- Serology
- [PCR]
- Cytology/Histopathology
- Clinical and imaging response to specific Rx
  - Usually improve >50% over neurological baseline in 7 to 10 days
Case 6
“Maria”

- Maria is 30 years old
- She was born in Bolivia and migrated to London 6 years ago
- She works as a waitress and office cleaner
- Maria is planning to be pregnant
- Does she require any parasitology tests?
Trypanosoma cruzi Life Cycle

1. Metacyclic trypomastigotes in hindgut
2. Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
3. Amastigotes multiply by binary fission in cells of infected tissues.
4. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.
5. Triatomine bug takes a blood meal (trypomastigotes ingested).
6. Epimastigotes in midgut
7. Multiply in midgut
8. Metacyclic trypomastigotes in hindgut

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CDC
http://www.dpd.cdc.gov/dpdx

= Infective Stage
= Diagnostic Stage
Neonatal *T. cruzi* infection

- From mother by haematogenous transplacental route
- Maternal parasitaemia rises in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
- Rates of transmission:
  - Almost 100% with HIV co-infection
  - 53% if mother acutely infected in pregnancy
  - Approx 5% in chronically infected mother
Neonatal *T. cruzi* infection

- Weak maternal innate and adaptive type 1 immune responses
- Haematogenous route through placental areas deprived of trophoblast
- Insufficient fetal/neonatal innate defences and parasite-specific type 1 immune response to control transmitted parasites
Neonatal *T. cruzi* infection

- Genotype TcV found in 80 to 100% of congenital cases in:
  - Argentina
  - Bolivia
  - southern Brazil
  - Chile
  - Paraguay
Neonatal *T. cruzi* infection

- Ideally treat women of child-bearing age BEFORE they become pregnant

- About 20-fold reduction of vertical transmission risk
Case 7
“Etetu”

• Age 40
• Migrated to London from Ethiopia 10y ago
• Illness started 5y ago
  – Fever, rigors, cough, joint pain, weight loss
  – Cachectic
  – Chest clear
  – Hepato-splenomegaly
Differential Diagnosis?
Differential Diagnosis?

- HIV-1 positive
  - CD4 55; viral load 4,740,500 copies/ml
Differential Diagnosis?

- HIV-1 positive
  - CD4 55; viral load 4,740,500 copies/ml
- Lymph node and liver biopsy:
  - *Leishmania donovani* PCR and culture positive
Differential Diagnosis?

- HIV-1 positive
  - CD4 55; viral load 4,740,500 copies/ml
- Lymph node and liver biopsy:
  - *Leishmania donovani* PCR and culture positive
  - Granulomas ?TB (microscopy and culture neg)
Sandfly Stages

1. Sandfly takes a blood meal (injects promastigote stage into the skin)
2. Promastigotes are phagocytized by macrophages
3. Promastigotes transform into amastigotes inside macrophages
4. Amastigotes multiply in cells (including macrophages) of various tissues
5. Sandfly takes a blood meal (ingests macrophages infected with amastigotes)
6. Ingestion of parasitized cell
7. Amastigotes transform into promastigote stage in midgut
8. Divide in midgut and migrate to proboscis

i = Infective Stage
d = Diagnostic Stage

CDC
http://www.dpd.cdc.gov/dpdx
Leishmania-HIV Co-infection

HIV infection increases the risk of developing Visceral Leishmaniasis by 100 to 2320 times in endemic areas.
“Etifu” Rx 1

- Jan to March year 2
  - Admission for relapse 1. Rx L-AMB / miltefosine
- May to Sept year 2
  - Miltefosine (50 to 100 mg/day)
- Sept year 2 to Sept year 4
  - Pentamidine 200mg IV every 3 weeks
“Etetu” Rx 2

- Oct year 4
  - Relapse 2; Rx L-AMB
- Oct to Dec year 4
  - L-AMB 4 mg/kg weekly
- Dec year 4
  - Pentamidine restarted
- Jan year 5
  - Relapse 3; L-AMB Rx course, then weekly until April year 5
“Etifu” Rx 3

- April to Sept year 5
  - Pentamidine every 3 weeks
- Oct year 5
  - Admitted for relapse 4: Rx L-AMB / miltefosine
- Dec year 5
  - Pentamidine restarted
Changing pattern of immunocompromise

Fletcher et al PLOS One 2015. 10 (4) e0121418

• HTD London 1995 to 2013
• 28 VL cases
  – 19 immunocompromised
    • 7 HIV positive, 5 on ARVs
    • 6 autoimmune disease all on immunomodulatory drugs
    • 2 haematological malignancy (CLL and T cell lymphoma)
    • 1 diabetes
    • 1 chronic alcohol excess
    • 1 multiple comorbidities
Case 8
A critical case

- 39y Afro-Caribbean male
- Grenada until 12y old
- Stage IVb T cell lymphoma
- 3 cycles of CHOP chemotherapy
- 3rd complicated by neutropenic sepsis
- Bled from duodenal erosions
- Transfusion; antibiotics; TPN
A critical case

- Developed small bowel obstruction
- Day 11: Laparotomy
- Necrotic nodes duodenal/jejunal flexure
- Thickened proximal small bowel
- Biopsies: see histology
A critical case
A critical case

• Reduced steroid dosage
• Oral ivermectin
• Oral albendazole
• But: Day 12 sputum still positive
• Commenced ivermectin subcutaneously (total of 15 doses)
• Larvae eventually cleared
Imported but long forgotten

*Strongyloides*
Strongyloides life cycle

Carlo Denegri Foundation Atlas
Clinical features of *Strongyloides* infection

- Asymptomatic
- Diarrhoea
- Malabsorption
- Larva currens
- Hyperinfestation
Larva currens
**Strongyloides treatment**

- Oral thiabendazole obsolete
- Oral albendazole less effective
- Oral ivermectin
- Rectal thiabendazole (unlicensed)
- Subcutaneous ivermectin (unlicensed)