A BITTER PILL TO SWALLOW

- Case presentation

Dr E Shoul
Wits University, Dept of Medicine
SA HIV Clinicians Society Conference
April 2016
Mr HM – 42 year old male from Johannesburg

**Background history:**
- Previously well
- Known with HIV, on ARVs since 2006
  - Uncertain initial regimen:
    - likely 3TC/ D4T/ EFV
    - then 3TC/ TDF/ EFV
    - now on FDC: FTC/ TDF/ EFV since April 2015
- No previous episodes of TB/ no other opportunistic infections
- No other chronic treatment taken apart from ARVs

**Social history:**
Works in construction - since 2004
Lives in a flat in Hillbrow with all amenities, with his 2 sons (aged 15 and 20) who are well
No exposure to pets, birds, livestock
Originally from Zimbabwe, last visited Zimbabwe over the December 2015 period
Noted lesions on the palate since 22/12/2015

- Lesions are painless, no difficulty swallowing or with phonation
- Denies any masses or ulcerations on the palate prior to this
- No preceding dental problems
- No history of sinus problems
History of the Presenting Complaint

- Mass enlarging - starting to impede phonation
- Remained painless, still able to swallow with no problems

- Referred to ENT for assessment and further management:
  - Skull x-ray done
  - Biopsy taken; told to follow up for results
  - CT scan booked for 2 days after initial consultation

**Working diagnosis:**
- Non-benign lesion of the palate for investigation
Initial blood results

Taken at ENT OPD on 11/01/2016

- **FBC:** 2.33 / 11.2 (MCV 88.5) / 280
- **Differential:** Not requested
- **U&E:** 136 / 4.6 / 98 / 27 / 6.7 / 71
- **CRP:** 14
CT BOS to clavicle:

- **Locally destructive soft tissue lesion left side of the palate:**
- Superiorly: inferior part of the maxillary bone with destruction of the bone
- Inferiorly: base of the tongue on the left with poor separation from the tongue
- Laterally: into the anterior masticator space and infratemporal region
- Medially: into the soft palate
- Associated areas of necrosis

**ABDO U/S:** Micro-abscesses noted in the spleen; mesenteric lymph nodes noted
What’s your differential diagnosis?
Patient H.M.

Intracellular fungal spores with discernible clear halos within macrophages

400X Magnification (Oil)
<table>
<thead>
<tr>
<th></th>
<th>22/01/2016</th>
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<tbody>
<tr>
<td>WCC</td>
<td>11.9</td>
<td>2.02</td>
<td>1.76</td>
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<tr>
<td>HB</td>
<td>11.5</td>
<td>10.7</td>
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<tr>
<td>MCV</td>
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<td>200</td>
<td>135</td>
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<td>TPHA</td>
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<td>Negative</td>
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<td>CD 4</td>
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<tr>
<td>TP</td>
<td>58</td>
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<td>ALBUMIN</td>
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<tr>
<td>GGT</td>
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<td>375</td>
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<td>ALT</td>
<td>15</td>
<td>192</td>
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<tr>
<td>AST</td>
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<td>ALP</td>
<td>81</td>
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Issues to consider

1. What is the clinical picture of histoplasmosis?
2. How do we diagnose it in our setting?
3. What is the recommended management and how can it be applied to the local context?
4. What are implications of treating histoplasmosis in someone on ARVS?
Different clinical spectra of histoplasmosis

Immune-competent

- Mild, self-limiting pulmonary illness
- Subacute pulmonary infection
- Acute diffuse pulmonary histoplasmosis
- Chronic pulmonary histoplasmosis

Immune-compromised

- Progressive disseminated histoplasmosis

Clinical picture – mimicking the mimicker
Disseminated Progressive Histoplasmosis

- Constitutional symptoms: fever, fatigue, weight loss - ± always
- Respiratory findings: cough and dyspnoea (about half)
- Hepatosplenomegaly
- Superficial lymph nodes
- Mucocutaneous features
- GIT/ Neuro (less common)

If you’re thinking TB – think Histoplasmosis

What is the value of “splenic microabscesses” on ultrasound?

-thinking outside the TB box

Most will be TB

HOWEVER

- Non-tuberculous mycobacterial infection eg. *Mycobacterium avium* complex infection (MAC)
- Salmonella spp.
- Lymphoma/ Leukemia/ Solid tumour metastasis
- Disseminated fungal infection (Candida spp., cryptococcus)
- Leishmaniasis
Diagnosing Fungal Infections
Diagnosing Fungal Infections

- **Culture** – blood or other tissue samples BUT long turn-around up to 4-6wks, coin-flip yield (around 50%)

- **Serology** – complement fixation or immunodiffusion (BUT: results delayed by few weeks)

- **Antigen detection** – *Histoplasma* antigen in urine and serum using antigen enzyme immunoassay – very sensitive

- **Direct microscopy** – peripheral blood or bone marrow aspirate: very low sensitivity

- **PCR** – directly from tissue or culture

- **Histology**

In Mr HM – combination of:

Laboratory Report
Date of report: 04-02-2016

Patient name: [Redacted]
Hospital number: [Redacted]
Referring laboratory: NHLS Charlotte Maxeke Johannesburg Academic Hospital
Reason for referral: Urine for Histoplasma antigen test
Test requestor: Dr M Venter
Contact details: Michelle.venter@gmail.com
Clinical history: 42-year-old man from Zimbabwe. HIV-infected with a CD4 count of 10 cells/μl. Has been on ART since 2006, claims adherence to ART, currently on FDC. He works as an excavator on construction sites (12 years), stays in Hillbrow and has no known exposure to birds. 1-month history of an enlarging palatal mass. On amphotericin B.
Specimen type: Urine for Histoplasma antigen test
Specimen collection date: 28/01/2016
Lab number: Unknown

Date of receipt at NICD: 28-01-2016

Histoplasma antigen assay (04-02-2016)
An investigational EIA was performed in duplicate on the urine sample:
   1. Test run 1: 24.235 EIA units (POSITIVE)
   2. Test run 2: 23.933 EIA units (POSITIVE)

Interpretation: A POSITIVE EIA implies the presence of Histoplasma galactomannan antigen in the urine. However, since this is an investigational assay that is currently being validated, culture and histopathological results must be considered before patient management is altered.

This test should not be used in isolation for diagnostic purposes.

Laboratory tests completed by: Maboto Mhlanga
Authorised: Nelesh Govender
Management

Histoplasmosis alone and implications in HIV with ARVs
Management depends on clinical syndrome

**No indication for antifungal therapy**

1. Mild acute pulmonary histoplasmosis
2. Localized pulmonary disease (Symptoms < than 4 weeks)
3. Rheumatologic complications
4. Pericarditis
   (Unless steroids given for severe pericarditis)
4. Mediastinal lymphadenitis
5. Asymptomatic granulomatous mediastinitis

**Treatment recommended**

1. Severe acute pulmonary disease (antifungal therapy + steroids)
2. Chronic cavitary pulmonary disease
3. Mild to moderate disseminated disease vs severe disseminated disease

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<th><strong>Induction phase</strong></th>
<th><strong>Maintenance phase</strong></th>
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<tr>
<td>Disseminated Progressive</td>
<td>Liposomal Amphotericin B x 1 – 2 weeks</td>
<td>Itraconazole 200mg tds x3/7 200mg bd x12mo.</td>
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<td>Histoplasmosis</td>
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<td>Alternative options</td>
<td>Other lipid formulations</td>
<td>?Fluconazole at high doses – less effective</td>
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<td>Deoxycholate Ampho B</td>
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Great if you live in the US

Not so great if you live in Southern Africa

No liposomal Ampho B
No itraconazole
No urinary antigen monitoring
No itraconazole monitoring

Murphy RA, et al. Open Forum Infect Dis 2015; March 23
Antifungal discontinuation in AIDS patients:

- At least 1 year of Itraconazole
- Negative blood cultures
- Serum and urine antigen levels $< 2 \text{ ng/mL}$
- CD 4 count above 150 cells/mm$^3$
- On HAART
Drug interactions – HAART vs Azoles

HAART

NRTIs – AZT/ ABC – not metabolised by cytochrome P450
NNRTIs – EFV: cleared by cytochrome P450, inhibitor of certain P450 enzymes – can increase levels of RTV
PIs – RTV potent inhibitor of cytochrome P450
  LPV/ ATV – metabolised by P450 system, weak inhibitors of certain enzymes

Azole Antifungals

- Extensively metabolised by cytochrome P450 system
- Competitive inhibitors of CYP isoenzymes
- Variable inhibitory capacity: ketoconazole > itraconazole > fluconazole
- Fluconazole and EFV: safe
- BUT fluconazole and NVP: increased NVP levels (monitor LFTs)
- Itraconazole and EFV/ NVP: decreased itraconazole levels (uncertain significance)
- Itraconazole and PIs: increased itraconazole concentration, prolong half-life, leads to accumulation
Plasma concentrations of itraconazole (solid line) and droxyitraconazole (dotted lines) in an HIV-infected patient with histoplasmosis.

A: Concentrations before ARVs
C: Concentration when ARVs at steady state and itraconazole at 200mg daily

Mr HM’s course

- Completed >14 days of Amphotericin B
- Will need itraconazole maintenance.
- Virological Failure
- Patient now needs to be changed to second line ARV’S
- Follow-up in Infectious diseases clinic
At presentation

After 1 week of Treatment
Thank you

Special thanks to:
Dr Michelle Venter, Dept of Medicine
Dr Kirsty Fearnhead, Dept of Pathology
Dr Stacey Bhikha, Dept of Medicine