HIV Clinician’s Society Conference

Unknown Case Presentation and Discussion:

A Palatal Mass and A Head-Scratcher

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Infectious Diseases Physician
Patient H.M:

- 42 year old male.
- Previously well.
- Known with Retroviral disease (RVD), on antiretrovirals (ARVs) since 2006.
  - (3 separate drugs, now on fixed-dose combination since April 2015).
- No previous episodes of TB.
- No other treatment taken apart from ARVs.
PATIENT HISTORY

Patient H.M:

- 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 6 months prior to his current presentation.
- Non-smoker.
- Denies ethanol use.
Patient H.M:

History of the Main Complaint:

- Noted lesions on the palate 2 months prior to his presentation:
  - Denies having experienced masses or ulcerations on the palate prior to this.
  - Lesions are painless, initially no problems swallowing or with phonation.
  - No preceding dental/ sinus problems.
  - Involves the left alveolar ridge and buccal mucosa.
  - Mass is now enlarging and starting to impede phonation, patient lost 2 teeth.
  - Remained painless, still able to swallow with no problems.

- No other lesions noted by the patient.
- Also gives a history of constitutional symptoms for 3 months.
**INITIAL INVESTIGATIONS:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>2,33 / 11,2 (MCV 88,5) / 280</td>
</tr>
<tr>
<td>U&amp;E</td>
<td>136 / 4,6 / 98 / 27 / 6,7 / 71</td>
</tr>
<tr>
<td>CD₄ Count</td>
<td>10 cells/μL</td>
</tr>
<tr>
<td>Viral Load</td>
<td>376 000 copies/ mL</td>
</tr>
<tr>
<td>LFT</td>
<td>5 / 3 / Pr 58 / Alb 34 ALP 81 GGT 26 AST 18 ALT 15</td>
</tr>
<tr>
<td>CRP</td>
<td>14</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Surface antibody negative, surface antigen negative</td>
</tr>
<tr>
<td>RPR / TPHA</td>
<td>Negative / Negative</td>
</tr>
<tr>
<td>Sputum GXP</td>
<td>Positive Rifampicin sensitive</td>
</tr>
</tbody>
</table>
STOP AND DISCUSS:

• LIKELY DIFFERENTIAL DIAGNOSIS FOR THE CURRENT PRESENTATION OF THE PATIENT?

• COULD HIS OCCUPATIONAL HISTORY PLAY A ROLE?

• NEXT STEPS?
HISTOPATHOLOGY OF THE LESION

Sections show ulcerated fragments of mucosa.
The lamina propria shows confluent sheets of epithelioid histiocytes with admixed lymphocytes and plasma cells.
Viral inclusion bodies are not identified.
There are no features of a neoplastic process in the sections examined.
The Ziehl-Neelsen stain is negative.
HISTOPATHOLOGY OF THE LESION

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Intracellular fungal spores some with discernible clear halos are identified within macrophages
The Grocott stain is positive in the fungal spores.

CONCLUSION:
Ulcerating mass involving the palate, left alveolar ridge and buccal mucosa:
The morphological features are in keeping with HISTOPLASMOSIS.
STOP AND DISCUSS:

- THE ROLE OF URINE HISTOPLASMA ANTIGEN TESTING IN THE SETTING OF IMMUNODEFICIENCY

- IS THERE A ROLE FOR MONITORING URINE HISTOPLASMA ANTIGEN IN RESPONSE TO TREATMENT?
HISTOPLASMA ANTIGEN ASSAY ON URINE: POSITIVE
Progressive Disseminated Histoplasmosis

- Antigen levels should be measured during therapy and for 12 months after therapy is completed to monitor for relapse (B-III).

- Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.
<table>
<thead>
<tr>
<th>Itraconazole</th>
<th>Beeprvir</th>
<th>Concentrations of itraconazole and/or beeprvir may be ↑.</th>
<th>Itraconazole dose should not exceed 200 mg/day. Monitor itraconazole concentration and adjust dose accordingly. Alternatively, consider switching to abline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>Possible bi-directional CYP3A4 inhibition and T exposure of both drugs.</td>
<td>Monitor for toxicities of both itraconazole and clarithromycin. Monitor itraconazole concentration and adjust dose accordingly. Alternatively, consider switching to abline.</td>
<td></td>
</tr>
<tr>
<td>Elafiruz</td>
<td>Itraconazole AUC ↓ 39%, Cmax ↓ 44% in PK studies. No change to elafiruz AUC. Failure to achieve therapeutic itraconazole concentrations has been reported.</td>
<td>Co-administration should be avoided if possible. If used in combination, monitor itraconazole concentrations and adjust dose accordingly.</td>
<td></td>
</tr>
<tr>
<td>Etravirine/elficit/lamivudine/lamivudine</td>
<td>Etravirine concentration may be ↑ &amp; lamivudine concentration may be ↓. Extent of the interaction unknown.</td>
<td>Dose adjustment with itraconazole may be necessary depending on the presence of other concurrent ARV drugs (e.g., PIs). Monitor itraconazole concentrations and adjust dose accordingly.</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Potential for inhibition of maraviroc metabolism and T in maraviroc concentration.</td>
<td>Decrease maraviroc dose to 150 mg twice daily.</td>
<td></td>
</tr>
<tr>
<td>Micosfumith</td>
<td>Itraconazole AUC ↓ 22%</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>Neviripine</td>
<td>Itraconazole Cmax ↓ 38%, AUC ↓ 61%; neviripine: no change</td>
<td>Monitor itraconazole concentrations and adjust dose accordingly. Monitor therapeutic efficacy.</td>
<td></td>
</tr>
</tbody>
</table>

**Itraconazole continued:**

<table>
<thead>
<tr>
<th>PIs</th>
<th>Potential for bi-directional CYP3A4 inhibition with T exposure of both drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritirubin</td>
<td>Itraconazole AUC ↓ 70%; potential for inhibition of ritirubin metabolism and T ritirubin exposure.</td>
</tr>
<tr>
<td>Ritiruplin</td>
<td>Itraconazole AUC ↓ 64%–88%; no change in ritiruplin concentrations.</td>
</tr>
<tr>
<td>Rifpilvirene</td>
<td>Potential T in rifpilvirene exposure or ↓ in itraconazole.</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Concentrations of itraconazole and telaprevir may be ↑.</td>
</tr>
</tbody>
</table>

Monitor for PI-associated toxicities; monitor itraconazole concentrations and itraconazole-associated toxicities. Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole concentrations and adjust dose accordingly; monitor for ritirubin-associated toxicities and consider monitoring ritirubin concentrations.
STOP AND DISCUSS:

• THE POTENTIAL PITFALLS IN TREATING ALL 3 CONDITIONS SIMULTANEOUSLY

• POTENTIAL TREATMENT OPTIONS AVAILABLE
Progressive Disseminated Histoplasmosis

Moderately severe to severe disease:

- Liposomal amphotericin B (3.0 mg/kg daily) for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) (A-I).

- Deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

Progressive Disseminated Histoplasmosis

Mild-to-moderate disease

• Itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) (A-II).

• Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

LARGEST COHORT IN THE LITERATURE OF TB AND HISTOPLASMOSIS CO-INFECTED CASES:

LARGEST COHORT IN THE LITERATURE OF TB AND HISTOPLASMOSIS CO-INFECTED CASES:

• 14 HIV-infected patients who had concomitant tuberculosis and histoplasmosis.
• Weight loss (85.7%), asthenia (78.5%), fever (64.2%).
• Death occurred in two patients.
• Relapse of both infections occurred in one patient.
• Moxifloxacin was substituted for rifampicin, with good outcomes noted for both infections.

HISTOPLASMOSIS REGIMEN
AMPHOTERICIN B
LIPOSOMAL AMPHOTERICIN B
ITRACONAZOLE
POSACONAZOLE
FLUCONAZOLE

ART REGIMEN
?? WHAT 3\textsuperscript{rd} DRUG SHOULD BE USED
PI
LOPINAVIR-RITONAVIR
ATAZANAVIR-RITONAVIR
INTEGRASE-INHIBITOR
DOLUTEGRAVIR

TUBERCULOSIS REGIMEN
RIFAMPICIN
RIFABUTIN
RIFAPENTINE
ISONIAZID
PYRAZINAMIDE
ETHAMBUTOL
? SUBSTITUTE RIF WITH A FLUOROQUINOLONE
AMPHOTERICIN B

• Randomized clinical trial:

• IV liposomal amphotericin B (3 mg/kg daily) more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily).
  • Induced a more rapid and complete response.
  • Lowered mortality.
  • Reduced toxicity.

ITRACONAZOLE

• Step-down therapy to oral Itraconazole:
  • 200 mg 3 times daily for 3 days.
  • 200 mg twice daily.
  • For a total of at least 12 months (AII).

Potential drug interactions between Itraconazole and both protease inhibitors and efavirenz:
• Advisable to obtain serum levels of Itraconazole after 2 weeks of therapy.
• Random serum level of at least 1.0 µg/mL is recommended.
ALTERNATIVES TO ITRACONAZOLE

Oral posaconazole and voriconazole:
• Reported to be effective for histoplasmosis in a small number of patients with AIDS.
• Reasonable alternatives for patients intolerant of Itraconazole who are only moderately ill (BIII).

Fluconazole
• Less effective than itraconazole for histoplasmosis.
• Moderately effective at 800 mg daily.
• May be a reasonable alternative at this dose for those intolerant of itraconazole (CII).

Echinocandins
• Not active against H. capsulatum
• Should not be used to treat patients with histoplasmosis (AIII).
**RETROVIRAL DISEASE**
- Changed to second-line ART (AZT/3TC/LOP-r)

**HISTOPLASMOSIS**
- Patient treated with deoxycholate Amphotericin B for 2 weeks
- Consolidation phase with Fluconazole 800mg daily PO while on TB treatment
- Continued on Itraconazole 200mg daily PO once TB treatment completed

**TUBERCULOSIS**
- Treated for 6 months in total
4 weeks after treatment
TAKE-HOME MESSAGES FROM THIS CASE

1) Opportunistic infections often co-exist: don’t stop looking because you’ve found one.
2) Drug-drug interactions should always be considered in these (and all) cases.
3) If you’re unsure, look it up.
Interaction Checker
Access our free, comprehensive and user-friendly drug interaction charts

Educational Videos
A series of mini-lectures on topics including pharmacology, HIV and drug-drug interactions

Prescribing Resources
Interaction tables, treatment selectors, clinical prescribing resources, and pharmacokinetic fact sheets

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Mobile Apps

Hepatitis Website

Cancer Website