HIV Clinician's Society Conference

Unknown Case Presentation and Discussion:

A Palatal Mass and A Head-Scratcher

Dr. M. Venter

Infectious Diseases Physician

PATIENT HISTORY

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.

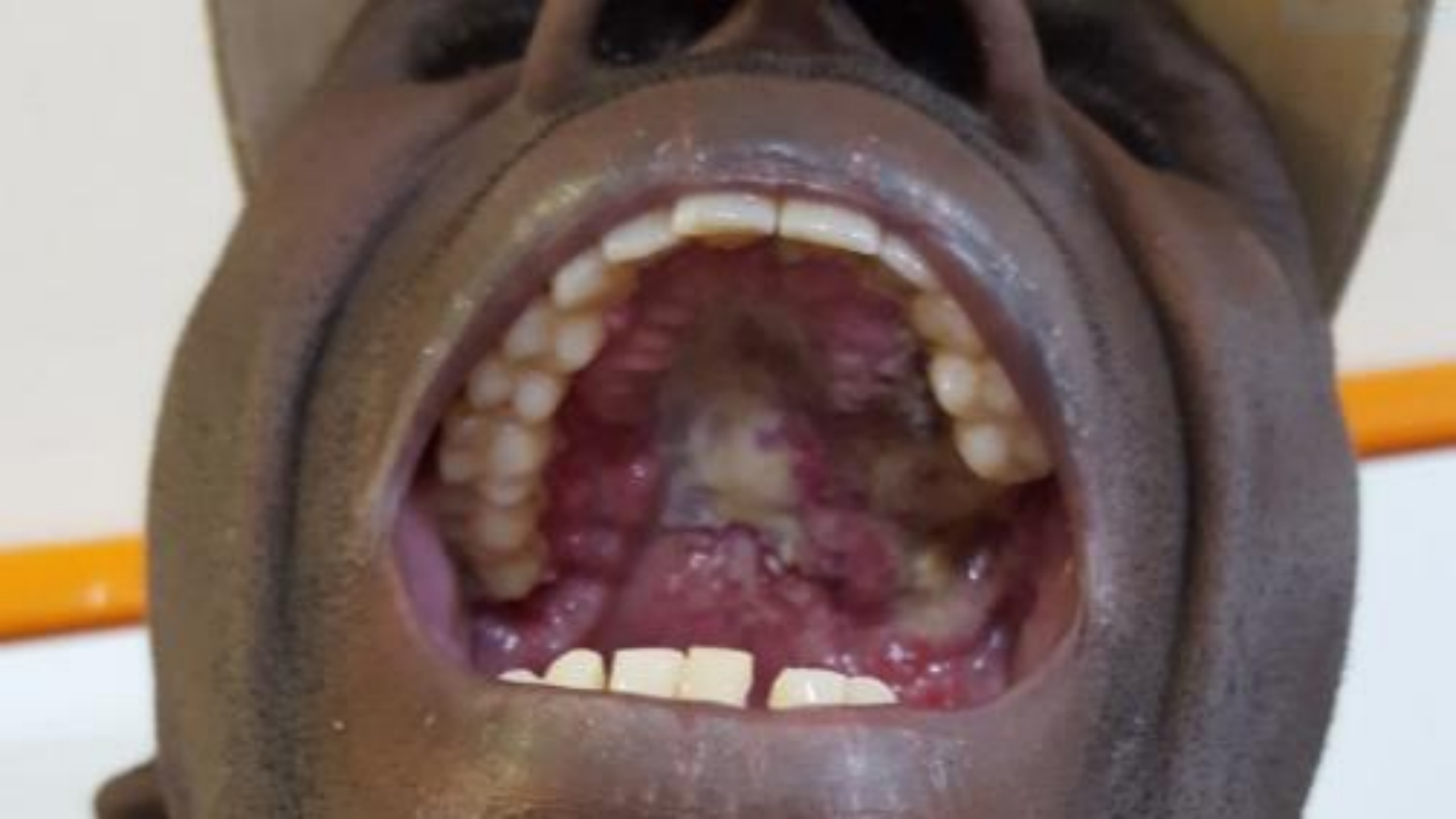
PATIENT HISTORY

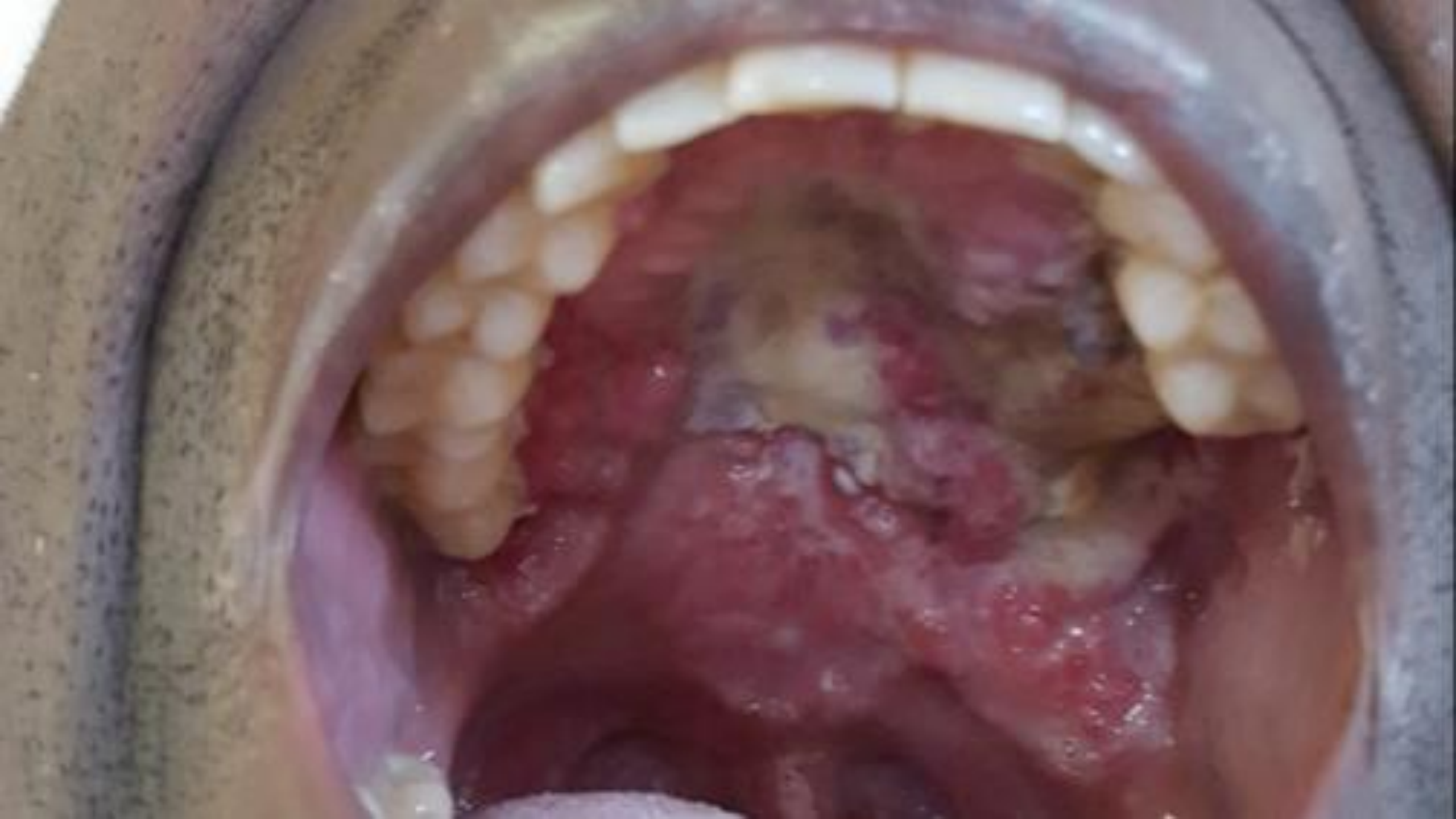
Patient H.M:

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:

Parameter	Result
FBC	2,33 / 11,2 (MCV 88,5) / 280
U&E	136 / 4,6 / 98 / 27 / 6,7 / 71
CD_4 Count	10 cells/ µL
Viral Load	376 000 copies/ mL
LFT	5 / 3 / Pr 58 / Alb 34 ALP 81 GGT 26 AST 18 ALT 15
CRP	14
Hepatitis B	Surface antibody negative, surface antigen negative
RPR / TPHA	Negative / Negative
Sputum GXP	Positive Rifampicin sensitive

STOP AND DISCUSS:

- LIKELY DIFFERENETIAL 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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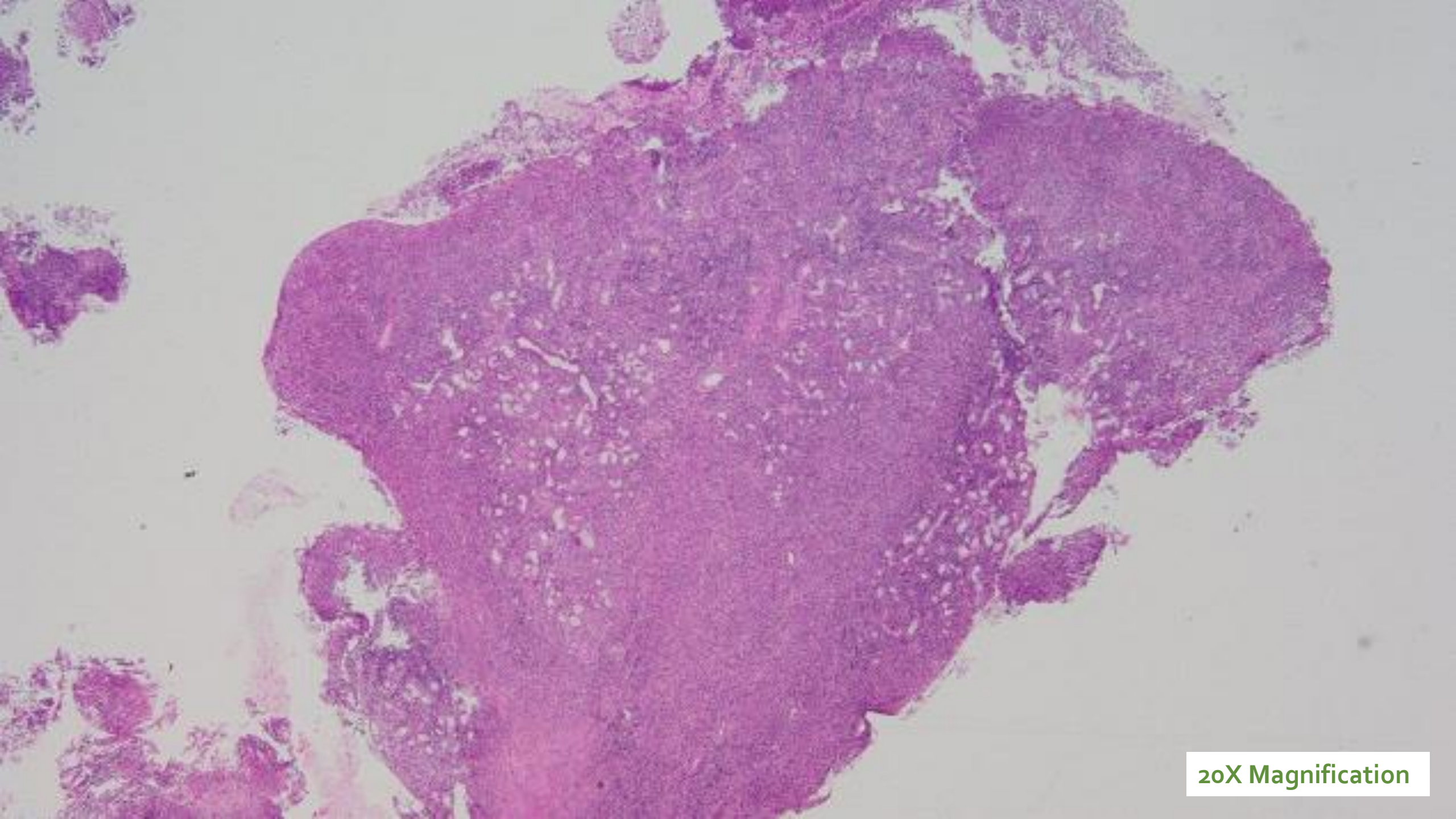
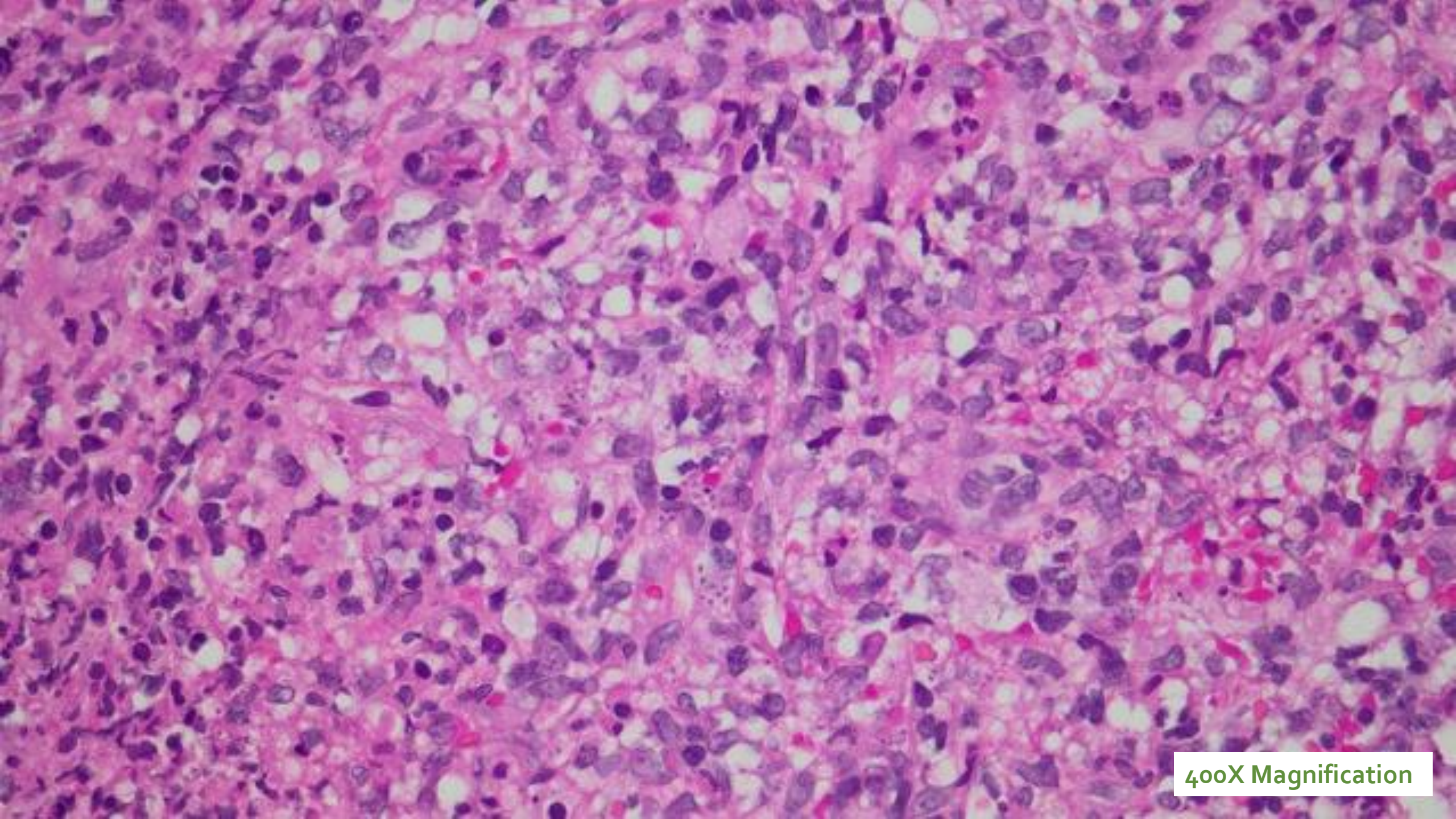
The Ziehl-Neelsen stain is negative.

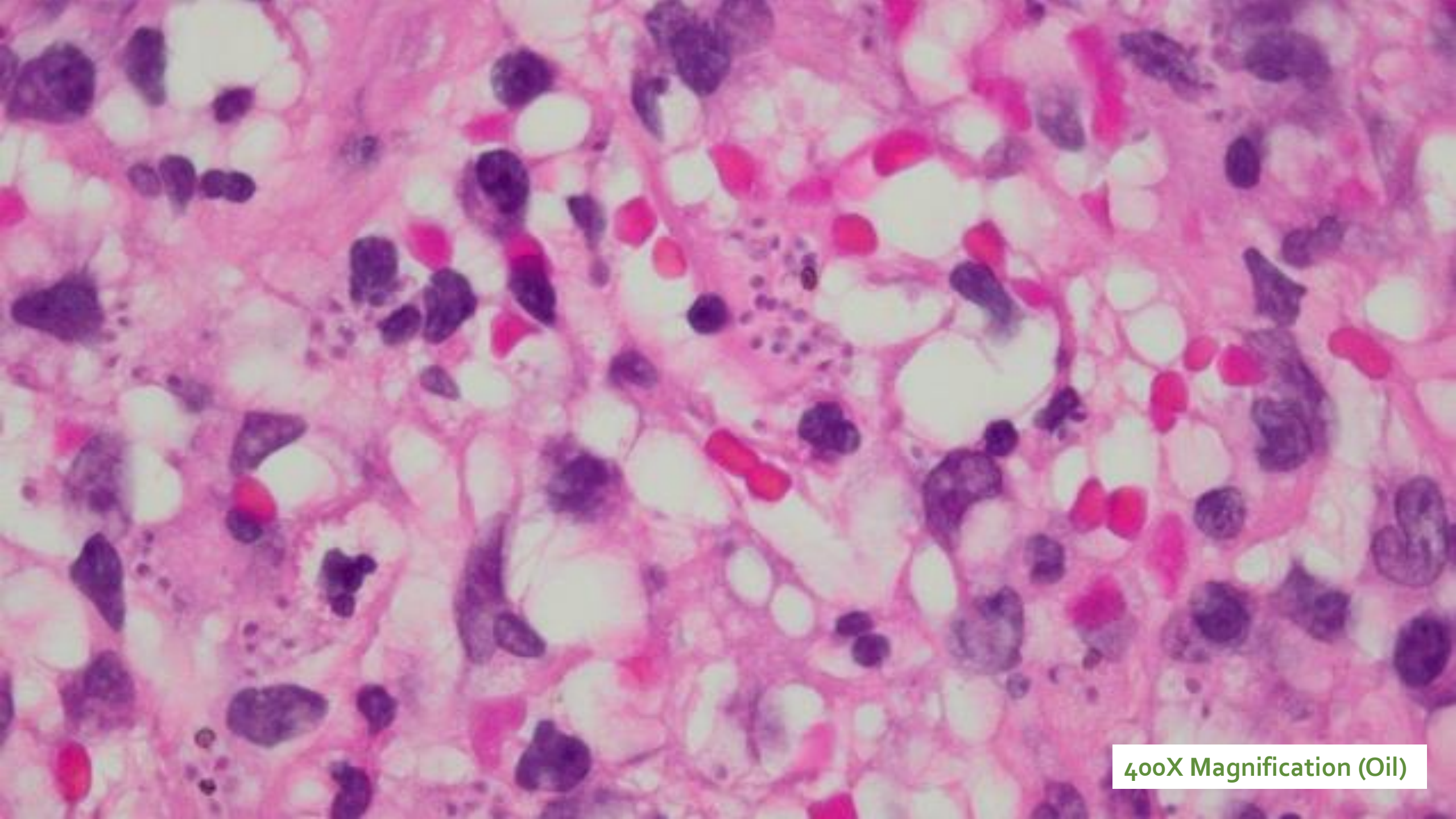
Intracellular fungal spores some with discernible clear halos are identified within macrophages
The Grocott stain is positive in the fungal spores.

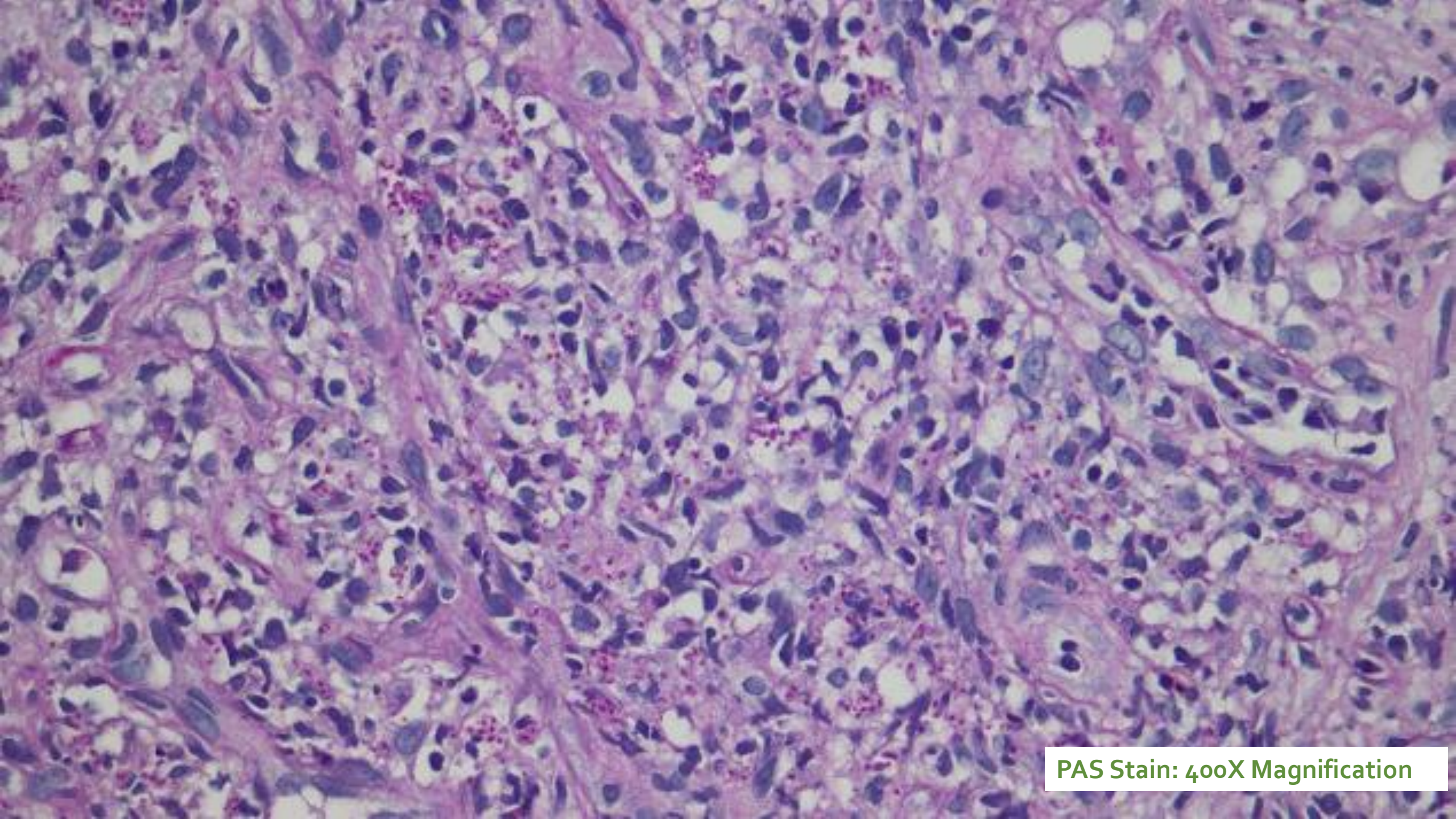
CONCLUSION:
Ulcerating mass involving the palate, left alveolar ridge and buccal mucosa:
The morphological features are in keeping with **HISTOPLASMOSIS.**

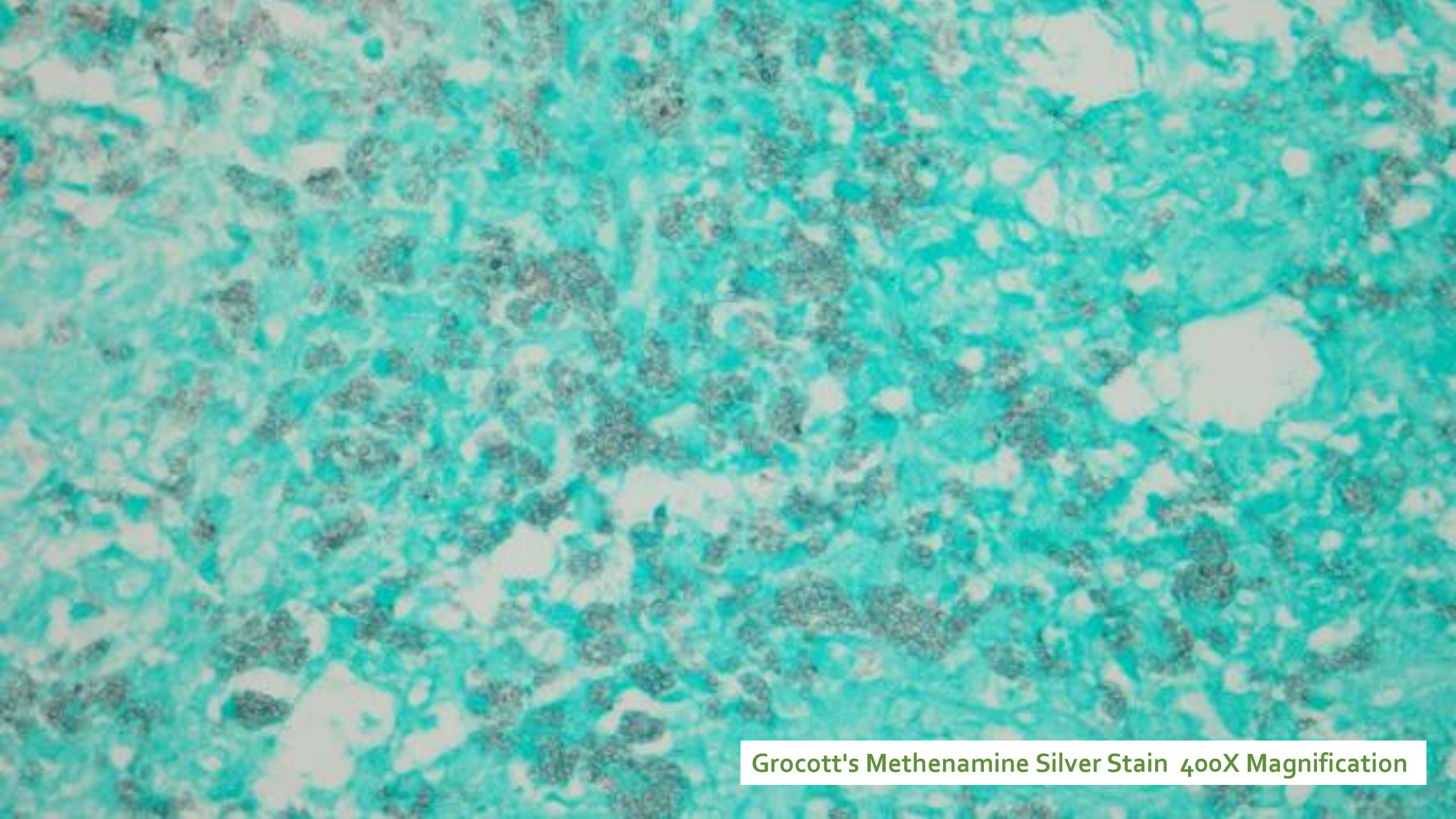


20X Magnification

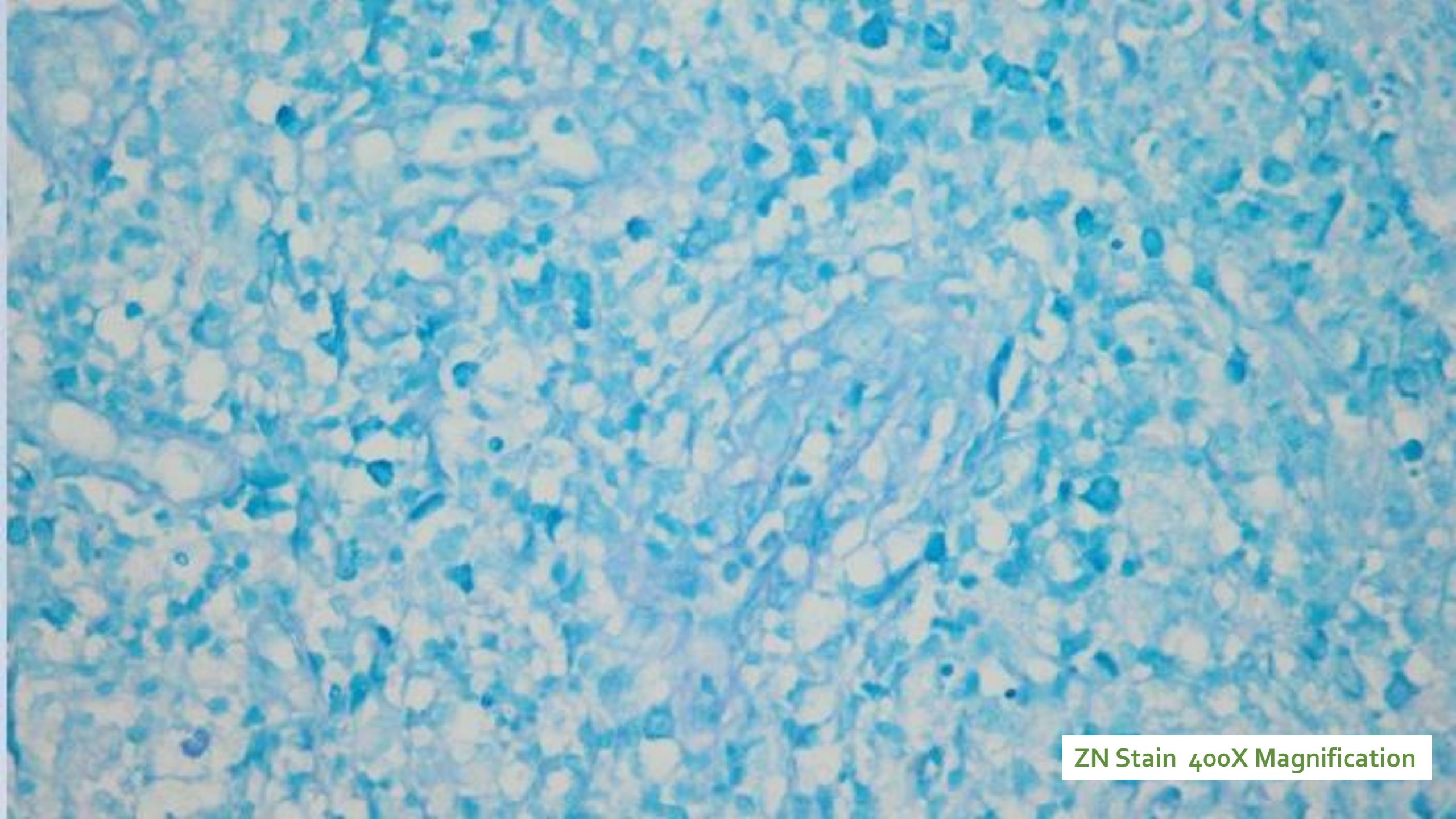

400X Magnification


400X Magnification (Oil)


PAS Stain: 400X Magnification



Grocott's Methenamine Silver Stain 400X Magnification



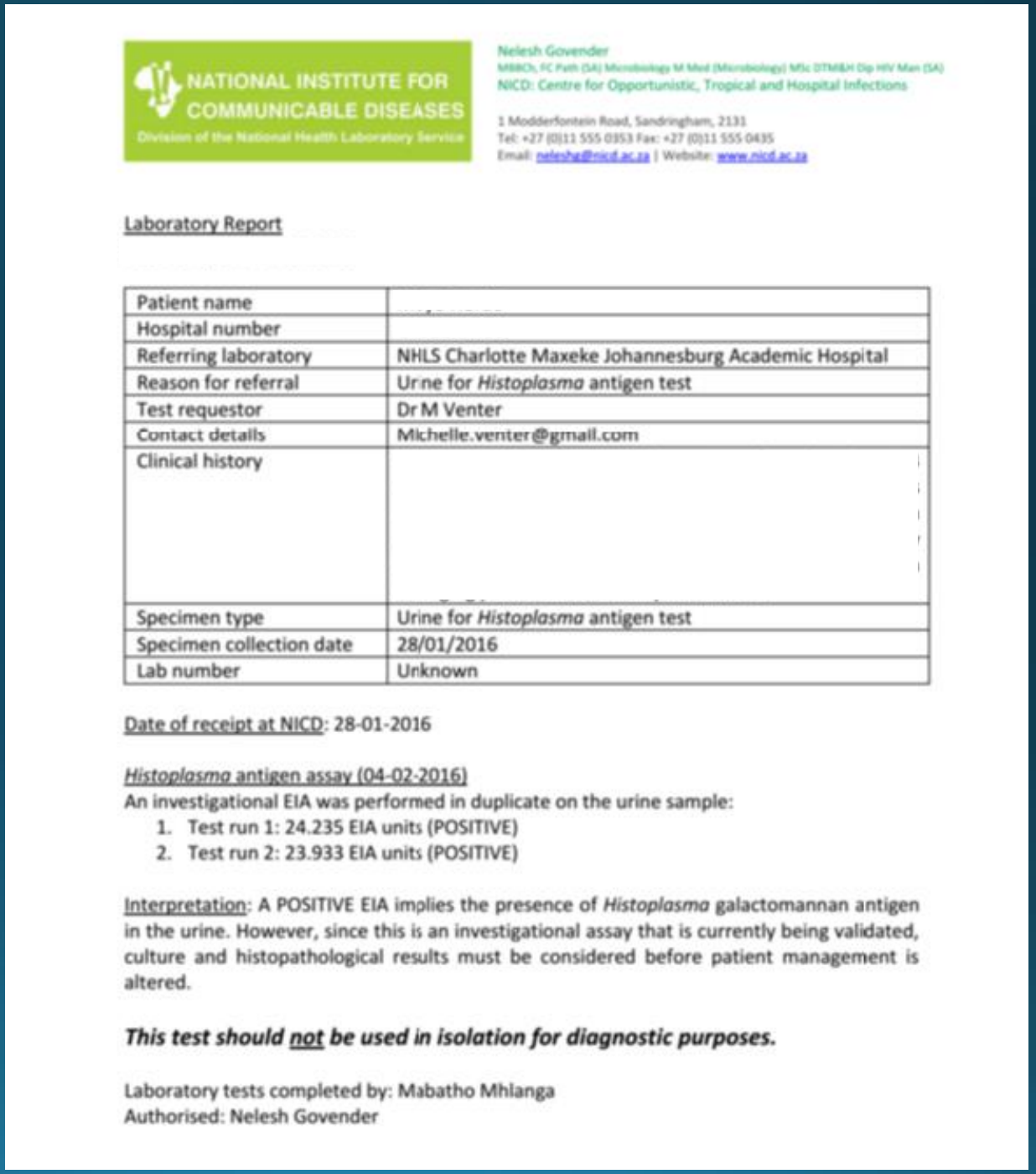
ZN Stain 400X Magnification

STOP AND DISCUSS:

- THE ROLE OF URINE HISTOPLASMA ANTIGEN TESTING IN THE SETTING OF IMMUNODEFICINCY
- IS THERE A ROLE FOR MONITORING URINE HISTOPLASMA ANTIGEN IN RESPONSE TO TREATMENT?

WORK-UP OF THE LESION

HISTOPLASMA ANTIGEN ASSAY ON URINE: POSITIVE



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Laboratory Report

Patient name	
Hospital number	
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	
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: Mabatho Mhlanga
Authorised: Nelesh Govender

Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America FREE

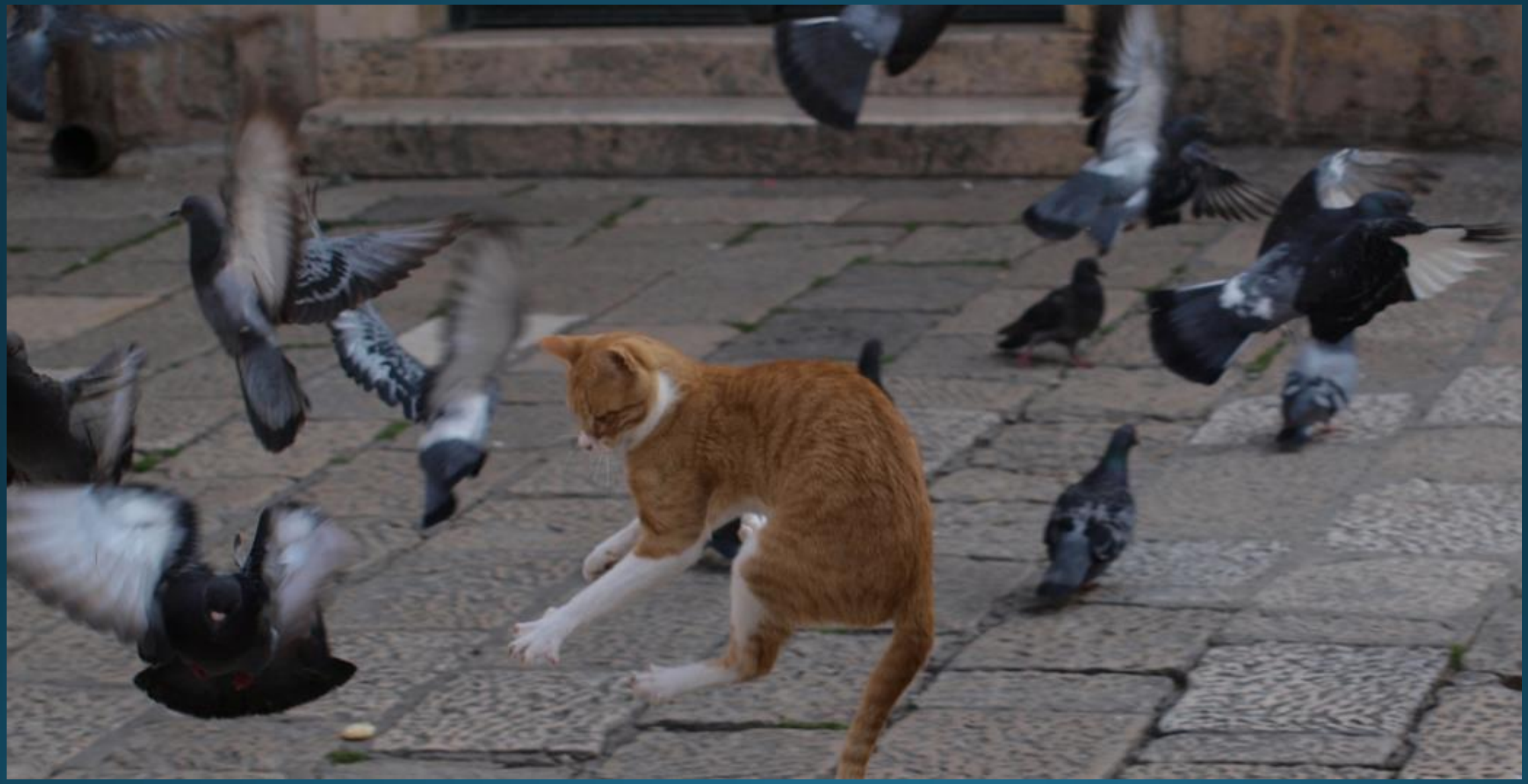
L. Joseph Wheat ✉, Alison G. Freifeld, Martin B. Kleiman, John W. Baddley, David S. McKinsey, James E. Loyd, Carol A. Kauffman

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.

TB

HIV



TB HISTOPLASMOSIS HIV

TB HISTOPLASMOSIS HIV

Itraconazole	Boceprevir	Concentrations of itraconazole and/or boceprevir may be ↑	Itraconazole dose should not exceed 200 mg/day. Monitor itraconazole concentration and adjust dose accordingly.
	Clarithromycin	Possible bi-directional CYP3A4 inhibition and ↑ exposure of both drugs.	Monitor for toxicities of both itraconazole and clarithromycin. Monitor itraconazole concentration and adjust dose accordingly. Alternatively, consider switching to azithromycin.
	Efavirenz	Itraconazole AUC ↓ 39%, C_{min} ↓ 44% in PK studies; No change to efavirenz AUC. Failure to achieve therapeutic itraconazole concentrations has been reported.	Co-administration should be avoided if possible. If used in combination, monitor itraconazole concentrations and adjust dose accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat, elvitegravir, and itraconazole serum concentration may be ↑	Avoid itraconazole >200 mg/day. Monitor itraconazole serum concentrations with co-administration.
	Erythromycin	Potential for bi-directional inhibition of metabolism and ↑ serum concentrations of both drugs.	Monitor for toxicities of both drugs, potential for QT prolongation; monitor itraconazole concentrations and adjust dose accordingly, or consider alternative azole or macrolide.
	Etravirine	Etravirine concentration may be ↑; Itraconazole concentration may be ↓. Extent of the interaction unknown.	Dose adjustment with itraconazole may be necessary depending on the presence of other concomitant ARV drugs (e.g., PIs). Monitor itraconazole concentrations and adjust dose accordingly.
	Maraviroc	Potential for inhibition of maraviroc metabolism and ↑ in maraviroc concentration.	Decrease maraviroc dose to 150 mg twice daily.
	Micafungin	Itraconazole AUC ↑ 22%	No dose adjustment necessary.
	Nevirapine	Itraconazole C_{max} ↓ 38%, AUC ↓ 61%; nevirapine: no change	Monitor itraconazole concentrations and adjust accordingly dose; monitor therapeutic efficacy.
Itraconazole, continued	PIs	Potential for bi-directional CYP3A4 inhibition with ↑ exposure of both drugs.	Monitor for PI-associated toxicities; monitor itraconazole concentrations and itraconazole-associated toxicities
	Rifabutin	Itraconazole AUC ↓ 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin exposure.	Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole concentrations and adjust dose accordingly; monitor for rifabutin-associated toxicities and consider monitoring rifabutin concentrations.
	Rifampin	Itraconazole AUC ↓ 64%–88%; no change in rifampin concentrations.	Co-administration should be avoided. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rilpivirine	Potential ↑ in rilpivirine exposure or ↓ in itraconazole.	No dose adjustment for rilpivirine; monitor for rilpivirine-associated toxicities. Consider monitoring itraconazole concentration and adjust dose as necessary.
	Telaprevir	Concentrations of itraconazole and telaprevir may be ↑	If co-administration is necessary, high doses of itraconazole (>200 mg/day) are not recommended. Monitor for toxicities to both drugs. Consider monitoring itraconazole concentration and adjust dose accordingly.

STOP AND DISCUSS:

- THE POTENTIAL PITFALLS IN TREATING ALL 3 CONDITIONS SIMULTANEOUSLY
- POTENTIAL TREATMENT OPTIONS AVAILABLE

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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).

Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. Oct 1 2007;45(7):807-825

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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).

Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. Oct 1 2007;45(7):807-825

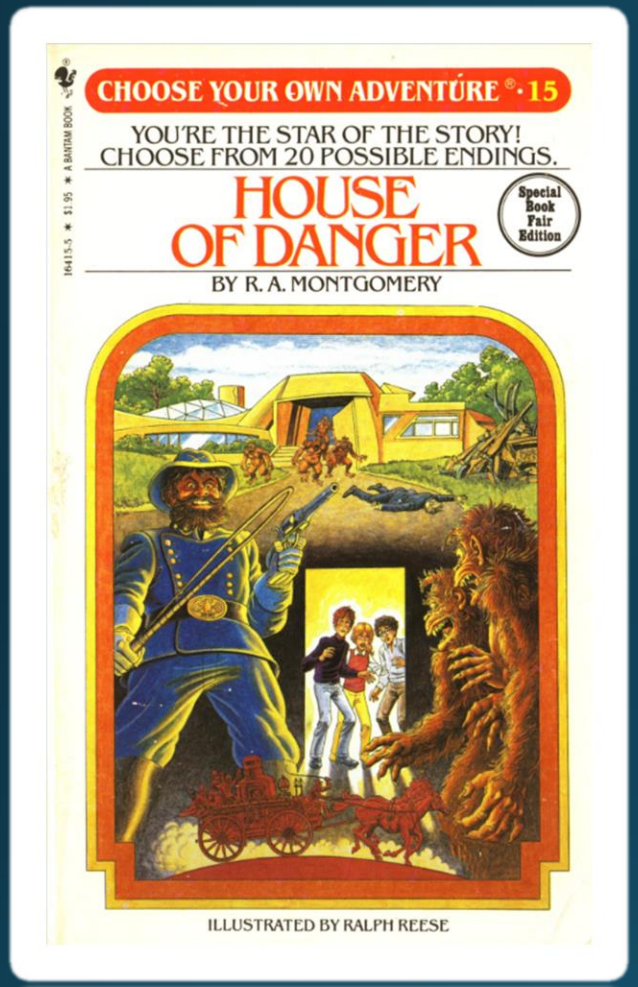
LARGEST COHORT IN THE LITERATURE OF TB AND HISTOPLASMOSIS CO-INFECTED CASES:

Agudelo CA et al: Am. J. Trop. Med. Hyg., 87(6), 2012, pp. 1094–1098

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.

Agudelo CA et al: Am. J. Trop. Med. Hyg., 87(6), 2012, pp. 1094–1098



HISTOPLASMOSIS REGIMEN

AMPHOTERICIN B
LIPOSOMAL AMPHOTERICIN B

ITRACONAZOLE

POSACONAZOLE

FLUCONAZOLE

ART REGIMEN

?? WHAT 3RD 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.

Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med. Jul 16 2002;137(2):105-109

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

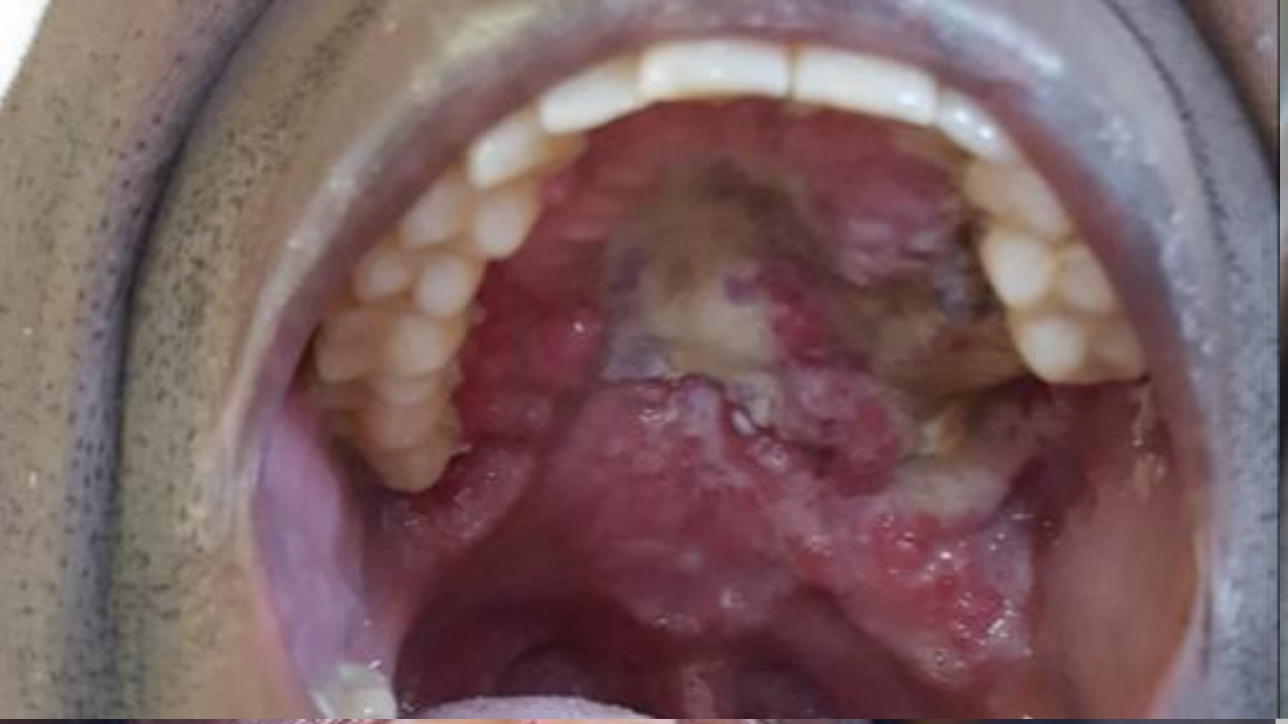
Patient treated with deoxycholate Amphotericin B for 2 weeks

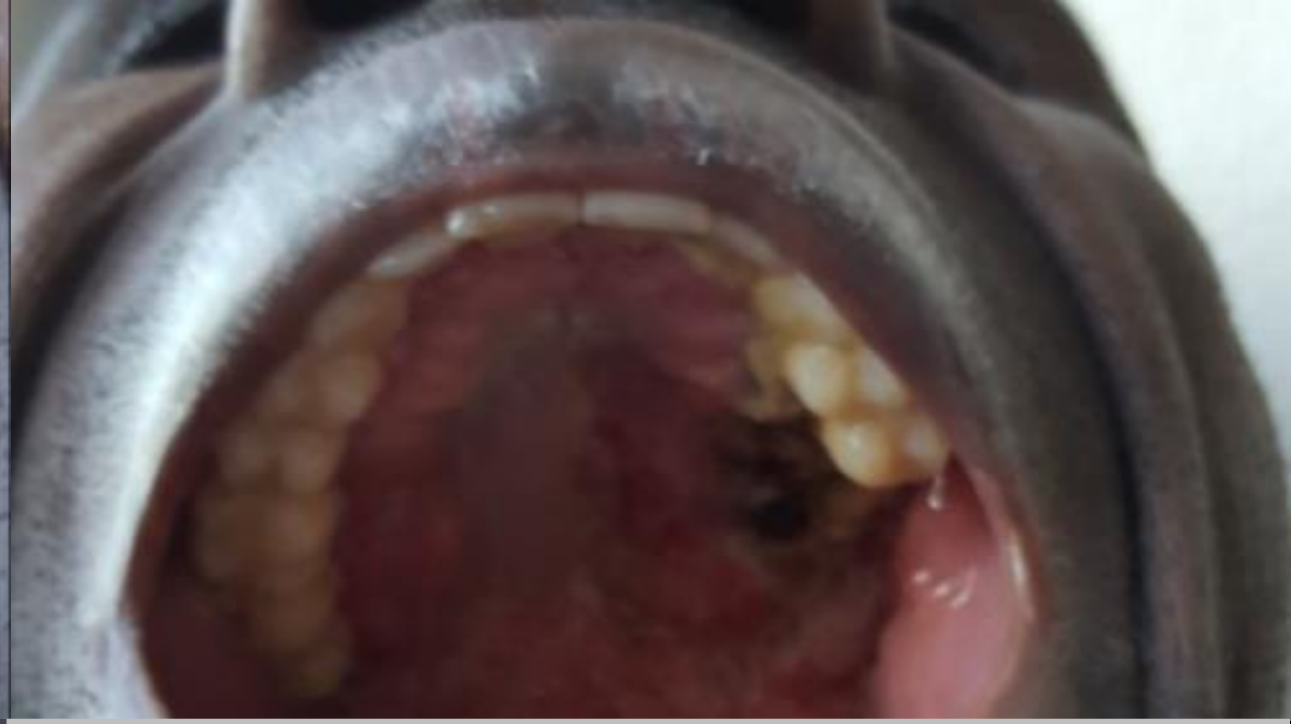
Consolidation phase with Fluconazole 800mg daily PO while on TB treatment

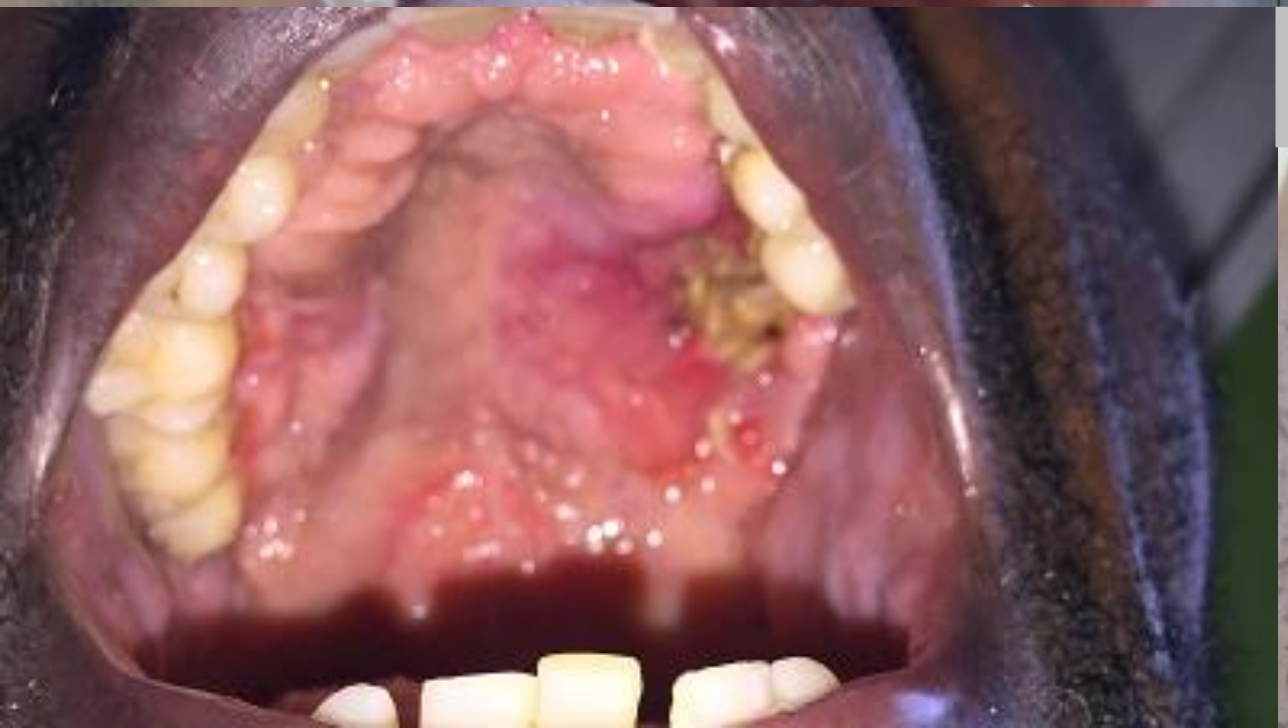
Continued on Itraconazole 200mg daily PO once TB treatment completed

TUBERCULOSIS

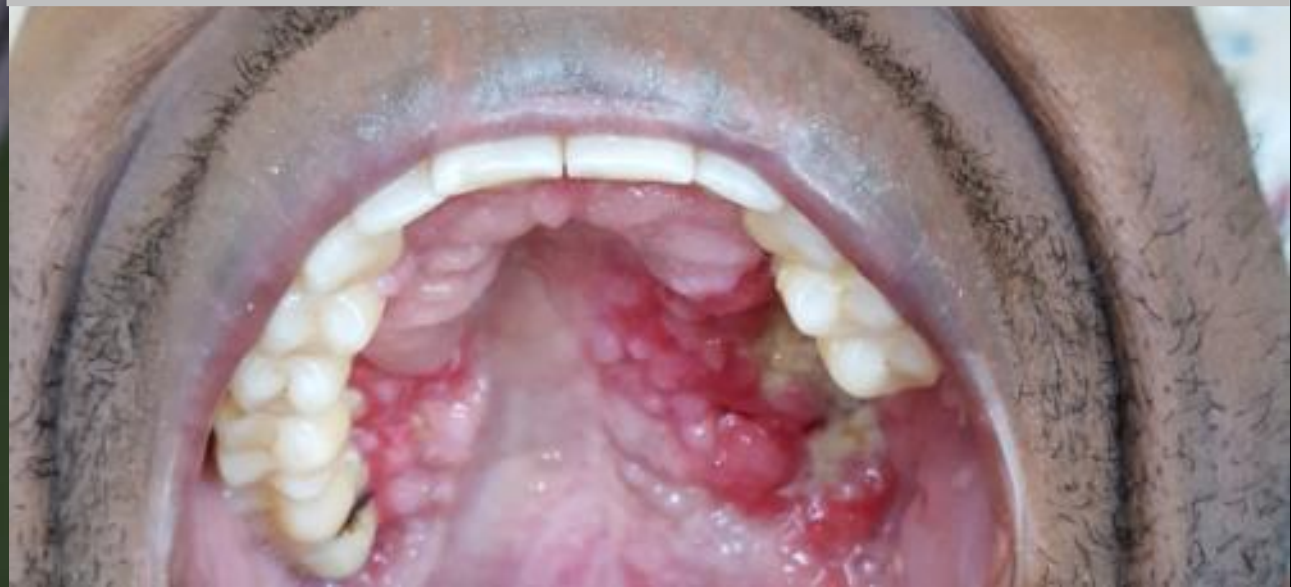
Treated for 6 months in total







4 weeks after treatment

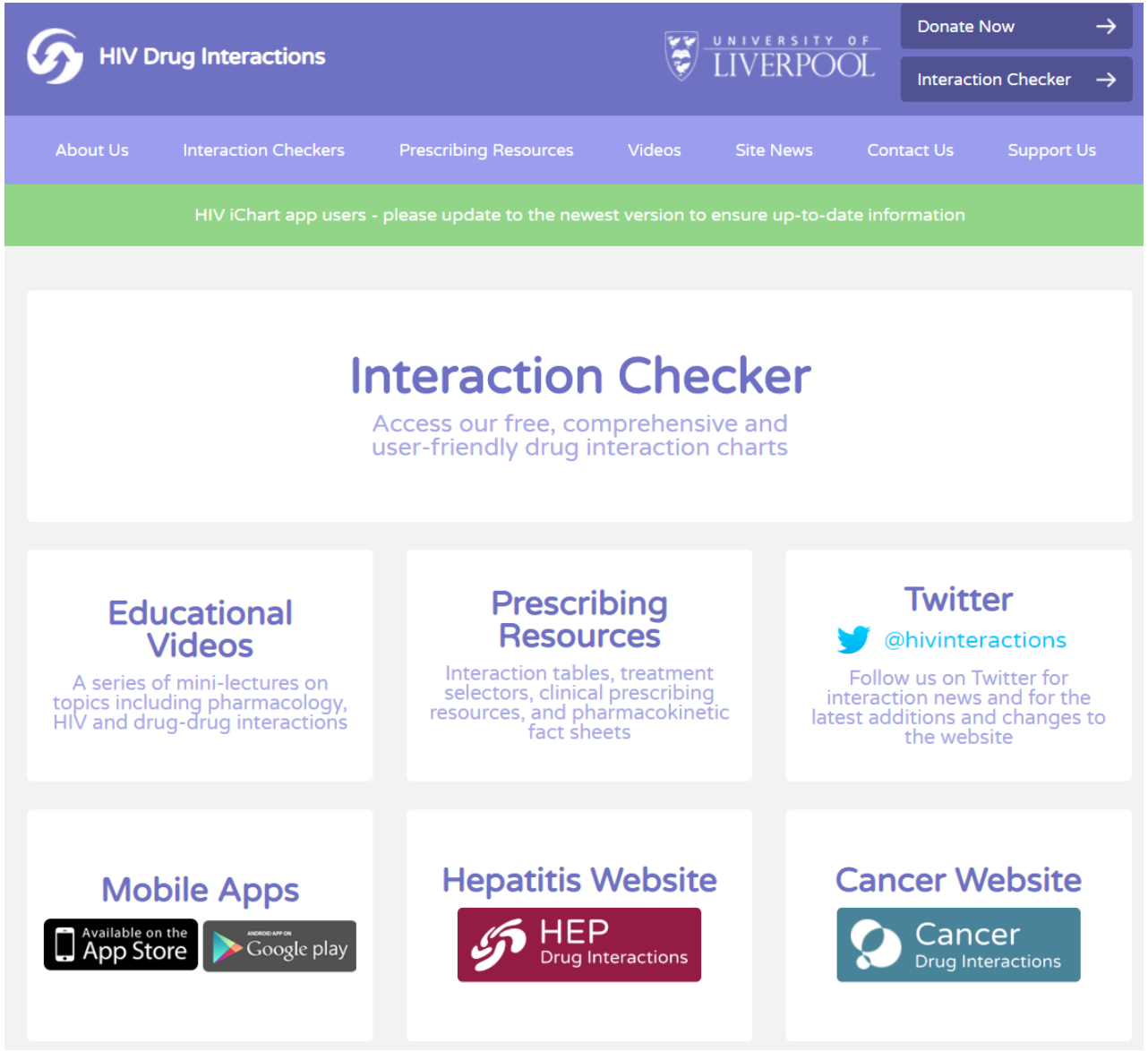


TAKE-HOME MESSAGES FROM THIS CASE

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.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