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ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Clinical Grand Round Case

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- Fever
- Skin rash
- Odynophagia

57 year old male Accountant

- UK born, lived in South Africa > 20 years
- New diagnosis of HIV, 2 months ago
  - CD4 count 11
  - HIV viral load 165,958 copies/mL

Background

- At time of HIV diagnosis, over 2 admissions, treated for
  - Late latent Syphilis (**+ve EIA, +ve TPPA**, -ve RPR, CSF normal –ve PCR)
  - *Pneumocystic jirovecii* pneumonia **PCR +ve** on BAL
    - **LOW Beta D Glucan 144pg/mL** (cut off 80pg/mL)
  - BAL and CSF AFB and fungal culture –ve
  - Mild confusion, MRI brain NAD, CSF clear, no growth
  - Severe oral/pharyngeal candidiasis
    - Responded to antifungals (2/52 high dose fluconazole)
  - Face and upper trunk skin lesions ?molluscum contagiosum
- Commenced tenofovir, emtricitabine and dolutegravir 2 months prior to third admission.

Travel history

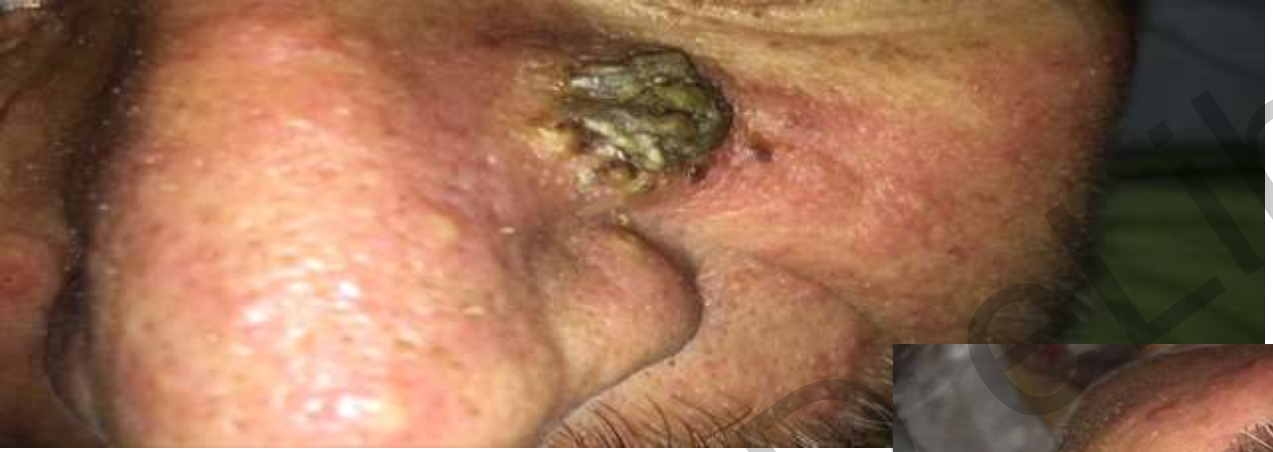
- Lived and worked South Africa for 20 years, travelled Botswana, Zambia, Zimbabwe
- Last 5 years tourism to India (Goa), Kenya, Marrekesh and Corfu

Represented to Hospital

- Fever
- Worsening skin rash
- Odynophagia

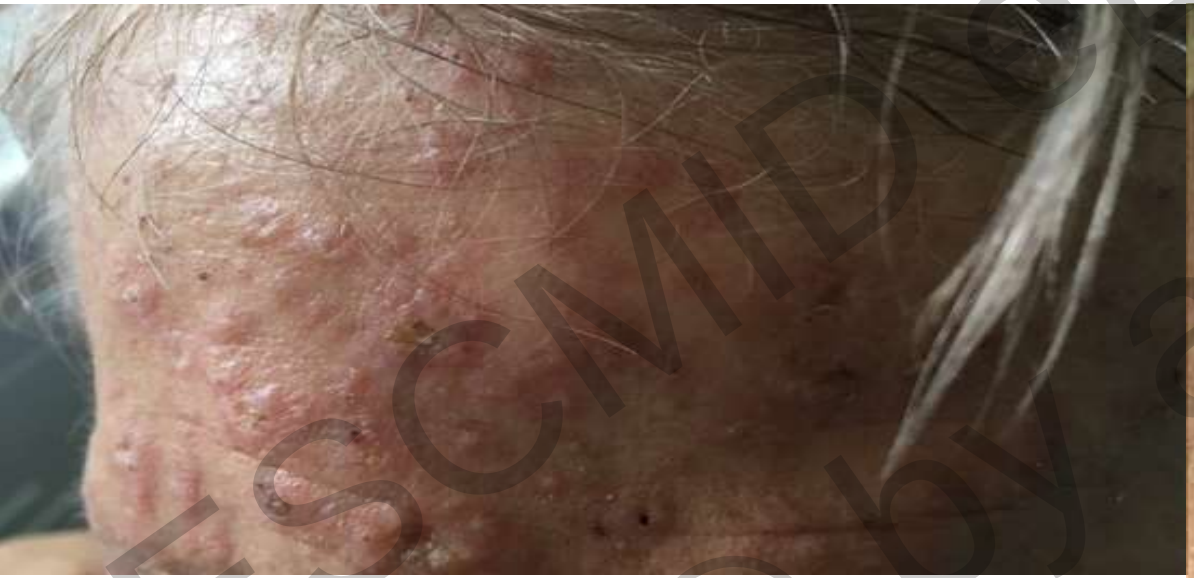
Examination Findings

- Cachexia
- Extensive oral ulceration
- Hyper-keratotic lesion on nose
- Widespread, erythematous papular lesions of face and trunk
- Mild confusion

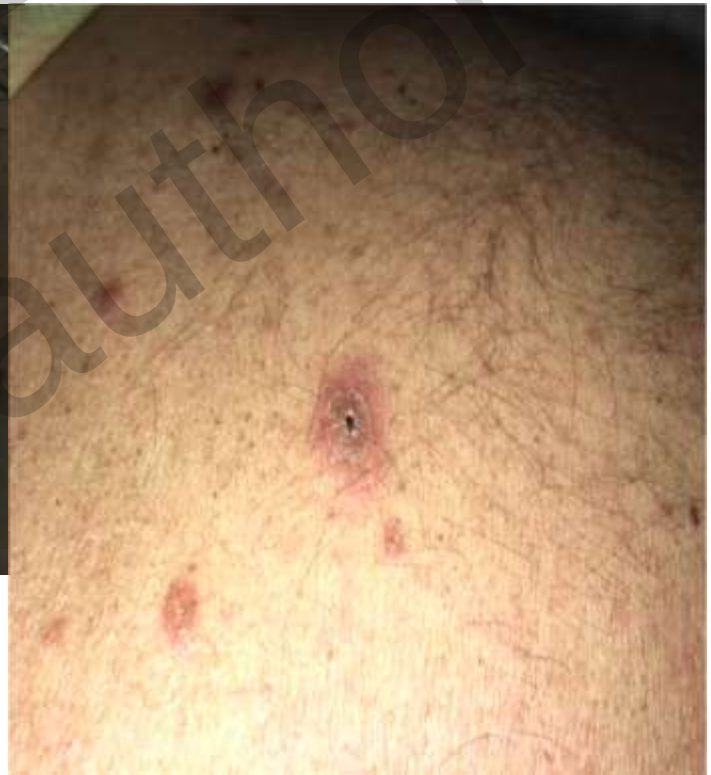


Photos courtesy of Dr. Claire Thomas

Forehead



Abdomen



Photos courtesy of Dr. Claire Thomas

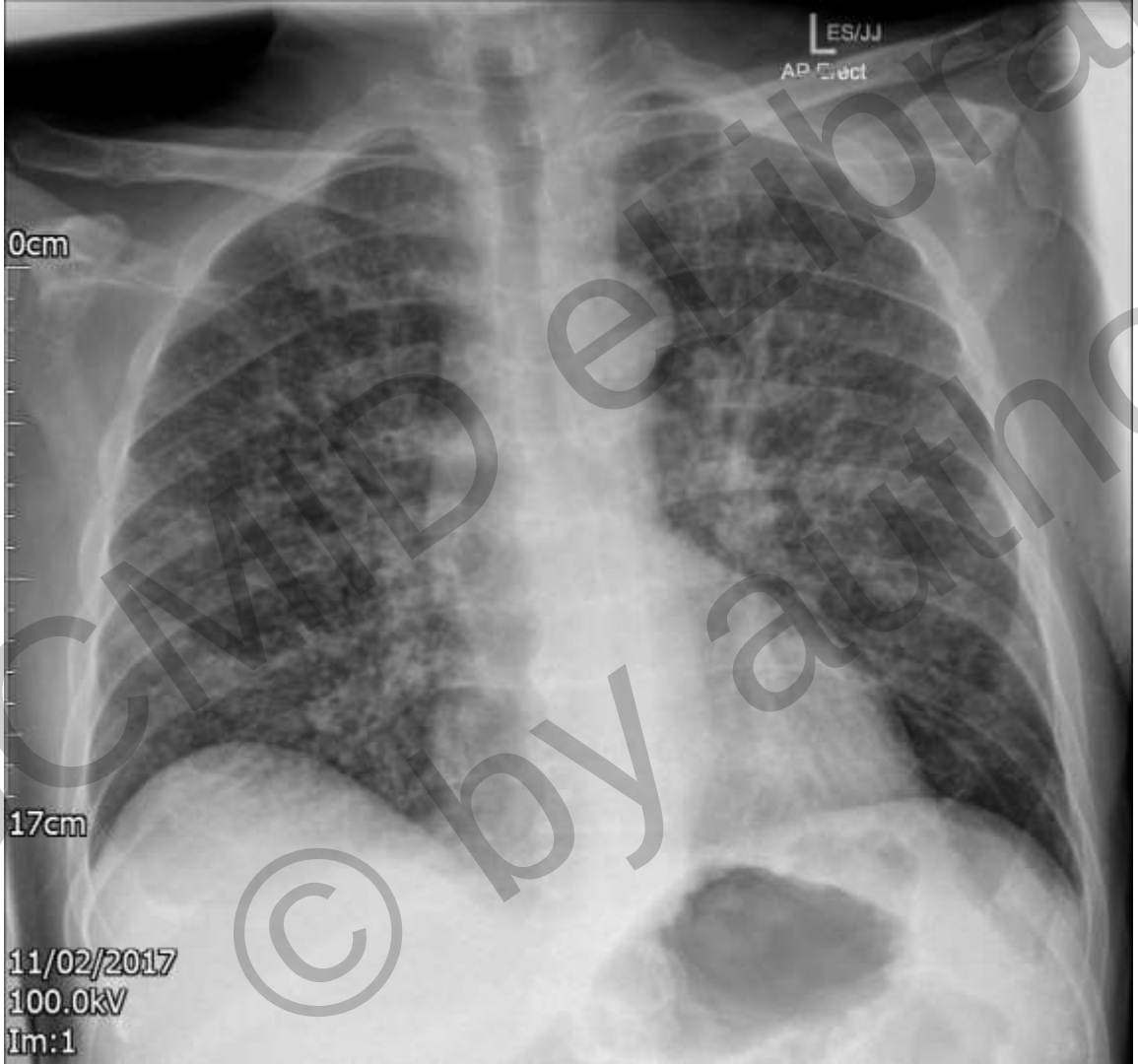
Blood results

Test	Result	Reference range
Haemoglobin	87	135-180 g/L
White cell count	4.5	4.0-11.0 X 10^9/L
Neutrophils	2.7	2.0-7.5 X 10^9/L
lymphocytes	1.3	1.0-4.5X 10^9/L
Eosinophils	0.0	0.0-0.4 X 10^9/L
Alanine Transaminase	50	7-55 U/L
Alkaline Phosphatase	389	45-115 U/L
Bilirubin	12	2.0-20 umol/L
Albumin	15	35-50 g/L
Sodium	126	135-145 mmol/L
Potassium	3.6	3.5-5 mmol/L
Urea	4.7	2.9-8.2 mmol/L
Creatinine	36	80-130 umol/L
C reactive protein	54	<5 mg/L

Panel differential diagnosis?

Management

- Broad spectrum antibiotics
- Anidulafungin 200mg loading then 100mg OD, for presumed severe candidiasis
- NG tube sited for nutritional support
- Cross sectional imaging planned
- Full infection screen sent off
- HIV status: CD4 51, VL undetectable



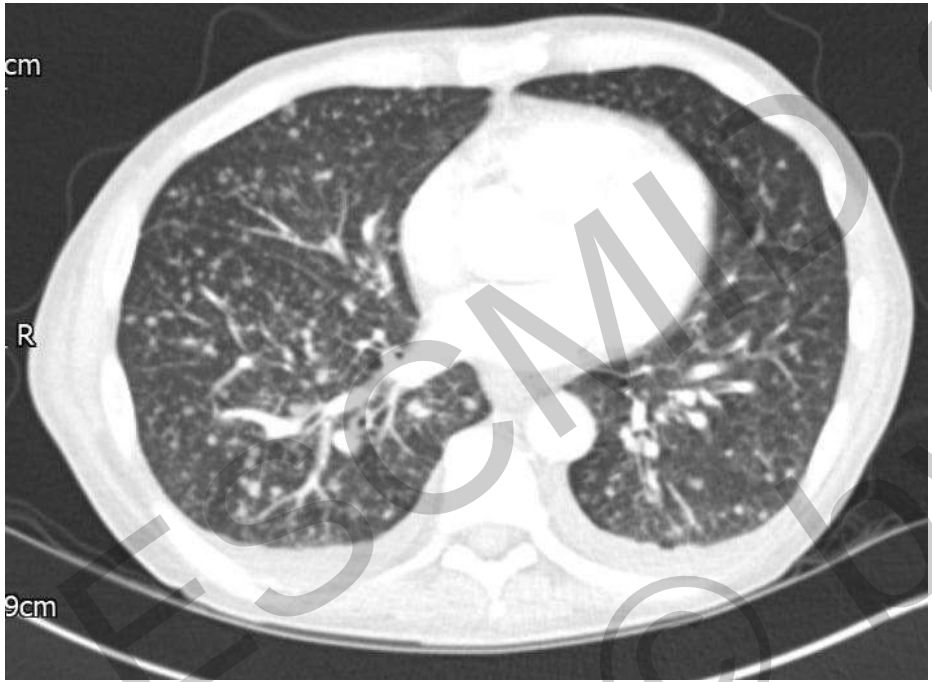
Deterioration 24 hours into admission

- Increased confusion
- Ongoing fever > 38.5°C
- Respiratory deterioration
- CRP 128

- Management
  - Piperacillin-tazobactam switched to meropenem 2g TDS
  - Aciclovir 10mg/kg added
  - CT head and lumbar puncture

Test	Admission bloods	Repeat	Reference range
Haemoglobin	87	88	135-180 g/L
White cell count	4.5	4.2	4.0-11.0 X 10^9/L
Neutrophils	2.7	3.3	2.0-7.5 X 10^9/L
lymphocytes	1.3	0.6	1.0-4.5X 10^9/L
Eosinophils	0.0	0.0	0.0-0.4 X 10^9/L
Alanine Transaminase	50	40	7-55 U/L
Alkaline Phosphatase	**389**	**687**	45-115 U/L
Bilirubin	12	13	2.0-20 umol/L
Albumin	15	11	35-50 g/L
Sodium	126	134	135-145 mmol/L
Potassium	3.6	3.2	3.5-5 mmol/L
Urea	4.7	3.7	2.9-8.2 mmol/L
Creatinine	36	38	80-130 umol/L
C reactive protein	**54**	**128**	<5 mg/L

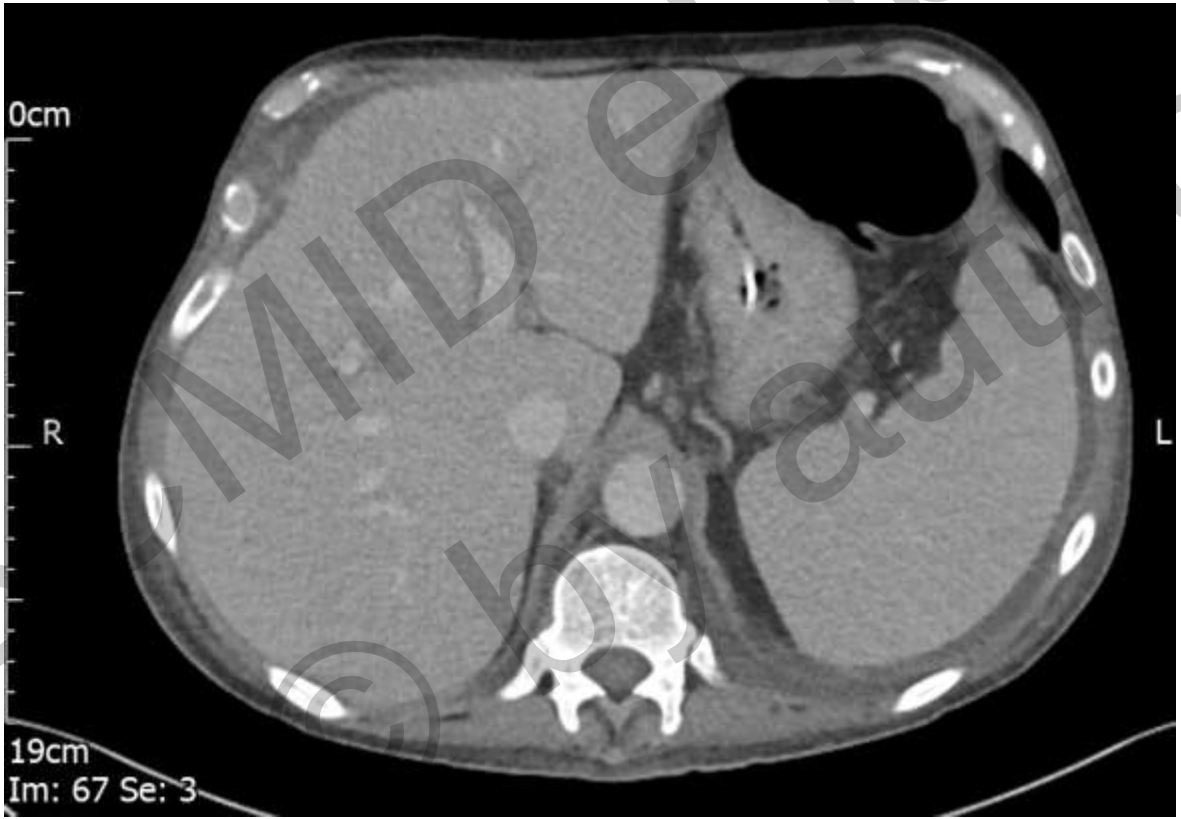
CT findings



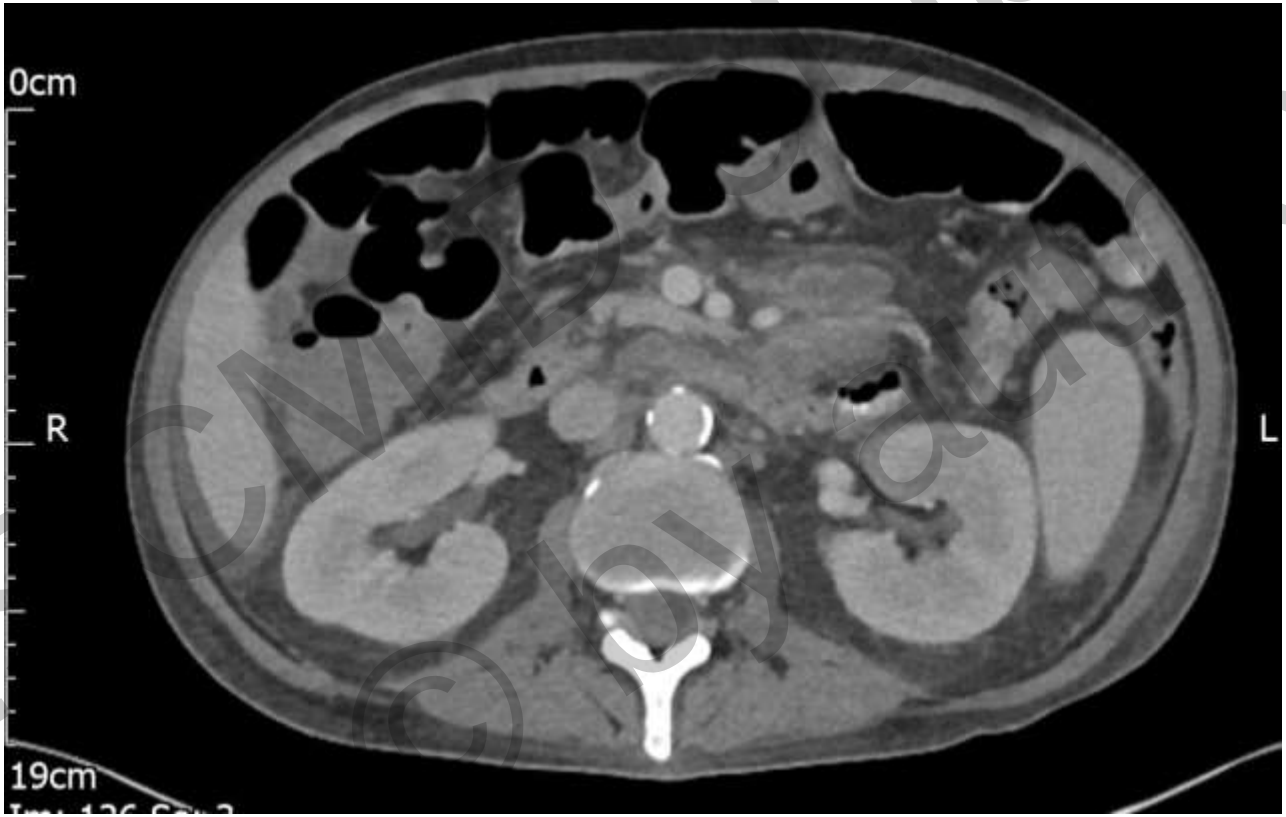
- Extensive pulmonary nodules
- Widespread axillary, mediastinal and intra-abdominal lymphadenopathy
- Splenomegaly
- Moderate ascites

“Features which would be consistent with mycobacterial disease”

CT abdomen



CT abdomen



Panel Management Plan

Further management

- Patient stablised on treatment
- Mycobacterial blood cultures repeated
- Urgent Bronchoscopy
- CT guided biopsy of intra-abdominal lymph nodes

- Chase biopsy result of skin and hard palate

Sample	Target	Result
Serum/EDTA	**CD4** HIV Viral load CMV viral load EBV viral load HHV8 viral load **Beta-D-glucan** **Aspergillus antigen** Histoplasma serology Hepatitis C Hepatitis B Sag/Core Ab **TB IGRA** CRAG	**51** Undetectable 448 copies/mL 244 copies/mL Pending **140 increase to 463pg/mL** **POSITIVE 1.57** (cutoff =1.0) NEGATIVE IgG POSITIVE RNA NEGATIVE NEGATIVE **INDETERMINATE** NEGATIVE
CSF	WCC 0 RCC 240, protein 0.41, glucose1.8 HSV, VZV, enterovirus, CRAG, syphilis, JC virus, AFB	 NEGATIVE
Bronchoalveolar lavage	Acid fast bacilli smear M.Tuberculosis complex PCR PCP PCR	NEGATIVE NEGATIVE NEGATIVE
Radiology	CT Brain	Diffuse cerebral atrophy

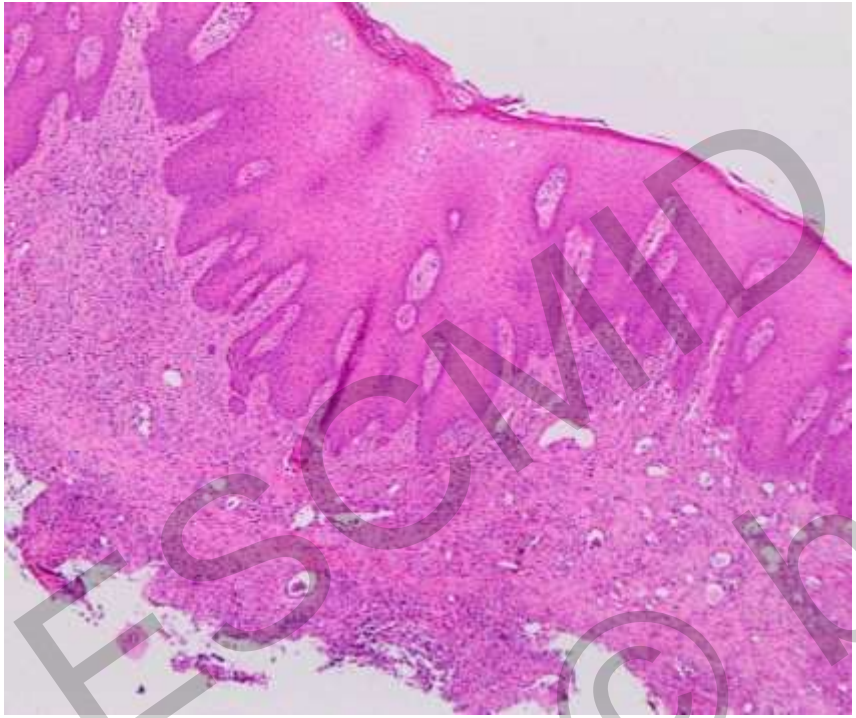
Further progress

- Oropharyngeal biopsy dropped into formalin (!)
  - None sent for MC&S
  - Histological examination in progress..
- Radiological abdominal biopsy unable to access lymph node- fluid aspirated

Management

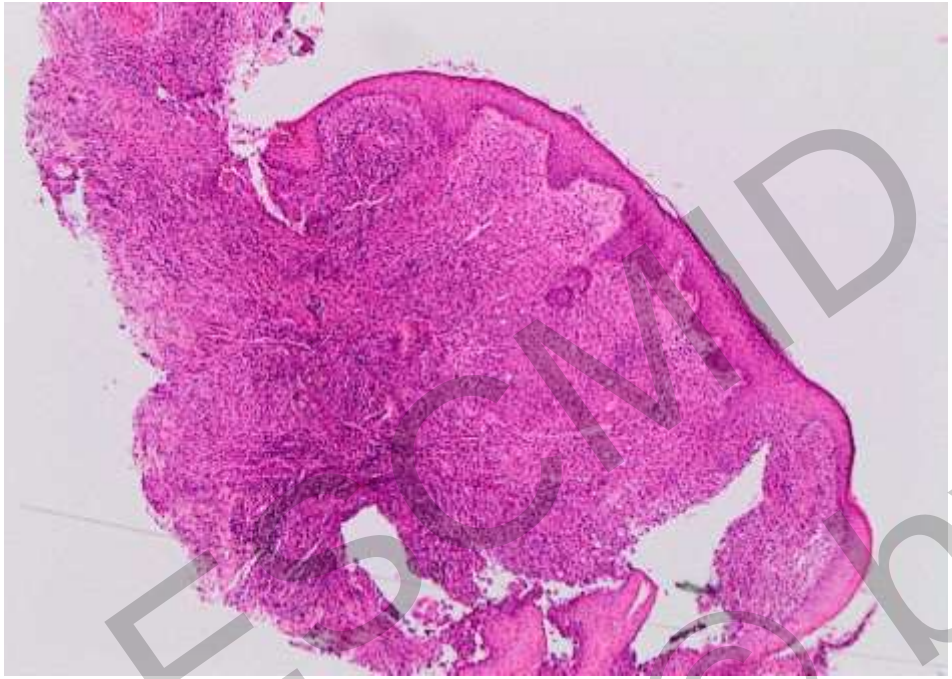
- Start quadruple therapy for Mycobacterium tuberculosis
- Rifampicin, Isoniazid (pyridoxime), Ethambutol, Pyrazinamide
- Aciclovir stopped as CSF negative and no evidence of HSV

Histology of hard palate



“Ulcerated squamous epithelium with hyperplasia and some nuclear atypia, inflamed granulation tissue but no definitive evidence of dysplasia or invasive malignancy”

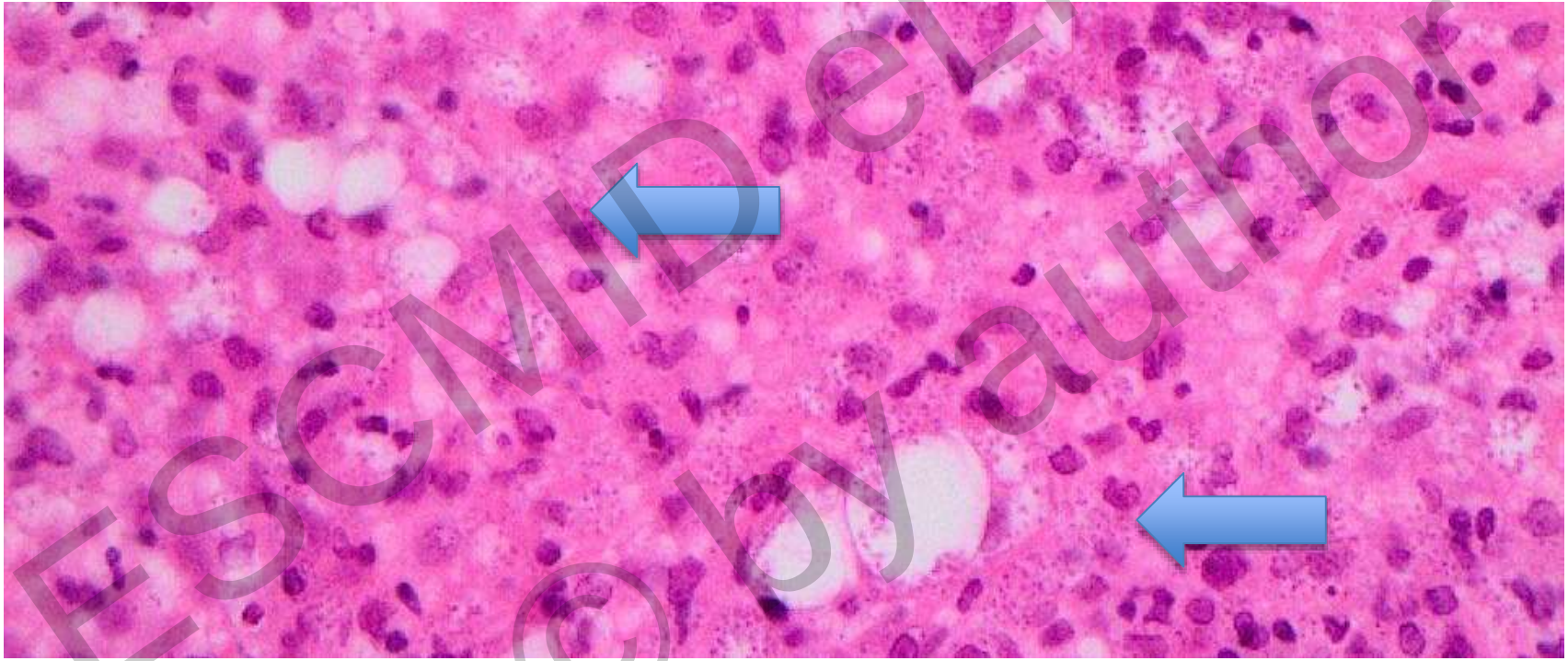
Histology of Nose lesion



"Multiple levels showing surface squamous epithelium and underlying dermis showing sheets of histiocytes which show tiny intracytoplasmic oval eosinophilic bodies with eccentric dot like nucleus and possible rod-like kinetoplast (amastigotes) no AFB or fungal hyphae identified.

Granulomatous and histiocytic inflammation consistent with leishmaniasis"

Nose Lesion H&E stain



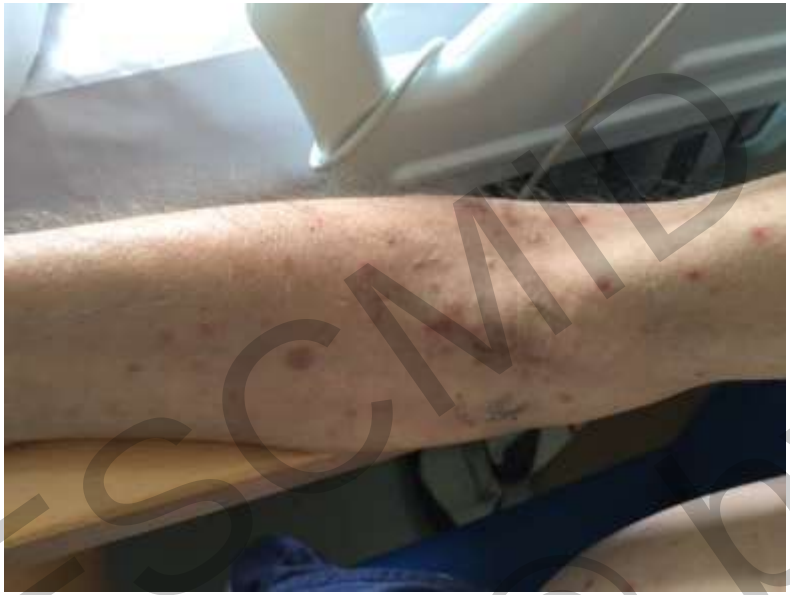
Differential diagnosis ?

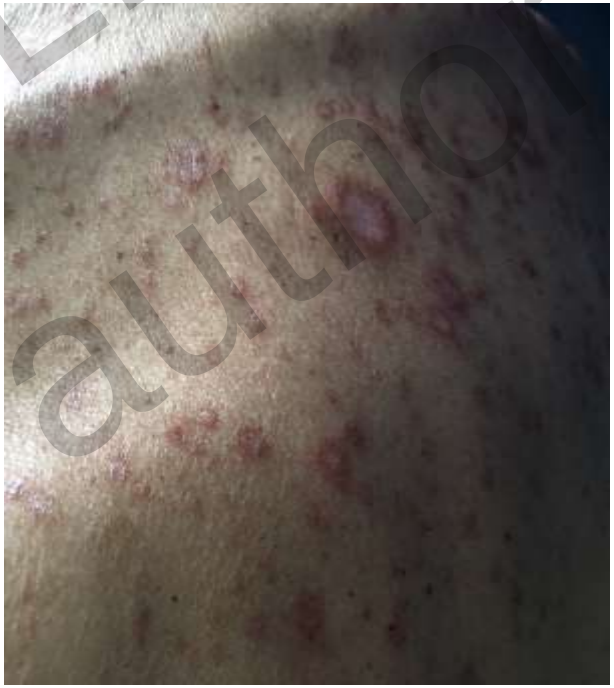
A. Disseminated Tuberculosis
B. Leishmaniasis
C. Disseminated Fungal infection
D. Immune Reconstitution Syndrome
E. None of the above
F. All of the above

Management

- Liposomal Amphotericin 3mg/kg commenced
- Bone marrow aspirate organised
- TB therapy continued
- Skin lesions unchanged

Skin lesions





Pictures courtesy of Dr. Claire Thomas

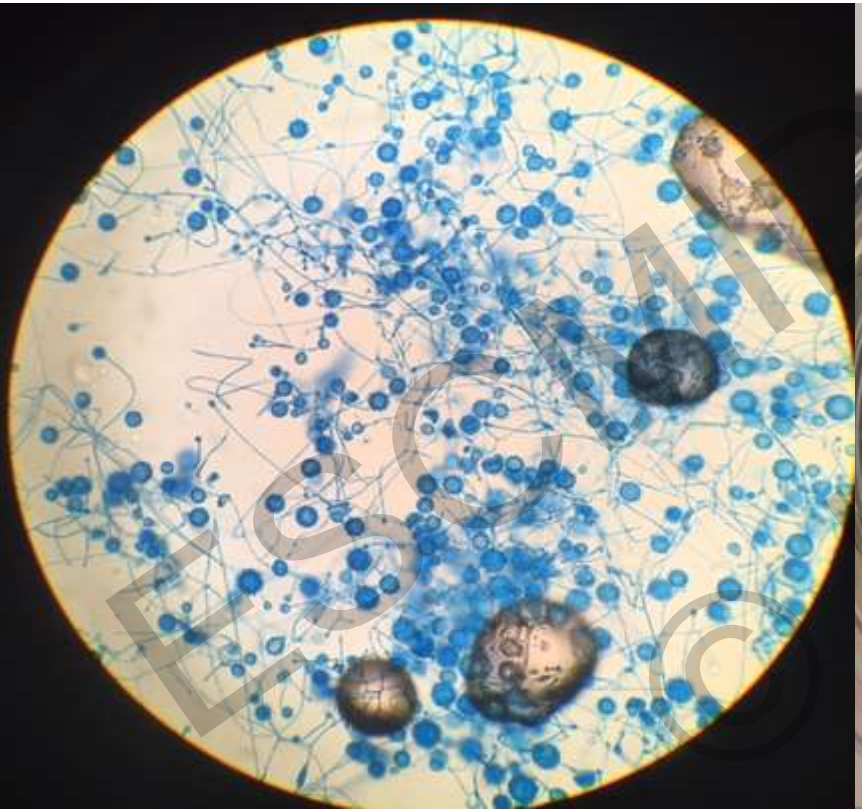
Bone Marrow Trephine & Aspirate

"Consistent with HIV related myelodysplasia, no evidence of Leishmania"

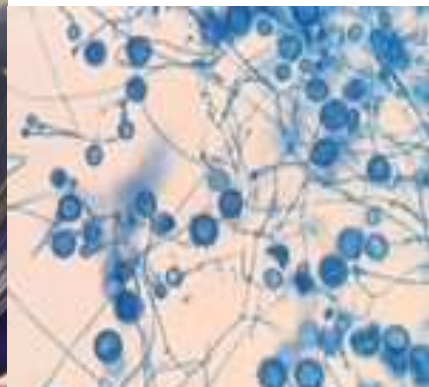
Further results from Bronchoscopy at 4.5 weeks…

25°C

37°C



Pictures courtesy of Dr. Claire Thomas & Dr. Christina Petridou



Dimorphic fungi

- Cultured after 4.5 weeks
- 37°C white yeast with ovoid thick walls
- 25°C hyaline hyphae with tuberculated macroconidia and cigar shaped microconidia

Final Microbiological Diagnosis

- Confirmed as ***Histoplasma capsulatum var capsulatum***

- Review of skin biopsy: **Intracellular Histoplasma**

Progress

- Anti-TB therapy and Meropenem stopped
- Liposomal Amphotericin 3mg/kg
  - Plan to step down to Itraconazole 200mg TDS after 4-6 weeks(CNS concerns), then 200mg BD for 12 months and review
  - Therapeutic drug monitoring after 5-7 days
    - aiming for pre-dose trough level of >0.5mg/L
- Slow, consistent clinical recovery
- Bone Marrow grew *Histoplasma capsulatum var capsulatum* after 2.5 weeks
- Beta D glucan 114→463, fell to 304 on treatment
- Histoplasma serology negative x2

Learning points

- *Histoplasma capsulatum* is globally endemic where a suitable environment exists
- Serology may be negative if HIV positive
- Long latent period
- *Histoplasma* can mimic the intracellular amastigotes of *Leishmania*
- **Prolonged** fungal culture (>5weeks) is required at 37°C and 25°C
- ?Disease severity and fungal markers attenuated by short courses of antifungals
- **<u>Biopsy skin lesions for fungal culture early</u>**

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