ECCMID Clinical Grand Rounds

VIENNA, AUSTRIA 2017

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History of Present Illness

- 65 year old African American man who presented to an outside hospital with the complaint of chronic right sided back pain, abdominal pain, headache and flank pain with an initial white blood cell count of 44.8 x 10^9 cells/L
- CT of the chest and abdomen (on presentation)
  - Single right upper lobe nodule
  - Retroperitoneal lymphadenopathy
  - T10 lytic lesion of the superior end plate
- Started on IV vancomycin and IV cefepime

Past Histories

- Past Medical History : no diagnosed medical problems
- Surgical History: R toe amputation due to trauma
- Outpatient medications : none
- Family history:
  - history of unknown type of leukemia in maternal uncle, other unspecified solid cancers in family members
- Alcohol, Tobacco, Illicit Drugs:
  - EtOH use 1-2 times per week, he was a former smoker with 15 pack year history (quit tobacco usage 2 months prior to admission), denies any illicit drug use or IV drug use

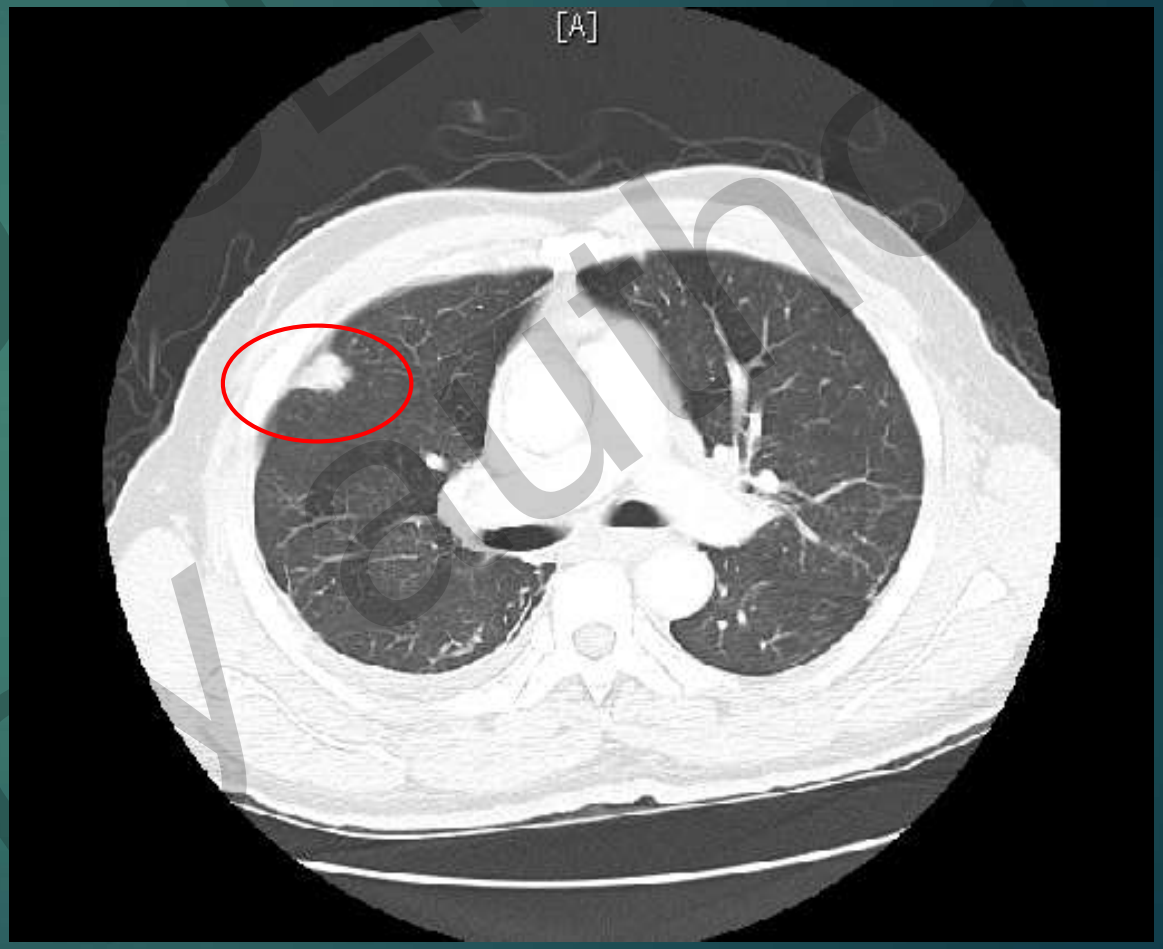
Physical Examination

- **Tmax 38.3C**, BP 177/94, HR 84, RR 18, pulse ox 100% RA
- HEENT: No significant findings
- **CVS: regular rate, normal rhythm, ns1s2, + 3/4 SEM left sternal border, + s4 , no carotid bruit, no JVD**
- Lungs: No significant findings
- Abdomen: No significant findings
- Back: **no tenderness to palpation over C/T/L spine, no paravertebral tenderness**
- GU: No significant findings
- Skin: No significant findings
- Ext: No significant findings
- Neuro: **No focal neurologic deficits, CN II-XII grossly intact**

Initial Laboratory Findings

- WBC: 44.8 x 10^9 cells/L (↑↑)
- Platelets 100 x 10^9 cells/L (↓)
- HgB 110 g/L/MCV 99.1 fL (↓)
  - Differential: 85% lymphocytes (↑), 30% neutrophils, no band forms, ANC 1.0, ALC 40,000 (↑↑)
- Normal Chemistries
- Pro-calcitonin 0.06

Initial Imaging



Differential Diagnosis?

Treatment Decision?

- Patient grew yeast in 2 out of 4 blood culture bottles (aerobic bottles)

Initial Treatment Plan

- He was empirically started on an echinocandin (IV Micafungin)
- After being started on IV micafungin he was transferred to our institution for a higher level of care
- Infectious Diseases consulted

Any Further Investigations?

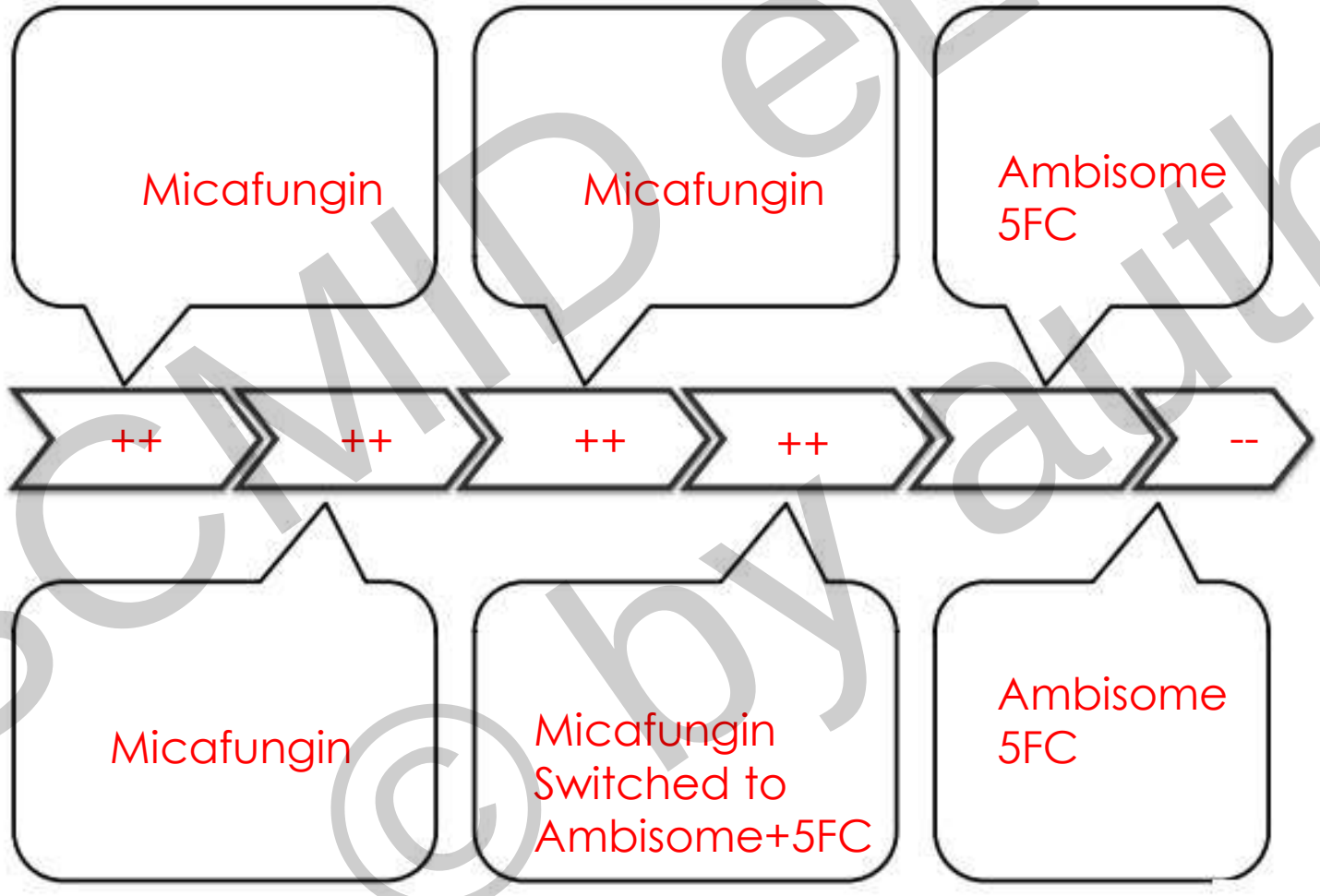
Hospital Course

Patient was immediately started on Liposomal amphotericin B + 5FC
Due to complaints of a headache and in the setting of destructive T10 lesion he also underwent a LP

Cryptococcus serum antigen : positive, titer: 1:320 (↑)

CSF Fluid	Results
Opening Pressure	33mmH_2O (↑)
WBC Count	456 cells/microL (↑)
Differential	Lymphocyte predominance
Glucose	48 mg/dL (↓)
Protein	60 mg/dL (normal)
Cryptococcal Antigen Titer	1:80 (↑)
CSF Fungal Culture	Cryptococcus Neoformans (Fluconazole MIC1)

Timeline



Diagnosis!

Blood culture identification

	Cryptococcus neoformans
Drug	MIC..
Fluconazole	4

Initial Flow Cytometry -peripheral blood

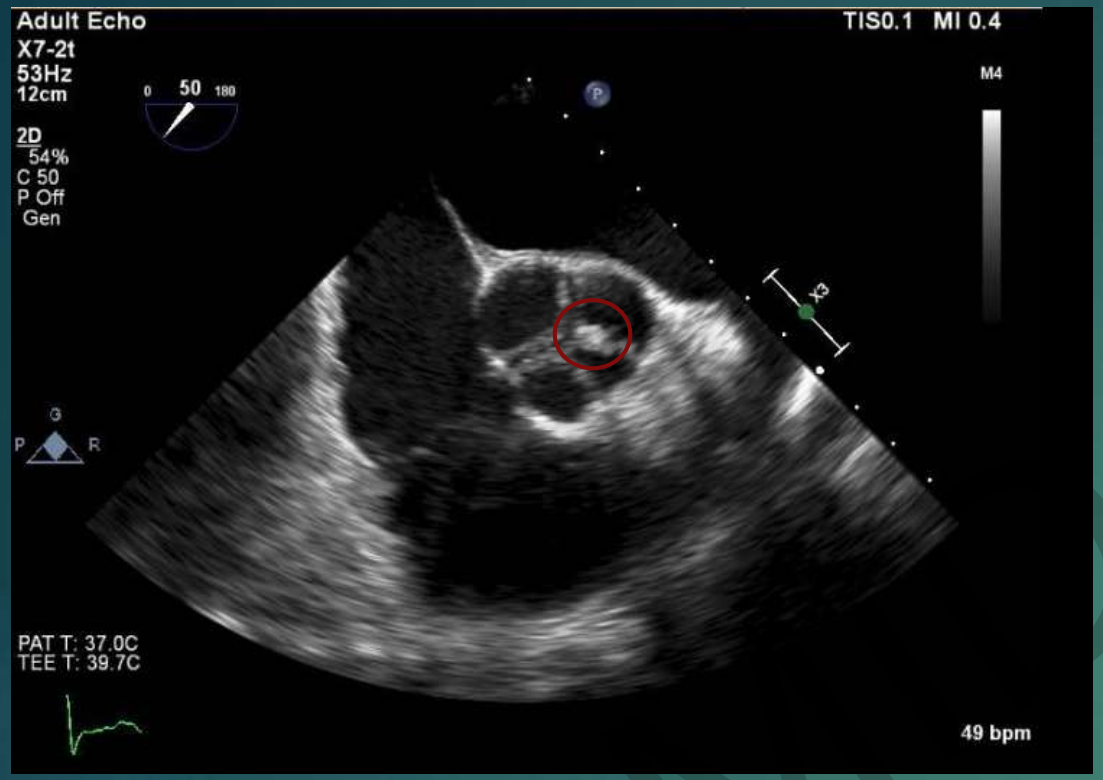
Most consistent with chronic lymphocytic leukemia
Or small lymphocytic lymphoma – B cell type

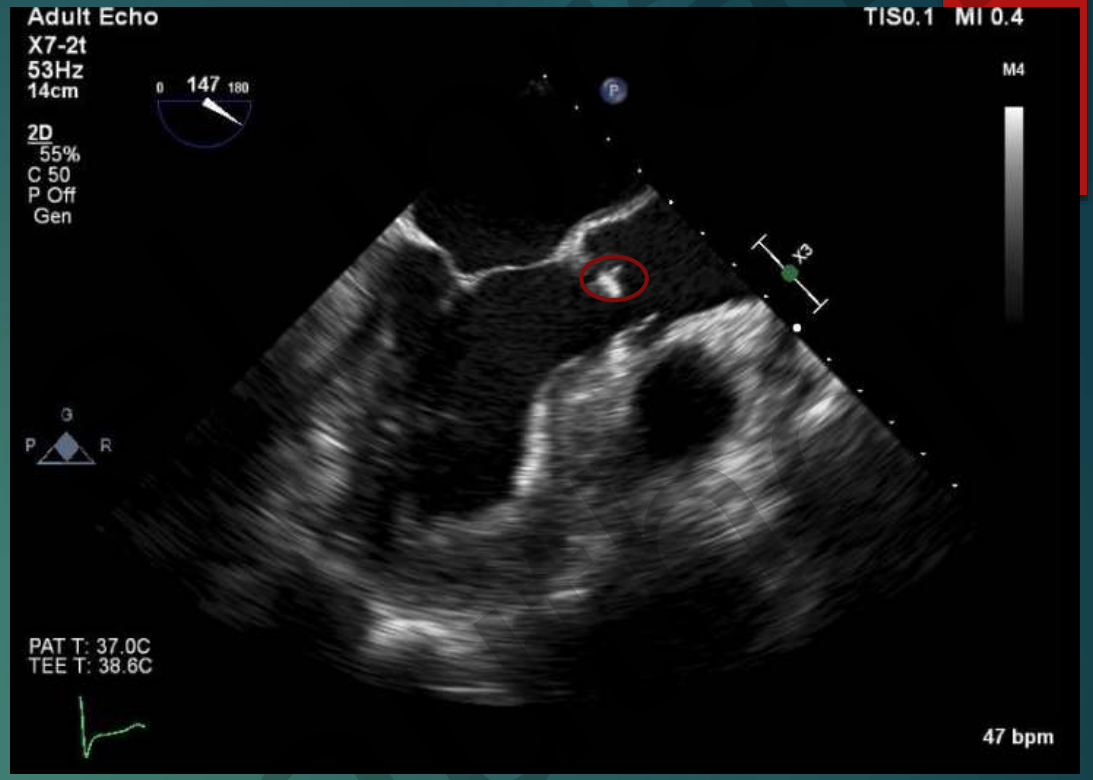
Cell Surface Marker Results

CLUSTER	SPECIFICITY	%GATED CELLS GATE # 1
CD2	Pan-T	4
CD3	Pan-T	5
CD4	Helper-T	3
CD8	Suppressor-T	1
CD5	T,B Subsets	97
CD7	T-ALL Ag.	4
CD10	Common ALL (CALLA)	<1
CD16	Natural Killer Cells	<1
CD56	Natural Killer Cells	5
CD19	Pan-B	95
CD20	Pan-B	94
CD22	Restricted-B	91
CD23	B Cells	61
Kappa		22
Lambda		77
CD38	Activated T/B cells, Blasts	12
FMC7	B cells	11
CD11c	Monocytic/HCL Ag	53

Interpretation

Flow cytometric immunophenotyping of peripheral blood, selectively gated using CD45 versus side scatter, discloses a CD45 bright lymphoid population dominated by CD19/20/22 positive B lymphocytes which coexpress CD5, partially express CD23 and CD11c (CD10 and FMC7 negative), and show monotypic expression of lambda light chain with dim fluorescence intensity. This phenotype is compatible with a B lineage lymphoproliferative disorder and is most characteristic of chronic lymphocytic leukemia/small lymphocytic lymphoma, B cell type. Clinical and morphologic correlation is required for definitive evaluation.



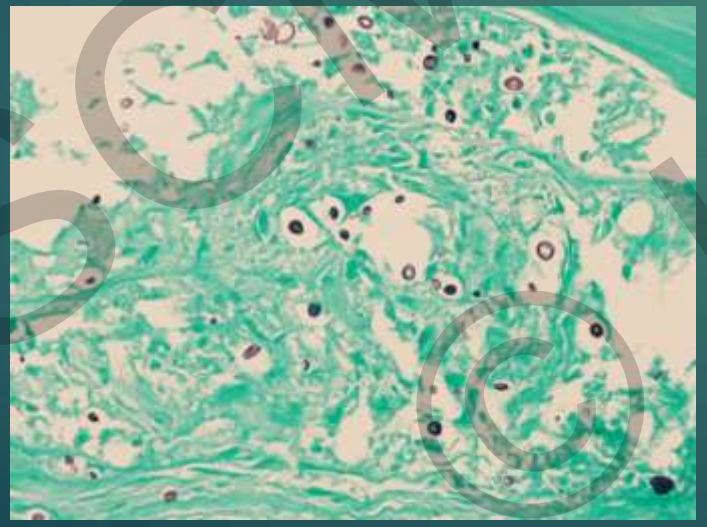


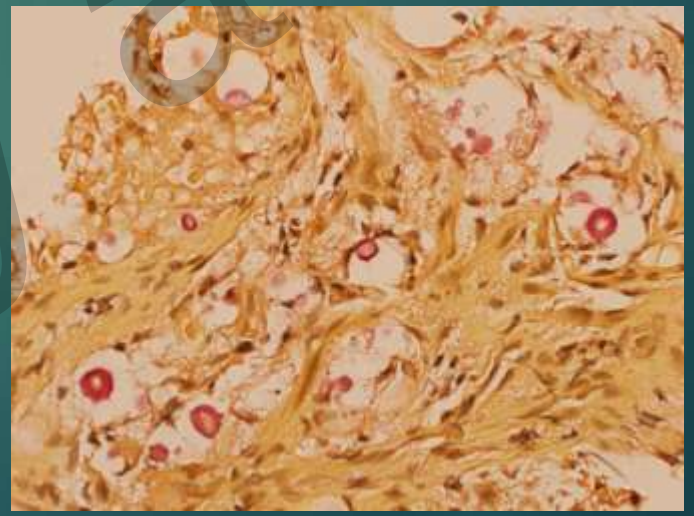
TEE Results:
There is calcification of the left coronary cusp of the aortic valve.
There is a small (8 mm) mobile mass attached to the cuff that likely is a vegetation.

IR/CT guided biopsy of T10 spinal lesion

Fungal Culture (Microbiology)

	Cryptococcus neoformans
Drug	MIC..
Fluconazole	6





Cryptococcal Endocarditis

- Very little literature on cryptococcal endocarditis
  - Most seen in prosthetic valve endocarditis
- Even less literature on native valve endocarditis
- 4-5 case reports ranging from 1957 to 2011

Clin Infect Dis. 2001 Jan;32(1):50-62. Epub 2000 Dec 12.

Pathogen(s)	1965–1971	1972–1979	1980–1987	1988–1995	Total
Aspergillus species[a]	18 (28)	20 (25)	14 (21)	14 (24)	66 (24)
Candida albicans	20 (31)	18 (23)	14 (21)	14 (24)	66 (24)
Non-*albicans* species of *Candida*[b]	15 (24)	26 (32)	19 (28)	16 (28)	76 (28)
Histoplasma	6 (9)	4 (5)	4 (6)	1 (2)	15 (6)
Other[c]	5 (8)	12 (15)	17 (25)	13 (22)	47 (17)
Total	64 (100)	80 (100)	68 (100)	58 (100)	270 (100)
Ratio of:					
Non-*albicans* species of *Candida* to *C. albicans*	0.75	1.4	1.4	1.1	1.2
Aspergillus to *Candida*	0.5	0.5	0.4	0.5	0.5

NOTE. Data are no. (%) of pathogens isolated except as otherwise indicated.

[a] Number of patients from which each pathogen was isolated was as follows: *A. fumigatus*, 25; *A. flavus*, 8; *A. niger*, 3; *A. clavatus*, 1; *A. terreus*, 5; *A. ustus*, 2; *A. nidus*, 1; *Aspergillus* unspecified, 11.

[b] Number of patients from which each pathogen was isolated was as follows: *C. glabrata/torulopsis*, 10; *C. tropicalis*, 10; *C. pseudotropicalis/kyfer*, 1; *C. parapsilosis*, 33; *C. krusei*, 4; *C. stellatoidea*, 2; *C. guillermondii*, 4; *C. paraktusei*, 2; non-*albicans* species of *Candida* unspecified, 12.

[c] Number of patients from which each pathogen was isolated was as follows: *Mucor* species, 3; *Trichosporon beigelii*, 1; *Trichosporon* species, 1; *Cryptococcus neoformans*, 3; *Pseudallescheria boydii*, 4; *Phialophora jeanselmei*, 3; *Curvularia lunata*, 1; *Trichophyton* species, 2; *Microsporum* species, 1; *Penicillium marneffei*, 3; *Fusarium* species, 1; *Paecilomyces* species, 6; *Penicillium chrysogenum*, 1; *Rhodotorula* species, 1; *Conidiobolus* species, 1; *Scedosporium* species, 1; *Engyodontium alba*, 1; *Wangiella dermatitidis*, 1; *Exophiala dermatitidis*, 1; *Saccharomyces* species, 1; unspecified fungus, 6.

Patient Outcome

- Continued liposomal amphotericin B + 5FC
- Cardiothoracic surgery deemed not a candidate for valve replacement
- Therapeutic lumbar punctures to manage his intra-cranial hypertension.
- MALDI-TOF which showed *Cryptococcus neoformans var. grubii*.
- Blood cultures cleared by day 5 of induction therapy

Take Home Message/Summary

- Unusual case of disseminated *Cryptococcus grubii* infection with
  - Endocarditis,
  - Spinal osteomyelitis
  - Meningitis
- Possible dysfunction of T-lymphocytes in a host with underlying CLL despite normal absolute neutrophil and lymphocyte counts
- This case highlights hematological malignancies as a well-known risk factor in the pre-AIDS era
- It also points to an inadequate choice of an echinocandin in an immunocompromised host with fungemia, where fungi other than *Candida* may be at play