Cryptococcal meningitis in a child with leukemia

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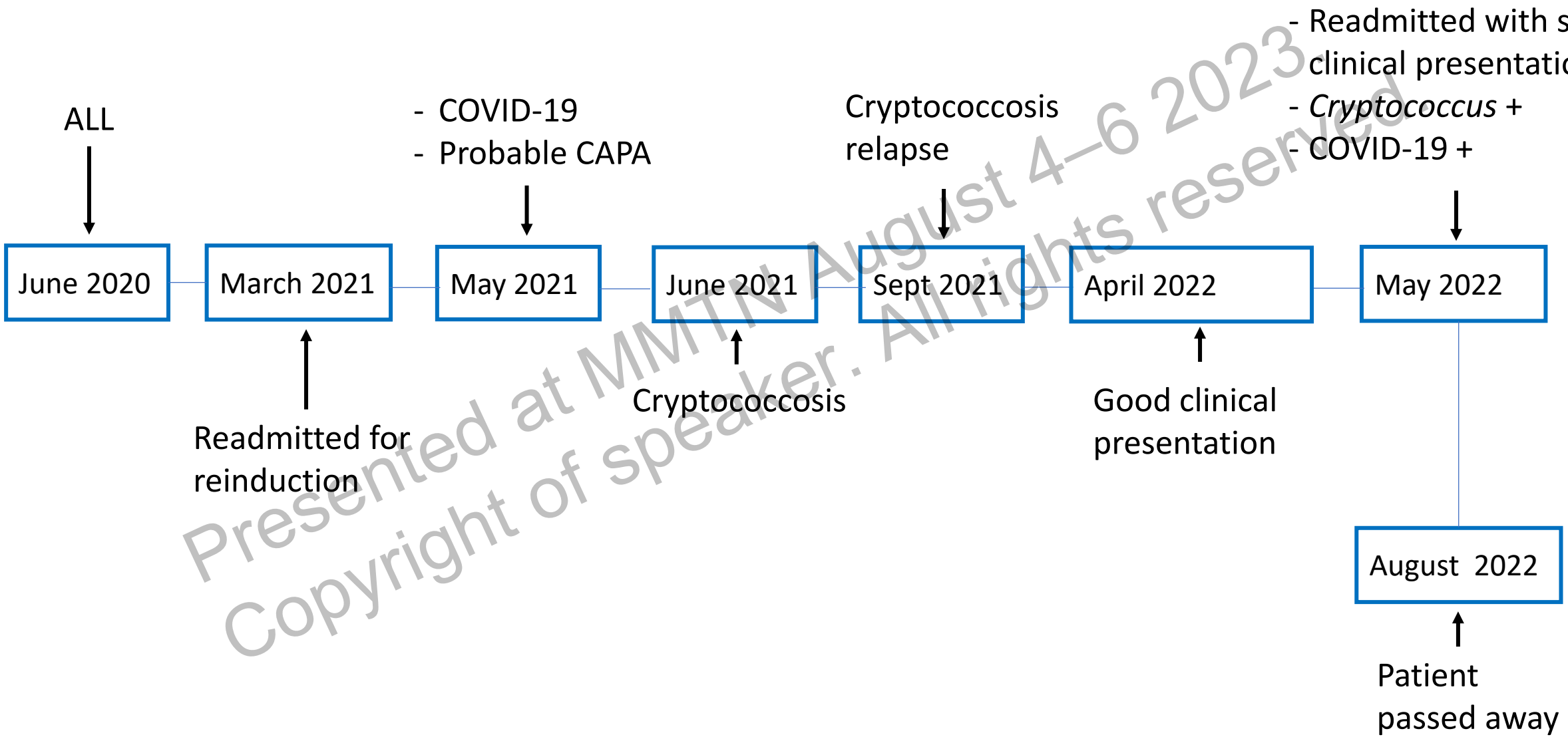
Cryptococcosis

- Cryptococcosis is caused by encapsulated yeast *C. neoformans* (serotype A & D) & *C. gattii* (serotype B & C).
- Nowadays they are elevated to become a separate species
- The source of infection is the environment (soil contaminated by birds dropping, tree hollows, etc.)
- The dehydrated spores are inhaled into the lung & may cause infection mainly the immunosuppressed patients.
- Infection can occur in various organs, esp. the brain
- We report an infection in a child with leukemia

Tree hollows with Cryptococcus
Courtesy of Dr. FE Siagian

Case report's timeline

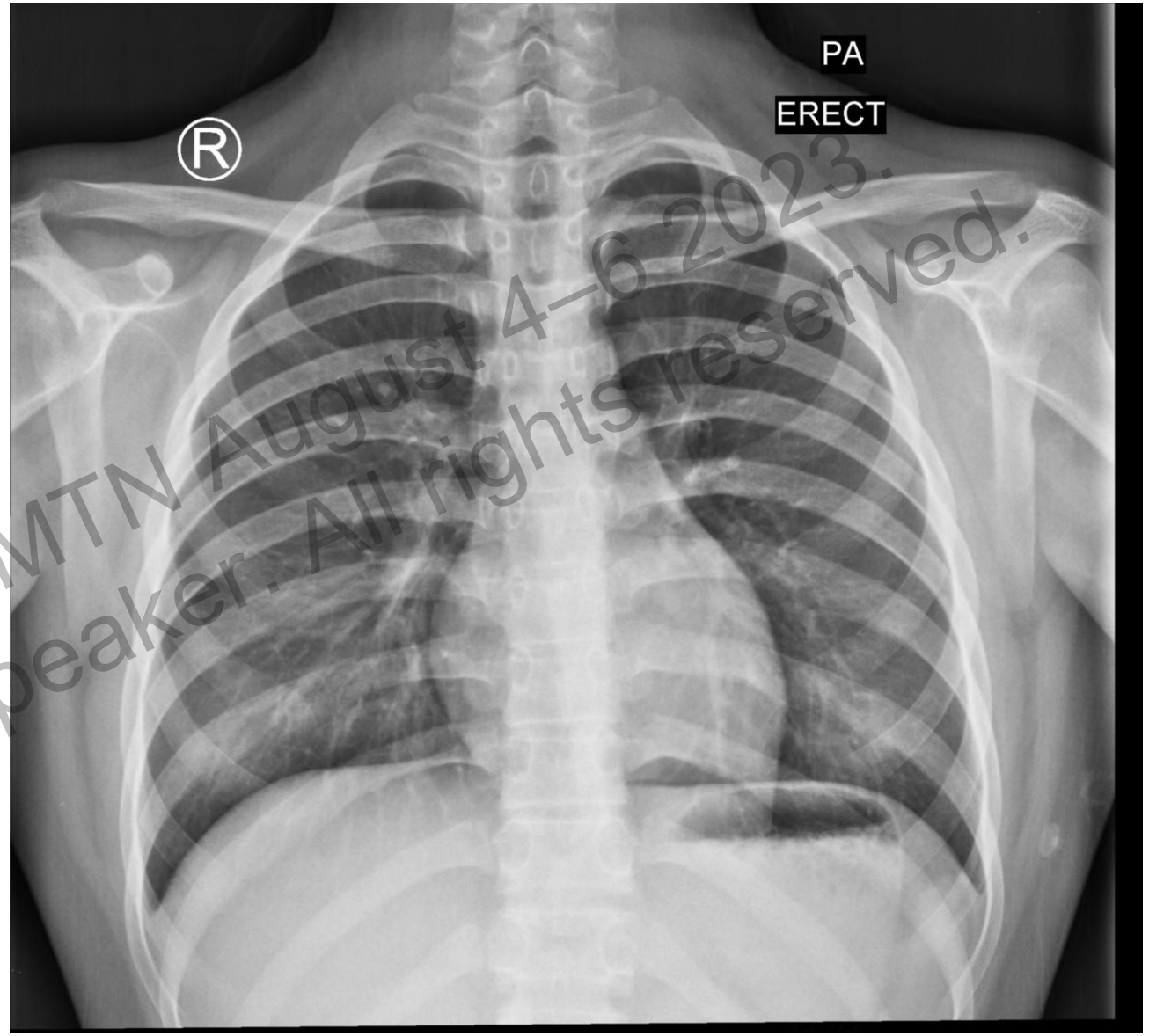


Case report

- A 14-year-old girl suffering from acute lymphocytic leukemia (ALL) since June 2020
- Underwent chemotherapy (oral prednisone, intra-venous vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine & 6 mercaptopurine (6MP) continued by high dose MTX. She completed the treatment
- Discharged from the hospital & in the maintenance therapy with 6 MP & MTX once a week intra thecal and vincristine.
- In March 2021, she was readmitted to the hospital for reinduction, but after first cycle of cytarabine she was suffering from fever, malaise and abdominal discomfort
- Source of infection was searched: the port of catheter on the chest is removed, the tips was cultured & *S. epidermidis* was isolated but blood cultures was negative. Antibiotic was given & clinically improved.

Case report – May 2021; COVID-19

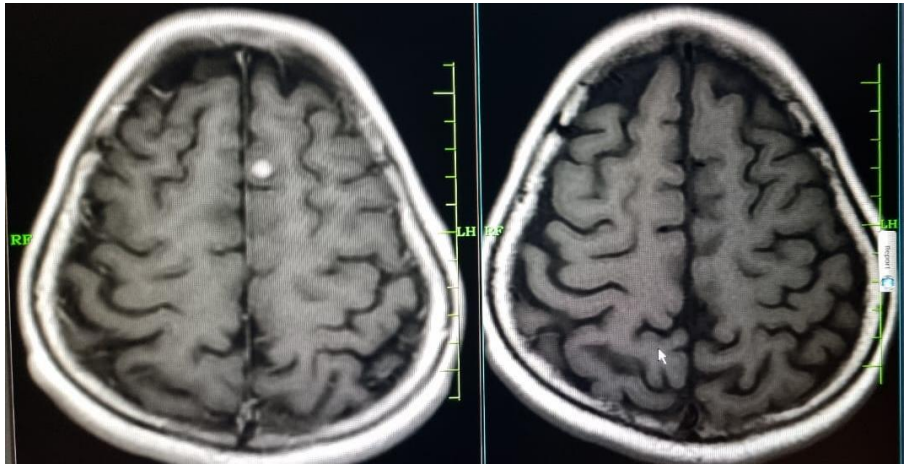
- COVID-19 was detected, the chemotherapy was stopped, CXR showed minimal infiltrate.
- Diagnosis: pneumonia (?)
- Serum *Aspergillus* GM was tested & the index was 1,8
- Probable CAPA.
- Voriconazole was administered for 5 days, continued by itraconazole. Significant improvement



Case report

- A month later (June 2021), complaining of headaches, but the temperature is a little bit above normal & itraconazole was continued.
- Brain MRI: small lesion in the left frontal lobe (5.5x5.5x5.5mm) with minimal perifocal edema. DD/ Chloroma (associated with ALL).
- General condition is good, & plan to be consulted to Neurology & Ophthalmology.
- 6 MP & MTX was restarted.

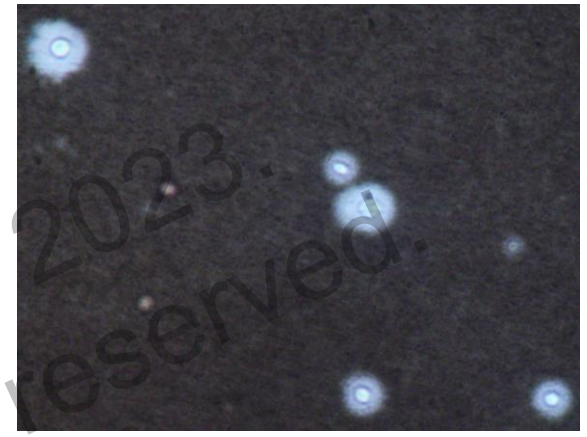
- Ophthalmology: Blurred due to optical neuropathy of ODS:
  - Prednisolone injection 4x250 mg/day for 3 days,
  - Continued by oral methylprednisolone 16 mg 2 tab/day, tapering off 1tab/day,
  - Citicoline 1000 mg.
  - Visual improvement after being treated



MRI with small lesion (June 11th 2021),

Cryptococcosis

- Fever & headache was worsened, an LP (for ALL) was conducted, *Cryptococcus* was found.
- Preparation for the administration of amphotericin B was done.
- High dose of fluconazole was administered (2×700 mg for 3 days cont by 2x 600 mg, 10 days).
- clinical improvement (no fever, no headache).
- At the request of the parents the patient was discharged from the hospital with oral fluconazole (2×200mg/day).
- July 30th 2021, MRI: improvement, compared to previous MRI, 4.5×5mm



India ink & CrAg positive, culture positive, susceptibility test; fluconazole was resistant.

Leucocytes were low

Date	Hb	WBC	Thrombocyte	Liver & renal function
1/5/21	9.7	2.58	168	Within the normal range
3/5/21	9.5	1.95	148	
5/5/21	9.8	1.44	144	
7/5/21	10.3	1.68	169	
4/6/21	9.2	1.02	237	

No blast cells, but neutropenia & lymphopenia were always found

In the 3rd week of September 21

- Readmitted to the hospital due to high fever (38°C) & seizures;
- WBC 0,93; Hb 8.0 thrombocyte 135
- LP was conducted: india ink positive, CrAg positive
- Ambisome was administered & showed clinical improvement; no seizure, headache endure (<), intra cranial pressure decrease
- Hypokalemia was corrected, renal & liver functions were within the normal range
- Discussion: give intra thecal amphotericin B 5mcg/48 h
- LP: India ink positive, culture negative, OP 12 cm H2O

In the 3rd week of September 21 - continued

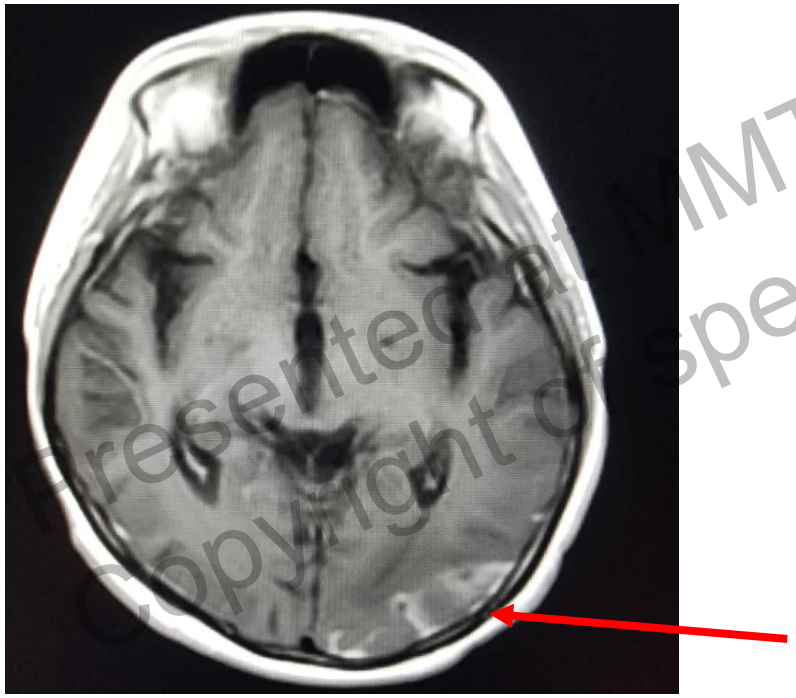
- Peripheral blood: WBC 5,53; Hb 9.2 thrombocytes 113, liver & renal function within the normal range,
- Clinical improvement, no headache, no fever, no seizure, the patient calm, but refuse to eat.
- After 2 weeks of ambisome treatment, cont. by fluconazole 2x200 mg, & intrathecal MTX
- Till the end of November LPs were conducted, the India ink is always positive but culture always negative

April 2022:

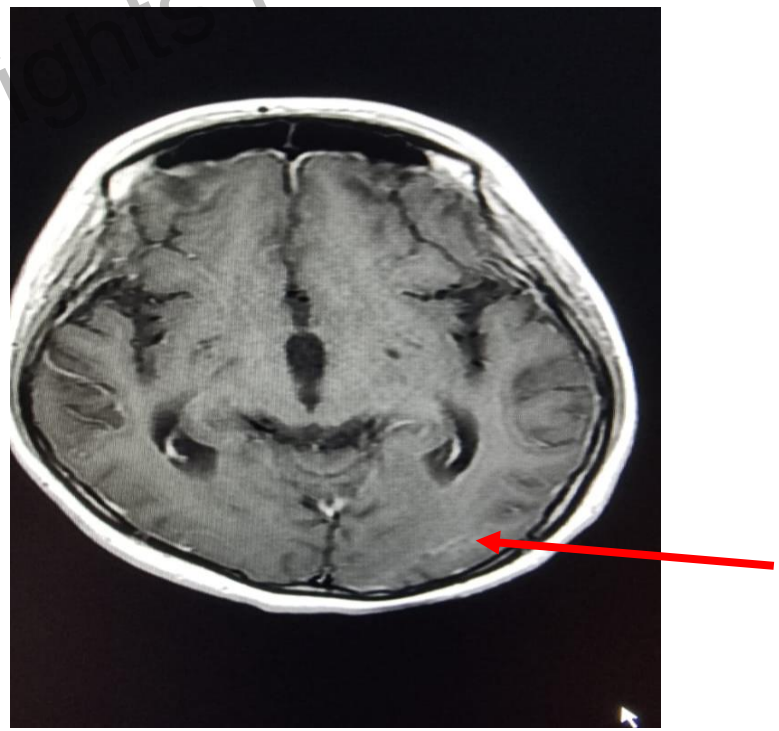
- Fluconazole 200 mg/day, low dose steroid, & maintenance with 6MP & MTX, clinically, radiology & laboratory result were good. Vision was improving. Periodic LPs performed gave positive TI results but cultures always negative.
- End of May 2022: Started complaining of intermittent headaches & worsening: severe headache, vomiting, photophobia. LP was conducted & the OP 60 cmH_2O, a bit cloudy, India ink positive, no malignant cells
- MRI: Meningo-encephalitis; leptomeningeal enhancement left temporo occipital region.
- Fluconazole was increase to 2× 400 mg/day IV; three days later LP, OP 84 cm, yellowish but clear, TI positive, culture 410 CFU, all AF were susceptible, & no malignant cell.

MRI brain: May 21st & June 18th 2022

Before Ambisome:
A lesion on left occipito-temporal lobe



After Ambisome:
Minimal leptomeningeal enhancement



Case report cont.

- Combined with fluconazole Ambisome was administered but only available for 7 days & will continued by Amphotericin B deoxycholate but her parents refuse instead ask for fluconazole only
- At the request of her parent, patient discharged from the hospital, with oral fluconazole 2× 400mg (at home it decreases into 2 × 300 mg). Before discharge from the hospital, patients was detected again suffering from COVID-19
- End of August patient passed away

Spinal fluid lab. investigation

LP (tgl)	India ink	Culture	Susceptibility	Serology
15/07/21	+	130 CFU	Fluc R, AmB S	Pos.
02/08/21	+	75 CFU	AmB+Fluconazole S	
20/09/21	+	140 CFU	AmB+Fluconazole S	
24/09/21	+	140 CFU	AmB+Fluconazole S	
12/10/21	+ (1-5)	-		
18/10/21	+ (0-1)	-		
25/10/21	+ (1-1)	-		
08/11/21	+ (1-1)	-		
08/12/21	+	-		
24/01/22	+	-		
07/04/22	+ (0-1)	-		
29/06/22	+ (1-1)	-		
08/07/22		-		pos

Discussion

- Cryptococcosis mostly infects HIV-infected patients, mainly causing meningitis, uncommon in malignancy & COVID-19
- Increasing number in non-HIV patients
- this patients with ALL & COVID 19 (2×) & received chemotherapy & steroids
- There is a weakening of immunity due to chemotherapy and steroids
- COVID-19 dysregulated immune response, its treatment cause the patient susceptible to fungal infections (CAPA, CAM & CAC). This patient had also been diagnosed with CAPA (GM *Aspergillus* index was 1.8).
- In malignancy, mortality due to cryptococcosis is high (57-85%) despite receiving amphotericin B therapy which also occurs in *Cryptococcus*-COVID-19.

Kontoyiannis et al , CID 2001; 32:e145–50; Wang et al. BMC Infect Dis. 2017; 17:463;
Sharma et al. Indian J Crit Care Med 2022;26(1):129–32. Chastain et al. *Ther Adv Infectious Dis.* 202; 9: 2–101

Cryptococcosis in COVID-19

Table 1. Laboratory Data.

		Day 0	Day 7	Day 30, discharge	Re-admission, Day 0
White-cell count (k/uL)	4.23-9.71	6.6	9.2	9.5	18.3
Red-cell count (M/uL)	3.70-5.20	4.93	4.29	3.21	4.5
Hemoglobin (g/dL)	11.0-15.0	15.5	13.6	10.7	14.6
Hematocrit (%)	33.0-45.0	45.2	39.4	31.5	45.8
Platelet count (k/uL)	130-400	138	148	168	177
Differential counts (k/uL)					
Neutrophils	1.50-7.00	4.5	8.1	7.8	17
Lymphocytes	0.85-3.20	1.4	0.4	0.8	1
Monocytes	0.20-0.80	0.7	0.6	0.7	1
Eosinophils	0.00-0.50	0	0	0.1	0
Basophils	0.00-0.10	0	0	0	0
C-reactive protein (mg/dL)	0.2-0.9	19.8	14.7	1.4	

- Thota et al., patient not recover until 6 weeks AF treatment

- Thota et al.,Neurohospitalist. 2022; 12: 96-99

Cryptococcosis in COVID-19

Table 1. Cerebrospinal Fluid (CSF) Studies

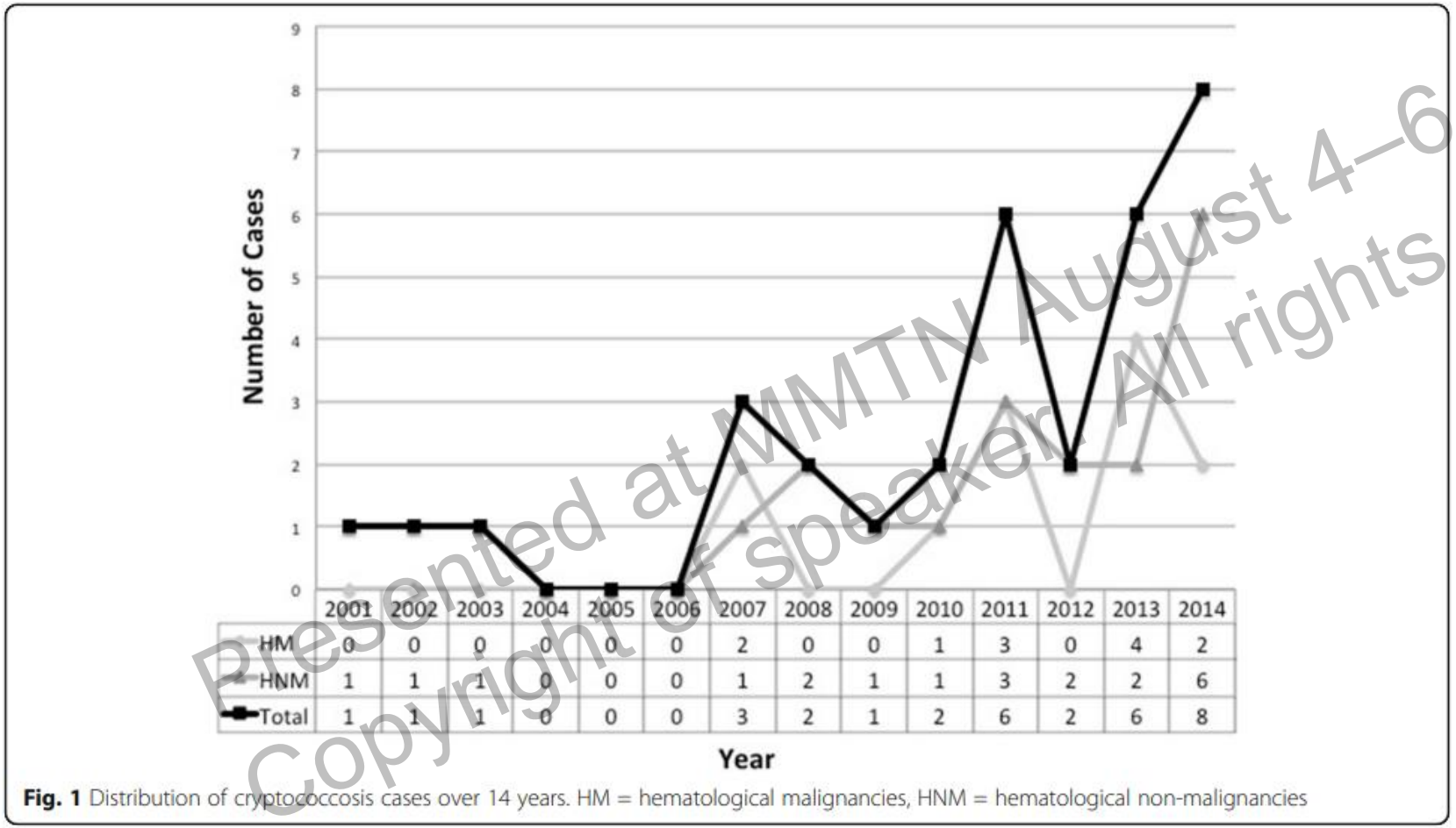
CSF Studies	Results	Normal Values
Color	Yellow	Colorless
Appearance	Clear	Clear
White blood cell count	97 cells/mcL	≤5 cells/mcL
Red blood cell count	392 cells/mcL	≤2 cells/mcL
Xanthochromia	Present	Absent
CSF polymorphonuclear cells	0%	No accepted reference interval
CSF mononuclear cells	100%	No accepted reference interval
Glucose	38 mg/dL	40–70 mg/dL
Protein	392 mg/dL	15–45 mg/dL
Enterovirus reverse transcriptase polymerase chain reaction	Negative	Negative
West Nile virus, CSF	IgG positive, IgM negative	IgG/IgM negative
Cultures	Cryptococcus neoformans	Negative

CSF studies demonstrated xanthochromia with hyperproteinorrhachia of 392, hypoglycorrhachia of 38, and mononuclear pleocytosis of 97.

- Prandecki AC et al., patient died

- Prandecki AC et al., 2023; 2:e220932.doi:10.7326/aimcc.2022.0932

Cryptococcosis in Haematology malignancy



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
HM	0	0	0	0	0	0	2	0	0	1	3	0	4	2
HNM	1	1	1	0	0	0	1	2	1	1	3	2	2	6
Total	1	1	1	0	0	0	3	2	1	2	6	2	6	8

Fig. 1 Distribution of cryptococcosis cases over 14 years. HM = hematological malignancies, HNM = hematological non-malignancies

- Rare in Haematology malignancy

Wang et al. BMC Infectious Diseases (2017) 17:463 DOI 10.1186/s12879-017-2561-z; Chastain et al. *Ther Adv Infectious Dis.* 202; 9: 2–101

Conclusion

- Cryptococcosis is starting to be widely reported among non-HIV patients
- Our patient has concomitant ALL and COVID-19 (2×)
- Both weaken the immune system that might be caused the cryptococcosis
- Recognizing cryptococcosis in these circumstances requires a high index of suspicion since its clinical presentation is not specific.

The team

- J. Bondan Lukito MD (pediatrician)
- I. Hussein MD (neurologist)
- D. Imran MD (neurologist)
- M. Sidik MD (opthalmologist)
- Sugento MD. (radiologist)
- R. Wahyuningsih MD (medical mycologist)
- R. Adawiyah MD (medical mycologist)
- I. Idris MD (clinical pathology lab)
- Edho Yuwono MD (clinical parasitologist)
- Nurse:
  - Julia Wiguna
  - Lilis Pujiastuti

Thank you very much

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