A Pair of Non-HIV, Non- Transplant Cryptococcal Meningitis Cases

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Introduction:

Non-HIV, Non-Transplant Cryptococcal Meningitis accounts for a significant burden of Cryptococcal Meningitis cases, with high mortality rates in the developed world despite appropriate therapy. Presentation is varied and can be sub-acute. It is a conditaion that often goes unrecognized or has a delayed diagnosis. This translates to worse outcomes in this patient cohort.

We present two cases of Non-HIV, Non-Transplant Cryptococcal Meningitis under our care in Beaumont Hospital in February 2021. We reviewed their clinical notes and investigations and performed a literature review of Non-HIV Cryptococcal Meningitis for the purposes of this case presentation

Patient A:

A 51 year old male was diagnosed with Non-HIV Cryptococcal Meningitis after presenting with fatigue, drowsiness and intermittent headaches over the past year.

The patient had multiple risk factors for immunosuppression including splenic lymphoma treated with Rituximab and Bendamustine, cardiac sarcoidosis on maintenance steroids, pan-hypogammaglobulinemia and T- cell lymphopenia.

He was started on induction therapy with ambisome 3mg/kg IV OD and flucytosine 25mg/kg PO QDS.

He initially remained clinically stable with no deterioration in GCS. Management continued as an inpatient due to his history of CKD and need for close renal monitoring on ambisome. Fluconazole was started as consolidation therapy.

The patient subsequently tested positive for Covid. He was given 5 days of remdesevir. However he deteriorated with increasing O2 requirement and was moved to ICU where he was intubated and ventilated. After a 12 day ICU admission, he unfortunately died due to respiratory failure secondary to Covid Pneumonitis.

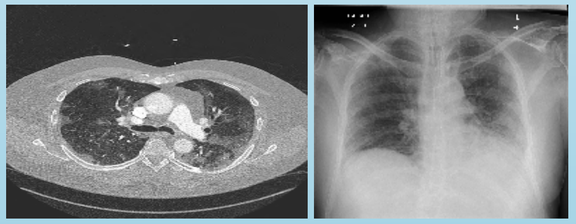

Figure A & B: CTPA and CXR showing bilateral infiltrates and ground glass changes of Covid pneumonitis

Patient B:

A 79 year old male presented with a two week history of headache, confusion and falls. He had no previous history of immunosuppression. HIV test on admission was negative and CT brain showed no acute abnormality.

Lumbar puncture was performed. CSF was CRAG positive and Cryptococcus Neoformans was grown on CSF culture.

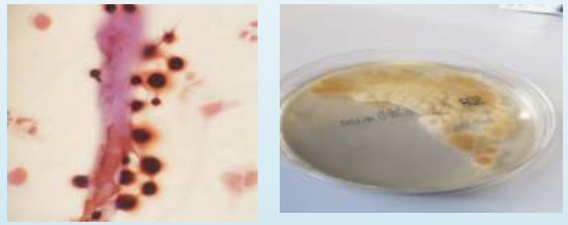

Figure C & D : Gram stain and culture of CSF - Cryptococcus Neoformans (Patient B)

Lumbar Puncture Results:

	WBC	Glucose (2.5-3.5)	Protein (15-45)	Opening pressure
23/02	112	2.4	78	Not checked
24/02	27	2.4	74	34 cm
25/02	84	2.4	80	31cm
02/03	148	2.3	67	34cm
04/03	32	1.8	91	37cm
08/03	68	1.7	152	11cm

He was commenced on induction therapy with ambisome and flucytosine. He required frequent therapeutic lumbar punctures and neurosurgical consultation due to persistently raised ICP throughout admission.

Patient B was also worked up for a diagnosis of sarcoid based on CT Thorax findings of multiple upper lobe predominant nodules and enlarged partially calcified mediastinal nodes with biopsy histology showing non-necrotizing granulomas most consistent with sarcoid.
After four weeks of induction therapy he was started on high dose fluconazole as part of the consolidation phase of treatment.

The patient subsequently had a deterioration in function. CT brain was performed which demonstrated increased hydrocephalus. VP shunt was placed, with significant improvement and facilitating discharge to a rehab unit.

Discussion:

These cases demonstarte the significant challenges assocaited with this rare condition.
Non-HIV CM accounts for approximately a third of cases of CM, with up to 30% mortality despite optimal therapy in the developed world. CM often goes unrecognized, or has a delayed diagnosis, among HIV-negative patients which translates to worse outcomes.

Lack of clinical experience, severe co-morbidities, age and irreversibility of immunosuppression are factors which likely contribute to delayed diagnosis in Non-HIV patients.

A US retrospective cohort study looking at data between 2000 and 2018 showed that patients with non-HIV cryptococcal meningitis had:

1. Higher CSF WBC count at the time of diagnosis

2. Higher rates of altered mental status on presentation

3. Higher rates of 90-day and 1-year all-cause mortality

Mortality rates were significantly higher in non-HIV/non-transplant patients at both 90 days (41.7% *versus* 8.3%, $p = 0.017$) and 1 year (41.7% *versus* 12.5%, $p = 0.047$)

There remains little understanding of the mechanisms of susceptibility for disease in Non-HIV Cryptococcal Meningitis and further immune studies are needed. The current guidelines are heavily weighted towards HIV Cryptococcal Meningitis and further prospective research is needed to identify the hallmarks of Non-HIV Cryptococcal Meningitis which would help facilitate early identification and intervention.

1. Motoa G, Pate A, Chastain D, et al. Increased cryptococcal meningitis mortality among HIV negative, non-transplant patients: a single US center cohort study. *Ther Adv Infect Dis*. 2020;7:2049936120940881. Published 2020 Jul 8. doi:10.1177/2049936120940881
2. Panackal AA, Wuest SC, Lin YC, et al. Paradoxical Immune Responses in Non-HIV Cryptococcal Meningitis. *PLoS Pathog*. 2015;11(5):e1004884. Published 2015 May 28. doi:10.1371/journal.ppat.1004884