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## Abstract

- Cryptococcus neoformans* infection (CN) can cause high morbidity and mortality among immunosuppressed patients. We performed a retrospective chart review of all patients infected with CN at our urban tertiary care hospital and identified distinct clinical characteristics and outcomes of CN in HIV-uninfected (HIV(-)) patients compared to HIV-infected (HIV(+)) patients.

## Background

- CN in HIV(-) patients can occur in those with solid organ transplantation (SOT), malignancies, autoimmune disease, or no apparent underlying disease. Clinical features and disease manifestations of CN in this population have been reported to be distinct from that of HIV(+) patients<sup>1,2,3,4</sup>.

## Methods

- We conducted a retrospective chart review of all patients with CN at Montefiore Medical Center, a tertiary care hospital comprised of 726-bed Moses Division and 396-bed Weiler Division, from Jan 2005 through March 2016.
- Clinical features, laboratory findings, and outcomes were reviewed.
- Variables were compared using Fisher's exact and Mann-Whitney U tests.

## Results

- From 2005 to 2016, there were 98 patients with CN, 35.7% of whom were HIV(-).
  - HIV(-) patients were older, had greater involvement of extra-CNS sites, less commonly had headaches, and had lower serum CrAg titers than HIV(+) patients (Table 1).
  - HIV(-) patients had higher CSF WBC, significantly higher CSF glucose and lower CSF culture positivity than HIV(+) patients (Table 2).
  - Mortality within 6 months of diagnosis was 9.5% in the HIV(+) and 22.9% in the HIV(-) group (Table 1).
- 40% of HIV(-) patients were solid organ transplant (SOT) recipients and 68.6% were on immunosuppressant therapy (Table 3).
  - 21.4% of SOT recipients had CN within 10 months of starting immunosuppressant therapy.
  - 21.4% of SOT recipients had a preceding (non-CN) infection prior to the diagnosis of CN.
  - One documented case of IRIS was found in a renal transplant patient.
  - One renal transplant patient had acute rejection of the graft.
- Median immunoglobulin level of HIV(-) patients were within the normal range (Table 1) but 3 patients had hypogammaglobulinemia (2 of them due to multiple myeloma and 1 undocumented).

**Table 1.** Clinical and laboratory findings among HIV-infected and HIV-uninfected patients with CN

Characteristics	HIV-infected (n=63)	HIV-uninfected (n=35)	P value
Male gender, No.(%)	49 (77.8%)	21 (60%)	0.10
Age, median years (range)	44 (18-69)	59 (20-87)	< 0.0001
Sites of infection, No.(%)			
CNS	43 (68.3%)	23 (65.7%)	
Pulmonary	6 (9.5%)	5 (14.3%)	
Skin, soft-tissue, or osteoarticular	1 (0.02%)	2 (5.7%)	
Fever, No.(%)	37 (58.7%)	16 (45.7%)	0.29
Headache, No.(%)	32 (50.8%)	10 (28.6%)	0.04
Abnormal neurologic findings, No.(%)	22 (34.9%)	15 (42.9%)	0.52
Serum cryptococcal antigen titer, median (range)	768 (2-65536)	64 (2-65536)	0.0004
Fungemia, No.(%)	23 (36.5%)	8 (22.9%)	0.18
CD4 T-cell count, median (range)	27 (1-261)	378 (2-1044) <sup>a</sup>	0.02
HIV RNA VL, median (range)	69,436 (75-7,500,000)	N/A	
IgG, median (range)	N/A	1,310 (547-4660) <sup>b</sup>	
IgM, median (range)	N/A	81.5 (24-343) <sup>c</sup>	
IgA, median (range)	N/A	373 (64-601) <sup>d</sup>	
Death within 6 months of diagnosis, No.(%)	6 (9.5%)	8 (22.9%) <sup>e</sup>	0.13

NOTE. Number of patients with data available, a=11, b,d = 9, c=10; N/A, not available  
e. Reasons of death – CM and sepsis (6 patients), sepsis (2 patients)

**Table 2.** CSF findings of patients with cryptococcal meningitis

CSF findings	HIV-infected (n=63)	HIV-uninfected (n=35)	P value
WBC, cells/mm <sup>3</sup> , median (range)	6 (0-590)	31 (0-1550)	0.08
Protein, g/l, median (range)	46 (6-249)	56.5 (8-622)	0.13
Glucose, g/l, median (range)	51 (5-683)	65 (8-125)	0.04
Positive CSF culture, No. (%)	26 (41.3%)	7 (20%)	0.04
Positive CSF cryptococcal antigen, No. (%)	43 (68.3%)	22 (62.9%)	0.66

**Table 3.** Variables associated with cryptococcosis in HIV-uninfected patients

Variable	No. (%) (n=35)
Type of immunocompromising condition	
Solid organ transplant (%)	14 (40%)
Malignancy (%)	6 (17.1%)
Autoimmune condition (%)	8 (22.9%)
Cirrhosis (%)	4 (11.4%)
Normal host (%)	2 (5.7%)
Likely undiagnosed HIV	1 (2.9%)
Type of transplant	
Liver	0
Heart (%)	1 (2.9%)
Kidney (%)	12 (34.3%)
Liver/Kidney (%)	1 (2.9%)
Receipt of immunosuppressant (%)	24 (68.6%)
Chronic steroid	21 (60%)
CNI (tacrolimus, cyclosporine)	13 (37.1%)
MMF	10 (28.6%)
Azathioprine	1 (2.9%)
Others <sup>1</sup>	7 (20.0%)
Infection preceding the diagnosis of CN <sup>2</sup>	3 (8.6%)
Concomitant viral infection	8 (22.9%)
CMV	3 (8.6%)
HCV	4 (11.4%)
BKV	2 (5.7%)
JCV	1 (2.9%)
Complications post-diagnosis <sup>3</sup>	2 (5.7%)

<sup>1</sup>Others include rapamycin, thalidomide, lenalidomide, tocilizumab, interferon/ribavirin, HyperCVAD, MTX, and cytarabine.

<sup>2</sup>Infections include JCV (1), EBV meningitis (1) and UTI (1). All occurred in SOT recipients.

<sup>3</sup>Complications include CNS IRIS (1) and acute rejection of the graft (1).

## Summary and Conclusions

- The highest burden of CN was in HIV(+) patients not taking ART.
- As described by others, we found distinct clinical features of CN in HIV(-) patients in regard to age, extraneural site involvement, CSF parameters, fungal burden, and mortality.
- Given increasing numbers of SOT recipients and use of potent immunosuppressive therapy, identification of factors that govern development of CN in HIV(-) patients are greatly needed.

## References

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