Association of CMV Viremia, IL-10 Responses, and 2-Week Mortality in Cryptococcal Meningitis

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BACKGROUND

- CMV (cytomegalovirus) viremia is strongly associated with increased mortality in persons with advanced HIV disease, particularly those with cryptococcal meningitis. It is unclear if CMV viremia is driving HIV-associated mortality, or if CMV serves as a sensitive biomarker of HIV-related immune dysfunction. We hypothesized that the upregulation of anti-inflammatory cytokines may provide a mechanistic explanation for the decreased survival observed in persons with CMV and cryptococcal meningitis co-infection.

METHODS

- Uganda participants from a clinical study of HIV-associated cryptococcal meningitis had cryopreserved plasma available (N=91).
- We measured human plasma IL-10 levels by Luminex assay and measured CMV viral IL-10 homolog using ELISA.
- CMV DNA concentrations were quantified by quantitative PCR with primers targeting UL83.
- Simple imputation was used to standardize cytokine values below or above assay limits of quantification.
- Univariate logistic regression examined the odds of log2-transformed cytokines being associated with CMV viremia.
- Univariate Cox regression determined association with 2-week mortality. No covariate adjustment or correction for multiple comparisons were made for this preliminary analysis.
- We graphed human IL-10 concentration by median tertile against two-week mortality, to look for evidence of a dose-response effect.

PLAIN LANGUAGE SUMMARY

Detecting CMV virus in the blood of a person with HIV and fungal brain infection showed that a person was more likely to have a blood biomarker called IL-10, which was a marker for increased risk of death.

Amongst persons with HIV-associated cryptococcal meningitis in Uganda, those with detectable CMV viremia had higher concentrations of human IL-10.

Higher concentrations of human IL-10 were associated with increased 2-week mortality.

Figure 1. Mortality at two-weeks by human IL-10 plasma concentration in HIV-associated cryptococcal meningitis.

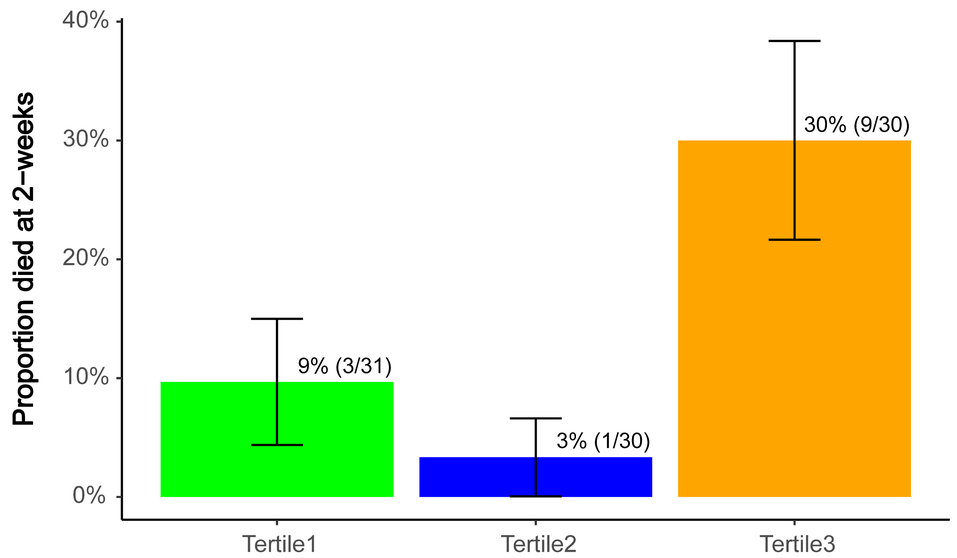


Figure 1 demonstrates median tertiles of human IL-10 concentration and the proportion who died in each tertile (overall p=0.008). The boundary of Tertile 1 and 2 was 29.8 pg/mL, while the boundary of Tertile 2 and 3 was 77.3 pg/mL. Human plasma IL-10 was significantly associated with 2-week mortality (Hazard Ratio=1.44; 95%CI, 1.05–1.99; p=.024). CMV IL-10 was not associated with mortality.

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RESULTS

Table 1: Baseline Demographics

Characteristic	CMV Viremia Present (N=23)	CMV Viremia Absent (N=68)	P-Value
Age, years	37 (30, 42)	34 (30, 42)	0.92
Male	13 (57%)	39 (57%)	0.94
Receiving ART at baseline	4 (17%)	17 (25%)	0.45
CD4 count, cells/μL	23 (5, 88)	29 (13, 69)	0.17
CMV viral load, IU/mL	569 (135, 36285)	--	--

Table 2: Baseline Cytokine Concentrations by Luminex

Analyte Concentration (pg/mL)	CMV Viremia Present	CMV Viremia Absent	P-Value
Human IL-10	70.0 (31.1, 238)	40.1 (16.5, 85.0)	0.024
CMV IL-10	0.00 (0.00, 1.35)	0.40 (0.00, 9.70)	0.049

Table 3: Odds Ratio for Risk of CMV by Logistic Regression

Analyte (Log_2 pg/mL)	CMV Viremia Present	CMV Viremia Absent	P-Value
Human IL-10	1.51	1.12, 2.11	0.010
CMV IL-10	0.73	0.52, 0.95	0.036

CONCLUSIONS

- Persons with HIV-associated cryptococcal meningitis and CMV viremia had higher concentrations human IL-10, but lower concentrations of CMV IL-10.
- Human IL-10 was associated with unadjusted 2-week mortality (while the presence of CMV viremia was not)
- This pattern suggests either non-overlapping causal variation, or alternate pathways of mediation that cancel out the net effect.
- Further investigations into the immunology of CMV viremia in advanced HIV populations is warranted.