Background: Multicentric Castleman's Disease (MCD) is a lymphoproliferative disorder common among HIV-positive patients caused by infection of Kaposi sarcoma-associated herpesvirus (KSHV). Despite high rates of HIV and KSHV rates in Malawi, Africa, MCD remains rare, likely due to underdiagnosis. Discovering biomarkers to predict response to treatment could improve outcomes for MCD patients. Methods: We analyzed bulk RNA-seq data from n=19 MCD patients enrolled in the Kamuzu Central Hospital Lymphoma Study, and n=15 non-MCD benign lymphadenopathy controls from UNC Hospital. DESeq2 was used for differential expression analysis, VirDetect was used to predict viral read counts and MiXCR was used to predict B-cell receptor profile. Results: MCD cases exhibited overexpression of mtorC1 and heme metabolism genes compared to controls. We identified two clusters of MCD cases by transcriptomic expression, with Cluster 2 (9/10) showing a male predominance compared to Cluster 1 (4/9). Cluster 2 displayed higher lactate dehydrogenase levels (p=0.016) at diagnosis. Survival and other clinical features did not significantly differ between clusters. Viral counts of Epstein Barr virus (p=0.24) and KSHV (p=0.5) were similar between the two, as well. Cluster 2 had a higher number of unique B-cell receptor clonotypes (1166 vs. 197, p=0.01). Discussion: Our findings suggest variations in immune responses to MCD pathogenesis among samples. The B-cell diversity observed in Cluster 2 may be due to increased activation and somatic hypermutation of background B cells. Future directions include identifying viral latency patterns by quantifying virus-transcribed mRNAs of Epstein Barr virus and KSHV.