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Low Cerebrospinal Fluid White Cell Counts and Mortality in HIV-associated Pneumococcal Meningitis

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Dear Editor,

We read with interest the case report by Duss and colleagues, "Pneumococcal meningitis without pleocytosis in a patient infected with HIV-1"[1]. We have previously noted similar findings in a large cohort of primarily HIV-positive adult patients being investigated for meningitis in South Africa[2]. Two of 57 (4%) of patients with culture confirmed pneumococcal meningitis had acellular (0 cells/μL) cerebrospinal fluid (CSF), and a further three (5%) had CSF white cell counts of ≤ 10 cells/μL with < 5 polymorphonuclear cells/μL. We have also recently reported results from a large national meningitis study in Botswana, including 238 cases of culture-confirmed pneumococcal meningitis[3]. A lack of CSF pleocytosis (total CSF WCC <5 cells/μL) was observed in 10% (24/238) of cases. Both studies reported results from laboratory-based surveillance studies, thus detailed individual data regarding HIV status and CD4 counts were lacking, however the vast majority of individuals with pneumococcal meningitis in both settings with HIV status data available

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were HIV-positive (97% in South Africa and at least 64% in Botswana) with low median CD4 cell counts (287 cells/μL and 221 cells/μL respectively)[2, 3].

Duss and colleagues speculate that that HIV-related immunosuppression could have hindered leucocyte migration through the blood–brain barrier, impairing effective immune control of *S. pneumoniae*. They further speculate that this resultant lack of inflammation could have contributed to the favourable outcome seen in their case[1].

We agree that it is highly plausible that HIV-related immunosuppression is likely to have contributed to the lack of an effective cellular immune response to *S. pneumoniae*, as we have described in detail in HIV-associated cryptococcal meningitis (CM)[4–6]. We have previously reported that a significant proportion of individuals with both HIV-associated CM and tuberculous meningitis (TBM) have acellular CSF (0 cells/μL in 16% and 5% respectively)[2]. However, in both CM[4, 6] and TBM[7–9] this lack of CSF white cell response is associated with increased rather than decreased mortality. In patients with HIV-associated CM the lack of an effective immune response at the site of infection, indicated by low CSF white cell counts, low levels of pro-inflammatory cytokines, and low levels of innate immune cell activation markers, is strongly associated with increased pathogen burden and death[4, 6].

Our recent data from the Botswana National Meningitis Study suggests that a paucity of CSF inflammation may also be a risk factor for poor outcome in HIV-associated pneumococcal meningitis[3]. Increased CSF white cell counts were significantly associated with lower 10-week mortality, with each $\log_{10}$ increase in WCC (cells/μL) associated with a hazards ratio for death of 0.77 (95% confidence interval 0.63–0.94, p=0.01) (Figure 1). Although prior smaller studies from African settings have not replicated this finding[10], and the very limited analyses of CSF cytokine levels in patients with HIV-associated pneumococcal meningitis have not revealed clear differences between survivors and those who died[10], our observation suggesting that a blunted inflammatory response in HIV-associated pneumococcal meningitis is associated with higher mortality could in part explain the lack of mortality benefit observed in trials of adjunctive corticosteroid therapy for pneumococcal meningitis in high HIV-prevalence settings [11].

An excess mortality risk associated with very low levels of CSF inflammation in HIV-associated pneumococcal meningitis is in keeping with the “host damage-response framework”[12], which explains microbial pathogenesis as a continuum, with host damage occurring as a result of microbial virulence or the host immune response[13]. The underlying immune environment in which infection occurs is thus critical to determining outcome. In the context of profound immune suppression such as advanced HIV-disease the lack of effective inflammation leads to unchecked pathogen replication and adverse outcomes; the appropriate management for which involves rapidly acting antimicrobial agents and possibly augmentation of effective immune responses[14]. Conversely, in the context of an intact immune system (or even HIV-infection with relatively high CD4 counts[13, 15] or following initiation of antiretroviral therapy[16–19]) excessive inflammation may lead to tissue damage and poor outcomes; the appropriate management for which involves suppression of detrimental inflammation (e.g. with corticosteroids in pneumococcal meningitis in HIV-

negative individuals[20]) and antimicrobial therapy. At which point inflammatory responses become detrimental rather than protective will likely vary from pathogen to pathogen and requires more study; but applying this conceptual framework to the management of pneumococcal meningitis may enable more appropriate treatments to be utilised, stratified by patient population or potentially individualised at the patient level, according to underlying immune status and the inflammatory response observed.

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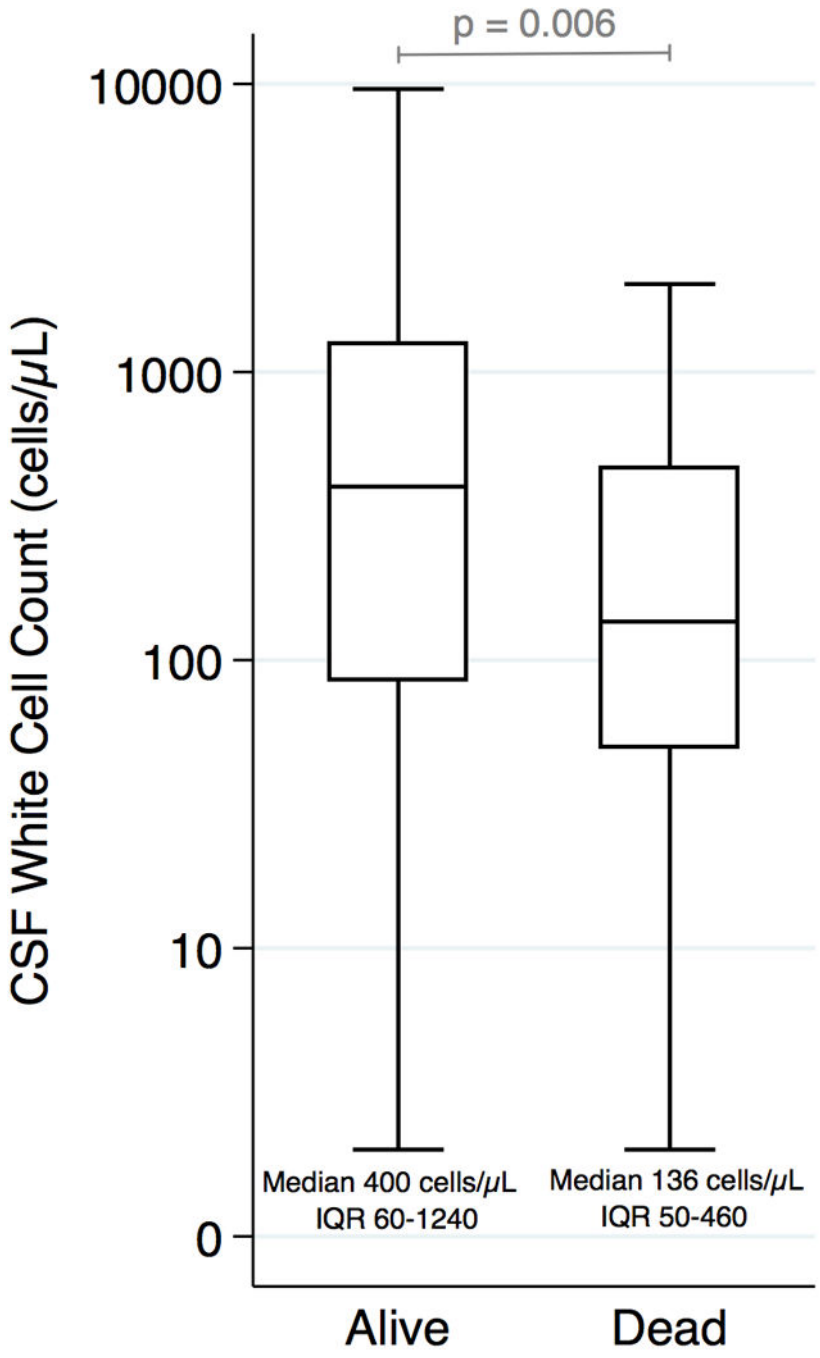

Figure 1.

Cerebrospinal fluid white cell counts in 238 patients with culture confirmed pneumococcal meningitis in Botswana, stratified by 10-week mortality (47% died, n=112). The box plots show median and interquartile ranges (IQRs), with whiskers indicating the range. The p-value was derived from a rank-sum test.