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SHORT COMMUNICATION

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Evaluation of IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ cytokines in HIV/HHV-8 coinfection

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Abstract

Imbalance in the immune response is one of the main pathogenic mechanisms of diseases related with *human immunodeficiency virus* (HIV)/*human gammaherpesvirus 8* (HHV-8) coinfection, such as Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman disease (MCD) and the Kaposi's sarcoma-associated herpesvirus inflammatory cytokine syndrome (KICS). However, significant changes in pro- and anti-inflammatory cytokine levels may be observed in HIV/HHV-8 individuals who are negative for KS, PEL, MCD, and/or KICS. In this study, serum levels of interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor nucrosis factor α (TNF-α) and interferon γ (IFN-γ) were assessed in 69 HIV and 48 HIV/HHV-8 individuals, all negatives for HHV-8-related diseases. The cytokines were measured by flow cytometry and analyzed by the Mann–Whitney test. The $p < .05$ and 95% confidence interval were considered in all analyzes. IL-4 ($p = .0155$), IL-6 ($p = .0036$), and IL-10 ($p = .0036$) levels were significantly higher in HIV/HHV-8 patients than in the HIV group. On the other hand, IL-2 ($p = .2295$), TNF-α ($p = .1216$) and IFN-γ ($p = .1178$) did not differ between the groups analyzed. To our knowledge, to date, this is the first report on significant differences in the levels of IL-4 and IL-6 in HIV versus HIV/HHV-8 individuals. Finally, these early findings are important as a prognostic tool and contribute to clarifying the HHV-8-host interaction.

KEYWORDS
cytokine, HHV-8, HIV, KSHV, pathogenesis

1 | INTRODUCTION

Human gammaherpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), *Herpesviridae* family, and *Rhadinovirus* genus, is the etiologic agent of Kaposi's sarcoma (KS) and has also been extensively associated with lymphoproliferative diseases (primary effusion lymphoma [PEL], multicentric Castleman disease [MCD], germinotropic lymphoproliferative disorder and HHV-8-positive diffuse large B-cell lymphoma, not otherwise specified).[1] In addition, HHV-8 infections have also been related to KSHV inflammatory cytokine syndrome (KICS).[2] Among these, KS, MCD, and KICS have often been reported in HIV/HHV-8 coinfected individuals.[1]

Similar to other herpesviruses, HHV-8 may have two infection cycles, lytic, or latent replication. The latent cycle has as its main objective the viral persistence, and the lytic phase is related to the

viral progeny and the infection of new cells.[3] Lytic replication is closely associated with the secretion of proinflammatory cytokines, which may be intensified by HIV infection in HIV/HHV-8 individuals. As a result, the pathogenesis of diseases associated with HHV-8, especially in HIV/HHV-8 individuals, is strongly influenced by an imbalance in viral and/or host cytokines.[1,2,4–8]

In KS, for example, in vitro and in vivo studies have reported that high concentrations of proinflammatory cytokines, such as IL-2, IL-4, IL-6 (from virus [vIL-6] or host [hIL-6]), interferon γ (IFN-γ) and tumor nucrosis factor α/β (TNF-α/β), and anti-inflammatory cytokines (e.g., IL-10) may be associated with the development of KS.[4–7,9–12] In MCD associated with HHV-8 infection, high levels of vIL-6, hIL-6, and IL-10 have also been related to the severity of the disease.[8] In the same way, in vitro and in vivo studies have suggested the participation of vIL-6, hIL-6, and IL-10, in addition to the vascular endothelial growth factor (VEGF), in the development of PEL.[6] Regarding KICS, high levels of IL-6 and IL-10 have also been associated with the severity of the syndrome.[2]

Imbalance in the immune response, indeed, is one of the main mechanisms involved in HHV-8-related diseases. However, it is also possible to observe significant changes in pro- and anti-inflammatory cytokine levels in HIV/HHV-8 individuals who are negative for KS, MCD, KICS, and/or PEL. These findings, in turn, may represent a prognostic tool for HHV-8 infections and contribute to a better understanding of the virus-host interaction. Considering this context and recognizing the participation of the previously mentioned cytokines on the pathogenesis of HHV-8 associated diseases, this study evaluated the serum levels of IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ cytokines in HIV monoinfected and HIV/HHV-8 coinfected patients, all negatives for KS, MCD, KICS, and/or PEL.

2 | MATERIALS AND METHODS

2.1 | Study population

This study is an analytical case-control study carried out with patients with HIV of both sexes, over the age of 18, from the *Ambulatório de Doenças Infecciosas e Parasitárias* at *Hospital das Clínicas*, *Universidade Federal de Pernambuco* (UFPE), Pernambuco, Brazil. Information about HIV viral load and TCD4 lymphocyte count were obtained from patients' records. All patients were on antiretroviral therapy (ART) and had no symptoms or clinical manifestations of diseases associated with HHV-8. The exclusion criteria were: individuals under 18 years old, pregnant women, patients diagnosed with lymphomas or KS, patients undergoing treatment for tuberculosis, individuals diagnosed with hepatitis B or C, hospitalized patients or users of cytokine modulating drugs. The study was approved by the ethics committee, process number CAAE-45156215.5.0000.5208 (Ethics and Research Committee of the Center for Health Sciences of the UFPE).

2.2 | Diagnosis of HHV-8 infection

The presence of immunoglobulin G against HHV-8 antigens was evaluated by in-house whole-virus ELISA, as described by Nascimento et al.[13]

2.3 | Cytokine quantification

The serum concentrations of IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ cytokines were evaluated by flow cytometry through the Cytometric Bead Array Flex set (BD Bioscience), according to the manufacturer's instructions. The samples were acquired using FACSCalibur equipment and analyzed by the FCAP array software v 3.0 (BD Bioscience).

2.4 | Statistical analyzes

Sociodemographic variables were assessed by the Fisher and χ^2 tests. The HIV diagnosis time and ART time were evaluated by the unpaired Student's *t* test. The cytokine and TCD4 lymphocyte levels were analyzed by the Mann–Whitney test. The $p < .05$ and 95% confidence interval were considered in all analyzes. Statistical analyzes were performed in the GraphPad Prism program v.6.0.

3 | RESULTS

A total of 117 individuals participated in the study, of which 69 and 48 were HIV and HIV/HHV-8 positives, respectively. The majority of participants was male, 61.5% (72/117), and the average age was 42.7 (±10.8) years old. The HIV diagnosis time was 6.6 (±5.9) and 7.9 (±6.3) years for patients with HIV and HIV/HHV-8, respectively (Table 1). The ART time was 5.6 (±5.4) and 6.8 (±5.7) years for patients with HIV and HIV/HHV-8, respectively (Table 1). The HIV diagnosis time and ART time did not differ significantly between HIV and HIV/HHV-8 patients, $p = .2616$ and $p = .2374$, respectively. Information on ethnicity, civil status, and education level are also shown in Table 1.

All patients had undetectable HIV viral load. The median TCD4 lymphocyte count was 560 and 595 cells/mm^3 for the HIV and HIV/HHV-8 groups, respectively. There was no significant difference in the TCD4 lymphocytes count ($p = .5532$).

Regarding the cytokine serum concentrations, IL-2 levels showed no significant difference between the HIV (median 5.470 pg/ml) and HIV/HHV-8 (5.365 pg/ml) groups ($p = .2295$) (Figure 1A). IL-4 concentrations, in turn, were higher in the HIV/HHV-8 (6.090 pg/ml) group when compared to the HIV (5.930 pg/ml) group ($p = .0155$) (Figure 1B). Serum levels of IL-6 were also significantly higher in HIV/HHV-8 individuals (8.280 pg/ml) when compared with HIV

TABLE 1 Study population

Variable	HIV ($n = 69$)	HIV/HHV-8 ($n = 48$)	p Value
Age	42.2 (±10.9)[a]	43.4 (±10.7)	–
Gender			.0528[b]
Male	37 (53.6%)	35 (73%)	
Female	32 (46.4%)	13 (27%)	
Ethnicity			.5055[c]
Mullato	39 (56.5%)	29 (60.4%)	
White	11 (15.9%)	10 (20.8%)	
Black	19 (27.5%)	9 (18.7%)	
Civil status			.5944[c]
Single	35 (50.7%)	29 (60.4%)	
Married	23 (33.3%)	11 (22.9%)	
Stable union	7 (10.1%)	5 (10.4%)	
Divorced	3 (4.3%)	1 (2.1%)	
Widower	1 (1.4%)	2 (4.2%)	
Educational level			.8105[c]
Elementary school	31 (45%)	19 (39.6%)	
High school	27 (39.1%)	23 (48%)	
University education	6 (8.7%)	3 (6.2%)	
Illiterate	5 (7.2%)	3 (6.2%)	
HIV diagnosis time	6.6 (±5.9)	7.9 (±6.3)	.2616[d]
ART time	5.6 (±5.4)	6.8 (±5.7)	.2374[d]

Abbreviations: ART, antiretroviral therapy; HIV, *human immunodeficiency virus*; HHV-8, *human gammaherpesvirus 8*.

[a]Standard deviation.

[b]p Value obtained by the Fisher test.

[c]p Value obtained by the χ^2 test.

[d]p Value obtained by the unpaired Student's t test.

(7.460 pg/ml) individuals ($p = .0036$) (Figure 1C). Serum IL-10 concentrations were significantly higher in the HIV/HHV-8 group (7.150 pg/ml) compared with the HIV group (6.950 pg/ml) ($p = .0036$) (Figure 1D). Serum concentrations of TNF-α (5.420 and 5.520 pg/ml for HIV and HIV/HHV-8 individuals, respectively) and IFN-γ (6.040 and 6.170 pg/ml for HIV and HIV/HHV-8, respectively) showed no significant differences between groups, $p = .1216$ and $p = .1178$, respectively (Figure 1E,F).

4 | DISCUSSION

Although the development of HHV-8-related diseases involves an imbalance in the immune response, significant differences in pro- and anti-inflammatory cytokine levels may also be observed in HHV-8 individuals, but who still present no signs and symptoms associated with infection.[1,2,4–8] In the present study, an increase in serum IL-4 concentrations was observed in HIV/HHV-8 coinfected individuals, all without any HHV-8-associated disease. Although the relationship between IL-4 and HHV-8 infection is poorly evaluated, to our knowledge, IL-4 difference between HIV versus HIV/HHV-8 individuals has not been described yet. To date, differences in IL-4 levels have previously been reported only in diseases associated with HHV-8, precisely in relation to KS.[12] It is possible that the increased IL-4 is related to the tropism of HHV-8 and its maintenance in the host. In vitro studies have shown a complex relationship between IL-4 and HHV-8. B cells can become permissive for HHV-8 infection when stimulated by IL-4; in addition, HHV-8 can inhibit IL-4 signaling, regulating cell apoptosis and favoring the viral latency.[11,14]

The IL-6 concentrations were also higher in HIV/HHV-8 individuals. Similar to that described for IL-4, this finding was not observed in previous studies that have assessed IL-6 levels in HIV versus HIV/HHV-8 individuals. To our knowledge, increased IL-6 has only been reported in individuals with KS, MCD, PEL or KICS.[2,6–8] Increased IL-6 is likely related to the interactions of HHV-8 proteins with host immunity. In vitro experiments, performed in HeLa cells, for example, have shown that K15, an HHV-8 protein expressed during the lytic cycle, can stimulate the secretion of IL-6, and that IL-6 secretion by KS spindle cells may be associated with tumor growth.[9,15]

Regarding IL-10, higher concentrations were found in individuals with HIV/HHV-8. This result corroborates Lidenge et al.[5] findings, but it differs from that reported by Lopes et al.,[7] who observed significantly higher levels of IL-10 in HIV monoinfected individuals. In Lopes et al.,[7] HIV and HIV/HHV-8 individuals were on ART for 7.5 (±5.2) and 11.0 (±6.1) years, respectively. In the present study, in turn, the ART time is very similar between the HIV and HIV/HHV-8 groups: 5.6 (±5.4) and 6.8 (±5.7) years, respectively. It is possible that the longer ART time in HIV/HHV-8 individuals in Lopes et al.[7] explains the difference between our findings, since ART can lead to decreased levels of IL-10.[16] Overall, the relationship between IL-10 and KS, MCD, PEL, and/or KICS has also been previously reported.[2,5–8] In this context, the increase in IL-10 in individuals negative for HHV-8-related diseases, in addition to IL-6 levels previously discussed, may represent a stage that precedes the development of diseases associated with HHV-8.

No significant difference in IL-2 levels was observed between individuals with HIV and HIV/HHV-8. Although proinflammatory cytokines are generally related to the induction of HHV-8 lytic replication, in vitro studies have not observed an increase in lytic replication of HHV-8 in cells infected with HIV and treated with IL-2.[10] In clinical trials, however, the use of IL-2 combined with IFN-β has been associated with an exacerbation of Epidemic KS.[4]

Although a slight increase in TNF-α levels was observed in coinfected individuals, the difference between the groups was not significant. These findings differ from those reported by Lopes et al.,[7] who observed a significant increase in the concentration of TNF-α in HIV individuals. It is possible that the difference in sample size between our study and that of Lopes (77 vs. 48 HIV/HHV-8 individuals, respectively) helps to explain the difference between the findings. Increased TNF-α has also been observed in KS, and in HHV-8-infected dendritic cells.[17] In addition, a previous study has also

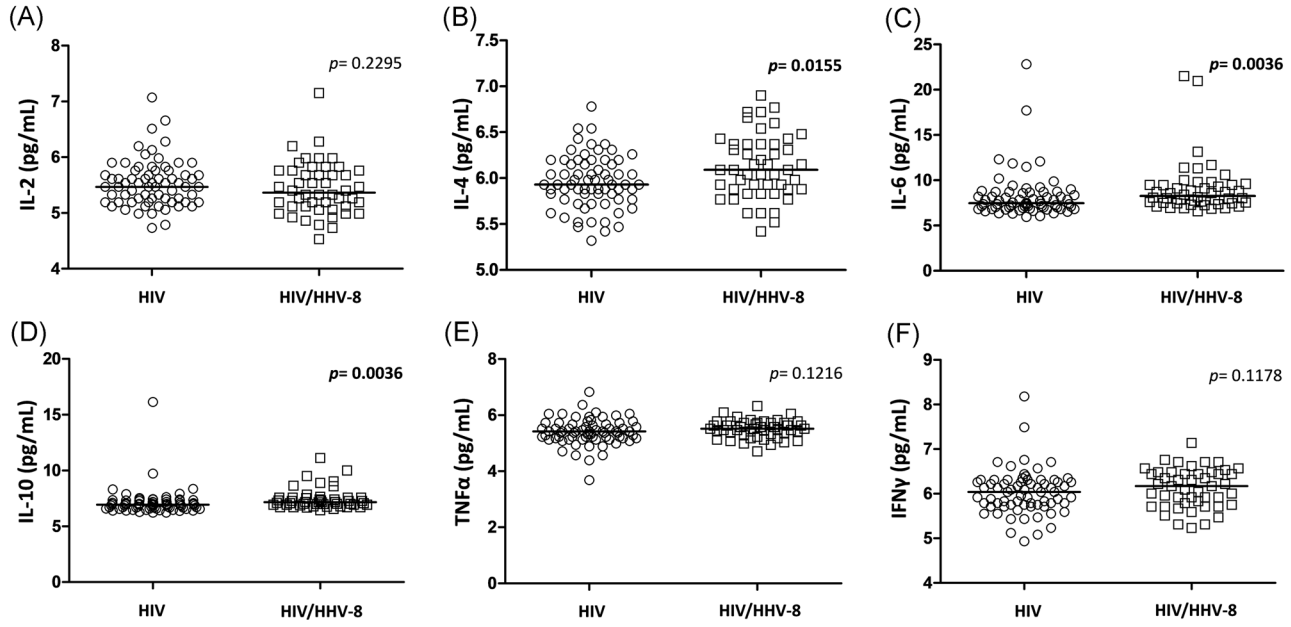

FIGURE 1 Serum concentrations of interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ) cytokines in *human immunodeficiency virus* (HIV) and HIV/Human gammaherpesvirus 8 (HHV-8) individuals. The cytokine concentrations were analyzed by the Mann–Whitney test. The $p < .05$ was considered as significant result

shown that HHV-8, via vFLIP/K13 viral protein, can inhibit TNF-α-mediated cell apoptosis.[18]

Similarly, a subtle increase in IFN-γ levels was observed in HIV/HHV-8 individuals, but that was not significantly different from the HIV group. This finding corroborates a previous study that compared IFN-γ in mono- and coinfected individuals.[19] On the other hand, some studies have demonstrated the influence of IFN-γ on HHV-8 infection.[10,20,21] IFN-γ was found, for example, in supernatants from both KS lesions and in peripheral blood mononuclear cell cultures, while in the uninvolved skin there was no detectable IFN-γ production.[20] IFN-γ production by TCD8 lymphocytes and monocyte-macrophages from KS lesions, in turn, was related to the formation of KS spindle cells with an angiogenic phenotype.[21] In addition, IFN-γ administration has also been associated with the induction of lytic cycle in HHV-8-infected cell culture, body-cavity-based lymphoma cell line.[10]

Despite the findings described here, it is important to highlight that the virus-host interaction is quite complex and involves genetic, phenotypic and environmental singularities, which are capable of influencing the clinical course of the infection. The study of these interactions, in turn, becomes more complicated in coinfection, when the virus–virus and virus–host-virus context must be carefully considered. To reduce these biases, all patients in this study had an undetectable HIV viral load and similar ART time. These issues are important, since HIV and ART can strongly influence cytokine levels.[16,22]

Considering the above, it is possible to conclude that the significant increase in serum levels of IL-4, IL-6, and IL-10, observed here, may have resulted from HHV-8 infection; this finding may contribute to elucidating the HHV-8-host interaction. Finally, since these cytokines, mainly IL-6 and IL-10, are related to the pathogenesis of KS, MCD, KICS, and/or PEL, monitoring their serum levels in HIV/HHV-8 individuals, still negative for HHV-8-related diseases, could have a prognostic value, alerting to the risk of developing the diseases previously discussed. This is a suggestion that can be considered in future prospective studies, which could also include other potential cytokines not evaluated in our study, such as VEGF and TNF-β.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Dayvson Maurício da Silva, Juliana Prado Gonçales, and Maria Rosângela Cunha Duarte Coêlho designed and performed the experiments. José Valter Joaquim Silva Júnior and Thaísa Regina Rocha Lopes interpreted the results and wrote the manuscript with support from Juliana Prado Gonçales and Maria Rosângela Cunha Duarte Coêlho. Luan Araújo Bezerra collected the data. Maria Rosângela Cunha Duarte Coêlho supervise the project, conceived the original idea and critically reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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