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Association of IL-6, IL-10 and CXCL10 serum concentrations with visceral Kaposi's sarcoma in people living with HIV/AIDS

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ABSTRACT

Human gammaherpesvirus 8 (HHV-8) is the etiologic agent of Kaposi's sarcoma (KS), one of the most common cancers in people living with HIV/AIDS. It is believe that the course of both HIV and HHV-8 infection is associated with the imbalance of anti- and/or pro-inflammatory cytokines. Here, we evaluated the IL-6, TNF-α, IL-10, CCL2 and CXCL10 serum concentrations in HIV- and HIV/HHV-8 (without KS) individuals, and in patients with cutaneous or visceral AIDS-KS. Serum concentrations of IL-6, IL-10 and CXCL10 were significantly higher in the AIDS-KS group compared to HIV and HIV/HHV-8 individuals. Similarly, the concentrations of theses cytokines were higher in patients with visceral than in those with cutaneous AIDS-KS. The TNF-α concentration was significantly higher in the HIV group compared to HIV/HHV-8 (with and without KS) individuals, and CCL2 levels did not present significant difference among the groups. The HIV viral load was undetectable in all patients from the HIV and HIV/HHV-8 groups. On the other hand, in the AIDS-KS group, most patients had detectable HIV viral load. In this context, we believe that the cytokine levels in AIDS-KS may be result of a complex interaction between HIV, HHV-8 and immunity.

1. Introduction

Human gammaherpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), belongs to *Herpesviridae* family and *Rhadinovirus* genus [1]. The Kaposi's sarcoma (KS) is one of the most common cancers in people living with HIV/AIDS (PLHA) [2]. The KS is a multifocal angioproliferative disorder of the vascular endothelium that may be classified into four forms: classic, endemic, iatrogenic and epidemic (AIDS-KS), according to clinical-epidemiological criteria [3].

Among these, the AIDS-KS stands out as being more aggressive. In addition to cutaneous involvement, the AIDS-KS often leads to visceral impairment, which may compromise lungs and/or gastrointestinal tract [3,4]. In these cases, it is possible observe cough, dyspnea and hemoptysis (in pulmonary involvement), and abdominal pain, diarrhea, weight loss, bleeding and vomiting (in individuals with gastrointestinal impairment) [5].

Regarding the greater severity of AIDS-KS, there is a consensus that only the immunodeficiency caused by HIV would not be enough for the AIDS-KS development [6]. The HIV Tat protein, for example, has been identified as one of the factors involved in the pathogenesis of KS, activating the HHV-8 lytic cycle by the JAK/STAT signaling pathway either by the induction of HHV-8 Rta protein [7,8]. *In vitro* studies have suggested that high concentrations of pro-inflammatory cytokines, such as IL-6, TNF-α, CCL-2 and CXCL-10, may be related to the development of KS [9–16]. On the other hand, anti-inflammatory cytokines, such as IL-10, have also been associated with the HHV-8 infection and/or AIDS-KS development [17–19].

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Despite the suggestions of several findings [9–16], rare studies have reported the association of the cytokines serum concentrations with the development or severity of AIDS-KS. Among them, Machado et al. [18], Lidenge et al. [19] and El-Mallawany et al. [20] related the IL-10 levels with the development of AIDS-KS [18,19], IL-10 levels with lymph node involvement in AIDS-KS [18] and IL-6 levels with AIDS-KS in children [20].

Therefore, based on evidence from previous *in vitro* and *in vivo* studies on the relationship between HHV-8 and immunity, especially regarding anti- and/or pro-inflammatory cytokines levels, we evaluated the serum concentrations of IL-6, TNF-α, IL-10, CCL2 and CXCL10 cytokines in HIV mono- and HIV/HHV-8 coinfected patients, and in individuals with cutaneous or visceral AIDS-KS.

2. Materials and methods

2.1. Study population

The study included PLHA of both sexes, older than 18 years, treated in the Reference Service for Infectious and Parasitic Diseases of the University Hospital at the Federal University of Pernambuco (HC-UFPE), Institute of Infectology Emílio Ribas (IIER) and in the Department of Infectious and Parasitic Diseases at the University of São Paulo Medical School (HCFM-USP). The exclusion criteria were individuals under 18 years old, with diagnostic of syphilis, hepatitis B, hepatitis C and human T-cell lymphotropic virus type 1/2 or pregnant women.

Initially, the participants were distributed into three groups: HIV monoinfected (HIV), HIV/HHV-8 coinfected without KS (HIV/HHV-8) and HIV/HHV-8 with KS (AIDS-KS). Participants with AIDS-KS were further divided into patients with cutaneous or visceral lesion. This latter group included individuals with cutaneous and gastrointestinal and/or pulmonary involvements. Information regarding the HIV viral load and TCD4 lymphocyte count were obtained from patients' records. All participants were receiving antiretroviral therapy (ART). The study was approved by the ethics committees of the institutions, process numbers 45156215.5.0000.5208 (HC-UFPE) and 55771116.0.1001.0065 (IIER, HCFM-USP).

2.2. Diagnosis for HHV-8 infection and KS

The patients were evaluated for presence of IgG against HHV-8 antigens by in-house whole-virus ELISA, as described by Nascimento et al. [21]. The diagnosis of KS was performed by: i) histological analysis of cutaneous lesions; ii) brochoscopy for evaluation of lung lesions; and iii) colonoscopy and endoscopy for analysis of gastrointestinal tract impairment.

2.3. Cytokine dosage

The serum concentrations of host IL-6, TNF-α, IL-10, CCL2 and CXCL10 cytokines were measured by flow cytometry through the Cytometric Bead Array (CBA) Flex set (BD Bioscience, San Diego, California, USA), following the manufacturer's instructions. The samples were acquired using FACSCalibur equipment and analyzed in the FCAP array software v 3.0 (BD Bioscience, San Diego, CA, USA).

2.4. Statistical analysis

The cytokine concentrations and TCD4 lymphocyte counts were analyzed by the Kruskal-Wallis and Mann-Whitney tests. The $p < 0.05$ *value* was considered as significant result. Statistical analysis were performed in the GraphPad Prism program v.6.0.

3. Results

3.1. Study population

A total of 146 PLHA participated of the study, of whom 31 were HIV monoinfected, 77 HIV/HHV-8 and 38 were with AIDS-KS. Of the 38 AIDS-KS individuals, 17 and 21 were with cutaneous or visceral impairment, respectively. Most of the individuals in all groups evaluated, mainly in AIDS-KS, was male. The ART use time and HIV diagnosis time were shorter in the AIDS-KS group compared to individuals with HIV or HIV/HHV8 (without KS). Individuals with AIDS-KS were also a littler younger than the other patients. Regarding the classification by the AIDS Clinical Trials Group (ACTG) system [22], all patients with cutaneous and visceral AIDS-KS were classified as T0 and T1, respectively (Table 1).

The HIV viral load was undetectable in all patients from the HIV and HIV/HHV-8 groups. Of the 38 patients with AIDS-KS, only nine presented undetectable HIV, of whom three and six were with visceral or cutaneous lesion, respectively. Of the 29 participants from the AIDS-KS group with detectable HIV viral load, 11 and 18 presented cutaneous or visceral involvement, with medians of 4.953 and 7.589 copies/mL, respectively.

Analysis of the TCD4 lymphocyte count showed that the values of the AIDS-KS group were significantly lower than the values of HIV and HIV/HHV-8 infected individuals ($p < 0{,}0001$). The medians of TCD4 lymphocyte count were 110.5, 635.5 and 782 cells/mm^3 for the AIDS-KS, HIV/HHV-8 and HIV groups, respectively. When the patients were distributed according to the severity of AIDS-KS, individuals with visceral disease had a TCD4 lymphocyte count significantly lower than patients with cutaneous lesions ($p = 0.0076$). The medians were 69 and 242 cell/mm^3 for visceral and cutaneous AIDS-KS, respectively. By the ACTG system, in relation to TCD4 lymphocyte count, 11 and 6 patients with cutaneous AIDS-KS were classified as I0 and I1, respectively. In addition, 4 and 17 patients with visceral AIDS-KS were defined as I0 and I1, respectively.

Table 1
Study population.

General characteristics	HIV (n = 31)	HIV/HHV-8 (n = 77)	AIDS-KS (n = 38)	AIDS-KS	
				Cutaneous (T0[1]) (n = 17)	Visceral (T1[1]) (n = 21)
Age[2]	43.9 (± 11.4)[3]	47.5 (± 10.3)	35.3 (± 10.8)	37.2 (± 11.9)	33.7 (± 9.9)
Gender					
Male	19 (61.3%)	50 (65%)	37 (97.4%)	17 (100%)	20 (95.3%)
Female	12 (38.7%)	27 (35%)	1 (2.6%)	0 (0%)	1 (4.7%)
HIV diagnosis time[2]	9.9 (± 6.2)	12.8 (± 6.4)	3.7 (± 5.4)	4.2 (± 6.5)	3.2 (± 4.6)
ART time[2]	7.5 (± 5.2)	11.0 (± 6.1)	2.2 (± 4.9)	2.6 (± 6.3)	1.9 (± 3.5)

[1] Classification according to AIDS Clinical Trials Group system.
[2] Years.
[3] Standard deviation.

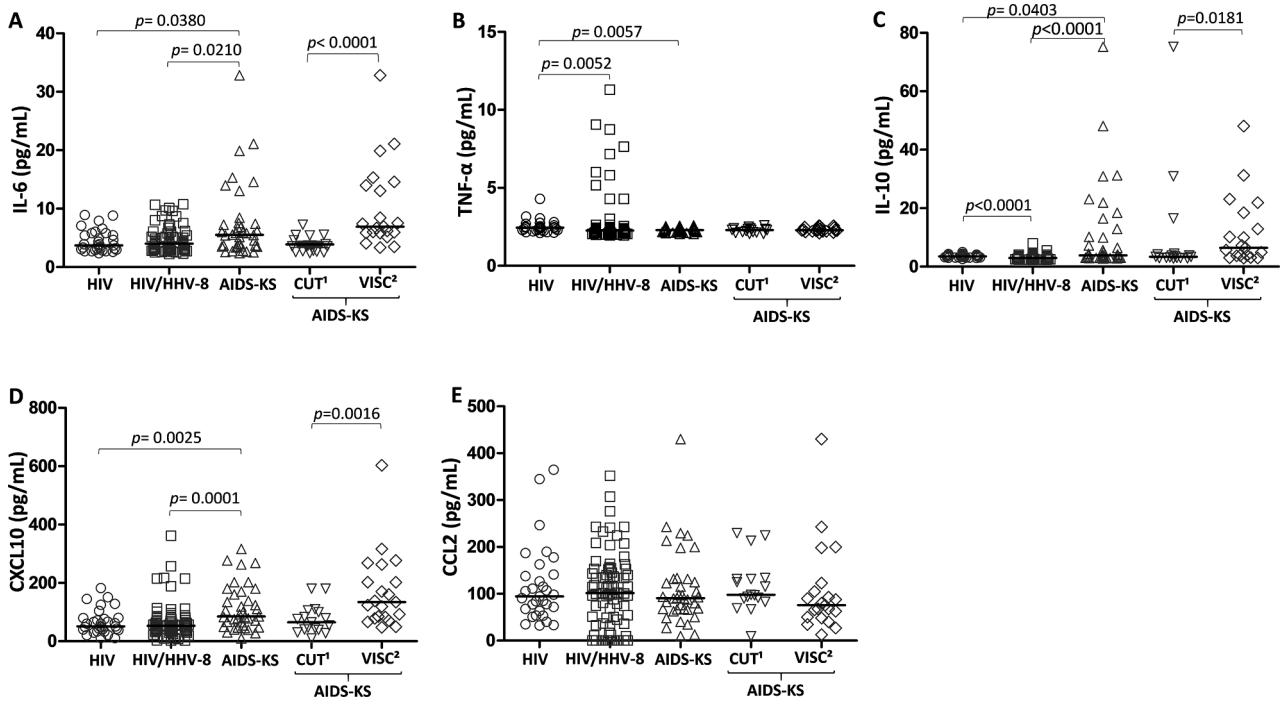

Fig. 1. Serum concentrations of IL-6, TNF-α, IL-10, CCL2 and CXCL10 cytokines in HIV, HIV/HHV-8 and AIDS-KS patients. [1]Cutaneous AIDS-KS; [2]Visceral AIDS-KS. The cytokine concentrations were analysed by the Mann-Whitney test. The $p < 0.05$ *value* was considered as significant result.

3.2. Dosage and cytokine analysis

The medians of IL-6 serum concentrations for the HIV, HIV/HHV-8 and AIDS-KS groups were 3.710, 4.040 and 5.515 pg/mL, respectively. The serum concentrations of IL-6 were significantly higher into the AIDS-KS group than in HIV ($p = 0.0380$) and HIV/HHV-8 ($p = 0.0210$) individuals (Fig. 1A). For TNF-α concentration, the medians were 2.440, 2.250 and 2.290 pg/mL for HIV, HIV/HHV-8 and AIDS-KS, respectively. The serum concentrations of TNF-α were significantly higher in HIV individuals than in the HIV/HHV-8 ($p = 0.0057$) and AIDS-KS ($p = 0.0052$) groups (Fig. 1B).

Regarding IL-10 concentrations, the medians were 3.490, 2.980 and 4.005 pg/mL for the HIV, HIV/HHV-8 and AIDS-KS groups, respectively. In the AIDS-KS group, IL-10 concentrations were significantly higher in relation to the HIV ($p = 0.0403$) and HIV/HHV-8 ($p < 0.0001$) groups. On the other hand, IL-10 concentrations in the HIV/HHV-8 group were significantly lower compared to HIV individuals ($p < 0.0001$) (Fig. 1C).

In relation to chemokines, CXCL10 concentrations presented medians of 50.69, 53.22 and 88.48 pg/mL for the HIV, HIV/HHV-8 and AIDS-KS groups, respectively. In the AIDS-KS group, CXCL10 concentrations were significantly higher compared to HIV ($p = 0.0025$) and HIV/HHV-8 ($p = 0.0001$) individuals (Fig. 1D). The CCL2 concentrations did not present significant difference among the evaluated groups, and the medians values were 94.36, 101.5 and 90.56 pg/mL for the HIV, HIV/HHV-8 and AIDS-KS groups, respectively (Fig. 1E).

When the participants from the AIDS-KS group were divided according to impairment, the medians of IL-6 concentration were 3.54 and 6.93 pg/mL for cutaneous and visceral AIDS-KS, respectively. The IL-6 concentrations were significantly higher in visceral patients than in those with cutaneous involvement ($p < 0.0001$) (Fig. 1A). Concerning TNF-α serum concentrations, no significant difference was observed between patients with cutaneous or visceral involvements, with medians of 2.300 and 2.280 pg/mL, respectively (Fig. 1B).

The IL-10 serum concentrations were significantly higher in patients with visceral than in those with cutaneous lesions ($p = 0.0181$) (Fig. 1C). For this cytokine, cutaneous and visceral AIDS-KS presented medians of 3.35 and 7.21 pg/mL, respectively.

The CXCL10 concentrations were significantly higher in patients with visceral involvement than in those with cutaneous form ($p = 0.0016$), with medians of 134.5 and 64.9 pg/mL, respectively (Fig. 1D). Similar to that described for the HIV and HIV/HHV-8 groups, no difference was observed in CCL2 concentrations between patients with visceral or cutaneous involvements, with medians of 97.50 and 75.81 pg/mL, respectively (Fig. 1E).

4. Discussion

Although KS is one of the most common cancers in PLHA, its pathogenesis is still unclear [2]. Among the mechanisms responsible for the pathogenesis of KS, *in vitro* and *in vivo* studies have suggested that high concentrations of anti- and/or pro-inflammatory cytokines may be related with the development and severity of KS [9–19].

In our study, we identified elevated concentrations of host IL-6 in the AIDS-KS group. Recently, El-Mallawany et al. [20] also observed elevated levels of IL-6 in a subset of children with KS. We believe that this relationship may be associated with the inflammatory role of IL-6 and angiogenesis related to IL-6-induced vascular endothelial growth factor [23]. Interestingly, it has been demonstrated that the K15 viral protein, expressed during the HHV-8 lytic cycle, stimulates the secretion of IL-6 in HeLa cells [12]. In addition, experiments performed in KS spindle cells associated IL-6 secretion with tumor growth [9].

After division of the KS group in patients with cutaneous or visceral lesion, IL-6 concentrations were significantly higher in the visceral AIDS-KS group. Elevated IL-6 concentrations have also been described in patients with multicentric Castleman's disease (MCD) and have been associated with disease severity [24]. More recently, increased host IL-6, as well as increased viral IL-6, has been associated with the development of KSHV inflammatory cytokine syndrome (KICS); a newly described disease affecting HIV/HHV-8 coinfected individuals [25].

In vitro and *in vivo* studies have related TNF-α level to HHV-8 infection or the development of KS [11,26–28]. In addition, the use of anti-TNF-α antibodies in the treatment of patients with joint involvement has resulted in the development of KS lesions [29,30]. Although in

these cases therapy often involves immunosuppression strategies, which may favor viral reactivation and the development of KS, these results contribute to reinforce the relationship between TNF-α and KS.

Interestingly, in our study, we did not observe elevated levels of TNF-α in HIV/HHV-8 patients, with or without KS. Here, the highest TNF-α serum concentration was observed in the HIV group. On the other hand, Machado et al. [18] found no significant difference between TNF-α level in individuals with AIDS-KS, classic KS and HIV. It is important to observe that, unlike our study, where HIV viral load was detected in some AIDS-KS patients, Machado et al. [18] do not comment on the HIV viral load in the evaluated individuals. Since TNF-α has been related to the course of HIV infection [31], we believe that the relationship between TNF-α and AIDS-KS should be analyzed also considering the influence of HIV in the HIV/HHV-8 coinfection.

We found high concentrations of CXCL10 in the AIDS-KS group. Similarly, Tso et al. [16] reported increased CXCL10 expression in AIDS-KS lesion samples. Experiments performed in HHV-8 infected THP-1 monocytes indicated that the CXCL10 expression may be associated with activation of the toll-like receptor 3 pathway [13]. After its secretion, CXCL10 may interact with vGPCR, an endothelial cell migration inhibitor, encoded by HHV-8 and expressed on KS endothelial cell. Binding of CXCL10 to vGPCR, in turn, abrogates the inhibition of migration, stimulating endothelial cell migration and the angioproliferative process [14].

Lidenge et al. [19] found higher concentrations of CXCL10 in HIV/HHV-8 individuals when compared to the AIDS-KS group. However, unlike our study population, some coinfected patients (without KS) in the study by Lidenge et al. [19] had detectable HIV viral load. The disagreement between our results may be related to HIV viremia, which is known to influence the CXCL10 serum concentrations [32]. In this same context, CXCL10 levels have been suggested as a hallmark in the clinical evolution of HIV infection [33].

We also observed higher concentrations of CXCL10 in the group with visceral AIDS-KS compared to individuals with cutaneous lesions. Although this is the first description of the association of this chemokine with the severity of AIDS-KS, some studies have suggested that CXC chemokines, such as CXCL10 and its CXCR3 receptor, may participate in the development, progression or metastasis of other cancers, such as colon cancer [34] and basal cell carcinoma [35].

Regarding IL-10, we showed high concentrations in the AIDS-KS group when compared with HIV and HIV/HHV-8 individuals. In addition, IL-10 concentrations were also significantly higher in patients with visceral AIDS-KS than in those with cutaneous lesions. It is possible that the serum increase of IL-10 favors the KS progression, since it suppresses the production of cytokines by Th1 lymphocytes and reduces the cell-mediated response to HHV-8 [36]. Interestingly, depending on the cellular context, anti-inflammatory cytokines may also play an anti-neoplastic role. Downregulation and/or inhibition of TGF-β signaling, for example, has been related to HHV-8 infection and the development of KS [37,38].

Part of our findings corroborates with Lidenge et al. [19], who reported significantly higher concentrations of IL-10 in AIDS-KS patients when compared to the HIV/HHV-8 group. Machado et al. [18] also found higher concentrations of IL-10 in AIDS-KS patients when compared to HIV monoinfected and classic KS individuals. However, Machado et al. [18] not observed difference between serum concentrations of IL-10 when compared patients with cutaneous and/or visceral AIDS-KS; the authors observed a significant increase of IL-10 only in KS patients with lymph node involvement.

Despite the *in vitro* observation of CCL2 secretion by KS spindle cells [10] and the high transcription of CCL2 gene into HHV-8 infected THP-1 monocytes [13], in our study there was no significant difference in CCL2 serum concentrations between the HIV, HIV/HHV-8 and AIDS-KS groups. In relation to these discordant findings, we believe that the development of *in vivo* models is important to provide new insights about the real participation of CCL2 in KS pathogenesis.

After the HIV *vs.* HIV/HHV-8 *vs.* AIDS-KS patients and cutaneous *vs.* visceral AIDS-KS comparisons, we observed significant decrease of TCD4 lymphocyte count in the AIDS-KS and visceral AIDS-KS groups. Indeed, immune deterioration and decreased in TCD4 count may result in the progression of AIDS-KS, in which the lesions tend to enlarge, multiply or coalesce [3]. On the other hand, it is possible that some ART treated HIV infected patients, with undetectable HIV viral load and relatively high TCD4 count, develop KS [39]. In this case, the presence of KS may be associated with the lower frequencies of naive T cells and increased frequencies of T cells with an immunosenescence phenotype [40].

It is interesting to note that most of our patients was male and that the median age of the AIDS-KS group was slightly lower compared to HIV/HHV8 (without KS) individuals. Although there is not yet an in-depth investigation into this relationship, some studies have also reported a higher prevalence of AIDS-KS in males [41–43] and in groups with a mean of 30–39 years [42–44].

In addition, it is also important to observe that our patients were recruited from medical centers located in distinct geographic regions from Brazil, specifically in the Northeast and Southeast regions. The analysis of dozens of DNA polymorphisms performed in the Brazilian population showed that the population is ancestrally admixed and has great genetic heterogeneity, even within the same population group [45–47]. However, molecular analysis of variance indicated a low degree of genetic differentiation between four Brazilian regions, North, Northeast, Central-East and Southeast. The exception was the Southern region, which has showed a considerable difference between the other regions [45–47]. Therefore, we do not believe that the cytokine levels observed in our study are influenced by regional differences.

Here, most individuals diagnosed with AIDS-KS had detectable HIV viral load and shorter ART use time than the HIV and HIV/HHV8 (without KS) individuals. In this context, it is also necessary to consider the influence of HIV and ART on the cytokine levels [48–50]. In addition to the influence of HIV on TNF-α and CXCL10, as previously discussed, several studies have reported the association of IL-10 and IL-6 cytokines with HIV infection [31,51–55]. Although not yet agreed, numerous studies have also reported the influence of ART on cytokine levels in HIV individuals [56]. In line with these findings, we believe that the cytokine levels observed in our study should be understood as the result of a complex interaction between HHV-8, HIV, ART and immunity. This is an essential issue, but one that is rarely considered and discussed in studies of AIDS-KS patients with detectable HIV viral load and/or under ART.

In conclusion, we reported high serum concentrations of IL-6, IL-10 and CXCL10 cytokines with both the presence and severity of AIDS-KS. Regarding severity specifically, to our knowledge, this is the first report of association of IL-6, IL-10 and CXCL10 cytokines with visceral AIDS-KS. Despite the need for further *in vivo* studies, including prospective analyses with larger groups, for a better understanding of HHV-8-immunity-disease interaction, we believe that these cytokines are important elements to the understanding of the pathogenicity mechanism of KS, mainly of AIDS-KS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Virus Taxonomy: 2018b Release. https://talk.ictvonline.org/taxonomy/ (accessed 10 Jul 2019).
[2] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108.
[3] M. Fatahzadeh, Kaposi sarcoma: review and medical management update, Oral. Surg. Oral Med. Oral Pathol. Oral Radiol. 113 (2012) 2–16.
[4] D. Ganem, KSHV infection and the pathogenesis of Kaposi's sarcoma, Annu. Rev. Pathol. 1 (2006) 273–296.
[5] F. Martellotta, M. Berretta, E. Vaccher, O. Schioppa, E. Zanet, U. Tirelli, AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies, Curr. HIV Res. 7 (2009) 634–638.
[6] B.C. Ensoli, C. Sgadari, G. Barillari, M.C. Sirianni, M. Stürzl, P. Monini, Biology of Kaposi's sarcoma, Eur. J. Cancer 37 (2001) 1251–1269.
[7] V. Varthakavi, R.M. Smith, H. Deng, R. Sun, P. Spearman, Human immunodeficiency virus type-1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus through induction of KSHV Rta, Virology 297 (2002) 270–280.
[8] Y. Zeng, X. Zhang, Z. Huang, L. Cheng, S. Yao, D. Qin, X. Chen, Q. Tang, Z. Lv, L. Zhang, C. Lu, Intracellular Tat of human immunodeficiency virus type 1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus: role of JAK/STAT signaling, J. Virol. 81 (2007) 2401–2417.
[9] S.A. Miles, A.R. Rezai, J.F. Salazar-González, M. Vander Meyden, R.H. Stevens, D.M. Logan, R.T. Mitsuyasu, T. Taga, T. Hirano, T. Kishimoto, AIDS Kaposi sarcoma-derived cells produce and respond to interleukin 6, PNAS 87 (1990) 4068–4072.
[10] F.L. Sciacca, M. Stürzl, F. Bussolino, M. Sironi, H. Brandstetter, C. Zietz, D. Zhou, C. Matteucci, G. Peri, S. Sozzani, Expression of adhesion molecules, platelet-activating factor, and chemokines by Kaposi's sarcoma cells, J. Immunol. 153 (1994) 4816–4825.
[11] B. Ensoli, M. Stürzl, P. Monini, Cytokine-mediated growth promotion of Kaposi's sarcoma and primary effusion lymphoma, Semin. Cancer Biol. 10 (2000) 367–381.
[12] M.M. Brinkmann, M. Pietrek, O. Dittrich-Breiholz, M. Kracht, T.F. Schulz, Modulation of host gene expression by the K15 protein of Kaposi's sarcoma-associated herpesvirus, J. Virol. 81 (2007) 42–58.
[13] J. West, B. Damania, Upregulation of the TLR3 pathway by Kaposi's sarcoma-associated herpesvirus during primary infection, J. Virol. 82 (2008) 5440–5449.
[14] J.P. Couty, M. Lupu-Meiri, Y. Oron, M.C. Gershengorn, Kaposi's sarcoma-associated herpesvirus-G protein-coupled receptor-expressing endothelial cells exhibit reduced migration and stimulated chemotaxis by chemokine inverse agonists, J. Pharmacol. Exp. Ther. 329 (2009) 1142–1147.
[15] E.A. Mesri, E. Cesarman, C. Boshoff, Kaposi's sarcoma and its associated herpesvirus, Nat. Rev. Cancer 10 (2010) 707–719.
[16] F.Y. Tso, A.V. Kossenkov, S.J. Lidenge, O. Ngalamika, J.R. Ngowi, J. Mwaiselage, J. Wickramasinghe, E.H. Kwon, J.T. West, P.M. Lieberman, C. Wood, RNA-Seq of Kaposi's sarcoma reveals alterations in glucose and lipid metabolism, PLoS Pathog. 14 (2018) e1006844.
[17] Z. Qin, P. Kearney, K. Plaisance, C.H. Parsons, Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes, J. Leukoc. Biol. 87 (2010) 25–34.
[18] P.R. Machado, K.J. Farias, J. Genre, C.J. Oliveira, P.M. Guedes, B.A. da Fonseca, Disseminated Kaposi's sarcoma in patients with HIV infection correlates to high serum levels of IL-10, Viral Immunol. 27 (2014) 356–360.
[19] S.J. Lidenge, F.Y. Tso, O. Ngalamika, J.R. Ngowi, Y. Mortazavi, E.H. Kwon, D.M. Shea, V. Minhas, J. Mwaiselage, C. Wood, J.T. West, Similar immunological profiles between African endemic and HIV1-associated Epidemic Kaposi's sarcoma patients reveal the primary role of KSHV in KS pathogenesis, J. Infect. Dis. 219 (2018) 1318–1328.
[20] N.K. El-Mallawany, P.S. Mehta, W. Kamiyango, J. Villiera, E.C. Peckham-Gregory, C. Kampani, R. Krysiak, M.K. Sanders, C. Caro-Vegas, A.B. Eason, S. Ahmed, G.E. Schutze, S.C. Martin, P.N. Kazembe, M.E. Scheurer, D.P. Dittmer, KSHV viral load and Interleukin-6 in HIV-associated pediatric Kaposi sarcoma-Exploring the role of lytic activation in driving the unique clinical features seen in endemic regions, Int. J. Cancer 144 (2019) 110–116.
[21] M.C. Nascimento, V.A. De Souza, L.M. Sumita, W. Freire, F. Munoz, J. Kim, C.S. Pannuti, P. Mayaud, Comparative study of Kaposi's sarcoma-associated herpesvirus serological assays using clinically and serologically defined reference standards and latent class analysis, J. Clin. Microbiol. 45 (2007) 715–720.
[22] S.E. Krown, C. Metroka, J.C. Wernz, Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee, J. Clin. Oncol. 7 (1989) 1201–1207.
[23] S.P. Huang, M.S. Wu, C.T. Shun, H.P. Wang, M.T. Lin, M.L. Kuo, J.T. Lin, Interleukin-6 increases vascular endothelial growth factor and angiogenesis in gastric carcinoma, J. Biomed. Sci. 11 (2004) 517–527.
[24] E. Oksenhendler, G. Carcelain, Y. Aoki, E. Boulanger, A. Maillard, J.P. Clauvel, F. Agbalika, High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients, Blood 96 (2000) 2069–2073.
[25] T.S. Uldrick, V. Wang, D. O'Mahony, K. Aleman, K.M. Wyvill, V. Marshall, S.M. Steinberg, S. Pittaluga, I. Maric, D. Whitby, G. Tosato, R.F. Little, R. Yarchoan, An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease, Clin. Infect. Dis. 1 (2010) 350–358.
[26] H.R. Hensler, G. Rappocciolo, C.R. Rinaldo, F.J. Jenkins, Cytokine production by human herpesvirus 8-infected dendritic cells, J. Gen. Virol. 90 (2009) 79–83.
[27] E. Ruocco, V. Ruocco, M.L. Tornesello, A. Gambardella, R. Wolf, F.M. Buonaguro, Kaposi's sarcoma: etiology and pathogenesis, inducing factors, causal associations, and treatments: facts and controversies, Clin. Dermatol. 31 (2013) 413–422.
[28] E.R. Knowlton, G. Rappocciolo, P. Piazza, L.M. Lepone, S.V. Nadgir, A. Bullotta, S.J. Berendam, J. Li, T.A. Reinhart, F.J. Jenkins, C.R. Rinaldo, Human herpesvirus 8 induces polyfunctional B lymphocytes that drive Kaposi's sarcoma, MBio 5 (2014) e01277–e1314.
[29] B. Bergler-Czop, L. Brzezińska-Wcisło, M. Kolanko, Iatrogenic Kaposi's sarcoma following therapy for rheumatoid arthritis, Postepy Dermatol. Alergol. 33 (2016) 149–155.
[30] G. Provenzano, A. Termini, C. Le Moli, F. Rinaldi, Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study, Ann. Rheum. Dis. 62 (2003) 680–681.
[31] A. Kumar, W. Abbas, G. Herbein, TNF and TNF receptor superfamily members in HIV infection: new cellular targets for therapy? Mediators Inflamm. 484378 (2013).
[32] R.P. Simmons, E.P. Scully, E.E. Groden, K.B. Arnold, J.J. Chang, K. Lane, J. Lifson, E. Rosenberg, D.A. Lauffenburger, M. Altfeld, HIV-1 infection induces strong production of IP-10 through TLR7/9-dependent pathways, AIDS 27 (2013) 2505–2517.
[33] J.M. Valverde-Villegas, R.M. de Medeiros, J.H. Ellwanger, B.R. Santos, M.G. Melo, S.E.M. Almeida, J.A.B. Chies, High CXCL10/IP-10 levels are a hallmark in the clinical evolution of the HIV infection, Infect Genet. Evol. 57 (2018) 51–58.
[34] K. Kawada, H. Hosogi, M. Sonoshita, H. Sakashita, T. Manabe, Y. Shimahara, Y. Sakai, A. Takabayashi, M. Oshima, M.M. Taketo, Chemokine receptor CXCR3 promotes colon cancer metastasis to lymph nodes, Oncogene 26 (2007) 4679–4688.
[35] B.K. Lo, M. Yu, D. Zloty, B. Cowan, J. Shapiro, K.J. McElwee, CXCR3/ligands are significantly involved in the tumorigenesis of basal cell carcinomas, Am. J. Pathol. 176 (2010) 2435–2446.
[36] E. Weiss, A.J. Mamelak, S. La Morgia, B. Wang, C. Feliciani, A. Tulli, D.N. Sauder, The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases, J. Am. Ac. Dermatol. 50 (2004) 657–675.
[37] J. Cai, T. Zheng, M. Lotz, Y. Zhang, R. Masood, P. Gill, Glucocorticoids induce Kaposi's sarcoma cell proliferation through the regulation of transforming growth factor-beta, Blood 89 (1997) 1491–1500.
[38] T.A. DiMaio, K.D. Gutierrez, M. Lagunoff, Kaposi's sarcoma-associated herpesvirus downregulates transforming growth factor β2 to promote enhanced stability of capillary-like tube formation, J. Virol. 88 (2014) 14301–14309.
[39] T. Maurer, M. Ponte, K. Leslie, HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load, N. Engl. J. Med. 357 (2007) 1352–1353.
[40] P. Unemori, K.S. Leslie, P.W. Hunt, E. Sinclair, L. Epling, R. Mitsuyasu, R.B. Effros, J. Dock, S.G. Dollard, S.G. Deeks, J.N. Martin, T.A. Maurer, Immunosenescence is associated with presence of Kaposi's sarcoma in antiretroviral treated HIV infection, AIDS 27 (2013) 1735–1742.
[41] R. Tedeschi, E. Bidoli, M.T. Bortolin, O. Schioppa, E. Vaccher, P. De Paoli, Plasma biomarkers of clinical response during chemotherapy plus combination antiretroviral therapy (cART) in HIV+ patients with advanced Kaposi sarcoma, Oncotarget 6 (2015) 30334–30342.
[42] E. Rohner, M. Kasaro, S.C. Msadabwe-Chikuni, K. Stinson, Z. Mohamed, H. Tweya, M. Egger, J. Bohlius, Treatment and outcome of AIDS-related Kaposi sarcoma in South Africa, Malawi and Zambia: an international comparison, Pan. Afr. Med. J. 24 (2017) 261.
[43] W. Mtonga, A. Mujajati, D. Munkombwe, A. Kalungia, L.T. Muungo, J. West, C. Wood, O. Ngalamika, Therapeutic outcomes in AIDS-associated Kaposi's Sarcoma patients on antiretroviral therapy treated with chemotherapy at two tertiary hospitals in Lusaka, Zambia, Curr. HIV Res. 16 (2018) 231–236.
[44] R. Bolanos, O. Martinez-Maza, Z. Zhang, S. Hussain, M. Sehl, J.S. Sinsheimer, G. D'Souza, F. Jenkins, S. Wolinsky, R. Detels, Decreased levels of the serum inflammatory biomarkers, sGP130, IL-6, sCRP and BAFF, are associated with increased likelihood of AIDS related Kaposi's sarcoma in men who have sex with men, Cancer Res. Front. 4 (2018) 45–59.
[45] N.M.O. Godinho, C.C. Gontijo, M.E.C.G. Diniz, G. Falcão-Alencar, G.C. Dalton, C.E.G. Amorim, R.S.S. Barcelos, M.N. Klautau-Guimarães, S.F. Oliveira, Regional patterns of genetic admixture in South America, Forens. Sci. Int. Genet. Suppl. Ser. 1 (2008) 329–330.
[46] T.C. Lins, R.G. Vieira, B.S. Abreu, D. Grattapaglia, R.W. Pereira, Genetic composition of Brazilian population samples based on a set of twenty-eight ancestry informative SNPs, Am. J. Hum. Biol. 22 (2010) 187–192.
[47] S.D. Pena, G. Di Pietro, M. Fuchshuber-Moraes, J.P. Genro, M.H. Hutz, S. Kehdy Fde, F. Kohlrausch, L.A. Magno, R.C. Montenegro, M.O. Moraes, M.E. de Moraes, M.R. de Moraes, E.B. Ojopi, J.A. Perini, C. Racciopi, A.K. Ribeiro-Dos-Santos, F. Rios-Santos, M.A. Romano-Silva, V.A. Sortica, G. Suarez-Kurtz, The genomic ancestry of individuals from different geographical regions of Brazil is more uniform than expected, PLoS One 6 (2011) e17063.
[48] J. Denner, M. Eschricht, M. Lauck, M. Semaan, P. Schlaermann, H. Ryu, L. Akyüz, Modulation of cytokine release and gene expression by the immunosuppressive domain of gp41 of HIV-1, PLoS One 8 (2013) e55199.
[49] J. Mait-Kaufman, E. Fakioglu, P.M. Mesquita, J. Elliott, Y. Lo, R.P. Madan, Chronic HIV infection is associated with upregulation of proinflammatory cytokine and chemokine and alpha defensin gene expression in colorectal mucosa, AIDS Res. Hum. Retroviruses 31 (2015) 615–622.
[50] Z. Wang, H. Shang, Y. Jiang, Chemokines and Chemokine Receptors: Accomplices for Human Immunodeficiency Virus Infection and Latency, Front. Immunol. 8 (2017) 1274.
[51] H. Ullum, M. Diamant, J. Victor, P.C. Gøtzsche, K. Bendtzen, P. Skinhøj, B.K. Pedersen, Increased circulating levels of interleukin-6 in HIV-seropositive

subjects, J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 13 (1996) 93–94.
[52] Venketaraman V, Morris D, Donohou C, Sipin A, Kung S, Oh H, Franklin M, Murad JP, Khasawneh FT, Saviola B, Guilford T, Donahue C. Role of cytokines and chemokines in HIV infection. HIV and AIDS-Updates on Biology, Immunology, Epidemiology and Treatment Strategies (2011) 281-300.
[53] Á.H. Borges, J.L. O'Connor, A.N. Phillips, F.F. Rönsholt, S. Pett, M.J. Vjecha, M.A. French, J.D. Lundgren, INSIGHT SMART and ESPRIT Study, Groups and the SILCAAT scientific committee. Factors associated with plasma IL-6 levels during HIV infection, J. Infect. Dis. 212 (2015) 585–595.
[54] Á.H. Borges, J.L. O'Connor, A.N. Phillips, J.D. Neaton, B. Grund, J. Neuhaus, M.J. Vjecha, A. Calmy, K.K. Koelsch, J.D. Lundgren, INSIGHT SMART Study and ESPRIT Groups, Interleukin 6 Is a stronger predictor of clinical events than high-sensitivity C-reactive protein or D-dimer during HIV infection, J. Infect. Dis. 214 (2016) 408–416.
[55] R.M. De Medeiros, J.M. Valverde-Villegas, D.M. Junqueira, T. Gräf, J.D. Lindenau, M.G. De Mello, P. Vianna, S.E. Almeida, J.A. Chies, Rapid and slow progressors show increased IL-6 and IL-10 levels in the Pre-AIDS stage of HIV infection, PLoS One 11 (2016) e0156163.
[56] K.I. Tasca, S.A. Calvi, Ldo R. Souza, Immunovirological parameters and cytokines in HIV infection, Rev. Soc. Bras. Med. Trop. 45 (2012) 663–669.