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ROSA HIOLANDA ABREU DE SOUSA

DESENVOLVIMENTO DO SARCOMA DE KAPOSI ORAL ASSOCIADO A CARGA VIRAL DO HIV, CD4 E RAZÃO DA CONTAGEM CD4+/CD8+

ORAL KAPOSI SARCOMA DEVELOPMENT IS ASSOCIATED WITH HIV VIRAL LOAD, CD4+ and CD4+/CD8+ RATIO COUNT

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Estomatologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master stomatopathology in stomatology area.

Orientador: Prof. Dr Helder Antônio Rebelo Pontes

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RESUMO

O Sarcoma de Kaposi (SK) é uma neoplasia maligna multissistêmica de origem endotelial, que pode exibir vários aspectos clínicos. Descrita pela primeira vez em 1972 pelo médico húngaro Moritz Kaposi, essa neoplasia compreende quatro subtipos diferenciados epidemiologicamente, onde o subtipo epidêmico é fortemente associado ao desenvolvimento de SK em pacientes vivendo com HIV/AIDS (Vírus da Imunodeficiência Humana/ Síndrome da Imunodeficiência Adquirida). A cavidade oral frequentemente é acometida pelas lesões produzidas pelo SK, onde 60% dos casos apresentam envolvimento oral e em 22% dos casos a mucosa oral é o local inicial de apresentação clínica do SK. Considerando a importância da compreensão dos aspectos relacionados ao desenvolvimento do SK em cavidade oral, este trabalho objetiva avaliar a influência da carga viral do HIV, a taxa de linfócitos CD4+ e CD8+ e a razão CD4 + / CD8 + no risco de desenvolvimento do SK oral. Os dados usados nesse trabalho foram obtidos de 62 pacientes HIV positivos, que foram divididos em dois grupos (32 com SK oral e 30 sem apresentação do SK em nenhuma parte do corpo). Posteriormente a regressão de Poisson foi aplicada a fim de investigar a associação entre o estado de imunossupressão e o desenvolvimento do SK oral, um valor de $P < 0,05$ foi considerado significativo. Foi observada uma relação expressiva entre os dados laboratoriais e o desenvolvimento de SK oral. Os resultados apontam que a contagem de CD4+ e a razão CD4 + / CD8 + estão fortemente associadas ao desenvolvimento de SK oral.

Palavras Chaves: Sarcoma de Kaposi. Câncer Oral. Diagnóstico.

ABSTRACT

Kaposi's Sarcoma (KS) is a malignant multisystemic neoplasm of endothelial origin, that shows various clinical aspects. Described for the first time in 1972 by the Hungarian doctor Moritz Kaposi, this neoplasm has four epidemiologically differentiated subtypes, where the epidemic is strongly associated with the development of KS in patients living with HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome). The oral cavity is frequently affected by lesions produced by KS, where oral involvement is observed in 60% of the cases, and 22% of the total cases have the oral mucosa as the starting point of clinical presentations of KS. Considering the relevance of understanding the aspects related to the development of KS in oral cavity, this work evaluates the influence of HIV viral load, CD4+ and CD8+ lymphocyte rate and the CD4 + / CD8 + ratio in the development of oral KS. The data used in this work was obtained from 62 HIV positive patients, that were divided in two groups (32 with oral KS and 30 without KS presentations in their body). Furthermore, a Poisson regression was used to evaluate the relation between the immunosuppressant state and the development of oral KS, a value of $P<0.05$ was considered significant. It was observed a strong relationship between the evaluated laboratory data and the development of oral KS. The results show that CD4+ rate and CD4+/CD8+ ratio are strongly associated with the development of oral KS.

Keyword: Kaposi's Sarcoma. Oral Cancer. Diagnosis.

SUMÁRIO

1 INTRODUÇÃO

O vírus da imunodeficiência humana (HIV) contribui para patogênese de inúmeras doenças incluindo alguns tipos de canceres considerados como definidores da Síndrome da Imunodeficiência Adquirida (do inglês acquired human immune deficiency syndrome/ AIDS) como Sarcoma de Kaposi (SK), Linfomas não Hodgkin (LNH) e Carcinoma cervical invasivo (CCV). Isso ocorre devido a uma desregulação imunológica provocada pelo HIV tornando permissivo a atividade de vírus oncogênicos como HHV8, EBV e HPV responsáveis pela expressão de vários genes que induzem a um processo neoplásico no hospedeiro infectado (Khan *et al* 2016; Yarchoan & Uldrick, 2018). A predisposição ao desenvolvimento neoplásico em pessoas vivendo com HIV/AIDS (PVHA) aumenta significativamente a mortalidade neste grupo (Angeletti, Zhang & Wood, 2008).

Segundo a UNAIDS estima-se que em 2018 cerca de 37,9 milhões de pessoas eram portadoras do vírus HIV, dos quais 1,1 milhão de pessoas morreriam de doenças relacionadas a AIDS (UNAIDS 2019), sendo o sarcoma de Kaposi (SK) o câncer mais comum entre pessoas vivendo com AIDS responsável por 19.902 mortes globalmente em 2018 (Pria *et al* 2019; Speicher *et al* 2016). O SK é um distúrbio angio-proliferativo caracterizado pela proliferação de células fusiformes de origem endotelial (Yarchoan & Uldrick, 2018). Descrito inicialmente em 1872 por Moritz Kaposi tendo como agente etiológico o Herpes Vírus Humano 8 (HHV8) (Angeletti, Zhang & Wood, 2008; Pria *et al* 2019). Existem quatro variantes do SK reconhecidas. Todas as formas apresentam o mesmo agente etiológico, HHV-8, porém, apresentam cursos clínicos diferentes. As formas clínicas descritas do SK são: SK clássico que afeta principalmente homens idosos do mediterrâneo, o SK africano (endêmico), e dois tipos ligados a imunossupressão que são o SK iatrogênico (associado a transplante) e o SK associado ao HIV / AIDS (epidêmico) (Angeletti, Zhang & Wood, 2008; Pria *et al* 2019; Speicher *et al* 2016)

O SK possui apresentação clinica diversificada e progressiva podendo exibir um aspecto de mácula de coloração vermelho-azulada, evoluindo para uma placa até chegar em uma apresentação nodular tumoral de envolvimento profuso, afetando desde tecidos cutâneos a vários órgãos particularmente o trato gastrointestinal, linfonodos, pulmões, ossos e mucosa oral (Yarchoan & Uldrick, 2018; Angeletti, Zhang & Wood, 2008). As lesões do SK geralmente envolvem a cavidade oral em 60 % dos casos, e cerca de 22% dos casos a mucosa oral é o local

inicial de apresentação clínica da doença, sendo associada a uma maior taxa de mortalidade quando comparadas com lesões cutâneas (Speicher *et al* 2016).

Poucos estudos têm sido publicados descrevendo os fatores contribuintes do desenvolvimento do SK em boca. Este estudo visou avaliar a influência da carga viral do HIV, dos níveis de linfócitos CD4 e CD8 e da relação CD4/CD8 com o aparecimento de lesões de sarcoma de Kaposi em boca.

2–ARTIGO: ARTIGO: ORAL KAPOSI SARCOMA DEVELOPMENT IS ASSOCIATED WITH HIV VIRAL LOAD, CD4+ and CD4+/CD8+ RATIO COUNT

Artigo submetido ao periódico Oral Sugery, Oral Medicine, Oral Pathology and Oral Radiology (Anexo 3)

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Running tittle: Oral Kaposi Sarcoma.

Keywords: cancer, oral, Kaposi's sarcoma, diagnostic.

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ABSTRACT

Objective: The purpose of the present research was to explore the association of HIV viral load, CD4+ and CD8+ counts and the CD4+/CD8+ ratio on the risk of oral Kaposi's sarcoma (KS) development.

Materials and methods: A total of 62 patients were retrieved from March 2008 to October 2020 from the files of two oral pathology centres. Clinical, laboratory and follow-up data were retrieved from their medical files. Poisson regression was used to explore the role of history of immunosuppression and its association with oral KS development. A P-value <0.05 was considered significant.

Results: Sixty-two patients were included in the present study (32 with oral KS and 30 with no presentation of lesions anywhere on the body). Patients with oral KS presented a mean age of 32.6 years, and male patients were more affected. The hard palate (15 cases; 46.8%) was the main anatomical site affected. The lesions were mostly presented as swellings (13 cases; 40.6%) and nodules (12 cases; 37.5%). Systemic manifestations were also observed, including candidiasis (4 cases; 12.5%), bacterial infection (3 cases; 9.3%), tuberculosis (3 cases; 9.3%), herpes simplex (3 cases; 9.3%) and pneumonia (3 cases; 9.3%). A significant correlation was observed between HIV viral load, CD4+ count and the CD4+/CD8+ ratio with oral KS development.

Conclusions: HIV viral load, CD4+ count and the CD4+/CD8+ ratio are associated with oral KS development.

INTRODUCTION

Kaposi's sarcoma (KS) is an uncommon, multifocal, angioproliferative lesion initially described by Moritz Kaposi in 1872[1,2]. The tumour is formed by the endothelial cells of blood and lymphatic vessels and shows a variety of clinical, epidemiological and immunophenotypic characteristics[3,4]. KS was classified epidemiologically by Antman and Chang in 2000: 1) the classic form occurs in middle-aged or elderly patients, 2) the endemic type is presented in Sub-Saharan Africa, 3) the epidemic category is AIDS associated and 4) the iatrogenic type is related to immunosuppression in patients receiving anti-rejection therapy for transplanted organs[5,6]. The aetiology of KS is associated with human herpesvirus-8 (HHV8) in all epidemiologic subtypes of the lesion[7,8].

KS is recognized as an AIDS-defining cancer, along with non-Hodgkin's lymphoma and invasive cervical cancer[3,8,9]. Clinically, lesions may be presented in the skin, oral mucosa, gastrointestinal tract, lymph nodes and lungs[8,10]. When the oral cavity is affected, lesions can demonstrate a variable morphology, from plaques to swellings with a purple or dark-brown appearance[6,11,12]. In addition, KS was identified as the second most common sarcoma of the oral cavity according to a multicentre study of oral sarcomas in the Brazilian population[11].

The prognosis for people living with HIV/AIDS (PLWHA) improved with the initiation of highly active antiretroviral therapy (HAART) in the mid '90s[13,14]. KS is the most common neoplasm in PVHA, even after que introduction of the HAART, which generated a significant decline in the KS occurrence rate, HIV+ patients, especially those with poor adherence to treatment or that did not received any kind of therapy, are 500 more susceptible to develop KS[15]. Despite significant advances in KS therapy, the innate immune system contributes significantly to treatment effectiveness[3-5]. HIV viral load, CD4+ and CD8+ levels and the CD4+/CD8+ ratio are all very important in the assessment of the patients' systemic condition[8,10].

Due to countless reports of KS as the first manifestation of HIV/AIDS, several clinical studies evaluating the patients' systemic condition have related KS development with HIV viral load, CD4+ and CD8+ levels and the CD4+/CD8+ ratio[16,17]. To the best of our knowledge, the association of patients' systemic condition and the development of oral KS has not been well established. Thus, the aim of this study is to evaluate the association of HIV viral load, CD4+ and CD8+ levels and the CD4+/CD8+ ratio with the development of oral KS.

MATERIAL AND METHODS

Study design and ethical approval

This research was developed on the files from two oral pathology centres of Brazil. Samples were retrieved from the centres over a period of 12 years (from March 2008 to October 2020). The diagnosis centres were João de Barros Barreto University Hospital, Federal University of Pará, Belém/Brazil and Instituto do Câncer do Estado de São Paulo (ICESP-FMUSP), São Paulo/Brazil. Expert oral pathologists from each centre evaluated the samples. The ethics committee of the João de Barros Barreto University Hospital approved this work. The patients' identities remained anonymous according to the Declaration of Helsinki.

Samples

KS in the oral cavity were recovered, and data regarding sex, age, location, clinical aspects, HIV/KS diagnosis and laboratory findings (HIV viral load, CD4+, CD8+ and CD4+/CD8+) were retrieved. Ranges of laboratory findings were classified following Taiwo & Hassan (2010), that categorize the count of CD4+ cells and the viral load in certain parameters, were CD4 $\geq$ 500/ml are classified as marginally immunodeficient, CD4 with values between 200/ml and 500ml are classified as lightly immunodeficient, and values below 200/ml are classified as severe immunodeficient. As for the viral load categorization, values less or equal to 10.000 copies/ml are classified as degree 1, while values above 10.000 copies/ml are classified as degree 2. In cases that oral KS was not confirmed, when patients refused to participate the research and when laboratory tests were not assessed represented the exclusion criteria. Lesions were diagnosed following the methods of our study group[19]. For a better diagnosis, all cases were also stained with CD34, D2-40 (podoplanin), Prox-1 and HHV8 (Figure 1).

Immunohistochemistry

For the immunohistochemical (IHC) polymer-based method, 3-μm-thick sections mounted on silanized slides were used. The sections were deparaffinized, rehydrated in graded ethanol solutions and submitted to antigen retrieval with EDTA/Tris buffer (pH 9.0) in an electric pressure cooker for 15 minutes. Following that, endogenous peroxidase activity was blocked with 20%-H2O2 with a single 15-minute incubation. The sections were then incubated with the diluted primary antibodies for two hours at room temperature. The high-sensitive visualization system EnVision G|2 System/AP, Rabbit/Mouse (Permanent Red) (code K535521-2, Dako)

was used. The IHQ reactions were revealed with Permanent Red (Dako), and counterstained with Carazzi's haematoxylin. Positive and negative controls were used to validate the reactions.

Data analysis

Means and percentages are presented as descriptive statistics. Poisson regression was used to explore the role of the prevalence of immunosuppression and the association of oral KS development, exploring viral load, CD4+, CD8+ and CD4+/CD8+ levels. A P-value <0.05 was considered statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY).

RESULTS

A total of 62 patients, including 32 patients with clinical presentation of oral KS (Table 1) and 30 patients with no KS lesions on the body were included in this research (Table 2).

Regarding patients with oral KS, a mean age of 32.6 years (range of 19–58 years old) was observed. Male patients were mostly affected, with a M:F ratio of 10.6:1. The hard palate (15 cases; 46.8%) was the main location of the lesion, followed by the alveolar ridge (6 cases; 18.7%), soft palate (6 cases; 18.7%), tongue (5 cases; 15.6%) and gums (5 cases; 15.6%). The mandible (2 cases; 6.2%), maxilla (1 case; 3.1%), lower lip (1 case; 3.1%) and upper lip (1 case; 3.1%) were less frequently seen. Lesions were presented as swellings (13 cases; 40.6%), nodules (12 cases; 37.5%), plaques (5 cases; 15.6%) and spots (2 cases; 6.2%). They showed purple (53.1%) and red colouration (15 cases; 46.8%). In addition, oral KS showed bleeding in 15 cases (46.8%) and pain in 14 cases (43.7%). The lesions were the first manifestation of HIV/AIDS in 23 cases (71.8%). Patients also showed lesions in the skin (10 cases; 31.2%), intestine (4 cases; 12.5%), stomach (4 cases; 12.5%), trachea (3 cases; 9.3%), lung (3 cases; 9.3%), eyes (1 case; 3.1%) and pharynx (1 case; 3.1%). Systemic comorbidities were observed in 16 cases (50%) and candidiasis (4 cases; 12.5%), bacterial infection (3 cases; 9.3%), tuberculosis (3 cases; 9.3%), herpes simplex (3 cases; 9.3%), pneumonia (3 cases; 9.3%), gastroenteritis (2 cases; 6.2%), syphilis (2 cases; 6.2%) and meningitis (2 cases; 6.2%) were most often seen.

The control group had a mean age of 41.6 years (range of 25–61 years), and male patients were more frequently affected than females, with a M:F ratio of 1.3:1. Oral

manifestation was observed in 5 patients (16.6%), and candidiasis (3 cases; 10%), oral herpes (2 cases; 6.6%) and hairy leucoplakia (1 case; 3.3%) were the manifestations seen. Systemic comorbidities were observed in all cases, and tuberculosis (14 cases; 46.6%), meningitis (5 cases; 16.6%), neurotoxoplasmosis (5 cases; 16.6%), bacterial infection (4 cases; 13.3%), scabies (2 cases; 6.6%), pneumopathy (2 cases; 6.6%) and syphilis (2 cases; 6.6%) were the main presentations.

Laboratory findings of patients who presented oral KS evidenced a mean HIV viral load of 149,487.6 copies/mL (range of 0–1,556,502 copies/mL), mean CD4+ count of 155.9 cells/mm^3 (range of 2–837 cells/mm^3), mean CD8+ count of 944.8 cells/mm^3 (range of 143–3056 cells/mm^3) and mean CD4+/CD8+ of 0.17 cells/mm^3 (range of 0.01–0.70 cells/mm^3). The control group showed a mean HIV viral load of 592,295.6 copies/mL (range of 69–6,254,071 copies/mL), mean CD4+ count of 112.5 cells/mm^3 (range of 10–540 cells/mm^3), mean CD8+ count of 996.6 cells/mm^3 (range of 229–4557 cells/mm^3) and mean CD4+/CD8+ count of 0.16 cells/mm^3 (range of 0.01–0.57 cells/mm^3).

Statistical analysis evidenced by the Poisson regression test for prevalence analysis that HIV viral load (HR 95% CI: 1.6517 [1.4681–4.2033]; p<0.0001), CD4+ level (HR 95% CI: 2.8058 [0.0667–8.5103]; p<0.0001) and CD4+/CD8 level (HR 95% CI: 1.7613 [0.7740–2.1304]; p<0.0001) were significantly associated with oral KS development.

DISCUSSION

Clinical and pathological information regarding oral KS is still very limited due to the diverse clinical presentation and because lesions are mostly presented in late manifestation of HIV/AIDS, when patients' systemic condition shows a severe debilitation[19-21]. The complete aetiopathogeneses of oral KS remains unclear, although HHV-8 represents the main etiological agent. It is well-established that combination of HHV-8 and impaired host immunity causes KS[22,23]. The patient's immune system is evaluated by laboratory analysis of HIV viral load, CD4+, CD8+ and the CD4+/CD8+ ratio, and their influence on clinical disease manifestation has been widely discussed[3,24,25]. Thus, the aim of the study was to correlate HIV viral load, CD4+, CD8+ and the CD4+/CD8+ ratio and their influence on oral KS development.

Clinically, oral KS demonstrated a male predominance, similar to previous literature[26,5,16]. The lesions were most commonly presented in young patients and rarely affect elderly individuals, despite some studies having shown an increase in HIV/AIDS infection and

the incidence of oral KS in patients aged 50 and over[27,28]. When presented in the oral cavity, KS is most frequently diagnosed in the hard and soft palate, although the tongue, gingiva, buccal mucosa and jaw bones may also be involved[2,11,26]. Oral tumours may present a wide diversity of presentations, varying from single spots to bleeding, painful and necrotic swellings[2,26]. They also may present colour alteration in the buccal mucosa due to their angiogenic origin, ranging from red to purple lesions[5,7,8,26].

The systemic affliction of HIV/AIDS patients generally causes, besides the oral cavity, development of KS in the skin, gastrointestinal and respiratory complex, consistent with the findings of the present study[29,30]. Systemic conditions commonly associated with immunocompromised patients were also observed, including oral presentation of candidiasis and herpes simplex, as well as systemic diseases including tuberculosis, pneumonia, gastroenteritis, syphilis and meningitis[31,32]. The evaluation of patients' systemic condition is very important to prevent the development of advanced disease stages and to decrease the presence of comorbidies[29,31].

Medical follow-ups of PLWHA generally involve a multidisciplinary assessment based on laboratory findings, including HIV viral load, CD4+, CD8+ and CD4+/CD8+, and other complementary exams when necessary[31]. However, there was an increase in the number of reports of oral KS as the first manifestation of HIV/AIDS, such increase was consistente with the findings of our study in which 71.8% of patients presented oral lesions as the first manifestation of the disease[16,17]

Thus, laboratory exams may be presented as a good option to evaluate patients' systemic condition[8,10,15,30]. The goal of this study was to explore the association of HIV viral load, CD4+, CD8+ and CD4+/CD8+ levels and oral KS development compared with a control group with no lesions on the body. Interestingly, HIV viral load, CD4+ and CD4+/CD8+ levels showed significant results when compared with the control group. Rezende et al.[33] and Chan & Pakianathan[34] observed a relationship of HIV viral load with AIDS-related KS, resulting in a significant relationship of HIV viral load and upper gastrointestinal KS, consistent with our findings. Many studies have explored the association of CD4+ cell count with AIDS-related KS, and they showed a significant correlation of KS development when a CD4+ cell count $\leq$200 cells/mm^3 was observed, similar to our results[35,36]. In addition, Poizot-Martin et al.[35] reported that a CD4+/CD8+ ratio $\leq$0.5 increased the risk of development of KS, corroborating our results as we showed a significant higher probability of developing oral KS with altered CD4+/CD8+

ratio levels. Hence, the clinical significance of HIV viral load, CD4+ count and the CD4+/CD8+ ratio is noteworthy in the development of oral KS.

More recently, KS genomics has gained attention over the past decades due to its remarkable pathogenic mechanisms. The association of the HHV-8 genome and KS development has been explored worldwide. It has been shown that more than 80 genes are expressed in the regulated transcriptional program that promotes latency with very limited viral expression or supports lytic replication with the production of progeny virions[37-39]. The cellular tropism of HHV-8 in KS includes epithelial, endothelial and B cells and more recently has been expanded to include neurons[39,40].

Despite the limitations on the number of patients to validate the current results, this is the first study to explore laboratory findings and oral KS development as an alternative method to improve diagnostic accuracy. Additionally, it is important to clarify that the CD8 + indices did not generate significant results related to the development of oral KS. knowledge of the influence of other etiologic factors is important to better establish the etiopathogenesis and pathogenesis of the disease, as well as to determine the gene alterations related to KS development.

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CONFLICT OF INTEREST STATEMENT

None.

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FIGURE LEGENDS

Figure 1. Histopathological and immunohistochemistry analysis of oral KS. A) Proliferation of spindle cells intermixed with numerous congested blood vessels (H&E, 100x). B) Spindle cells with significant pleomorphism and presence of blood-filled slits like spaces (H&E, 200x). Immunohistochemistry reaction showing positivity for HHV-8 (DAB, 200x) (C), CD34 (DAB, 200x), D2-40 (podoplanin) (DAB, 200x) and Prox-1 (DAB, 200x).

Figure 2. Different clinical presentations of oral KS in the analysed patients. A) A 35-year-old male patient presented a painful swelling in the hard palate with superficial areas of necrosis. B) A 39-year-old male patient with a nodular lesion in the hard palate. C) A 31-year-old male patients demonstrated extensive bleeding and a necrotic lesion in the hard palate. D) A 58-year-old male patient presented a bleeding nodule in the hard palate. E) A 30-year-old male patient showed an asymptomatic purple spot in the hard palate. F) A 25-year-old male patient was presented with a necrotic lesion and bleeding in the hard palate associated with posterior teeth, as well as two nodules in the soft palate. G) A 23-year-old male patient demonstrated a bleeding and painful swelling in the posterior tongue with necrotic areas. H) A 41-year-old male patient was referred with an ulcerated swelling in the hard palate. I) A 25-year-old male patient presented with a painful and ulcerated lesion in the lower lip.

TABLE LEGENDS

Table 1. Clinicopathological features of patients affected by oral KS.

Table 2. Clinicopathological features of patients from the control group who did not present with oral KS.

Table 3. Laboratory findings of the analysed patients.

Table 4. Poisson regression analysis.

Table 1. Clinicopathological features of patients affected by oral KS.

	Sex/Age	Location	Clinical aspect	Color	Bleeding	Pain	1st sign of HIV/AIDS	Other affected sites	Comorbidities
Case 1	M/22	Hard palate	Swelling	Purple	N	N	Y	None	None
Case 2	M/21	Tongue/Hard palate	Nodule	Red	Y	Y	N	Skin/Trachea/Lung/Intestine	Gastroenteritis/bacterial infection
Case 3	M/23	Tongue	Swelling	Purple	Y	Y	Y	None	Disseminated candidiasis
Case 4	M/58	Hard palate	Nodule	Purple	Y	N	Y	None	Neurosyphilis
Case 5	M/29	Gum	Swelling	Purple	N	Y	Y	None	Tuberculosis/Syphilis
Case 6	M/34	Gum	Swelling	Red	Y	Y	Y	None	Bacterial infection
Case 7	M/31	Hard palate/Alveolar ridge	Swelling	Purple	Y	N	Y	Skin/Eyes	None
Case 8	M/22	Soft palate	Plaque	Red	N	N	Y	None	Herpes/Candidiasis
Case 9	M/27	Hard palate	Nodule	Purple	N	N	N	None	Herpes/Pneumonia
Case 10	M/36	Hard palate/Alveolar ridge/Tongue	Swelling	Purple	Y	Y	Y	Skin/Trachea	Bacterial infection
Case 11	M/37	Alveolar ridge/Mandible	Swelling	Purple	N	Y	N	Skin/Lung/Stomach	Tuberculosis/Erysipelas
Case 12	M/25	Hard palate/Soft palate/Alveolar ridge	Swelling	Purple	Y	Y	N	None	None
Case 13	M/19	Hard palate	Nodule	Red	Y	N	Y	None	None
Case 14	M/21	Mandible	Plaque	Red	Y	Y	Y	None	None
Case 15	M/30	Maxilla	Swelling	Purple	Y	Y	Y	Skin/Stomach/Intestine	Meningitis

Case 16	F/27	Soft palate	Plaque	Red	Y	Y	Y	None	Meningitis/Candidiasis
Case 17	M/25	Lower lip	Swelling	Red	N	Y	Y	None	None
Case 18	F/30	Soft palate	Nodule	Red	Y	Y	N	None	Tuberculosis/Syphilis
Case 19	M/39	Hard palate	Nodule	Purple	Y	N	Y	None	Herpes/Ulcerative enterocolitis
Case 20	M/28	Tongue/Hard palate	Nodule	Red	Y	Y	Y	Stomach/Intestine	Cytomegalovirus/Pneumonia
Case 21	M/46	Soft palate	Plaque	Red	N	N	Y	None	None
Case 22	M/37	Gum	Nodule	Red	Y	Y	N	None	Pneumonia/Gastroenteritis/Septicemia/Agranulocytosis/Candidiasis
Case 23	M/44	Tongue	Nodule	Purple	N	N	Y	None	Lymphoma
Case 24	M/33	Hard palate/Gum	Nodule	Red	N	N	N	Skin	None
Case 25	M/30	Hard palate	Nodule	Red	N	N	Y	Skin/Stomach/Intestine	None
Case 26	M/30	Hard palate	Spot	Purple	N	N	Y	None	None
Case 27	M/36	Hard palate/Gum	Plaque	Purple	N	N	Y	Skin	None
Case 28	M/29	Alveolar ridge	Swelling	Red	N	N	Y	Skin	None
Case 29	F/41	Soft palate	Swelling	Purple	N	N	Y	Lung/Pharynx	None
Case 30	M/44	Alveolar ridge	Swelling	Red	N	N	N	Trachea	None

Case 31	M/50	Upper lip	Nodule	Purple	N	N	Y	Skin	None
Case 32	M/41	Hard palate	Spot	Purple	N	N	N	None	None

Table 2. Clinicopathological features of patients from the control group and did not present oral KS.

	Sex/Age	Oral manifestation	Comorbidities
Case 1	M/44	Oral herpes	Tuberculosis/Scabies/Pneumopathy
Case 2	M/44	None	Tuberculosis/Meningitis
Case 3	M/39	None	Osteomielitis
Case 4	M/55	None	Pneumocystosis/Pneumopathy
Case 5	M/44	None	Tuberculosis
Case 6	M/40	None	Syphilis/Erysipela/Osteonecrosis
Case 7	F/27	None	Cryptococosis
Case 8	F/44	None	Bacterial infection
Case 9	F/61	None	Tuberculosis/Meningitis
Case 10	F/43	Candidiasis	Neurotoxoplasmosis/Collelitiase/Herpes Zoster
Case 11	F/32	None	Cryptococosis/Neurotoxoplasmosis/Tuberculosis
Case 12	F/25	Candidiasis	Tuberculosis/Genital warts/Cerebral cryptococosis/Scabies
Case 13	F/48	Candidiasis/Hairy leukoplakia	Pneumocystosis
Case 14	F/46	None	Bacterial infection
Case 15	M/25	None	COVID-19
Case 16	M/60	None	Tuberculosis
Case 17	M/39	None	Neurotoxoplasmosis/Pneumocystosis/Meningitis
Case 18	F/43	None	Tuberculosis
Case 19	F/37	None	Neurotoxoplasmosis
Case 20	M/28	None	Meningitis
Case 21	M/55	Oral herpes	Syphilis/Pneumonia
Case 22	M/43	None	Neurotoxoplasmosis/Tuberculosis
Case 23	M/37	None	Tuberculosis/Pancreatitis
Case 24	M/38	None	Tuberculosis
Case 25	M/32	None	Histoplasmosis
Case 26	M/44	None	Bacterial infection
Case 27	F/30	None	Tuberculosis
Case 28	F/56	None	Tuberculosis
Case 29	F/53	None	Bacterial infection
Case 30	M/29	None	Tuberculosis/Meningitis

Table 3. Laboratory findings of the analyzed patients.

	Oral KS				**Control Group**			
	HIV Viral load (copies/mL)	CD4+ (cells/mm^3)	CD8+ (cells/mm^3)	CD4+/CD8+ (cells/mm^3)	HIV Viral load (copies/mL)	CD4+ (cells/mm^3)	CD8+ (cells/mm^3)	CD4+/CD8+ (cells/mm^3)
Case 1	91442	216	1399	0.15	ND	185	741	0.25
Case 2	232	131	1186	0.11	101	158	524	0.30
Case 3	156799	179	1788	0.10	4751	93	995	0.09
Case 4	233346	103	1296	0.08	205	209	1635	0.13
Case 5	0	71	410	0.17	616182	121	2134	0.06
Case 6	2495	101	1208	0.08	50024	540	1206	0.45
Case 7	144680	91	882	0.10	598890	19	257	0.07
Case 8	505865	31	652	0.05	478	98	312	0.31
Case 9	28988	57	789	0.07	587462	19	925	0.02
Case 10	402	379	600	0.63	3242533	155	586	0.26
Case 11	1556502	142	1593	0.09	6488	57	229	0.25
Case 12	289329	15	500	0.03	67783	10	229	0.04
Case 13	>500000	123	655	0.19	6254071	163	4557	0.04
Case 14	53298	23	1313	0.02	11396	57	877	0.06
Case 15	>500000	2	227	0.01	8859	103	570	0.18
Case 16	323026	5	200	0.03	24143	113	1242	0.09
Case 17	3916	71	672	0.11	49970	50	1543	0.03
Case 18	21395	674	3056	0.22	312211	35	275	0.13
Case 19	121334	99	455	0.22	114701	85	1345	0.06
Case 20	72592	31	627	0.05	581167	18	758	0.02
Case 21	313784	30	536	0.06	1629621	168	1150	0.15

Case 22	162098	143	559	0.26	259	109	2067	0.05
Case 23	0	837	1445	0.58	327000	12	1200	0.01
Case 24	137	380	1178	0.32	131519	216	2097	0.10
Case 25	101999	82	559	0.15	11025	28	259	0.11
Case 26	1211	340	1355	0.25	9107	151	526	0.29
Case 27	4359	11	853	0.01	1803218	66	504	0.13
Case 28	5708	200	1741	0.11	70272	196	343	0.57
Case 29	248412	59	599	0.10	663068	64	522	0.12
Case 30	0	66	913	0.07	69	78	292	0.27
Case 31	41006	199	845	0.24	-	-	-	-
Case 32	273	100	143	0.70	-	-	-	-

Table 4. Poisson regression analysis.

Laboratory findings	**HR (95% CI)**	**P-value**
HIV viral load	1.6517 (1.4681 - 4.2033)	<0.0001
CD4+	2.8058 (0.0667 - 8.5103)	<0.0001
CD8+	2.4227 (1.2668 - 7.0260)	0.3818
CD4+/CD8+	1.7613 (0.7740 - 2.1304)	<0.0001

Figure 1. Histopathological and immunohistochemistry analysis of oral KS.

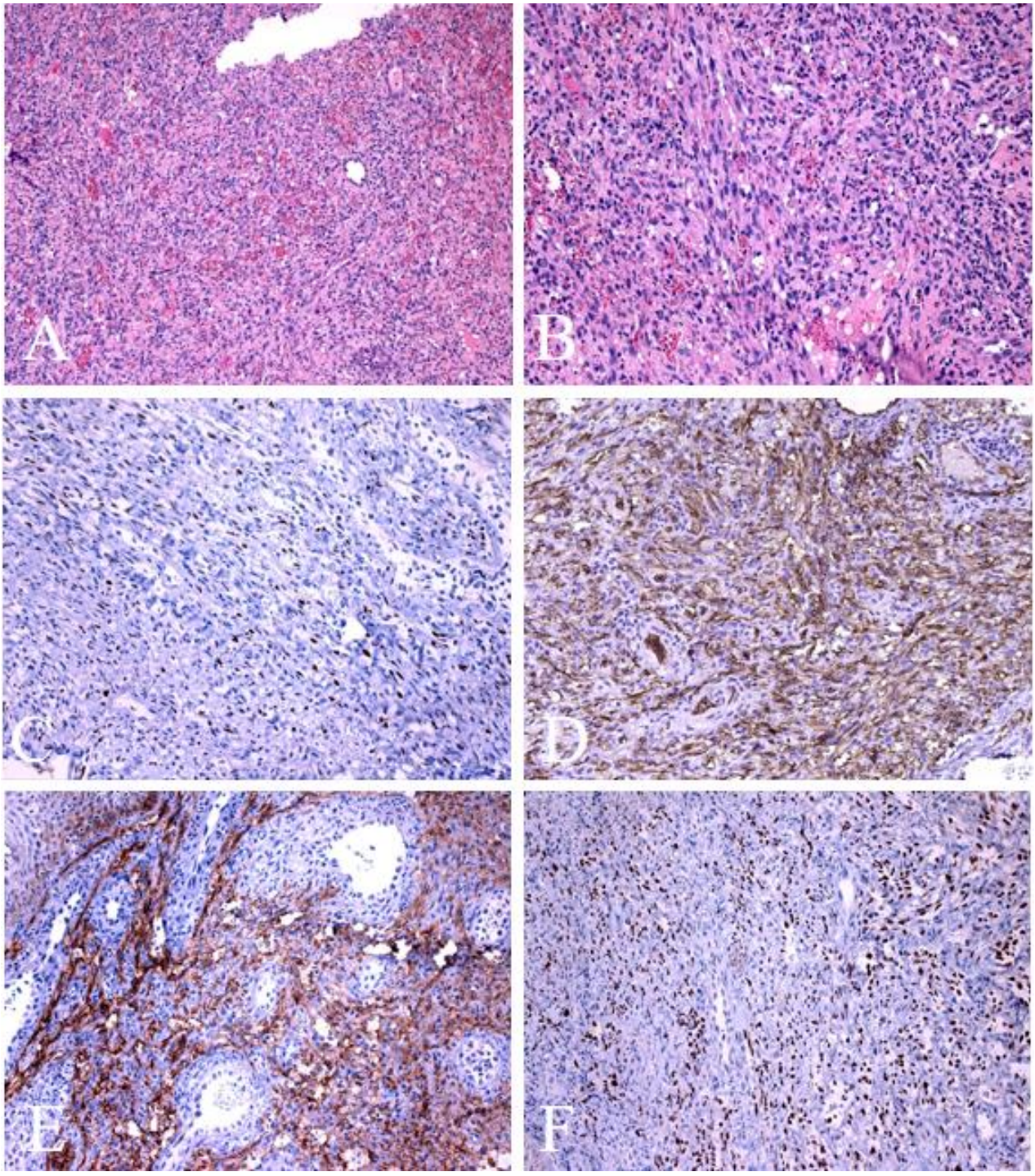
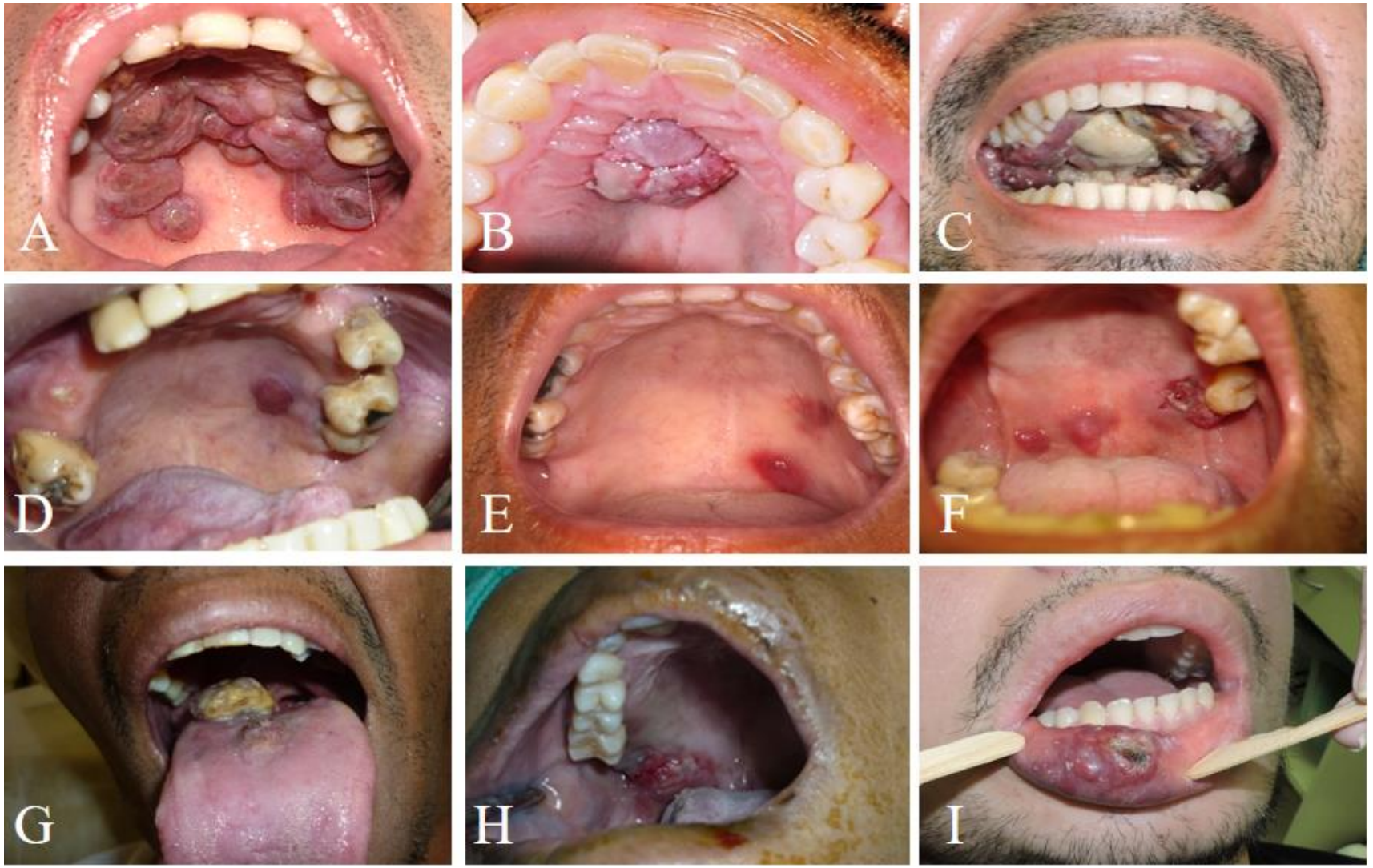


Figure 2: Clinical presentations of oral KS



3-CONCLUSÃO

Este trabalho demonstrou que as taxas de CD4+ e razão CD4+/CD8+ e carga viral do HIV exibem associação significativa no desenvolvimento de Sarcoma de Kaposi oral. Até onde podemos identificar, este trabalho foi o primeiro estudo a explorar a correlação de dados laboratoriais de perfil imunovirológico de pacientes vivendo com HIV/AIDS com o desenvolvimento do SK oral, contribuindo deste modo, para compreensão da patogênese envolvida no desenvolvimento do Sarcoma de Kaposi oral.

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ANEXOS

Anexo 1: Certificado do Comitê de Ética em Pesquisa

UFPA - HOSPITAL UNIVERSITÁRIO JOÃO DE BARROS BARRETO DA UNIVERSIDADE FEDERAL DO PARÁ

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Avaliação dos níveis de CD4 e da carga viral de pacientes portadores do vírus da imunodeficiência humana que apresentem neoplasias malignas de boca.
Pesquisador: HÉLDER ANTÔNIO REBELO PONTES
Área Temática:
Versão: 2
CAAE: 28202120.9.0000.0017
Instituição Proponente: Hospital Universitário João de Barros Barreto - UFPA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.483.768

Apresentação do Projeto:
Emenda para inclusão como membro da equipe de pesquisa de Rosa Hiolanda Abreu de Sousa, aluna do Programa de Pós-Graduação em Estomatopatologia da Faculdade de Odontologia de Piracicaba/ Universidade Estadual de Campinas, no presente projeto, considerando que a pesquisa servirá de subsídio para elaboração de sua dissertação de mestrado sob orientação do Prof. Dr. Hélder Antônio Rebelo Pontes. Encaminhado conforme requerido a carta de anuência da UNICAMP.

Existem poucos trabalhos no Brasil que avaliam a prevalência de neoplasias malignas de boca em pacientes portadores do vírus HIV, bem como estudem sua correlação com marcadores laboratoriais de acompanhamento, portanto, esse estudo terá como finalidade Avaliar os níveis de CD4 e da carga viral de pacientes portadores do vírus da imunodeficiência humana que apresentem neoplasias malignas diagnosticadas em um centro de referência do Brasil em comparação com um grupo controle de pacientes diagnosticados com o HIV não acometidos por neoplasias malignas. Isto ocorrerá por meio da análise de prontuários e exames no período de janeiro de 2007 a dezembro de 2019. Serão selecionados prontuários de pacientes com
sorologia positiva para HIV por centros de testagem do Sistema Único de Saúde que não apresentem neoplasias de boca e que apresentem neoplasias de boca com diagnóstico confirmado

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através de análise histopatológica. Sendo avaliados sexo, idade, contagem de linfócitos CD4, carga viral, sobrevida e evolução. Os dados serão organizados na tabela do Excel. De acordo com os resultados, vamos observar se há correlação da presença das neoplasias malignas bucais em pacientes HIV+ com seus níveis de CD4 e com a carga viral em comparação a um grupo controle,além de verificar padrões clínico-patológicos. Portanto, esse trabalho pode ser uma fonte de estudos de pesquisas futuras em outros centros de referência. A identificação das manifestações orais dessas neoplasias é importante, uma vez que pode sugerir possível infecção pelo HIV em um indivíduo que desconhece sua condição sorológica. Ao lado disso, a identificação dessas neoplasias em um paciente sabidamente infectado pode sinalizar a progressão da infecção pelo HIV e a necessidade de início ou ajuste da terapia na terapia antirretroviral.

Objetivo da Pesquisa:
Avaliar os níveis de CD4 e da carga viral de pacientes portadores do vírus da imunodeficiência humana que apresentem neoplasias malignas diagnosticadas em um centro de referência do Brasil em comparação com um grupo controle de pacientes diagnosticados com o HIV não acometidos por neoplasias malignas.

Avaliação dos Riscos e Benefícios:
Riscos:
Os riscos com a pesquisa em questão serão mínimos. Estes são em relação ao risco de quebra da confidencialidade e privacidade dos usuários. Entretanto, serão tomadas todas as medidas necessárias para proteção e minimização dos mesmos. Os pesquisadores envolvidos garantem que não utilizarão das informações coletadas nos prontuários para manter qualquer contato com os usuários e/ou familiares.

Benefícios:
Os benefícios com a realização da pesquisa e análise dos resultados incluem a avaliação da relação de marcadores laboratoriais com neoplasias malignas em pacientes soropositvos. Além disso, estimar a sobrevida e evolução dos mesmos, podendo ser uma fonte de estudos de pesquisas futuras em outros centros de referência.

Comentários e Considerações sobre a Pesquisa:
Pesquisa relevante.

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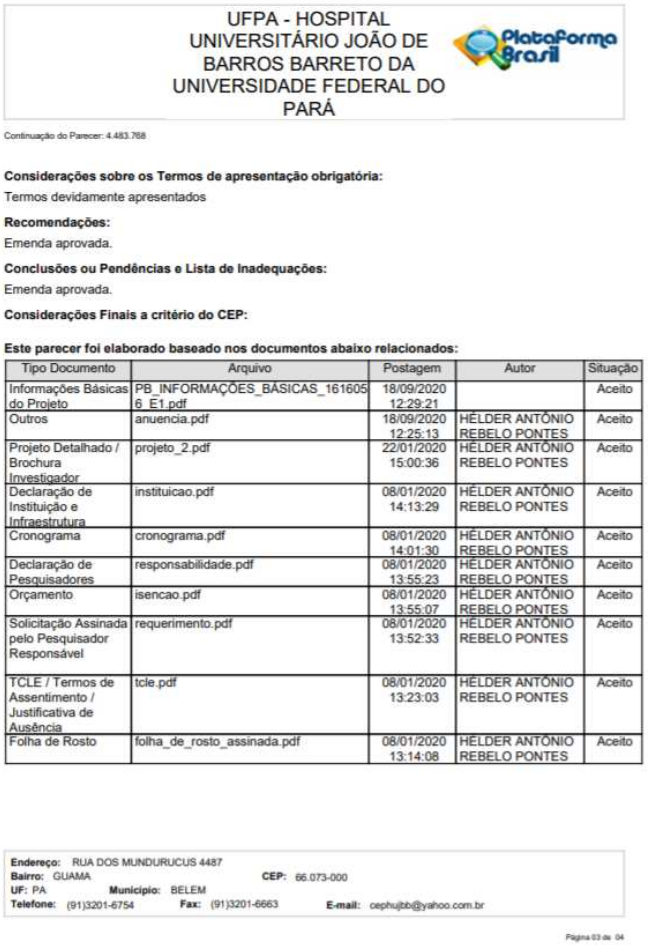
Anexo 1: Certificado do Comitê de Ética em Pesquisa



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Continuação do Parecer: 4.483.768

Considerações sobre os Termos de apresentação obrigatória:

Termos devidamente apresentados

Recomendações:

Emenda aprovada.

Conclusões ou Pendências e Lista de Inadequações:

Emenda aprovada.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1616056_E1.pdf	18/09/2020 12:29:21		Aceito
Outros	anuencia.pdf	18/09/2020 12:25:13	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Projeto Detalhado / Brochura Investigador	projeto_2.pdf	22/01/2020 15:00:36	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Declaração de Instituição e Infraestrutura	instituicao.pdf	08/01/2020 14:13:29	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Cronograma	cronograma.pdf	08/01/2020 14:01:30	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Declaração de Pesquisadores	responsabilidade.pdf	08/01/2020 13:55:23	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Orçamento	isencao.pdf	08/01/2020 13:55:07	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Solicitação Assinada pelo Pesquisador Responsável	requerimento.pdf	08/01/2020 13:52:33	HÉLDER ANTÔNIO REBELO PONTES	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	tcle.pdf	08/01/2020 13:23:03	HÉLDER ANTÔNIO REBELO PONTES	Aceito
Folha de Rosto	folha_de_rosto_assinada.pdf	08/01/2020 13:14:08	HÉLDER ANTÔNIO REBELO PONTES	Aceito

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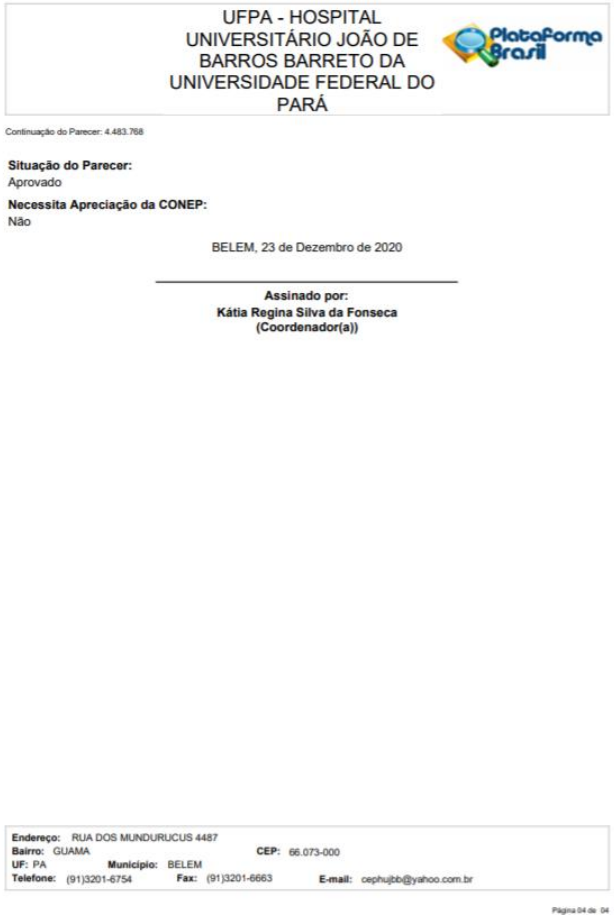

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Continuação do Parecer: 4.483.768

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

BELEM, 23 de Dezembro de 2020

Assinado por:
Kátia Regina Silva da Fonseca
(Coordenador(a))

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Anexo 2: Certificado de Originalidade e Prevenção Contra Plagio.

ORAL KAPOSI SARCOMA DEVELOPMENT IS ASSOCIATED WITH HIV VIRAL LOAD, CD4+ COUNT and CD4+/CD8+ RATIO - R3

RELATÓRIO DE ORIGINALIDADE

25%	12%	23%	4%
ÍNDICE DE SEMELHANÇA	FONTES DA INTERNET	PUBLICAÇÕES	DOCUMENTOS DOS ALUNOS

CORRESPONDER A TODAS AS FONTES(SOMENTE AS FONTES IMPRESSAS SELECIONADAS)

17%

★ Pablyanne Tereza Louzada Guedes, Flavia Sirotheau Correa Pontes, Ana Carolina Prado-Ribeiro, Leticia Rodrigues-Oliveira et al. "HIV POSITIVE PATIENTS WITH ORAL KAPOSI'S SARCOMA: AN OVERALL SURVIVAL ANALYSIS OF 31 PATIENTS.", Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 2020

Publicação

Excluir citações	Desligado	Excluir correspondências	Desligado
Excluir bibliografia	Em		

Anexo 3: Comprovante de Submissão do Artigo

Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology

ORAL KAPOSI SARCOMA DEVELOPMENT IS ASSOCIATED WITH HIV VIRAL LOAD, CD4+ COUNT and CD4+/CD8+ RATIO

--Manuscript Draft--

Manuscript Number:	
Article Type:	Case Report (online only)
Keywords:	Cancer; oral; Kaposi's sarcoma; diagnostic.
Corresponding Author:	Hélder Antônio Rebelo Pontes, Ph.D João de Barros Barreto University Hospital Belém, BRAZIL
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	Hélder Antônio Rebelo Pontes, Ph.D
Abstract:	Objective: The objective of the present research was to explore the association of HIV viral load, CD4+ and CD8+ counts and the CD4+/CD8+ ratio on the risk of oral Kaposi's sarcoma (KS) development. Materials and methods: A total of 62 patients were retrieved from March 2008 to October 2020 from the files of two oral pathology centres. Clinical, laboratory and follow-up data were retrieved from their medical files. Poisson regression was used to explore the role of history of immunosuppression and its association with oral KS development. A P-value <0.05 was considered significant. Results: Sixty-two patients were included in the present study (32 with oral KS and 30 with no presentation of lesions anywhere on the body). Patients with oral KS presented a mean age of 32.6 years, and male patients were more affected. The hard palate (15 cases; 46.8%) was the main anatomical site affected. The lesions were mostly presented as swellings (13 cases; 40.6%) and nodules (12 cases; 37.5%). Systemic manifestations were also observed, including candidiasis (4 cases; 12.5%), bacterial infection (3 cases; 9.3%), tuberculosis (3 cases; 9.3%), herpes simplex (3 cases; 9.3%) and pneumonia (3 cases; 9.3%). A significant correlation was observed between HIV viral load, CD4+ count and the CD4+/CD8+ ratio with oral KS development. Conclusions: HIV viral load, CD4+ count and the CD4+/CD8+ ratio are associated with oral KS development.