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DOCTORAL THESIS

OROPHARYNGEAL MANIFESTATIONS IN IMMUNOSUPPRESSED PATIENTS

SUMMARY

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KEY WORDS

immunosuppression; HIV-AIDS; COVID-19; oropharyngeal lesions; opportunistic infections; biological therapy; oral candidiasis; clinical dentistry; immunosuppressive treatment

CURRENT STATE OF KNOWLEDGE

1. INTRODUCTION

In the context of the topic "Oropharyngeal Manifestations in Immunocompromised Patients," this research aimed to study the complexity and diversity of oral and pharyngeal clinical manifestations in immunocompromised patients, particularly those affected by HIV/AIDS, COVID-19, and those undergoing biological therapies. Situated at the intersection of dentistry, infectious medicine, and immunology, this research topic significantly contributes to the understanding of how immunosuppressive diseases affect oral health and the quality of life of patients.

1.1. Research motivation

Immunosuppression, whether caused by human immunodeficiency virus (HIV) infection, oncological treatments, or autoimmune diseases, is frequently associated with a variety of oropharyngeal manifestations, ranging from opportunistic infections to chronic and autoimmune lesions. These manifestations not only affect the general health of patients but can also become clinically relevant symptoms for diagnosing and monitoring the progression of the underlying disease.

The study was initially conceived in 2018 to analyze the impact of HIV/AIDS infection on oral health, particularly in the context of a lack of antiretroviral therapy or insufficient treatment. However, with the onset of the COVID-19 pandemic, the research focus expanded. Immunosuppression and SARS-CoV-2 infections have brought to light new oropharyngeal clinical manifestations, from dysgeusia (taste alterations) to herpetiform lesions and salivary gland inflammations. This shift in the global medical context required a rethinking of the

research project to include the analysis of oral manifestations in COVID-19 patients, thus offering a comprehensive approach to the phenomenon.

Additionally, biological and oncological therapies used to treat various autoimmune conditions and cancers have also been associated with oropharyngeal manifestations, including opportunistic infections and adverse drug reactions. An increasing number of patients have been treated with such therapies, and their effects on oral health have become a clinical area of interest.

Therefore, the research is driven by the need to better understand the complexity of oropharyngeal manifestations in immunocompromised patients, especially in light of the new challenges posed by the pandemic and the widespread use of biological therapies.

1.2. Research objectives

The main objective of this research is to determine the impact of oral and oropharyngeal lesions and manifestations in immunocompromised patients on their general health and the progression of their underlying diseases. Specifically, the research aims to identify the role of these manifestations in diagnosing and monitoring the progression of immunodepressive diseases such as HIV/AIDS, COVID-19, and various forms of autoimmune diseases treated with biological therapies.

The secondary objectives include:

- Investigating the frequency and typology of oropharyngeal manifestations in HIV/AIDS-infected patients, both before and after starting antiretroviral therapy.
- Evaluating oral manifestations in immunocompromised patients diagnosed with COVID-19, to determine whether these manifestations are specific to the viral infection or expressions of pre-existing immunosuppression.
- Analyzing the correlation between CD4 cell count, CD4/CD8 ratio, viremia, and the severity of oropharyngeal manifestations in seropositive patients.
- Studying the side effects of biological therapy on oral health, particularly in patients treated for psoriasis.

1.3. Research methodology

The research was conducted on a population of immunocompromised patients, including HIV-positive patients, psoriasis patients undergoing biological therapy, as well as patients diagnosed with COVID-19. The study took place between 2018 and 2023, divided into two major stages: the pre-pandemic stage, focusing on some HIV/AIDS patients, and the pandemic stage, which included COVID-19 patients and those treated with biological therapies.

1.3.1. Study design

The study was observational and clinical in nature, based on a quantitative approach. The cohort of HIV-positive patients included individuals in various stages of the disease, both before and after initiating antiretroviral therapy. These patients were clinically monitored, with periodic evaluations of oropharyngeal manifestations and correlations with immunological parameters such as CD4 cell count and viremia. COVID-19 patients were selected based on the severity of the disease and the presence of immunosuppression. Both patients with pre-existing immunosuppression and those who developed immune complications following SARS-CoV-2 infection were analyzed. For patients undergoing biological therapies, the research focused on evaluating the side effects of these treatments on oral health. The mentioned study cohorts were compared with a cohort of healthy patients who presented to the specialized service for a comprehensive evaluation of their oral and dental status.

1.3.2. Research methods and tools

The methods used in the research included:

- Detailed clinical examination of the oral cavity and pharynx to identify lesions, infections, and inflammations.
- Laboratory tests for evaluating immunological markers (CD4 cell count, CD4/CD8 ratio, viremia).
- Statistical analysis to correlate clinical manifestations with immunological and demographic data of the patients.
- Self-assessment questionnaires on patients' quality of life to measure the impact of oral lesions on their general health.
- The collected data were processed and analyzed using statistical analysis software, such as SPSS, to determine the statistical significance of identified correlations.

PERSONAL CONTRIBUTION

The PhD thesis titled “Oropharyngeal Manifestations in Immunocompromised Patients” is structured into a general theoretical part and a special contribution that includes four research studies and a case study.

2. RESEARCH STUDY 1

2.1. General objective

The study aims to investigate the oropharyngeal manifestations in immunocompromised patients infected with SARS-CoV-2, with a special focus on the impact on oral health and identifying possible correlations between these manifestations and the overall state of immunosuppression. Additionally, the goal is to determine the frequency and severity of these manifestations in infected patients, exploring whether they are a direct consequence of the infection or exacerbated by pre-existing conditions.

2.2. Materials and methods

The study was conducted between January 26 – February 26, 2021, by distributing an online questionnaire through social media. The questionnaire, designed in Google Docs, was structured into several sections to collect demographic data, medical history, and oral hygiene behaviors. The first section included general data about the participants' age, gender, and geographic location, as well as any existing comorbidities. The second section focused on oral hygiene habits, while the third tracked the presence and severity of oropharyngeal manifestations both before and after contracting COVID-19. Questions were also included regarding the loss of taste and smell and access to dental services during the pandemic.

2.3. Results

The study included 310 participants, the majority of whom (85.5%) were women, with 85.4% coming from urban areas. The average age of participants was 41 years. A significant percentage of patients (24.8%) reported chronic comorbidities, including cardiovascular diseases (12.9%) and autoimmune diseases (7.4%). A notable aspect of the study is the decrease in the incidence of certain oral conditions after contracting SARS-CoV-2, such as aphthous stomatitis, which dropped from 38.39% to 3.55%, pharyngitis (from 42.90% to 4.84%), and tonsillitis, which decreased from 47.74% to 1.61%. On the other hand, gingival bleeding showed a more moderate reduction, from 47.10% to 17.10%.

Table 1: Oropharyngeal manifestations before and after COVID-19

Oral Manifestation	n1	p1	p1(%)	n2	p2	p2(%)	p1-p2(%)	z	p
Oral candidiasis	35	0.1129	11.29%	4	0.0129	1.29%	10.00%	5.128	0.000
Oral herpes	109	0.3516	35.16%	6	0.0194	1.94%	33.23%	10.642	0.000
Aphthous stomatitis	119	0.3839	38.39%	11	0.0355	3.55%	34.84%	10.655	0.000
Tongue infection	5	0.0161	1.61%	1	0.0032	0.32%	1.29%	1.641	0.101
Tonsillitis	148	0.4774	47.74%	5	0.0161	1.61%	46.13%	13.321	0.000
Pharyngitis	133	0.4290	42.90%	15	0.0484	4.84%	38.06%	11.117	0.000
Tooth pain	225	0.7258	72.58%	35	0.1129	11.29%	61.29%	15.464	0.000
Gingival bleeding	146	0.4710	47.10%	53	0.1710	17.10%	30.00%	8.000	0.000
Periodontal pockets	58	0.1871	18.71%	4	0.0129	1.29%	17.42%	7.229	0.000

n1: Number of cases before COVID-19; p1: Proportion of cases before COVID-19; p1 (%): Percentage of cases before COVID-19; n2: Number of cases after COVID-19; p2: Proportion of cases after COVID-19; p2 (%): Percentage of cases after COVID-19; p1-p2 (%): Percentage difference between before and after COVID-19; z: z-value of the statistical test; p: p-value of the statistical test (statistical significance)

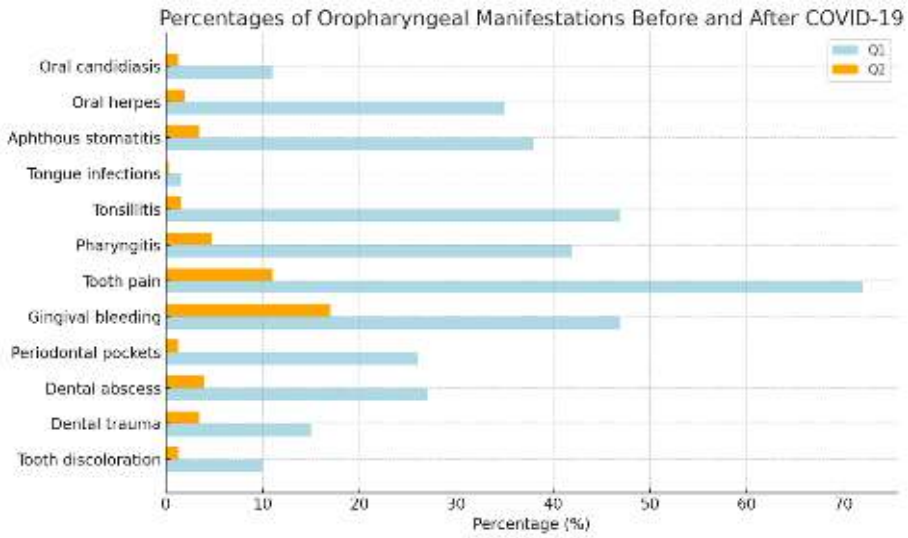

Figure 1: Graphic representation: Q1 – Oropharyngeal manifestations before COVID-19, Q2 – manifestations after COVID-19 infection

The study also found that 68% of participants reported loss of taste and smell, highlighting the significant impact of the infection on these senses.

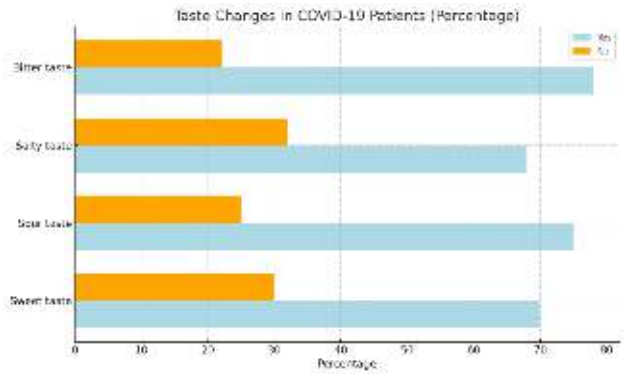

Figure 2: Percentage representation of patients who experienced changes in different taste categories.

The study's conclusions regarding the loss of taste and smell in SARS-CoV-2-infected patients show that these manifestations are common and significant. Approximately 68% of participants reported an alteration in their sense of smell, and nearly 25% noticed changes in their taste perception, regardless of the type of taste (bitter, salty, sweet, or sour).

3. RESEARCH STUDY 2

3.1. General objective

The main objective of Study No. 2 was to identify significant differences in oropharyngeal manifestations between SARS-CoV-2-infected patients and an uninfected control group. Through this comparative approach, researchers aimed to analyze the impact of COVID-19 on oral health, focusing on symptoms such as oropharyngeal pain, ulcers, and taste and smell alterations. Additionally, the study investigated whether the virus has the capacity to invade and reproduce in oral cavity cells, which could explain the occurrence of specific clinical manifestations.

Secondary objectives included evaluating the incidence of oropharyngeal manifestations and other comorbidities in COVID-19 patients, analyzing symptoms associated with respiratory failure, hypertension, liver diseases, and diabetes. The study also explored the presence and severity of oropharyngeal symptoms based on the age and gender of the patients..

3.2. Materials and methods

The study was conducted at the Constanța Clinical Infectious Diseases Hospital between April 2021 and October 2022. Two groups were analyzed: 52 patients hospitalized with a COVID-

19 diagnosis and 52 patients from the CONTROL group who were not infected with SARS-CoV-2. The COVID-19 group consisted of 30 men and 22 women, with an average age of 45.3 years, while the control group had a similar distribution, with an average age of 44.1 years. The examination of patients included detailed evaluations of the oral cavity and paraclinical tests, such as tests for identifying fungal and bacterial infections. Additionally, data on oral hygiene, oropharyngeal manifestations, and patients' interactions with dentists were collected. The questionnaires completed by the participants included questions about oral hygiene practices, oral symptoms associated with COVID-19, and taste and smell changes. The results were statistically analyzed using chi-square and t-tests to assess the differences between the two groups. It was found that oral lesions such as ulcers, herpetiform lesions, and salivary gland inflammations frequently occur in these patients and may aggravate their overall health condition. Moreover, early symptoms like dysgeusia have proven to be important signs in the early identification of COVID-19 infection, especially in immunocompromised patients.

3.3. Results

The study highlighted significant differences between the COVID-19 group and the CONTROL group regarding oropharyngeal manifestations. In SARS-CoV-2-infected patients, symptoms such as candidiasis (36.5%), herpes (40.4%), and stomatitis (46.2%) had a higher incidence. In contrast, symptoms such as glossitis, tonsillitis, and pharyngitis were more frequent in the CONTROL group.

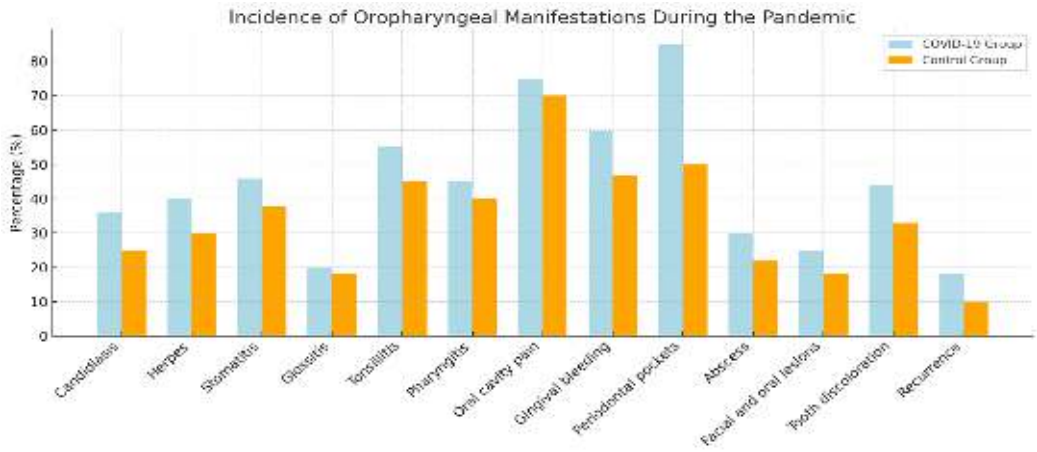

Figure 3: Incidence of oropharyngeal manifestations between the two groups

Candida and herpes were significantly more frequent in COVID-19 patients, with a prevalence of 36.5% and 40.4%, respectively, compared to 26.9% and 30.8% in the CONTROL group. Stomatitis was also more present in the COVID-19 group, with a prevalence of 46.2%,

compared to 38.5%. Other manifestations, such as changes in tooth color, were more frequent in COVID-19 patients (69.2%), indicating a direct influence of the infection on oral health.

The study also showed that COVID-19 patients experienced more severe oral health symptoms. Oral cavity pain was reported by 75% of COVID-19 patients, compared to 69.2% of those in the CONTROL group. Similarly, changes in tooth color were reported by 69.2% of COVID-19 patients, compared to 53.8% of CONTROL group patients.

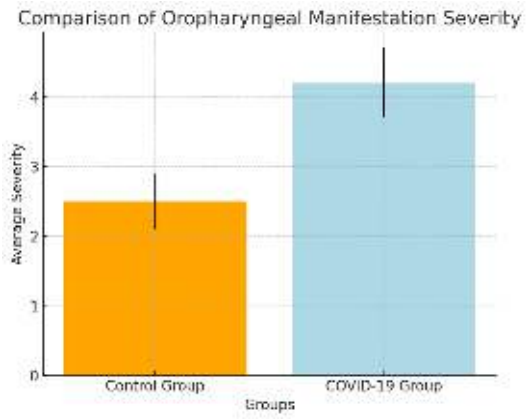

Figure 4: Average severity of oropharyngeal manifestations (MOF)

Regarding taste and smell-related symptoms, changes in tooth color were reported by 69.2% of COVID-19 patients, compared to 53.8% of those in the CONTROL group. Loss of taste and smell was a common symptom among COVID-19 patients, supporting the hypothesis that SARS-CoV-2 infection significantly impacts taste and olfactory senses.

Statistical analyses showed that COVID-19 patients had a higher incidence of candidiasis, herpes, and stomatitis compared to the CONTROL group, with these differences being statistically significant. However, symptoms such as glossitis, tonsillitis, and pharyngitis were more frequent in the CONTROL group, suggesting that not all oropharyngeal manifestations are more severe in SARS-CoV-2-infected patients.

The study also emphasized the importance of oral hygiene practices. However, statistical analyses showed no significant differences between patients who brushed their teeth once a day, twice a day, or more frequently. The same was true for the use of mouthwash. These results suggest that oral hygiene practices did not have a major impact on the incidence of oropharyngeal manifestations in COVID-19 patients.

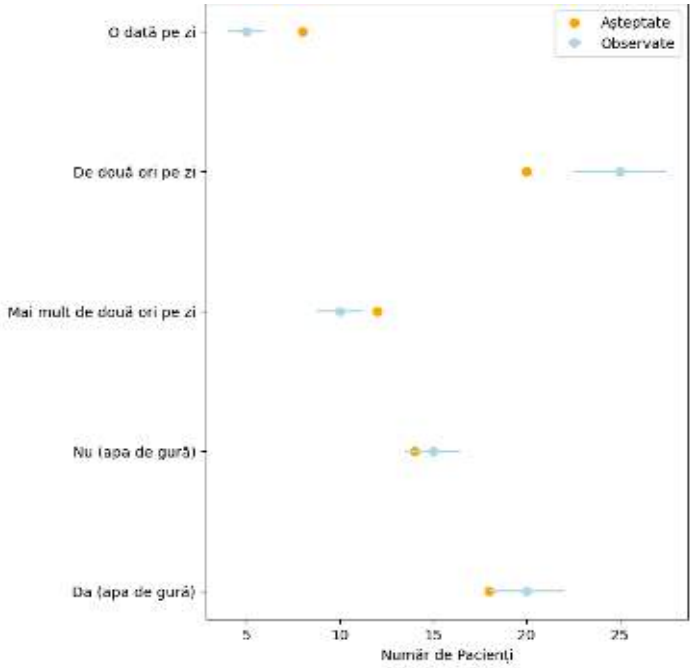

Figure 5: Forest plot for oral hygiene practices and oropharyngeal manifestations (observed and expected results)

4. RESEARCH STUDY 3

4.1. General objective

Research Study No. 3 aims to investigate the impact of oropharyngeal lesions and manifestations in HIV-infected patients, compared to a control group and COVID-19-infected patients. The main goal of the research is to correlate these manifestations with immunological markers and the effectiveness of antiretroviral therapy and biological therapies. Additionally, the study seeks to evaluate the frequency and severity of oropharyngeal manifestations in immunocompromised patients and to determine their influence on quality of life.

Another key objective is to determine how chronic immunosuppression, specific to HIV patients, and acute inflammation, characteristic of COVID-19 patients, influence the severity and type of oropharyngeal manifestations. These manifestations are analyzed and correlated with CD4 and CD8 lymphocyte levels, which are indicators of immune system health.

4.2. Materials and methods

The study was conducted on a cohort of 52 HIV-diagnosed patients undergoing antiretroviral therapy, and a control group of 52 healthy individuals. Clinical evaluation included detailed dental examinations, imaging investigations, as well as paraclinical tests to analyze

immunological markers (CD4, CD8, CD3). The frequency and severity of oral lesions in these patients were also evaluated.

To assess the oropharyngeal manifestations and how they are influenced by immune status, patients completed detailed questionnaires about their oral health, specific manifestations, and history of interaction with the dentist. In HIV patients, the questionnaire included questions about specific disease symptoms, while COVID-19 patients were evaluated for oropharyngeal symptoms that appeared during the SARS-CoV-2 infection. Statistical analysis included comparisons between the patient cohorts, using statistical tests to identify significant differences in immunological markers and oropharyngeal manifestations. Additionally, the study sought to correlate this data with the severity of the infection and the overall impact on patients' oral health and quality of life.

4.3. Results

The study highlighted significant differences between HIV-infected patients and those in the COVID-19 group regarding oropharyngeal manifestations and immunological parameters. In HIV patients, CD4 lymphocyte levels were significantly lower (300 cells/mm³) compared to COVID-19 patients (600 cells/mm³). This difference indicates severe immunosuppression in HIV patients, which explains their increased susceptibility to opportunistic infections and specific oropharyngeal manifestations.

Table 2: Differences between HIV and COVID-19 patients regarding immune and inflammatory markers.

Variable	HIV (Mean ± SD)	COVID-19 (Mean ± SD)
CD3 Lymphocytes	1100 ± 250 cells/mm³	1500 ± 300 cells/mm³
CD4 Lymphocytes	300 ± 80 cells/mm³	600 ± 120 cells/mm³
CD8 Lymphocytes	800 ± 150 cells/mm³	700 ± 140 cells/mm³
CD4/CD8 Ratio	0.5 ± 0.1	0.86 ± 0.2
CD3 Lymphocytes (%)	60% ± 5%	70% ± 6%
CD4 Lymphocytes (%)	20% ± 3%	30% ± 5%
CD8 Lymphocytes (%)	45% ± 4%	40% ± 5%
Interleukin 6	12 ± 3 pg/ml	8 ± 2 pg/ml
C-reactive Protein	10 ± 4 mg/L	6 ± 2 mg/L
Total Lymphocytes	1.0 ± 0.3 x10^9/L	1.8 ± 0.5 x10^9/L
Eosinophils	0.2 ± 0.1 x10^9/L	0.3 ± 0.1 x10^9/L
Fibrinogen	500 ± 60 mg/dl	350 ± 50 mg/dl
Objective Oropharyngeal Manifestations	65% ± 7%	40% ± 6%

Additionally, HIV patients had a higher mean CD8 lymphocyte count of 800 cells/mm³, compared to COVID-19 patients (700 cells/mm³). This increased CD8 count reflects a compensatory immune response but is insufficient to effectively combat infections. The CD4/CD8 ratio in HIV patients was significantly lower (0.5), underscoring a profound imbalance in their immune system compared to COVID-19 patients, whose CD4/CD8 ratio was 0.86.

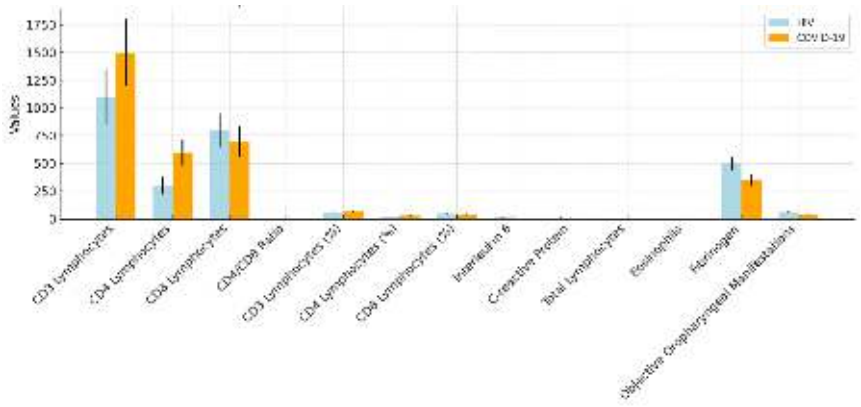

Figure 6: Comparison of values between HIV and COVID-19

Oropharyngeal manifestations, such as candidiasis and herpes, were much more frequent in HIV patients. 65% of them presented with such manifestations, compared to 40% of COVID-19 patients. Oral candidiasis, a common fungal infection in HIV patients, was present in 55% of them, while only 36.5% of COVID-19 patients experienced this manifestation.

Statistical analysis also showed that HIV patients generally have a higher susceptibility to bacterial and fungal infections compared to COVID-19 patients and the CONTROL group. Secondary bacterial infections were present in 55% of HIV patients, compared to only 10% in the CONTROL group. Additionally, fungal infections affected 45% of HIV patients, compared to just 5% of those in the CONTROL group.

Table 3: Comparative analysis of the prevalence of secondary infections between HIV patients and the CONTROL group.

Variable	HIV Group (Mean ± SD)	CONTROL Group (Mean ± SD)
Bacterial infections (%)	55% ± 6%	10% ± 3%
Fungal infections (%)	45% ± 5%	5% ± 2%
Viral infections (%)	35% ± 4%	8% ± 2%

In conclusion, the study highlighted that HIV patients are at a higher risk of oral complications and secondary infections due to chronic immunosuppression, while COVID-19 patients experience acute manifestations related to severe inflammation caused by the viral infection.

5. RESEARCH STUDY 4

5.1. General objective

Study No. 4 had the main objective of evaluating and comparing oropharyngeal manifestations in patients with severe vulgar psoriasis undergoing biological therapies (secukinumab, adalimumab, and risankizumab) compared to a CONTROL group of healthy patients. The research aimed to identify possible correlations between oropharyngeal manifestations and the degree of immunosuppression induced by biological treatments. Another important objective was to analyze the efficacy and safety of biological therapies to assess whether these therapies negatively influence oral health and to provide informed clinical recommendations for optimizing patient treatment.

Secondary objectives included determining the incidence and severity of oropharyngeal manifestations in patients treated with biological therapies and analyzing differences compared to the CONTROL group. Additionally, the research sought to evaluate whether oropharyngeal manifestations could serve as early indicators of compromised immune responses or systemic conditions, offering diagnostic value in patient management.

5.2. Materials and methods

The study was conducted on a group of 42 patients with severe vulgar psoriasis undergoing biological therapies and a CONTROL group of 52 healthy patients. Patients in the treatment group were treated with secukinumab, adalimumab, and risankizumab, with the main goal being to evaluate the impact of these treatments on oral health.

Patients underwent detailed clinical examinations to identify the presence of oropharyngeal conditions such as oral candidiasis, herpes, aphthae, tongue infections, glossitis, tonsillitis, pharyngitis, and gingival bleeding. Additionally, questionnaires were completed to determine the frequency and severity of these manifestations and their impact on the patients' quality of life. Laboratory analyses included monitoring biological and immunological parameters to correlate oropharyngeal manifestations with the degree of immunosuppression induced by biological therapies. The study also compared dental hygiene methods between the group receiving biological therapies and the CONTROL group to evaluate whether these methods influenced the frequency of oropharyngeal manifestations.

5.3. Rezultate

The study results showed significant differences between patients undergoing biological therapies and those in the CONTROL group regarding the incidence and severity of oropharyngeal manifestations. Patients treated with secukinumab, adalimumab, and risankizumab had a significantly higher prevalence of oral infections and other dental problems compared to the CONTROL group.

For example, oral candidiasis was reported in 30% of patients treated with biological therapies, while in the CONTROL group, the incidence was only 15%. Herpes had a prevalence of 40% in the biological group compared to 20% in the CONTROL group, and aphthae were reported by 44% of treated patients compared to only 22% in the CONTROL group.

Table 4: Frequency of oropharyngeal manifestations

Manifestation	Biological Therapies (%)	Control Group (%)
Oral candidiasis	30%	15%
Herpes	40%	20%
Aphthae	44%	22%
Tongue infections	36%	18%
Tonsillitis	50%	25%
Pharyngitis	40%	20%
Tooth pain	60%	30%
Gingival bleeding	56%	28%
Periodontal pockets	52%	26%
Dental abscesses	54%	27%
Lip lesions	50%	25%
Tooth discoloration or changes	44%	22%

Tongue infections, tonsillitis, and pharyngitis also had a higher incidence in the treated group, with percentages of 36%, 50%, and 40%, respectively, compared to 18%, 25%, and 20% in the CONTROL group.

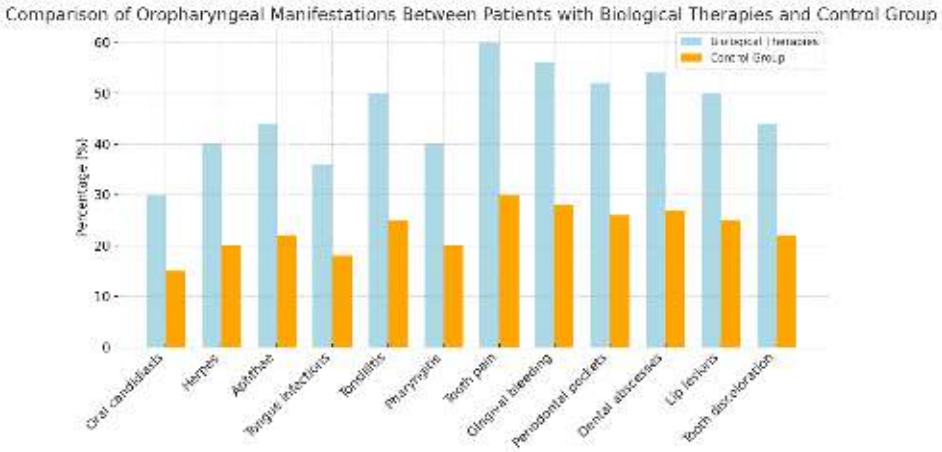

Figure 7: Frequency of oropharyngeal manifestations (MOF) between the patient groups

Regarding other dental problems, tooth pain and gingival bleeding were much more common among patients treated with biological therapies. 60% of these patients reported tooth pain, and 56% reported gingival bleeding, compared to 30% and 28% of patients in the CONTROL group. Periodontal pockets and dental abscesses were also more frequent in the treated group, with rates of 52% and 54%, respectively, compared to 26% and 27% in the CONTROL group.

Statistical analyses confirmed that the observed differences between the two groups are significant. The chi-square test showed p-values below the 0.05 threshold for all oropharyngeal manifestations, indicating that patients treated with biological therapies have a significantly higher risk of developing these conditions than healthy patients.

The study also showed that patients treated with biological therapies used more rigorous dental hygiene methods than those in the CONTROL group. Tooth brushing and the use of mouthwash were reported by 40 and 35 patients in the biological group, respectively, compared to 30 and 25 patients in the CONTROL group. However, these more rigorous methods did not reduce the prevalence of oropharyngeal problems among treated patients, suggesting that the immunosuppression induced by biological therapies is a determining factor in the occurrence of these conditions.

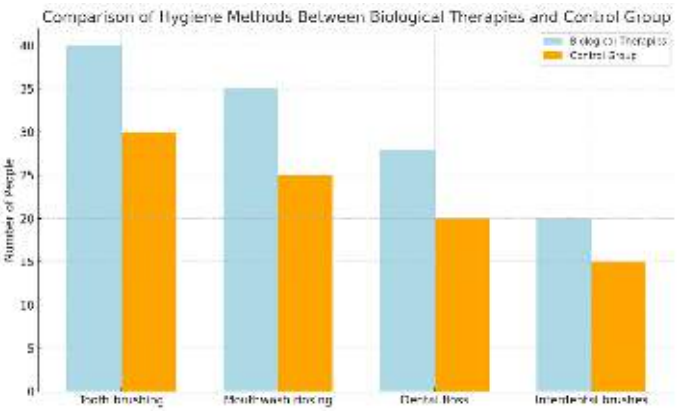

Figure 8: Comparison of hygiene methods

Logistic regression analysis showed that the degree of immunosuppression induced by biological therapies is a significant predictor of the occurrence of oropharyngeal manifestations.

6. CASE STUDY

6.1. General objective

The presented case study's main objective was to evaluate a rare case of plasmablastic lymphoma (PbL) in a patient with concurrent HIV and SARS-CoV-2 infections. In this context, clinical manifestations, disease progression, and treatment response, including antiretroviral therapy and chemotherapy, were analyzed. A secondary objective was to examine the impact of SARS-CoV-2 infection on the progression of plasmablastic lymphoma and treatment response in HIV patients. The role of Epstein-Barr virus (EBV) in the pathogenesis of plasmablastic lymphoma was also investigated, considering the association of EBV infection with various lymphomas in immunocompromised patients. Another secondary objective was to correlate the presence of Epstein-Barr virus with the severity and progression of plasmablastic lymphoma to determine the virus's influence on the patient's prognosis and response to treatment.

6.2. Materials and methods

The study focused on a 51-year-old smoker who had a severe SARS-CoV-2 infection in October 2020. After being discharged following 18 days of treatment, the patient developed a rapidly progressing ulcerative tumor lesion in the oral cavity, extending to the left mandible, upper dental arches, and palate. Associated symptoms included profuse sweating, severe fatigue, loss of appetite, and a weight loss of approximately 7 kg. Laboratory investigations revealed several abnormalities, including anemia, leukopenia with lymphopenia, and elevated inflammatory markers. Serological tests were negative for hepatitis B and C but positive for HIV and Epstein-Barr virus IgG, with high levels of EBV DNA. To evaluate the disease's extent, the patient underwent a series of imaging investigations, including cranial, pulmonary, and abdominal computed tomography (CT), which showed numerous osteolytic lesions and ground-glass opacities in the lungs, indicating post-COVID sequelae and bilateral lymphadenopathy.

6.3. Results

The study's first hypothesis suggests that concurrent SARS-CoV-2 and HIV infections negatively influence the evolution and prognosis of plasmablastic lymphoma. In this case, the tumor lesion in the oral cavity progressed rapidly after the SARS-CoV-2 infection, and the patient's overall condition significantly deteriorated. The systemic inflammatory response induced by SARS-CoV-2, combined with severe immunosuppression caused by HIV, accelerated the progression of plasmablastic lymphoma, contributing to the severity of symptoms and poor treatment response.

The patient was treated for COVID-19 with remdesivir, tocilizumab, and dexamethasone, but these treatments likely had a negative impact on lymphoma progression. Corticosteroids, in particular, may interfere with the efficacy of chemotherapy and antiretroviral therapy, contributing to a poor prognosis. The patient experienced rapid and aggressive tumor growth, and imaging investigations revealed multiple osteolytic lesions in the cranial vault and extensive lymphadenopathy. These findings support the hypothesis that SARS-CoV-2 infection worsens plasmablastic lymphoma progression in HIV patients. The patient required complex therapeutic interventions, including chemotherapy, radiotherapy, and antiretroviral therapy, but the prognosis remained poor due to multiple complications and poor treatment response.

The study's second hypothesis proposes that EBV plays a key role in the development and progression of plasmablastic lymphoma in HIV patients. In this case, serological tests showed high levels of EBV DNA (213,000 copies/mL), confirming an active EBV infection. The presence of this virus has been associated with the malignant transformation of plasma cells and uncontrolled proliferation, characteristic of plasmablastic lymphoma.

CONCLUSIONS

The research studies in this doctoral thesis highlighted that immunocompromised patients, whether suffering from HIV, receiving biological therapies, or affected by SARS-CoV-2 infection, have an increased risk of developing severe oropharyngeal manifestations. Oropharyngeal lesions such as oral candidiasis, glossitis, ulcers, and opportunistic infections were frequently reported in all patient groups, with varying prevalence depending on the degree of immunosuppression and the underlying condition. These manifestations not only affect the

quality of life of patients but also represent an important clinical marker of general health status and disease progression.

A central aspect of the research was evaluating the correlation between CD4/CD8 cell levels and oropharyngeal manifestations in HIV patients and other forms of immunosuppression. The results showed that patients with low CD4 lymphocyte counts are more likely to develop severe oropharyngeal lesions, such as candidiasis, herpes, and oral ulcers. At the same time, patients with better immune responses, characterized by a balanced CD4/CD8 ratio, had fewer clinical oral manifestations.

The studies also provided a detailed analysis of the impact of biological and antiretroviral therapies on oropharyngeal health. While these therapies have brought significant benefits in controlling the underlying disease, they are not without risks. Patients undergoing biological treatments, such as adalimumab or secukinumab, showed a higher incidence of oropharyngeal infections, particularly oral candidiasis and herpes. At the same time, antiretroviral treatments reduced the prevalence of oral lesions in HIV patients, but did not completely eliminate the risk.

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