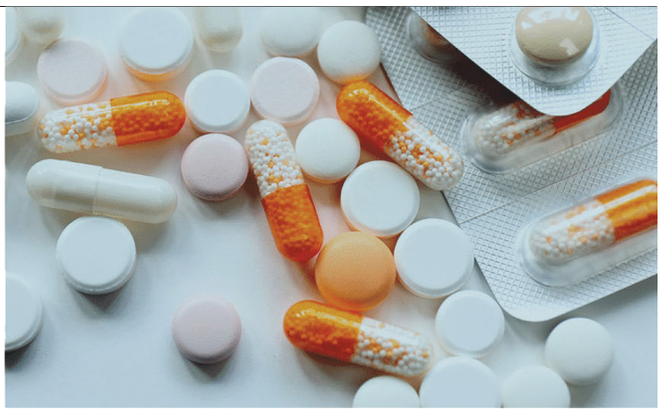

ABSTRACT

ADR IN ODONTOIATRIA (ADR-O)

Reazioni avverse a farmaci

Stato dell'arte e prospettive

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Dental School Lingotto
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Responsabile scientifico
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Adverse reaction by tonic water: a case report

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Background: Quinine is an alkaloids that have a long history of use in medicine. The observation of beneficial effects of quinine was initially made by the indigenous people of the Amazon. It has antipyretic and analgesic effects as well as an antiparasitic effect, making them useful in the treatment of acute malaria. This substance is also useful in the treatment of nocturnal leg cramps, cardiac arrhythmias, and occasionally some neurologic diseases. Quinine is also widely used in tonic water and furthermore, this is an unintentional source of poisoning in "street" heroin. This appears to be a problem in the U.S.(1).
The scientific literature reports that quinine is a common cause of severe drug-induced disorders, such as thrombocytopenia (DITP) and drug-induced thrombotic microangiopathy (DITMA). Recognizing the frequency and severity of DIPT and DITMA, the U.S. Food and Drug Administration has established stringent regulations related to medicinal quinine production and accessibility.
In addition to these adverse reactions, many additional disorders were described. They included chills, fever, hypotension, neutropenia, disseminated intravascular coagulation, painful acral cyanosis, liver toxicity, respiratory failure, rhabdomyolysis, and systemic cutaneous reactions(2). The diversity of these unexpected additional disorders often causes diagnostic uncertainty and could also obscure the quinine aetiology.
Here we report an uncommon oral adverse reaction to quinine in the tonic water.
Case presentation: A 28-year-old female patient was referred to the Department of Oral Medicine and Surgery of the University of Parma for recurrent episodes of stomatitis. She had three episodes in 6 months with ulcerated erythematous lesions on the lips and oral cavity (tongue and hard palate) (Fig.1-3). She had a negative history of systemic diseases and didn't take any medication. The first diagnostic hypothesis was herpetic gingivostomatitis, and an antiviral drug was prescribed. She always responded well to the therapy, but the blood test markers for Herpes Human Virus 1 and 2 (HHV 1-2) showed a negativity of immunoglobulin M (IgM) and only a positivity of IgG for HHV-1. So, we investigated with the patient about the intake of drugs, food or some particular substance and, after about 6 months, she remembered the assumption of Schweppes, coinciding with the last two oral manifestations. Checking the ingredients of the drink, we noticed the presence of "quinine". Eventually, the patient, questioning her family, finds out that the grandmother had had a severe allergic reaction after the assumption of quinine, which had been given to her in wartime. So, we proposed allergy tests for quinine, which confirmed its intolerance. Based on these findings, it was established a diagnosis of erythema multiforme by adverse reaction to quinine, contained in the tonic water.
Conclusions: Quinine, even with only minute exposure from common beverages, can cause severe adverse reactions involving multiple organ systems. So, it is important to establish an accurate diagnosis and offer adequate recommendations to the patient with the consumption of this product.

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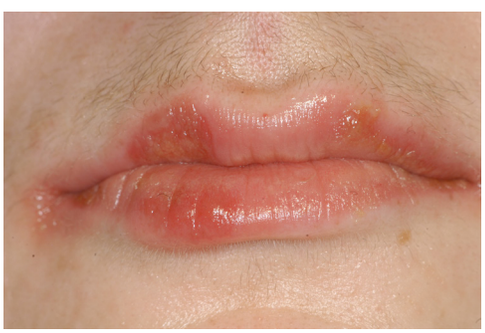

Fig. 1

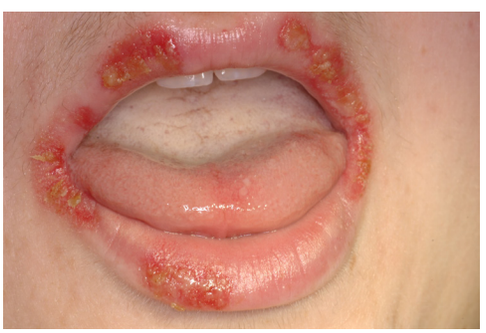

Fig. 2

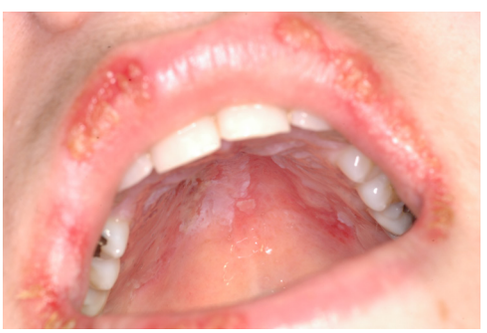

Fig. 3

Oral melanin pigmentations associated to letrozole, a case report

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Background: Oral melanin pigmentations can be the manifestations of several local and systemic conditions (e.g. Addison's disease, Peutz-Jeghers syndrome, Laugier-Hunziker syndrome) including side effects of many drugs administration. Drugs associated with oral melanin hyperproduction and deposition within the basal layer cell of the epithelium, connective tissue or both include nicotine, minocycline and cyclophosphamide, among others. It is not known if melanin hyperproduction is the result of direct stimulation of drugs on oral melanocytes or if there is the activation of specific pathways leading to the final effect of oral pigmentation occurrence. It should be borne in mind that oral melanocytes are usually inactive.
Treatment of oral pigmented lesions (surgical excision) is usually not required, apart from aesthetic reasons.
Letrozole is an aromatase inhibitor medication that is used in the treatment of breast cancer. It prevents aromatase from producing estrogens by competitive, reversible binding to the heme of its cytochrome P450 unit. The most common side effects are sweating, hot flushes, arthralgia and fatigue.
To the best of our knowledge, oral melanin pigmentations have never been described as a side effect of letrozole.
Here we describe a case of multiple oral pigmentations, due to melanin production, that occurred after letrozole administration.
Case presentation: A 54-year-old woman in post-menopause started therapy with letrozole (2.5mg/day) under the supervision of oncologists at the Breast Unit of Academic Hospital of Parma for the recurrence of a breast carcinoma (BC) which had been previously treated through surgery and tamoxifen. At anamnesis, the patient referred that the first occurrence of BC dated six years before and that she had been in good systemic conditions in the last 5 years.
After approximately 2 weeks of letrozole administration, the patient noticed the development of several asymptomatic dark macules in the oral cavity.
At the clinical evaluation, the oral mucosa appeared affected by multiple flat, non-ulcerated brown lesions with quite well-defined margins (Fig.1). Lesions were localized on the vestibular upper adherent gingiva and on the hard palate. A provisional diagnosis of the drug(letrozole)-associated melanin pigmentations was hypothesized. Following the biopsy, the histopathological evaluation confirmed the presence of melanin presence in the basal layer of the epithelium and in the superficial portion of connective tissues (where it was partially included in macrophages). As no other (known) possible causes of oral melanin pigmentations were present, a final diagnosis of a (possible) side effect of letrozole administration was rendered. No treatment was proposed and lesions remained unchanged during follow-up.
Conclusions: We can only hypothesize that the present case report represents an effective side effect of letrozole administration. Our hypothesis is based on the close temporal proximity between the beginning of therapy and oral lesions appearance altogether with the exclusion of all known causes of oral pigmentations (e.g. Laugier-Hunziker syndrome).

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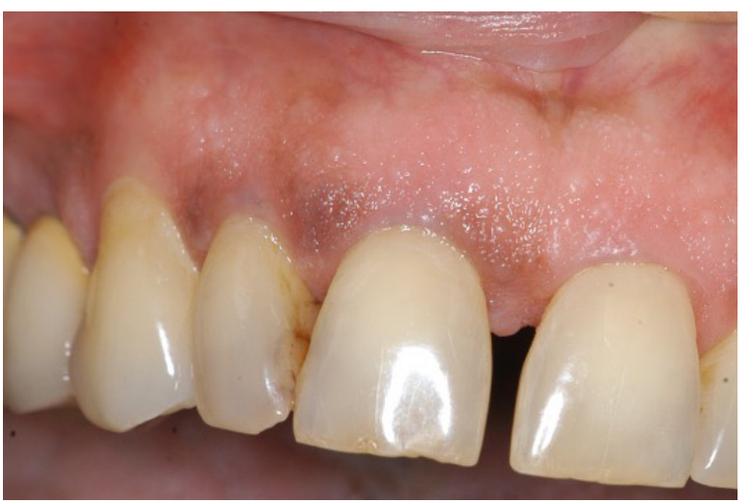

Fig. 1

Naproxen-induced oral pemphigus after anti-flu vaccination: a case report

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Background: Pemphigus is a rare and life-threatening group of autoimmune blistering diseases that affect the skin and mucous membranes. Multiple potential contributors to the disruption of immune tolerance have been identified, encompassing factors such as genetic predisposition, diseases (infections, cancer, and other autoimmune conditions), medications, pregnancy, hormonal fluctuations, dietary influences, emotional stress, and various environmental factors.
A broad spectrum of most commonly prescribed drugs, such as anti-hypertensive, anti-convulsant, anti-microbial, and anti-inflammatory drugs can favor the manifestation of oral pemphigus. We report a case of naproxen-induced pemphigus after anti-flu vaccination.
Case presentation: The patient, a 55-year-old woman with Down syndrome, was accompanied by her caregiver to the Dental Clinic. She presented with crusty lesions on the lips, red atrophic round lesions on the labial mucosa and ulcerative lesions with edema on the tongue(Figure 1). The onset of the oral lesions occurred three days after initiating therapy with naproxen (500 mg every 12 hours) for a recent back trauma. An anti-flu vaccination was administered the week before the trauma. No cutaneous lesions were observed. Serological tests for vesiculobullous disease were prescribed, and an oral biopsy was performed. The laboratory analysis revealed positive anti-desmoglein 3 antibodies. The histological examination disclosed epithelial-connective tissue detachment, with no positivity to direct immunofluorescence for tissue-bound autoantibodies. The patient received topical corticosteroids (betamethasone 4mg/vial, two rinses a day with half a vial for two weeks, then one rinse a day for one week), topical itraconazole (one rinse per day for two weeks) and lanolin cream (two applications per day on the lips for three weeks). A complete resolution of the lesions was observed after a month.
Conclusions: Drug-induced pemphigus is likely both a biochemical and immunologic process. The chemical structure of certain inciting agents has been found to contribute to the cell-to-cell dyshesion.
Drugs inducing pemphigus can be classified based on their chemical structure, with the main groups being thiols drugs, phenol drugs, and non-thiol/phenol drugs. Some of the most noteworthy thiols reported as triggering pemphigus are penicillamine, captopril, and tiopronine. The literature suggests thiol drugs promote acantholysis by stimulating enzymes like plasminogen activator, which disaggregate keratinocytes and inhibit enzymes that promote keratinocyte aggregation. Phenol drugs disrupt the integrity of cellular adherence mechanisms by stimulating keratinocytes to release proinflammatory cytokines. The release of tumor necrosis factor-alpha and interleukin-1 from cells drives complement and protease activation, which contribute to acantholysis. The most noteworthy phenols include aspirin, heroin, rifampin, and levodopa. Many non-thiol and non-phenol drugs have also been classically described in pemphigus. These agents may cause acantholysis through alternative pathways such as the activation of autoantibodies or altering the target antigen structure on keratinocytes. Examples of these agents include non-steroid, anti-inflammatory drugs, and calcium-channel blockers. Concurrent medications other than the implicated drugs were considered responsible for drug-induced pemphigus, especially furosemide and naproxen. Some vaccines against rabies, tetanus-diphtheria, influenza, and hepatitis B have been reported to induce or exacerbate pemphigus. Regarding this specific case, we can speculate that naproxen possibly facilitated the development of mucosal lesions, especially in light of the concomitant administration of the anti-flu-vaccine. Naproxen, a non-steroidal anti-inflammatory drug (NSAID), may modulate the immune system by affecting inflammatory pathways. It could have influenced cytokine production and immune cell function, potentially contributing to an altered immune response. Simultaneously, the anti-flu vaccine stimulated the immune system to produce an antibody response against influenza antigens. The precise mechanism might have involved the dysregulation of immune cells, increased production of autoantibodies, or alterations in the target antigen structure on keratinocytes. The synergistic effects of these agents may have triggered or exacerbated the immunologic processes underlying pemphigus in this patient. Finally, it is noteworthy to report the complete disappearance of oral lesions, quite atypical for oral pemphigus, which makes this mucosal reaction more similar to erythema multiforme for its transient nature.

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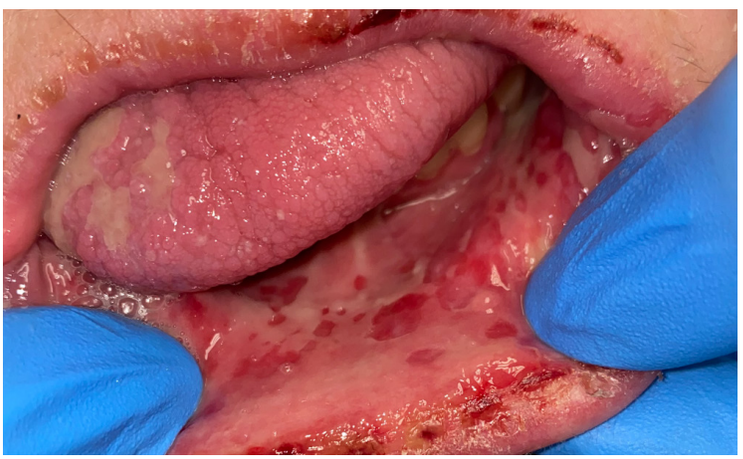

Fig. 1

Hydroxychloroquine-Induced Oral Hyperpigmentation in a Patient with Systemic Lupus Erythematosus: A Rare Clinical Presentation

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Background: Hydroxychloroquine (HCQ), originally designed for malaria, is used in treating Systemic Lupus Erythematosus (SLE). Noted adverse effects include dermatological complications, with a focus on oral mucosa hyperpigmentation. A recent review highlights reactive hyperpigmentation induced by these drugs, underscoring the need for understanding oral drug-related adverse effects in autoimmune diseases like SLE treated with antimalarial drugs[1]. HCQ influences various intracellular processes, including anti-inflammatory, and immune responses. The complications of chronic use are diverse, ranging from gastrointestinal symptoms and skin issues to severe cardiovascular, neurosensory, and ocular complications[2]. The pigmentation induced by HCQ involves complex mechanisms, including extensive adherence to melanin, which reveals for predominance of bluish-grey staining on the hard palate, providing valuable insights into the anatomical distribution of drug-induced pigmentation[1]. The complex interplay of drug dosage, duration, and pigmentation mechanism adds nuance to adverse effects understanding. Diagnosis relies on history and clinical signs with pigmentation generally reversible post-discontinuation, but limited information on reversibility necessitates further research.
Case presentation: The patient under consideration is a 66-year-old female diagnosed with SLE. Her medical history is notable for chronic autoimmune liver disease, positive Anti-Hbc and negative HBV-DNA. Additionally, she exhibits autoimmune thyroid disease, managed with levothyroxine replacement therapy, and has a history of gallbladder microlithiasis.
The diagnosis of LES was initially established in the year 2000, characterized by episodic arthritis, xerostomia, and xerophthalmia. Initial treatment involved azathioprine; however, this regimen was discontinued due to an allergic reaction. Subsequently,

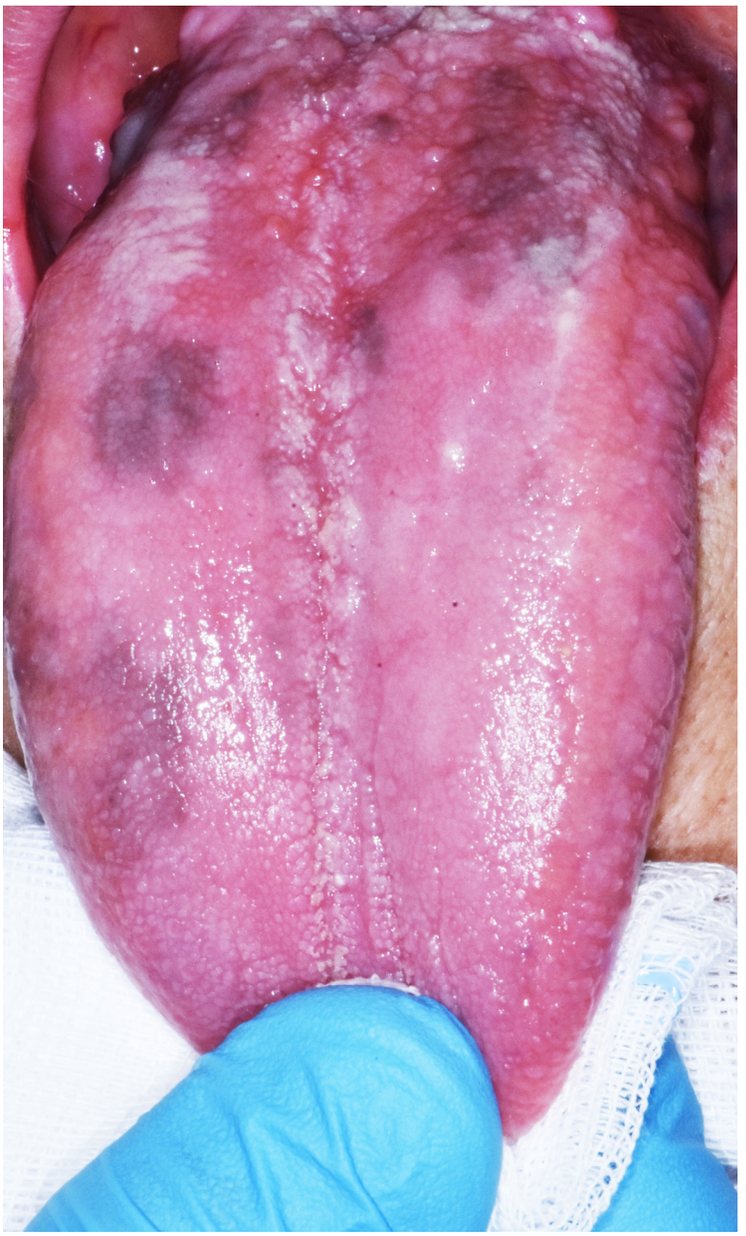

Fig. 1 *Dorsal view of the tongue showcasing diffuse grey-blue lesions, predominantly affecting the middle to the posterior third of the dorsal surface, sparing the anterior two-thirds on the left side.*

hydroxychloroquine (Plaquenil) was initiated at a dosage of 1 tablet twice daily, serving as the primary therapeutic approach for SLE.
In June 2022, during the most recent clinical evaluation at the Internal Medicine, Hepatobiliary, and Intestinal Diseases Unit of the "P. Giaccone" Policlinic in Palermo (Italy), the patient reported the onset of patchy, dark lesions on the tongue. These lesions, as reported by the patient, initially appeared in 2006 at smaller sizes, gradually extending in both size and number over a 16-year timeframe and a biopsy has never been performed. Consequently, she was referred for specialized oral examination at the Dentistry and Oral Medicine Clinic for Fragile Patients within the same institution.
Upon objective examination, the patient presented with diffuse gray-blue lesions on the dorsal surface of the tongue. The clinical figure accompanying this report vividly captures the distinctive nature of these lesions, showcasing the overlapping patterns and diverse pigmentation shades (Figure 1). Notably, the patient remained asymptomatic despite the distinct visual presentation of the lesions. The assessment also revealed an absence of associated symptoms such as pain or discomfort.
The clinical oral findings, while unique, present a diagnostic challenge and prompted further investigation into the potential relationship between the observed oral lesions and the ongoing hydroxychloroquine treatment, necessitating a comprehensive analysis of drug-induced adverse effects in the context of SLE patients. Based on a thorough review of the patient's clinical history and medication regimen, a conclusive diagnosis of drug-induced oral pigmentation has been established. Currently, the patient is actively undergoing follow-up care to monitor and manage the condition, the medication was maintained according to the recommendations of the rheumatologist and hyperpigmentation showed no changes in its presentation.
Conclusions: This exploration of oral manifestations in SLE patients underscores challenges in diagnosing HQC-related adverse reactions. The interplay of autoimmune diseases, drug mechanisms, and pigmentation distribution necessitates a multidisciplinary approach. Despite case report limitations and evidence scarcity, this study serves as a foundation for future research, promoting a deeper understanding of drug-induced effects in autoimmune disorders. Collaboration among specialists is essential for optimal SLE patient care.

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Rare Oral Squamous Cell Carcinoma Associated with Prolonged Hydroxyurea Treatment: A Case Report

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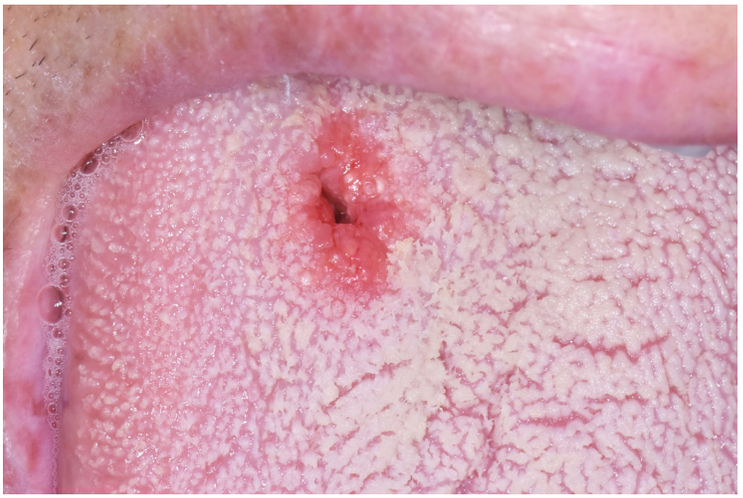

Fig. 1 *The ulcerative lesion on the right posterior dorsal surface of the tongue exhibits everted, raised, indurated, and erythematous margins.*

Background: Hydroxyurea (HU) is a widely used therapeutic agent for various hematological disorders, including chronic myelogenous leukaemia, polycythemia vera, and essential thrombocythemia. Despite its effectiveness, the utilization of HU is linked to numerous adverse effects, particularly alterations in the skin and mucosa, along with an elevated predisposition to tumorigenesis.
Patients subjected to prolonged HU regimens frequently present changes in their skin and mucous membranes, with well-documented occurrences such as pigmented lesions in the oral cavity and the development of oral ulcers. The carcinogenicity of HU is ascribed to its mutagenic characteristics and the impairment of DNA repair mechanisms, particularly when exposed to external factors. Prolonged administration of HU has been notably associated with the occurrence of cutaneous squamous/basal cell carcinomas (1). Nevertheless, instances of oral cancer arising from prolonged HU treatment are exceedingly infrequent and have been sparingly recorded in the scientific literature[2-3].
Case presentation: A 78-year-old man was referred to the Oral Medicine Clinic at the "P. Giaccone" Polyclinic in Palermo in February 2023 for an oral examination. The patient had a notable medical history of polycythemia vera diagnosed twenty years ago, for which he has been undergoing continuous treatment with HU. The reason for his visit was related to the persistence and enlargement of a lesion over the past three months. The patient reported no known risk factors for oral cancer and affirmed a non-smoking and non-alcoholic lifestyle. His prior oral and dental records showed no evidence of lesions on the oral mucosa, and there is no documented history of oral or other malignant conditions. During the oral examination, an ulcerative lesion with an endophytic appearance was identified on the posterior dorsal surface of the tongue, measuring 20 mm in maximum diameter. The margins of the lesion were everted, raised, and indurated. The lesion was non-bleeding and non-painful (Figure 1). Magnetic Resonance Imaging (MRI) of the head and neck revealed no lymphadenopathy. A biopsy specimen demonstrated fragments massively infiltrated by atypical neoplastic tissue with indicative characteristics of squamous cell carcinoma. Consequently, the patient was referred to an oncologist for further diagnostic and therapeutic management.
Conclusions: The presented case underscores the rare occurrence of oral cancer associated with prolonged HU treatment. While the literature extensively documents cutaneous squamous/basal cell carcinomas HU-related, instances of oral cancer arising from such treatment are exceedingly infrequent and scarcely recorded. This case highlights the complex challenge of balancing the therapeutic benefits of chronic HU in hematological disorders with the associated risk of rare but serious adverse effects such as the rare occurrence of oral malignancies. The observed chronology and clinical signs strongly suggest a plausible association between HU and the occurrence of oral cancer, although notably, similar case reports are scarce in the existing literature. The carcinogenic potential of HU, attributed to its mutagenic characteristics and interference with DNA repair mechanisms, necessitates careful monitoring and consideration in prolonged treatment regimens. Furthermore, this case serves as a reminder of the importance of comprehensive oral examinations in patients undergoing prolonged HU therapy. Timely identification and intervention are essential for optimizing patient outcomes and minimizing the impact of adverse effects associated with this widely used therapeutic agent. The potential lethality and unique presentation of cutaneous carcinomas, coupled with the simultaneous occurrence of oral malignancies reported in the literature[3], emphasize the critical importance of vigilant monitoring and comprehensive assessments in individuals subjected to prolonged HU regimens. These collective insights contribute to the evolving understanding of the adverse effects

associated with HU and advocate for heightened awareness and proactive management strategies in clinical practice.

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Mucous Membrane Pemphigoid Manifesting in the Oral Cavity Following SARS-CoV-2 Vaccination

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Background: Vaccination campaigns targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been pivotal in controlling the global spread and severity of COVID-19. However, a surge in mucocutaneous adverse reactions related to SARS-CoV-2 vaccines, including autoimmune mucocutaneous blistering diseases, has been consistently reported (1). This case report aims to shed light on the onset of Mucous Membrane Pemphigoid (MMP) following the administration of the third dose of the mRNABNT162b2 vaccine (Comirnaty® /Pfizer/BioNtech).
Case presentation: A 72-year-old female, with a history of breast cancer on maintenance therapy and severe osteoporosis treated with Denosumab, presented with painful oral lesions persisting for over six months. The oral lesions manifested nine days after receiving the third dose of the mRNABNT162b2 vaccine. Previous attempts to address the condition with antibiotics and antifungal medications by her general physician and dentist were unsuccessful. Intra-oral examination revealed generalized bullous and erythematous areas, along with ulcerations at the upper and lower gingivae, extending bilaterally to the vestibular fornix and the right buccal mucosa (Figure 1). Other mucosal membranes and skin were unremarkable. A biopsy was performed on the bullous lesions present at the upper right gingiva, revealing sub-epithelial detachment in histopathology. Direct immunofluorescence microscopy illustrated linear deposition of IgG and IgA antibodies at the basement membrane zone, along with predominant granular deposition of C3 at the same sites. The patient's serum, examined through ELISA, exhibited elevated anti-BP-180 antibodies (116 U/ml; normal <20 U/ml), while anti-BP-230 antibodies were within normal limits (5 U/ml; normal <20 U/ml). Considering the temporal association between the onset of bullous lesions and SARS-CoV-2 vaccination, a diagnosis of Mucous Membrane Pemphigoid (MMP) localized at the oral mucosa was established. Initial treatment with topical betamethasone sodium phosphate tablets (0.5 mg diluted in water) as a mouthwash three times daily for three weeks did not yield a response. Subsequently, systemic prednisone at a dose of 0.5 mg/kg (25 mg/day) was prescribed for one week, followed by a gradual tapering dosage, leading to complete clinical remission in three weeks (Fig D). The patient has undergone one year of follow-up and remains in clinical remission without the need for ongoing therapy.
Conclusions: This case underscores the emergence of Mucous Membrane Pemphigoid in the oral cavity subsequent to SARS-CoV-2 vaccination. The occurrence of autoimmune bullous diseases post-vaccination raises critical questions regarding potential pathogenic mechanisms, urging further investigation. To date, a variety of orofacial manifestations related to Covid-19 vaccination have been reported, ranging from erythema multiforme-like reactions, oral lichenoid lesions, to oral mucositis (2). While the majority of these reactions are mild-to-moderate and self-limiting, severe cases of oropharyngeal pemphigus vulgaris have also been documented. This diversity in manifestations underscores the need for heightened awareness among oral healthcare providers regarding the potential development of autoimmune bullous diseases with

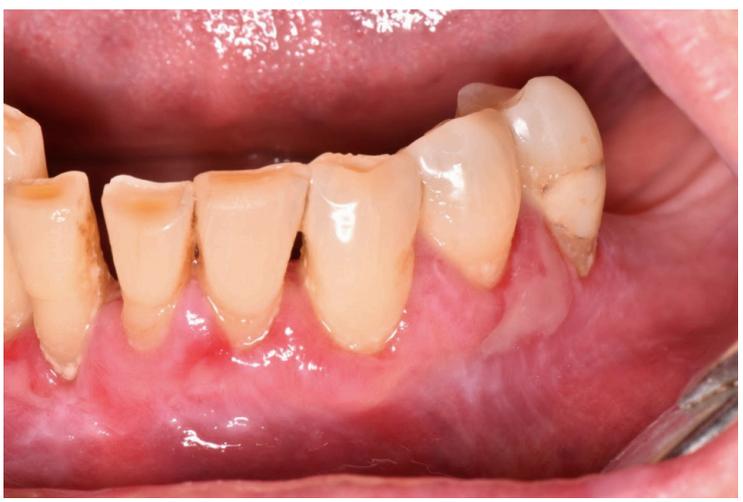

Fig. 1

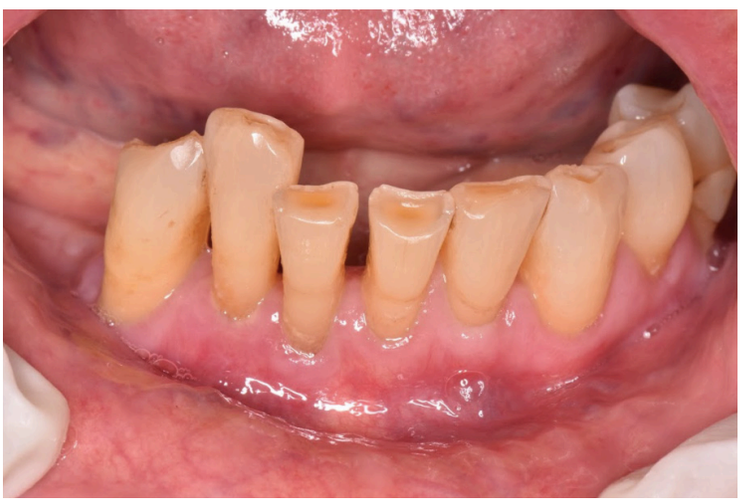

Fig. 2

exclusive oropharyngeal involvement after COVID-19 vaccination. Potential pathogenic mechanisms underlying the occurrence of adverse events in Covid-19 vaccinated patients are far from being clarified, and only a temporal correlation may be suggested. The complex interplay between the host's immune response, the vaccine components, and individual predispositions necessitates comprehensive investigation. This case emphasizes the significance of interdisciplinary collaboration in unraveling the complexities surrounding mucocutaneous adverse reactions post-vaccination. In conclusion, increased vigilance and collaboration between medical disciplines are essential for comprehending and addressing the implications of such adverse events in vaccinated individuals. The early diagnosis of autoimmune bullous diseases is crucial, as timely intervention can significantly impact patient outcomes. As we delve deeper into the realm of vaccine-related adverse reactions, ongoing research and collaboration will be instrumental in enhancing our understanding and refining vaccination strategies.

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Imatinib-induced mucosal hyperpigmentation of the hard palate in a patient with chronic myeloid leukemia: A case report

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Background: Pigmented oral mucosal lesions present a diagnostic challenge, encompassing a spectrum from benign conditions like oral melanotic macules to malignant entities such as oral malignant melanoma: the etiology can stem from physiologic and environmental causes (ethnic pigmentation, smoking-associated melanosis, dental amalgam tattoo), malignant neoplasms, and pathologic causes arising from manifestations of systemic diseases and syndromes (e.g. Peutz-Jeghers syndrome, Addison's disease). A notable contributor to pigmentation, accounting for 10%-20% of acquired hyperpigmentation cases, is the use of certain medications, including phenothiazines, amiodarone, oral contraceptives, and tetracyclines. Imatinib mesylate (Gleevec®) functions as a tyrosine kinase inhibitor with specificity towards the BCR-ABL protein in chronic myeloid leukemia (CML), c-kit, and platelet-derived growth factor receptors. It is usually used for the treatment of CML and gastrointestinal stromal tumors. Common Imatinib-related adverse effects encompass superficial edema, nausea, muscle cramps, diarrhea, and cutaneous reactions such as rash and superficial edema. Hypopigmentation is a recognized and frequent side effect, whereas hyperpigmentation is deemed rare but potentially underreported, particularly in the context of intraoral manifestations. The objective of this clinical case presentation is to elucidate hyperpigmentation within the oral cavity associated with Imatinib usage.

Case presentation: A 30-year-old Caucasian man was referred in March 2023 to the Oral Medicine Unit of the University of Foggia by his general dentist following a finding of a dark blue/grey pigmented area of the hard palate, which the patient reported having noticed it already 2 years ago, without morphological changes. His medical history included CML, for which he had been taking 400 mg/die imatinib since 2013 (10 years). He had no other underlying medical conditions and took no other medications. In the past, the patient denied having taken medications that in the scientific literature are related to the development of pigmentation. Laboratory examinations revealed no abnormalities in hematological data. He was a never-

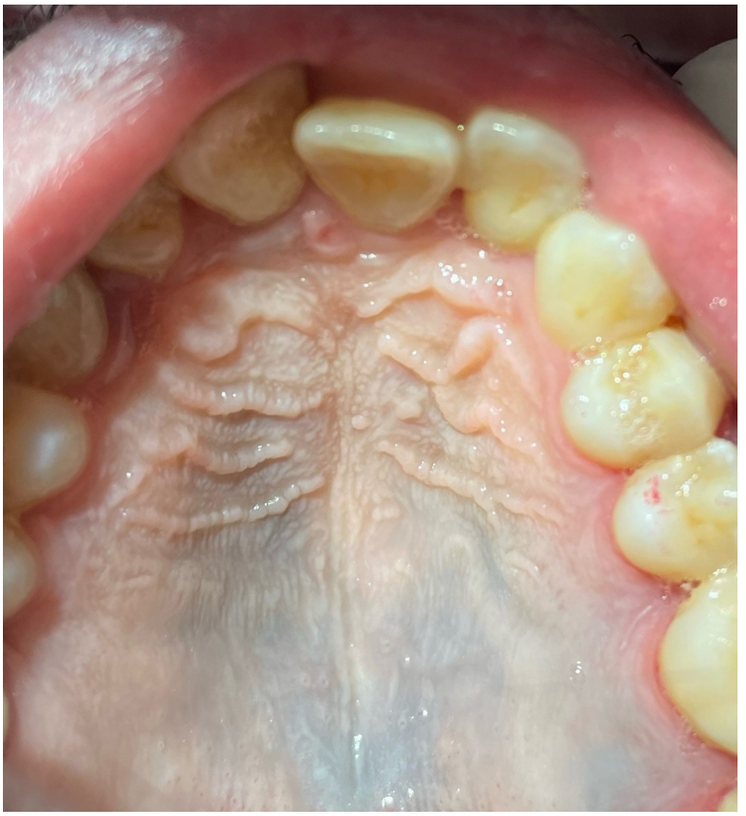

Fig. 1

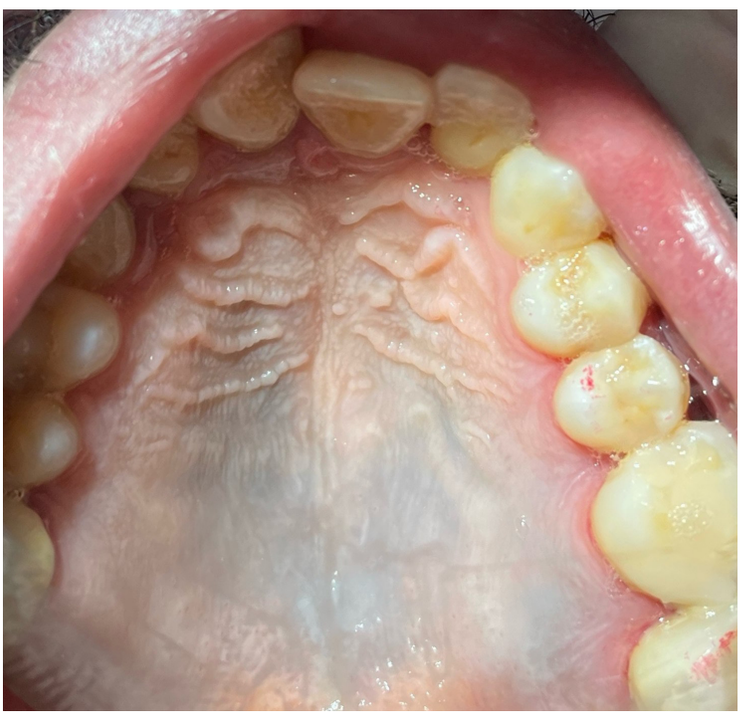

Fig. 2

smoker and consumed alcohol occasionally and there was no history of trauma to the hard palate. On oral mucosa examination, there was a bluish macular pigmentation which almost completely affects the middle and posterior region of the hard palate, without evidence of extension to the soft palate. The pigmented area was asymptomatic and did not blanch on pressure. Furthermore, the lesion was not associated with leukoplakia, erythema, induration, ulceration, or speckling and there were no other areas of extraoral or cutaneous pigmentation. The site, extension, and absence of current or previous dental amalgam restorations, led us to exclude exogenous pigmentation; normal blood tests with a correct hormonal and electrolytic profile and the absence of further symptoms or extraoral signs allowed us to exclude a systemic cause or a syndromic state; by applying the ABCDE algorithm and especially considering the persistence of the lesion for more than 2 years we have potentially excluded the possibility of a malignant lesion. Considering the positive medication history for Imatinib and the current scientific literature, no biopsy of the lesion was executed and probable diagnosis of medication-related pigmentation by Imatinib was performed. However, we applied a close follow-up strategy every 3 months to evaluate any differences in the clinical picture. Since there were no changes after 3 follow-ups and considering that the patient continued to take the drug for the chronic myeloid leukemia, the possibility that the hyperpigmentation is due to the use of Imatinib, and the absence of malignancy is further confirmed. To avoid an invasive and annoying procedure such as a biopsy, we will continue to monitor the patient closely for another 8 months or so, reserving the possibility of a biopsy should doubtful clinical signs appear.

Conclusions: Oral hyperpigmentation associated with Imatinib is considered benign and inconsequential, rendering interventions or suspension of the drug unnecessary. Therefore, both dentists and physicians must be cognizant of mucosal pigmentation as a rare occurrence in patients undergoing imatinib therapy. Additionally, practitioners should diligently conduct a comprehensive pharmacological history to identify potential correlations between drug use and oral lesions.

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Resolution of drug-induced oral lichenoid reaction after drug suspension: a case report

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Background: The oral lichenoid reactions (LR) caused by drug use were first reported in 1929. LR consists of oral lesions clinically similar to those caused by oral lichen planus, except for a marked erythematous/erosive component and a unilateral distribution of the lesions, particularly on the genial mucosa and on the dorsum and lateral margin of the tongue. Furthermore, unlike lichen planus, in these cases the underlying cause is identifiable. Although the pathophysiology of oral lichenoid reactions is still unclear, they can be induced by various systemic medications and direct contact with dental restoration materials. In recent years an increase in lichenoid reactions has been observed, especially in poli-medicated patients. The vast range of medications on the market and the higher drug intake among patients than in the past can be used to explain this escalating LR. The most common medications related to LR are nonsteroidal anti-inflammatory drugs and antihypertensives, including -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers. When the drugs listed above are assumed in combination, they act synergistically increasing the risk of LR onset. Finally, it should be underlined that LR belongs to a group of oral lesions known as "potentially malignant disorders" (OPMD), as a reduced number of cases may undergo malignant transformation, recognizing these lesions from the outset is indispensable for proper management and follow-up.

Case presentation: We report a case of a 79-year-old female who was admitted to the Oral Medicine Unit of University Hospital Policlinico "Paolo Giaccone" in Palermo (Italy) for the presence of white and red lesions on the right buccal mucosa associated with a burning sensation. The patient reported the appearance of the present lesion several years ago. His personal history includes hypertension, arteriosclerosis, mitral valve regurgitation, type 2 diabetes mellitus, chronic hepatitis C infection, and depressive disorder. His medical history includes Metformin, Trazodone, Perphenazine, Vortioxetine, Clopidogrel, Candesartan, Carvedilol, and Lercanidipine. The extraoral examination did not reveal any abnormalities. Clinical examination revealed the presence of white reticular lesions associated with red areas on the right retromolar trigone and the right genial mucosa (Figure 1). The patient experienced pain and a burning sensation when eating spicy food. The primary suspicious diagnosis included oral lichen planus and lichenoid lesions. Then, based on the patient's medical history, to exclude oral lichenoid lesions diagnosis, the attending physician

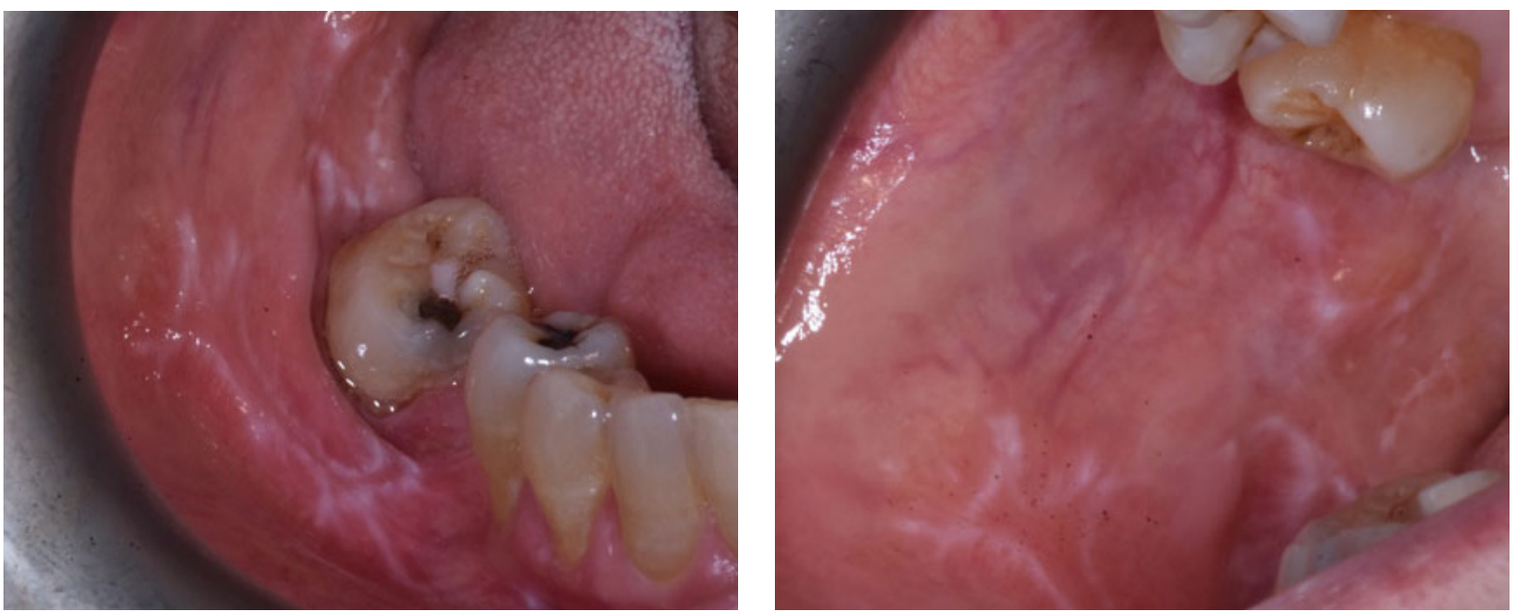

Fig. 1 *Clinical features at the first visit.*

was asked to evaluate and possibly re-modulate the antihypertensive therapy the patient was taking. The patient underwent odontoplasty of the particularly sharp teeth and topical corticosteroid therapy (i.e., clobetasol propionate) to try to reduce the inflammation and discomfort. One month after the doctor changed the drug therapy, withdrawing one of the three antihypertensive drugs (Candesartan), the patient presented to our attention for a new oral examination. Encouragingly, a significant improvement was observed in the previously afflicted oral lesions, as illustrated in Figure 2. The confirmation of the diagnosis of LR is the recovery of the lesions one month after quitting the medication. So, the adverse event was reported to the Italian drug agency through the required notification procedure. After 18 months, the patient is currently under regular follow-up with no signs of recurrence.

Conclusions: LR is an oral adverse drug reaction that belongs to the group of OPMDs. Since predicting the risk of transformation of LR remains a significant challenge in oral medicine practice, in the face of all these types of injuries, one must adopt an approach that includes the monitoring of ADR and a close follow-up, considering it is a case of OPMD. Moreover, a multidisciplinary approach is fundamental to the management of LR.

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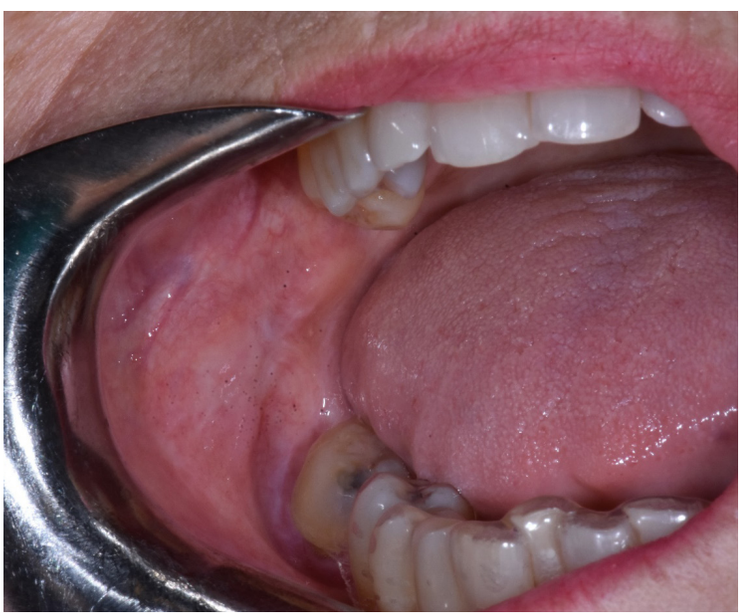

Fig. 2 *Clinical features one month later.*

Angiotensin receptor blockers-induced gingival hyperplasia: a case report

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Background: According to the World Health Organization, hypertension affects 1 in 3 adults worldwide. The most prescribed antihypertensive drugs are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers. Drug-induced gingival overgrowth (DIGO), also known as gingival hyperplasia (GH), is an oral adverse drug reaction (ADR) associated with the use of anti-hypertensive drugs, including olmesartan, a drug belonging to the group of ARBs. DIGO is a side effect with a multifactorial etiology that seems to be initiated by the interaction between drugs and fibroblasts in the gingiva. Some categories of medications, in particular antihypertensive drugs including ARBs, may interfere with the synthesis and function of collagenases, interfering in the degradation of collagen. The consequence is a larger amount of extracellular collagen tissue within the gums. Moreover, a genetic predisposition could also influence and trigger the inflammation process promoting gingival fibroblast functional heterogeneity, collagenolytic activity, drug metabolism, and impair collagen synthesis. Clinically, the gingival hyperplasia generally manifests as a painless enlargement of the papilla which proceeds to include the gingival margin, eventually developing to cover a substantial portion of the crown of the tooth. In advanced stages, gingival enlargement may affect normal oral hygiene practice and interfere with masticatory functions, gradually becoming a source of pain. Although gingival hyperplasia is a well-known adverse drug reaction, due to polypharmacology, sometimes identifying which drug is involved may not be easy. The treatment of DIGO consists of causal periodontal therapy, a change of the drug therapy associated with ADR by the prescribing doctor, and, when necessary, gingivectomy and gingivoplasty.
Case presentation: We report a case of a 57-year-old male who was admitted to the Oral Medicine Unit of University Hospital Policlinico "Paolo Giaccone" in Palermo (Italy) for the presence of a gingival enlargement. The patient reported the appearance of the present lesion approximately one year before. The lesion was not associated with pain. His personal medical history includes hypertension, diabetes, and anxiety disorder. His drug history includes olmesartan, metformin, aripiprazole, sertraline, and alprazolam. The extraoral examination did not reveal any abnormalities. Clinical examination revealed the presence of a gingival enlargement of approximately 4 cm in the 3rd quadrant which extended from 3.2 to 3.4, almost entirely covering these teeth (Figure 1). During examination, no change in color and surface and no present tendency to bleed were

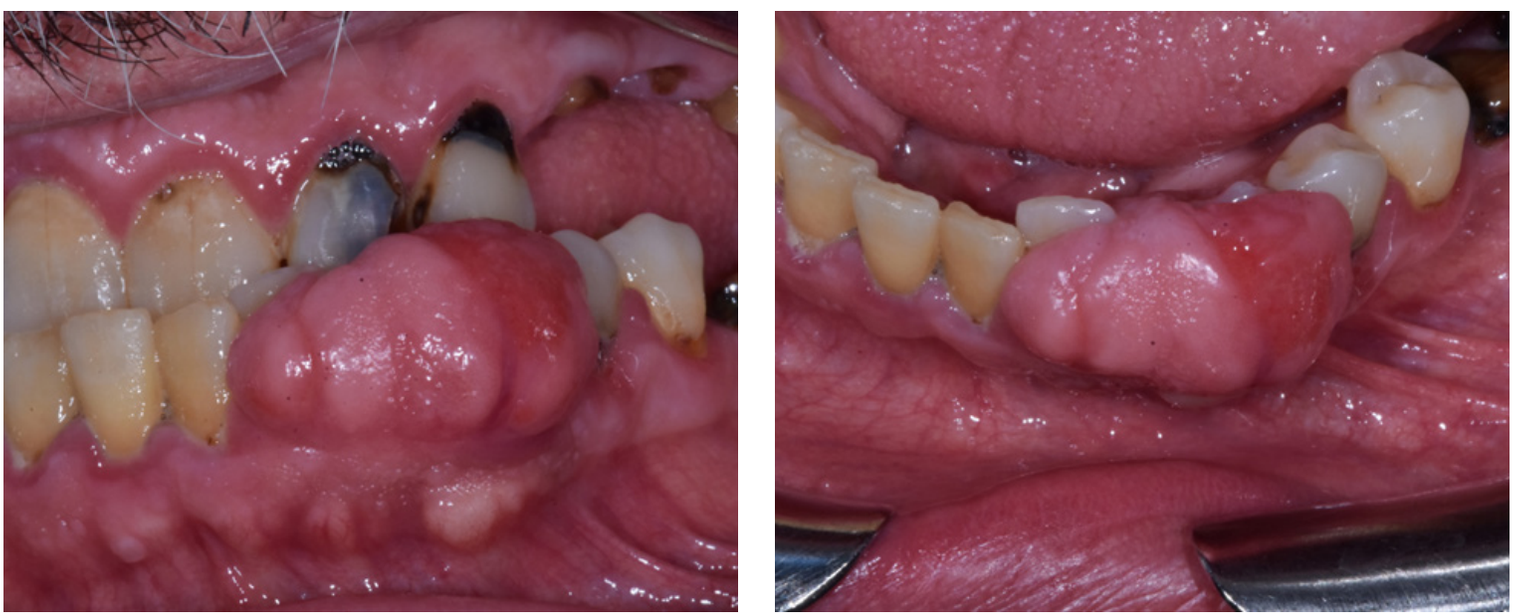

Fig. 1 *Clinical features at the first visit.*

observed. Moreover, a modest presence of plaque was detected. The patient underwent a radiological examination to complete de diagnostic process. The orthopantomography revealed the presence of different root residues in all 4 quadrants. Then, the patient underwent causal periodontal therapy and root residues extractions. Regarding the gingival enlargement, due to the patient's drug history, the primary diagnosis suspicious was an adverse drug reaction; specifically, to ARB (olmesartan). Then, the prescribing physician was asked to consider the possible replacement of olmesartan with one antihypertensive drug containing a different molecule. The patients assumed several medications related to adverse drug reactions, including psychotropic drugs (aripiprazole, sertraline, and alprazolam), which are related to xerostomia, sialorrhea, geographic tongue, candidiasis, and burning mouth syndrome. Nevertheless, in literature, only olmesartan has been associated with other cases of GH. The patient was evaluated one month after the causal periodontal therapy and medication change and although he improved slightly, the lesion persisted. Therefore, the patient underwent surgical excision of the lesion via gingivectomy and subsequently gingivoplasty. The histopathological examination revealed the accumulation of collagenous components in the extracellular matrix of gingival connective tissues accompanied by varying degrees of inflammation. Moreover, the adverse event was reported to the Italian drug agency through the required notification procedure. One year after the drug change the patient is currently under regular follow-up. During the last check-up visit, a month ago, the patient presented caries at the cervical level of 3.2, 3.3, and 3.4, but no signs of recurrence (Figure 2).

Case presentation: DIGO is an oral ADR associated with several types of medications, including olmesartan. DIGO is a benign disease that can affect the aesthetics and consequently the patient's quality of life. Oral health specialists must recognize these changes in the early stage of ADR development and provide appropriate diagnosis and treatment processes. Since the change of drug therapy by the prescribing doctor plays an important role in the management and treatment of DIGO, good communication between the dentist and general practitioner and the multidisciplinary approach is of fundamental importance in this difficult task: reporting adverse drug reactions.

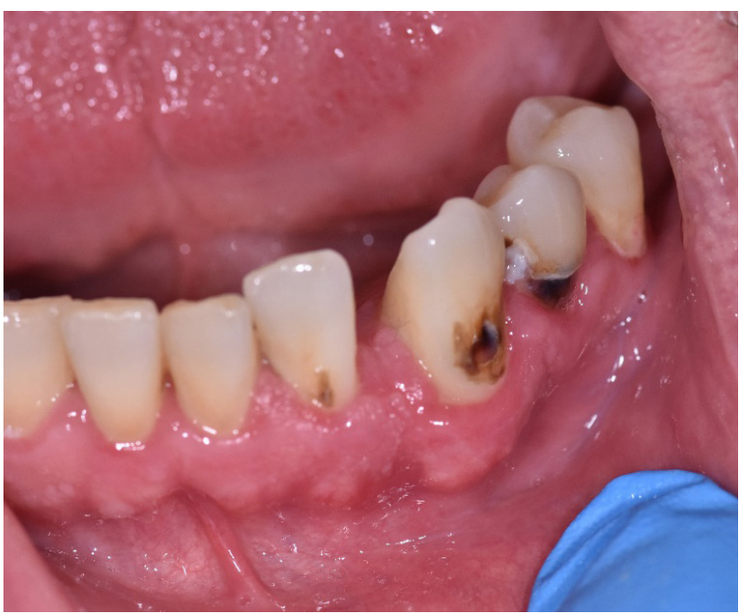

Fig. 2 *Clinical features at the follow-up visit.*

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Palatal lichenoid reaction associated to the use of clotrimazole

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Background: Oral lichenoid reactions (OLRs) are clinically and histologically indistinguishable from Oral Lichen Planus (OLP), caused by known identifiable factors. The primary causes that can induce OLRs are classified into 3 groups, represented by drugs, Graft Versus Host Disease, and dental materials, above all amalgam. The main drugs that may induce OLRs include antihypertensives, antimalarials, hypoglycemic drugs, and NSAIDs. Clotrimazole is an antifungal drug commonly used to treat oral candidiasis and vaginal fungal infections. Clotrimazole is generally well-tolerated with few side effects, including nausea, vomiting, oral discomfort, itching, and increased liver enzymes. Oral administration of antifungal drugs causes more frequent side effects than topical application.
Case presentation: A 72-year-old Caucasian female, a non-smoker and non-drinker, presented to our attention due to a diffuse white patch on her hard palate. The anamnestic data revealed hypothyroidism, under treatment with Levothyroxine for about 10 years. More recently, she underwent a 19-day course with Clotrimazole Troche 10 mg for a previously diagnosed oral candidiasis. The patient completed the Clotrimazole Troche treatment in the U.S.A., as this medication is not commercially available in Italy. The troches were applied in contact with the hard palate for 20 minutes four times a day. The oral candidiasis resolved, but after a 10-day suspension of clotrimazole treatment, she reported the onset of a new lesion on the hard palate. The lesion appeared white, non-removable, with a lichenoid aspect, and without symptoms. The patient underwent a biopsy of the lesion, followed by pathological analysis. The histopathology report indicated the presence of a sub-epithelial lymphomonocytic infiltrate, with vacuolization of the basal epithelium and orthokeratosis.
Both clinical evaluation and histological examination confirmed the diagnosis of OLR. The patient underwent treatment with Clobetasol propionate 0.05% twice a day for 2 weeks, resulting in the complete disappearance of the lesion. At the follow-up the patient did not show OLR recurrence.
Conclusions: Currently, there are no reports of OLRs associated with the use of clotrimazole. However, Literature has documented few cases of OLRs linked to the use of ketoconazole. Both clotrimazole and ketoconazole belong to the same class of antimycotic drugs (azoles), acting by inhibiting fungal growth through the targeting of ergosterol biosynthesis. Additionally, common side effects are reported. In this case, the contact with the clotrimazole tablet with the oral mucosa caused a local effect probably due to a systemic autoimmune reaction. The adverse effect described occurred as a result of applying the drug in contact

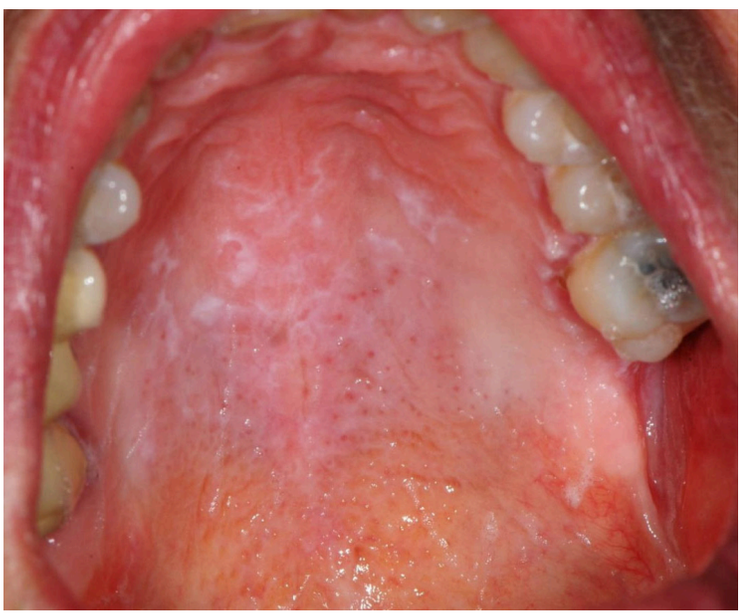

Fig. 1 *White, non-removable striae showing a lichenoid aspect on the hard palate before Clobetasol propionate 0.05% treatment.*

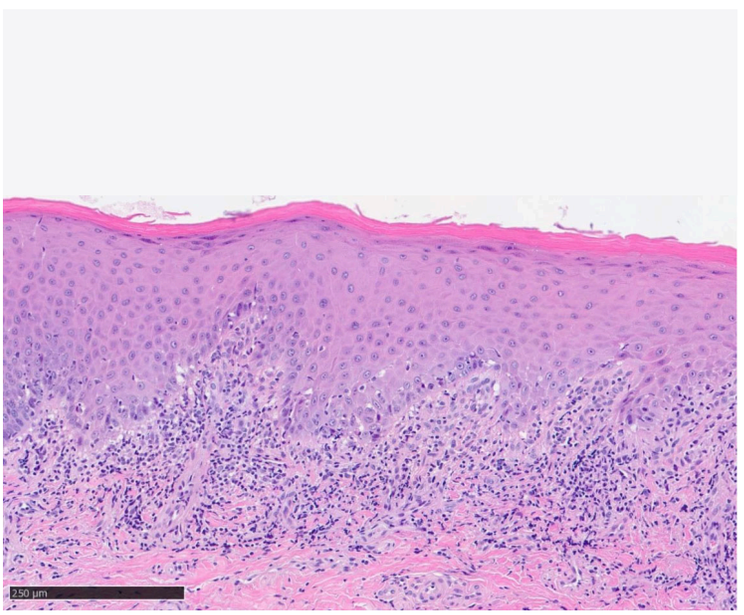

Fig. 2 *Pathological analysis of the lesion showing a sub-epithelial lymphomonocytic infiltrate, with vacuolization of the basal epithelium and orthokeratosis.*

with the oral mucosa, and there is not enough data to ascertain if a similar effect would have arisen with systemic or oral administration of the medication.
A reference to the DoTS (dose, time, and susceptibility factors) criteria of Adverse Drug Reactions (ADRs) was considered to elucidate the relationship between the use of clotrimazole and the onset of an OLR. Anamnestic data revealed that the patient had not recently taken other drugs that could cause the lesion, increasing the probability that the lesion was caused by clotrimazole according to the temporal criteria of DoTS. Additionally, the absence of susceptibility factors in the medical history links the onset of the lesion only with the intake of clotrimazole. Another supporting evidence for the causal relationship, was the non-recurrence of the lesion after treatment with clobetasol. As per ADRs classification, the OLR can be considered a type B reaction. Indeed, it is dose-independent and not predictable based on the pharmacology of clotrimazole. Clotrimazole should be considered as potential drug causative of ADRs.

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An unusual case report of labial and genital angioedema following the application of ligosan periodontal gel

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Background: Ligosan® 140 mg/g periodontal gel is a topical preparation of doxycycline hyclate 14% in polyglycolide gel, indicated in the adjuvant treatment of periodontitis in adults with depth pockets ≥ 5 mm. Recent randomized trials have demonstrated the effectiveness of topical tetracyclines in the adjuvant therapy of peri-implantitis. The topical preparation of doxycycline is generally well tolerated: a randomized controlled trial that recruited 128 patients with moderate/advanced chronic periodontitis, treated with supportive periodontal therapy and followed for three years, did not record any adverse reactions. Furthermore, a double-blind randomized controlled multicenter study, which recruited 111 patients with moderate/severe periodontitis treated with the same therapy mentioned before, reported only two adverse events, one case of gingival swelling and one of dysgeusia. The few trials existing in the literature, which have evaluated the use of Ligosan® in peri-implant support therapy, have not reported adverse reactions. Systemic, cutaneous- mucosal and anaphylactic reactions have an unknown recurrence, not definable on the basis of the available data. The present work describes a clinical case in which the use of Ligosan®, as peri-implantitis non-surgical treatment, caused a systemic adverse reaction.

Case presentation: A 63-year-old male patient, smoker, has been suffering from moderate periodontitis since the age of 42. Approximately nine years ago, he underwent a non-surgical periodontal therapy and prosthetic rehabilitation with the placement of dental implants on the unrecoverable dental elements. The periodic controls showed recurrence appearances of periodontal disease with probings > 5mm and bleeding with grade 2 in numerous sites. The radiographic full status indicated the appearance of infra-bone pockets in several teeth and peri-implantitis disease in sites 2.6-2.7 with a 30% and a 50% of bone loss in 2.6 and 2.7 corrispectively. Clinically, the patient presented gingival edema, bleeding and probing > 5-6 mm. His medical history included surgery for prostate cancer and arterial hypertension treated with ramipril for 5 years. After a preliminary scaling treatment under local anesthesia with 4% articaine and 1:100,000 adrenaline, the patient underwent non-surgical debridement of the peri-implant site, followed by topical application of Ligosan® gel; 15 minutes later, he was discharged, in normal clinical conditions. After about 3 hours the patient contacted the dental clinic by telephone, worried by the development of labial edema, followed by genital edema localized to the glans; he did not report any respiratory symptoms and the blood pressure was within the normal range. Therapy with prednisone 50 mg and cetirizine 10 mg orally was immediately prescribed. The following day, the solidified gel residue was removed from the peri-implant

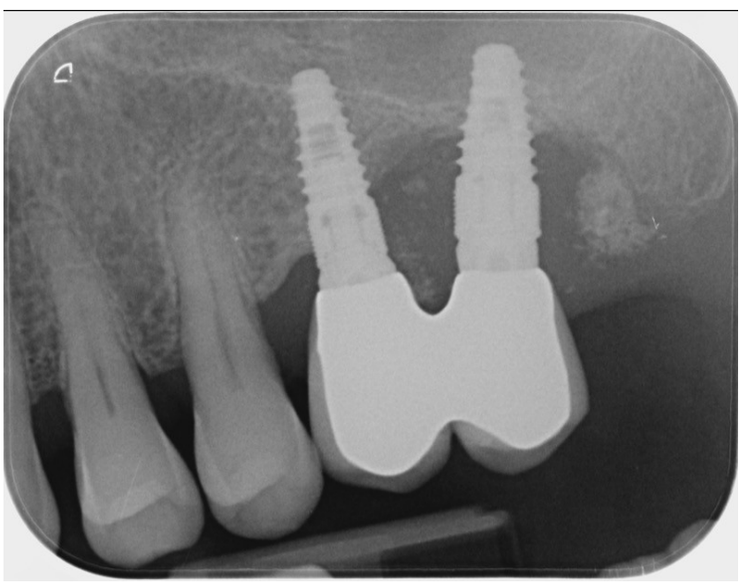

Fig. 1 *Periapical X-ray of implant sites 2.6-2.7*

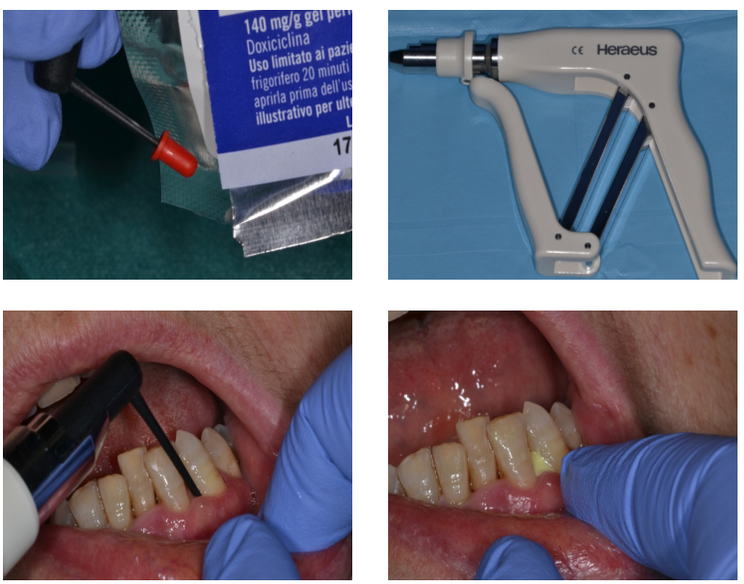

Fig. 2 *Method used for the injection of Ligosan ® inside the periodontal pocket.*

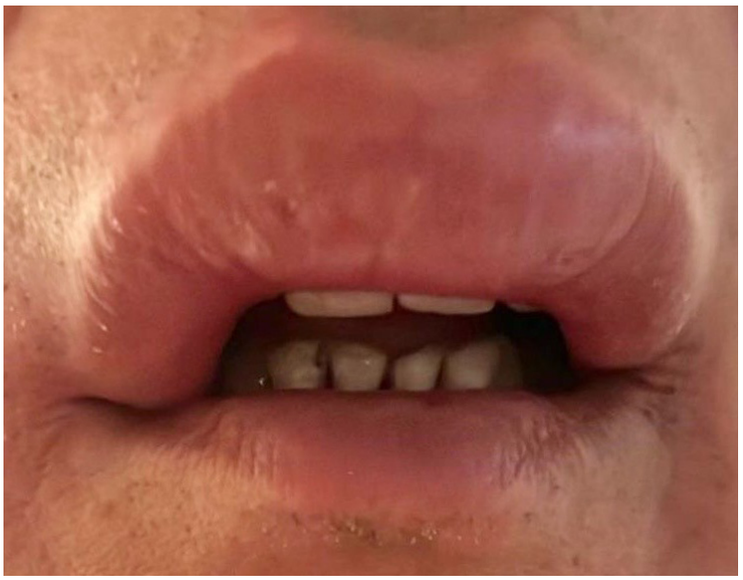

Fig. 3 *Labial edema contained on the upper lip after 3 hours from the injection of Ligosan® Frontal view.*

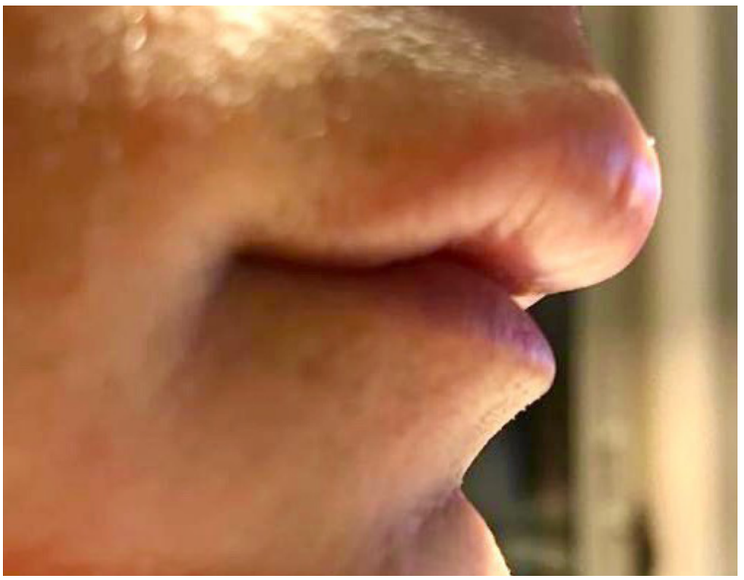

Fig. 4 *Labial edema contained on the upper lip after 3 hours from the injection of Ligosan® Lateral view.*

pocket and the patient continued the pharmacological therapy for the following three days, with gradual resolution of the labial and genital angioedema. Since the patient achieved the complete healing on the fourth day, we suspended the prednisone and we suggested the continuation of the antihistamine for a further 2 days. The suspected adverse drug reaction was appropriately reported to the National Pharmacovigilance Network of the Italian Medicines Agency (provisional Id 45367).

Conclusions: Topical preparations are widely used in the dental field. Although, the currently available data do not allow the frequency to be defined, systemic adverse reactions to local release active ingredients are possible and with an unpredictable severity. A better knowledge of the possible adverse reactions to topical preparations is desirable, considering that in Italy their clinical use is permitted to non-medical healthcare personnel as well, who are often not prepared to deal with medical emergency situations.

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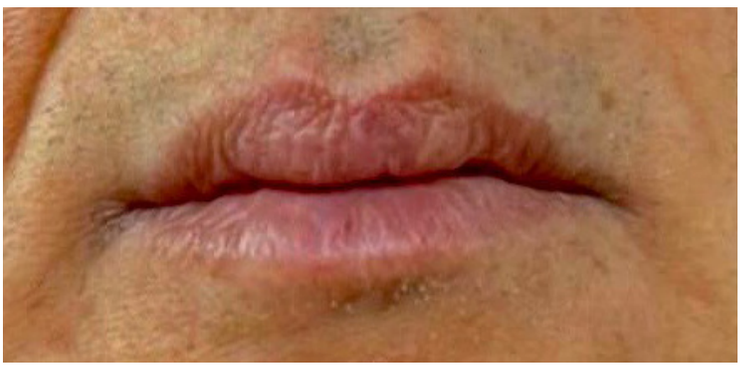

Fig. 5 *Resolution of the labial angioedema after 3 days of pharmacological therapy. Frontal view.*

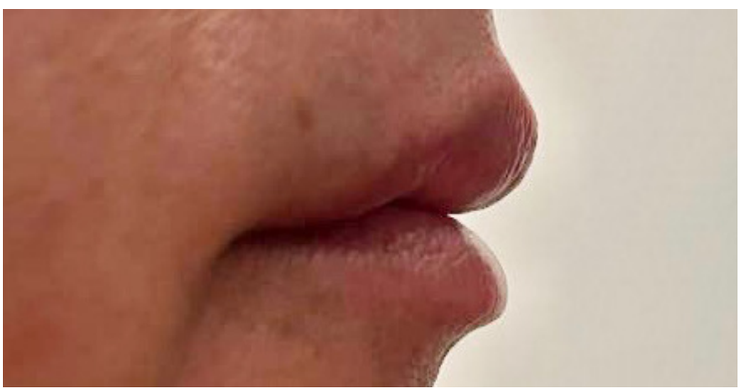

Fig. 6 *Resolution of the labial angioedema after 3 days of pharmacological therapy. Lateral view.*

Multiple immune-related adverse-events of the oral mucosa secondary to Pembrolizumab for advanced-stage cutaneous melanoma

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Background: Immune-checkpoint-inhibitors (ICIs) are considered a major discovery in clinical oncology due to their ability to disrupt the natural history of certain, otherwise non-curable, malignant conditions[1]. Although these agents have successfully demonstrated a significant extension for disease-free-remission among many cancer survivors, they are commonly associated with a range of adverse-events (AEs) caused by the uncontrolled activation of the immune-system[2]. Herein we present a case of multiple AEs of the oral mucosa following initiation of Pembrolizumab in a patient with advanced-stage cutaneous melanoma.

Case presentation: A 52-year-old-male with a medical history of hypertension, hyperlipidemia, hypothyroidism, and bipolar-disorder presented in June 2023 to the University of Maryland, School of Dentistry for full-mouth rehabilitation. The patient reported a 4-week history of xerostomia in addition to a diffuse burning sensation of the oral mucosa with specific sensitivity to spicy/acidic foods with extent to the labial commissures. A recent recurrence of a stage-III melanoma of the left arm which was currently being treated with the programmed death-1 (PD-1) inhibitor pembrolizumab (Keytruda®) 2 mg/kg every 6 weeks was also reported. The patient's medications included levothyroxine, valsartan, atorvastatin, and carbamazepine. Following the delivery of a permanent zirconia bridge, a clinical consultation from an oral medicine specialist was requested. Clinical intraoral examination revealed an (1) diffuse erythema of the maxillary gingivae extending from tooth 1.4 to 2.3; a (2) bilateral lichenoid lesions of the buccal mucosa and ventrolateral tongue characterized by extensive reticular striations/keratotic papules, and surrounded by diffuse erythema and focal ulcerations; (3) white detachable/scrapable plaques of the bilateral lower-vestibule and FOM; (4) mild erythema of the labial commissure associated with cutaneous fissuring and crusting, and (5) moderately dry oral mucosa with limited FOM salivary pooling and saliva discharge from the parotid ducts (Fig. 1). Given the presentation, a clinical

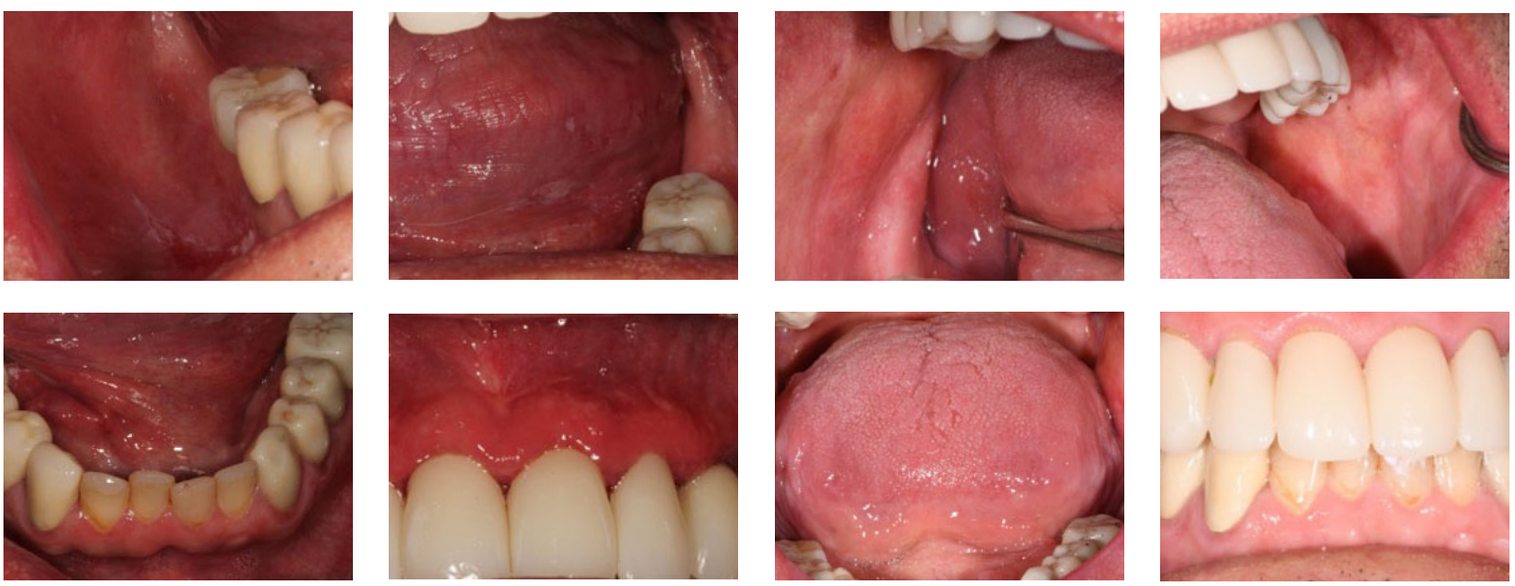

Fig. 1 *Multiple lichenoid reactions of the bilateral buccal mucosa; diffused erythema of the attached gingiva; white detachable/ scrapable plaques of the bilateral lower-vestibule and FOM.*

Fig. 2 *Regression of the oral LR, with faint residual reticular areas on bilateral buccal mucosa.*

diagnosis of oral candidiasis, angular-cheilitis, pembrolizumab-induced xerostomia and lichenoid-hypersensitivity reactions of the oral mucosa were rendered. Therapeutic management consisted of nystatin 100.000 UI/mL oral rinses, dexamethasone 0.5 mg/0.5 ml topical solution up to BID-QID if needed for 3 months.
Patient returned for follow-up in 8 weeks and clinical examination revealed an almost complete resolution of the oral lesions with mild residual lichenoid and erythematous areas on the bilateral buccal mucosa (Fig. 2) still consistent with pembrolizumab-associated oral-LR but with no signs of active disease. The patient's burning sensation improved dramatically with only a slight sensitivity to hot/acidic foods. The patient completed his last immunotherapy session in October 2023, and remains in oncologic remission.
Conclusions: Immune-checkpoint inhibitors (ICIs) have been exponentially used through the last 10 years, revolutionizing the standards of cancer treatment. Accordingly, frequent immune-related adverse events (irAEs) were described in the literature. Martins et al, reported an overall risk of developing at least one AE from ICIs up to 60%, with ipilimumab being the most commonly reported and atezolizumab having the best overall safety profile/lower risk of any AE[1]. The range of pembrolizumab-related AEs varies between <1% for hepatic complications with low-dose regimens, up to 19% for GI-tract AEs with high-dose-regimens[1]. Although less frequent, oral irAEs were also described in literature. Shazib et al. presented 13 patients treated with PD-1/PDL-1 inhibitors, 8 (61.5%) of which were treated with pembrolizumab; of them, 50% developed lichenoid mucositis (LM), one patient EM-like oral lesions, whereas one patient had oral-GVHD reactivation[2]. Similarly, Pergolini et al. presented 13 cases treated with ICIs for advanced solid tumors3. Overall, almost 80% (n=10) of their cohort were treated with pembrolizumab, with 50% (n=5) of them showing oral LM (n=4) and oral candidiasis (n=1). Accordingly, our patient developed oral LM, angular-cheilitis, oral candidiasis, xerostomia/salivary-hypofunction. Whereas LM and xerostomia are well-documented as irAEs, fungal infections emerging during immunotherapy have raised doubts if they are directly related to ICIs, develop secondarily to salivary-hypofunction or as a consequence of local corticosteroid treatment. Our patient developed oral candidiasis/angular-cheilitis before topical corticosteroid treatment, therefore we consider both the xerostomia/salivary-hypofunction, and the ICI as the likely potential etiologic factors involved.
Patients receiving prolonged ICIs should be carefully monitored by oral-health-providers for oral complications resulting from the use of immune-modulating drugs. The oral complications, as illustrated in this case are easily managed and may prevent unnecessary delays in oncologic management, as may occur with premature withdrawal of oncologic agents to appease oral symptoms.

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White tongue and straight hair in a patient with chronic hepatitis C: a case report and review of the literature

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Background: The antiviral treatment for chronic HCV with Interferon alfa or PEG Interferon alfa combined with Ribavirin leads to many skin side effects like alopecia, vasculitis, cutaneous necrosis, eczema, lichenoid lesions, dry skin, pruritus, psoriasis, vitiligo. During this combination therapy tongue and gums hyperpigmentation both in dark-skinned as well as Caucasian have been also reported. There are also two case reports of a complete and acquired straightening of hair due to the administration of the same drugs.
Case presentation: We described the first case of a patient with a chronic HCV infection who developed a white and spongy tongue and also an acquired straightening of hair, during combination therapy with PEG Interferon alfa and Ribavirin.
Conclusions: The pathogenetic mechanism of this white tongue associated with hair straightening is unclear. In our case, the absence of the most important diseases or drugs associated with this phenomenon, and, in particular, the progressive oral lesions remission one month after the end of therapy, and their complete remission at three months from the end of the last drug administration, lead us to the association of the PEG- INF-2a plus Ribavirin with this abnormalities. However, the limited data present in the literature do not allow us to confirm with certainty a cause-effect relationship between the drugs and these side effects.

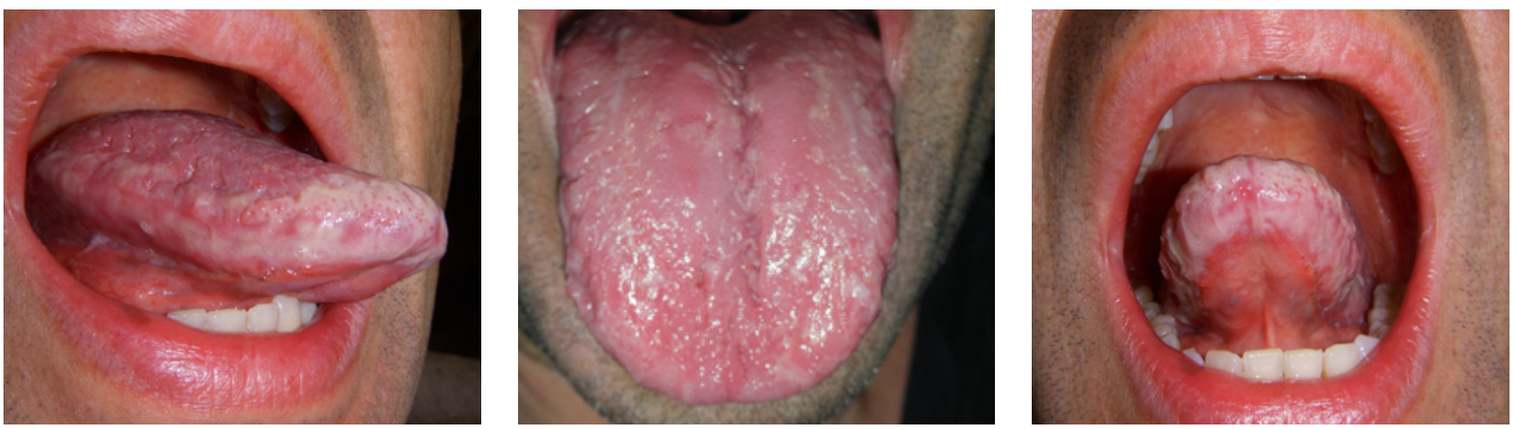

Fig. 1 *White tongue after treatment.*

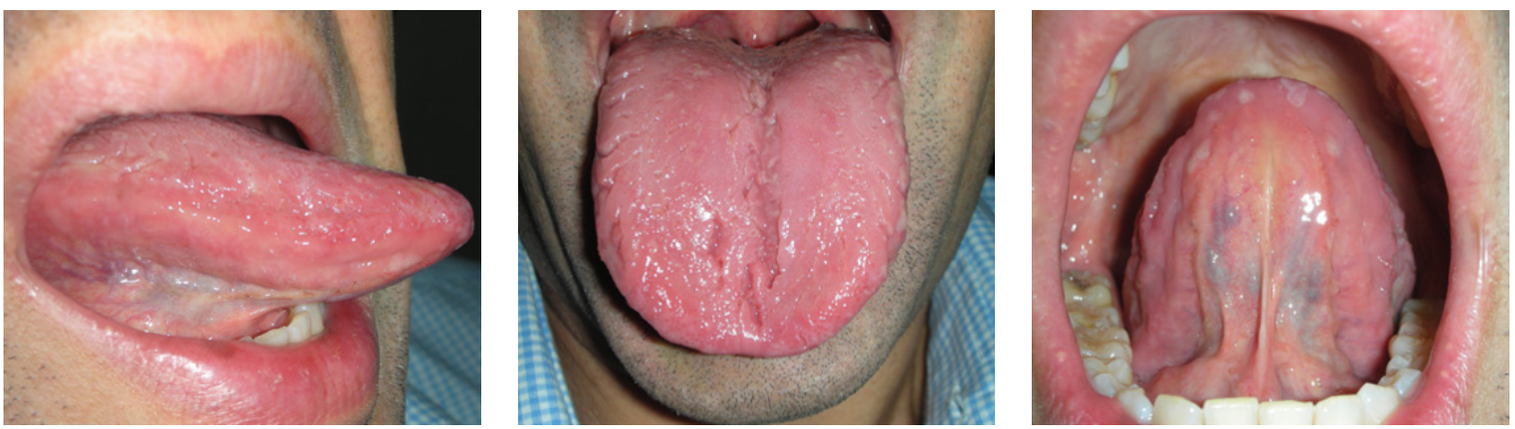

Fig. 2 *Remission of clinical signs three months after the end of the last drug administration.*

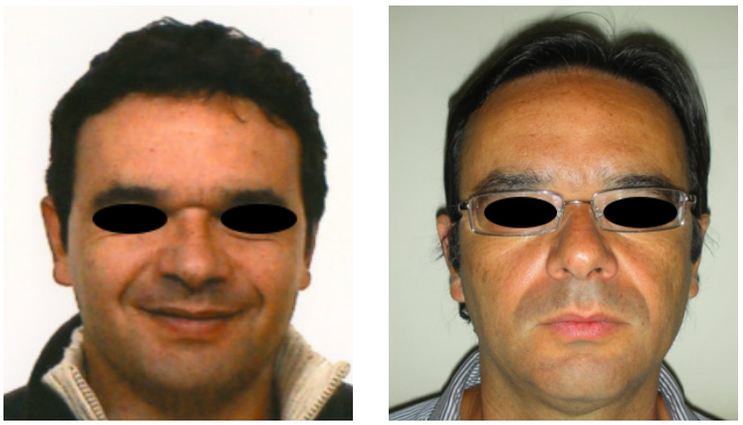

Fig. 3 *Figure A: pre-treatment patient with curly hair. Figure B: patient with straight hair during the treatment.*

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A case of low-dose methotrexate-induced oral ulcers in a patient with rheumatoid arthritis

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Background: Methotrexate (MTX) is an immunomodulator that functions as an antagonist of folic acid and is widely used at high doses as a chemotherapeutic agent for the treatment of lymphomas, leukemia and some solid tumors.
At low doses (below 25 mg/week), it exerts anti-inflammatory effects and is used for the treatment of several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, pemphigoid, or psoriasis. However, by inhibiting crucial enzymes in the biosynthesis of purines and pyrimidines MTX not only targets high turnover cells like inflammatory and malignant cells but inevitably also affects epithelial cells causing oral mucosal lesions. Oral ulcers have been reported in 11%-17% of patients treated with MTX at low doses. We describe a case of MTX-related oral mucositis completely regressed after MTX discontinuation.
Case presentation: A 68-year-old patient was referred for non-regressing multiple widespread oral ulcers and erosions arisen two months before. Ulcerative lesions were also associated with reticular-like red and white areas (Fig.1A). Sites involved included mucosae of both upper and lower lips, cheeks, and lateral borders of the tongue. Systemic medications included rivaroxaban 2,5 mg twice/day for deep vein thrombosis prevention, methotrexate 17,5 mg/week for rheumatoid arthritis, olmesartan medoxomil 10 mg/daily for hypertension, pantoprazole 20 mg for gastric protection, atorvastatin for hyperlipidemia regulation. Methotrexate (MTX) intake started 2 years before, but the dosage had been recently increased from 7,5 mg/ week to 17,5 mg / week due to worsened rheumatoid arthritis control.
Previous short-term treatment with methylprednisolone 16 mg tablets (suspended at the time of referral) reportedly ameliorated the ulcerative lesions but was not resolutive.
Differential diagnoses included oral lichen planus, autoimmune blistering diseases, recurrent aphthous stomatitis, allergic reactions, viral and bacterial infections, coeliac disease, agranulocytosis, and adverse drug effects. The patient underwent oral biopsy sampling for microscopic evaluation and direct immunofluorescence (DIF). Thereupon, the patient was prescribed prednisolone 25 mg/day tablets for intense oral pain. After 15 days of steroid therapy lesions slightly decreased in size but did not regress. Moreover, results from the histology were not informative showing not specific signs of erosive chronic inflammation and areas of hyper-parakeratosis, cellular atypia and overexpression of immunohistochemical markers. DIF was also negative for IgG, IgM, IgA, C3, Fibrinogen.
To rule out drug-induced mucositis, the rheumatologist was asked to reduce/discontinue methotrexate therapy if allowed by guidelines for rheumatoid arthritis clinical management. Two weeks after MTX discontinuation complete clinical resolution could be noted (Fig.1B). The persistence of clinical remission at the end of steroid tapering, confirmed the diagnosis of MTX associated mucositis. MTX was finally switched with leflunomide 20 mg by the rheumatologist.
Conclusions: Despite oral mucositis is a well-recognized side

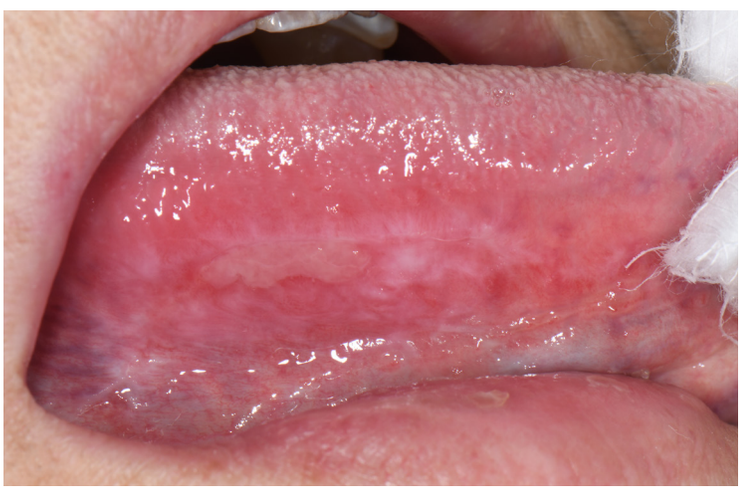

Fig. 1A

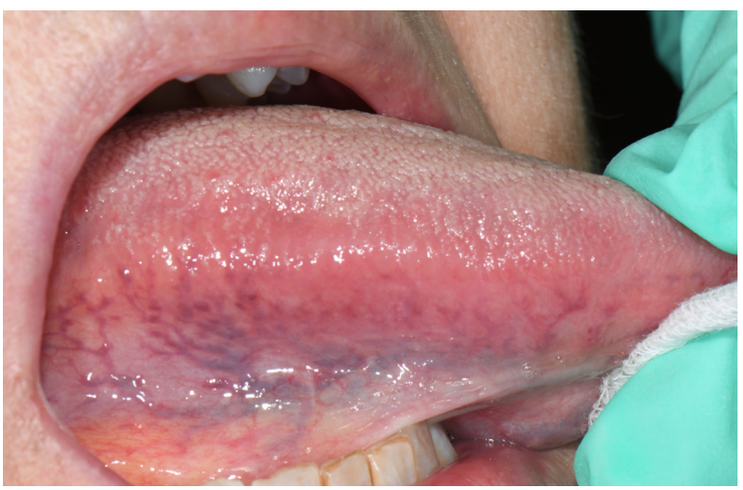

Fig. 1B

effect of MTX its diagnosis can be challenging. Indeed, the clinical and histological characteristics are not always diagnostic. Clinical presentation may range from apthous like ulcers/deep irregular ulcers to diffuse mucositis mimicking lichenoid lesions. Histologic examination may help for excluding malignancies or autoimmune disorders but great heterogeneity in histologic results have been reported including non-specific ulceration, presence of irregular and hyperplastic epithelial layers with atypical nuclei, lymphocytic infiltrate with lichenoid appearance. Accurate medical history is thus essential for correct interpretation.
Most studies suggest that in MTX-related oral mucositis a dose-dependent relationship may exist. The present case seems to support this hypothesis since oral ulcers developed soon after the dose of MTX was raised. Lesions tend to regress within three weeks after MTX discontinuation as occurred in the present report. Recent studies seem to suggest a potential beneficial effect of folic or folinic acid supplementation on the incidence of stomatitis, but results need further confirmation.
In conclusion, interdisciplinary collaboration among oral medicine specialists, pathologists and MTX prescribers is essential for a prompt recognition and management of MTX-related oral adverse events.

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Oral Lichenoid Bullous Reaction Induced by ß-Blockers: A Case Report

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Background: Oral lichenoid reactions or oral lichenoid lesions constitute a condition that exhibits clinical and histological similarities with oral lichen planus. Clinically, oral lichenoid reactions can be similar to forms of oral lichen planus, including reticular, plaque-like, erythematous, erosive, bullous, or ulcerative. The onset of oral lichenoid drug reactions appears to subsequent to administration of some medications, such as antihypertensive drugs, beta-blocker, oral hypoglycemic drugs. This report details a case of bullous oral lichenoid reactions, potentially related to beta-blocker assumption.

Case presentation: A 37-year-old woman with Turner syndrome, hypothyroidism, and cardiac arrhythmia, and currently in treatment with beta-blocker medication for 3 years, presented to the Unit of Oral Medicine with Dentistry for Fragile Patients (AOUP "Paolo Giaccone" of Palermo) for a chief complaint of oral pain. About three months ago, she observed the emergence of red lesions on the gingiva, accompanied with a burning sensation, particularly in the region of the upper left first premolar. No other medications are referred during previous months. No alterations were detected during the extraoral examination. Intraoral exam revealed widespread desquamative gingivitis with red lesions on the gums and ulcers on the gingival, especially on the upper left first premolar. (Fig. 1-2). Firstly, differential diagnosis included oral lichenoid reactions and oral lichen planus and other immune-mediated diseases. To confirm the diagnosis, blood test and an incisional biopsy were conducted. The histopathological examination disclosed a stratified squamous epithelium with mild acanthosis, likely corresponding to the detached "roof" of a bullous lesion (Fig. 3). Additionally, a fragment of stromal connective tissue exhibited marked chronic inflammatory infiltrate on one side (no band-like aspect), with modest ectasia and vascular congestion of the capillaries. These findings collectively supported the clinical diagnosis of "drug-induced lichenoid (bullous) reaction." No significant results of blood test were reported. So, it was prescribed topical applications of clobetasol propionate, a targeted therapeutic measure aimed at alleviating painful symptoms and reducing discomfort and inflammation caused by desquamative gingivitis. At the same time, according to the prescribing specialist, the medication beta-blocker was replaced, considering it as an adverse event that was reported to the Italian drug agency by the known notification procedure. Our management determined a swift and notable relief from oral lesions, with a clinical amelioration of oral condition (Fig. 4). To ensure comprehensive care and monitor the patient, a regimen of regular follow-up appointments has been established. Follow-ups represent as a platform for continuous assessment, allowing for the adjustment of the treatment plan as needed and ensuring the sustained well-being of the patient. The collaboration between the medical team and the patient in this

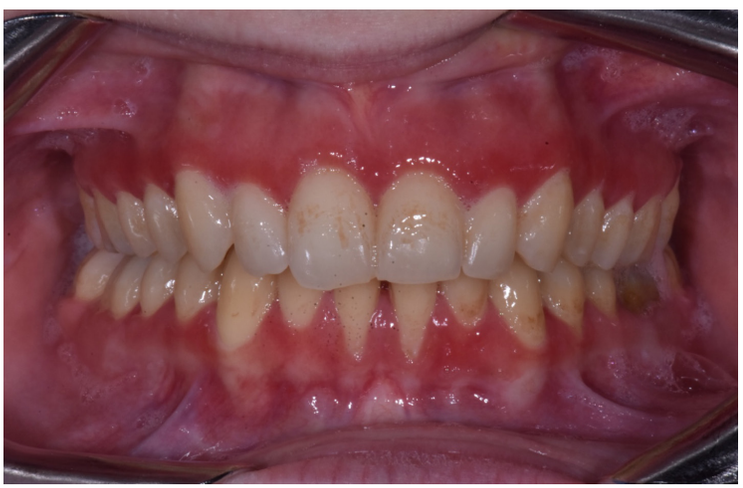

Fig. 1 *Clinical image red lesions on the gums.*

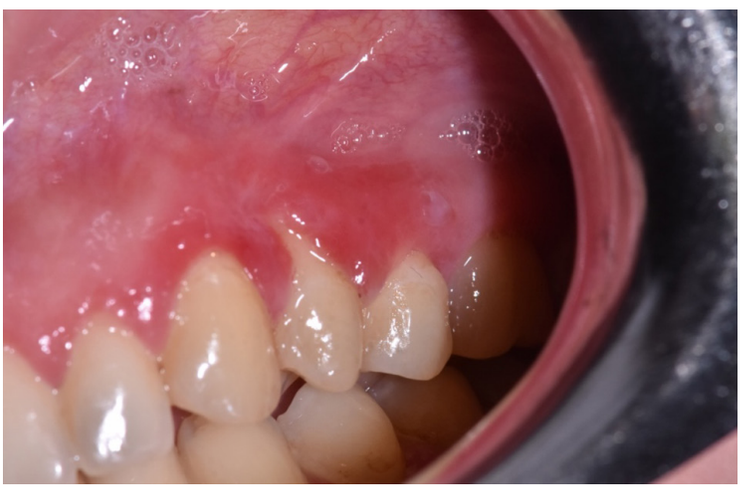

Fig. 2 *Clinical image of red lesion around the upper left first premolar.*

follow-up process is crucial for achieving optimal outcomes and maintaining oral health.

Conclusions: The aim of this case report is to describe a rare occurrence of oral mucosal reaction related to a drug, particularly Bisoprolol, a beta-blocker, which rarely leads to such lesions (1/1000 cases). Complete healing has been observed after discontinuation of the medication. Differential diagnosis can be challenging, since many conditions could overlap many clinical and histopathological diseases. It emphasizes the importance of experience and knowledge of healthcare professionals for early recognition, identification and management of oral adverse events related to medication. Despite being a matter of controversy, the diagnosis and follow-up of these lichenoid lesions appear even more crucial due to the potential risk of malignant transformation.

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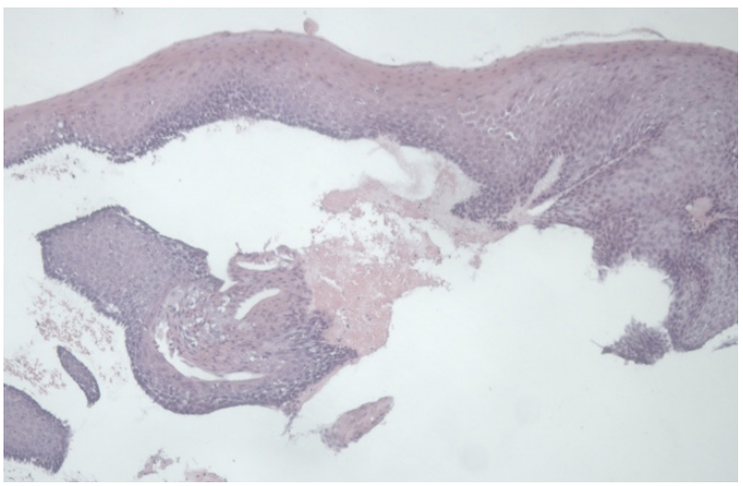

Fig. 3 *Histological image of the analyzed biopsy sample.*

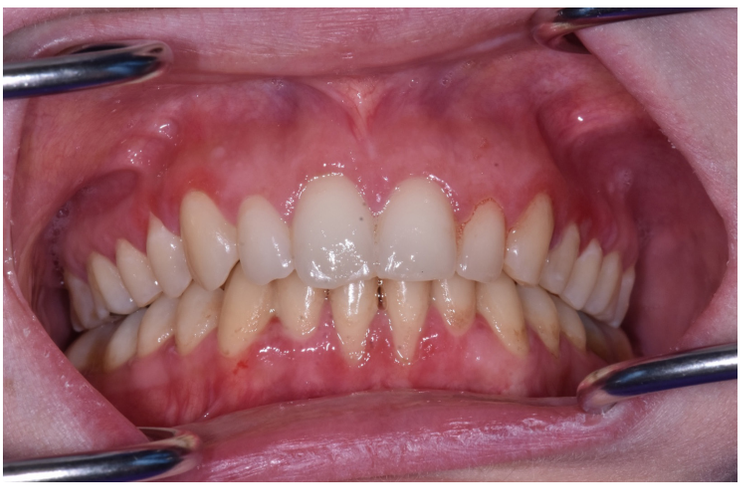

Fig. 4 *Fifteen days after the replacement of the beta-blocker, gingival mucosa.*

Cisplatin-Induced Necrotizing Stomatitis: A Case Report

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Background: Oral stomatitis represents a widespread and devastating side effect of antitumor therapies, significantly compromising the patient's quality of life and potentially jeopardizing their life due to severe infections and delays in antitumor treatments. In the past, this issue has been widely overlooked and underestimated. Several chemotherapeutic drugs can result in mucositis and stomatitis as an adverse effect on the oral cavity. This report details a rare case of chemotherapy-induced necrotizing stomatitis, potentially associated with cisplatin therapy. Recognition of so rare pathological conditions is crucial for the accurate and timely clinical and symptomatic management.
Case presentation: A 54-year-old woman with metastatic colorectal neuroendocrine carcinoma presented at the Unit of Oral Medicine with Dentistry for Fragile Patients at the "Paolo Giaccone" University Hospital in Palermo. She referred to be undergone to one cycle of cisplatin treatment two weeks ago, and to present from few days pain and widespread oral cavity lesions. The patient affirmed that she had not taken any other medications in the months leading up to the present. The extraoral examination did not reveal any alterations, while the intraoral examination showed a condition of chronic periodontitis with diffuse horizontal bone resorption (stage II periodontitis) and many white lesions on gingiva of some sextants. In details, these lesions were present on the gingival mucosa of the upper arch on both the vestibular and palatal sides (Fig 1A-B), as well as on the gingival mucosa of the lower arch on both the vestibular and lingual sides (Fig B-C). The lesions were removable and consisted of fibrin covering underlying ulcerated areas. Given the medical history and clinical presentation, a possible diagnosis of chemotherapy-induced necrotizing stomatitis was established. The suspension of the cisplatin treatment was prescribed after consultation with the oncologist. After, the patient underwent a session of causal periodontal therapy, received low-level laser therapy, and received a prescription of topical medical treatments. These included a mouthwash containing benzydamine hydrochloride for pain management and application of an oral gel enriched with hyaluronic acid.

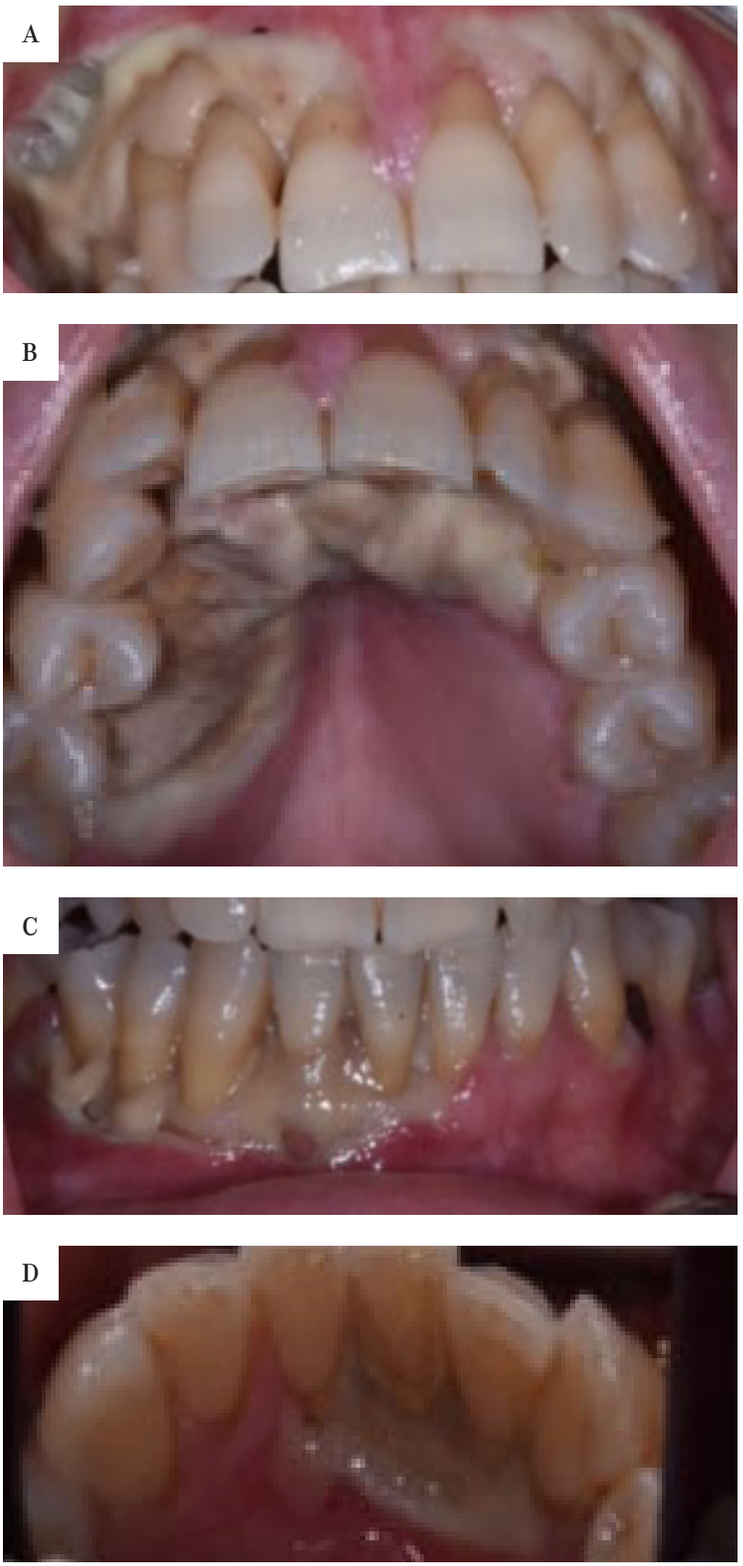

Fig. 1 *Clinical images of ulcerative oral cavity lesions due to chemotherapy-induced necrotizing stomatitis.*

During the follow-up visit (one month), a significant improvement was observed both clinically and symptomatically. The lesions completely healed, especially in the upper arch on the palatal side and in the lower arch on both the vestibular and lingual sides (Fig. 2 B-C-D). Some residual lesions persisted only on the vestibular side of the upper arch (Fig. 2 A). A second session of low-level laser therapy was carried out, and the at-home topical medical treatment was continued. This adverse event is reported to the Italian drug agency by notification procedure. Unfortunately, the patient passed away before the final check-up.

Conclusions: Oral stomatitis is a common complication arising from cancer treatments, and ulcerative and necrotizing stomatitis due to cisplatin is a rare occurrence (1 in 1000 cases). The presence of a chronic inflammatory condition such as periodontitis could have triggered the necrotizing stomatitis. Thanks to the recent publication of the MASCC/ISOO clinical guidelines for mucositis secondary to cancer treatment, updated data on incidence, pathophysiology, consequences, and therapeutic options provide support to professional healthcare specialists with an evidence-based tool specifically designed for the clinical environment to facilitate the management of mucositis in cancer patients. The importance of prevention, oral care, and comprehensive communication with the patient cannot be emphasized enough. These are fundamental elements for enhancing the quality of life, which is already compromised, for cancer patients. The reporting of adverse reactions plays a crucial role in expanding knowledge and disseminating information about new adverse events that may not yet be known.

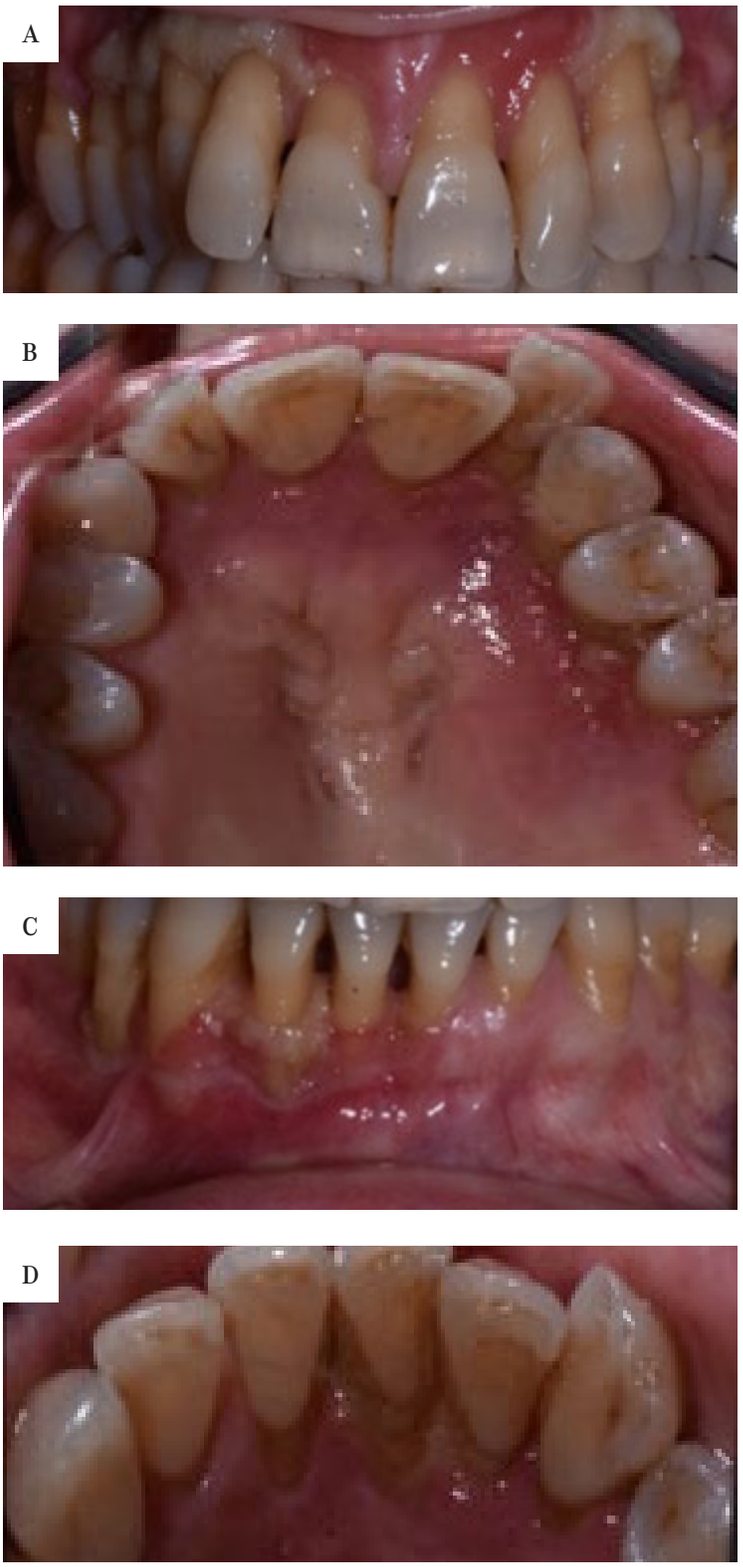

Fig. 2 *Clinical images of healing of chemotherapy-induced lesions after low-level laser therapy and topical medical treatment.*

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Section amlodipine-induced gingival hyperplasia: a case report

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Background: Drug-induced Gingival Overgrowth (DIGO) is a side effect of some medications used in non-dental settings such as anticonvulsants (phenytoin), immunosuppressants (cyclosporine) and antihypertensive calcium channel blockers (nifedipine and amlodipine).
Amlodipine belongs to the third generation of calcium antagonist and the association of gingival hyperplasia with the administration of this drug is rare. According to the literature, the incidence of amlodipine-induced gingival hypertrophy varies from 1.7% to 3.3%. Men are 3.3 times more likely to develop gingival hypertrophy than women.
We report a case of amlodipine-induced gingival enlargement in a hypertensive patient taking amlodipine at a dose of 5 mg.
Case presentation: A 80-year-old male with a large gingival tissues hypertrophy especially on II quadrant gingiva, referred to the Oral Pathology Unit of CIR-Dental School, University of Turin. The patient reported that he was unable to wear his removable partial upper prosthesis.
His medical history reported arterial hypertension under therapy with Amlodipine 5mg once daily.
According to the blood tests the blood count, VES and protein C are within normal range.
His dentist has already started scaling and root planning sessions. Suspecting gingival hypertrophy induced by amlodipine, it was decided to continue with the causal periodontal therapy and to perform an incisional biopsy in area 2.3 and 2.4 in order to confirm the hyperplastic nature of the lesion.
Histopathological report revealed the presence of polypoid fragments of oral mucosa with mild chronic inflammatory infiltrate, predominantly sub- and intraepithelial lymphocytic, marked stromal fibrosis and hyperplasia of the epithelium, a morphological picture compatible with gingival hyperplasia.
After about one month the patient suspended the therapy with amlodipine but the gingival hyperplasia involving vestibular and palatal areas 2.3 and 2.4 with difficulty in correctly inserting the prosthesis remained unchanged. Therefore it was decided to proceed with a large corrective gingivectomy by diode laser.
Conclusions: The etiology of drug-induced gingival overgrowth is not entirely understood but it has now become quite clear that a multifactorial role may be involved in its cause. Treatment consists of stopping the offending drug if possible with the patient's physician consent and providing effective oral hygiene measures, professional tooth cleaning, scaling, and root plannin. If gingival enlargement persists, after careful consideration of the previously mentioned approaches, these cases need to be treated by surgery.

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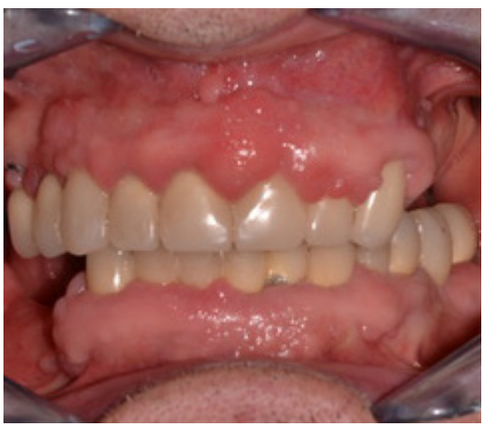

Fig. 1 *Frontal buccal photo of both dental arches.*

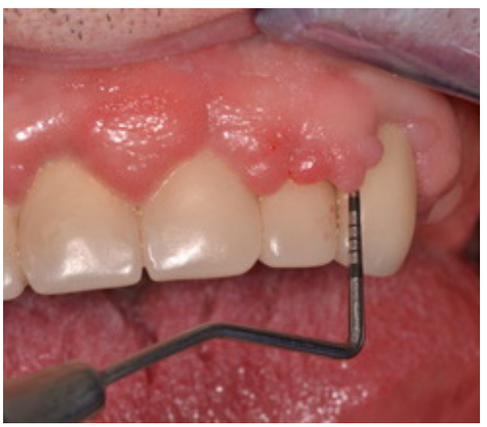

Fig. 2 *Frontal vestibular photo of quadrant II.*

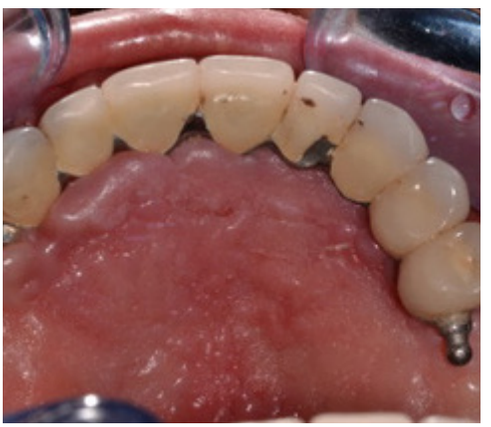

Fig. 3 *Upper occlusal photo.*

Oral lesions postinjection of the first administration of Pfizer-BioNTech SARS-CoV-2(BNT162b2) vaccine

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Background: COVID-19 has been strongly associated with dysgeusia, but several oral manifestations have also been described in patients infected by SARS-CoV2. There is growing evidence that angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of SARS-CoV-2, is highly expressed on the epithelial cells of the tongue and of the salivary glands, which may explain the development of dysgeusia: it is possible that SARS-CoV- 2 can infect and replicate in oral keratinocytes and fibroblasts, causing oral manifestations. However, there is still a question in COVID patients about whether oral lesions may be also a secondary manifestations resulting from the patient's systemic condition.
Case presentation: A 34 year-old healthy woman, with no medical history of allergic reactions and not undergoing chronic systemic pharmacological therapies, presented with diffuse and painful oral lesions. These appeared two days after the first administration of Pfizer-BioNTech SARS-CoV- 2 (BNT162b2) vaccine. She reported no fever after the shot, but mild diffuse joint pain, asthenia and local pain in the injection site. At clinical examination, diffuse ulcerative lesions on the floor of the mouth were observed, associated with oral erythema of the ventral surface and anterior area of the tongue. The lip mucosa appeared dry and inflamed, with mild signs of angular cheilitis. The patient also referred swelling of the lips and oral gingiva, where multiple small erosive ulcers were present. The lesions were treated with topical antibacterial agents and moisturizing lip balm. At the one-week follow-up, the lesions were gradually healed, but still present on both margins of the tongue and lower lip. Signs of angular cheilitis remained. At day 15, complete mucosal healing was achieved. Subsequently, the patient underwent allergological cutaneous tests, planned before the second vaccine administration. These resulted positive for polysorbate 80, in particular ID 1:10 with refresh-sterile eye drops, used an alternate source of polysorbate. Other allergy testing for pegilate was negative. The day after allergy test, the patient reported swelling of the lips and diffuse oral burning sensation, which lasted for 2 days. Due to the reaction following the first administration of the vaccine and the positive allergological results of proven allergy to the excipient, patient did not receive the second administration of the vaccine.
Conclusions: Given the clinical picture of the patient, it could not be excluded during the first clinical examination that the lesions could be due to a COVID-19 infection already ongoing at the time of the first administration of the vaccine, although the patient recently had confirmation of negative nasopharyngeal swab. The oral lesions appeared after 48 hr since the first injection with BNT162b2 vaccine. In addition, allergic reactions can also occur after vaccination, although oral side effects of systemically administered vaccines are extremely rare. Recently, a case of oral mucositis due to a hypersensitivity triggered by ChAdOx1 COVID-19 vaccination has been reported, with similar lesions to those here described. However, these two vaccines differ: ChAdOx1 consists of a nonreplicating viral vector while BNT162b2 is a m-RNA vaccine and they consist of different excipients triggering the human immune system with different pathways. Since the patient showed an important reactivity to polysorbate 80 during allergological tests with evident skin reaction and reappearance of oral signs and symptoms, it is plausible to associate the oral manifestations with the administration of the vaccine. Polysorbate 80 is used to make the m-RNA fat-soluble, and it is generally used to encapsulate the monofilament of the m-RNA, which otherwise is unstable in physiological conditions, and otherwise, it could not perform its function. It is known to be able to cause a cross-link reaction with one of the components of the BNT162b2 vaccine. The nano-particle possibly involved in the cross-link reaction with Polysorbate 80 is named Poly(ethylene glycol) (PEG), which has been proven to improve stability and immunogenicity of vaccine particles. Possible adverse reactions to PEG are already known in literature and have already been specifically indicated as a possible adverse effect to the BNT162b2 vaccine.

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Pigmented lesions and white spots of the oral mucosa after therapy with Epclusa®

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Background: Hepatitis C virus (HCV) infection influences morbidity and mortality worldwide. Sofosbuvir/Velpatasvir (Epclusa®) is an antiviral oral medication labeled for the treatment of adults with chronic HCV infection.
Epclusa® is taken orally once a day for 12 weeks and it is generally well tolerated.
Cause-effect relationship between the administration of a specific drug and the appearance of pigmented lesions in the oral cavity are documented. Lesions may appear immediately or after a longer period. The duration of the lesions depends on each prescription and often it is dose dependent. Evidence of disappearance of the lesions after the withdrawal of the causing medication has not been found. Currently, the mechanism that causes the pigmentation is unclear. It is believed that it could be due to an increase in the number of melanocytes, an increase in melanin synthesis or deposit of metabolites (derived from the drugs) in the tissue. Some medications may also generate a change in the colouring of the hard tissues such as the alveolar bone or the tooth. These lesions are not known to have a tendency to malignancy. The published literature records antineoplastic drugs as the most frequent pharmacological family related to the appearance of melanocytic pigmentation, followed by antimalarial medicines. It has been reported an association between antituberculosis medications and hyperpigmented macules and lichenoid papules in the oral cavity. Biologic agents are being used with increasing frequency for the management of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis and in oncology, and reports of lichenoid reactions have begun to appear in the literature.
Case presentation: A female patient, aged 54, moderate smoker, non-drinker, suffering from chronic hepatitis C, underwent antiviral therapy with Epclusa® with good clinical response and negative HCV-RNA detection after 12 weeks. The medical history refers to arterial hypertension, treated orally, for some years, with association of amlopidine/perindopril.
The patient is sent to evaluate the appearance of brown pigmentations of the gums and the floor of the mouth. The affected sites are vestibular gingiva of 1.1, 2.1, 2.2, 2.3, and the vestibular gingiva of 3.2, 4.1, 4.2, 4.3, while on the floor of the mouth there are homogenous white spots and striae, alternating with brown pigmentations. There is also an increase in gingival volume of the lower incisor area.
Oral lesions are asymptomatic. The patient states that lesions appeared three weeks after the end of therapy with Epclusa®, excluding that they were pre-existing. Her dentist, who has been following the patient for many years, says that he has never previously observed the aforementioned lesions.
Two incisional biopsies were performed with histological evaluation:

- in area 4.3: "oral mucosa including melanotic stain";
- on the left floor of the mouth, on a white/brown spot: "oral mucosa with marked chronic sub-epithelial phlogosis, presence of numerous stromal melanophages, hyperplasia and hyperparacheratosis of the epithelium. No evidence of dysplasia".

The follow-up, carried out every 6 months for two years, highlighted the stability of the spots and pigmentations of the oral mucosa.

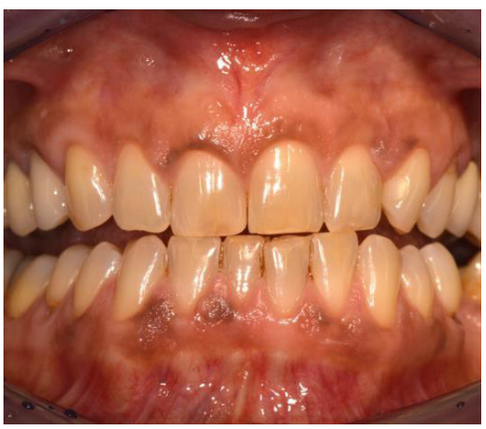

Fig. 1 *Pigmented lesions of the vestibular gum*

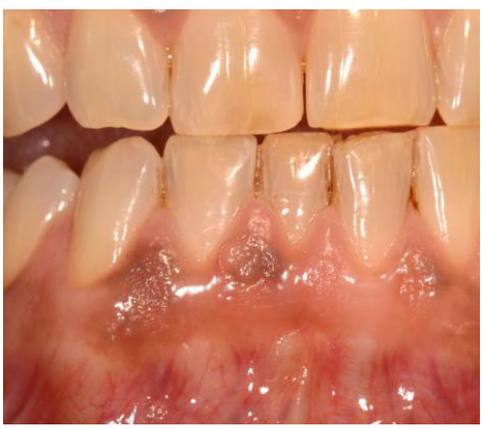

Fig. 2 *Increased gingival volume and brown pigmentations of the gum of vestibular lower incisors area*

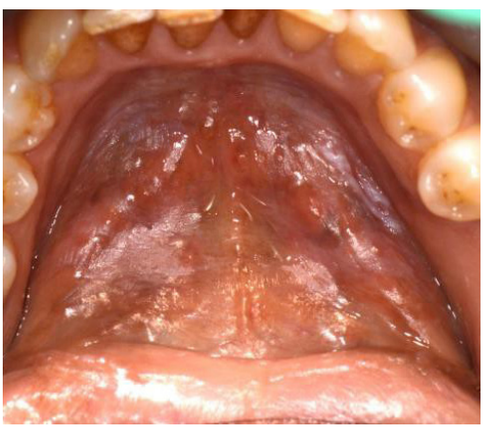

Fig. 3 *White spots and brown pigmentations of the floor of the mouth*

Suspicion of adverse reaction to the drug Epclusa® is raised. The prescriber of the drug has communicated the suspected adverse reaction to the National Pharmacovigilance Network of the Italian Medicines Agency.

Conclusions: The appearance of pigmentations and white spots of the oral mucosa after the intake of Epclusa® is not currently reported on the technical sheet of the drug, and in the medical literature there are no similar case reports. Further reports of suspected similar adverse reactions are necessary to establish a causal relationship between the drug and the oral manifestations described.

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Major salivary gland atrophy in chronic graft versus host disease

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Background: The oral cavity is one of the most common site of morbidity when chronic graft versus host disease occurs following stem cell transplant therapy to treat haematologic malignant pathologies. In literature some risk factors associated with cGVHD are reported: increasing patient age, use of an unrelated donor, conditioning total body irradiation and a preceding history of acute graft versus host disease.Furthermore, Peripheral Blood Stem Cell transplant seems to have major risk than bone marrow transplant. The mechanism of Graft host disease (GVHD) is based on donor T lymphocytes that recognise antigenic disparities between the donor and the recipient, activating an inflammatory response which causes tissue damage. Cutaneous, hepatic and ocular manifestations coexist with oral lesions in cGVHD. The HLA upregolation and cytokine abnormalities are involved in major salivary gland dysfunction. The clinical symptoms of the oral cavity include erythema, lichen planus, candidosis, ulceration, mucoceles, atrophy, fibrosis, hyperkeratosis, increased risk of oral squamous cell carcinoma and salivary gland dysfunction with related xerostomia and limited mouth-opening. The salivary glands diseases include hypo-function, similar to that of the Sjogren's syndrome, and changes in the biochemical composition of the saliva, such as decreased salivary immunoglobulin A (IgA), with resulting increased risk of systemic infections, decreased inorganic phosphate and increased [Na+], [Cl−], albumin and immunoglobulin G (IgG)(1). The reduction of the salivary flow determines a higher incidence of oral mucosal infection, dental caries and decreasing food intake. The Sjogren's cohort symptoms often include xerophthalmia, too. The cGVHD is characterized by the following histopathological features at the level of the salivary glands: there is a lobular and periductal lymphocyte TCD8 (over than CD4) infiltrate, that induces destruction of the acini and consequently the atrophy and the fibrosis of the major and minor salivary glands (2). Conditioning regimens maybe promote the salivary glands' dysfunction; literature suggests that the total body irradiation during conditioning could be a risk factor for GVHD-related salivary gland disease. Different studies revealed that both human and animal models have a reduction in the salivary flow rate in case of cGVHD. Minor salivary glands are involved, too. The treatment is based on the use of cholinergic agonists like pilocarpine to restore the salivary flow, or the use of 'artificial' saliva (2).

Case presentation: In our study, we report the case of a male patient affected by acute lymphoblastic leukaemia, who was treated with bone marrow transplant in 2013, when he was 26 years old. Nine years after the stem cell transplant, he reported a GHVD characterized by major salivary glands severe atrophy and multiple oral cavity lesions. At physical examination he presented tongue surface depapillation (Fig.1), mucosal erosive lesions on the palate and of the labial commissure region (Fig.2), hyperkeratosis on cheek's mucosa and verruciform lesions on tuber maxillae. However, the most important symptoms reported by our patient are severe xerostomia, burning mouth, disgusting taste, swallowing difficulties and reduced mouth-opening, related to salivary glands atrophy. Clinically, the parotid and the submandibular glands have decreased volume (Fig.3), confirmed by imaging. At the US (ultrasound) examination, the parotid glands are not well defined and the submandibular glands are characterized by a significant decrease in volume with feather edges. Also the facial MRI shows a significant parotid (Fig.4) and submandibular (Fig.5) glands

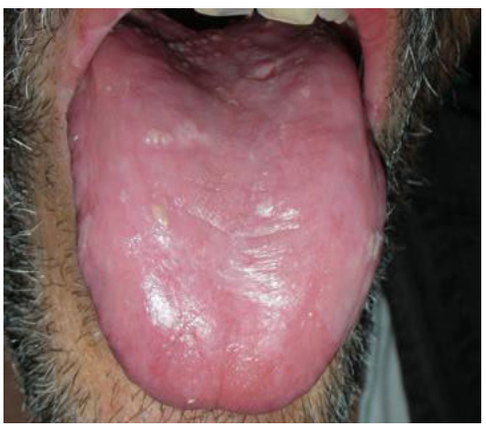

Fig. 1 *Tongue surface depapillation.*

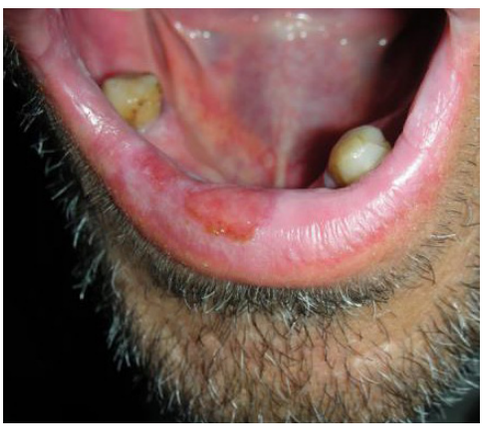

Fig. 2 *Mucosal erosive lesion.*

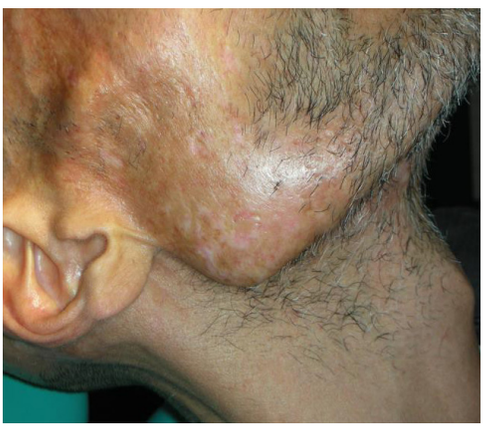

Fig. 3 *Parotid and the submandibular glands decreased volume.*

atrophy. To complete the diagnostic workout, the patient underwent a scintigraphy that validated the reduced salivary glands activity. Due to the severity of the salivary glands atrophy, the only possible treatment was the use of artificial saliva.

Conclusions: In conclusion, our case report reveals that salivary gland atrophy, associated with the oral cavity lesions and other tissues damage, is an uncommon but important manifestation of chronic graft versus host disease after stem cell transplant.

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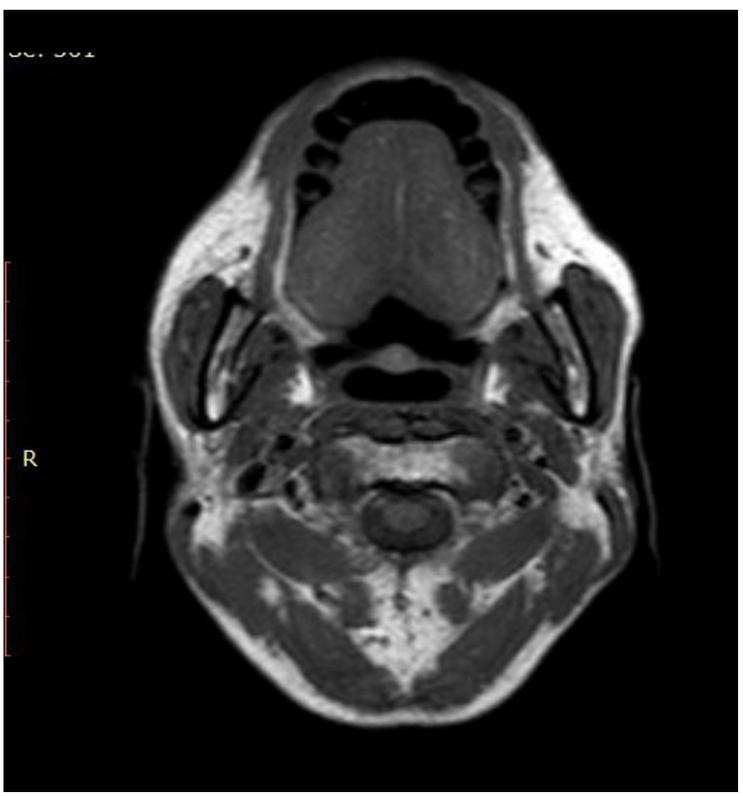

Fig. 4 *MRI shows a significant parotid gland atrophy.*

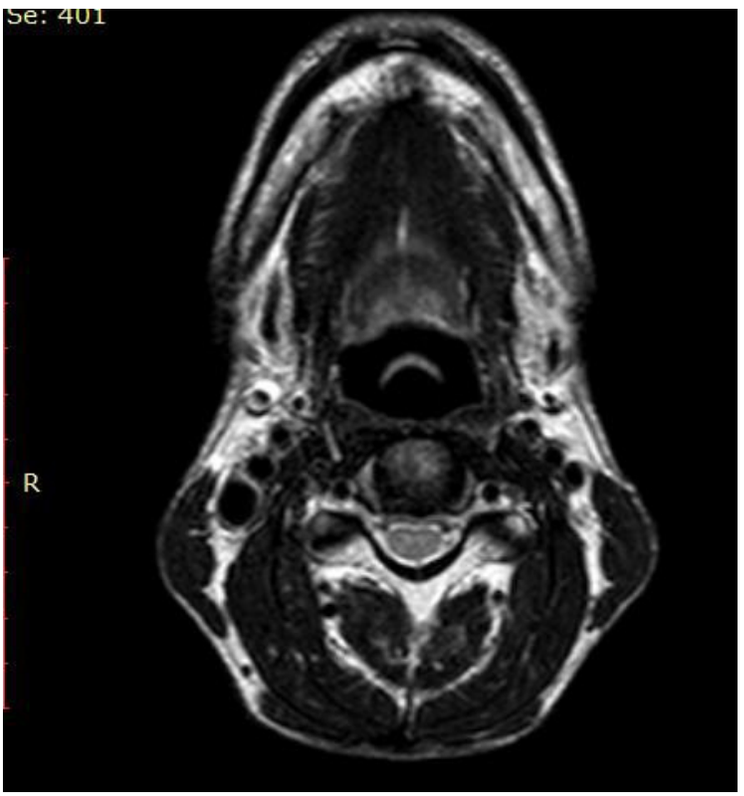

Fig. 5 *MRI shows submandibular gland atrophy.*

Imatinib-related pigmentated palate: a relatively uncommon evenience in oral medicine

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Background: Imatinib mesylate (IM) is a tyrosine-kinase inhibitor (TKI) commonly employed as a first-line medication in the management of oncohematological conditions such as chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. This medication is generally well-tolerated, and patients undergoing this therapy show a higher survival rate with mild side effects, including cutaneous hypopigmentation, edema, rash, lichenoid reactions, nausea, headache, Stevens-Johnson syndrome, and graft-versus-host-like disease (GvHD). Additionally, less commonly reported but paradoxical side effects include mucous hyperpigmentation and gray hair re-pigmentation. (1) In the oral cavity, the palate is the most affected site. Pigmentation extension is a dose-dependent phenomenon. The underlying pathogenesis is still unclear and numerous hypotheses have been made.
Case presentation: In June 2023, a 59-year-old Caucasian man was referred to our department for the evaluation of a diffuse palatal pigmentation (fig.1). His medical history revealed that he was treated for CML with IM 100 mg, 4 tablets every evening since 2015. The patient, a former smoker until 1993, also had grade B gastroesophageal reflux disease (GERD) and was on treatment with pantoprazole and anhydrous magaldrate. He reported the onset of a blue palatal pigmentation for approximately the past 8 years, for which he was first evaluated by a dermatologist. The dermatologist then referred him to his general dental practitioner, who subsequently referred the patient to a tertiary center for oral medicine. Anamnestic data excluded a history of melanoma or previous pigmented lesions in the oral cavity.
The pigmented lesion was exclusively located on the hard palate and appeared homogeneous and flat, without any raised or ulcerated area. Ultrasonographic evaluation of locoregional lymph nodes did not reveal any significant alterations. Since the lesion fulfilled all DoTS criteria for being an Imatinib adverse drug reaction (ADR) (2), a biopsy was not performed, and a clinical diagnosis of Imatinib-related oral pigmentation was provided, also following the diagnostic algorithm suggested by Donnell et al. (3). The patient was then monitored with follow-up appointments every six months, and to date, there have been no variations in the texture, color, and size of the lesion.
Conclusions: Less than 100 cases of pigmentations induced by Imatinib are reported in the Literature. Hyperpigmentation of the oral mucosa can be associated with skin depigmentation and, in some cases, hair re-pigmentation. Many pathogenetic hypotheses regarding palatal involvement in these pigmentations have been formulated. Some studies suggest that on palatal mucosa, the large number of melanocytes makes the accumulation of their metabolites more evident. An alternative hypothesis suggests that drug metabolite deposition may induce apoptosis in melanocytes. Finally, it has been proposed that the correlation between CML and Imatinib-induced pigmentations is not coincidental. In fact the c-KIT mutation, distinctive of this neoplasm, leads to the overactivation of this receptor compared to non-mutated receptors, causing palatal hyperpigmentation. However, there are still no prospective studies supporting other mechanism, thus the pathogenesis remains still unclear.
The diagnostic approach for these lesions should involve a thorough ABCDE clinical examination that includes the evaluation of symmetry, regularity of borders, color variations, lesion size, and changes over time. The absence of previous or synchronous pigmentated malignant tumors, negative findings for ABCDE parameters, the evaluation of any cutaneous manifestations, and the positive medical history for DoTS criteria, should be indicative elements supporting the clinical diagnosis of drug-induced oral pigmentation. Consequently, validation of these elements can support the clinical diagnosis as reliable, avoiding an invasive procedure as the palatal biopsy. Given the benign nature of the lesion, active treatments are unnecessary, requiring only limited follow-ups.

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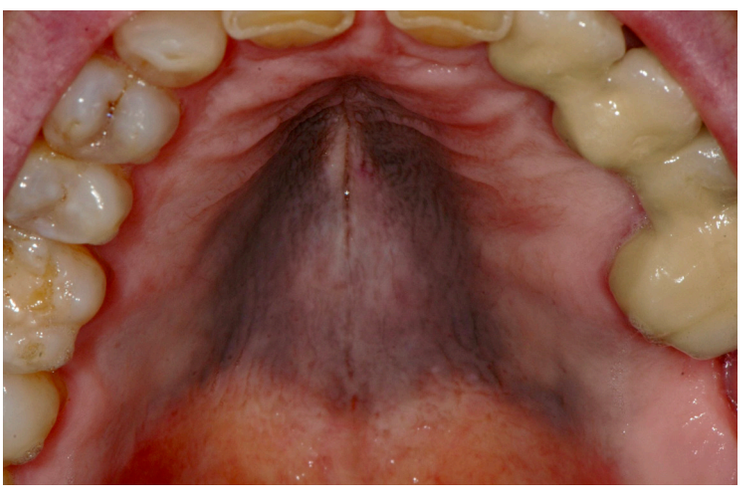

Fig. 1 *Palatal pigmentation induced by Imatinib Mesylate*

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Oral ulcers as an adverse effect to the administration of Bendamustine + Rituximab, in the treatment of Non-Hodgkin's Lymphoma and Zolendronic Acid for antiresorptive therapy

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Background: Rituximab, is a molecule belonging to the category of Monoclonal Antibodies, is indicated in adults in association with Bendamustine for the treatment of Non-Hodgkin's Lymphoma, follicular lymphoma in stage III-IV or also in maintenance therapy for the treatment of patients with follicular lymphoma that responds to induction therapy and is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia. Rituximab binds to a CD20 protein found on the surface of B lymphocytes. This protein is also found on the surface of most B lymphocytes that cause some forms of low-grade non-Hodgkin's lymphoma. Rituximab works by attacking both malignant and normal B lymphocytes; As a defense mechanism, the body is able to quickly replace any damaged normal white blood cells, thereby significantly reducing the risk of side effects. However, cases of adverse effects following the administration of this therapy are described in the literature, especially when these administrations exceed approximately the fourth dose. Adverse effects are often traced back to non-specific symptoms such as nausea, vomiting or flu-like syndromes but can also consist of the appearance of oral cavity ulcers with very significant burning symptoms. These lesions appear large and can arise in any area of the oral cavity. In addition to the patient's state of discomfort created by the painful symptoms, the consequence is the impossibility of proper nutrition, worsening the state of defecation that cancer patients are forced to face due to their underlying pathology.(1).

Case presentation: A 56-year-old patient comes to our observation for burning pain on the right anterolateral lingual belly and mandibular attached gingiva on the lingual side. In recent pathological history the patient presents osteoporosis, hypothyroidism and Non-Hodgkin's lymphoma. The patient took Eutirox for the treatment of hypothyroidism, D-Base and Zolendronic Acid as therapy for osteoporosis. As prophylactic therapy for opportunistic infections the patient took Aciclovir and Pantoprazole as a proton pump inhibitor. The most demanding pharmacological therapy is represented by the administration of Rituximab 375 mg/m2 intravenously on the first day of chemotherapy and Bendamustine 90 mg/m2 intravenously on the second and third day for a cyclic duration of 6 total cycles of chemotherapy. The patient begins to feel a dull but progressive pain from the lingual margin to the lingual apex; the pain also includes the keratinized gum of the mandibular arch. These symptoms arise after administration of maintenance Rituximab at a dosage of 375 mg/m2 intravenously every 2 months. On clinical examination, the presence of ulcers of approximately 2 cm in diameter is noted in the left ventral lingual area and in the area of the right lingual anterior margin. (Figure 1) After the clinical evaluation and the prescription of blood chemistry tests, incisional biopsies of the lesions were performed. The pathological picture is compatible with the diagnosis of eosinophilic ulcers of the oral mucosa. Corticosteroid therapy with Prednisone 25 mg for 7 days is prescribed and complete healing of the oral

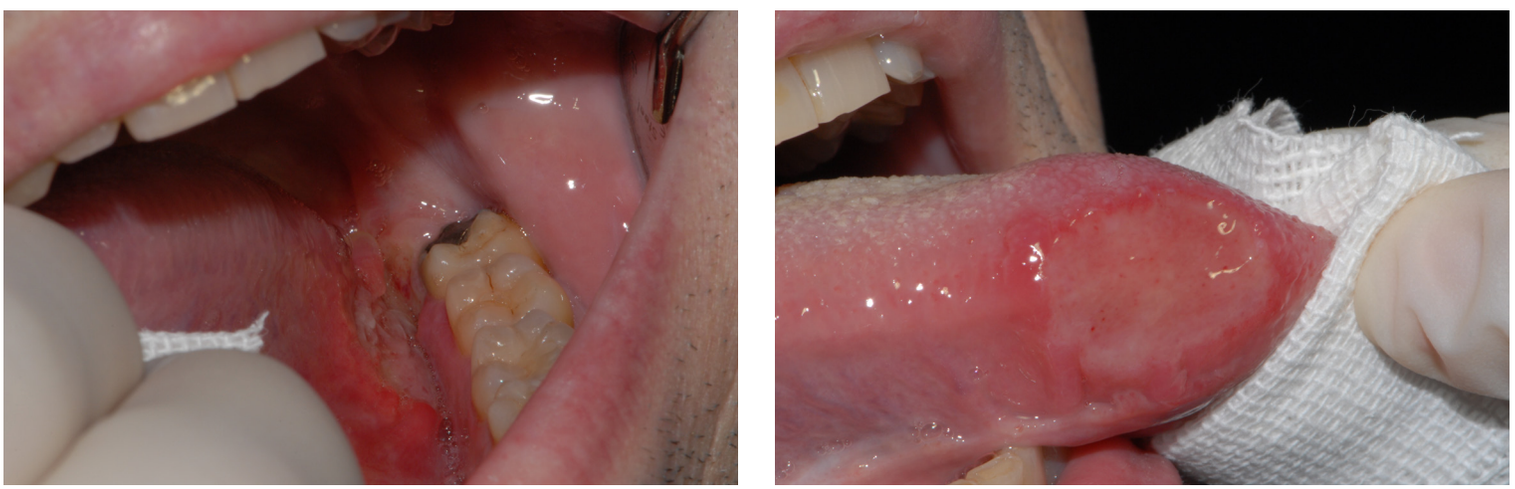

Fig. 1 *Ulcer of the left lingual belly and ulcer of the right anterior lingual margin.*

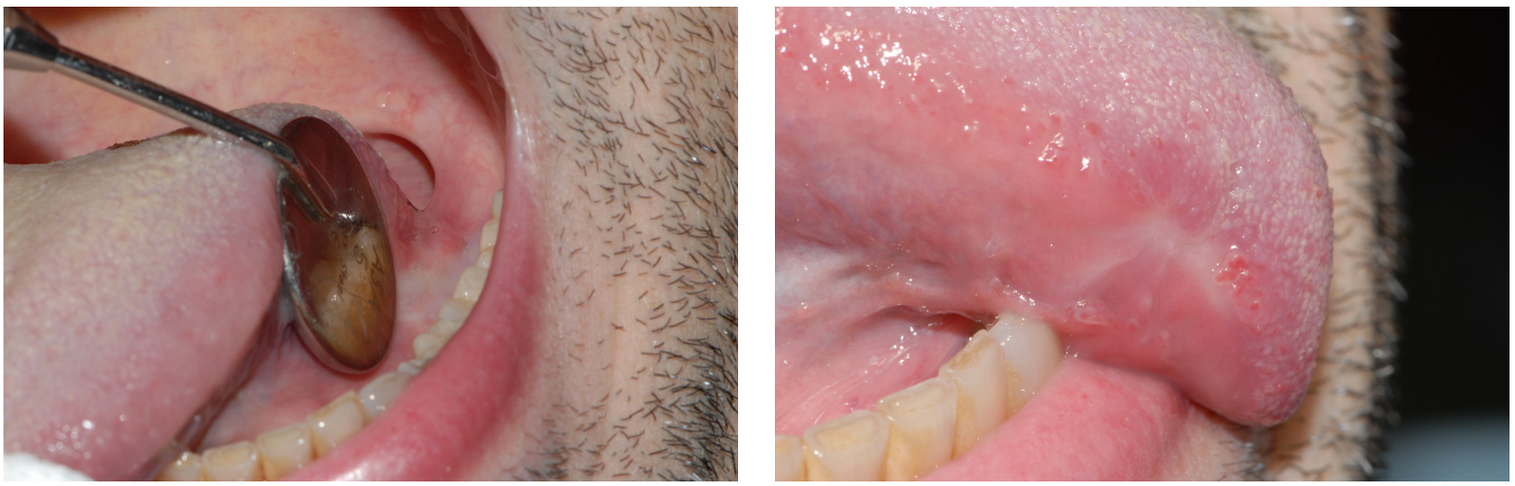

Fig. 2 *Healing of ulcers after cortisone therapy*

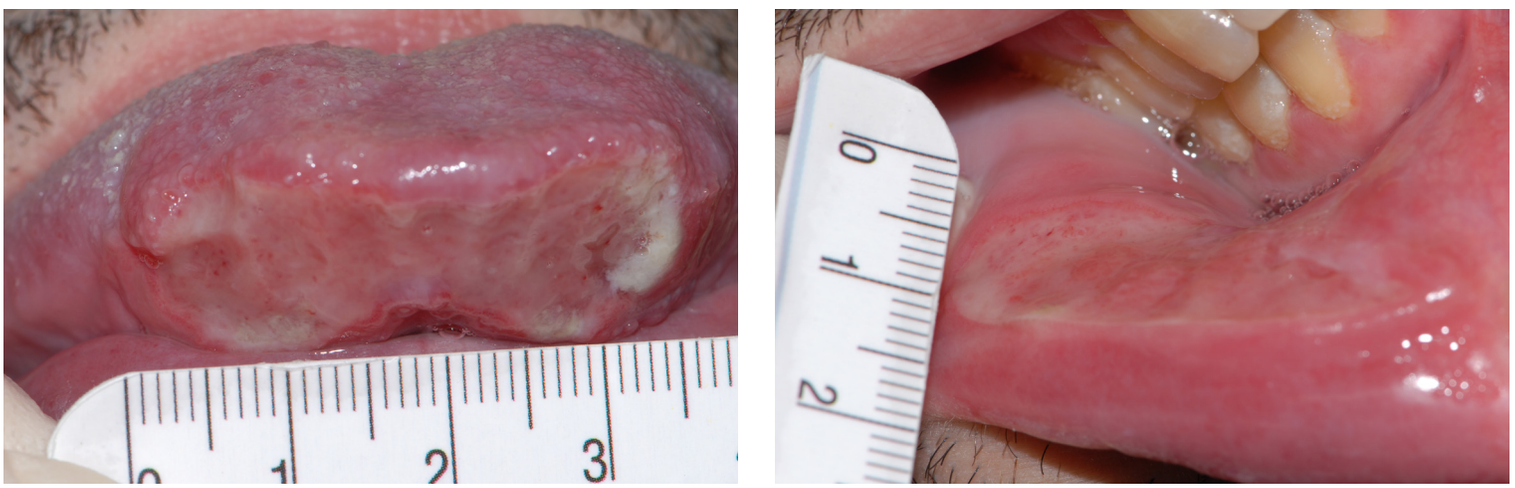

Fig. 3 *Ulcerative lesions of the lower and apex of the tongue appearing after the administration of Zolendronic Acid.*

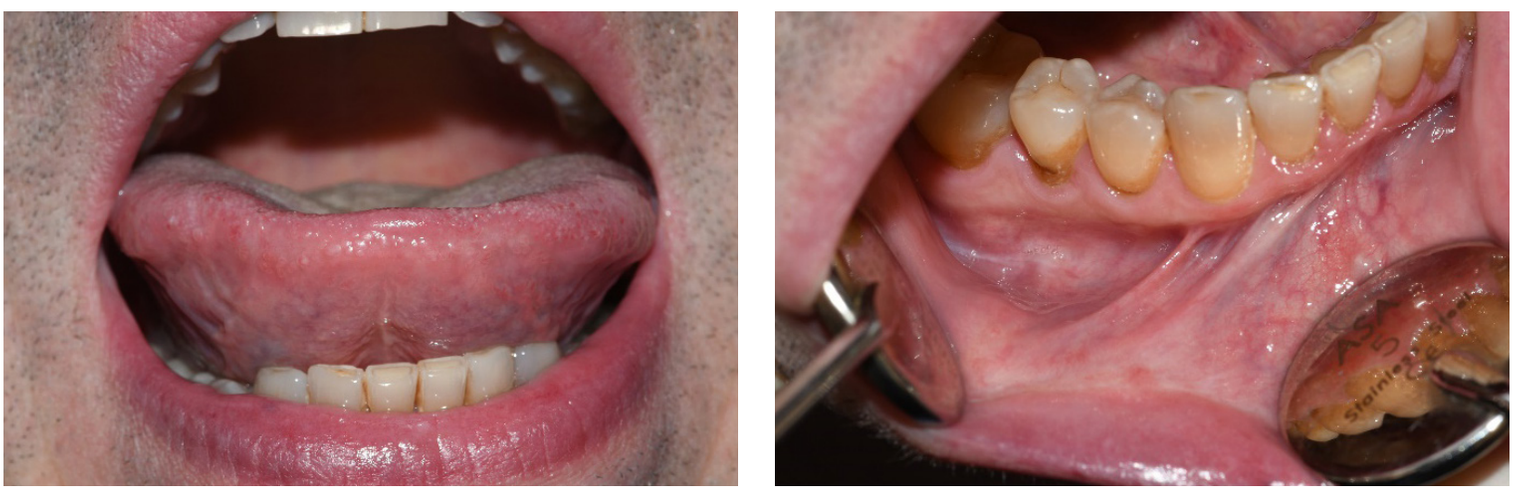

Fig. 4 *Follow Up 4 weeks after intralesional administration of Triamcinolone Acetonide 0.8 ml 32 mg.*

ulcers is achieved. (Figure 2) 30 days after healing of the ulcers, the patient is administered a further infusion of Zolendronic Acid for antiresorptive therapy. After the second administration, the onset of further ulcers larger than 3 cm was noted on the upper and lower lip and on the lingual apex. (Figure 3) These lesions are accompanied by highly painful symptoms, accentuated by feeding and speaking. In this case we decided to proceed with a Corticosteroid therapy of Triamcinolone Acetonide 0.8 ml 32 mg administered via intralesional injections. 2 weeks after the therapy we noticed a 50% reduction in the diameter of the lesions with improvement in the painful symptoms. After another two weeks we noticed complete healing of the lesions with the complete absence of symptoms.
Conclusions : Rituximab and Zolendronic Acid are very important molecules for their therapeutic purpose, unfortunately they present adverse effects which are described in the literature.(2)(3) Among these there are ulcerative lesions of the oral cavity which can be large and particularly debilitating for the patient. The task of the oral doctor is to recognize the patient's comorbidities and act with targeted therapy to prevent the lesions from becoming excessively debilitating, compromising the patients' quality of life.

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Hydroxychloroquine-Induced Gingival Hyperpigmentation: A Case Report

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Background: Hydroxychloroquine (HCQ), an antimalarial drug extensively employed in the management of systemic lupus erythematosus and various rheumatic disorders, exerts its therapeutic impact through anti-inflammatory and immunomodulatory mechanisms. The connection between quinine-derived medications and oral mucosa pigmentation was initially documented by Lippard and Kaeur in 1945(1). A recent scoping review, aimed at evaluating the incidence of oral pigmentation induced by chloroquine or hydroxychloroquine, identified 19 scientific papers, collectively describing 44 cases of chloroquine and hydroxychloroquine-induced oral pigmentation(2). Interestingly, only 14 of these cases were associated with HCQ. This observation can be ascribed to the clinical efficacy of hydroxychloroquine, which parallels that of chloroquine but with a lower level of toxicity. The etiology of pigmentation appears to be linked to the heightened affinity of HCQ to melanin as experimental evidence has demonstrated the ability of hydroxychloroquine to bind to melanin, forming a melanin-drug complex. This aligns with histopathological findings, revealing brown-colored pigment granules in basal cells and collagen fibers, consistent with previous reports(3). The duration of treatment before the onset of pigmented lesions exhibits considerable variability as studies focusing on oral mucosa lesions have reported a mean interval of 4.9 years(2).
Case presentation: A 23-year-old female was referred for grey/brown gingival hyperpigmentation. The lesions were limited to oral cavity and no other cutaneous or mucosal site was involved (Fig.1). Four years before the patient underwent hospitalization for proteinuria (258 mg/24h). ANA were negative but a biopsy revealed membranous glomerulonephritis with evidence of immune deposits at mesangial and basal level. The patient received a diagnosis of lupus-like membranous glomerulonephritis but since ANA were negative and proteinuria was minimal no therapy was suggested. The following year ANA became slightly positive (1:160 speckled anti DNA EIA) and proteinuria increased (465 mg /24h). The patient was prescribed hydroxychloroquine 300mg daily for two years until the lesions appeared. Except for ANA, blood tests including ACTH levels were within normal levels. A biopsy sampled from mandibular gingiva revealed a hyperpigmentation of the basal epidermal layer without significant increase of melanocytes. Deposits of pigment within the collagen fibres of the lamina propria were also identified (Fig.2). Such findings were consistent with the clinical suspect of drug induced melanosis. Thus, diagnosis of HCQ induced pigmentation was based on medical history, clinical presentation and histological examination. The appearance of lesions after the start of hydroxychloroquine excluded a physiological pigmentation and raised the suspect of a drug-induced hyperpigmentation. Likewise, normal ACTH levels excluded Addison. Similarly, Laugier-Hunziker syndrome, a rare acquired pigmentary condition often linked to longitudinal melanonychia, was excluded from consideration since lesions were limited to gingiva and no signs of hyperpigmentation were noted in nails or other cutaneous sites. Typically, no specific

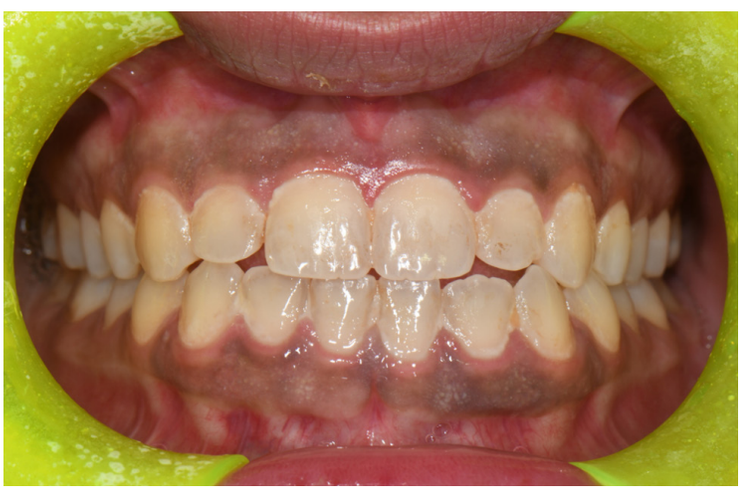

Fig. 1

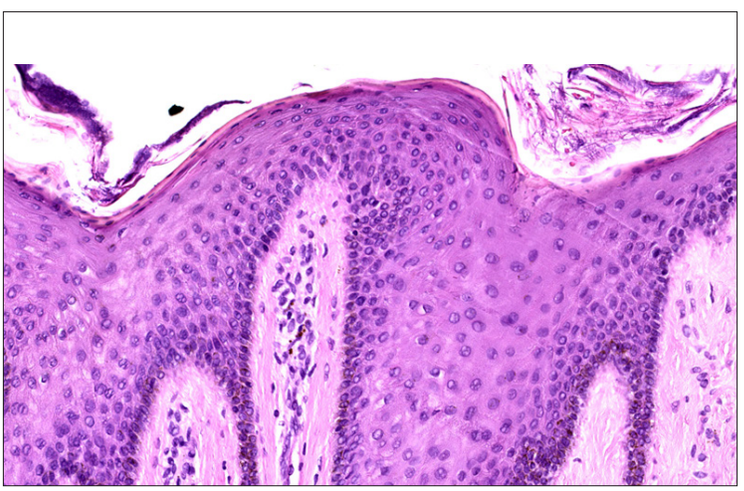

Fig. 2

treatment is recommended for hydroxychloroquine-induced oral pigmentation. However, HCQ prescription was suspended as instances of spontaneous regression after discontinuation of therapy have been documented in the literature4. Unfortunately, the oral lesions persisted despite the suspension of therapy for over a year.
Conclusions: In summary, this case underscores the rare occurrence of hydroxychloroquine-induced oral pigmentation in a patient diagnosed with lupus-like membranous glomerulonephritis. Notably, the clinical presentation, medical history and histological examination were pivotal in confirming the drug-induced nature of the pigmentation, ruling out other potential causes. Moreover, evidence regarding the reversibility of oral pigmentation induced by HCQ remains limited as discontinuation did not lead to resolution. However, while ophthalmologic evaluation is advisable for detecting signs of retinopathy, oral pigmentation should not be regarded as a marker of drug toxicity. Therefore, decisions regarding drug withdrawal should be made by carefully assessing the risks and benefits associated with the underlying disease.

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Drug-Induced Gingival Overgrowth by Antihypertensive Therapy: A Case Report

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Background: Gingival overgrowth, related to medications like anticonvulsants, calcium channel blockers (CCBs), and immunomodulators, is an uncommon but clinically significant condition. The incidence of gingival hyperplasia has been observed in 19.6% of patients on CCBs. Gingival hyperplasia could cause difficulty in speech and mastication, and determine poor oral hygiene, and poor aesthetic appearance. This case report elucidates the intricate presentation of gingival overgrowth in a patient undergoing combination therapy with the antihypertensive Tripliam® (amlodipine, perindopril, and indapamide).
The authors offer a comprehensive exploration of the clinical presentation and propose effective strategies for managing this adverse drug reaction (ADR).

Case presentation: A 62-year-old female patient, affected with arterial hypertension and in therapy with Tripliam® and Nebivolol from one year, presented at the Unit of Oral Medicine with Dentistry for Fragile Patients (AOUP "Paolo Giaccone," Palermo, Italy). The patient reported the recent onset of gingival swelling in the upper arch, occasionally accompanied by tenderness and bleeding.
During an intraoral examination, diffuse gingival enlargement affecting marginal, attached, and interdental gingiva on both the buccal and lingual/palatal aspects in the upper dental arch was revealed, particularly in the zone II of the sextant (Fig. 1). This enlargement was characterized by a widespread, relatively avascular, smooth, and nodular swelling of the gums. The condition led to significant coverage of dental crowns by the surrounding tissues. Despite undergoing professional oral hygiene and home-based treatments, including a five-day course of spiramycin tablets followed by a 0.20% chlorhexidine mouthwash for 15 days, no improvement in the gingival enlargement was observed. The diffuse enlargement affecting marginal, attached, and interdental gingiva suggested a pervasive inflammatory response. Considering that the onset of gingival enlargement coincided with the initiation of Tripliam®, and with documented potential ADR associated with this medication, a request was made for discontinuation. Gingival overgrowth, a rare but documented side effect of Tripliam®, prompted a judicious evaluation and subsequent therapeutic modification. After a positive assessment, the attending physician approved the replacement of Tripliam® with losartan as a new antihypertensive medication. Following the medication switch, there was a swift and marked reduction in the gingival symptoms. A follow-up examination a month later revealed improvement in the gingival area of the II sextant, even without additional prescribed therapies or procedures (Fig. 2).
This substantial improvement in the area of the II sextant not only validated the appropriateness of the therapeutic switch but

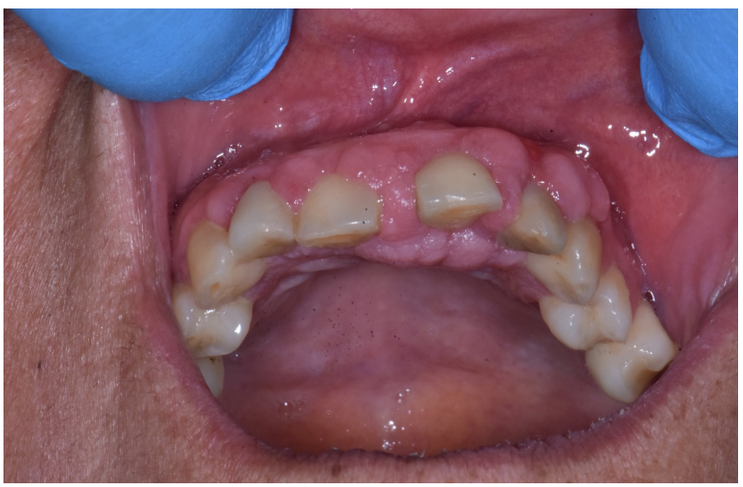

Fig. 1 *Diffuse gingival hyperplasia affecting marginal, attached, and interdental gingiva of the II sextant.*

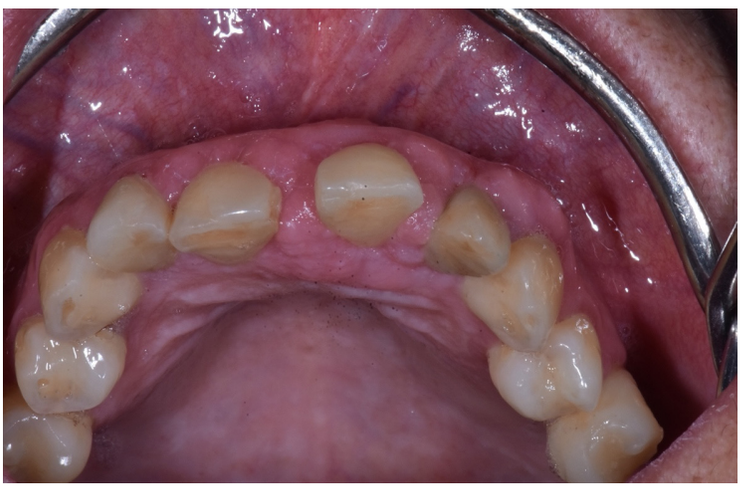

Fig. 2 *Improvement in the gingival area of the II sextant.*

also highlighted the potential reversibility of drug-induced oral manifestations. The patient is scheduled for ongoing monitoring in the coming months to ensure sustained improvement and evaluate any potential long-term effects of the new antihypertensive medication.

Conclusions: This case underscores the importance of recognizing gingival overgrowth as a complex outcome of the Tripliam® antihypertensive regimen. The consequences of gingival overgrowth are substantial, extending beyond mere aesthetic concerns. Associated issues encompass potential challenges in chewing, compromises in phonetics, and impacts on the aesthetics of the smile. Some of the related concerns involve difficulties in pronunciation, and effects on the overall visual appeal of the smile. Moreover, the increased gingival volume can foster the formation of gingival pockets, creating an environment conducive to bacterial proliferation. This, in turn, may contribute to the development of more severe gum diseases, escalating the risk of persistent inflammation and structural damage. The effective management outlined here emphasizes the crucial role of a customized, multidisciplinary strategy in addressing antihypertensive-induced gingival overgrowth. Our report provides valuable insights that form a foundation for healthcare professionals to adopt vigilant monitoring and timely intervention in instances of ADR associated with complications arising from antihypertensive drugs. The findings underscore the necessity of a comprehensive approach, involving collaboration among various medical disciplines, to address and mitigate the impact of medication-induced complications, ultimately enhancing the quality of life for patients and promoting overall oral health..

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Adverse Drug Reaction to Atezolizumab-Bevacizumab Combination Therapy in a Patient with Hepatocellular Carcinoma: A Case Report

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Background: Atezolizumab (ATZ) is a humanized monoclonal antibody, specifically an engineered IgG1 Fc antibody, targeting programmed cell death ligand 1 (PD-L1). In combination with bevacizumab (BVZ), it is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not undergone previous systemic therapy.
The heightened immune activation triggered by PD-L1 inhibitors in normal tissues can lead to various types of significant adverse drug reactions (ADRs), including severe mucocutaneous adverse reactions.
While the well-established efficacy of ATZ and BVZ is recognized, a growing body of evidence also underscores the emergence of ADRs including Stevens-Johnson syndrome (SJS).
This case report delves into a rare manifestation of oral ADR in a patient dealing with an HCC diagnosis.
This individual, undergoing first-line systemic therapy featuring ATZ and BVZ, unfolds a compelling narrative that prompts a deeper exploration of the intricate interplay between therapeutic benefits and unintended complications associated with these drugs.
Case presentation: A 55-year-old man, diagnosed with cryptogenic liver cirrhosis-associated liver tumor, sought specialized consultation at the Unit of Oral Medicine with Dentistry for Fragile Patients (AOUP "Paolo Giaccone," Palermo, Italy).
His medical history revealed HCC in two areas (S6-S7 measuring 5.5 cm and S5 measuring 1.4 cm) with invasion of a portion of the liver's portal system, associated with A6-grade hepatic cirrhosis per the Child Pugh classification. In 1990, he underwent liver resection and spleen removal due to a gunshot wound.
In March 2023, he was admitted to the Complex Gastroenterology and Hepatology Unit (AOUP "Paolo Giaccone," Palermo, Italy) for a chronic liver disease reassessment. Following a single ATZ and BVZ infusion for the primary pathology, the patient experienced fever, asthenia, muscle pains, and stomatitis in the subsequent week, unresponsive to topical chlorhexidine therapy. After fever resolution but with severe worsening of oral issues, a specialist consultation was sought from the Complex Gastroenterology and Hepatology Unit at the Unit of Oral Medicine with Dentistry for Fragile Patients.
In May 2023, the patient presented for observation, complaining of burning and pain in the oral cavity.
The extraoral examination revealed signs of inflammation, significant swelling, edema, blisters, and ulcers of the lower lip, with exudate containing traces of blood. Hemorrhagic vesicles in the oral cavity and dried blood clots with blood crusts along the vermilion border of the lower lip, combined with documented adverse effects of

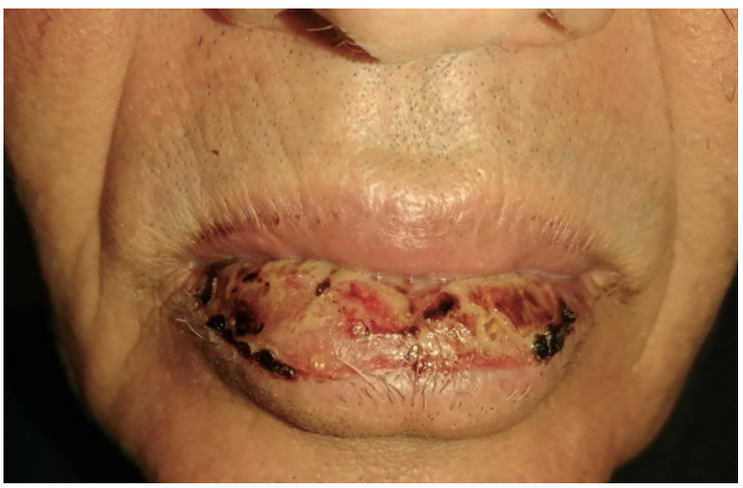

Fig. 1 *Swelling, blisters, and blood crusts along the vermilion border of the lower lip.*

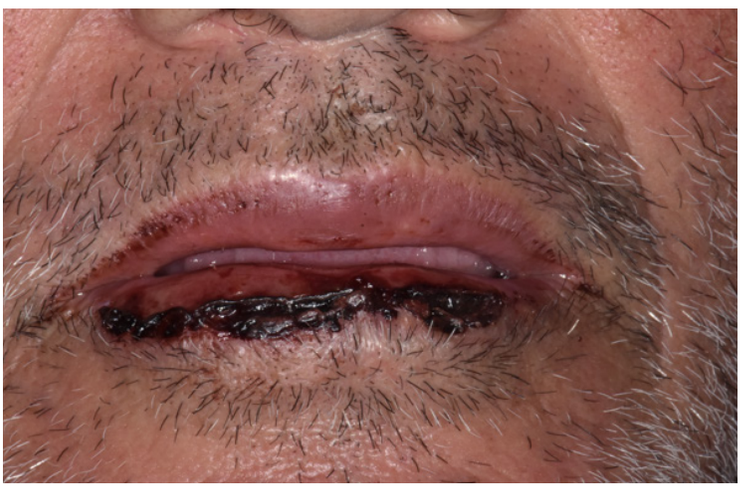

Fig. 2 *Reduced swelling and disappearance of most blood crusts*

combination therapy, led to the suspected diagnosis of SJS (Fig. 1) With a suspicion of an ADRs to ATZ and BVZ administration, a drug suspension request was made to the prescribing physician. Following a positive assessment, the patient returned for a follow-up visit two weeks after therapy discontinuation, showing significant improvement in pain symptoms and overall clinical status, including reduced swelling and disappearance of most blood crusts (Fig. 2) Up to date, the patient is closely monitored.

Conclusions: ADRs can significantly impact a patient's quality of life and disrupt oncological treatment. Thus, possessing sufficient knowledge, ensuring timely monitoring, and implementing appropriate management of these events are crucial.

This clinical case highlights the rarity and profound clinical impact of ADRs associated with ATZ and BVZ administration. Management, contingent upon agreement with the prescribing physician and aligned with the patient's primary pathology, may involve drug suspension and/or therapy re-modulation. The prompt identification and suspension of the offending agent led to a notable improvement in the patient's oral symptoms, emphasizing the critical role of vigilant monitoring and individualized management in mitigating ADRs.

The implications of this case extend beyond the individual patient, stressing the need for heightened surveillance in cohorts undergoing advanced oncological therapies. This investigation reveals potential complications that can significantly impact both symptomatology and overall quality of life.Timely and effective ADRs management is crucial for enhancing patient compliance and guiding decisions on discontinuing immunotherapy. Further in-depth clinical studies are necessary to identify biomarkers serving as useful predictors for both treatment efficacy and adverse effects, enabling specialists to determine the optimal balance for effective oncological treatment.

In the era of innovative oncological interventions, additional research efforts are indispensable for a comprehensive understanding of the frequency, underlying mechanisms, and optimal management strategies of such intricate ADRs in oncologic populations.

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Anti TNF-α induced mucous membrane pemphigoid. A contradictory manifestation

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Background: Mucous membrane pemphigoid (MMP) is a chronic, autoimmune subepithelial blistering disease involving the mucous membranes and rarely the skin; the pathophysiology of MMP is not completely understood. BP180 (collagen XVII) and laminin 332 are the main autoantigens of MMP, with the linear deposition of IgG, IgA, or C3 along the epithelial basement membrane zone (BMZ) as peculiar feature(1). TNF-α blockers (or anti TNF-α) are biologic drugs involved in the treatment of various diseases such as psoriasis vulgaris, rheumatoid arthritis, inflammatory bowel disease and unresponsive skin bullous pemphigoid (BP)(2,3). Anti TNF-α adverse reactions including BP manifestation are described in literature; such autoimmune reactions are triggered by drug molecules or metabolites that acts as antigens in the BMZ. The pathogenesis of pemphigoids induced by anti TNF-α is still unclear but is related to the interaction of different immune pathways(2).
Case presentation: In January 2023, a 40 year-old woman was referred to investigate a recurring desquamative gingivitis. Since November 2022, she reported the outbreak of gingival inflammation and tense mucosal bullae that leaves no scars when collapsing and completely recovers in 5 days or less.
She had history of autoimmune urticaria, axial spondylarthritis, hypothyroidism, episodes of fever and allergy to non-steroidal anti-inflammatory drugs. The patient was following a program for medical assisted reproduction.
Drug history was disclosed: anti TNF-α etanercept (Benepali®), 1/week IM since 1yr; omalizumab (Xolair®), a mAb that binds to and neutralizes IgE, 2/month since 1 yr.; buprenorphine (Busette ®), opioid transdermal patch, 1/month since 2yr; rupatadine (Pafinur®), antihistaminic, 1/day; levothyroxine (Tirosint®), hormonal substitute, daily.
In correlation to a scheduled 2 week etanercept suspension for seasonal flu vaccination, she noticed an improvement of her oral condition.
The oral examination showed overall gingival inflammation along with lesions including erosion, blisters and their residual, involving both gingiva and lining mucosa (Fig. 1, 2 and 3); the Nikolsky sign was negative. Extraoral examination revealed no lesions, scars, crust or bullae involving nasal mucosa or conjunctiva. Other than the known autoimmune urticaria, no skin lesions were disclosed on scalp, arms, trunk and legs. Considering the patient medical history, the oral complains and the findings, a mucosal biopsy and blood sampling were proposed.
Two tissue samples were taken under local anesthesia, to perform histological examination as well as direct immunofluorescence (DIF). In addition, indirect immunofluorescence (IIF) and ELISA test were performed on patient serum.
While histology described a chronically inflamed mucosa, DIF resulted positive for IgG and C3 along the basement membrane and IIF revealed a positive IgG titer on monkey esophagus substrate (dilution 1:10) (Fig. 4; A, IgG; B, C3; C, IIF; D, NC16a biochip MMP). Moreover, an ELISA for IgG autoantibodies against BP180 and BP230 yielded 52,64 U/ml and 2,43 U/ml, respectively (cut off value, 9 U/ml). Based on clinical observation and test results, the diagnosis of

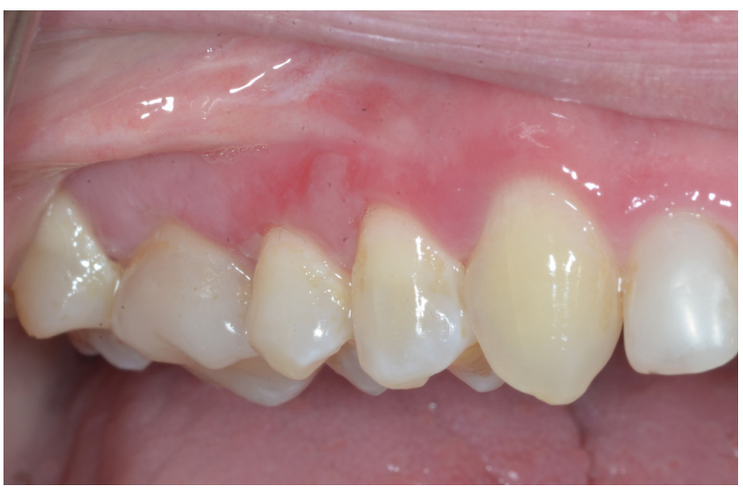

Fig. 1

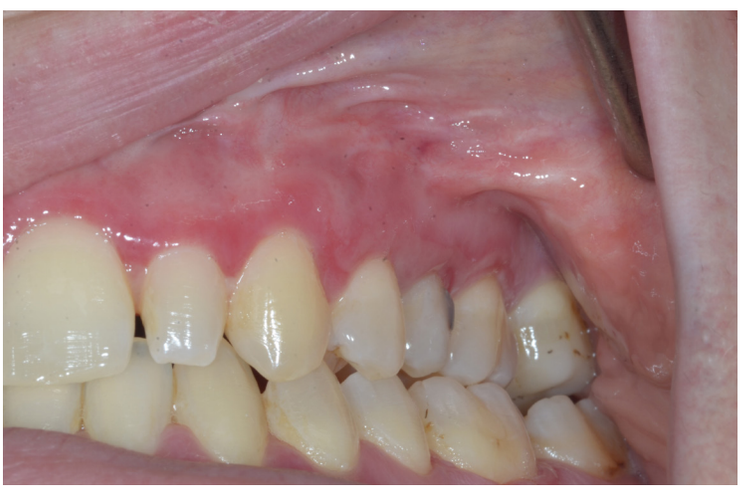

Fig. 2

MMP was suggested.
During follow-up (FU), the potential association between etanercept injection and blisters development was directly observed. Again, another scheduled 2 week etanercept suspension for vaccination led to mucosa healing and no new blisters manifestation (Fig. 5). Moreover, during the FU period, the patient had one dose/week as prescribed, and lesions systematically reappeared 2 or 3 days after injection.
Galenic formulation of clobetasol propionate 0.05% in Orabase, 1:1, for application into a tailor-made mouthguard was prescribed; administration was then slowly adjusted from twice-a-day to 1 to 3 application a week until November 2023. Nystatin mouthwashes were associated.
Conclusions: Except for the scheduled suspension, etanercept injections were regularly administered 1/week from the beginning of FU (10 months); during such period, MMP lesions chronically arise but were tamed by the topical therapy, as well as symptoms. Moreover, a recent switch to certolizumab pegol (Cimzia®), an anti Tnf-α administered twice-a-month, did not prevent MMP lesions development but resulted in less frequent manifestation.

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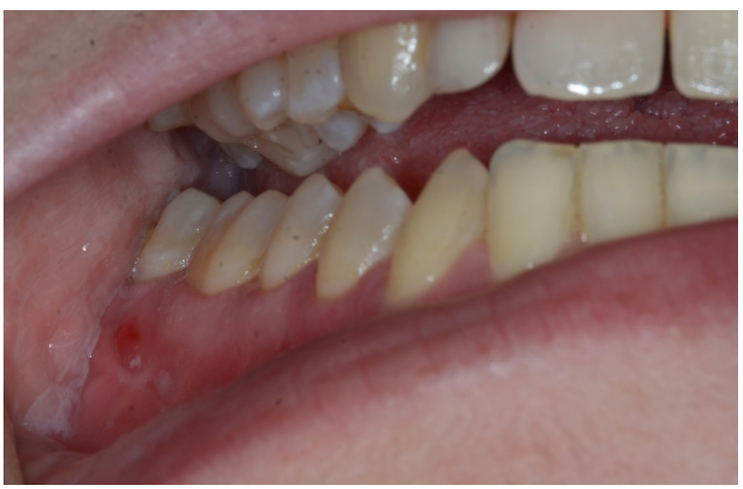

Fig. 3

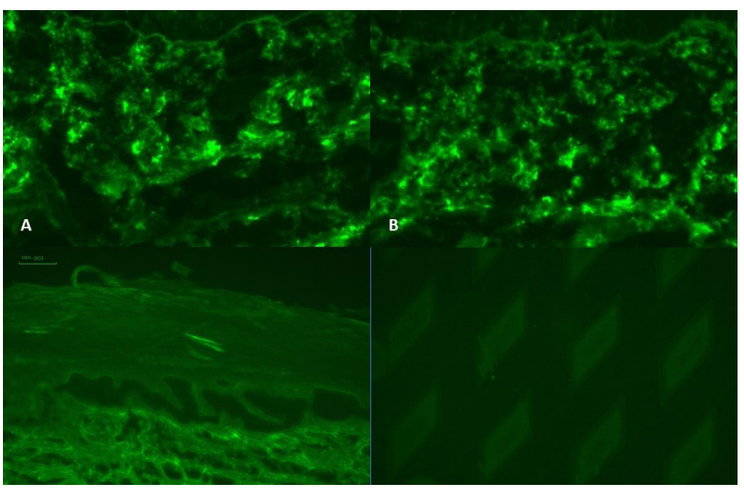

Fig. 4

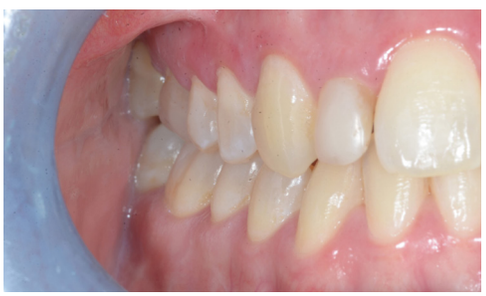

Fig. 5A

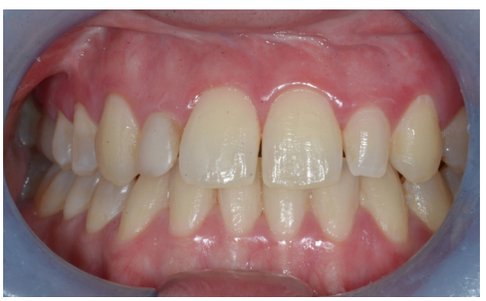

Fig. 5B

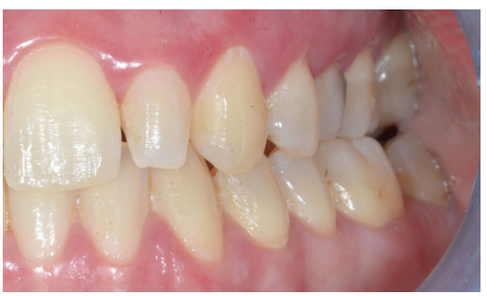

Fig. 5C

Diffuse gingival hyperplasia as adverse drug reaction in a pediatric patient with nephronophthisis: a case report

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Background: Nephronophthisis is a rare autosomal recessive renal cystic disease induced by the mutation of the nephrocystin genes (NPHP1-11, NPHP1L), which causes impairment of the ability of the kidneys to concentrate solutes, chronic tubulointerstitial nephritis, cystic renal disease progressing to end-stage renal disease (ESRD). Nephronophthisis has two clinical subtypes depending on the age of onset of ESRD: infantile-onset, juvenile-, adolescent- or adult-onset phenotypic continuum. In those patients, diffuse gingival hyperplasia can occur as an adverse drug reaction because of the chronic intake of calcium antagonists, immunosuppressants, or antiepileptic drugs. The objective of this report is to show the surgical management of diffuse gingival hyperplasia as an adverse drug reaction in a pediatric patient with juvenile nephronophthisis.
Case presentation: In July 2023, a thirteen-year-old male patient showing diffused gingival hyperplasia was referred to the Complex Unit of Odontostomatology of the University of Bari Aldo Moro, Italy. The diffuse gingival hyperplasia caused the failure of the exfoliation of the deciduous teeth, the absence of several permanent teeth, and difficulty chewing and swallowing, so much so that feeding with a tube inserted via percutaneous endoscopic gastrostomy (PEG). In addition, the patient showed diffuse cavities because the gingival hyperplasia prevented the parents from carrying out domiciliary oral hygiene procedures. To understand the causes of such a condition, the authors collected the medical history of the patient and found that the child received a nephronophthisis diagnosis, experienced cerebral ischemia that resulted in focal epilepsy, hearing loss, and blindness, and underwent a combined kidney-liver transplant at the age of nine years old. Every day, the patient received supplementation of 2 gr sodium bicarbonate, 250 mg biliary acids, and 50 mg trivalent iron; 2 mg melatonin; immunosuppression by 500 mg mycophenolic acid and 6.5 mg tacrolimus; antiepileptic therapy by 210 mg phenytoin and 3.75 mg nitrazepam; every two days, the patient also received 5 mg prednisone. In addition, the patient supplemented cholecalciferol once per week. The patient couldn't undergo a panoramic radiogram because of severe psychomotor delay; thus, the authors performed computed tomography under conscious sedation and found the agenesia of several permanent teeth. The patient underwent standard blood tests, an electrocardiogram, a chest x-ray, and an anesthesiologic visit to receive dental treatments under general anesthesia. To avoid prolonged general anesthesia, the authors divided the persistent deciduous teeth extractions, the diode laser gingivectomies, and the restorations of the exposed decayed permanent teeth into two sessions. In September 2023, the authors extracted the five persisting lower deciduous teeth (7.1, 8.1, 8.3, 8.4, and 8.5); in addition, the authors performed diode laser gingivectomy to expose four permanent teeth (4.2, 4.5, 4.6 and 3.2). The authors' protocol for diode laser gingivectomy used a continuous power output of 7 W and contact technique incision together with local anesthesia by mepivacaine 3% without epinephrine. Anyway, the authors

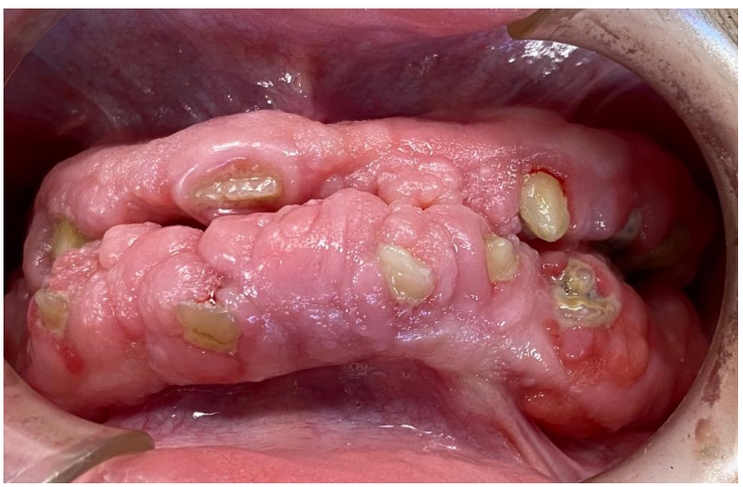

Fig. 1 *Diffuse gingival hyperplasia in a thirteen-year-old pediatric patient suffering from nephronophthisis.*

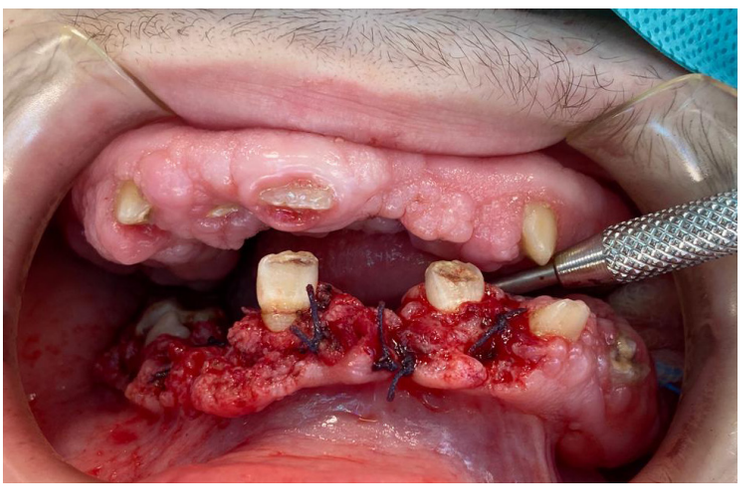

Fig. 2 *Thirteen-year-old pediatric patient after the first surgical laser treatment.*

experienced abundant bleeding as an intraoperative complication; thus, treated sites received vicryl resorbable stitches. The authors sent samples of the excised gingiva for histological examination. After discharge, the authors instructed the parents to administer acetaminophen for postoperative analgesia. The complete healing of the treated sites occurred without postoperative complications after three postoperative weeks. The patient is still waiting for the second treatment session because of several delays depending on the unstable state of his general health.

Conclusions: In the current case, diffuse gingival hyperplasia occurred as an adverse drug reaction induced by the chronic concomitant administration of immunosuppressants and antiepileptics. Gingivectomy is a necessary surgical intervention as the first step to allow normal feeding in those patients; anyway, intraoperative bleeding is a major issue to manage even if using coagulative cutting systems such as the diode laser. Eventually, prolonged follow-up is mandatory to avoid recurrences in the treated sites and decide the timing of continuation of the treatment.

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Allopurinol and tiopronin adverse muco-cutaneous reaction. A Challenge-Dechallenge-Rechallenge approach

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Background: Tiopronin is commonly used to prevent cystine kidney stones by forming a soluble complex called cystine-tiopronin disulfides. Allopurinol is indicated to treat hyperuricemia, gout and kidney lithiasis. It induces acid uric decrease in plasma level and uric excretion due to the inhibition of xantina oxidase. Adverse effects have been reported for them both, being allopurinol one of the most frequently reported drug involved in oral lichenoid reaction.

Case presentation: A 66 years-old man came to our attention for extensive oral mucositis. At physical examination diffuse oral erosions associated to mild white patches were observed on vestibular mucosa, dorsal and ventral tongue (Fig. 1). Erosive lesions were also observed on the nasal mucosa and the patients reported the presence of similar lesions involving genitals. Erosive-crusty cutaneous lesions involved the trunk, dorsum and limbs (Fig. 2). Two months before a dermatologist prescribed with lip emollients, vitamin A and E supplements and silver sulfadiazine cream for cutaneous lesions with no significant response. A recent oral biopsy showing "ortho-parakeratotic hyperkeratosis with band infiltrate and signs of aggression of basal keratinocytes showing focal vacuolar degeneration" was consistent with an interface cell-mediated mucositis. At anamnesis he was on treatment with tiopronin and allopurinol for kidney lithiasis and reported the onset of oral symptoms 6 months after starting treatment. Clinical, histological and chronological features were suggestive for mucocutaneous Adverse Drug Reaction (ADR). Prednisone (50 mg/day) was prescribed, and the nephrologist agreed to stop tiopronin and allopurinol.

Mucocutaneous erosive lesions and related symptoms had a complete remission in 3 weeks. Prednisone was stopped in 6 weeks after tapering, even if the patient still had white oral lichenoid and erythematous cutaneous lesions. Six months later, after nephrologist's prescription, the patient started tiopronin again. In one-week, erosive oral lesions occurred leading to immediate tiopronin interruption with spontaneous regression of the oral lesions within 2 weeks. A similar reaction was observed 8 months later when allopurinol was prescribed again. Oral lesions appeared in a few days and the interruption of therapy allowed their spontaneous regression within 2 weeks.

Conclusions: The potential association of allopurinol to oral lichenoid reaction/mouth sores is renowned and reports about tiopronine can be found. In the present case, the clinical indication for nephrological treatment allowed us to observe the patient in a quasi-challenge-dechallenge-rechallenge protocol with distinct assessments for the 2 drugs. This is of outmost importance as almost 90% of the reported ADR lack such information.

Other than mucocutaneous involvement, Allopurinol Hypersensitivity Syndrome has been previously described as including vasculitis, rash, eosinophilia, hepatitis, and progressive renal failure and several Steven-Johnson Syndrome associated cases have been reported. Even if the underlying mechanisms are unknown, an immune dysregulation has been suggested to be

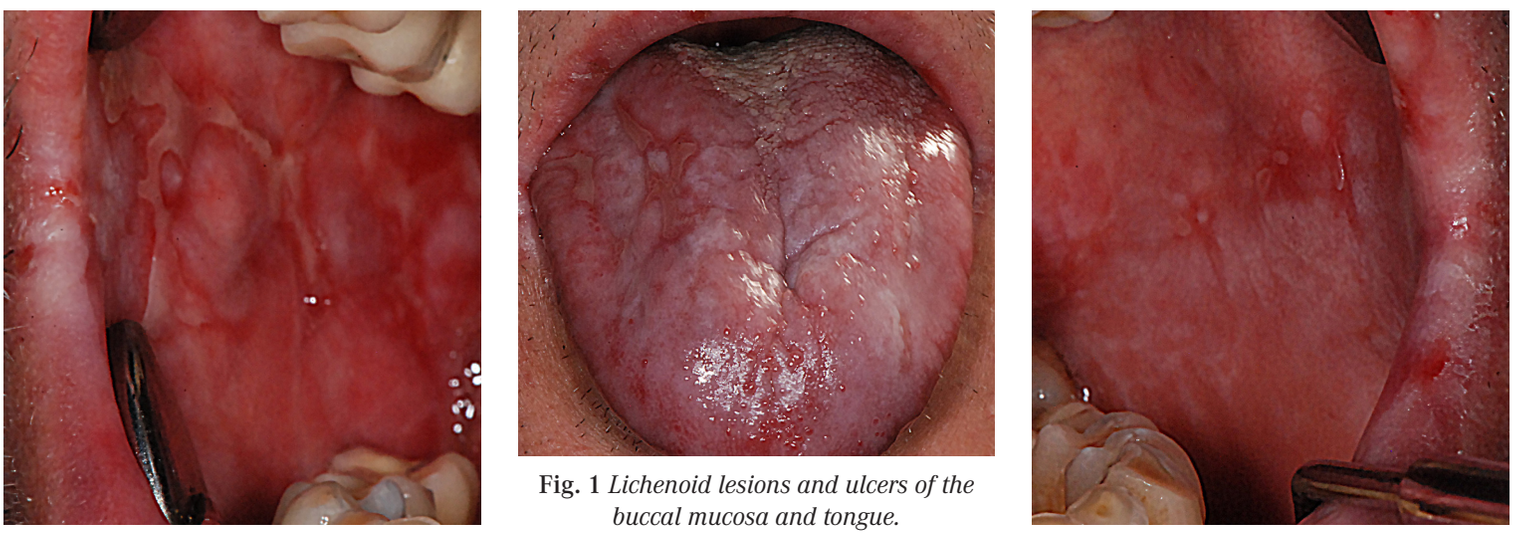

Fig. 1 *Lichenoid lesions and ulcers of the buccal mucosa and tongue.*

involved in the pathogenesis.
Likewise, sulfhydryl drugs, including tiopronin, can be responsible for lichenoid reaction. Along with oral mucositis, the reported tiopronin adverse reaction include pruritus, pemphigus, maculopapular exanthems, erythema multiforme and eczematous eruptions.
The concomitant Adverse Reaction to two chemically unrelated drugs could suggest a multi-drug hypersensitivity syndrome (MDHS), characterized by a massive T-cell stimulations. MDHS clinical manifestations include exanthema (mild to severe), Drug Reaction with Eosinophilia and Systemic Symptoms, and Erythema Multiforme major.
Since 2002, in the AIFA (Agenzia Italiana del Farmaco) reports (https://bi.aifa.gov.it/SASVisualAnalyticsViewer/VisualAnalyticsViewer.jsp) 2536 ADRs to allopurinol can be found, equally distributed by gender: 64% of patients had skin manifestations but no reports engaged the oral mucosa. About Tiopronin 13 ADRs have been reported, with only 1 case of cutaneous involvement and none engaging the oral mucosa.

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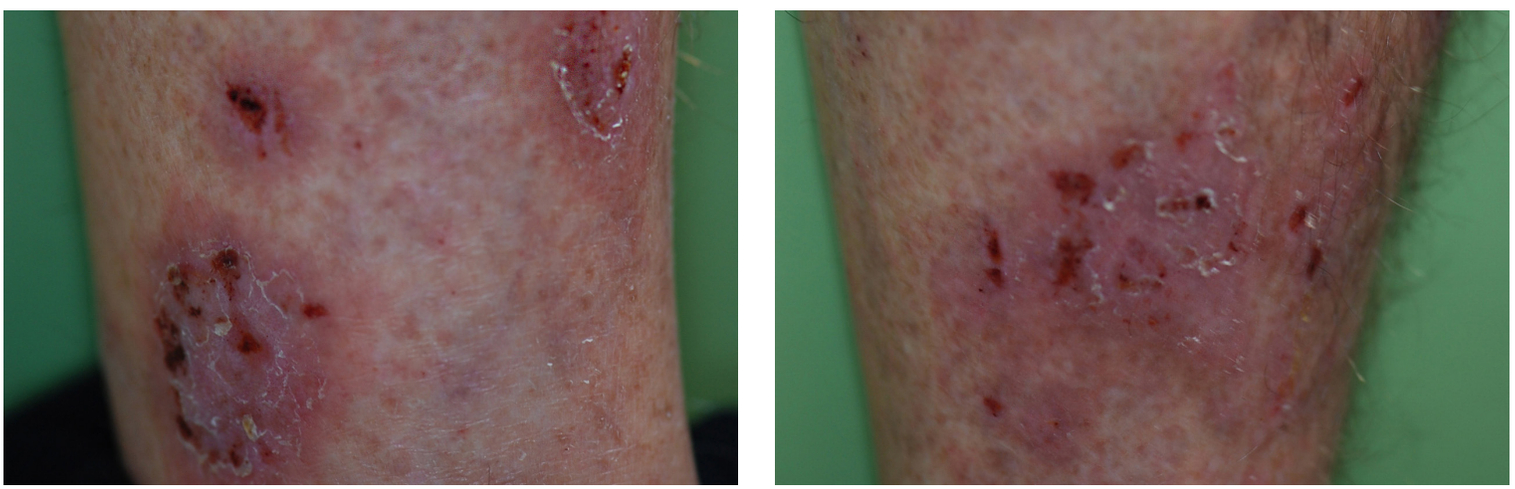

Fig. 2 *Erosive-crusty cutaneous lesions of the legs*

Angina bullosa haemorrhagica: an unusual case related to long-term usage of inhaled glucocorticoids

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Background: Angina bullosa haemorrhagica (ABH) is an uncommon dermatosis characterized by the sudden onset of well-defined red or magenta blisters filled with blood on the oral mucosa, mainly affecting the soft palate. The tongue and the buccal mucosa can also be involved. ABH has been described more commonly in individuals aged between 40 and 80 years, presenting either as a single tense blood blister or, less frequently, as multiple blisters. Such bullae are completely benign and self-limiting, rapidly expanding and rupturing spontaneously within 24 to 48 hours after their onset. While the exact etiopathogenesis of ABH remains unclear, factors contributing to its development have been identified. Local trauma, chronic use of inhaled glucocorticoids (GCs), dental procedures, and systemic diseases such as hypertension and diabetes are the main triggering factors. This case report describes a case of ABH caused by inhaled GCs.

Case presentation: A 62-year-old male came to our department referring the sudden appearance of multiple blood-filled blisters on the right cheek mucosa. The onset of lesions began 24 hours before. A detailed medical history was carried out, revealing a 10-year use of Angiotensin Receptor Blockers (ARB) for the treatment of hypertension and a 6-year use of inhaled glucocorticoids (GCs) for the treatment of Chronic Obstructive Pulmonary Disease (COPD). Furthermore, the patient had a history of smoking for over 20 years. Clinical examination of the oral mucosa revealed three intact and painless hemorrhagic bullae on the right cheek mucosa. The blisters varied in size: 13 mm x 13 mm in diameter, 10 mm x 10 mm in diameter and 5 mm x 5 mm in diameter [Figure 1]. Blood blisters were ruptured during examination with a dental mirror, leaving erosive areas.

Clinical laboratory tests including complete blood count and differential, prothrombin time, and activated partial thromboplastin time resulted within normal range, so it was possible to rule out blood dyscrasias such as thrombocytopenia and Von Willebrand's disease. In addition, a differential diagnosis with erythema multiforme, dermatitis herpetiformis, mucous membrane pemphigoid (PMM) and pemphigus vulgaris (PV) was done. Serum circulating autoantibodies targeting BP180, BP230, Dsg1, Dsg3, Col VII were evaluated through indirect immunofluorescence (IIF) and ELISA resulting negative. Moreover, our patient did not show other dermatological manifestation, so diseases included in the differential diagnosis were excluded.

Considering the patient's typical history, clinical and laboratory findings, and adherence to the diagnostic criteria for ABH presented by Oridoni et al. [2], a final diagnosis of angina bullosa haemorrhagica was established without performing a rather invasive biopsy. The patient was reassured about the benign nature of the disorder and placed under follow-up. At the 1-week and 3-week appointments, the lesions appeared completely healed without scarring [Figure 2].

Conclusions: This report shows a case of ABH with some unusual features: the lesions were multiple and located on the cheek mucosa. The pathogenesis of ABH is hypothesized to involve a mechanical

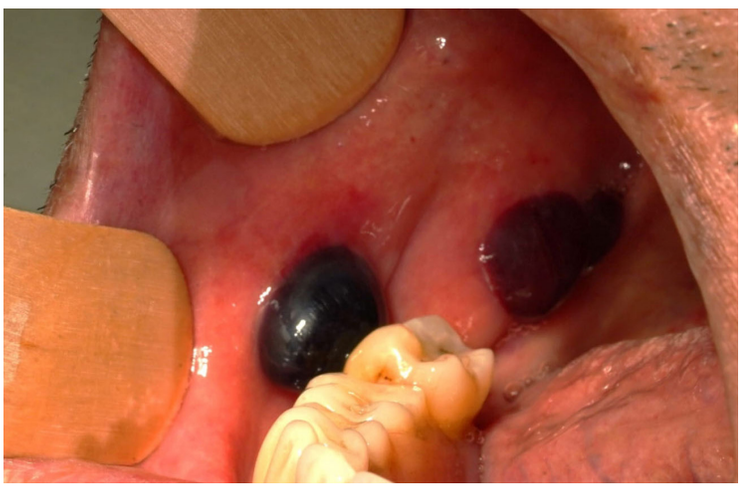

Fig. 1 *Three tense haemorrhagic blisters on the right cheek mucosa.*

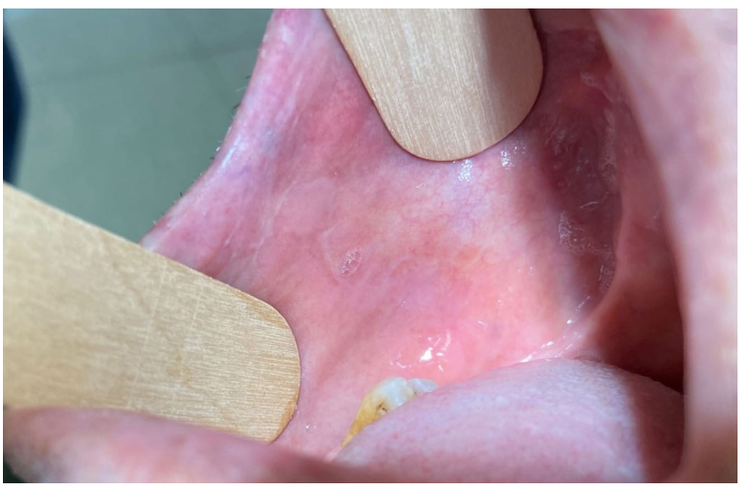

Fig. 2 *Cheek mucosa completely healed one week after the onset of lesions.*

instability in the epithelial-connective tissue connection, predisposing the nonkeratinized mucosa to the damage. Furthermore, topical GCs, known for inducing cutaneous atrophy, may contribute to the disorder's development. It appears that skin atrophy induced by topical GCs involves the synthesis of lipocortin protein, which inhibits the activity of phospholipase A2 (PLA2) reducing the release of arachidonic acid (AA). Consequently, the inflammatory process is suppressed and both mitotic activity and protein synthesis result impaired. AA is also involved in the coagulation cascade: free AA is a precursor for thromboxane A2, which is a vasoconstrictor and inducer of platelet aggregation. Therefore, the reduced release of AA leads to the inactivation of the coagulation cascade. Given all these data and the alignment of the patient's condition with the DoTS (Dose, Time, Susceptibility factors) criteria [3] for inhaled glucocorticoids adverse drug reactions (ADRs), long-term inhaled GCs therapy is proposed as the primary triggering factor in our patient.

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The curious case of the Imatinib-related hard palate dark hyperpigmentation: our experience

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Background: Glivec or imatinib mesylate is a medication that inhibits the Abelson (ABL) tyrosine kinase, that is expressed as a deregulated fusion protein, termed BCR–ABL, in the most cases of chronic myeloid leukaemia (CML) and is produced by an aberrant chromosome rearrangement that fuses the genes encoding to form the Philadelphia chromosome. Actually, Glivec (imatinib) is related to great results as target therapy but as all the medication, has already known drug-related adverse reactions such as thrombocytopenia, leukopenia, myalgia, but between the rare adverse-reaction we recognize the hyperpigmentation of the mucosa.
Case presentation: A 44-year-old male affected by chronic myeloid leukaemia and in treatment with Glivec was referred by his general practitioner for the accidental finding of hard palatal mucosa pigmentation. The patient noticed the presence of the lesion but he didn.t refer any pain or occupying-space mass sensation or bleeding or blood-taste in oral cavity, and his dentist noticed hyperpigmentation black area on the palatal mucosa during routine dental examination, and promptly recommended a maxillofacial consultation. The patient didn't perform bone marrow transplantation for chronic myeloid leukaemia, and he was being treated with imatinib mesylate 400 mg/d for 2 years. According to his oncologist, the patient had not received hydroxyurea, prednisone, chloroquine, or minocycline in the last 2 years. The patient didn't refer other imatinib-adverse reactions such as leukopenia and anaemia. The patient didn't refer to smoke or any palatal trauma or any kind of acute or history of chronical inflammatory disease of the oral cavity or in the hard palatal mucosa area. No skin or nail pigmentation was evident, and he was unaware of any changes in cutaneous pigmentation. Clinical examination showed that the hard palate had a homogeneous gray-black discoloration, non-elevated, non-ulcerated, symmetric and with well-defined margins, not tender and not painful. The rest of the oral mucosa was normal and hadn't any relevant lesions. Biopsy was performed and revealed melanosis with the presence of apoptotic melanocytes. Pathogenetic hypotheses include the Imatinib mesylate stimulation of the melanogenesis, resulting from activation rather than inhibition of the c-kit receptor, but there are also few hypotheses related to lichenoid reaction that regresses, or apoptosis of melanocytes and melanin incontinence, which is caused by increased concentration of imatinib. We performed a short-term (2-4-6-months) follow up and a long-term (12-18-24-30-36 months) follow up, and the lesion didn't change after 36 months its features. The lesion disappeared completely 11 months after the imatinib-suspension without residual lesions or residual chromatic alteration.
Conclusions: The knowledge about drug-associated adverse reactions could be very useful for both patients and medical professional black hyperpigmentation is fundamental in patient management in order to avoid confusion with other systemicdiseases, but it also protects the patient from unnecessary anxiety, testing, and other adverse effects in the medical follow up of this kind of patients.

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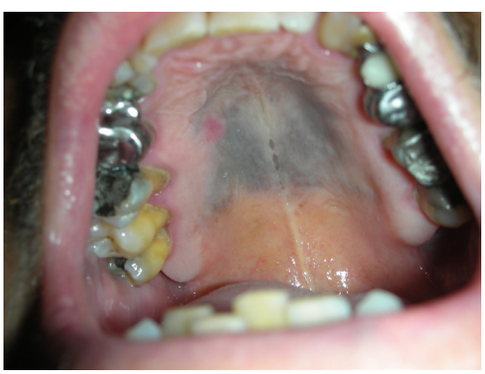

Fig. 5A

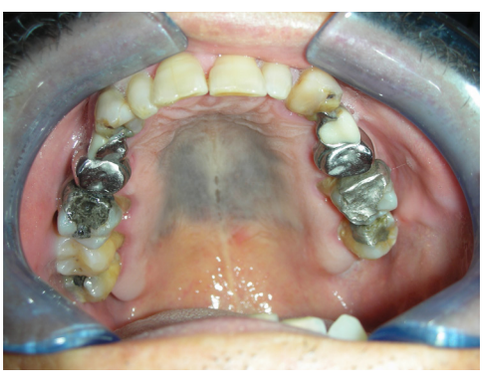

Fig. 5B

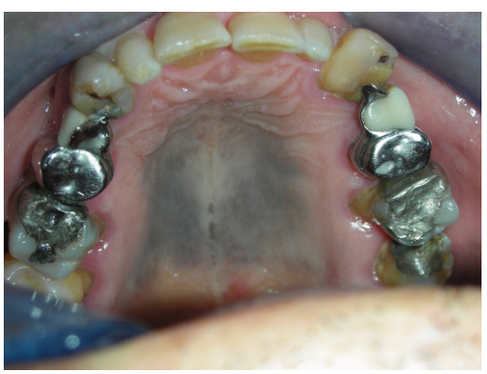

Fig. 5C

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