

CASE REPORT

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Oral mucosal changes caused by nicotine pouches: case series

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Abstract

Oral nicotine pouches are the latest products in the tobacco industry. They are manufactured by large tobacco companies and entice tobacco or nicotine addicts, although the products are presented as a 'harmless choice'. Nevertheless, dentists and oral health specialists worry about oral mucosal changes due to product interactions with the oral mucosa. Unfortunately, there are no case reports of oral mucosal changes from nicotine pouches that are also investigated histopathologically. The aim of the present study was to visually and histopathologically investigate oral mucosal changes in nicotine pouch users. An online retrospective survey regarding medical and dental health, dietary habits, and tobacco consumption habits was conducted ($n = 50$). Respondents were selected for further intraoral and histopathological investigation based on the inclusion criteria. All five respondents had oral lesions that were histopathologically analyzed. Visually, the lesions varied in form and intensity, but all appeared white at the location where the pouches were placed. Histopathological analyses revealed parakeratosis with acanthotic epithelium, intraepithelial and connective tissue oedema, and chronic inflammatory infiltration with lymphocytes and macrophages. Participants received information about nicotine cessation and oral health recommendations. In conclusion, nicotine pouches significantly impacted oral mucosa with white lesions that revealed important changes at the cellular level.

Keywords Nicotine pouches, Oral lesions, Oral mucosa, Parakeratosis

Introduction

Nicotine addiction is one of the most common addictions worldwide, including in the United States, according to the results of the 2021 National Survey on Drug Use and Health [1]. Currently, cigarettes are still the most popular product used, but depending on the age group, the use of tobacco and nicotine products is changing, and other forms of tobacco or nicotine are being used. Nicotine vaping is the most popular among young adults

(18-25-year-olds), but its use decreases with increasing age [2, 3]. Conventional cigarettes, on the other hand, are used at the same frequency as other tobacco products, such as nicotine pouches, smokeless tobacco, and cigars [4, 5]. People are increasingly choosing odourless and smokeless products such as nicotine pouches, which can be used without social restrictions; for example, in school classes, during training, indoors [6]. As mentioned in the study by Tattan-Birch and colleagues, the use of nicotine pouches has increased in recent years, especially among young males who were recent cigarette users and who used other nicotine products [7].

Oral nicotine pouches are the latest products in the tobacco industry; they are manufactured by large tobacco companies and entice tobacco or nicotine users [6]. Nicotine pouches look similar to Swedish snus—both are

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manufactured in small sachets with different flavours and placed under the lip [8, 9]. The difference is that nicotine pouches do not contain tobacco, whereas Swedish snus does [10, 11]. Therefore, the sale of nicotine pouches in the European Union is legal, but the sale of Swedish snus is illegal and allowed only in Sweden [12]. Currently, some European countries have already banned nicotine pouches due to the high levels of nicotine [13] (Parliamentary question - E-002498/2023). In contrast, in the Baltic states, especially in Latvia, distributors of nicotine pouches are opening new markets and advertising alternatives to cigarettes with fewer health problems [14]. Therefore, these products are becoming more accessible and popular in society. Sales of oral nicotine pouches have increased since 2016 in the United States, and sales rose even more during the COVID-19 pandemic in 2019 and 2020 [15].

Interestingly, there is an association between nicotine products and increased willingness to use them, with fewer perceived harmful effects, based on the manufacturer's label "This product contains tobacco-free nicotine (TFN)..." that is placed on the package. Moreover, this "warning" plays an important role in use among young individuals because it raises "awareness" [16]. The average nicotine level of conventional cigarettes is approximately 6–12 mg per cigarette, depending on the brand [17]. Nicotine levels in nicotine pouches range from 1.79 to 47.5 mg per pouch [18], resulting in the use of 3–10 or more pouches per day, which can lead to enormous levels of daily nicotine intake [19]. Disposable e-cigarettes contain 39 to 48 mg of nicotine in one pod [20].

Tobacco-free nicotine products are suggested as a smoking cessation strategy in some countries, but as the nicotine product is still highly addictive, new addictions develop with local oral changes as a side effect [8]. Moreover, a study among United States physicians concluded that 40% of professionals do not have any information about nicotine pouches, and 22% of physicians advised patients to use nicotine pouches as an alternative to smoking but did not mention knowing about any risks or any other future harms that could affect the oral mucosa [21, 22]. Therefore, dentists should be the first specialists to inspect the oral mucosa for possible changes and inform patients about potential harmful effects on oral health [3].

Nicotine pouches are prone to cause not only local toxicological responses but also systemic responses, according to studies of oral epithelial cells and bronchial epithelial cells. As nicotine pouches are available with different flavours, the greatest cell response was observed for spearmint- or tobacco-flavoured nicotine pouches [23]. These flavours are the most popular among nicotine pouch users [24]. Moreover, manufacturers include

synthetic coolants that reduce sensory irritancy resulting from product usage and increase appeal [25].

Increased use of smokeless tobacco is associated with the development of oral leukoplakia and head and neck cancer [26]. Currently, there are no studies about nicotine pouches and oral cancer, possibly because nicotine pouches are relatively new products on the market. Based on the available studies, local oral lesions are observed when the product is used regularly [27]. Both nicotine and tobacco flavourings have cytotoxic effects on oral mucosal cells [2, 28]. A previous study indicated that smokeless tobacco users have a 2-fold greater prevalence of oral cell dysplasia [29]. Increased micronuclei, frequency of binucleated cells, karyolysis, and karyorrhexis were observed in smokeless tobacco users [30]. Moreover, parakeratosis, dyskeratosis, and hyperkeratosis were also detected in smokeless tobacco users [31].

As mentioned above, there are many research papers about smokeless tobacco's harmful effects on the oral cavity, but there is no histopathological evidence about oral changes due to nicotine pouch usage. Therefore, the aim of the present study was to visually and histopathologically investigate the oral mucosa of nicotine pouch users.

Materials and methods

Research ethics

This study was approved by the Ethics Committee of Riga Stradins University (No. 22/28.01.2016). All participants signed informed consent forms and consented to the collection of biological material, the photographing and publishing of images of their oral cavities, and the publication of this study. This study adhered to the guidelines of the Declaration of Helsinki.

Respondent inclusion

An online retrospective survey regarding medical and dental health, dietary habits, and tobacco consumption habits was conducted and published in the university student council group from August 2022 to April 2023 ($n=50$). Based on the answers from the questionnaire, respondents were selected for further investigation based on the following inclusion criteria: 18–35 years of age; no systemic diseases or medical conditions; no daily medication intake or systemic antibiotics for at least 1 year [32]; not pregnant [33]; no periodontitis; daily use of nicotine pouches/smokeless tobacco for at least 2 years; and no use of other forms of tobacco/nicotine products.

Oral examination and sample collection for histopathological examination

Respondents who met the inclusion criteria ($n=7$) then underwent an oral cavity examination, which consisted of status dentalis, oral cancer examination [34], and

basic periodontal examination [35]. This was performed by two independent examiners, certified dentists with a dental practice in Riga. Respondents with basic periodontal examination scores of 3 or 4 were excluded from this study ($n=2$). If oral mucosal changes were present, the changes were photographed (Canon, EOS 80D, Oita, Japan), and samples of the mucosal tissue were collected.

Infiltration anesthesia was induced with 40 mg/ml of Septanest forte with adrenaline 1/100,000 (Septodont, Saint-Maur-des-Fosses Cedex, France). Soft tissue excision (5 mm in diameter, 3 mm thick) was then performed with a sterile scalpel, and tissue samples were placed in Eppendorf tubes (5.0 ml, Sigma-Aldrich, Darmstadt, Germany) with formaldehyde solution at a ratio of 1:15. The samples were stained with hematoxylin and eosin and examined under a microscope (at 40x, 100x, and 600x magnification).

Instructions on preventive oral care after the biopsy were provided to the respondents. Additionally, participants received information about nicotine cessation in their native language [36] at two points: after the clinical examination and after the results of the histopathological examination.

Results

Five nicotine pouch users met the inclusion criteria. Each respondent's tobacco history, intraoral examination description, and histopathological analysis are described further.

Respondent No. 1

History

Male, 28 years old. This individual brushed his teeth twice a day but did not floss. He used dental mouthwash and interdental brushes. Additionally, he used nicotine

pouches for over 7 years, consuming 5–10 sachets daily with each sachet containing 10.9 mg of nicotine.

Intraoral examination

The individual had good oral hygiene. White lesions of varying densities were found above teeth d12–d15, beneath the upper lip, in the vestibulum. The most concentrated white lesions were observed on the buccal mucosa (see Fig. 1). The lesion felt dense upon palpation. Oral hygiene was moderate, with teeth exhibiting large fillings, caries, and discoloration.

Histopathological examination

Parakeratosis was observed (Fig. 2a). There was slight disruption in epithelial polarity, with moderate inflammatory infiltration in the subepithelial zone. Mucosal oedema and significantly expanded capillaries were noted (Fig. 2b). Additionally, the individual exhibited expanded capillaries with individual neutrophils (Fig. 2c).

Respondent No. 2

History

Male, 27 years old. This individual brushes his teeth twice a day but does not floss or use dental mouthwash or interdental brushes. He has been using nicotine pouches for the past 4 years, having previously used smokeless tobacco. Approximately 10 pouches are used daily, each containing 10 mg of nicotine. Previously, he used snus with 17.6 mg of nicotine per sachet. Each pouch is used for 60 min or more and is placed under the upper lip in the vestibulum, alternating between sides from d13 to d23.

Intraoral examination

White leathery lesions were found above teeth d12–d22 on the gingiva and frenulum (Fig. 3). Line-like white lesions were observed under the right side of the lip and above teeth d13–d11 (Fig. 4). These lesions appeared thin and were not palpable. Oral hygiene was moderate, with evidence of gingival bleeding and calculus, but no active caries were detected.

Histopathological examination

A fragmented biopsy revealed hyperplastic multilayer flat epithelial fragments of the oral mucosa with underlying subepithelial fibrous stroma (Fig. 5a). Mucosal epithelial regeneration was evident, with slight disruption in epithelial polarization. Minimal inflammatory changes were noted in the subepithelial zone, along with parakeratosis (Fig. 5b). Additionally, individual capillaries with perivascular lymphocytes and macrophages were observed in the subepithelial zone, with swollen capillary endothelium (Fig. 5c).



Fig. 1 White lesion in the right buccal area and vestibulum of the upper lip. Intraoral photograph of Respondent No. 1

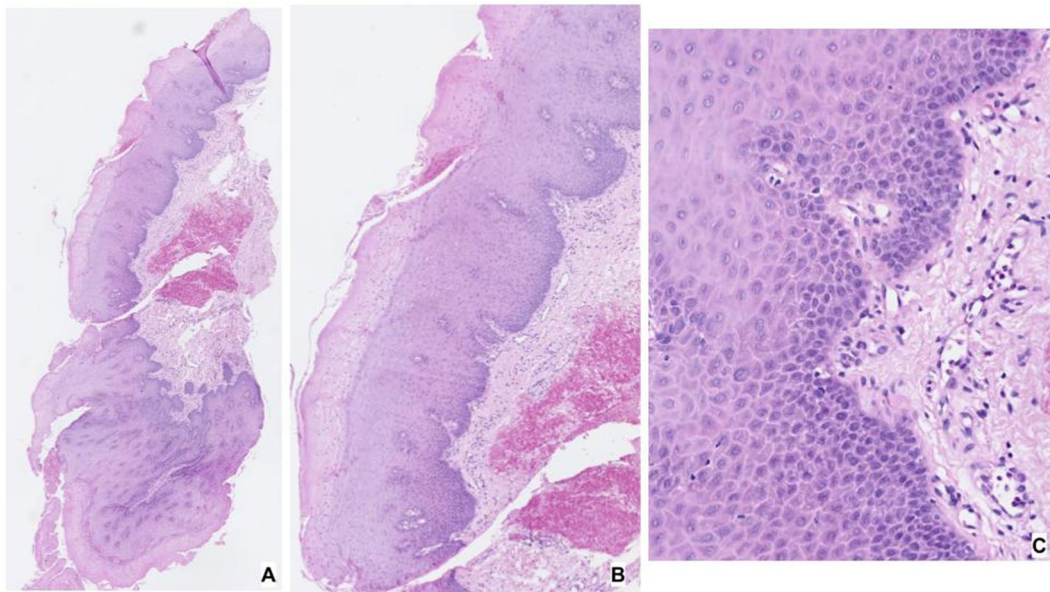


Fig. 2 Histopathological features of oral lesions of Respondent No. 1. (H&E, original magnification 40x (A); 100x (B); 600x (C))



Fig. 3 White leathery lesions on the gingiva and oral tissue above teeth d12-d22, the frenulum and lip



Fig. 4 White line-like lesions under the right area of the lip, above teeth d13-d11

Respondent no. 3

History

Male, 32 years old. This individual brushes his teeth twice a day and uses dental floss and interdental brushes. He has used nicotine pouches for 5 years, consuming 5–7 sachets per day. Each sachet is used for 30 min and is placed under the upper lip in the central area above the frenulum.

Intraoral examination

Visible white linear lesions were observed above tooth d21, near the frenulum (Fig. 6). Oral hygiene was good, and there were no signs of caries or gingival bleeding.

Histopathological examination

There was an increase in mucosal and submucosal thickness. The multilayered flat epithelium exhibited acanthotic thickening with interconnected acanthotic growth (Fig. 7a). Alterations were noted in the mucous membranes, with intraepithelial lymphocytes and relatively dense chronic inflammatory infiltration observed in the subepithelial zone (Fig. 7b). Moderate intraepithelial oedema and oedema in the connective tissue were also observed. Lymphoid infiltrates with a nodular appearance were present (Fig. 7c).

Respondent no.4

History

Male, 27 years old. This individual brushed his teeth once a day and did not floss or use mouthwash. He used nicotine pouches for 5 years, each sachet containing 20 mg of nicotine; prior to that, he used smokeless tobacco for 7 years, with each sachet containing 17.6 mg of nicotine.

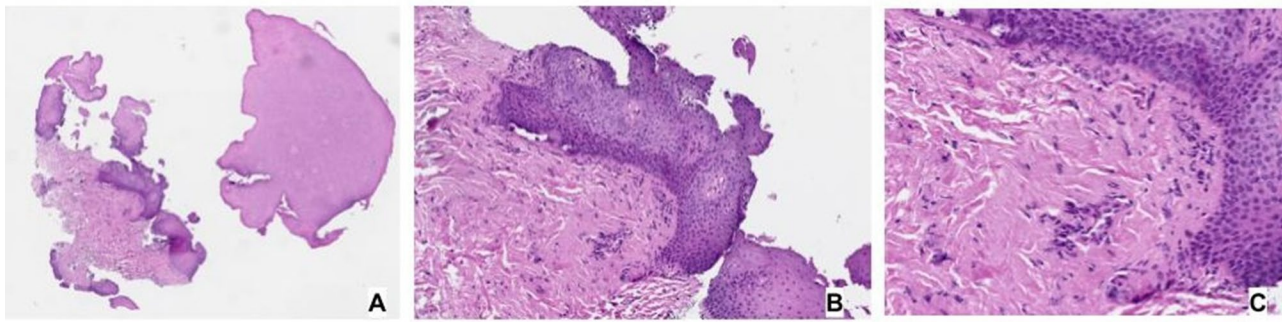


Fig. 5 Histopathological features of the oral lesions of Respondent No. 2. (H&E, original magnification 40x (A); 100x (B); 600x (C))



Fig. 6 White linear lesions above tooth d21, near the frenulum

He used ten sachets per day, placing them under the upper lip near the frenulum.

Intraoral examination

A white homogeneous lesion was observed above teeth d11-d21, with the densest lesion noted on the frenulum (Fig. 8). Oral hygiene was poor, characterized by plaque accumulation on the teeth, gingival bleeding, and active caries.

Histopathological examination

The individual exhibited mucosal lesions characterized by acanthotic thickening of multiple flat epithelia and areas of low mucosa with inflammation (Fig. 9a). Subepithelial infiltration showed a dense collection of lymphoid elements. Submucosal and intraepithelial oedema indicated a dense capillary network (Fig. 9b). Visible intraepithelial oedema and stretched intercellular bridges of the multilayered flat epithelium were observed (Fig. 9c).

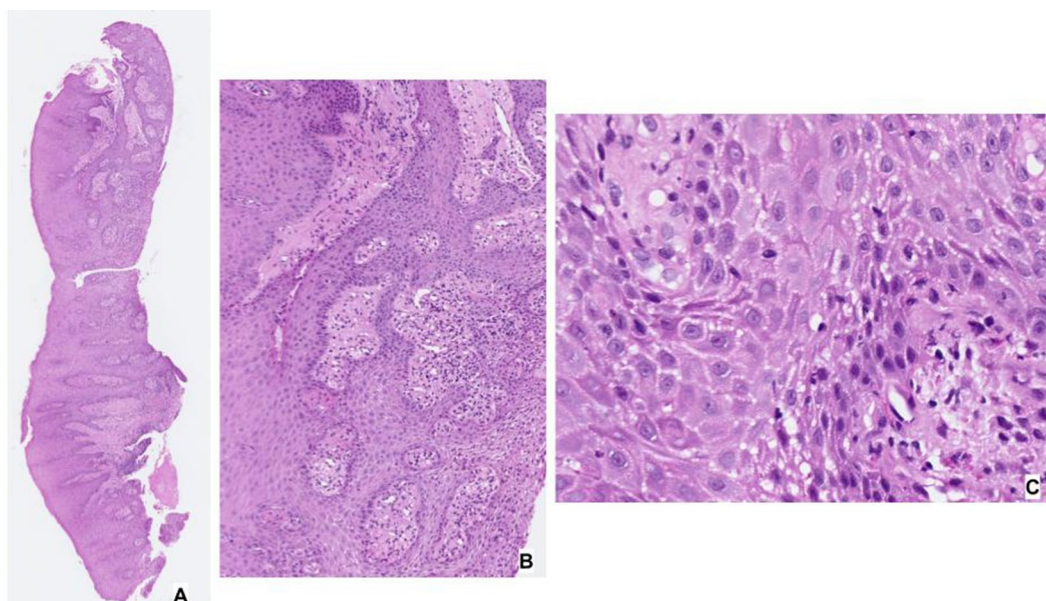


Fig. 7 Histopathological features of oral lesions in Respondent No. 3. (H&E, original magnification 40x (A); 100x (B); 600x (C))



Fig. 8 White homogenous lesions in the frenulum area

Respondent No. 5

History

Male, 28 years old. This individual brushes his teeth twice a day but does not floss or use mouthwash or interdental brushes. Dental visits are irregular. He has used smokeless tobacco for over 5 years, consuming approximately 10 sachets per day. Sachets are consistently placed under the upper lip in the central area and used for 30–45 min each.

Intraoral examination

White linear lesions were observed above teeth d13–d23 on the frontal gingival tissue and vestibulum (Fig. 10). The lesions were not palpable. Oral hygiene was moderate, with no active caries detected.



Fig. 10 White linear lesions above teeth d13–d23

Histopathological examination

The submucosa exhibited marked acanthotic mucosal thickening (Fig. 11a). Dense chronic inflammatory infiltration, primarily composed of lymphocytes, accompanied by a dense capillary network, was observed (Fig. 11b). The epithelium showed maintained polarity and differentiation. Intraepithelial oedema was also noted (Fig. 11c).

Discussion

Our research provides insight not only into the usage habits of nicotine pouch users but also offers a visualization of oral mucosal changes and histopathological analysis of the lesions, revealing both macro- and microscopic examinations.

As seen above, oral mucosal changes tend to occur at the same location where sachets are placed. Although lesions differ in size, pattern, and thickness, they commonly appear white. If the sachets are placed closer to soft moving tissue, e.g., the frenulum, lesions tend to look like white lines. In other cases, lesions appear more

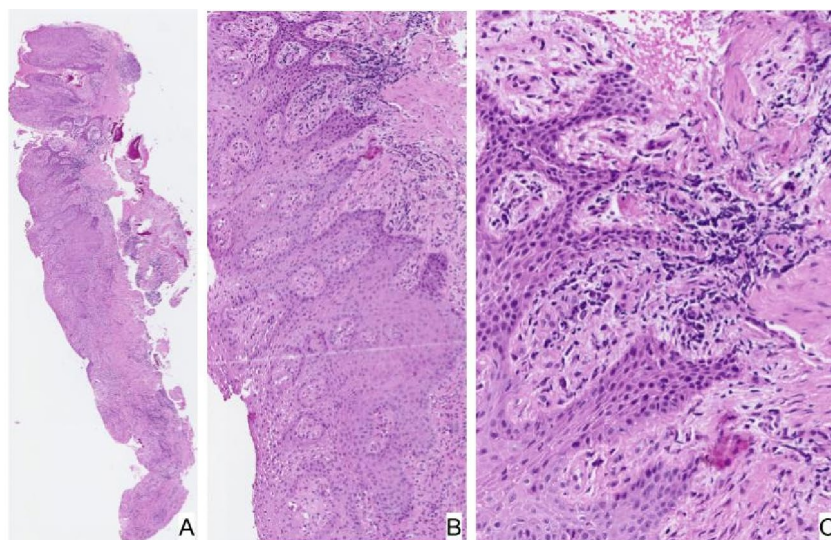


Fig. 9 Histopathological features of the oral lesions of Respondent No. 4. (H&E, original magnification 40x (A); 100x (B); 600x (C))

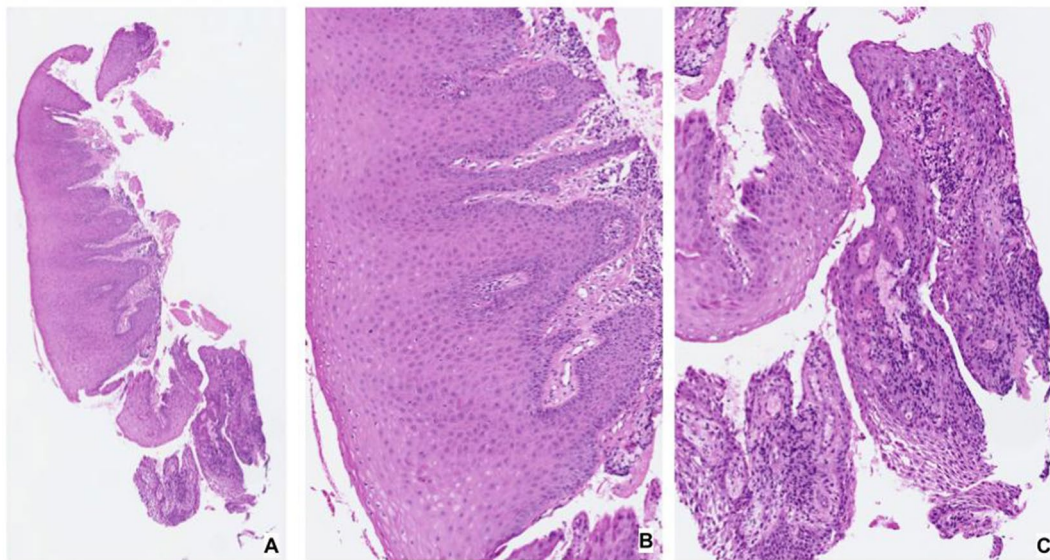


Fig. 11 Histopathological features of oral lesions of Respondent No. 5 (H&E, original magnification 40x (A); 100x (B); 600x (C))

cloud-like with varying intensities. Some lesions are wrinkled. Similar oral findings were detected by Müller [37]. Oral mucosal changes from smokeless tobacco have been well documented [38–40]. This study was the first to detect oral mucosal changes from nicotine pouches. Therefore, due to the lack of similar studies, our results could be compared to studies on smokeless tobacco-induced mucosal changes.

The results indicated that the epithelium was acanthotic with mutually anastomosing acanthotic growths. These results are similar to other studies, although more specific to smokeless tobacco than to nicotine pouches [37]. Subepithelial dense chronic inflammatory infiltration with lymphocytes and macrophages was detected in the samples from our respondents. Lymphoid infiltrates with crush effects were also observed. Intraepithelial and connective tissue oedema and a swollen capillary endothelium were detected. Similarities were found with the study by Woo, where similar lesions were categorized as reactive, chemical-induced contact lesions [41].

Parakeratosis with acanthosis is a histopathological feature of leukoplakia [42]. However, dysplasia was revealed in 5–25% of leukoplakia biopsy samples [43]. Leukoplakia is a clinical diagnosis, but a biopsy is needed for a definitive diagnosis [44]. According to the World Health Organization, oral epithelial dysplasia is associated with an increased risk of progression to squamous cell carcinoma [45]. During the COVID-19 pandemic, although there was a significant delay in the diagnosis of oral squamous cell carcinoma, inpatient services for treating this condition were not disrupted [46, 47]. Women are at greater risk for oral cancer from smokeless tobacco use than men [48], but as seen from our and other studies, smokeless

tobacco is preferred by men. Research has shown that if a healthy individual stops using smokeless tobacco, oral lesions can resolve within 6 weeks to 6 months [49, 50]. If the lesion does not resolve, a biopsy is strongly indicated [37]. If the lesion changes in appearance, lesion removal and regular observation of the mucosa may be necessary [51]. Currently, there is no evidence that lesions vanish after the cessation of nicotine pouch use, but this topic should be investigated in the future.

Based on the results from respondents' survey, a transition from snus to nicotine pouches was observed in two respondents due to easier purchase availability, which was possible after 2019 when nicotine pouches entered the market [52]. In contrast, other respondents used only nicotine pouches; according to the survey, they started to use nicotine pouches when they first appeared on the market in the United States. Although the survey of the respondents was concise, the possible involvement of human factors cannot be ruled out because some of the respondents used other tobacco products occasionally (e.g., at gatherings), which could affect oral changes.

Although some respondents used nicotine pouches or snus for only 5 years, oral mucosal changes were already visually detected. Nevertheless, we could not definitively detect when the lesion occurred due to ethical reasons, but within 5 years, changes in cellular levels were detected. In other research, when respondents switched from snus to nicotine pouches, oral lesions disappeared. These findings should be interpreted with caution because this was a very short-term investigation (only 6 weeks), and the authors of that research had connections with nicotine pouch manufacturers [53]. Moreover, several studies on nicotine pouches have been funded by the

tobacco industry, leading to doubts about the reliability of these studies [54, 55].

One of the exclusion criteria in the survey was multiple product usage every day, e.g., e-cigarettes and snus. It was challenging to find respondents who used only one product, possibly due to the fact that flavored tobacco products increase interest in using multiple products simultaneously [56]. Nicotine pouch flavorings are harmful to the periodontal innate immune system [57]. Flavorings themselves can increase addiction, e.g., users of tobacco products with menthol flavoring have greater nicotine dependency than users of other flavorings [58]. This is a concerning fact not only for nicotine pouch users but also for e-cigarette users, where the choice of flavors is large, and advertising is strong [59].

It is well known that “heavy smokers” are those who smoke more than 25 cigarettes a day, but “light smokers” are those who smoke fewer than 25 cigarettes a day [60]. Although there was no categorization for snus or nicotine pouch users, based on the answers of respondents, we decided that if respondents used more than 10 sachets/pouches per day, they were categorized as “heavy sachet users”, but those who used fewer than 10 sachets/pouches were categorized as “light sachet users”. Therefore, 3 respondents were “heavy sachet users”, but 2 respondents were “light sachet users”.

Nicotine pouch manufacturers recommend using one pouch for approximately 30 min [61]; however, based on the answers from the survey, respondents tended to exceed this time, even using the sachets for 1 h or more. The consequences and effects of prolonged use could be investigated in future research, supplementing research on nicotine pouches.

Typically, one snus or nicotine pouch container consists of 20–24 portions, depending on the manufacturer [62]. The content of nicotine in one sachet varies. Moreover, respondents usually tend to switch products with different nicotine contents during use; therefore, nicotine intake in the bloodstream changes. The nicotine content of sachets varies from 6 mg per sachet to even 20 mg per sachet. Moreover, nicotine absorption through sachets depends on the pH of the sachet. The greater the pH, the greater the ability of nicotine to be absorbed through the oral mucosa [63, 64]. Therefore, if the pH of sachets is near pH 10, nicotine can be transformed into almost 99% freebase nicotine, which is more bioavailable and can cross the oral mucosa faster and more rapidly, increasing the amount of nicotine in the bloodstream [65]. Some users believe that smokeless tobacco is less harmful than cigarettes because it is smoke-free [66]. However, if a smoker of conventional cigarettes absorbs approximately 0.5–1.6 mg of nicotine per cigarette [67], then the majority of nicotine, which is more than 80%, is released within 20 min [68]; therefore, this negates the assumption that

nicotine sachets are less harmful yet are very addictive [69].

Limitations of the study include a small sample size and the retrospective nature of the survey. Given this information, it would be compelling to conduct a study with a larger cohort of respondents. This study could classify participants based on the duration of nicotine pouch consumption and the type of oral lesions observed. Such a study could provide deeper insights into the correlation between long-term nicotine pouch use and specific oral health outcomes.

Conclusions

Nicotine pouches caused changes in the oral mucosa, presenting as white homogeneous lesions typically located at the sites where the pouches were placed. Histopathological analyses revealed parakeratosis with acanthotic epithelium, intraepithelial and connective tissue edema, and chronic inflammatory infiltration with lymphocytes and macrophages.

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Author contributions

Conceptualization, Sintija Miluna-Meldere; Formal analysis, Sarlote Vanka; Investigation, Sintija Miluna-Meldere, Maris Sperga and Dagnija Rostoka; Methodology, Sintija Miluna-Meldere and Dagnija Rostoka; Project administration, Sarlote Vanka; Supervision, Ingus Skadins, Juta Kroica and Dagnija Rostoka; Writing – original draft, Sintija Miluna-Meldere; Writing – review & editing, Ingus Skadins, Juta Kroica and Dagnija Rostoka. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was approved by the Ethics Committee of Riga Stradins University (No. 22/28.01.2016).

Informed consent

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Competing interests

The authors declare no competing interests.

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