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ORAL LICHEN PLANUS POST COVID-19 VACCINATION: REPORT OF TWO CASES

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Ключові слова: *COVID-19, червоний плескатий лишай порожнини рота, вакцина проти SARS-CoV-2, клінічний випадок*

Abstract. Oral lichen planus post COVID-19 vaccination: report of two cases. Samoilenko A.V., Oryshchenko V.Yu., Strelchenia T.M. *Manifestations of coronavirus disease 2019, caused by SARS-CoV-2 virus, are diverse and can vary from asymptomatic infection to respiratory failure needing intensive care. Vaccines against SARS-CoV-2 focusing on the spike glycoprotein have shown promise in diminishing the spread of Covid-19. Adverse effects, however, are associated with every vaccination. Currently, there are literature reports of some cases of lichen planus eruption following COVID-19 vaccine injection. Oral lichen planus is a relatively common immune-mediated dermatologic disorder that can occur isolated or associated with cutaneous lichen planus. Postvaccination lichen planus has previously been reported in the literature as a rare adverse event following various vaccinations, especially hepatitis A and B, influenza, and varicella. The majority of patients presented with classic cutaneous lichen planus, although some reports highlighted primarily mucosal involvement. Herein we describe two rare cases of erosive-ulcerous oral lichen planus among SARS-CoV-2 vaccine recipients. The first is a case of a 67-year-old male who developed mucocutaneous lichen planus 5 days after administration of the single-dose of Ad26.COV2.S COVID-19 vaccine. In the second case, a 56-year-old female presented with reactivation of oral lichen planus after receiving a first dose of Pfizer COVID-19 vaccination 2 days earlier. The mechanism of the association between vaccines and lichen planus is not known, it is attributed to cell-mediated autoimmunity. Although there is currently no evidence of a causal relationship between SARS-CoV-2 vaccination and lichen planus, these clinical observations suggest that the COVID-19 vaccine is a possible key initiating event leading to the development or recurrence of this disease.*

Реферат. Червоний плескатий лишай слизової оболонки порожнини рота після вакцинації проти COVID-19 (два клінічні випадки). Самойленко А.В., Орищенко В.Ю., Стрельченя Т.М. *Прояви коронавірусної хвороби 2019, викликаної вірусом SARS-CoV-2, різноманітні й можуть варіюватися від безсимптомного перебігу до дихальної недостатності, що потребує інтенсивної терапії. Вакцини проти SARS-CoV-2, зосереджені на спайковому глікопротеїні, показали перспективу щодо зменшення поширення COVID-19. Однак побічні ефекти пов'язані з кожною вакцинацією. Наразі в літературі є повідомлення про деякі випадки червоного плескатого лишаю на тлі вакцинації проти COVID-19. Червоний плескатий лишай слизової оболонки порожнини рота є відносно поширеним імуноопосередкованим дерматологічним розладом, який може зустрічатися ізольовано в порожнині рота або поєднуватися із проявами на шкірі. Поствакцинальний плескатий лишай раніше описувався в літературі як рідкісний побічний ефект після різних щеплень, особливо проти гепатиту А і В, грипу та вітряної віспи. Більшість таких пацієнтів мала класичні шкірні прояви захворювання, однак у деяких звітах наголошувалося переважно на ураженні слизової оболонки порожнини рота. Ми наводимо два рідкісні клінічні випадки ерозивно-виразкової форми червоного плескатого лишаю з ураженням слизової оболонки порожнини рота серед реципієнтів вакцини проти SARS-CoV-2. Перший пацієнт– це 67-річний чоловік, у якого через 5 днів після введення однодозової Ad26.COV2.S COVID-19 вакцини розвинулися симптоми червоного плескатого лишаю з одночасним ураженням як слизової оболонки порожнини рота, так і шкіри. У другому випадку 56-річна жінка звернулася з приводу реактивації червоного плескатого лишаю порожнини рота через 2 дні після отримання першої дози COVID-19 вакцини Pfizer. Механізм зв'язку між вакцинацією та червоним плескатим лишаєм наразі достеменно не відомий, але його пов'язують із клітинним автоімунітетом. Хоча на цей час немає доказів причинно-наслідкового зв'язку між вакцинацією проти вірусу SARS-CoV-2 і червоним плескатим лишаєм, але наведені клінічні спостереження свідчать про те, що вакцина проти COVID-19 є можливою ключовою ініціюючою подією, що призводить до розвитку або рецидиву цього захворювання.*

The massive spread of the novel coronavirus infection COVID-19 worldwide, which started at the end of 2019 in China, and the enormous death toll called for the high vaccine coverage of the population [1]. To address the clinical and public health threat of the COVID-19 pandemic, in addition to traditional vaccines (inactivated vaccines), vaccines using a variety of platforms have been made available. The most innovative vaccines (viral vector (adenovirus) vaccines and nucleic acid-based vaccines) use the next-generation platforms and their action is in introducing sequences that encode the SARS-CoV-2 spike protein, that plays a crucial role in penetrating host cells and initiating infection [2].

Adverse effects are known to be associated with every vaccination [2, 3]. Current COVID-19 vaccines with an accelerated vaccine development timeline have shown numerous adverse reaction patterns that may occur following immunization [2]. Many of these findings have been reported to be localized injection site reactions, but uncommonly, especially in genetically predisposed individuals, immune-mediated dermatologic disorders, such as lupus erythematosus, pemphigus, atopic dermatitis, erythema multiforme, herpes zoster, and lichen planus have developed following COVID-19 vaccine injection [4].

The aim of our work was to present two rare cases of erosive-ulcerous oral lichen planus (OLP) triggered by COVID-19 vaccination.

MATERIALS AND METHODS OF RESEARCH

There are presented two clinical cases: a 67-year-old male patient and a 56-year-old female patient who attended our University Clinic, Faculty of Dentistry, Dnipro State Medical University presenting multiple white lesions and erosions in the oral cavity following COVID-19 vaccination.

In order to determine the possible association between COVID-19 vaccine administration and onset of OLP symptoms, relevant information was reviewed, including the medical history (prior lichen planus, clinical course, treatment course); history of current vaccination against the SARS-CoV-2 virus (vaccine type, vaccination strategy). In addition, the time interval between COVID-19 vaccination and the development of the first OLP manifestations of the disease has been analyzed.

Patients were examined according to the traditional scheme [5] followed by histological examination [6]. A careful and detailed intraoral examination was provided. Taking into account the possibility of involvement of other sites in the lichen planus manifestations, the skin of the extremities, trunk, scalp, and nail were also examined. Photographic fixation was carried out using intraoral camera Canon with a ring flash (MacroRing lite MR-14EX) and dent-o-care mirrors from Filtrop.

Laboratory tests included a blood count test, ESR, blood glucose test, and urinalysis. Since the association between lichen planus and liver diseases is well known, in which hepatitis B and C virus infections play an important role, serological studies were carried out to detect antibodies to hepatitis B and C viruses [7].

All other possible differential diagnoses were also ruled out. The clinical differential diagnosis of our cases included systemic lupus erythematosus, chronic atrophic and hyperplastic candidiasis, pemphigus, allergic stomatitis, and erosive form of leukoplakia.

In the first clinical case (a 67-year-old male patient), the clinical diagnosis of the erosive-ulcerative form of oral lichen planus was confirmed by histology. Second case (a 56-year-old female patient) was diagnosed based on clinical evaluation which is acceptable according to the scientific literature [7]. Histology was not performed due to patient refusal. According to the pathognomic appearance of a bilateral lace-like pattern (Wickham's striae) next to erosions on buccal mucosae, we diagnosed this cases as erosive-ulcerative OLP.

We continued to follow up patients over the next year post treatment.

The methodology of the research study takes into consideration the ethical, legal and regulatory norms and standards for research set forth in the "Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects" adopted by the 64th World Medical Association General Assembly (October 2013). Research study also conforms to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine adopted by the Council of Europe (ETS No. 164, April 1997). The research study was considered and approved by the Research Ethics Committee of the Dnipro State Medical University (protocol No. 1 dated February 10, 2020). Before the study, written informed consent for participating in our study was obtained from the patients. In the form the patients have also given their consent for their images and other clinical information to be reported in the journal.

Case presentation 1.

A 67-year-old male patient V. presented with a one-week history of intractable burning and pain in conjunction with acidic, spicy and salty foods intake, inability of solid food intake.

When asked about possible triggers, the patient denied any signs of infection, changes in medication or stress before. He associated onset with the Janssen Ad26.COV2-S (Johnson & Johnson) vaccination 2 weeks prior. The patient felt discomfort during food

intake on his buccal mucosa 5 days after the administration of the vaccine against COVID-19. Patient used chamomile solution rinse to alleviate his symptoms before seeking help from us. Despite that, the lesions gradually had increased in number and size.

He had concomitant hypertension. He was on antihypertensives (Amlodipine 5 mg) for two years, a smoker for the past twenty years. The patient did not start new medication during the previous month. He did not use any new personal oral hygiene products the year before.

Thus, a review of potential triggers of OLP was significant only for intramuscular injection of COVID-19 vaccination. In addition, a few days before immunization, the patient underwent a routine preventive examination in our clinic, which allowed us to completely exclude OLP history.

Oral examination showed the fibrin-coated ulcers surrounded by reticular white lines in a lace-like pattern (Wickham's striae) on both buccal mucosae (Fig. 1A, 1B). The patient also had an ulcer with a brown crust and numerous keratinized papules on the left lower vermillion, which formed white lines on the periphery of the affected area (Fig. 1C). The lesion measured 2.1 × 0.7 cm and extended from 41 distally to 33 tooth. Patient wears a fixed partial metal-ceramic denture with 42 and 32 abutment teeth. This lip lesion was caused by physical trauma during chewing, which was consistent with the Koebner phenomenon, another pathognomonic sign of OLP.

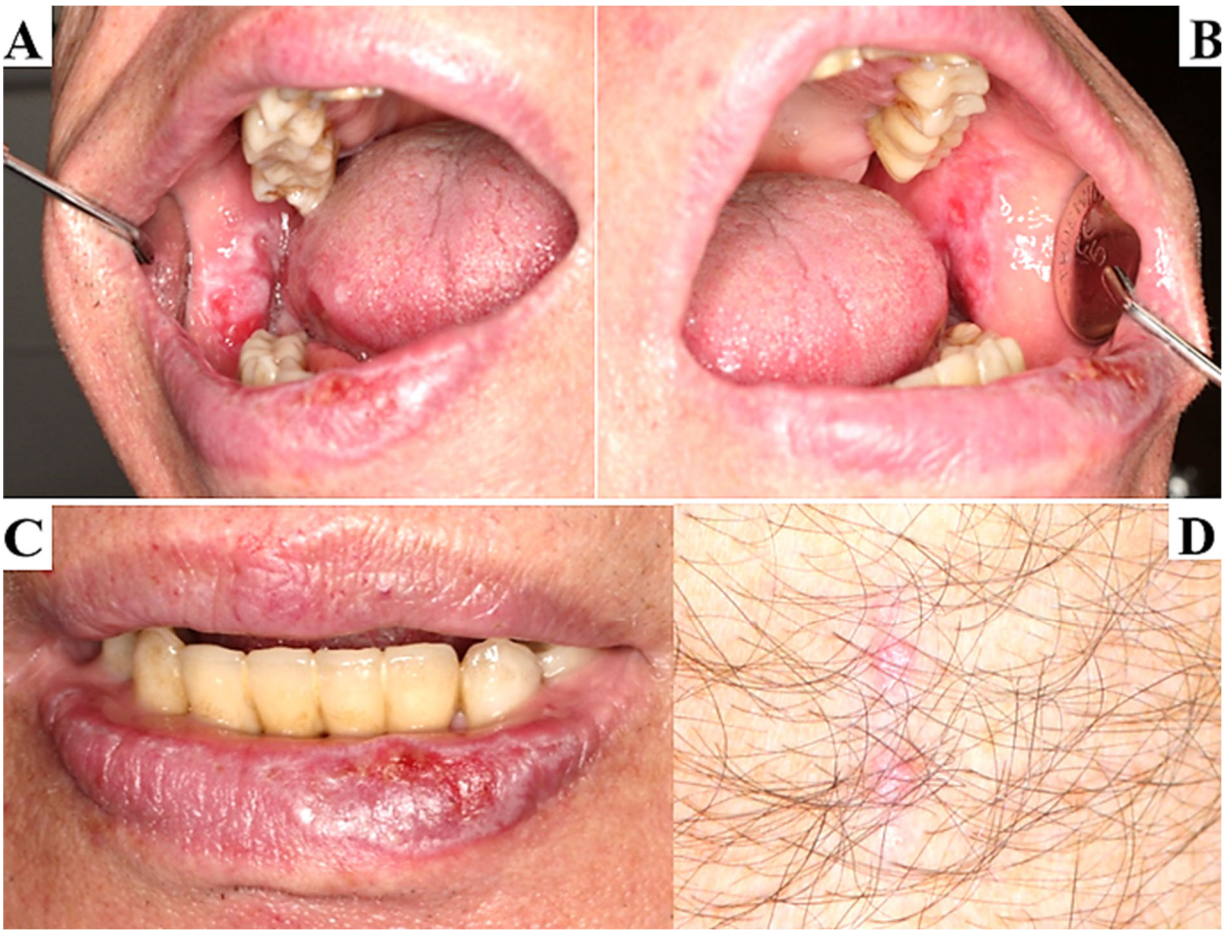

Fig. 1A, 1B – grouped keratinized papules in a lace-like pattern (Wickham's striae) and focal ulcerations of the (A) right buccal and (B) left buccal mucosa.
Fig. 1C – crusted ulcer secondary to bite trauma (Koebner phenomenon) and characteristic grouped papules in Wickham's striae on the left lower vermillion lip.
Fig. 1D – skin lesion, magnification: polygonal, pink, scaly papules on the periumbilical area merged into plaques

After a detailed oral examination, and OLP suspected, extra-oral areas were also examined. Scattered, pink, 1- to 3-mm scaly papules were found on the back and periumbilical skin area. Some were coalescing into plaques (Fig. 1D).

A biopsy specimen obtained from the right buccal mucosa showed apoptotic basal keratinocytes with band-like lymphocytic cell infiltration in the upper lamina propria, consistent with clinical diagnosis of OLP.

Patient's basic hematological parameters were evaluated and found to be within normal limits. Neither hepatitis B virus (HBV) nor HCV infection was detected.

In view of the clinical picture, the timing of the lichenoid eruption with respect to the vaccination and the histopathologic findings, an erosive-ulcerous OLP likely triggered by the COVID-19 vaccination has been diagnosed.

The patient was instructed to rinse oral cavity with 0.05% solution of chlorhexidine after meals three times a day, followed by application of steroid gel Trimistin to the oral lesions, which contained the triamcinolone acetonide. Trimistin gel also contains a broad-spectrum antimicrobial agent miramistin, which protects the oral mucosa, including against fungal infection and treatment with antifungal drugs, which is almost always required when the number of steroids applications exceeds once a day [8].

Topical application of retinoid Corneregel® has been prescribed as a second-line therapy. Corneregel® has keratoplastic properties due to the active substance dexpanthenol. The patient applied gel five times a day before meals to epithelize the oral mucosa.

The patient was consulted by a dermatologist and also applied Trimistin onto the skin eruptions twice a day.

During the treatment period, the patient was advised to follow a soft bland diet and give up smoking. Home care instruction was given regarding rinsing and gentle brushing with a soft tooth brush.

After 3 weeks, the lesion was completely suppressed. The skin lesions resolved during two weeks with hyperpigmentation.

After the disease is resolved, the patient returned for a complete periodontal evaluation. The patient was made aware that, unless the local irritans are removed, OLP may return or become chronic.

We continued to follow up patient over the next year post treatment. No recurrence has been noted during the follow-up period of 1 year.

Case presentation 2.

A 56-year-old female patient K. presented with complaints of pain and burning sensation in oral cavity augmented by chewing and swallowing which resulted in poor alimentation. She reported the oral eruption had started two days after the first dose of BNT162b2 (Comirnaty®; BioNTech and Pfizer) vaccination.

Initially she visited a private dental clinic, where she was diagnosed with oral lichen planus, given that two years ago, the patient had clinically confirmed diagnosis of OLP. Dentist did not associate oral lesions with COVID-19 vaccination. The patient was treated to regularly use topical applications with sea buckthorn oil. However, due to further worsening of symptoms, the patient was referred to our clinic for further consultation.

Upon detailed taking of the medical history and analysis of the patient's medical record, it was established that two years prior, after stress, the patient had a typical form of OLP. Since then, there have been no recurrences.

She had not started any new medications the year before and was not taking any drugs chronically. Patient maintained good oral hygiene and denied using new personal oral hygiene products.

Oral examination revealed the bilateral symmetric extensive buccal lesions of the well-demarcated red erosions with multiple keratinized papules and network of whitish lines, compatible with Wickham's striae (Fig. 2A, 2B). There was no source of irritation or evident reason of local trauma on those sites.

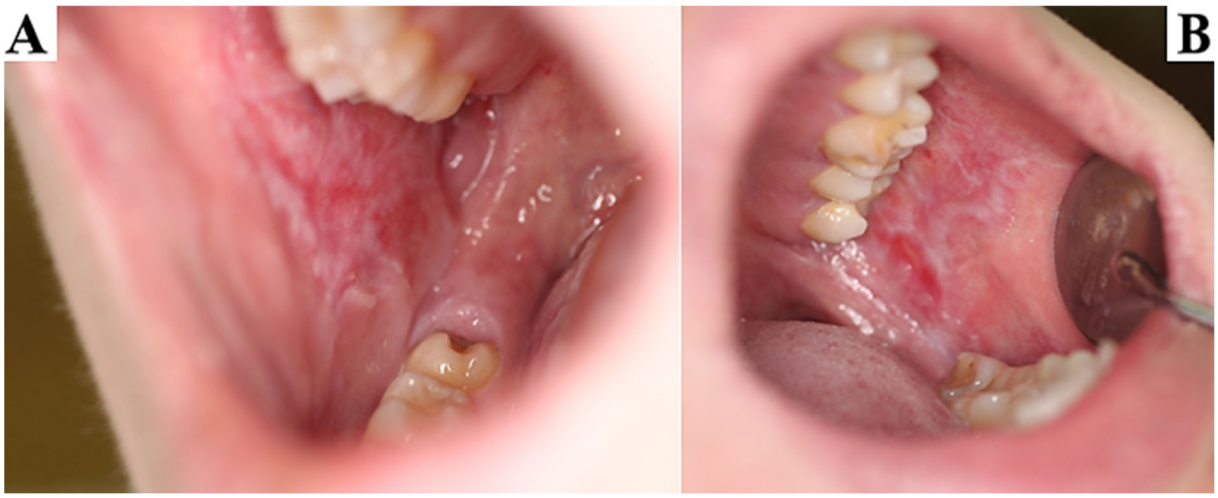

Fig. 2A, 2B – grouped keratinized papules in a lace-like pattern (Wickham's striae) and erosions on the (A) right buccal mucosa and (B) left buccal mucosa

The patient presented with only oral manifestations without the involvement of skin, nail lesions.

Oral biopsy was not performed because of the patient's refusal.

Routine laboratory tests were within normal ranges. Serologies for hepatitis C virus (HCV) and HBV were negative.

According to pathognomonic clinical picture of Wickham's striae and the history of OLP, we diagnosed this case as an exacerbation of OLP (erosive-ulcerous form).

Though an approach to make a comprehensive treatment plan was similar to the first clinical case, the woman was advised to regularly use a topical corticosteroid. In 3 weeks of follow-up, the patient informed about inconsistent and minimal use of topical corticosteroids with the symptoms persisted, and during this period she received a booster dose of the Pfizer vaccine.

After a month of treatment with Triamcinolone acetonide (Trimistin gel) with the supplementary use of a 0.05% Chlorhexidine mouth rinse and topical application of Corneregel® under our control, the eruption gradually resolved and finally disappeared.

During a 1 year' follow-up period no recurrence was noted.

RESULTS AND DISCUSSION

Lichen planus (LP) is a T-cell–mediated inflammatory chronic disorder that affects oral mucosa as well as skin, genital mucosa, scalp, and nails [7]. It is one of the most common dermatological diseases presenting in the oral cavity [8].

Oral lesions may be the only manifestation of disease in many cases. Contrarily to cutaneous manifestations, OLP tends to be chronic, recurrent, and difficult to treat. According to the World Health Organization, since 2005 OLP has been considered as a precancerous condition [7].

White papules that usually coalesce, forming a network of lines (Wickman's striae), are the pathognomonic feature to define a lesion as OLP. The lesions are usually bilateral with relatively symmetric appearance [9]. The most frequently affected site of the involvement is the buccal mucosa, followed by the tongue, gingiva and lower lip.

The imbalance between epithelial regeneration and T-cells mediated destruction is responsible for the clinical varieties of OLP. The typical (reticular), papular and plaque-like forms are usually painless and are known as the "white" variants of OLP. The "red" variants of OLP are the atrophic (erythematous), erosive-ulcerative and the bullous forms which symptoms range from mild discomfort to episodes of intense pain [9, 10].

Histopathological examination reveals hyperkeratosis, "saw-tooth" rete ridges, band-like cell infiltrate of CD4+ and CD8+ T cells in the superficial dermis with degeneration of basal keratinocytes. Such changes suggest an immune-mediated disease [7,10].

Although the clinical and histological criteria have been established to diagnose OLP, to date, no causal factor has been identified [7, 11]. Environmental factors such as emotional and/or physical stress, infections (including hepatitis B and C viruses, and Helicobacter pylori), allergens, medications (such as beta-blockers, nonsteroidal anti-inflammatory drugs, antimalarials, diuretics, and oral hypoglycemics) and mechanical trauma are believed to be involved in the beginning of the autoimmune process [7, 10].

At the same time, LP is known as one of the side effects of different types of vaccines which supports the possibility of a relationship between the disease and vaccines [12]. Cases of lichenoid eruptions developing after vaccination against hepatitis A and B, influenza, varicella, rabies, herpes zoster and combined vaccination against diphtheria, pertussis, and tetanus vaccination have been widely discussed in the literature.

The time interval between vaccine administration and onset of symptoms of lichen planus varied from one day to 120 days after vaccination, but the critical period, the so-called marker period, was equal to the first 2 weeks from injection. If clinical manifestations of the disease appear during this period, it gives reason to suggest that the vaccine can be considered as a trigger factor for lichen planus [12].

The majority reports highlight primarily cutaneous involvement with the lower frequency of mucosal and nail involvement. Vaccine-associated lichen planus may not be distinguished clinically and histopathologically from the classical ones [3, 12]. Now, it is also not clear which specific component in the vaccine initiates this lichenoid eruption, whether this is a combination of vaccine ingredients or a single ingredient such as an immunogenic material, an adjuvant, a stabilizer, or preservative [12].

Our report of two clinical cases of OLP after COVID-19 vaccination supplements literature data about rare cases of lichen planus associated with vaccination against the new virus SARS-CoV-2 [13, 14, 15, 16, 17, 18].

According to vaccine type, most patients (91.7%) were vaccinated with a gene therapy-based SARS-CoV-2 vaccines: 66.7% received an mRNA-based vaccine [17, 18] and 25% – a viral vector vaccine [13,16]. Only one subject was vaccinated with the classical inactivated vaccine [15]. Our patients also received new generation vaccines, namely a viral vector vaccine (Janssen Ad26.COV2-S (Johnson &

Johnson)) and an mRNA vaccine (BNT162b2 (Comirnaty®; BioNTech and Pfizer)).

Among these patients, three-quarters developed a new onset of lichen planus, while one-quarter experienced a reactivation of pre-existing lichen planus. Our clinical observation was divided equally: one clinical case of OLP was registered for the first time, in another one – recurrence of the disease was diagnosed.

All patients had cutaneous and mucosal involvement, nails and hair were not involved. These reported cases indicated that lichen eruptions might arise equally on the skin [16] and on the oral mucosa [13, 17, 18], and in several cases of OLP was observed simultaneously with extraoral eruption [15]. Oral manifestation was dominated by the painless typical (reticular) form of OLP. In contrast, our patients were diagnosed with erosive-ulcerous form of OLP, and, to our knowledge, this is the first attempt ever made to report the so-called red variant of OLP manifestation after SARS-CoV-2 vaccine administration.

All cases showed a clear temporal relationship between the administration of the vaccine and the onset of symptoms, suggesting that lichen planus may be an adverse event after SARS-CoV-2 vaccine administration, especially in susceptible individuals. Lichenoid eruptions occurred 2–14 days after the first (4 pts, median: 5 days) [16] or the second dose (6 pts, median: 9 days) [15, 17, 18] of vaccine. Two patients developed lichen planus in a week after administration of the SARS-CoV-2 vaccine (Ad26.COV2-S), administered as a single dose [13]. In our study, the onset of OLP in the first clinical case began on day 5 after COVID-19 vaccination with the Janssen vaccine and two days after the administration of the first dose of the Pfizer vaccine, when the patient had an exacerbation of OLP. These data also confirm the aforementioned time dependence.

Thus, the period of increased risk of lichenoid eruption associated with vaccines against COVID-19 is primarily within the 2 weeks after vaccination, which may give an important clue to the diagnosis of post-COVID-19-vaccination OLP.

Regarding the prevalence of OLP associated with vaccination against COVID-19, current information is limited by a few studies and further evidence is needed.

Study by Hertel M. et al. [17] found that the incidence of OLP or oral lichenoid lesions (OLL) was significantly higher in patients who received COVID-19 (cohort I) vaccination compared to subjects who were not vaccinated (cohort II). For this, initial cohorts of 274,481 vaccinated and 9,429,892 not vaccinated patients were retrieved from the TriNetX database (USA). Among cohort I, 146 individuals developed OLP/OLL in 6 days after COVID-19 vaccination (88 and 58 subjects received mRNA- and adenovirus vector-based vaccines), whereas in cohort II, 59 patients were newly diagnosed with OLP/OLL in 6 days after visiting the clinic for any other reason. The risk of developing lichenoid eruptions was calculated as 0.067% vs. 0.027%, for vaccinated and not vaccinated patients [24]. Unfortunately, the study did not single out cases of OLP, which does not allow us to draw final conclusions.

McMahon et al. [19] analyzed the reports of patients with cutaneous reactions to SARS-CoV-2 vaccination. This study relied on the biopsy reports that were entered in the International COVID-19 dermatology registry from December 24, 2020 to May 19, 2021. Histopathological characteristics of LP following SARS-CoV-2 vaccination were detected by board-certified dermatopathologists in only four (6.89%) biopsy reports, while of the 803 cases, only 58 (7%) cases had biopsy reports available for review. The authors concluded that overall registry case numbers may not be representative of the true prevalence of vaccine-induced LP, as providers were less likely to biopsy more-common or easily recognized conditions [19].

The mechanism of post-COVID-19- vaccination OLP is not definitively known. One of common hypotheses, most often cited in the research literature, originates in the theory of cell-mediated autoimmunity when the presence of antigens on the surface of epithelial basal cells trigger an abnormal T-cell cytotoxic reaction [12,16, 13, 14, 15]. Vaccination induces a Th1 cell response and the subsequent release of pro-apoptotic cytokines, which may play a key role in the pathogenesis of lichen planus.

It cannot be ruled out that the occurrence of OLP after COVID-19 vaccination could be a simple coincidence. However, the temporal correlation as well as absence of any of the classical risk factors in our cases and in previous reports are suggestive for vaccine related OLP, and that the vaccine alone represents a triggering factor necessary for immune alteration sufficient for the development of OLP.

Thus, it seems unlikely that the occurrence of OLP in our patients is accidental, as also evidenced by the fact that there were no recurrences of OLP during the following 12 months after treatment.

This report is limited by insufficient clinical information to draw definitive conclusions regarding the association between the pathogenesis of OLP and vaccination against COVID-19. To confirm these claims, further research and evaluation are needed, including data of official reporting system of adverse events from the COVID-19 vaccination.

CONCLUSION

1. Presented two clinical cases of erosive-ulcerative oral lichen planus are most likely related to vaccination against COVID-19.

2. It can be hypothesized that vaccines against COVID-19 (mainly innovative vaccines) can trigger oral lichen planus, either as a new disease or a reactivation of previously diagnosed one, but proof of association as well as exact mechanism of development wait for further investigation.

Contributors:

Samoilenko A.V. – conceptualization, writing – original draft, writing – review & editing, resources, data curation;

Oryshchenko V.Yu. – writing – original draft, wriing – review & editing;

Strelchenia T.M. – visualization, writing – review & editing.

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