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CASE REPORT

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Management of a carcinoma in situ of the tongue margin, using a Nd:YAG laser, cross-linked hyaluronic acid (xHyA) gel and a porcine pericardium resorbable membrane: a case report

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Abstract

Background Oral tongue squamous cell carcinoma is the most prevalent cancer of the oral cavity. To date, the mainstay management for carcinoma in situ of the oral cavity is the surgical radical removal of the neoplastic tissue. This paper describes a new approach in the management of an in situ carcinoma of the tongue margin, treated surgically by the use of Nd:YAG laser, the application of cross-liked hyaluronic acid (xHyA) gel and the placement of a resorbable porcine pericardium membrane (PPM).

Case presentation The case involves a 49-years old male patient with no history of smoking and alcohol use, who presented a non-homogeneous leukoplakia of the right tongue border. The biopsy revealed high-grade lichenoid dysplasia, corresponding to severe epithelial dysplasia or carcinoma in situ (Tis), characterized by full-thickness dysplasia without stromal invasion.

Conclusions The case shows that the combined use of Neodimium laser surgery, xHyA gel and PPM is a viable option for promoting soft tissue regeneration in the oral cavity, enabling excellent clinical results in terms of healing medium-sized surgical defects. In addition, compared with other options for the reconstruction of surgical defects of the tongue, the clinical use of the association between these two materials has several biological advantages due to the absence of donor sites and high patient tolerability.

Keywords Nd:YAG laser, Cross-linked hyaluronic acid, Resorbable porcine pericardium membrane, Oral early carcinoma

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Background

Oral potentially malignant disorders (OPMDs) are a group of mucosal disorders that may precede the diagnosis of oral squamous cell carcinoma [1, 2]. The most common OPMDs in the oral cavity is oral leucoplakia (OL), which has a highly variable rate of malignant transformation risk ranging from 0.13 to 34.0% [3, 4]. The malignant transformation (MT) of OL appears to be heavily dependent on specific risk factors, such as tobacco and alcohol abuse, advanced age, female gender, oral site of lesion, non-homogeneous clinical type, and the presence of epithelial dysplasia [5].

There is a correlation between the lesion site and malignant transformation, and OLs of the border or ventral surface of the tongue have a higher risk of developing in OSCC (55,4%) [5].

An International multi-institutional analysis conducted in 2020 revealed an increasing incidence of oral tongue squamous cell carcinoma (OTSCC), which also affects young patients (≤ 45 years) without defined risk factors [6].

The mainstream treatment for early stage OTSCC without any lymph node involvement is transoral resection of the lesion with free margins [7], commonly considered adequate in the range of 0.5 cm to 1.0 cm, in width and thickness.

The case involves the surgical management of a lesion diagnosed as carcinoma in situ (characterized by full-thickness epithelial dysplasia without stromal invasion), located on the tongue margin through the use of Nd: YAG laser for lesion excision and the combination of cross-linked Hyaluronic Acid gel and a porcine pericardium resorbable membrane to promote healing of the surgical site.

Cross-linked hyaluronic acid is a hygroscopic and viscoelastic substance [8] endowed with bacteriostatic [9], anti-inflammatory [10, 11], and anti-oedematous [12] properties. Furthermore, it promotes tissue regeneration by taking part and accelerating healing steps [13, 14] and counteracting ROS action [15]. The porcine pericardium membrane acts as a mechanical barrier, thus protecting the surgical site. In addition, it enhances xHyA properties.

Case presentation

The following clinical case involves a 49 years old male patient who presented with a non-homogeneous leukoplakia located on the right tongue margin.

The lesion, which had been present for 5 months before the first visit to our clinic, was approximately 4.0 cm x 2.0 cm in size (Fig. 1).

The patient did not report any symptoms, and denied smoking or alcohol consumption. Furthermore, no

Fig. 1 Non-homogeneous leucoplakia of the right tongue margin

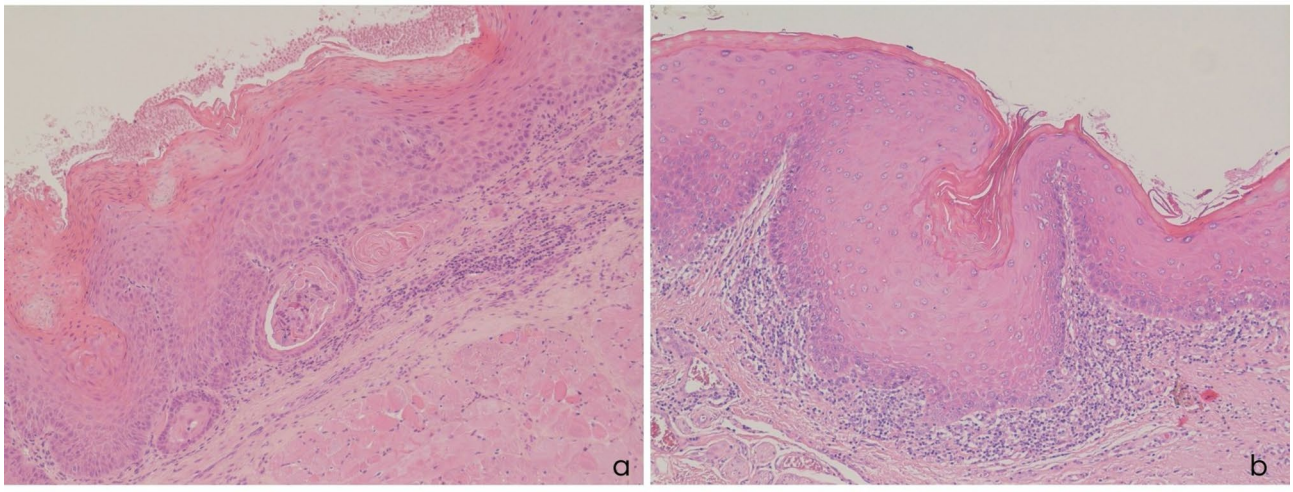

Fig. 2 **a**. and **b**. Microscope images of the incisional biopsy specimen

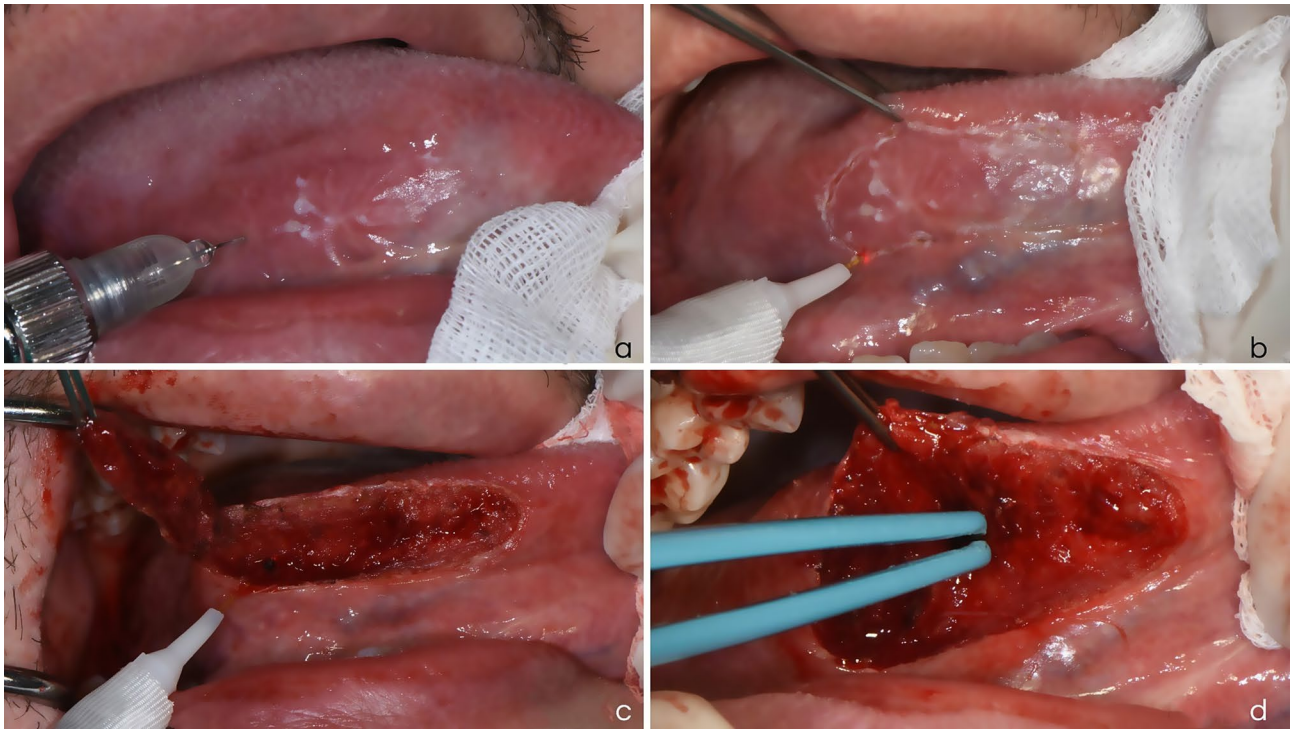

Fig. 3 **a**. Loco-regional anesthesia performed close to the lesion margins; **b**. Drawing of the perimeter of the area to be removed using the Nd:YAG laser; **c**. Excision performed with Nd:YAG laser; d. Management of deep arterial bleeding using a bipolar clamp

current or previous systemic pathologies or therapies have been reported. It was decided to proceed by performing an incisional biopsy of the lesion, which revealed high-grade lichenoid dysplasia, consistent with carcinoma in situ (Tis) (Fig. 2a, b). Because of the histological nature of the lesion, the patient was required to undergo an MRI (Magnetic Resonance Imaging) with and without contrast medium and an ultrasound scan of the lymph nodes in the neck, which allowed us to rule out any lymph node involvement.

Therefore, surgery was performed with the excision of the entire lesion. After loco-regional anaesthesia (Fig. 3a), excisional margins were identified, including free margins of 1 cm in width and depth (Fig. 3b). Excision was performed using a Neodymium yttrium aluminium garnet laser (Nd: YAG laser 1064 nm, 64 Hz, 35 W fiber: 300 µm, fluence: 658 J/cm^2, power density: 49.5mW/cm^2) (Fig. 3c). Although the Nd: YAG laser guarantees good haemostasis, a bipolar clamp was necessary to manage deep arterial bleeding (Fig. 3-d). Subsequently,

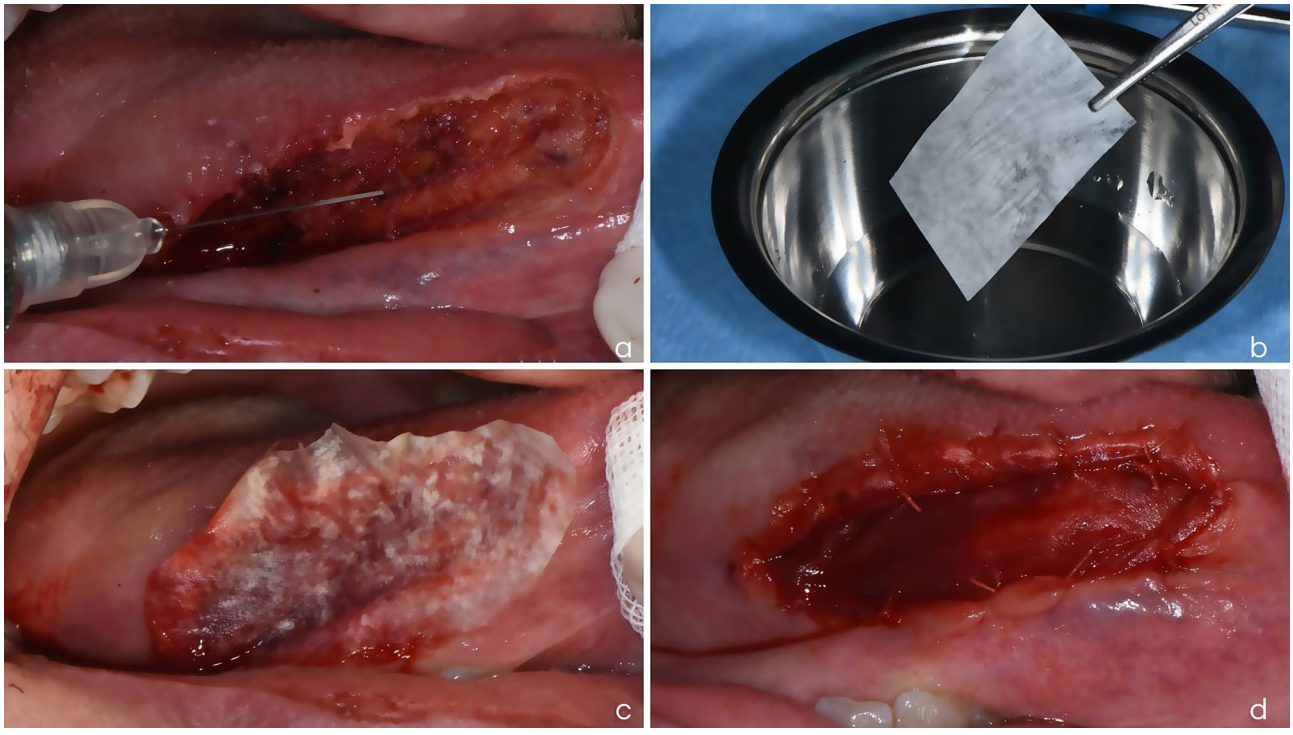

Fig. 4 **a**. Application of xHyA gel at the bottom of the surgical wound; **b**. Porcine pericardium resorbable membrane hydrated with physiological saline; **c**. Porcine pericardium resorbable membrane placed on the wound; **c**. Porcine pericardium resorbable membrane fixed with resosrbable stiches

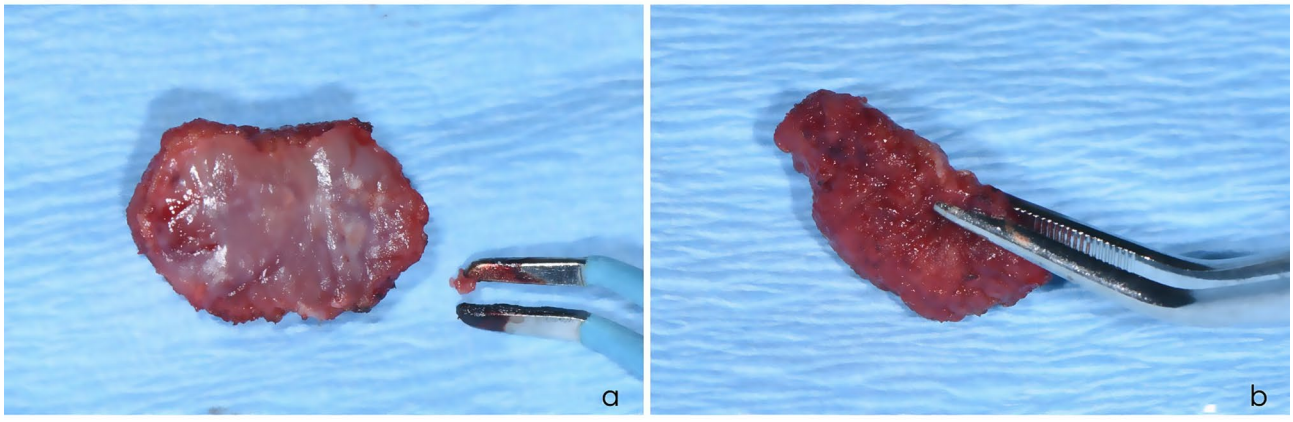

Fig. 5 **a**. Size of the removed piece (4.0 cm x 2.0 cm); **b**. Thickness of the removed piece (2.0 cm)

hyaluronic acid gel (composition: 1.6% cross-linked hyaluronic acid and 0.2% native hyaluronic acid) was applied at the bottom of the surgical wound, delivered using a syringe (Fig. 4a). Thereafter, a porcine pericardium resorbable membrane was hydrated with physiological saline (Fig. 4b), shaped following the defect outline, and placed on the injury (Fig. 4c). The membrane was fixed with single resorbable stitches (Vicryl 5/0) (Fig. 4d). In Fig. 5a and b, it is possible to observe the size of the piece removed and its thickness (4.0 cm x 2.0 cm x 2.0 cm). Histological analysis of the post-operative sample confirmed the diagnosis of carcinoma in situ (Fig. 6).

At the one-week postoperative follow up, early re-epithelization of the site and the complete absence of signs of inflammation were observed (Fig. 7a). In addition, no postoperative impairment of the muscles has been reported. Moreover, the patient reported the complete absence of post-operative pain, thus no need to take painkillers even in the days immediately after surgery.

At two-week follow-up, the restitutio ad integrum of the area was fully achieved (Fig. 7b).

The next follow-up, one month after the intervention, showed the presence of a slight scar retraction, which progressively reduced in size, as visible at the four-month

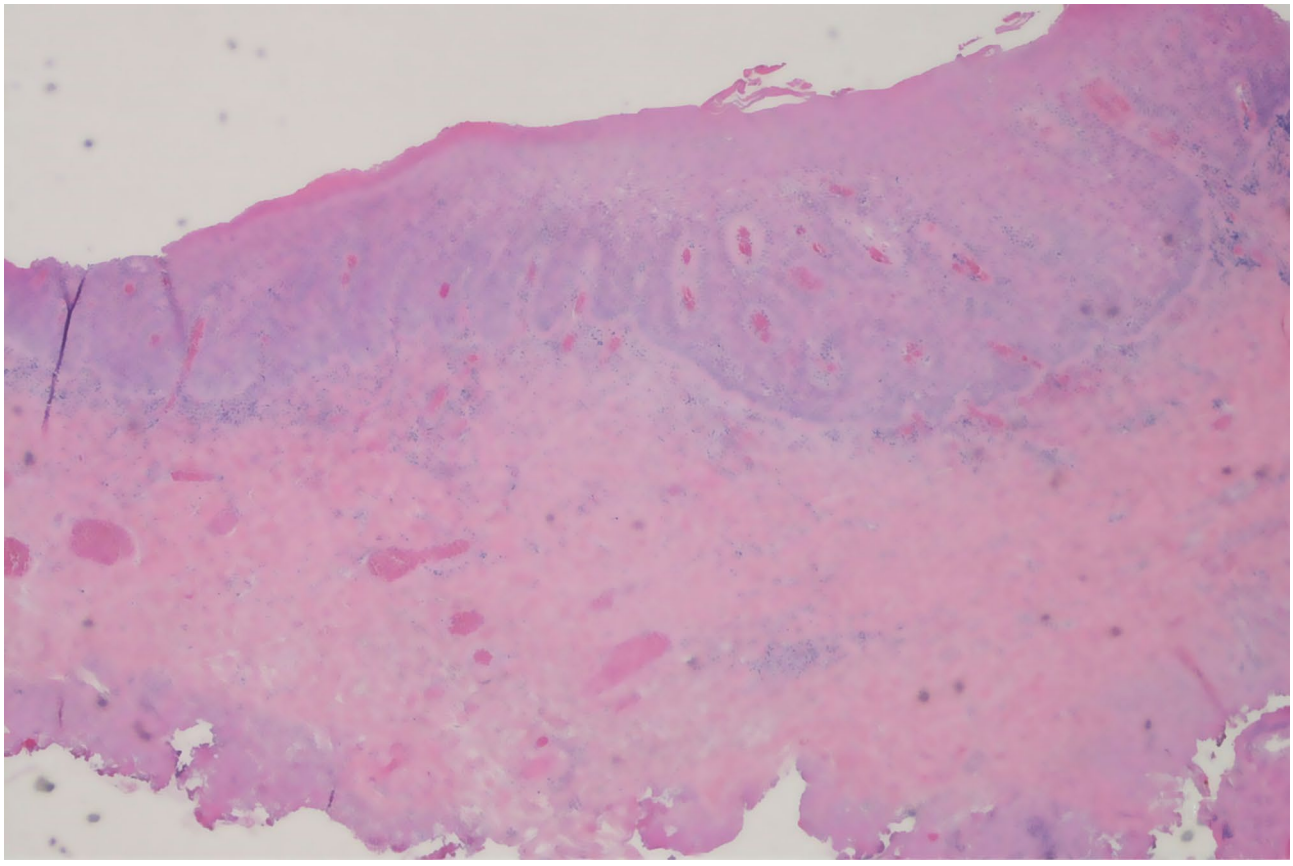

Fig. 6 Microscopic image of the post-operative sample

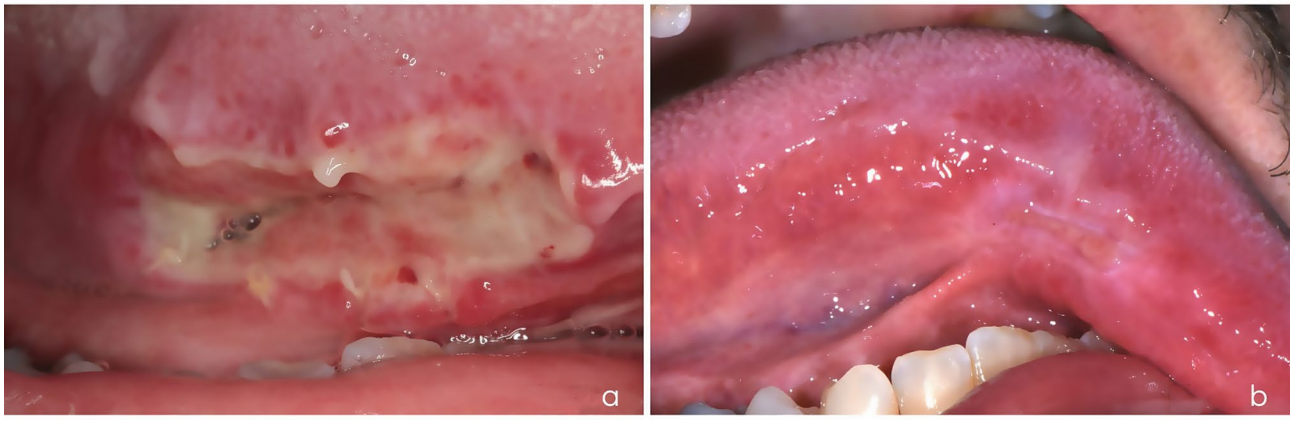

Fig. 7 **a**. One-week follow-up; **b**. Two-week follow-up

follow-up (Fig. 8a). After eight months, optimal healing of the surgical site was observed without any signs of recurrence (Fig. 8b).

Discussion and conclusions

Oral tongue squamous cell carcinoma is the most prevalent cancer of the oral cavity (25–40% of all oral malignancies) [16]. OTSCC is characterized by aggressive behaviour because of its unusual histologic makeup, against which the tongue is not equipped to protect itself and respond to tumor invasion and metastasis [17].

According to the literature, surgical intervention represents the mainstream treatment for early oral tongue squamous cell carcinoma without any evidence of nodal invasion (T1-T2, N0) [18], which provides the removal of oncological tissue and free margins, commonly considered adequate in the range of 0.5 cm to 1.0 cm [7].

Fig. 8 **a**. Four-month follow-up; **b**. Eight-month follow-up

Surgical treatment using Neodimium laser provides both intraoperative and postoperative benefits, representing a technique that needs of physicians and patients [19].

The Nd: YAG laser wavelength is well absorbed by melanin and haemoglobin, which justifies its excellent haemostatic effect [20], reducing bleeding, and thus ensuring good visibility of the surgical field during the procedure. Moreover, the laser wave acted in depth by extending up to 4–5 mm in this direction. This feature of the laser beam ensures that, in addition to the cutting effect, the Nd: YAG laser performs a photobiostimulant effect on deep tissues [21], thus promoting a more rapid and optimal healing of soft tissue wounds and improving pain relief and OHRQoL as it reduces post-operative discomfort.

The extent of surgical intervention is strictly correlated to tumor dimension, and consequently, indications for tongue reconstruction differ based on the type of glossectomy performed. Considering that the primary aim of tongue reconstruction is the restoration of its morphology and functionality, small volume defects can be managed by primary and secondary intention or through soft tissue grafts [22]. Semple reconstruction with primary and secondary intention is associated with good outcomes; however, in the case of midsize defects, grafts are indicated. Reconstructive treatment options for medium-sized surgical defects include buccal myomucosal local flaps (Facial Artery Myomucosal Flap - FAMM, FAMM reverse, Bozola, Zhao, and others) [23, 24], split-thickness skin grafting (STSG) [25] and biologics grafts [26].

Although autologous grafts still represent a surgical option, several disadvantages such as additional surgical intervention, differences in colour and texture, and the limited amount available for harvest make these grafts less suitable [27]. In addition, donor site morbidity and operative time justify the inclination to prefer xenogeneic collagen grafts [22].

In this case report, we assessed the effectiveness of the association of cross-linked hyaluronic acid and a porcine pericardium membrane to promote healing of the surgical defect due to their biological features and regenerative potential.

Hyaluronic acid (or hyaluronan) is a glycosaminoglycan formed by a disaccharide unit (D-glucuronic acid and N-acetylglucosamine) that repeats up to 50,000 times.

This molecule is naturally present in human organisms as a constituent of ECM and, is involved in many processes, including cell signalling, wound repair, tissue regeneration, morphogenesis, matrix organization and pathobiology [28].

Crosslinking of pure HA polymers (xHyA) is achieved using specific reagents that induce the formation of cross-linked inter- and intra-molecular bonds between several hyaluronic acid polymers. This structure confers higher resistance to mechanical stress and slower degradation compared to the native form [29].

The clinical use of xHyA guarantees several advantages, such as the maintenance of postoperative functional integrity of the treated anatomical structure, reduction of postoperative pain [28], acceleration of the healing process [14], promotion of neoangigenesis [30], bacteriostatic action, and lower risk of infection [9].

In particular, in the wound healing process, low molecule weight Hyaluronic Acid (LMW-HA) plays a pivotal role as a promoter of early inflammation, increasing the concentration of proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-8 (IL-8) [31]. The inflammatory phase is crucial: immune cells clear the wound from bacteria and damaged tissue and attract and activate fibroblasts, inducing the proliferation phase of the healing process [32]. Obviously, moderation of the inflammation process is needed in order to proceed toward a healing response. In a somewhat contradictory role to its inflammatory stimulation functions, hyaluronan may also act as

a moderator of inflammation [33], which is decisive stabilizing the granulation tissue matrix, particularly in its high molecular form.

In the case presented, the use of hyaluronic acid is not properly aimed at treating the cancerous lesion: the application of the product takes place after the complete excision of the lesion (with extension into healthy tissue of 1.0 cm in width and depth) in order to promote tissue regeneration of the surgical site.

Native porcine pericardium resorbable membranes are highly biocompatible. The aforementioned characteristic is the result of accurate cleaning processes, performed using supercritical carbon dioxide (scCO2) [34].

The porcine pericardium resorbable membrane acts as a barrier by separating the surgical site from the oral cavity environment. Furthermore, it promotes blood clotting and allows cell adhesion [35, 36]. In addition, its clinical use is justified on the grounds that, when applied to a site already impregnated with hyaluronic acid, it enhances HA effects and further reduces its degradation time [37].

The association between cross-linked hyaluronic acid and porcine pericardium membranes is widely used in dentistry. Their osteoinductive action has been extensively documented in the literature [38, 39], and their effectiveness has been verified in several oral treatments [40].

Specifically, in periodontology, xHyA and native porcine pericardium resorbable membranes are used for non-surgical periodontal therapy [12], guided bone regeneration, GBR [41, 42], management of gingival recessions [43, 44], treatment of peri-implantitis [45], and sinus floor augmentation [46].

We opted for the association of these two materials to assess their effectiveness in promoting the regeneration of small soft tissue (skin and muscle) defects, achieving promising results. In particular, the patient reported no post-operative pain and, consequently, he did not report needing to take painkillers as a result of the surgery; furthermore, rapid healing of the tissue, complete absence of inflammation signs at re-evaluations, no functional impairment, and no changes in aesthetics has been recorded.

In conclusion, our application of a novel therapeutic approach involving Neodimium laser surgery, cross-linked hyaluronic acid, and resorbable porcine pericardium membranes after the removal of pre-malignant lesions associated with oral lichenoid dysplasia/carcinoma in situ has demonstrated positive outcomes in terms of wound healing. However, it is imperative to acknowledge that despite the encouraging initial results, the efficacy of this intervention in preventing recurrence or impeding the progression to oral tongue squamous cell carcinoma remains uncertain.

Longitudinal studies and extended follow-up periods are warranted to comprehensively evaluate the long-term effectiveness and potential benefits of this combined therapeutic approach.

Regarding follow-up times, the monitoring of patients is ensured by the fact that all subjects treated for OTSCC are part of a long-term follow-up schedule: the protocol in our Operative Unit is to perform two ultrasound scans for neck lymph nodes evaluation and one magnetic resonance imaging (MRI) to be carried out annually for five years.

Additionally, ongoing research efforts should focus on elucidating the underlying mechanisms involved in the pathogenesis of oral lichenoid dysplasia/carcinoma in situ and determining how the implemented therapy may influence the natural course of the disease.

While our current findings suggest promise in terms of wound healing, the ultimate goal of preventing malignant transformation necessitates continued exploration and refinement of therapeutic strategies. This conclusion underscores the importance of ongoing research endeavors and collaborative efforts within the medical community to advance our understanding of oral lichenoid dysplasia and enhance the development of targeted and more effective therapeutic interventions.

Author contributions

R.I.: writing- original draft; writing- review and editing (equal); I.G.: Supervision (equal); M.M.: Supervision (equal); J.C.L.: writing—review and editing; P. V.: Methodology. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests

The authors declare no competing interests.

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