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Malignant Transformation of Oral Leukoplakia After 16 Years: A Case Report and Literature Review

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Abstract

Oral leukoplakia (OL) is the most common oral potentially malignant disorder. Evidence on time to malignant transformation is scarce. A lifelong, time-dependent risk of malignant transformation has been reported. Despite numerous studies of risk factors for shorter time to transformation, there are currently no predictors that can reliably forecast the timing in an individual case. We present a clinical case of OL that persisted for a prolonged period and underwent malignant transformation after sixteen years.

Keywords: oral potentially malignant disorder, oral leukoplakia, malignant transformation, time to malignant transformation, risk factors

Introduction

Oral leukoplakia (OL) is defined as a “predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer” [1]. OL is the most common member among the group of oral potentially malignant disorders, with reported prevalence rates in the global population between 3.41% and 4.11%, varying across world regions [2], [3], [4]. A concerning trend toward increasing OL cases worldwide is reported, with approximately a twofold rise over the past 20 years [2], [5].

A current and widely discussed issue in the literature concerns OL and the risk of malignant transformation over time [6], [7]. Data regarding time to malignant transformation is limited [8]. Meta-analyses on time to transformation are hampered by heterogeneity in outcome and data reporting—absolute mean values in days, months, or years; time intervals; and cumulative incidence [8].

Reported malignant transformation rates for OL range between 3.5% and 9.8%, with annual malignant transformation rates of 1.56%–6.3% [9], [10], [11], [12], [13]. Patients with OL are reported to have a lifelong risk of 30%-50% of malignant transformation [14].

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Overall, literature reports on time to malignant transformation of OL are few. A mean time of 6 years has been reported, but transformation can also occur after a very long period of up to 15 years [15]. According to Jr Sol, the risk for malignant transformation is highest within the first two years [16]. Other authors report an increasing risk over time —1.3% in the first 3 years, 2.4% by year five, and 4% by year ten — emphasizing the need for long-term follow-up [17]. The exact individual risk for malignant transformation unfortunately cannot be pointed out [7]. Nevertheless, it is reported that in approximately 6.6% of cases the malignant transformation will occur after an unknown period [7]. Long-term follow-up is therefore emphasized because of the persistent risk of malignant change [16].

Moderate and severe epithelial dysplasia has been identified as a risk factor for more rapid malignancy [15]. Anatomical localization on the lateral border of the tongue is also identified as a risk factor for earlier transformation, with reported time to malignancy of 6.4 years [18], [15]. Although a non-homogeneous clinical appearance is generally considered a risk factor for earlier transformation, Bagán Sebastián did not find statistically significant associations [15]. Saito reported a time to malignancy of 4 years for multifocal OL and 9 years for localized lesions [19]. A systematic review and meta-analysis reported that patients with OL who continue smoking have a higher risk of disease progression [7]. Despite this increased risk, 73% of patients with confirmed OL continue to smoke cigarettes and only 27% quit [16].

Long-term clinical follow-up of all OL patients is warranted regardless of the presence or absence of risk factors because of the known potential for changes in lesion characteristics and the uncertain malignant potential over time [15], [7]. Any OL — whether with mild, moderate, or severe epithelial dysplasia, carries an increased risk of malignant transformation over time; therefore, long-term follow-up is prudent given the risk of malignancy [7], [10].

In the following we present a case of a long-standing multifocal oral leukoplakia involving the floor of the mouth, the ventral surface, and the lateral borders of the tongue bilaterally, which underwent malignant transformation after a period of 16 years.

Case Description

A 45-year-old woman with OL of the mucosa of the floor of the mouth and the ventral surface of the tongue for 16 years was reported to the oral and maxillo-facial clinic “Alexandrovska” hospital. The patient was first examined and photographed by P. Stanimirov at the eighth year after the onset of OL (Figure 1), revealing a white, thick, relatively homogeneous plaque widely involving the sublingual mucosa and the ventral tongue. The patient was a smoker (15 cigarettes daily for 20 years) and was advised then to stop smoking completely and to undergo follow-up. During the first two years thereafter (the ninth and tenth years from onset of OL), she attended regular check-ups, but afterwards subsequently discontinued follow-up.

In 2021 (sixteen years from onset of OL) the patient came for a clinical examination after a long absence with new complains of an intraoral exophytic mass (Figure 2). The patient reported that over the preceding years the OL had enlarged, but even though she did not seek any medical consultations. Over the years the patient had periods of reduction and cessation of smoking, followed by relapse, and reported that for four years has quit smoking. On the current clinical examination we noted clinical progression of the OL, which had spread onto the tongue bilaterally

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along both mandibulolingual sulci when in comparison with earlier photographs (Figure 1). A sublingual area exhibited verrucous proliferation appearing as a firm, rough, white exophytic nodular lesion on a narrower base arising from the sublingual mucosa (Figure 2). Comprehensive mucosal examination of the previously documented lesion (Figure 1) showed overall peripheral expansion toward the lateral tongue margins, significant non-homogenity, and erythematous areas.

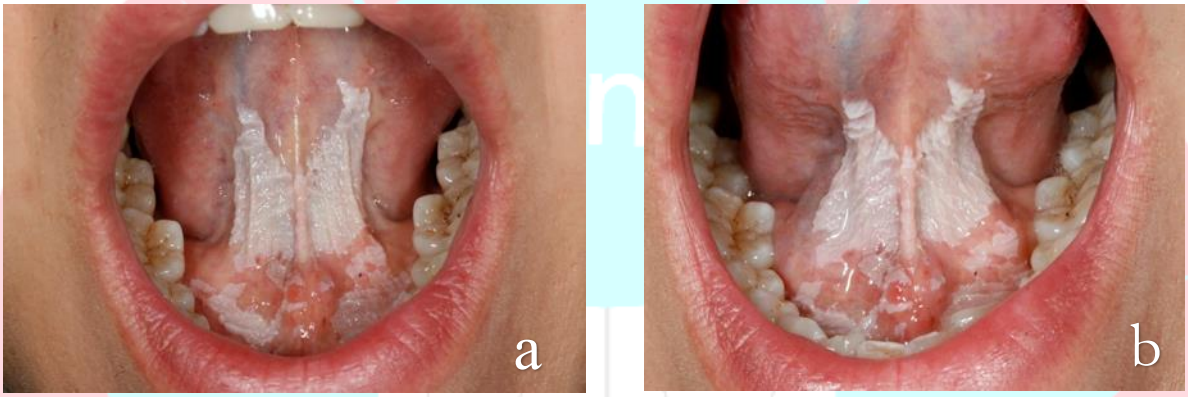

Figure 1. Clinical appearance of oral leukoplakia eight years earlier.

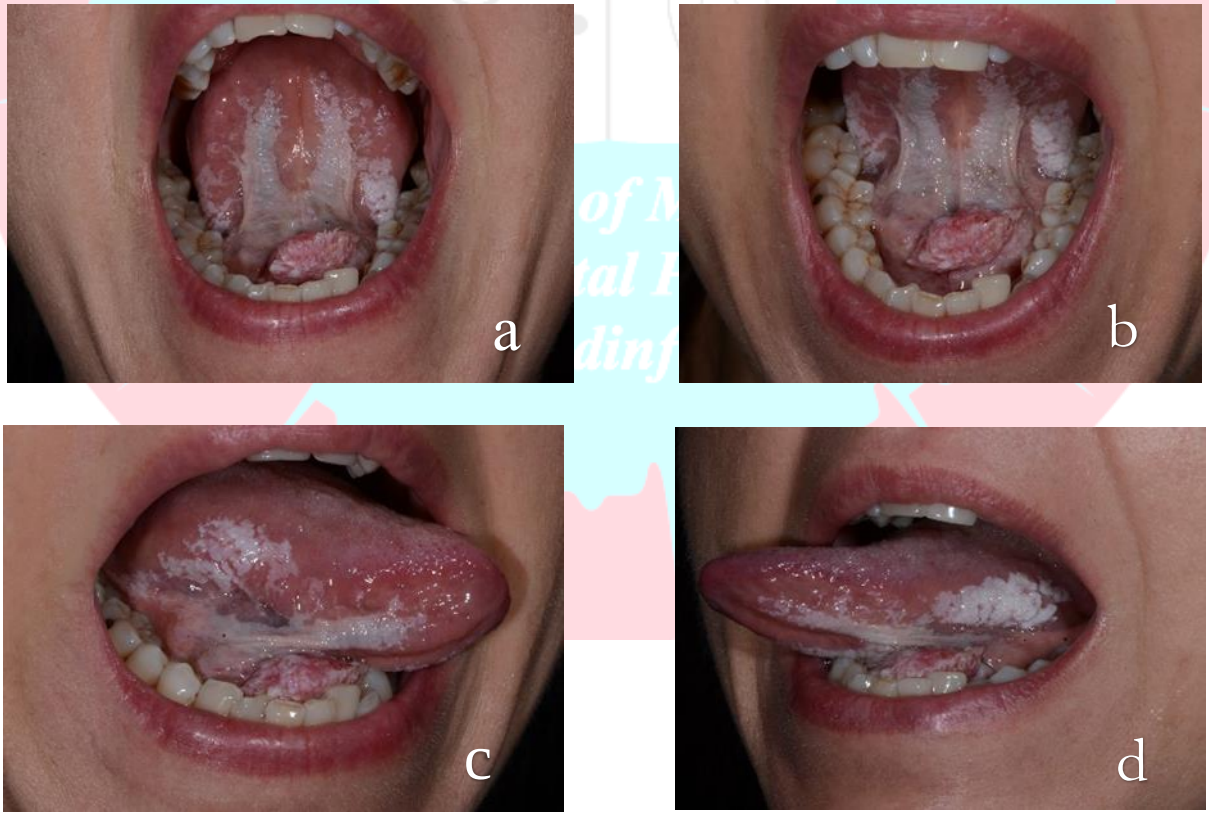

Figure 2. Clinical findings at the time a malignant transformation was established. Multifocal non-homogeneous leukoplakia involving the floor of the mouth, ventral surface, and lateral borders of the tongue bilaterally (2c, 2d). Sublingually- an

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exophytic nodular lesion, firm on palpation, with a verrucous surface developing within the field of OL (2a, 2b). Incisional biopsy of the nodular lesion revealed a verrucous squamous cell carcinoma with transition to conventional squamous cell carcinoma.

An incisional biopsy was performed, confirming malignant transformation with a verrucous squamous cell carcinoma transitioning to conventional invasive squamous cell carcinoma. The tumor was removed by wide excision lateral to the tumor mass; however, the resection margins traversed a field of leukoplakia (Figure 3). Histopathology showed verrucous carcinoma with transition to conventional microinvasive squamous cell carcinoma, depth of invasion up to 1 mm; the verrucous mass was excised with negative margins (R0), with a mean clearance to inked margins of 10 mm; the stratified squamous mucosa present in the specimen showed focal mild dysplasia and hyperkeratosis; final staging: pT1(mi) R0.

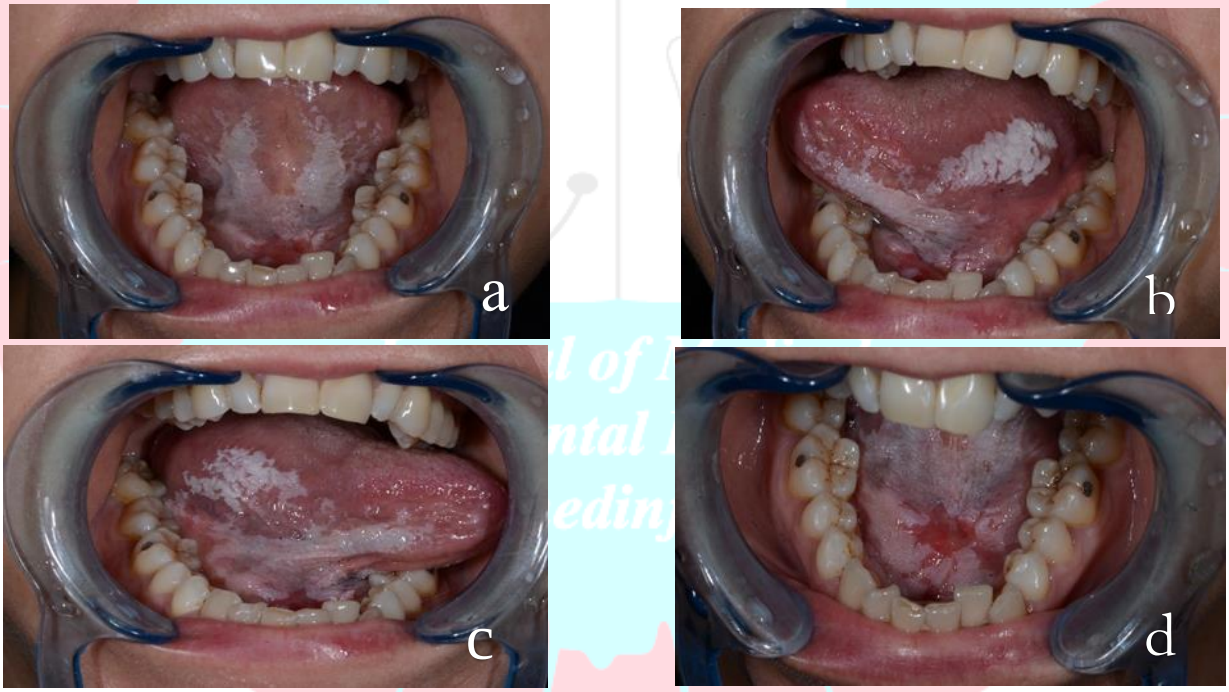

Figure 3. (a,b,c,d) Preoperative local clinical status.

The patient was advised to undergo long-term, strict surveillance with clinical examinations every 2 months throughout the year, combined with monthly ultrasound examinations of the regional cervical lymph node basin, and additional cross-sectional imaging—CT/MRI/PET-CT as needed at the discretion of the treating physician.

Six months postoperatively, on clinical examination a new lesion on the right lateral tongue border was observed. A new incisional biopsy demonstrated a moderately differentiated keratinizing squamous cell carcinoma of the right lateral tongue (Figure 4). A metastatic progression on the neck on level II (right) was also observed.

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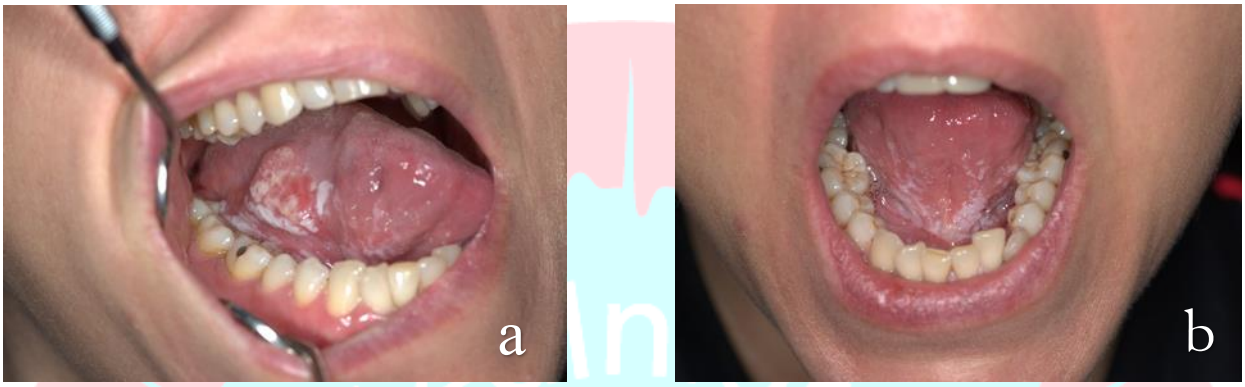

Figure 4. Unfavorable course with expansion of oral leukoplakia and a non-homogeneous clinical appearance; development of a new area on the right lateral tongue border suspicious for a new neoplasm within the OL field (4a). Postoperative status sublingually – no local recurrence after previous operative treatment (4b).

Excision of the tumor (according to NCCN recommendations) and a radical neck dissection were performed. Histopathology revealed a moderately differentiated (G2) squamous cell carcinoma of the right tongue with broad infiltration into underlying skeletal muscles; worst pattern of invasion (WPOI) - 4; a mild-to-moderate peritumoral inflammatory reaction with predominantly lymphoplasmocytic infiltrate; metastases in 2 of 23 examined lymph nodes at level II.
Four months after the second operation, the patient reported that she had not undergone the recommended adjuvant postoperative radiotherapy. Examination showed disease progression with advanced regional metastatic disease with soft-tissue infiltration, not amenable to surgical treatment, and she was referred for radiotherapy with chemotherapy/immunotherapy. Despite the treatment, the disease progressed rapidly, leading to death a few months later.

Discussion

Literature data on the time to malignant transformation of OL vary [15], [16]. A mean interval of 6 years to cancer progression has been reported [3]. The first two years after diagnosis are cited as with the highest risk of malignant transformation [16]. The risk of malignant transformation is considered to remain high even 11 years after OL diagnosis in the study by [12]. In our case, OL underwent malignant transformation after a long interval of 16 years. Evren emphasizes the need for long-term clinical follow-up of OL and underscores that the risk of malignant transformation cannot be accurately predicted despite the clinical, histological, and molecular risk factors investigated in the literature [12]. In our patient we observed multiple negative factors: continuation of smoking after OL diagnosis, non-homogeneous clinical appearance, multifocality, size over 200 mm² and localization on the floor of the mouth and lateral tongue border. The case illustrates the necessity of long-term surveillance, a view widely supported in the literature [15], [20], [21], [8]. Malignant transformation of OL in patients under regular follow-up is diagnosed at an earlier cancer stage compared with those without regular or any clinical control [20]. In our case

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the patient discontinued follow-up for 8 years until malignant transformation occurred. A clear risk factor here is that the patient continued smoking for 12 years after the initial OL diagnosis, consistent with observations by Pimenta-Barros and Jr Sol that most patients continue smoking [7], [16]. The patient also noted an increase in size and a change in the clinical appearance of OL, but did not seek medical help. In our practice we often observe that patients with oral potentially malignant disorders or with oral squamous cell carcinoma continue to smoke or report smoking less. Many state that they quit and then resume; overall, our impression is that they do not fully realize—or would rather not attempt to understand—the adverse consequences associated with this risk factor. This has also been emphasized by Alamoudi [22]. In our clinical practice, all patients with oral potentially malignant disorders are instructed in self-examination and awareness of their oral mucosal status and are informed to present for evaluation as soon as possible if they notice mucosal changes. Ilkay [20] also recommends this self-monitoring approach to recognize early signs of malignant transformation. In our case, malignant transformation did not arise at a single focal site; within six months essentially the entire affected region transformed into invasive, aggressive squamous cell carcinoma. This observation recalls the classic publication by Slaughter describing the so-called “condemned mucosa” concept [23]. Retrospectively, one might ask: “Why did you wait, and why did you not remove the leukoplakia when first seen?”, or: “What would have happened if the leukoplakia had been removed earlier?”—a contentious question. This highlights the need to improve patient understanding and awareness of the condition and the necessity of regular follow-up.

Conclusion

Oral leukoplakia is the most common oral potentially malignant disorder, with an unknown individual risk of progression to carcinoma. At present, no prognostic factors can precisely predict the risk of malignant transformation in an individual case. Our case demonstrates that progression to squamous cell carcinoma may occur after a long interval of 16 years. The progression did not present as a localized event at a single site but as an aggressive disease affecting the entire region of the floor of the mouth and tongue. Strict, long-term clinical surveillance of OL cases is prudent to enable early detection of unfavorable changes in individual patients and to allow earlier treatment when indicated. This case reflects both the unpredictable course of OL and the challenges related to motivating smoking cessation, ensuring strict long-term follow-up, and fostering awareness of potential consequences in patients with OL.

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