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Case Report

SYNCHRONOUS ORAL SQUAMOUS CELL CARCINOMA IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS: AN UNCOMMOM PRESENTATION

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs, including the oral mucosa. Although SLE has been recognized as an oral potentially malignant disorder (OPMD), malignant transformation within lupus-related oral lesions is exceptionally rare.

Case report: This report describes a 77-year-old woman with SLE who developed three synchronous oral carcinomas—two verrucous carcinomas and one conventional oral squamous cell carcinoma (OSCC)—after years of chronic, treatment-refractory mucosal lesions. Histopathological examination revealed multifocal epithelial dysplasia and carcinoma, suggesting a phenomenon of field cancerization (FC). The patient, who lacked classical risk factors such as tobacco or alcohol use, was treated successfully with radiotherapy, achieving complete remission and no recurrence after 18 months of follow-up. The present report highlights the potential role of chronic inflammation and long-term immunosuppression in oral carcinogenesis in SLE. It also underscores the diagnostic challenges in differentiating lupus lesions from other OPMDs and the importance of serial biopsies for early detection of dysplastic transformation.

Conclusion: The coexistence of FC and SLE has not been previously reported, and this case contributes novel clinical and histopathological evidence supporting the inclusion of SLE among conditions predisposing to multifocal oral cancer.

KEYWORDS: lupus, autoinmune diseases, oral, cancer.

Statement of Clinical Significance

Systemic lupus erythematosus-associated oral lesions may undergo malignant transformation even in the absence of classic risk factors. Persistent or atypical lesions require close monitoring and serial biopsies, as early detection of dysplasia could enable timely intervention and improve patient outcomes.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is an entity that may develop from pre-existing lesions in approximately 20% to 30% of cases[1]. These lesions, known as oral potentially malignant disorders (OPMDs), have the capacity to transform into OSCC at varying rates of malignant transformation. Among them, one of the least studied is systemic lupus erythematosus (SLE)[2,3].

SLE is a chronic, multisystemic autoimmune disease characterized by immune system dysfunction that can affect multiple organs, including the skin, joints, kidneys, heart, and central nervous system[4].

The etiopathogenesis of SLE is complex and multifactorial, involving genetic, environmental, hormonal factors, and possibly exposure to certain infectious agents. Although the precise mechanisms are not yet fully understood, chronic inflammation mediated by the immune system is known to play a central role in its development and progression. SLE is caused by an autoimmune reaction involving the innate and adaptive immune systems, where an abnormal immune response is directed to nucleic acid-containing cellular particles. The over production of antibodies targeting these nucleic acids, known as antinuclear antibodies (ANAs), is characteristic of SLE. Moreover, the anti-Smith (anti-Sm) antibody, which is an auto-antibody directed against a component of the spliceosome, is highly specific to SLE, with 20-40% SLE patients versus approximately 1% healthy individuals carrying them[5]. SLE has been recognized as an OPMD, particularly when it involves the lip[3]. A recent meta-analysis

revealed a significantly increased risk of OSCC in patients with SLE, with a reported risk ratio of 2.69 compared to the general population. Additionally, the prevalence of OSCC in patients with SLE has been estimated at approximately 10%[6,7]. Given its malignant potential, it is crucial that patients with SLE are closely monitored, particularly in areas of the oral mucosa where lesions may persist or undergo changes over time. The literature contains few reported cases of malignant transformation in SLE-related lesions, and therefore the available evidence on this phenomenon remains limited[8].

Field cancerization (FC) is a concept introduced by Slaughter in 1953. He described the development of multiple foci of malignant transformation within a field of tissue—primarily epithelial—that has been exposed to carcinogens or predisposing genetic alterations. FC suggests that OSCC does not arise as an isolated cellular event, but rather as an anaplastic tendency involving numerous cells simultaneously. This leads to a multifocal cancer development process occurring at different rates throughout the entire field in response to a carcinogen, with tobacco use being the most common[9]. FC is a phenomenon that helps explain the development of new tumors in patients who have already developed OSCC, as well as the occurrence of synchronous or metachronous tumors in different areas of the oral mucosa, which may or may not be associated with previous OPMDs.

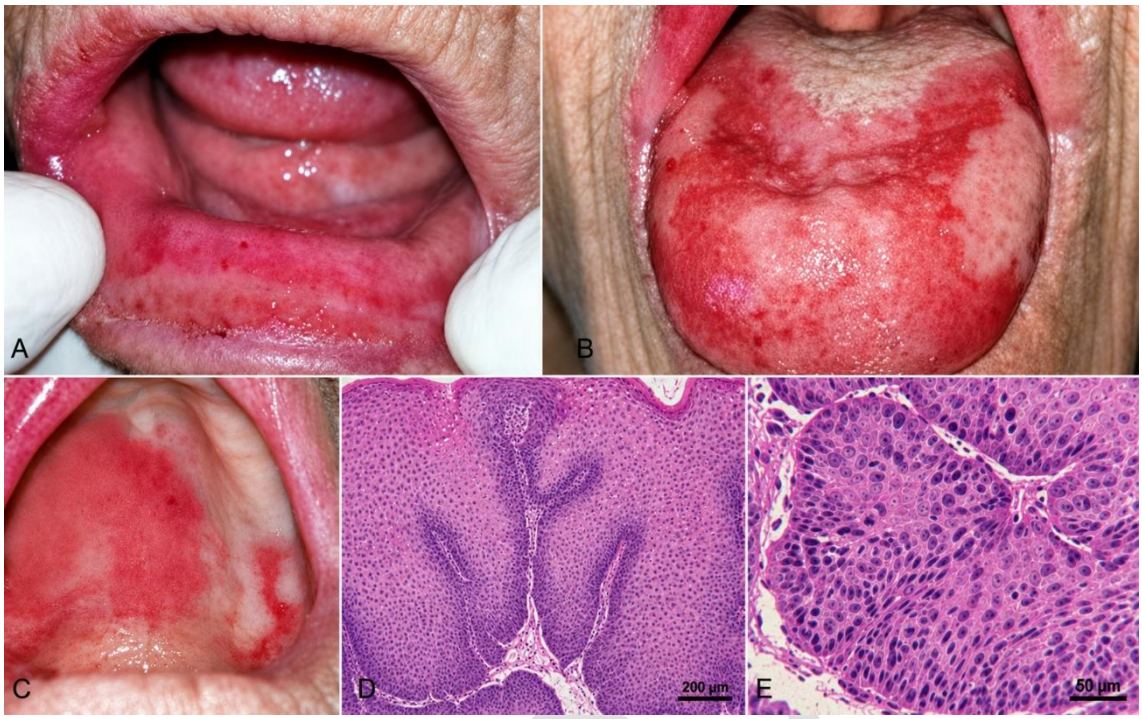
The identification of areas of the oral mucosa prone to cancer development is based on the detection of molecular patterns within regions that are genetically altered, even when they appear clinically and histologically normal. These areas are referred to as peritumoral cancer fields[10]. Although FC can affect clinically healthy-appearing mucosa[11], some authors have proposed clinical patterns that may be associated with this phenomenon, most often adjacent to OPMDs. Among the OPMDs, proliferative verrucous leukoplakia (PVL) and OLP are considered to have a stronger association with FC-related processes. Similarly, lesions that demonstrate dynamic clinical behavior during follow-up—such as multicentric patterns in patients with OLP or PVL exhibiting a lichenoid morphology—have also been associated with FC, albeit with some controversy[12,13].

To the best of our knowledge, the presence of FC in SLE has not been reported in the literature to date. This study aims to present a clinical case of a patient with SLE who developed dysplastic lesions of the oral mucosa during follow-up, which were refractory to treatment and showed an unusual progression to OSCC and verrucous carcinoma (VC). The patient subsequently demonstrated a satisfactory response to oncologic treatment.

CASE PRESENTATION

A 77-year-old female patient presented in 2017 with multiple painful oral lesions of two years' duration. She also had cutaneous lesions diagnosed as psoriasiform lupus and SLE, treated with azathioprine 50 mg, affecting the trunk and upper and lower extremities. There were no other relevant pathological or family history findings. The patient was a non-smoker and did not consume alcohol.

According to the medical history, during 2017 and 2018, the patient was followed by a healthcare service due to multiple erosive and erythroplasic lesions on both buccal mucosae, lower labial mucosa, palate, and tongue. These lesions partially responded to treatment with corticosteroids and immunosuppressants (Tacrolimus 0.1% ointment, Betamethasone 0.05%, Hydrocortisone 0.05% cream combined with Mupirocin for perioral lesions). The patient experienced alternating periods of intense oral burning and symptom-free intervals. After two years of follow-up with intermittent symptoms, she was referred to our service, where an extensive erythroplasic velvet-like area with burning sensation was observed, and a biopsy was performed. The specimen demonstrated squamous stratified epithelium that exhibits acanthosis with pleomorphic cells along all epithelial layers with intense cellular atypia and nuclear pleomorphisms, increased nucleoli and hyperchromatism confirming a diagnosis of a severe epithelial dysplasia (Figure 1).



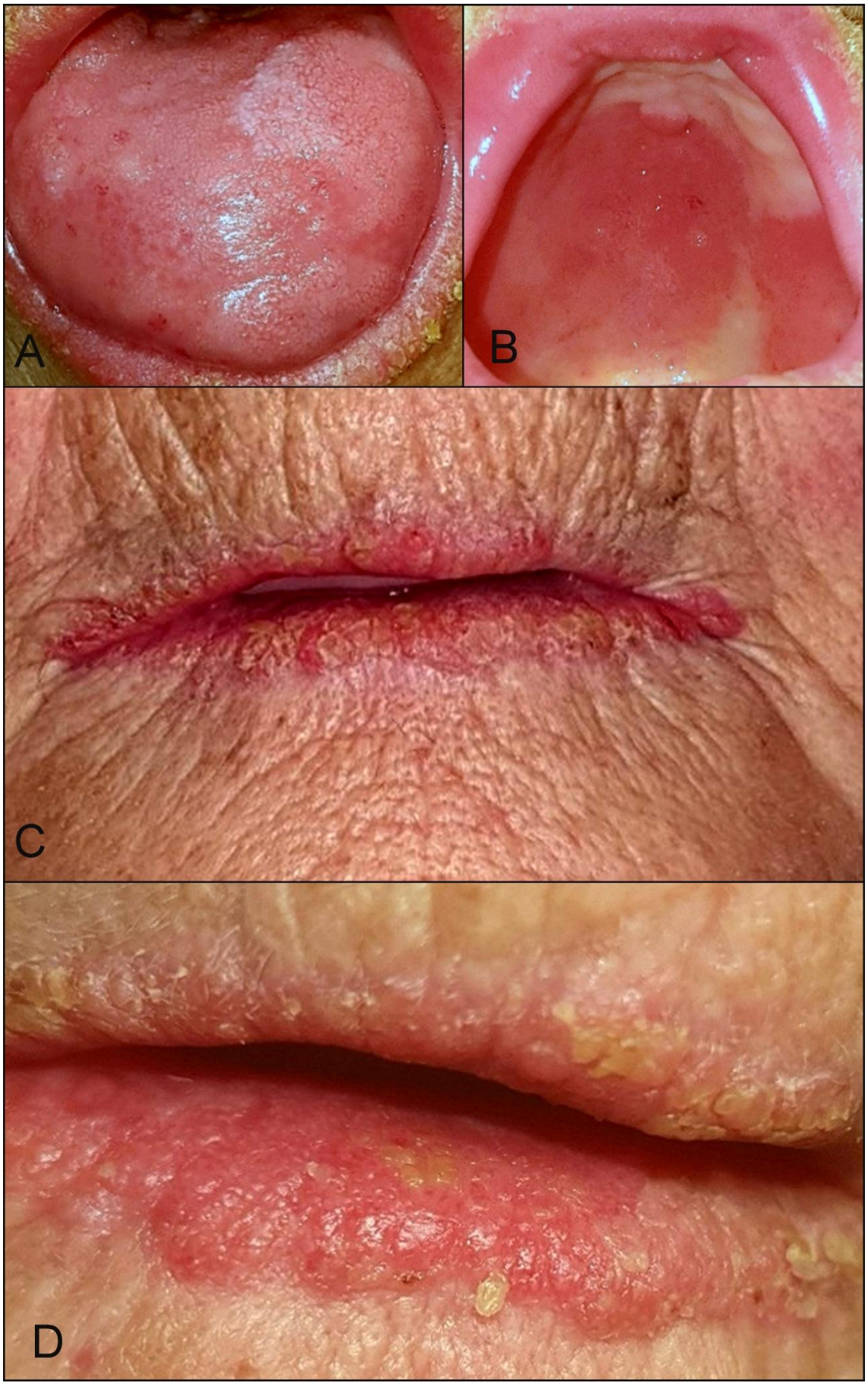
(A) Superficial erosion of the upper labial mucosa causing burning sensation and discomfort. (B) Erosive lesions on the lateral borders and dorsum of the tongue, showing depapillated areas with significant symptomatology. All lesions were refractory to topical antifungal and immunosuppressive therapy. (C) Red, velvety-mate erythroplakia-like lesion on the palate with a papillary and non-regular surface. (D–E) Histological sections showing stratified squamous epithelium with marked acanthosis and epithelial dysplasia involving all epithelial layers.

Due to the COVID-19 pandemic, the patient did not return for follow-up.

In 2021, the patient returned with multiple painful oral lesions and intense sialorrhea. Additionally, she showed poor general condition with weight loss, asthenia, chronic fatigue, exacerbation of cutaneous lesions due to discontinuation of SLE medication and limited mouth opening because of severe fibrosis in the perioral area, which hindered oral examination.

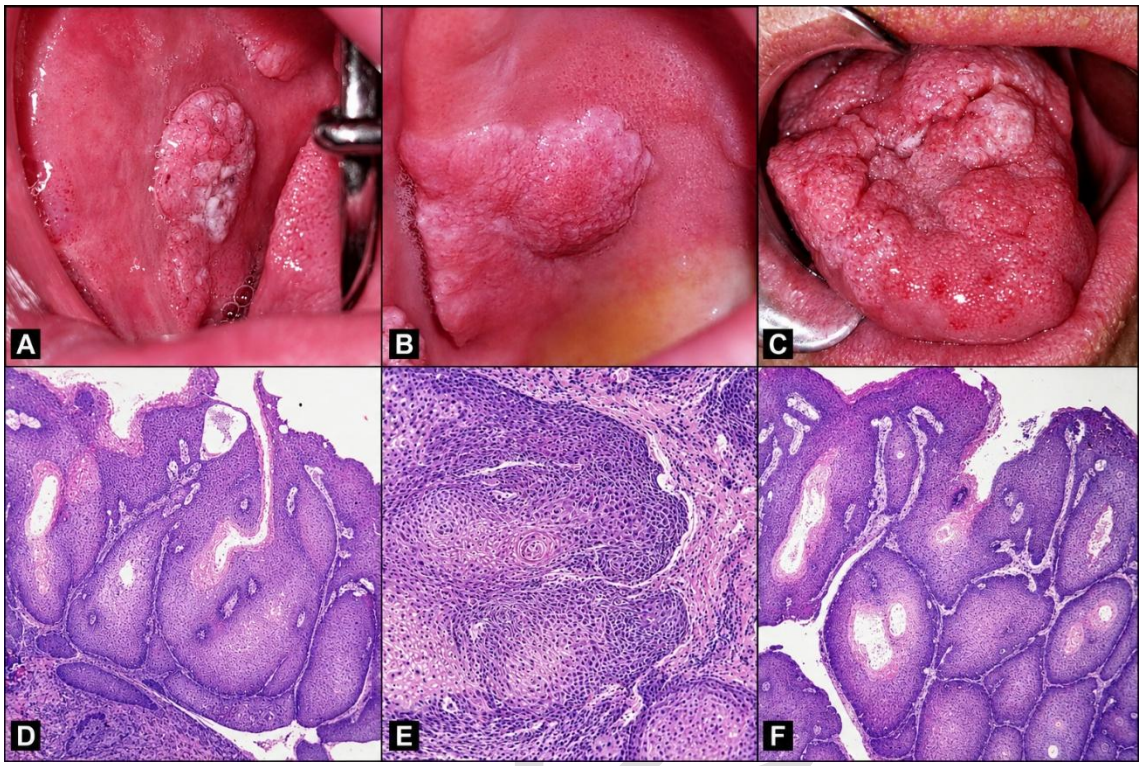
Multiple papillary lesions, some whitish, were observed throughout the oral cavity, along with scaly and crusted lesions on both lips resembling cheilocandidiasis, although there was no response to antifungal treatment (local and systemic ketoconazole and fluconazole). Laboratory tests revealed hypochromic anemia (3,200,000 RBC), 5300 WBC, erythrocyte sedimentation

rate of 45 mm, positive C-reactive protein, and positive antinuclear antibodies (ANA) with a fine granular nuclear pattern at a titer of 1:160. The patient was referred again to her rheumatologist, and new diagnostic biopsies were recommended, but she refused all further medical consultations (Figu


A
B
C
D

(A) The ulcers and erosions on the dorsal surface of the tongue shown in Figure 1 evolved into whitish papillary-like lesions. (B) The erythroplakic lesion on the palate progressively expanded, showing a slow but progressive spread. (C–D) On the labial vermilion, multiple irregular crusts and scales with a desiccated appearance and spontaneous pain were observed. A papillary or micropapillary clinical pattern of the lesions was also evident. At this stage, the patient declined to undergo biopsy.

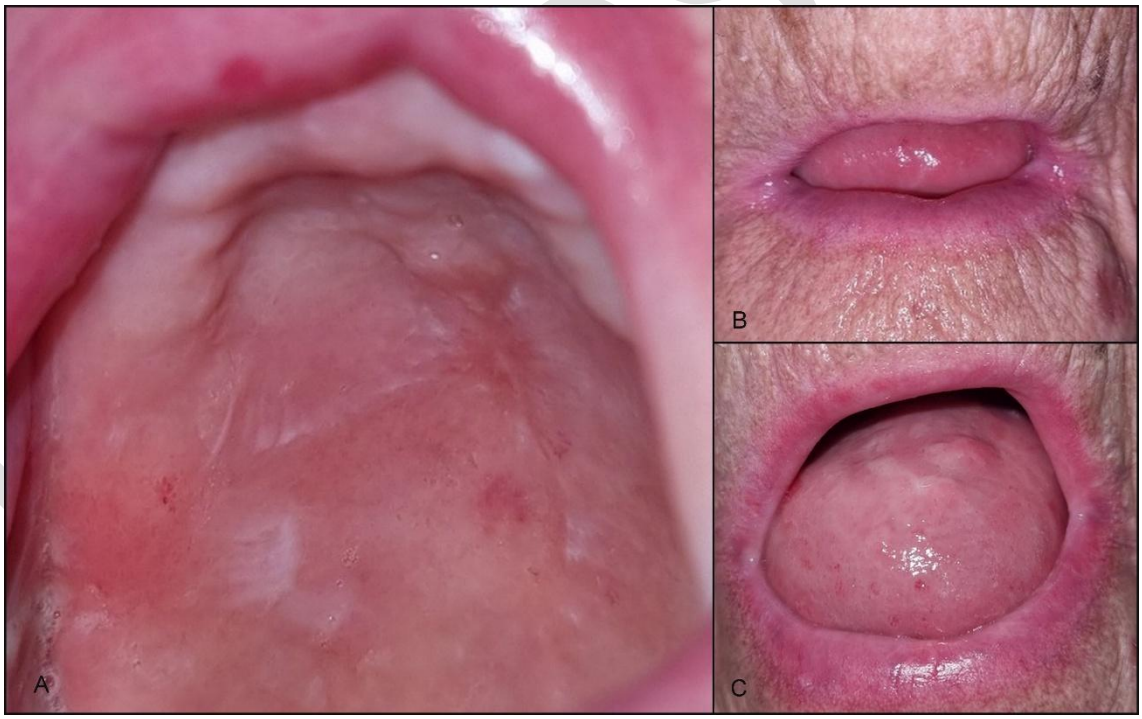
In February 2024, the patient presented again with multiple painful tumoral lesions. Clinical inspection revealed three synchronous papillary, slightly indurated tumoral lesions. Multiple biopsies were immediately performed, confirming two verrucous carcinomas located on the buccal mucosa and tongue, microscopically characterized by a well-differentiated squamous epithelium, without prominent dysplasia displaying a prominent exophytic and papillomatous component without connective tissue invasion and one well-differentiated squamous cell carcinoma on the palate, showing microscopically pleomorphic epithelial cells with atypia and nuclear pleomorphisms infiltrating the connective tissue (Figure 3).



(A) Nodular and tumoral lesion with an irregular surface, showing verrucous areas and a sessile base, surrounded by a red erythroplakic zone and superficial foci of hyperkeratosis. The lesion involved the posterior region of the buccal mucosa. (B) Verrucous tumor extending over the hard palate and the residual ridge of the right maxilla, broad in surface extension. Note the papillary or micropapillary surface pattern, similar to the other two synchronous tumors. (C) Tumor with a papillary surface and verrucous areas occupying the entire dorsal surface of the tongue; at the periphery, discrete but extensive papillary tumoral elevations were evidenced, all painful upon palpation. The three lesions were firm to palpation but showed limited induration. The lower panels show the corresponding histological images for each case. (D) Verrucous carcinoma demonstrating a well-differentiated exophytic lesion with well-defined pushing borders extending below the level of the adjacent epithelium. (E) Well-differentiated oral squamous cell carcinoma showing islands of pleomorphic epithelial cells infiltrating the connective tissue. (F) Verrucous carcinoma with a well-differentiated epithelium, displaying a prominent exophytic and papillomatous component without connective tissue invasion.

The patient was referred to the head and neck oncology committee for management.

Fractionated radiotherapy was administered with a daily tumor dose of 2.75 Gy, totaling 55 Gy. Additionally, peritumoral margins were irradiated with lower doses (daily 2.4 Gy; total 48 Gy) over one month of treatment. At a two-month follow-up after completing radiotherapy, the patient exhibited moderate mucositis, intense xerostomia, and complete resolution of the tumoral lesions. Leukoplakia-like lesions, possibly residual, were observed on the palate. Complete resolution of the previously observed scaly and crusted lesions on the semilabial mucosa was also noted. The patient is being monitored every three months, with one and a half years of follow-up and no evidence of recurrence or relapse (Figure 4).



Radiotherapy treatment showing complete resolution of the lesions and decent clinical outcome. (A) At the site of the former verrucous lesion, a faint whitish area can be identified. (B) The lip, previously affected by scaly and crusted lesions, appears free of lesions, with only mild post-radiotherapy dermatitis—suggesting that the previous alterations were likely dysplastic in origin. (C) Dorsal surface of the tongue showing excellent healing and complete remission of the tumoral and peripheral papillary lesions.

Figure 5 illustrates the clinical timeline of disease evolution over a nine-year period, including the onset of oral lesions, diagnostic procedures, histopathological findings, therapeutic interventions, development of synchronous oral carcinomas, radiotherapy treatment, and clinical outcome during follow-up.

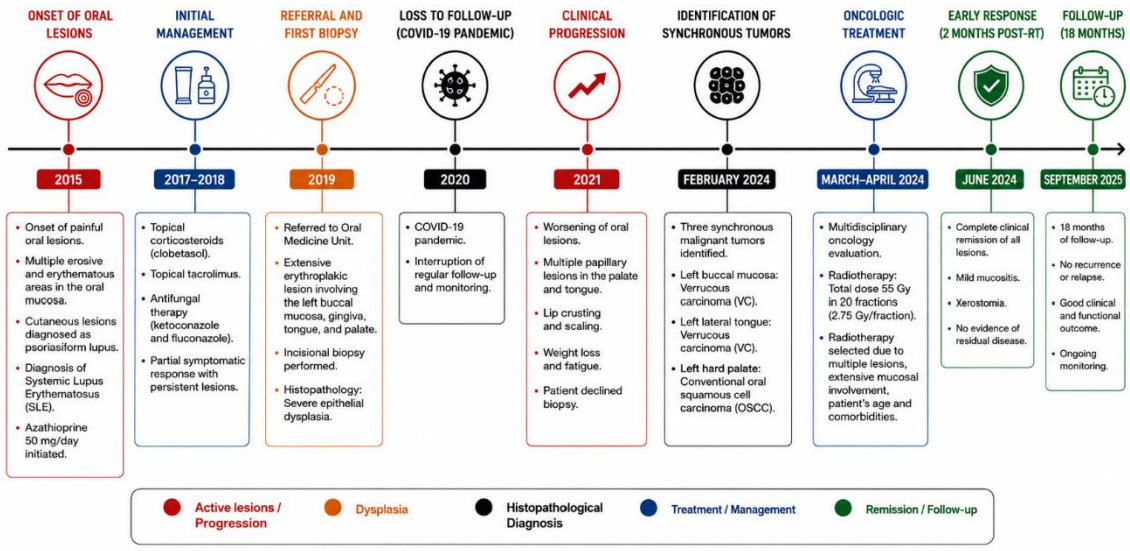


Figure 5. Clinical timeline summarizing disease evolution from the onset of oral symptoms to the final oncologic outcome. The timeline illustrates the progression of oral lesions, diagnostic procedures, histopathological findings, therapeutic interventions, development of three synchronous oral carcinomas, radiotherapy treatment, and clinical follow-up. Color coding was used to facilitate interpretation: red indicates active lesions and disease progression; orange, epithelial dysplasia; black, histopathological diagnosis; blue, therapeutic interventions; and green, remission and follow-up status. VC = verrucous carcinoma; OSCC = oral squamous cell carcinoma; RT = radiotherapy.

DISCUSSION

The development of OSCC in patients with SLE has led to the consideration of this entity as a possible OPMD[6]. The available literature is limited and somewhat controversial, making it difficult to find cohort studies of SLE patients who develop OSCC lesions during follow-up[3]. This clinical scenario is truly uncommon for several reasons. First, because the patient, despite lacking

classical risk factors, developed three synchronous carcinomas with different histological subtypes (conventional OSCC and VC), after a previous history of multiple lesions that were refractory to treatment and difficult to diagnose. The long-term follow-up of these lesions, together with the lack of timely interventions—mainly due to their extensive involvement of large areas of the oral mucosa and the patient's poor adherence to the proposed treatment—led to multiple malignant transformation events, a phenomenon that could represent the FC.

Moreover, this case presents a series of significant clinical challenges. The seven-year progression of the oral lesions—from erosive and erythroplakic manifestations to the development of VC and OSCC—highlights the complexity of managing FC in a context of chronic immunosuppression and associated comorbidities. Due to the absence of serial biopsies from the early stages, it was difficult to determine whether these lesions could have been related to the patient's underlying comorbidity. Lupus-related oral lesions have been reported to display various clinical patterns. Among the most frequent, reticular-like lesions stand out, which are clinically difficult to differentiate from oral lichen planus. The most common oral manifestations include painful ulcers, erythematous areas, keratotic plaques, and purplish lesions that may affect the lips, buccal mucosa, palate, and tongue[8]. These are usually described as well-defined erythematous or erosive areas with central white papules surrounded by radiating white striae. Such lesions are not only relevant for disease diagnosis but also have a significant impact on patients' quality of life, interfering with eating and speech[3,8]. Early identification of these lesions is essential, as they may represent one of the first clinical signs of SLE. Although standardized criteria for classifying oral lesions in SLE do not exist, the presence of oral ulcers—together with other systemic manifestations—is included among the diagnostic criteria for the disease.

We believe that the lack of clinical response to the therapeutic approach used at that time (antifungal agents and topical immunosuppressants) may also be associated with the presence of multiple epithelial dysplasia fields within the oral mucosa, which over time eventually developed into multifocal carcinomas. One possible explanation for the persistent and treatment-refractory behaviour of

the lesions is that part of the clinically affected mucosa may have already harboured genetically altered epithelial clones. Such alterations could remain clinically active despite therapies directed primarily toward inflammatory or infectious conditions (candidosis). Although this hypothesis cannot be confirmed in the present case, the subsequent development of multifocal carcinomas within previously affected mucosal areas raises the possibility that widespread epithelial instability was already present during earlier stages of disease evolution. This scenario poses not only a diagnostic challenge but also a therapeutic one, since it involves extensive areas of the oral mucosa, making conventional surgical resections—typically indicated for more localized OPMD cases—difficult to perform.

FC describes the genetic alterations that occur in the oral mucosa with a multicentric pattern, which are often found adjacent to the tumor site. This phenomenon explains the development of synchronous OSCCs, disease recurrence, and the emergence of new secondary primary tumors[14]. The different theories addressing FC in OSCC suggest that areas adjacent to clinically normal mucosa are also exposed to mutagens, facilitating the development of abnormal genetic alterations. The main molecular changes considered hallmarks of FC include mutations in oncogenes and tumor suppressor genes, loss of heterozygosity, and genomic instability. These genetically altered cells acquire the ability to develop and expand the neoplastic field. Normal mucosal cells are replaced by mutated precancerous cells carrying preneoplastic genetic signatures, rendering the epithelia more susceptible to additional genetic or epigenetic insults. Eventually, this process may lead to the development of local recurrences or the emergence of new secondary primary tumors[15]. In our case, it was evidenced that in oral mucosa showing histological evidence of previous epithelial dysplasia—but with a clinical phenotype difficult to classify within the already described OPMDs—multiple squamous cell carcinomas and their verrucous histological variants developed. These lesions arose not only in areas where previous lesions had been present, but also in regions of clinically normal mucosa that exhibited evident molecular alterations (for example, the buccal mucosa). Another noteworthy finding is that FC, as previously described, is a phenomenon associated with the multifocal action of a mutagenic or carcinogenic

agent or a combination of both, such as tobacco and alcohol, which are the most frequently studied[16]. In the present case, however, the patient did not present any of the classical risk factors for OSCC, the chronic systemic inflammation associated with SLE or the immunosuppression resulting from its treatment could have contributed to the oral carcinogenesis. Although molecular confirmation was not available in the present case, the coexistence of severe multifocal epithelial dysplasia, extensive multicentric oral lesions persisting over several years, and three synchronous carcinomas arising in distinct anatomical sites constitutes a clinicopathological pattern highly suggestive of a FC. Importantly, the concept of FC was originally proposed to explain the occurrence of multicentric tumors and second primary neoplasms based on clinical and histopathological observations, whereas molecular markers were incorporated later to further characterize the biological basis of these alterations. Recent evidence suggests that chronic inflammation, immune dysregulation, and autoimmune diseases may contribute to field effects independent of traditional carcinogenic exposures such as tobacco and alcohol[16,17]. Given the patient's longstanding systemic lupus erythematosus, chronic oral inflammatory lesions, absence of conventional risk factors, and multifocal malignant transformation, an immune-mediated field effect represents a biologically plausible explanation for the observed clinical evolution. Nevertheless, in the absence of molecular analyses, field cancerization should be interpreted as a strongly supported clinicopathological hypothesis rather than a molecularly confirmed diagnosis.

In this regard, it is interesting to consider that OSCC associated with OPMD, also known as sequential OSCC, may develop in the context of FC within extensive or multifocal OPMDs, such as oral submucous fibrosis, proliferative verrucous leukoplakia, or oral lichen planus[1,18]. Although evidence of FC has been demonstrated in clinically normal oral mucosa, studies addressing this phenomenon in OPMDs remain limited[10]. Bagan et al. proposed that proliferative verrucous leukoplakia, considered one of the OPMDs with the highest rate of malignant transformation, could be regarded as an entity that represents the essential features of FC, given its ability to develop OSCC at multiple foci following a multicentric pattern[19,19]. Interestingly, in our clinical case, the manifestation of extensive multifocal and multicentric erythematous plaques with

dysplastic histology could correspond to the FC phenomenon described above. However, a limitation of this report is the absence of histopathological diagnosis during the first years of patient follow-up, when the oral lesions were empirically treated as SLE. One of the main diagnostic challenges of this case lies in the lesions that preceded the onset of malignant tumors, which showed, upon histopathological examination, a papillary epithelial configuration with epithelial dysplasia. Nevertheless, from a clinical standpoint, these lesions would not fulfill any of the diagnostic criteria for OPMD according to the latest WHO 2020 consensus.

The presence of multiple and multifocal red plaques with a micropapillary surface pattern represented an unusual clinical presentation within the spectrum of OPMD. In this regard, Villa et al. included erythematous, erythroplakic, and atrophic areas among the diagnostic criteria for proliferative verrucous leukoplakia, highlighting their association with an increased risk of malignant transformation and OSCC development[20]. However, in the present case, during seven years of evolution, no white lesions compatible with PVL were detected. Interestingly, during post-radiotherapy follow-up, whitish areas resembling the early stages of PVL were noted on the palate.

Another important aspect to highlight is that the previously biopsied lesion did not show the typical histopathological features of SLE (such as the presence of a mixed juxtaepithelial and perivascular inflammatory infiltrate and areas of acanthosis in the surface epithelium)[8]. Therefore, we cannot affirm that the oral lesions were typical of this entity, even though the patient had this underlying comorbidity. This is a relevant point, as cases of malignant transformation of SLE-related oral lesions reported in the literature rarely specify whether the malignant change occurred within typical lupus lesions or whether it was associated with the development of another well-known OPMD in a patient with SLE. This also raises the question of whether the malignant transformation was related to SLE per se, or rather to dysplastic processes linked to long-term immunosuppression resulting from treatment[3]. A noteworthy clinical feature was the presence of scaly-crusted lesions on the lips and commissures, which were initially treated as cheilocandidiasis associated with SLE without improvement, but showed complete remission—similar to the peritumoral red areas—after radiotherapy.

This finding suggests that these lesions may have harbored similar molecular alterations, reflecting an extensive FC phenomenon. Therefore, in the context of FC and multiple synchronous OSCCs, the presence of reddish labial lesions with scaling and crusting that do not respond to local therapy should be considered a warning sign. In line with previous reports, such labial lesions could be associated with the higher incidence of lip carcinoma usally reported in SLE[21].

FC in the context of SLE raises critical questions regarding the role of chronic medication-associated immunosuppression, persistent inflammation, and the inherent immunological alterations of the disease as potential factors in the initiation and progression of OPMD or malignancies[22]. However, based on this single case report, it is impossible to ascertain whether the development of multiple synchronous OSCCs was directly related to the underlying disease or to the prescribed medication. The discontinuation of medication and the exacerbation of cutaneous lesions, together with anemia and elevated C-reactive protein levels, indicate a state of systemic inflammation and possible immune dysfunction that may have contributed to tumor progression.

Oral lesions in patients with SLE can mimic a variety of conditions, including oral lichen planus, pemphigus vulgaris, and candidiasis[4,8]. The presence of scaly and crusted lesions on the lips, initially interpreted as cheilocandidiasis, highlights the need for a thorough diagnostic approach and the consideration of multiple etiologies. Therefore, performing serial biopsies during the follow-up of these patients is crucial to enable the early identification of dysplastic changes and to establish an accurate diagnosis. The clinical management of such cases requires close collaboration among rheumatologists, oral medicine specialists, oncologists, radiotherapists, and oral pathologists in order to establish and discuss therapeutic options and to develop an individualized treatment plan.

Surgical resection remains the treatment of choice for both VC and OSCC, with the strongest evidence supporting its use as a curative modality[23]. Nevertheless, alternative approaches such as radiotherapy or chemoradiotherapy may be considered in selected patients, particularly when tumors are extensive, multifocal, technically difficult to resect, or when surgery would result in unacceptable morbidity or is contraindicated due to the patient's

clinical condition. In the present case, the multidisciplinary head and neck oncology board—including maxillofacial surgeons, radiation oncologists, medical oncologists, oral medicine specialists, and pathologists—carefully evaluated the presence of three synchronous malignant lesions involving distinct anatomical sites, extensive multifocal mucosal involvement, severe perioral fibrosis with limited mouth opening, advanced patient age, and the significant functional and aesthetic morbidity anticipated from multiple extensive surgical procedures. Considering these factors, definitive radiotherapy was selected as the most appropriate therapeutic strategy, aiming to achieve comprehensive disease control while preserving oral function and minimizing treatment-related morbidity. Notably, radiotherapy resulted in complete clinical remission of all three carcinomas and was also associated with the disappearance of previously documented dysplastic areas of the oral mucosa. Two months after completion of radiotherapy, the patient presented with only mild oral mucositis and showed an excellent clinical response, characterized by complete remission of all three carcinomas and resolution of the previously documented dysplastic mucosal alterations. Clinicians should maintain a high index of suspicion for FC and carefully monitor patients with VC who exhibit concomitant OPMD, given their increased risk for multifocal malignant transformation and the development of synchronous or metachronous carcinomas.

Conclusion

This case allowed the identification of FC phenomena and the development of multiple OSCCs in a patient with SLE, a disease considered an OPMD according to the WHO. Patients who develop FC represent diagnostic and therapeutic challenges. The publication of this case may contribute to scientific knowledge and improve the care of patients with similar presentations in the future.

Artificial Intelligence Disclosure

The timeline presented in Figure 5 was generated using OpenAI ChatGPT (GPT-5) and its integrated image-generation tools. The authors designed, supervised, reviewed, and edited all scientific content included in the figure and take full

responsibility for its accuracy and interpretation. The image was used exclusively as a graphical aid to summarize clinical information already described in the manuscript and does not constitute primary research data.

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AUTHORS' CONTRIBUTIONS

GG, FG. Conceptualization

GG, RP, BABA. Data Curation

GG, FG, PB, BABA Formal Analysis

GG, FG, PB Methodology

GG, RP Resources

PB, RP, BABA Supervision

PB Visualization

GG, PB, FG Writing – Original Draft Preparation

GG, RP, BABA Writing – Review & Editing

CONFLICT OF INTEREST STATEMENT

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Ethics approval:

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