Tongue squamous cell carcinoma and oral lichen planus: a rare case report of a pregnant woman

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Key Clinical Message

Squamous Cell Carcinoma (SCC) of oral mucosa is increasingly affecting younger individuals, particularly in the tongue. SCC can develop from disorders like Oral Lichen Planus (OLP). This case highlights the first known instance of OLP and SCC in a pregnant woman, suggesting hormonal changes and HPV as possible risk factors.

Keywords :

Oral Lichen Planus; Squamous Cells Carcinoma; Pregnant Woman; Precancerous Condition; Tongue Neoplasms.

Introduction

Squamous cell carcinomas (SCC) represent more than 90% of the upper aerodigestive tract cancers and can affect the mucosa of the oral cavity, pharynx and larynx. Worldwide, they represent the 8^{th} most common cancer and even rank 2^{nd} when the risk factors tobacco and alcohol are simultaneously present [1]. It has been reported that these cancers are 15 times more frequent when tobacco and alcohol are consumed

synergistically [2]. Indeed, the alcohol-smoking patient, in his 6^{th} decade of age with a low socio-economic lifestyle, is considered to be the most frequent patient profile of SCC in the upper aerodigestive tract, and more specifically the oral SCC [1]. However, recently, two other population profiles are emerging for the oral SCC, with an increasing trend in elderly women, possibly linked with denture trauma and toxic exposure [3] and a tendency of increasing tongue cancers in young white women [4] [5]. While HPV infection was associated with the increasing incidence of oropharyngeal cancers in nonsmoker young patients, no evident association with oral and tongue cancer in young women has been found. Tobacco and alcohol consumption seem to have a limited link with these two patient profiles [6] [3]. Other risk factors, such as cannabis consumption, environmental factors, dietary factors, body mass index, dental hygiene, immunosuppression, genetic and familial factors, viral infection, and co-morbidities have been suggested [7]. Some inflammatory diseases and potentially malignant disorders are also likely to degenerate and may be linked to the increased incidence of SCC. Among these, lichen planus is reported.

Lichen planus (LP) is a chronic muco-cutaneous inflammatory disease which can affect the skin and appendages, but more frequently the mucosal membranes and more specifically the oral mucosa. Oral lichen planus (OLP) affects 1 to 2% of the population with a slightly higher prevalence in women (60 to 65%) [8] [9]. The average age of onset is between 30 and 60 years of age. Clinical and histological diagnosis criteria of OLP has been well defined and updated in a recent report published by a group of experts in a workshop organized by the collaborating center of the World Health Organization (WHO) for oral cancer in the UK. These criteria, mainly based on clinical characteristics, are summarized in table 1 [10].

OLP is often discovered during a routine consultation and progresses in flare-ups, with phases of remission and exacerbation. The lesion is preferentially located on the cheek mucosa and at the lower vestibular side, but is also detected on the dorsal surface and lateral edges of the tongue, as well as on the attached gingiva [11]. After several years of evolution, OLP is characterized by mucosal atrophy and fibrosis. The physiopathology of OLP is still not elucidated and relies on immunological hypotheses, and may be associated with some autoimmune pathologies like chronic hepatitis, myasthenia gravis, ulcerative colitis [11].

Since several clinical studies have shown that OLP has an increased risk of malignant transformation, the WHO has classified this entity among "Oral Potentially Malignant Disorders" [10]. Potentially malignant lesions are a morphological alteration of the tissue in which cancer has a greater chance of occurring than in tissue without apparent modification [12]. Even though the incidence and the risk of OLP to evolve into cancer has been widely discussed, controversies exist between authors [13] [14] [15]. The difficulty is to understand whether OLP has an intrinsic potential for malignant transformation and whether this is accentuated by other factors.

Although rare, some cases of tongue cancer in pregnant women have been previously reported, but not arising from a potentially malignant disorder : [16] [17] [18]. Among signaling pathways involved in tumor development, pregnancy induces physiological changes that may promote neoplastic growth, such as changes in vascular networks, elevated metabolism, increased circulating growth factors, and hormonal responses, which may be amplified mediated by estrogen and progesterone receptors [19].

Hereafter, we report a rare case of a young pregnant patient presenting a tongue SCC diagnosed concomitantly with an OLP.

Case History/Examination

We report the case of a 36-year-old healthy patient, with no history of alcohol or tobacco consumption, married and a housewife. She originated from North Africa and came two years earlier to France with her husband. At the time of medical check consultation, the patient was a primiparous pregnant woman with 32 weeks of amenorrhea. She consulted the dentistry emergency department of Montreuil hospital in July 2012 for "discomfort on the tongue and pain in the last two months". The patient noticed the appearance of "white spots" on her tongue for several months, following the development of "a mass" associated with pain and discomfort.

Palpation of the cervical lymph-node zone reveals submandibular and right cervical lymphadenopathy. Intraoral examination showed an ulcerative lesion around 2cm-wide, with everted irregular borders (Figure 1A). The lesion was located at the middle third of the tongue, on the right lateral border. Palpation revealed bleeding on contact and sublesional induration. The examination of the whole oral mucosa surface showed the presence of reticulated lichen planus on the inner surface of the cheek and on the lateral edges of the tongue with streaks in white to opaline networks (Figure 1B and 1C)

Differential diagnosis, investigations and treatment

The clinical aspect of the lesions guided the diagnosis toward a squamous cell carcinoma on oral lichen planus, despite the young age of the patient and the absence of tobacco and alcohol history. What was surprising was the concomitance of pregnancy with the appearance of this tongue lesion. Biopsies were performed on three different areas of the lesion and the anatomopathological result was requested urgently. It was obtained after 48 hours and confirmed the SCC diagnosis.

A complete local and general radiological examination was carried out to explore the tumor lesion and its extension. A CT scan and Magnetic Resonance Imaging (MRI) of the tongue and the cervicothoracic region showed the absence of local extension of the tumor and the presence of bilateral submandibular adenomegaly of inflammatory type.

The Multidisciplinary Consultation Meeting, with the participation of gynecologists, decided to induce delivery at 35 weeks of amenorrhea before treating the cancer. Our patient gave birth to a girl through a cesarean procedure. The baby weighed 2,400 gr, her Apgar score was 10 and pH equal to 7,4.

The Positron Emission Tomography (PET scan), performed just after the early-induced delivery, showed an intense focal hyper uptake at the right lateral edge of the tongue with hypermetabolic lymph-node formation at the right subdigastric level.

The surgical decision was to perform a right lateral partial glossectomy, associated with a right lymph node dissection - according to the PET scan results - two weeks after delivery. The anatomopathological examination of the partial glossectomy specimen showed a well-differentiated infiltrating squamous cell carcinoma measuring 2 cm in long axis, with the presence of perineural sheaths and a few lymphatic emboli (Figure 2). No lymph-node metastasis was found after right lymph-node dissection. Human papillomavirus (HPV) infection was investigated by immunostaining with the P16 protein and was negative, but PCR was not done to confirm the presence of the viral DNA. The tumor was classified: T1N0M0. The post-surgery healing was favorable.

Outcome and follow-up

Patient follow-up is favorable, at 18 months, the patient showed no recurrence and new erosive lesions appeared on the left lateral border of the tongue, but the biopsy did not show epithelial dysplasia (Figure 3A and 3B). At 6 years, a new biopsy concluded that there was no malignancy. The last follow-up appointment in February 2021 indicates that the clinical examination of the mucosa and lymph nodes is completely satisfactory.

The reported case shows that pregnant women may have tongue SCC, even if rarely, can be associated with a potentially malignant lesion such as OLP. The hypothesis of disruption of the patient's immune system, linked to her pregnancy or a possible activation of oncogenic viruses, could explain the transformation of OLP into SCC, but more investigation for proving association with hormonal modification during pregnancy is needed. It is important to focus on early detection and early intervention for pregnant women with a regular oral examination, especially of the tongue, to detect early signs of cancer. All areas of suspected oral inflammatory mucosa or potentially malignant lesions OLP-like should be biopsied and monitored with regularity to exclude malignancy. The practitioner must inform the patient of the potential risk of transformation of the OLP.

Discussion

The aim of reporting this case was mainly to discuss the possible links between malignant transformation to oral SCC in physiological conditions such as pregnancy, in order to better understand the physiopathology underlying this transformation, especially in a potentially malignant condition like OLP, diagnosed concomitantly to the oral cancer. It is interesting to notice that, although similar cases are still rare, an increasing tendency of tongue cancer's incidence has been described in recent years in young women [20].

Indeed, oral cancers, especially SCC, are usually diagnosed in older men with heavy tobacco and alcohol consumption. However, it is interesting to note that recently, the frequency of oral cancer affecting young people has increased, particularly in young women between 18 and 44 years of age [18]. Several epidemiological studies, such as that of Murphy et al, noticed in 2016 a 60% increase in tongue cancers in patients under the age of 40 when comparing cohorts from 1973 to 1984 and from 1985 to 1997 [19]. Deneuve and al. confirmed in their study published in 2021 a significant increase of the incidence of tongue cancer in women aged 30 and 40 in France from 1990 to 2018 [4]. The incidence of tongue cancer also increased significantly in the United States between 2001 and 2019, more particularly in women under 50 years old according to Burus et al, 2024 [5]. In addition, It is important to emphasize that the age of first pregnancy is increasing and the age at which cancers occur is decreasing. Taking into account these two parameters, it is therefore likely that the incidence of malignant tumors during pregnancy will increase in the coming years [22].

Tobacco and alcohol consumption are known to be associated with oral cancer, but not in young patients. Other risk factors are also being studied, such as viral infections, particularly human papillomavirus, oral traumatism, oncogenic factors and genetic predisposition [17]. Some pathological or physiological conditions can accelerate the malignant transformation of oral lesions, among which inflammatory diseases and pregnancy are the most studied [23].

Indeed, cancer may occur approximately in 1 out of 1,000 pregnancies. The most frequent cancer types encountered during pregnancy are breast cancers (46%) and hematological cancers (18%) [17]. With lower frequency, cervix, ovary, brain cancers and melanomas may be associated with pregnancy. Oral cancers are rare and occur in only 2% of pregnancy cancer cases [18] with 65% of diagnoses made after the first trimester of pregnancy and an average mortality rate of 36 % [17] [24].

Concerning OLP, it has been classified as an Oral Potentially Malignant Disorder (OPMD) by the WHO experts. The term "potentially malignant" has been introduced in 2007 [12] because "precancerous" implies that the malignant transformation is the most likely evolution of all these lesions, which is often not the case. Since 2020, OPMDs are associated with an increased risk of occurrence of cancers of the lip or oral cavity [10].

The frequency of malignant transformation of OLP differs among authors. It is estimated between 2 to 5%, based on some studies with a follow-up duration of 6 to 10 years [11]. A review of the literature in 2014, screening a large sample of patients (7,806 patients) from 16 retrospective selected studies, showed a frequency of 0 to 3.5% [25]. Another review relying on retrospective studies over a 77-year period, showed a frequency ranging from 0 to 12.5% [26]. A slight female predominance has been noted and the most common site of malignant transformation is the tongue [27] [25]. The most recent meta-analysis was published in 2019 [28] grouped 82 studies with 26,742 patients. It revealed a reported OLP malignant transformation of 1.14% and a statistically significant increased malignant transformation risk for the tongue (RR=1.82). They conclude that the malignant transformation potential of OLPs is probably underestimated in the literature given that most authors consider OLPs, oral lichenoid lesions (OLLs) and lichenoid reactions (LRs) to be low-risk OPMDs.

Patients with lichenoid lesions were also sometimes included in the past in studies evaluating the transformation rate of OLP, as the diagnosis criteria of OLP have progressively changed and became more accurate from 2003 to 2020. The disappearance of the criterion: "absence of epithelial dysplasia" from the past OLP description may also be confusing. Indeed, the experts group recommends not to use the term "oral lichenoid dysplasia" to describe OLP or lichenoid disorders with an epithelial dysplasia. They recommend to describe each entity separately, which may be confusing for cases described before 2020.

The mechanisms underlying the malignant transformation of the OLP give rise to several hypotheses: chronic inflammation is the most discussed. Indeed, inflammation may damage keratinocytes DNA, through a phenomenon of oxidative stress, which may over time result in cancer. The resulting intraepithelial neoplasia may become invasive after several years of alternation between inflammatory and scarring states of OLP [29].

Concerning the described clinical case, this hypothesis does not explain the malignant transformation, as the appearance of OLP, which seems recent or even concomitant with the appearance of the malignant transformation. In addition, the clinical form diagnosed was not atrophic. The latter represent the most likely OLP stage to degenerate with the erosive form. Adding to the concomitancy of OLP diagnosis with SCC, our patient was in a particular physiological state, with a primiparous pregnancy. Changes that occur in the immune system during pregnancy are widely studied and are potentially likely to promote neoplastic growth.

These changes include an increase in progesterone and glucocorticoids. These hormones may affect T cell differentiation, varying the Th1/Th2 balance. T helper type 1 (Th1) cells are mainly involved in cell-mediated immunity (production of pro-inflammatory cytokines) while T helper type 2 (Th2) cells are involved in the stimulation of humoral immunity (production of anti-inflammatory cytokines). These two hormones inhibit the development of Th1 and increase the development of Th2 [30]. Th2 cytokines predominate during pregnancy and would inhibit the proliferation and function of natural killer cells which are important in the immune regulation and suppression of tumors, thus potentially promoting neoplastic growth [23]. Progesterone Induced Blocking Factor (PIBF) therefore reduces inflammatory phenomena (inflammatory cytokines, production of non-cytotoxic antibodies, inhibition of NK) in order to create immune-tolerance between the mother and the fetus to carry the pregnancy at term [31]. However, some authors show that the effect of waning antitumor immunity during pregnancy is slight and does not affect the prognosis [22].

The association of human papillomavirus (HPV) in oral cancer is also well discussed in the literature. Patients concerned are almost younger, with no alcohol-smoking intake, and a trans-suspected sexual transmission with oropharynx preferential localizations. In fact, HPV was found to be associated with approximately 45.6% of SCC of the oropharynx versus 10.5% for oral SCC [32]. The analysis of histological samples of a great cohort of patients confirms these data and found only 2.2% oral SCC positive for HPV DNA and only 7.9% with an immunopositive P16 marking [33]. For OLP, the levels of HPV 16 and 18, were found significantly higher on OLP lesions than on healthy mucosa, and that more specifically in atrophic or erosive OLP forms [34]. However, the tongue, which appears to be the most common site of oral cancers during pregnancy, does not have a propensity for HPV receptors unlike posterior oropharyngeal cancer [18].

Concerning the choice of maintaining the pregnancy or aborting and starting treatment, Mhallem Gziri et al, in 2011, shows in their review including 17 cases of pregnant women with tongue cancer, a wide variation in treatment strategy, illustrating the lack of standardization of treatment when tongue cancers are treated during pregnancy. There are basically two treatment schemes. First, the child may be deliberately aborted or put at risk by major surgery during pregnancy. Second, the patient may compromise by minimizing risk to the fetus but using less than ideal treatment. No treatment modality is entirely free from immediate or delayed risk to the fetus and only the magnitude of the risk is reduced [17].

For cancer treatment, the fetus is exposed to one or more risks linked to surgery and anesthesia in all stages of pregnancy. During the first trimester, teratogenic effects of drugs and spontaneous abortion are the most serious problems. It is possible to end the pregnancy in order to concentrate on cancer treatment depending on the tumor stage. The second trimester is relatively the safest time to perform surgery, but it still carries considerable risk to the fetus. It is more complicated to end a pregnancy, that's why there is a strong possibility at this stage of performing oral cancer treatment while continuing the pregnancy. All along pregnancy, the risk of hypoxemia exists, and in the third trimester, premature term may result from anesthesia and surgery. That is why a cesarean section may be performed after 30 to 34 weeks of gestation, or labor may be induced [22]. It is recommended to consider termination of pregnancy if the tumor is large or metastasized at an early age of pregnancy, thereby complicating fetal and maternal outcomes [18].

The management of pregnant patients with tongue cancer has evolved over time. The review of Murphy et al. [21] identified the treatment procedures described for 32 cases of pregnant women with SCC of the tongue. The authors excluded cases of regional recurrence of SCC of the tongue during pregnancy. Surgery was found to increasingly play an important role in the management of these patients. For this, several criteria have been proposed to maximize the smooth running of these surgeries. Rapid induction is recommended to decrease the risk of miscarriage and deep vein thrombosis. Continuous and strict monitoring of circulation, respiration, maternal and fetal heart rate intraoperatively is recommended. Adequate monitoring to avoid hypotension, hypoglycemia, hypothermia, premature contractions or fetal distress is also necessary. On the surgical side, the procedure must be carried out quickly, taking care to minimize blood loss. Because cell-mediated and humoral immunity are impaired during pregnancy, the risk of postoperative infection is high. Antibiotic therapy is therefore recommended. Sufficient maternal analgesia is important, also to avoid premature contractions. It is important to avoid the use of teratogenic drugs (such as tetracycline antibiotics and phenobarbital). The combination of pregnancy and surgery induces a hypercoagulable state that favors the development of thromboembolism and, therefore, preventive anticoagulant treatment is necessary. Taking care of maternal well-being is the best guarantee to ensure the health of the fetus. [17] [21].

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Author contributions

David Moretti and Ihsene Taihi involved in data collection, literature review, and manuscript writing. Nadia Benlagha involved in clinical data collection and reviewed the manuscript. Joel Cucherousset involved in histopathological data collection and reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of interest

None.

Consent

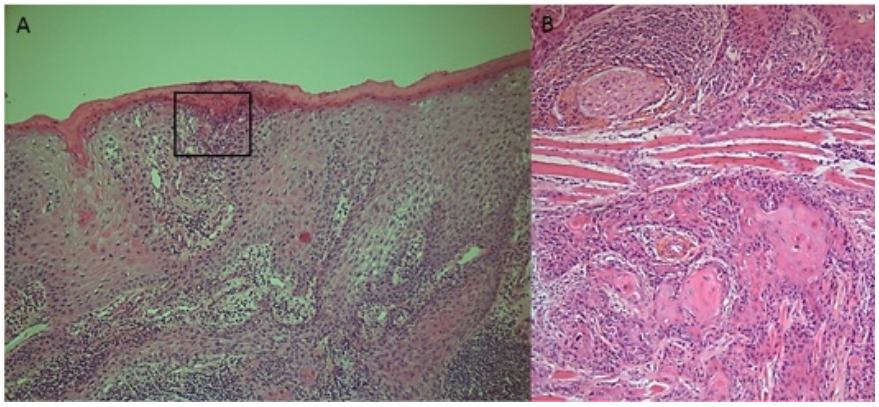
A written informed consent was obtained from the patient to publish this case report in accordance with the journal's patient consent policy.

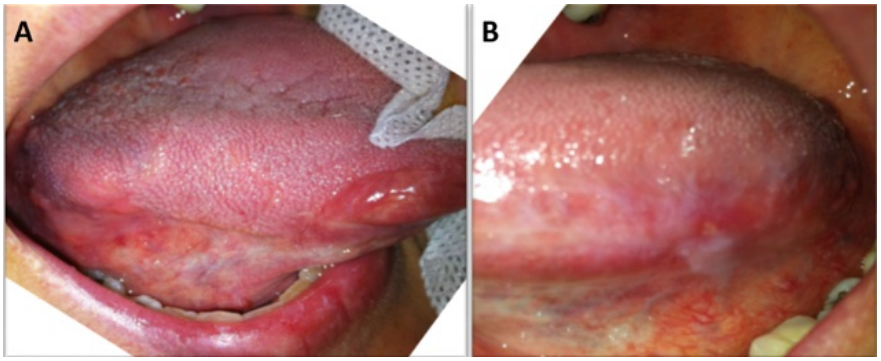
Figure 1. *Clinical examination of the clinical case. (A) Squamous cell carcinoma on the lateral right side of the tongue, with a reticular lichen planus. (B) Reticular lichen planus on the lateral left side of the tongue, with no symptoms. (C) Reticular lichen planus on the cheek mucosa, with no symptoms.*

Figure 2. *Histological examination of the tumor after surgical glossectomy: squamous cell carcinoma differentiated and infiltrant.*

Figure 3. *Follow-up at 18 months after surgery (A) Right side: healing very well and no recurrence. (B) Left side: an erosion appeared on the reticular LPO, biopsy showed no epithelial dysplasia.*

Table 1. Diagnosis criteria of lichen planus in 2024





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