

## Tongue squamous cell carcinoma in a patient with systemic sclerosis: A case report

<sup>1</sup>Fatemeh Bagheri <sup>2</sup>Hamed Mortazavi <sup>\*3</sup>Maryam Baharvand

<sup>1</sup>Postgraduate Student, Dept. of Oral Medicine, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

<sup>2</sup>Associate Professor, Dept. of Oral Medicine, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

<sup>\*3</sup>Associate Professor, Dept. of Oral Medicine, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: marbahar@gmail.com

### Abstract

**Objective:** Systemic sclerosis (SS) is a chronic autoimmune disease of connective tissue, which involves skin and internal organs, and results in collagen deposition and fibroblasts activation. Studies have reported a higher risk of malignancy in patients with progressive systemic sclerosis (PSS). The aim of this study is to report a case of tongue squamous cell carcinoma (SCC) in a patient with PSS.

**Case:** A 46-year-old woman with SS presented to the Department of Oral Medicine of Shahid Beheshti University of Medical Sciences Dental School with chief complaint of an ulcer on her tongue. During intraoral examination, an asymptomatic ulcer measuring 2.0×1.5 cm was discovered on the right lateral border of the tongue. Incisional biopsy under local anesthesia was performed and histopathological report confirmed presence of squamous cell carcinoma. After further evaluation, surgery was performed, followed by three sessions of brachytherapy and six sessions of chemotherapy. After 26 months of follow-up, there was no evidence of recurrence.

**Conclusion:** Periodic screening examinations are necessary to discover possible malignancies in primary stages in patients with SS.

**Key words:** Squamous Cell Carcinoma, Systemic sclerosis, Tongue.

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### Introduction:

Systemic sclerosis is a rare connective tissue disorder involving the skin and internal organs. It is characterized by high fibroblastic activation and collagen deposition. In a systematic review Bonifazi reported the prevalence of scleroderma to be between seven to 489 cases per million individuals, with geographic location playing an important role in disease distribution (1). The two common types of SS include progressive skin scleroderma with involvement of extremities, face, body, kidneys, and other internal organs, and limited skin scleroderma (2). Systemic sclerosis is caused by damage to endothelial cells, with their subsequent

activation and peri vascular inflammation, consisting of different types of inflammatory cells. Also, extracellular matrix deposition, tissue destruction, and different chemokines and cytokines, such as Transforming Growth Factor  $\beta$  (TGF-  $\beta$ ), are involved in the pathogenesis of this disease. Transforming Growth Factor  $\beta$  increases cell growth and differentiation, and collagen and protein matrix synthesis, which results in decreased production of a collagenase enzyme named matrix metalloproteinase (3).

Raynaud's phenomenon is one of the first signs of SS. Increase in skin thickness (scleroderma) is one of the hallmarks of SS, which begins from hands and spreads proximally to the extremities, torso, and face. This condition occurs within the

first three to five years of the disease. Other skin manifestations include telangiectasias, hypo- or hyper-pigmentation, and calcinosis. After skin involvement, alimentary tract involvement is the most common feature of SS, which manifests in the form of dysphagia. Pulmonary fibrosis, kidney and heart involvement and abnormalities in autonomic, peripheral, and cranial nerves are seen in this condition as well. Oral manifestations include microstomia, xerostomia, telangiectasias, tongue stiffness, gingival recession, and difficulty in speech. Pulmonary fibrosis and pulmonary hypertension are among the most serious causes of death in more than 50% of patients suffering from SS (1, 2).

Management of scleroderma includes treatment of vascular complications such as Raynaud's phenomenon, and immunosuppressive therapy, which inhibit connective tissue proliferation (3). Additionally, multiple studies have reported a higher risk of malignancies in patients suffering from PSS compared to general population. Possible mechanisms include impairment of carcinogen clearance, defects in immune system, familial susceptibility, and increased susceptibility to malignant transformation(4). In a cohort study of 769 patients with PSS, Derk, *et al.* (2005) found six cases of SCC of the tongue and reported a higher risk of this malignancy in these patients (5). There have been case reports of SCC of the skin, oesophagus and the lips in patients with scleroderma (6-8). The aim of this study is to report a rare case of SCC of the tongue in a female patient with PSS.

### Case:

A 46-year-old female patient presented to the Department of Oral Medicine of Shahid Beheshti University of Medical Sciences Dental School with the chief complaint of an ulcer on her tongue over the previous two months. She was diagnosed with SS two years prior to admission, for which she was on prednisolone,

colchicine, and azathioprine. In addition, she had a history of hypertension, which was controlled with captopril. She had no family history of cancer among her first-degree relatives. Physical examination was significant for multiple telangiectasias on her face, stretched lips (fish mouth appearance) (Figure 1), limited mouth opening, and thickening of her fingers skin.



**Figure 1- Multiple telangiectasias on the face and stretched lips in our patient with PSS**

Oral examination revealed an ulcer measuring 2.0×1.5 cm in the right lateral border of her tongue with rolled borders, but no induration was felt on palpation (Figure 2).

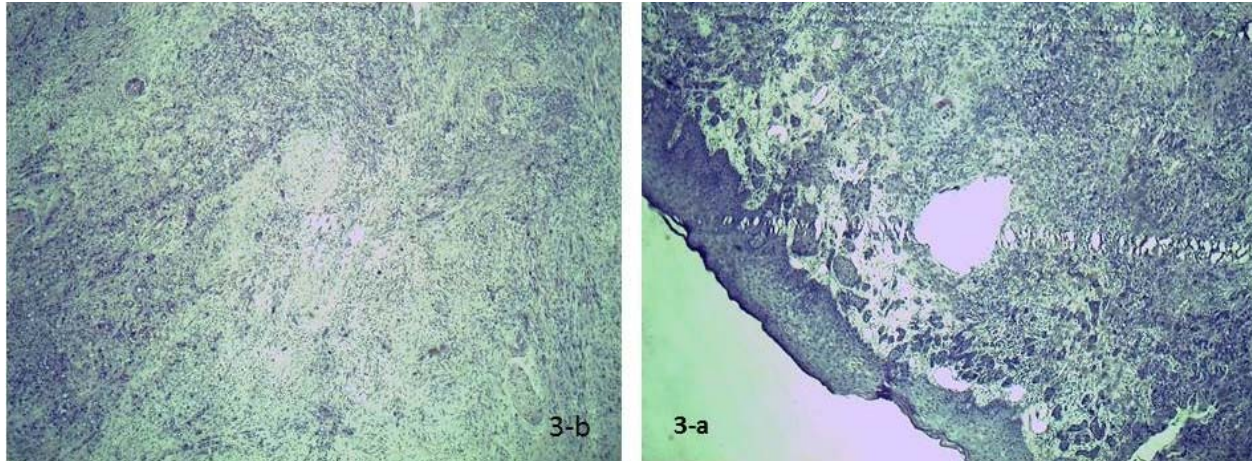


**Figure 2- A rolled-border ulcer on the lateral border of the tongue in our patient with PSS**

Because the ulcer was exclusively in the soft tissue, there was no need to request radiographic imaging. There was no submandibular or cervical lymph node involvement. An incisional biopsy was performed under local anesthesia and histopathological examination revealed a malignant epithelial tumor, composed of islands of squamous cells with pleomorphism, keratin

pearl formation, hyperchromatism, a few mitotic figures, and giant nuclei. Tumor cells in most areas were arranged as scattered individual cells penetrating deep into the connective tissue.

Invasion of tumor cells into vessels and bundles were also evident and a diagnosis of SCC was made (Figure 3).



**Figure 3a, b- Malignant epithelial tumor, composed of islands of squamous cells with pleomorphism, keratin pearl formation, hyperchromatism, a few mitotic figures, and giant nuclei. Tumor cells in most areas were arranged as scattered individual cells penetrating deep into the connective tissue.**

The patient was referred to the Cancer Institute of Tehran University of Medical Sciences for further evaluation and treatment. Subsequently, the patient underwent surgical resection of the tumor. Upon neck dissection, there was evidence of perineural, muscular, and lymph node involvement. Surgical excision of the lesion was followed by three sessions of brachytherapy and six courses of chemotherapy (cisplatin and 5-Fluorouracil). After 26 months of follow-up, there was no evidence of recurrence.

### Discussion:

The association between PSS and malignancies has been mentioned in previous studies (5), but continues to remain an area of debate. According to some studies, the incidence of malignancy among patients with SS ranges from 3.6 to 10.7% with the mean of 6.3 % (4). A case of alveolar cell carcinoma was the first report linking SS with cancer (9). Despite studies by

Black, *et al.* in 1982 (10) and Chatterjee, *et al.* in 2005 (11), which showed no increased risk of cancer in patients with PSS, many other studies have shown an increased risk of cancer in these patients (4,5,12). Lung cancer is the most common malignancy in patients with SS, followed by breast cancer, and gastrointestinal malignancies (4-5-9). Derk, *et al.* in 2005 demonstrated that patients with PSS had a 25fold higher frequency of tongue carcinoma compared to general population. They identified nine patients with SCC of the oral cavity and pharynx, six of which had SCC of the tongue (5). In 2009, Petrov, *et al.* reported the first case of SCC of the tongue in a patient with scleroderma (8). The current case report confirms prior reports and shows a higher risk of malignancy in patients with PSS.

Factors involved in the pathogenesis of both PSS and malignancy are reported to be the same. Viral infections and exposure to certain chemicals are among these factors. One hypothesis about the pathogenesis of oral cancer in patients with PSS is exposure of the oral

cavity to environmental factors, such as betel nut, perchloroethylene, and herbal medicines containing aristolochic acid, which can result in malignancy and fibrosis (5).

Malignancy may be seen in patients with both limited or diffuse forms of SS. Wooten *et al.* (2008) stated that female sex, the average age of 58 years old and systemic form of SS increase the risk of malignancy (4). In a study by Derk, *et al.* (2005) all patients with scleroderma, which had SCC of the tongue, were involved with diffuse form of the disease (5). After further evaluation, they concluded that SCC of the tongue occurred at least one year after diagnosis of PSS was made, with the average age of 56.3 (11.1) years. The case reported by us was similar to the previous studies in terms of patient sex and diffuse skin involvement. However, our patient was diagnosed with another malignancy about a decade earlier. Also, she was diagnosed with SCC of the tongue two year after being diagnosed with SS.

On the other hand, malignancy in patients suffering from PSS may be the result of the medications used to treat it (4). Immunosuppressant (cyclophosphamide, methotrexate, azathioprine) may predispose patients to malignancies (13). However, according to Hesselstrand (14), there is no such a relationship between scleroderma treatment and developing cancer. In a study by Derk, *et al.* (2005), half of the patients who had both PSS and SCC of the tongue received D-penicillamine as the treatment for PSS. Our patient has been receiving azathioprine but not D-penicillamine

(5).

Despite its rarity, tongue cancer is the second most common malignancy of the oral cavity (5). Tobacco and heavy alcohol use are two exogenous agents that increase the risk of oral cancer (15). In the study by Derk, *et al.* (2005), 33% of patients had a positive family history of cancer and only one patient had an additional risk factor such as tobacco and alcohol use (5). Our patient had none of these risk factors. She did not use to smoke nor drink alcohol, and had no family history of cancer. It seems that PSS and exposure to immunosuppressant might predispose her to oral cancer. Since the majority of patients with SS undergo immunosuppressive therapy, periodic screening to diagnose malignancy at early stage is imperative.

### **Conclusion:**

Given the increased risk of malignancy in patients suffering from scleroderma and PSS, periodic screening and follow up examination are necessary in order to detect possible malignancies at an early stage in this group of patients.

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### **Conflict of Interest: “None Declared”**

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