Post-radiotherapy recurrence of conventional oral squamous cell carcinoma showing sarcomatoid components: an immunohistochemical study

Túlio Morandin Ferrisse¹, Audrey Foster Lefort Rocha¹, Maria Letícia de Almeida Lança¹, Heitor Albergoni Silveira¹², Luciana Yamamoto Almeida¹, Andreia Bufalino¹, Jorge Esquiche León²

How to cite: Ferrisse TM, Rocha AFL, Lança MLA, et al. Post-radiotherapy recurrence of conventional oral squamous cell carcinoma showing sarcomatoid components: an immunohistochemical study. Autops Case Rep [Internet]. 2021;11:e2020219. https://doi.org/10.4322/acr.2020.219

ABSTRACT

Spindle cell squamous cell carcinoma (SpSCC) is a rare biphasic malignant neoplasm, uncommonly affecting the oral cavity. The SpSCC diagnosis is difficult, especially when it exhibits inconspicuous morphology, inadequate tissue sampling, or association with an exuberant inflammatory reaction. Post-radiotherapy recurrent SpSCC occurring at the same site of conventional SCC is a rare phenomenon. A 59-year-old man was complained of “painful injury on the tongue” with 20 days of duration. He reported smoking and alcohol consumption. Medical history revealed conventional SCC on the tongue treated with surgery and radiotherapy 10 years ago. Intraoral examination showed a polypoid lesion with ulcerated areas, measuring 3 cm in diameter, on the tongue and floor of the mouth, at the same site of previous conventional SCC. The microscopical analysis showed small foci of carcinomatous component admixed with an exuberant inflammatory reaction. Immunohistochemistry highlighted the sarcomatoid component. Both malignant components were positive for EMA, CD138, p40 (deltaNp63), p63, and p53. Moreover, CK AE1/AE3 evidenced the carcinomatous component, whereas vimentin stained the sarcomatoid component. The Ki-67 was >10%. The current case emphasizes the importance of immunohistochemistry in the differential diagnosis of SpSCC from mimics and documents a rare complication of Ionizing Radiation.

Keywords
Squamous cell carcinoma; Squamous Cell Carcinoma of Head and Neck; immunohistochemistry; radiotherapy

INTRODUCTION

Squamous cell carcinoma (SCC) accounts for about 90% of the oral and oropharyngeal cancers. Oral cavity SCC (OSCC) is the most common malignancy of the head and neck region.¹ The tobacco smoking and alcohol consumption are the main etiological factors of the OSCC.² In the last decades, human papillomavirus (HPV) has emerged as a major etiologic factor for oropharyngeal SCC (OPSCC) and on the lips, the ultraviolet radiation plays a central role in the carcinogenesis.²⁻⁴ The OSCC includes several...
histopathological variants, including verrucous, basaloid, adenoid, spindle cell, adenosquamous and undifferentiated. The understanding of its microscopic peculiarities is fundamental for correct diagnosis and consequently adequate treatment.\(^5\)

Spindle cell SCC (SpSCC) of the head and neck region is a rare, biphasic neoplasm with aggressive behavior.\(^6\) The main sites of occurrence are the upper aerodigestive tract, larynx, and hypopharynx; nevertheless, in the oral cavity, the occurrence is rare, accounting for less than 1% of all SCCs.\(^7\) The clinical presentation of SpSCC usually vary from exophytic, polypoid mass with an ulcerated surface to an infiltrative ulcer and the histopathological characteristics exhibit a dysplastic epithelium with foci of infiltration and connective tissue stroma containing numerous spindle-shaped cells, many of them round to oval in shape with eosinophilic and vacuolated cytoplasm, nuclear hyperchromatism and atypical mitoses.\(^8,9\) Interestingly, SpSCC after radiotherapy treatment in some conventional SCC patients have been reported.\(^10\) Thus, a detailed clinicopathological analysis of similar cases is encouraged to better understand their pathogenesis, treatment, and prognosis.\(^11\)

**CASE REPORT**

A 59-year-old male Caucasian patient was referred with the main complaint of “wound in the tongue” lasting 20 days. On the clinical examination, a painful, exophytic, polypoid lesion was observed with approximately 3 cm in diameter associated with ulcerative areas on the floor of the mouth with extension to the adjacent tongue (Figure 1).

On the extraoral examination, nothing of note was identified. According to the patient, the lesion started 30 days ago, and it increased in size. The medical history was remarkable for a previous diagnosis of well-differentiated SCC in this same region 10 years ago (Figure 2), clinically presented as an ulcerated lesion, being the patient staged as T3N0M0.

The treatment consisted of surgery and conventional external beam radiotherapy with 70 Gy in 35 sessions. An incisional biopsy was performed, and the histopathological analysis revealed a biphasic tumor consisting of a carcinomatous component evidenced by dysplastic and infiltrative epithelium, focal formation of keratin pearls and an intense inflammatory cell infiltrate permeating a sarcomatoid component (Figure 3).

The immunohistochemical analysis (Figure 4 and 5) showed positivity for cytokeratin AE1/AE3 highlighting the carcinomatous component, while that vimentin strongly stained the sarcomatoid component. Moreover, EMA, CD138, p40 (deltaNp63), p63, and p53 highlighted both carcinomatous and sarcomatoid components. Of them, only the EMA expression was weak and focal in the sarcomatoid component. S100 protein was negative. The Ki-67 labeling index was >10%. The final diagnosis was SpSCC, and the patient...
was referred to the oncologist. The patient was submitted to tumor resection and complementary radiotherapy with a total dose of 70 Gy even as the first radiotherapy 10 years ago. After 1-year of follow-up, no sign of recurrence or alteration was observed.

**Figure 2.** Histopathological features of oral SCC: neoplastic epithelium with conventional pattern (Original magnification, A, x10; B, x20) (H&E stain).

**Figure 3.** Histopathological features of SpSCC: Biphasic tumor consisting of infiltrating neoplastic epithelium in close relationship to spindle cells (H&E, A, x10; B, x20). Dysplastic epithelium and overt pleomorphism of the spindle cells in the sarcomatoid component (H&E, C, x20; D, x20).
DISCUSSION

SpSCCs of the head and neck region are rare variants of SCC, representing less than 3% of all head and neck SCCs. The most frequently involved sites in the oral cavity are the lower lip, tongue, and gingiva. Microscopically, SpSCC is characterized by the presence of two distinct morphological components, carcinomatous and sarcomatoid or spindle cell proliferation, with both components of epithelial origin. Post-radiotherapy SpSCC is a rare complication. Interestingly, the current case is the third SpSCC originated after surgical resection and radiotherapy of conventional SCC, with both tumors being diagnosed in the same location, at the head and neck region. Taking into consideration that radiotherapy has beneficial effects in the SCC treatment, the development of SCC after radiotherapy is uncommon and deserves special attention to better understand its pathogenesis, treatment, and prognosis.

A systematic review conducted by Brown et al. in OSCC shows no difference in local recurrence between patients who underwent surgical treatment alone and surgical treatment with postoperative radiotherapy. On the other hand, overall survival seems to be relatively lesser in those patients receiving surgical treatment with postoperative radiotherapy. Therefore, these results indicate the need for more randomized clinical trials and possible changes in cancer treatment protocols, aiming to improve the quality of life of these patients. Additionally, according
Figure 5. Immunohistochemical analysis of the SpSCC on consecutive serial tissue sections. A – Positive reaction for p40 (deltaNp63) in both sarcomatoid and carcinomatous components; as well as in B – positivity for p63; C – The sarcomatoid component showing positive nuclear staining for p53; and D – Ki-67 (>10%) (A and B x20, C and D x10).

Studies have shown that some tumor types may originate due to exposure to different types of radiation. It is not possible to determine from histopathological examination whether a tumor occurring in a radiation field has been induced by radiation. However, there are reports in the scientific literature of malignant neoplasms, either SCCs or sarcomas, which appeared after treatment with radiotherapy.

The cause of tumor development in the radiation field may be explained for dose-response effects and the tumor type. For example, the Colleman study noted that the induction of sarcomas requires higher doses, especially in thyroid and breast, since lower doses may induce leukemia. For SCC, scientific researches demonstrating the exact amount of dose for carcinogenic induction were not found; however, for SpSCC cases arising after radiotherapy treatment from conventional SCC, the amount of radiation used appears to be sufficient to induce carcinogenesis. A total radiation dose may vary between 50-70 Gy for SCC in the head and neck region.

According to Baker et al. study, fibrosis, and vascular changes induced by radiotherapy may be responsible for the development of secondary malignant neoplasms. The radiation can induce chromosome aberrations such as asymmetrical rearrangements that may be observed at the first mitosis in tumor cells, and normal-cells. Radiation may also induce high levels of micronuclei standing acentric fragments or whole chromosome loss at anaphase. Thus, further studies of the tumor microenvironment and cell pathways can clarify the possible mechanisms involved in cases of recurrence and neoplasms induced by radiation.
The nonneoplastic effects of radiation on mucosal tissues are dependent on the type of tissue irradiated. The most typical alterations occur in the lamina propria, submucosa, and deep soft tissues of the mouth, pharynx, larynx, and genitalia, which reveal fibrosis and lack or paucity of inflammatory exudate, followed by fibrinous exudate, atypical fibroblasts, and necrosis. Noteworthy, the radiation-induced mesenchymal stromal cell alterations can mimic a malignant neoplasm, either carcinoma or sarcoma.24-26 Thus, strict clinicopathological correlation, supported by immunohistochemistry, is necessary to achieve a correct diagnosis.

We also conducted a literature review considering recurrence in cases of SpSCC in the head and neck region and other information such as demographic data, primary tumor, location, treatment, and time of recurrence.7,9,10,27-34 In most cases, the location of recurrence and the initial site of involvement were the same. The initial treatment most commonly used was a combination of surgery and radiotherapy, and surgery alone was often associated with recurrence. The time of recurrence ranged from 2 months to 11 years. Table 1 shows the clinicopathological features of primary conventional SCC and recurrence as SpSCC, and Table 2 shows the clinicopathological features of primary SpSCC and recurrence as SpSCC. It is worth noting that twenty cases of recurrent SpSCC were not included in the tables due to lack of clinicopathological data.35-37 According to our literature review, there are forty-four cases of recurrent SpSCC in the head and neck region, of which only nine cases originated from conventional SCC. The present study relates to the tenth case.

The histopathological diagnosis of SpSCC in the head and neck region is often difficult due to embryologically and anatomically complex area, small sample sizes of biopsy, and often inflammatory cell infiltrate admixed with malignant cells. Moreover, because SpSCC may present four histopathological patterns, including monomorphic, pleomorphic, biphasic, and myxoid, the diagnosis is challenging. In addition, the microscopic distinction of SpSCC from other malignant mesenchymal spindle cell neoplasms may require aid from immunohistochemistry.38 The correct understanding of these histopathological aspects is fundamental to achieve the correct diagnosis. In the present study, the sarcomatoid component of the SpSCC was obscured by an intense inflammatory cell infiltrate.

However, after immunohistochemical analysis, the spindle cells revealed positivity for EMA, CD138, p40 (deltaNp63), p63 and p53, with significant proliferative index (Ki-67, >10%). Our findings are in agreement with other reported SpSCC cases.39,40

| Study                     | Age (y)/Sex | Location             | Tx       | Recurrence | Site of recurrence | Primary Tumor | Tx | Time to recurrence (y) |
|---------------------------|-------------|----------------------|----------|------------|--------------------|---------------|----|------------------------|
| Takata et al.27           | 50/M        | Gingiva              | S+Rad    | SpSCC      | Oropharynx         | SCC           | S+Chm | 18                     |
|                           | 83/F        | Buccal mucosa        | Rad      | SpSCC      | Buccal mucosa      | SCC           | S+Rad+Chm | 5                      |
|                           | 71/F        | Tongue               | Rad      | SpSCC      | Gingiva            | SCC           | S    | 2                      |
|                           | 76/M        | Gingiva/FoM          | S+Rad    | SpSCC      | Tongue             | SCC           | S    | 11                     |
| Minami et al.28           | 58/F        | Esophagus            | Rad      | SpSCC      | Oropharynx         | SCC           | S    | 11                     |
| Kinra et al.10            | 56/M        | Larynx               | S+Rad    | SpSCC      | Oropharynx         | SCC           | S    | 3                      |
| Oktay et al.7             | 55/F        | Tongue               | S+Rad    | SpSCC      | Tongue             | SCC           | S+Rad | 8                      |
| Manickam et al.29         | 62/M        | Larynx               | S+Rad    | SpSCC      | Larynx             | SCC           | S    | 3                      |
| Okuyama et al.30          | 62/F        | Tongue               | Surg     | SpSCC      | Tongue             | SCC           | S    | 4                      |
| Index case                | 49/M        | Tongue               | S+Rad    | SpSCC      | FoM/Tongue         | SCC           | S+Rad | 10                     |

Legend: Chm: chemotherapy; F: female; FoM: floor of the mouth; M: male; S: surgery; SCC: squamous cell carcinoma; Rad: radiotherapy; SpSCC: spindle cell squamous cell carcinoma; Tx: treatment; y: years.
Table 2. Clinicopathological features of primary SpSCC and recurrence as SpSCC in the head and neck region

| Study                        | Age(y)/sex | Ethnicity | Location                  | Tx     | Recurrence | Site of recurrence | Primary tumor | Tx     | Time to recurrence (yr) |
|------------------------------|------------|-----------|---------------------------|--------|------------|-------------------|---------------|--------|------------------------|
| Ferrisse TM, Rocha AFL, Lança MLA, et al. | N/A        | N/A       | Tongue                   | Rad    | SpSCC      | Tongue            | SpSCC         | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Tongue/FoM               | Rad    | SpSCC      | Tongue/FoM        | SpSCC         | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Retromolar trigone/ Palate| Rad    | SpSCC      | Retromolar trigone/ Palate | SpSCC | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Lower lip                | Rad    | SpSCC      | Lower lip         | SpSCC         | N/A    | N/A                    |
| Leventon and Evans[^11]      | N/A        | N/A       | Buccal mucosa            | Rad    | SpSCC      | Buccal mucosa     | SpSCC         | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Buccal mucosa            | S      | SpSCC      | Tongue            | SpSCC         | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Oropharynx               | S+Rad  | SpSCC      | Oropharynx        | SpSCC         | N/A    | N/A                    |
| N/A                          | N/A        | N/A       | Tongue                   | Surg   | SpSCC      | Tongue            | SpSCC         | N/A    | N/A                    |
| Su et al.[^32]               | 52/M       | N/A       | Buccal mucosa            | S+Rad  | SpSCC      | Buccal mucosa     | SpSCC         | N/A    | 0.6                    |
| 32/M                         | N/A        | N/A       | Tongue                   | S      | SpSCC      | Tongue            | SpSCC         | N/A    | 0.2                    |
| 51/M                         | N/A        | N/A       | Buccal mucosa            | S      | SpSCC      | Buccal mucosa     | SpSCC         | N/A    | 2.2                    |
| Iqbal et al.[^33]            | 42/M       | N/A       | Lip                      | S+Chm  | SpSCC      | Lip               | SpSCC         | N/A    | 2.7                    |
| 59/M                         | N/A        | N/A       | Gingiva                  | S      | SpSCC      | Gingiva           | SpSCC         | N/A    | 1.1                    |
| 52/M                         | N/A        | N/A       | Tongue                   | S+Rad+Ch | SpSCC   | Tongue            | SpSCC         | N/A    | 1.7                    |
| 51/M                         | N/A        | N/A       | Tongue                   | Surg   | SpSCC      | Tongue            | SpSCC         | N/A    | 0.2                    |
| 46/M                         | N/A        | N/A       | Lip                      | S+Rad  | SpSCC      | Lip               | SpSCC         | N/A    | 0.7                    |
| 67/M                         | N/A        | N/A       | Buccal mucosa            | S+Rad  | SpSCC      | Buccal mucosa     | SpSCC         | N/A    | 0.5                    |
| 60/M                         | N/A        | N/A       | Tongue                   | S+Rad  | SpSCC      | Tongue            | SpSCC         | Surg   | 3.7                    |
| 63/M                         | N/A        | N/A       | Tongue                   | S+Rad  | SpSCC      | Tongue            | SpSCC         | Surg   | 1.7                    |
| Ohba et al.[^34]             | 72/F       | Asian     | Buccal mucosa            | S+Rad+Ch | SpSCC   | Submandibular region | SpSCC         | Ch+Rad | 1.0                    |
| Al-Bayaty and Balkaran[^9]   | 73/F       | Black     | Gingiva/Mandible         | Surg   | SpSCC      | Gingiva/Mandible  | SpSCC         | N/A    | 0.5                    |

Legend: Chm: chemotherapy; F: female; FoM: floor of the mouth; M: male; N/A: not available; Rad: radiotherapy; S: surgery; SpSCC: spindle cell squamous cell carcinoma; Tx: treatment; y: years.
CONCLUSION

Post-radiotherapy recurrent SpSCC occurring at the same site of well-differentiated SCC is a rare phenomenon, usually related to poor prognosis. Herein we report the fourth case in the head and neck region. The histopathological diagnosis can be challenging, because, in some cases, the immunohistochemical analysis is necessary for the correct diagnosis. Further studies assessing recurrent SpSCC after radiotherapy are encouraged better to understand their pathogenesis, treatment, and prognosis.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. http://dx.doi.org/10.1002/ijc.29210. PMid:25220842.

2. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer. 2011;11(1):9-22. http://dx.doi.org/10.1038/nrc2982. PMid:21160525.

3. Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15. http://dx.doi.org/10.1016/S1470-2045(12)70137-7. PMid:22575588.

4. Shield KD, Ferlay J, Jemal A, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin. 2017;67(1):51-64. http://dx.doi.org/10.3322/caac.21384. PMid:28076666.

5. Pereira MC, Oliveira DT, Landman G, Kowalski LP. Histologic subtypes of oral squamous cell carcinoma: prognostic relevance. J Can Dent Assoc. 2007;73(4):339-44. PMid:17484800.

6. Gupta R, Singh S, Hedau S, et al. Spindle cell carcinoma of head and neck: an immunohistochemical and molecular approach to its pathogenesis. J Clin Pathol. 2007;60(5):472-5. http://dx.doi.org/10.1136/jcp.2005.033589. PMid:16731596.

7. Oktay M, Kokenek-Unal TD, Ocal B, Saylam G, Korkmaz MH, Alper M. Spindle cell carcinoma of the tongue: a rare tumor in an unusual location. Patholog Res Int. 2011;2011:572381. http://dx.doi.org/10.4061/2011/572381. PMid:21403898.

8. Romañach MJ, Azevedo RS, Carlos R, de Almeida OP, Pires FR. Clinicopathological and immunohistochemical features of oral spindle cell carcinoma. J Oral Pathol Med. 2010;39(4):335-41. http://dx.doi.org/10.1111/j.1600-0714.2009.00843.x. PMid:20002980.

9. Al-Bayaty H, Balkaran RL. Spindle cell carcinoma of the mandible: clinicopathological and immunohistochemical characteristics. J Oral Biol Craniofac Res. 2016;6(2):160-3. http://dx.doi.org/10.1016/j.jobcr.2015.08.009. PMid:27195215.

10. Kinra P, Srinivas V, Sinha K, Dutta V. Post irradiation spindle cell carcinoma of tonsillar pillar. Case Rep Med. 2011;2011:325193. http://dx.doi.org/10.1155/2011/325193. PMid:22203850.

11. Parikh N, Desai N. Spindle cell carcinoma of the oral cavity: a case report of a rare entity and review of literature. J Acad Adv Dent Res. 2011;2(2):31-6. http://dx.doi.org/10.1177/2229411220110206.

12. Chuang R, Crowe DL. Understanding genetic progression of squamous cell carcinoma to spindle cell carcinoma in a mouse model of head and neck cancer. Int J Oncol. 2007;30(5):1279-87. http://dx.doi.org/10.3892/ijo.30.5.1279. PMid:17390032.

13. Brown JS, Shaw RJ, Bekiroglu F, Rogers SN. Systematic review of the current evidence in the use of postoperative radiotherapy for oral squamous cell carcinoma. Br J Oral Maxillofac Surg. 2012;50(6):481-9. http://dx.doi.org/10.1016/j.bjoms.2011.08.014. PMid:22196145.

14. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone: report of 11 cases. Cancer. 1948;1(1):3-29. http://dx.doi.org/10.1002/1097-0142(194805)1:1<3::AID-CNCR2820010103>3.0.CO;2-7. PMid:18867438.

15. Maghami EG, St-John M, Bhuta S, Abemayor E. Postirradiation sarcoma: a case report and current review. Am J Otolaryngol. 2005;26(1):71-4. http://dx.doi.org/10.1016/j.amjoto.2004.08.005. PMid:15635588.

16. Koshy M, Paulino AC, Mai WY, Teh BS. Radiation-induced osteosarcomas in the pediatric population. Int J Radiat Oncol Biol Phys. 2005;63(4):1169-74. http://dx.doi.org/10.1016/j.ijrobp.2005.04.008. PMid:16054775.

17. Plichta JK, Hughes K. Radiation-induced angiosarcoma after breast-cancer treatment. N Engl J Med. 2017;376(4):367. http://dx.doi.org/10.1056/NEJMicm1516482. PMid:28121510.

18. Murray EM, Werner D, Greeff EA, Taylor DA. Postirradiation sarcomas: 20 cases and a literature review. Int J Radiat Oncol Biol Phys. 1999;45(4):951-61. http://dx.doi.org/10.1016/S0360-3016(99)00279-5. PMid:10571202.

19. Coleman CN. Secondary neoplasms in patients treated for cancer: etiology and perspective. Radiat Res. 1982;92(1):188-200. http://dx.doi.org/10.2307/3575854. PMid:7134383.

20. Huang SH, O’Sullivan B. Oral cancer: current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir
This study carried out jointly between the São Paulo State University (UNESP), School of Dentistry, Araraquara, São Paulo, Brazil and Ribeirão Preto Dental School (FORP/USP), University of São Paulo, Ribeirão Preto, São Paulo, Brazil.
Authors’ contributions: Túlio Morandin Ferrisse, Audrey Foster Lefort Rocha and Maria Leticia de Almeida Lancã contributed to the clinical and microscopic analyses and the review of the literature. Heitor Albergoni Silveira and Luciana Yamamoto Almeida contributed with the immunohistochemical analysis and the manuscript writing. Andreia Bufalino and Jorge Esquiche León, contributed to the manuscript design, final data analyses and critical review.

Ethics statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

Conflict of interest: The authors have no conflict of interest to declare.

Financial support: Luciana Yamamoto Almeida (2016/02713-2), Heitor Albergoni Silveira (2018/12734-2) and Jorge Esquiche León (2016/11419-0) have received research Grants from State of São Paulo Research Foundation (FAPESP). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Submitted on: November 7th, 2019
Accepted on: June 15th, 2020

Correspondence
Jorge Esquiche León
Universidade de São Paulo (USP), Faculdade de Odontologia de Ribeirão Preto, Departamento de Estomatologia, Saúde Coletiva e Odontologia Legal, Patologia Oral
Av. Café, s/n, Bairro, CEP CEP 14040-904, Ribeirão Preto, SP, Brasil
Phone: +55 (16) 3315-4063
jleon@forp.usp.br