Acantholytic squamous cell carcinoma of the gingiva: report of a case and review of the literature

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Adenoid squamous cell carcinoma differs from common squamous cell carcinoma in histologic features and its aggressive nature. Microscopically, the tumor shows cystic degeneration of the neoplastic epithelium, producing a prominent alveolar pattern and pseudoglandular structures with acantholytic cells. It occurs most commonly on the lips, rarely intraorally, and it is associated with a poor prognosis. This case concerns a 72-year-old woman who presented with the chief complaint of burning tongue and soreness of the lips. Clinical examination revealed an ulcerated and elevated mass on the edentulous left maxillary ridge, beneath the base of a partial denture. An incisional biopsy rendered the diagnosis of adenoid squamous cell carcinoma. The patient was referred to a specialized maxillofacial surgery center for diagnostic work-up and treatment. She underwent partial maxillectomy and radiotherapy, and 17 months after treatment, she died of uncontrollable recurrence. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e67-e71)

Acantholytic squamous cell carcinoma (ASCC) is an uncommon histopathologic variant of squamous cell carcinoma (SCC), characterized by marked acantholysis in the cancer nests leading to a pseudoglandular or pseudovascular appearance.1 It was first described by Lever in 1947 as adenoacanthoma of the sweat glands.2 Synonyms include adenoid SCC, pseudoglandular SCC, SCC with gland-like features, angiosarcoma-like SCC, and pseudovascular adenoid SCC.3

ASCC is more frequent on the skin, where it accounts for 2%-4% of all SCC.1 The sun-exposed areas of the skin, particularly on the head and neck of elderly men, are more commonly affected.4 Sporadic cases have been reported in various mucosal membranes and internal organs.5,6 A review of the English-language literature revealed 22 cases of ASCC on the vermilion border of the lips7 and 12 cases in the oral mucosa.5-13

A case of ASCC on the maxillary gingiva is reported here, and all previously published intraoral cases are reviewed.

CASE REPORT

A 72-year-old caucasian woman was referred by her dentist for evaluation of a painless lesion on the maxilla. The patient had noticed the lesion approximately 2 months before and attributed it to trauma caused by a removable partial denture. No symptoms were reported. Her presenting complaints were burning tongue and soreness of the lips that were partially relieved after a short course of chlorhexidine mouthwash. The patient did not smoke tobacco or drink alcohol, and her medical history was significant only for hypercholesterolemia.

Clinical examination revealed an irregular mass, measuring ~1.7 x 1 cm, with a central ulceration on the posterior left mandibular ridge (Fig. 1). It had a rough nodular surface with white and red areas and was hard but nontender on palpation. The lesion was totally covered by the base of a partial denture, whereas the rest of the supporting maxillary mucosa showed features consistent with denture stomatitis. A dental radiograph showed irregularity at the crest of the alveolar ridge (Fig. 2).

The presumptive diagnosis was SCC, and a partial biopsy was performed under local anesthesia. The tissue was fixed in 10% buffered formalin. On gross examination, the specimen measured 1.2 x 0.5 cm and was white and friable. Microscopic examination showed a fragment of gingival mucosa covered by dysplastic epithelium with parakeratin plugs (Fig. 3, A). The underlying connective tissue was infiltrated by nests of pleomorphic neoplastic epithelial cells, with large and irregular nuclei and prominent nucleoli, originating from the overlying epithelium. In some nests, marked acantholysis of the neoplastic cells resulted in the formation of irregular clefts and pseudoglandular structures lined by a single layer of atypical cuboidal or cylindrical cells; acantholytic cells with intense eosinophilic cytoplasm and cellular debris were noted within the clefts (Fig. 3, B). Atypical mitoses were recognized. The surrounding connective tissue was collagenized, highly vascularized, and infiltrated by lymphocytes and plasma cells. No periodic acid–Schiff–positive material

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was identified intracellularly or within the pseudoglandular structures.

Immunohistochemical examination showed cytoplasmic staining of most neoplastic epithelial cells for pan-cytokeratin AE1/AE3 (Novocastra; Leica Biosystems, Newcastle, U.K.; dilution 1:100; Fig. 4) and membranous staining for E-cadherin (Novocastra; dilution 1:50). However, E-cadherin was not expressed in most of the cells lining the clefts or the pseudoglandular structures (Fig. 5), and positive staining in acantholytic cells was interpreted as an artifact. Neoplastic cells did not react for cytokeratin (CK) 7 (Novocastra; dilution 1:100), CK20 (Novocastra; dilution 1:100), carcinoembryonic antigen (CEA; Novocastra; dilution 1:100), and cancer antigen 125 (CA125; BioGenex Laboratories, San Ramon, CA; dilution 1:50). Ki-67 (Novocastra; dilution 1:100) showed high proliferative activity of the tumor cells (>40%). The findings were consistent with an ASCC.

The patient was referred to a specialized maxillofacial surgery center for further diagnostic work-up and treatment. There were no regional or distant metastases or other primary malignancies. She underwent partial maxillectomy without neck dissection, followed by radiotherapy (30 cycles), but 10 months after completing the treatment she developed extensive local recurrence, involving the temporomandibular region, and generalized lymphadenopathy. She refused further treatment and 7 months later, she died of disease.

**DISCUSSION**

Since the first description of a case of intraoral ASCC reported by Goldman et al. in 1977, 12 more cases have been reported in the English-language literature, including the present one (Table I). In 2 cases, the initial diagnosis of SCC was modified to
ASCC in autopsy, after recurrences and death of the patients.\textsuperscript{8} Nine patients were male and 4 female. The age ranged from 50 to 86 years, with an average age of 62.6 ± 10.6 years. Five lesions were located on the tongue, 4 on the floor of the mouth, 3 on the gingiva (2 maxillary, 1 mandibular), and 1 on the buccal mucosa. Although the small number of intraoral ASCC reported so far precludes conclusions, it seems that its main clinical features are consistent with those of conventional oral SCC. Our case is only the second reported ASCC to affect the maxilla.

Microscopically in ASCC, the pseudoglandular or pseudovascular structures are usually found in the deeper portions of a typical SCC and do not contain sialomucins.\textsuperscript{1,3} They are lined by atypical squamous epithelial cells that are positive for high-molecular-weight CK, and occasionally for epithelial membrane antigen and involucrin.\textsuperscript{1,3,12} In contrast, they do not express glandular markers, i.e., low-molecular-weight CK, CEA, or CA125.\textsuperscript{1} Alterations in the expression of molecules that mediate cell-cell and cell–extracellular matrix adhesion of adult epithelial cells, such as E-cadherin, syndecan-1, and β-catenin, have been associated with acantholysis and the biologic behavior of ASCC.\textsuperscript{5,11,14} In oral SCC, E-cadherin expression has been variously reported as present in the cells lining the pseudoglandular structures in 2 tumors,\textsuperscript{5} absent in 2 tumors,\textsuperscript{6} or ectopically expressed in the cytoplasm in 4 tumors.\textsuperscript{11} In the present case, E-cadherin was located in the squamous areas, but not in the cells lining the pseudoglandular structures.

Oral ASCC should be differentiated from adenosquamous carcinoma, mucoepidermoid carcinoma of minor salivary gland origin, ductal involvement of a conventional SCC, and angiosarcoma.\textsuperscript{5} Adenosquamous carcinoma is an aggressive variant of SCC that shows an in situ or infiltrative SCC combined in its deeper portion, but not admixed, with a ductal adenocarcinoma.\textsuperscript{15} In contrast to ASCC, the duct-like structures of the adenosquamous carcinoma contain intraepithelial or intraluminal sialomucins and the lining cells show ductal differentiation. Mucoepidermoid carcinoma of minor salivary gland origin rarely shows involvement of the overlying epithelium, whereas mucous cells and intraepithelial and ductal sialomucins are always recognized.\textsuperscript{3,15} In addition, most cells, except squamous cells, are strongly and diffusely CK7\textsuperscript{16}, but CK20−.\textsuperscript{3,15} Extension of a conventional SCC along salivary ducts is an uncommon phenomenon that is usually seen in SCC of the floor of the mouth, where cancer cells replace the normal ductal cells.\textsuperscript{17} Abrupt transition of normal ductal epithelium to carcinoma is characteristic, with the normal luminal cell being CK7+/CK20−.\textsuperscript{18}

In view of the above, the case of an ASCC in the floor of the mouth reported by Kusafuka et al.\textsuperscript{5} is unusual, because the “inner flat cells” lining the pseudoglandular nests were CEA+, CA125+, CK7+, and CK20−, an immunoprofile more consistent with a salivary gland tumor. Although CK7 positivity may be seen in SCC, it is usually focal and weak.\textsuperscript{16} In a breast ASCC, coexpression of glandular (CK8/18) and squamous-type (CK5/13) keratins, combined with a high and variable chromosomal instability, lack of expression of hormone receptors and Her-2, and overexpression of epidermal growth factor receptor and p53, was considered to be consistent with an origin from adult mammary gland stem cells, combined with squamous cell differentiation.\textsuperscript{19}
In the variant of ASCC termed pseudovascular adenoid SCC or angiosarcoma-like SCC, anastomosing spaces and channels that mimic the neoplastic vessels of angiosarcoma are formed. In addition, intense vascularity of the tumor stroma in ASCC may give the erroneous impression of a vascular tumor. In contrast to an angiosarcoma, the cells of ASCC are negative for endothelial markers, such as CD31, CD34, and von Willebrand factor. Cytokeratins should not be considered to be a distinct discriminating criterion, because malignant endothelial cells occasionally may be positive. Recently, endothelial differentiation marker Fl-1 has been recommended as a discriminator between those tumors, because it was negative in 3 cases of oral ASCC, but positive in 1 oral angiosarcoma.

Ultraviolet radiation is implicated in the pathogenesis of cutaneous ASCC, because most tumors develop on sun-exposed surfaces that shows features of actinic keratosis, whereas radiation therapy has been implicated in 2 intraoral cases.

ASCC of the skin shows a more aggressive biologic behavior than typical SCC, and multiple lesions as well as association with other primary tumors, in particular SCC, have been reported. Although the follow-up period in the 9 oral ASCC with available data is rather short for conclusions, it should be noticed that 5 patients died of the disease after 46 months after diagnosis, 4 of them after extensive locoregional recurrence 26 months after diagnosis; interestingly, in the present patient the tumor recurred in 10 months. High proliferation index and intracytoplasmic accumulation of the $\gamma$-2 chain of laminin and $\beta$-catenin have been associated with an unfavorable prognosis. Loss of E-cadherin and syndecan-1 is suggestive of dyscohesion of cancer cells that is thought to promote invasion, and diminished E-cadherin expression has been seen in poorly differentiated and invasive oral SCC. Reports of more cases of ASCC would possibly help to elucidate the role of acantholysis in the biologic behavior of oral SCC.

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REFERENCES


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