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Intra-oral Acantholytic Squamous Cell Carcinoma: 55 Cases. Is this Variant more Aggressive?

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Abstract

We aimed to collect and analyze available cases of intraoral acantholytic squamous cell carcinoma (aSCC), that consisted of the authors' cases and cases derived from the existing literature, with an emphasis on the pathological staging and patient outcome. Our research question was whether aSCC is more aggressive than conventional SCC. The literature was searched for documented cases of aSCC involving the intra-oral mucosa, excluding those from the lips and tonsils, and seven new cases were added from our files. The authors compared the obtained aSCC data to existing data for conventional SCC. Fisher Exact or Pearson's χ^2 tests were used for categorical variables. Fifty-five cases of intraoral aSCC were reviewed, of which 48 were retrieved from the literature. Analysis of the published cases was reinforced by contacting the authors of all the papers with incomplete data for further clarifications. The most common sites of aSCC were the tongue (24/55) and the maxilla/maxillary gingiva and/or palate (11/55). The overall survival rate was 36/53 (67.9%) with a mean follow-up period of 22 months against 62.5% for conventional SCC ($p = 0.6$). No statistically significant difference between the two variants of the tumor with respect to the oral cavity was detected. The differences in age, sex, survival rate, staging, and locations were not statistically significant. Based on the available data from 55 cases, there is no evidence to suggest that aSCC is more aggressive than conventional SCC in intraoral cases.

Keywords Acantholytic squamous cell carcinoma · Squamous cell carcinoma · Prognosis · Survival · Recurrence · Oral cavity

Introduction

Acantholytic squamous cell carcinoma (aSCC) (also termed as adenomatoid squamous cell carcinoma or adenoacanthoma) is an uncommon histological variant of squamous cell carcinoma (SCC) that may appear as a flesh-colored nodule and is characterized by a typical SCC pattern in combination with pseudoglandular structures, dyskeratotic cells, and prominent acantholysis within tumor islands [1–3]. This acantholysis develops owing to the loss of desmosomal adhesion proteins that leads to an impaired cell–cell adhesion. The acantholytic cells may appear extremely bizarre, large, or multi-nucleated. If mucicarmine staining is applied in histopathology, it may reveal no intracytoplasmic mucin. In immunohistochemistry, while Cytokeratin-14 and MNF-116 (pankeratin) are equally expressed in both conventional and acantholytic SCC areas of the lesions, Claudin-1 expression is enhanced and E-cadherin staining is decreased only in acantholytic areas [1–6]. It must be noted, however, that

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the transmembrane protein Claudin-1 overexpression is not specific for aSCC and may be found in various other disorders. A negative E-cadherin membrane staining is indicative for various types of carcinoma. Traditionally, aSCC is considered as a more aggressive variant compared to conventional SCC [2–6].

Specifically for the maxillo-facial area, aSCC of the lip, a site close to the skin, was previously attributed to sun exposure, but intraoral cases cannot be explained by this etiology thus probably bear a different pathway of pathogenesis. The purpose of this study was to present seven new cases of intraoral aSCC and to analyze the existing literature on the intraoral variant of aSCC, with an emphasis on the pathological staging and patient outcome. We aimed to investigate whether aSCC is indeed more aggressive than conventional SCC.

Methods

The goal of the study was to collect and analyze the largest number of the oral aSSC cases to date. Three strategies were implemented: 1) the initial literature search (the PRISMA protocol for the systematic review), 2) contacting the authors of the papers published after 2000 with incomplete data for further clarifications, and 3) the collection of additional cases of the oral aSCC in the authors' hospitals.

Strategy 1: The Initial Literature Search

The literature was searched for adequately documented cases of aSCC published between 1977 and September 2020. The rationale of choosing 1977 as the starting point was based on the preliminary analysis of previously published reports. There were detailed reports on aSCC published in the 1960s [7–9], but the authors used currently outdated classifications of staging and treatment approaches that made adequate comparison and analysis rather difficult. Medline's PubMed, Embase, ScienceDirect, and Google Scholar were searched using the keywords such as "adenomatoid SCC", "adenoacanthoma", "pseudo-glandular SCC", "angiosarcoma-like SCC", "aSCC", AND "oral cavity", "nasal sinuses", OR "mouth". References of published papers were also searched for additional cases. Search results were limited to original human studies with properly described cases of aSCC of the oral cavity.

The search for cases was restricted to the intra-oral mucosa and excluded those from the lips (vermilion area), and the tonsils (oropharynx). Therefore, only the oral cavity cases were analyzed. The selected cases had to include the following ten variables: age, gender, location of aSCCs, information on clinical presentation, the size of the lesion, pathological stage, detailed histological report, risk factors, treatment, and follow-up. Reports without adequate substantial data, abstracts only, conference summaries, meta-analyses, and duplicate data were excluded. Applying this strategy, we initially selected 36 articles but only 24 of them remained after the exclusion criteria were applied. A total of 26 adequately reported cases were retrieved during Stage 1 of the research.

Strategy 2: Eliminating Incomplete Data

Stage 2 contacts with the authors of the papers with incomplete data brought additional data to the current research. The authors contacted corresponding authors of nine articles published after 2000 to clarify their case descriptions in an attempt to eliminate incomplete data. Seven of them promptly responded that added the necessary data to additional eight cases. Therefore, cases with a relatively full description of a case but with only one variable missing (for example, the treatment of the lesion was not indicated or risk factors were not documented) have also been included in the analysis.

Strategy 3: The Search for Additional Cases

Seven new cases have been prospectively collected by the authors from January 2016 to December 2020 (with follow-up to May 2021) at the hospitals in Israel and Uzbekistan. They have been combined with the previously published cases in one group, tabulated, and analyzed.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (amended 2013) as reflected a *priori* after approval by the Institutional Review Board—Helsinki committee.

Comparison between aSCC and SCC

To evaluate if aSCC is more aggressive than conventional SCC in oral cavity cases, the authors compared the obtained aSCC data to that of SCC. The SCC data on clinical presentation, the typical size of the lesion, pathological staging distribution, risk factors, treatment, and follow-up were extracted from case reports, general descriptive publications of the last decade [10–13] and the SEER Cancer Statistics Review 1975–2017 [14].

Analysis

The cases of aSCC were compared with extracted SCC data using the Fisher Exact test or Pearson's χ^2 test for categorical variables (gender, diagnostic findings, staging, management, outcome). The *t*-test was used to assess differences between patients of the two groups for a continuous variable (age). The correlation coefficient "r"

was calculated to detect possible connections between analyzed variables and gender and age of the patients. The data were statistically evaluated by SPSS, Standard version 17.0 (SPSS, Chicago, IL, 2007). As the numerator was less than 100, all references to percentage were changed to a fraction. The level of significance for all analyses was set at $p < 0.05$, but for analysis of the lesion sizes and staging, we also assessed whether findings remained after Bonferroni correction for multiple comparisons that corresponded to an adjusted $\alpha = 0.025$.

Results

A total of 41 full-description cases of intraoral aSCC were analyzed (literature: 34 cases; authors: seven cases; mean age 61.5 ± 9.6 y, range 38–92 y). In addition to these full-description cases, 14 cases were described as a group in one publication without detailed case-by-case descriptions except indication of location, staging, and the outcome [15]. Therefore, the analysis of location was performed for 55 cases, the analysis of staging for 52 cases, and the outcomes analysis was performed for 53 cases. The full study data are presented in a table in the Supplementary data. Pathological staging for the newly added cases was assessed according to the 7th edition of the American Joint Committee of Cancer (AJCC) [16]. The authors decided to use the 7th edition instead of newly published 8th edition as this edition was in use when the majority of the analyzed literature cases were reported.

Analysis of the Intraoral aSCC Cases

The male to female ratio was 3:2. The clinical presentation was known in 41 cases and was dominated by exophytic ulcerated lesion (15/41) and exophytic lesion (13/41) followed by only ulcerated lesions (6/41) and polypoid lesions (2/41). Two cases presented erythroleukoplakia, two appeared as nodular, and in one case the lesion was described as "diffuse swelling". Invasion to adjacent structures was mentioned in 13 cases (13/41), in six cases the tumor penetrated the maxillary sinus, five of these were bone invasions, and the Wharton's duct was affected in two cases. The rest of the cases (28/41) did not present invasion to adjacent structures. The distribution of the lesion sizes (retrieved for 39 cases) was as follows: T1 (˂2 cm) – 11/39, T2 (2–4 cm) – 7/39, T3 (4–6 cm) – 10/39, and T4 – 11/39.

For all 55 cases selected for analysis, the location of the lesion was clearly indicated. Most of them were on the tongue and on the mucosa of the maxilla, while the floor of the mouth, the buccal mucosa, and the mandibular gingiva were less involved (Table 1). For the pathological staging, most of the cases (23/52) were at stage 4, and in three cases the pathological stage was not documented. A description of 40 cases documented risk factors indicating 24 patients without them. Smoking (11/40), denture/orthodontic appliances use (3/40), and diabetes mellitus (2/40) were documented (Supplemental Table S1).

The overall survival rate (those who were free of the disease and those who suffered from recurrence but still alive) was 36/53 with a mean follow-up period of 22 months. Among 17 patients (17/53) who died of the disease, 11 died in the first year and six others died in four years. Among nine patients (9/53) who suffered from tumor recurrence, six

Table 1 The comparison between data squamous cell carcinoma (SCC) and acantholytic squamous cell carcinoma (aSCC) of the oral cavity

Variable	SCC	aSCC	P
General (41 aSCC cases)			
Age, y	62–63	61.5	0.9 (t-test)
Sex, M:F ratio	2:1	1.5:1	0.5 (Fisher Exact test)
Survival rate	62.5%	36/53 (67.9%)	0.6 (Fisher Exact test)
Smoking	75%	11/40 (27.5%)	0.01 (less) (Fisher)
Pathological stages III and IV	65%	32/52 (61.5%)	0.4*(Pearson's χ^2 test)
Location			
Tongue	25%–40%	24/55 (43.6%)	0.02 (more)
The floor of the mouth	15%–20%	6/55 (10.9%)	0.02 (less)
Palate/maxilla	5%–24%	11/55 (20.0%)	1
Buccal	2%–10%	6/55 (10.9%)	0.03 (more)
Mandibular	2%–10%	8/55 (14.5%)	0.02 (more)

Out of 55 analyzed cases, 41 cases had full description and for 14 cases only location, staging, and outcome were indicated. P values: "more"–more frequent than in SCC cases, "less"–less frequent that in SCC cases. The analysis for locations was performed with the Pearson's χ^2 test

*The statistical difference was not maintained after Bonferroni correction for multiple comparisons

remained alive during their follow-up periods (not always 22 months).

Comparison between aSCC and SCC of the Oral Cavity

The comparison is presented in Table 1. The only statistically significant differences between the two types of carcinoma in respect to the oral cavity can be seen in their location within the cavity ($p = 0.03$ or 0.02). The differences between other variables, including age, sex, survival rate, and staging are not statistically significant. Within the risk factor topic, smoking was not the main risk factor for aSCC and this is the only statistically significant difference between aSCC and SCC cases ($p = 0.01$) besides the location issue. The treatment options for both SCC and aSCC – surgery, radiotherapy, chemotherapy – were identical.

Discussion

We presented the analysis of the largest to date group of 55 aSCC cases of the oral cavity. It has been suggested in the literature that aSCC may be more aggressive than conventional SCC but the issue has not been resolved, possibly due to the rarity of this type of SCC in general, and in intra-oral location in particular. This question is not purely theoretical. If aSCC patients represent a higher risk category in comparison with SCC patients, they should be targeted with more aggressive and/or novel therapies. ASCC occurring in skin [17, 18], prostate [19], breast [20], and larynx [21] were classified as aggressive. In the head and neck region, it was reported that aSCC of the nasopharynx was more aggressive than skin aSCC [22]. In regard to intraoral tumors, the aggressiveness of the tumor was stressed for aSCC of the maxilla [23] and the tongue [24].

The opposite viewpoint was expressed by Nappi et al. [25] who indicated that cutaneous aSCC usually "behaved in an indolent manner." In 2011, Garcia and Crowson [26] conducted an in-depth literature search and found out that "analysis of the published evidence does not support the assumption that ASCC is a more-aggressive tumor." The same viewpoint was also expressed by Ogawa et al. in 2017 [27]. While these reports dealt with cutaneous aSCC, the intraoral cases were not analyzed.

Some diagnostic problems may arise with aSCC because this tumor is a subject for a significant morphologic mimicry in nondermal locations [28]. While our results suggest that features of acantholysis are not important for intraoral SCC cases with respect to prognosis, it is important to recognize the entity so it is not confused with adenocarcinoma. Such mimicking-dependent confusion was described for pulmonary, gallbladder, and esophageal adenocarcinomas and aSCC cases [29–31]. There was only one such mimicking case described in the analyzed literature on intraoral cases. Terada described a case that was diagnosed as aSCC but the tumor appeared to be positive for "squamous cell carcinoma markers (CD5/6, CK34βE12, and p63) and adenocarcinoma markers (CEA, CA19-9, CA125, MUC1)" at the same time [32]. However, once the diagnosis is recognized there is no prognostic significance of the histological variant of aSCC with respect to conventional SCC.

Our results seem to be more in favor of the opinion that intraoral aSSC is not more aggressive than conventional SCC of this location. Analyzing the same topic, Garcia and Crowson lamented that "published data are scant and contradictory" [26]. We also were not fully satisfied with the results of our literature search and documentation in the cases or case series reviewed and that is why the additional clarification strategy was implemented (see Supplement data Table S1). Case reports and case series can be very useful for clinicians, as long as they are well documented.

Limitations

The limited number of documented cases of aSCC does not enable us to differentiate survival in different stages of the disease. The second limitation is that our analysis concentrated on intraoral cases of aSCC and cannot be generalized for other locations. For example, the above-mentioned report on prostate aSCC indicated two-year survival rate for the entire cohort as 37.8% and 78% for those patients who underwent prostatectomy [19]. The survival rate of 36/53 (67.9%) among the analyzed cases of oral aSCC is somewhere between these numbers, but it is evident that aSCC may express itself differently in different locations. Another limitation of the analysis was that the publications describing SCC might contain cases of acantholytic, conventional SCC, and variants that may be not exclusive for non-aSCC.

Conclusion

Published data concerning intraoral aSCC are not appropriately documented. However, based on the available data there is no evidence to suggest that the acantholytic variant of SCC is more aggressive than conventional SCC in intraoral cases.

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Authors contributions MA—Conceptualization; Methodology; Investigation—raw data collection in Israel; Data curation; Project administration; Supervision; Writing—review & editing; Approval of the final version of the manuscript. ON—Conceptualization; Methodology; Data curation in Israel; Writing—original draft; Writing—review &

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Data availability Supplementary Table 1

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (amended 2013) as reflected a *priori* after approval by the Institutional Review Board—Helsinki committee.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish Not applicable.

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