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ORIGINAL ARTICLE

Exploring the Aggressiveness of Sarcomatoid Carcinoma of the Oral Cavity – an Institutional Experience

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Abstract

Background: Sarcomatoid variant of squamous cell carcinoma in the oral cavity is a rare biphasic variant of squamous cell carcinoma. This aggressive variant of squamous cell carcinoma is characterized by invasive growth with marked local recurrence and distant metastasis resulting in poor prognosis. Sarcomatoid carcinoma can occur over a wide age range, incidence increases with older age and is a male-predominant disease. **Methods:** 23 patients with histologically proven Sarcomatoid SCC or with a sarcomatoid component (Group A) were compared with 23 randomly chosen patients with clinical stage IV (Group B) disease at the time of diagnosis, within the same time period and comparison was made between disease free survival and overall survival. **Results:** In group A, the mean DFS was found to be 12.4 months raging from 1 month to 36 months. 6 patients were therafter lost to follow follow up, in 11 patients the mean overall survival was found to be 8.72 months (ranging from 2 to 18 months) whereas 6 patients are alive till date. In group B, the mean DFS was found to be 19.56 months ranging from 6 months to 33 months. 4 patients succumbed to the disease with a mean overall survival of 24.25 years (ranging from 18 to 33 months), 4 patients were lost to follow up and the rest are alive till date. **Conclusion:** Sarcomatoid carcinoma of the oral cavity is an extremely rare but aggressive variant of conventional squamous cell carcinoma. We have to systematically understand their clinical, morphological and immunohistochemical features which is critical for their accurate diagnosis which aids in correct patient management. After radical surgery and adjuvant radiation therapy, strict follow up for development of recurrence and distant metastasis should be done.

Keywords Prognosis · Aggressiveness · Overall survival · Disease free · Survival · Sarcomatoid

Introduction

Sarcomatoid variant of squamous cell carcinoma is a rare biphasic variant of squamous cell carcinoma characterized by dysplastic surface squamous epithelium and a stromal element consisting of invasive spindle cells [1]. It has been proven by studies that conventional squamous cell carcinoma and the sarcomatoid constituents monoclonally arise from a single stem cell. This aggressive variant of squamous cell carcinoma is characterized by invasive growth with marked local recurrence and distant metastasis resulting in poor prognosis [2]. One thought is that, under extremely rare conditions, the pathogenesis of sarcomatoid carcinomas is due to transformation of a particular subset of poorly differentiated squamous carcinomas. Sarcomatoid carcinoma can occur over a wide age range, incidence increases with older age and is a male-predominant disease. Older age, consumption of alcohol, tobacco usage in any

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form and previous exposure to radiation therapy (RT) may act as additional risk factors. On the whole, the mortality rate of sarcomatoid carcinoma is higher than conventional squamous cell carcinomas with better outcomes associated with early stage and extraoral tumors [3]. Recently, there has been a shred of light on the predictive role of the pre-operative and postoperative inflammatory parameters (NLR, PLR, and LMR) and histopathological parameters in determining the prognosis and survival.

outcomes of these patients [4]. In this study, we aim to analyse the oncological outcome of these tumours by reviewing the tumour biology, recurrence rate, distant metastasis and overall prognosis of 23 patients between July 2018 to May 2021 in our institution.

Materials and Methods

Inclusion and Exclusion Criteria

In this study, all the patients between > 18 and < 80 years at diagnosis with histopathologically proven sarcomatoid carcinoma of the oral cavity (confirmed by immunohistochemistry) without any evidence of metastases who underwent treatment at our institute between July 2018 and May 2021 were included.

Patients with known distant metastasis were excluded from the study.

Patients with a prior history of squamous cell carcinoma who developed recurrence at the same site or a second primary in the oral cavity without any evidence of distant metastasis were also enrolled for the study.

Management Criteria

All the patients whose lesions were surgically resectable at baseline underwent upfront surgery with modified neck dissection and appropriate reconstruction. The patients who had gross disease involving vital structures and deemed unresectable at baseline, received induction chemotherapy or neoadjuvant chemotherapy (NACT) with the idea of downstaging the disease and make it resectable. Taxotere-Platinol-fluorouracil or the TPF regimen was used for induction chemotherapy. Post-surgery, the patients with high-risk features on the histopathological report were treated with adjuvant chemoradiation or radiotherapy as per the standard guidelines.

Tumour Biology

Assessed by clinical characteristics and histopathological data, such as age, gender, site of lesion, tumour size, tumour histology, lympho-vascular emboli (LVE), perineural invasion (PNI), margin status, depth of invasion, worst pattern of invasion, regional lymph nodal status with or without extra nodal extension.

Diagnosis

All these cases were diagnosed to be sarcomatoid carcinoma of the oral cavity histopathologically and confirmed by IHC by the same histopathology team of our institution. On microscopic examination diagnosis of sarcomatoid carcinoma was done if a biphasic tumour consisting of conventional clusters of squamous epithelial cells and proliferating atypical spindle cells which were positive for hematoxylin and eosin (H&E) staining was observed. Confirmation by IHC was done by the presence of the markers CK, EMA, AE1/AE3 HMWCK, P16, and CD10.

Post treatment completion, patients were kept on regular follow up and suspicious recurrent lesions on clinical and radiographical examination were subjected to histopathological examination for confirmation. Metastatic work up was done using CT Thorax and abdomen or a PET CT scan.

Patients were followed up for a minimum of 1 year and assessed for recurrence, development of distant metastasis, disease free progression and overall survival.

These patients with histologically proven Sarcomatoid SCC or with a sarcomatoid component (Group A) were compared with 23 randomly chosen patients with clinical stage IV (Group B) disease at the time of diagnosis, within the same time period and comparison was made between disease free survival and overall survival. We defined overall survival as the time period from the diagnosis of the disease to death due to disease or any cause. Disease free survival was defined as the time period from diagnosis till the disease relapsed (local regional or metastatic).

Results

In group A, a total of 23 patients with sarcomatoid carcinoma were included in the present study cohort. All baseline characteristics and clinicopathological features are presented in Table 1. The mean age of the patients at presentation was found to be 49.65 years (IQR: 30–78 years). The majority of the patients were male (91.30%) with poorly differentiated SCC (47.82%) at the time of initial diagnosis. Four of 23 patients had.

received radiotherapy previously. The most common habit in patient's cohort was found to be tobacco.

chewing (11/23) and a few of them (9/23) had multiple habits such as alcohol consumption and smokeless tobacco. Four patients had advanced staged tumours who

Table 1 Patient Parameters

VARIABLES	GROUP A (n = 23)	GROUP B (n = 23)	P value
Age			
> 50 years	10	15	
< 50 years	13	08	
Sex			
Male	21	19	
Female	2	4	
Habits (Tobacco/alcohol)			
Yes	22	19	
No	1	4	
Site			
Tongue	5	03	
Buccal mucosa	15	20	
Maxilla	3	00	
NACT	4	9	
Response to NACT			
Complete Response	0	2	
Partial response	0	4	
No/Minimal Response	4	3	
Previous RT	4	0	
T size			
> 4 cm	10	4	
< 4 cm	13	19	
LVI			
Present	10	08	
Absent	13	15	
PNI			
Present	15	06	
Absent	08	17	
WPOI			
> 3	23	17	
< 3	0	07	
DOI			
> 10 mm	14	16	
< 10 mm	09	07	
Lymph Nodes			
Positive	07	06	
Negative	16	17	
Staging			
TI-T2	04	00	
T3-T4	19	23	
Adjuvant Therapy			
Only RT	16	14	
Adjuvant CT + RT	07	09	
None	00	00	
DFS			
> 6months	16	22	
< 6months	07	01	
Overall survival			
> 12months	02	04	
< 12months	09	00	
Lost to follow up	06	04	
Alive till date	06	14	

received NACT followed by surgery and 15 patients underwent upfront surgery followed by adjuvant treatment and 4 patients had recurrent disease where they had received prior adjuvant therapy. Post operatively, 15/23 patients received adjuvant radiation.

In group B, 23 randomly chosen clinically stage 4 patients with histologically proven Squamous cell carcinoma who were diagnosed during the same time period were included. All baseline characteristics and clinicopathological features are presented in Table 1. The mean age of the patients at presentation were 53.91 years (IQR: 39–74 years). Males were predominant (82.60%) in the study with moderately differenciated (56.52%) carcinomas at the time of initial diagnosis. 9 patients had received prior neo-adjuvant chemotherapy because of advanced disease and the rest had undergone upfront surgery. The most common habit in this patient cohort was found to be smoking in 10 patients followed by guthkha chewing in 9 patients. Post operatively all patients received adjuvant radiotherapy and 9 among them received concurrent chemotherapy.

In group A, the mean DFS was found to be 12.4 months raging from 1 month to 36 months. 6 patients were therafter lost to follow follow up, in 11 patients the mean overall survival was found to be 8.72 months (ranging from 2 to 18 months) whereas 6 patients are alive till date.

In group B, the mean DFS was found to be 19.56 months ranging from 6 months to 33 months. 4 patients succumbed to the disease with a mean overall survival of 24.25 years (ranging from 18 to 33 months), 4 patients were lost to follow up and the rest are alive till date.

Discussion

Sarcomatoid Carcinoma is an unusual variant of squamous cell carcinoma and portrays a biphasic histologic picture with an invasive spindle cell component and many types of epithelium ranging widely from mild dysplasia to invasive carcinoma [1] (Fig. 1a and b). It was first described by Virchow in 1864. He labeled it as carcinosarcoma, suggesting it to be a "collision tumor" between a carcinoma and sarcoma [5–7]. In 1900, Krompecher suggested that the tumour consists of an epithelial origin with "dedifferentiation" to a spindle cell morphology and coined the term "sarcomatoid carcinoma" to describe it [6, 7]. In 1957, Lane proposed to use the term "pseudocarcinoma" suggesting that it may actually be a squamous cell carcinoma with an atypical reactive stroma [6, 7]. The majority of the tumour is comprised by spindle cells, with occasional regions having epithelioid pattern. These tumours exhibit typical growth patterns, presence of invasive or related dysplasia/carcinoma in situ components distinguish sarcomatoid

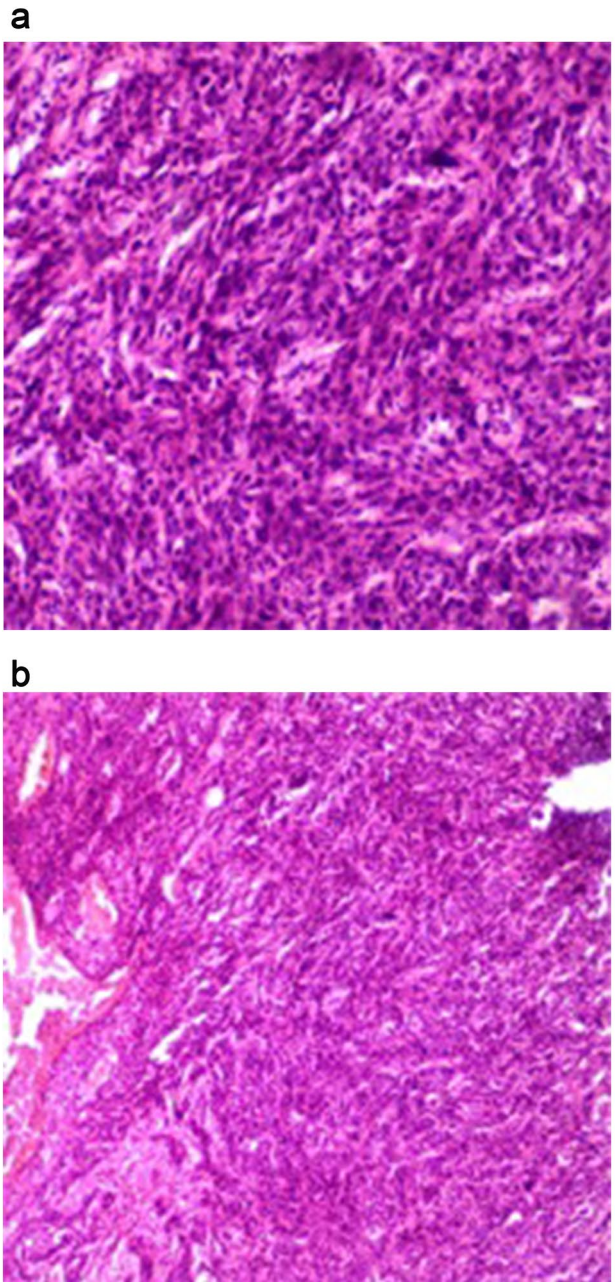

Fig. 1 **a** HP view - H&E stain shows spindle shaped atypical cells with hyperchromatic nuclei and moderate cytoplasm. **b** LP view - H&E stain shows spindle shaped atypical cells arranged in sheets

carcinomas from other primary sarcomas or melanomas [8]. Immunohistochemistry (IHC) is used to identify markers for epithelial differentiation (pan-CK, EMA, or p63) for diagnosis of head and neck sarcomatoid carcinomas [9]. However, if the expression of epithelial markers are negative, it does not exclude the possibility of sarcomatoid carcinoma because the epithelial differentiation within the tumour is highly variable. It is believed that the tumour cells undergo mesenchymal differentiation and it is the most widely accepted hypothesis for sarcomatoid carcinoma [9]. Other factors like radiation, prior trauma, tobacco usage, smoking and alcohol consumption are proposed to be the key factors in this conversion mechanism. Some believe that patients who have been previously irradiated are more likely to get converted and radiation appears to play a major role in this case. Newer radiation therapy modalities such as intensity-modulated RT (IMRT) reportedly increase the risk of secondary malignancies [10]. A reason for this might be that normal tissues are exposed to a lower radiation dose of radiation but the total dose of body exposure is somewhat increased. Tissues around the primary tumor are especially at risk for transformation. However, distinguishing criteria between secondary malignancies from radiation induced malignancies still remains unclear [11]. Cahan et al. [12] was the first to present a diagnostic criteria for radiation induced sarcoma, which included a minimum latency of 5 years from previous RT however, some authors believe that even shorter periods of latency would be acceptable. In our study 4 patients had received prior RT, however the latency periods were 2.1 years, 2.3 years, 23 months and 21 months post RT respectively. Therefore, we cannot comment definitely whether these patients developed radiation induced sarcomatoid carcinomas or de novo secondary malignancies in such a short period of time. Sarcomatoid carcinoma though relatively common in other sites in the body, is uncommon in the oral cavity and accounts for less than 1% of all tumors of oral regions [7]. In the oral cavity, the frequent sites involved are lower lip (42%), tongue (20%), alveolar ridge or gingiva (19%) [13]. In our study the most frequent site of involvement was the buccal mucosa in 65.2% of the cases followed by tongue in 21.7% of the cases. It has been noted that prolonged tobacco usage (both chewable and smoked forms) and consumption of alcohol are strong pre disposing factors for the development of conventional squamous carcinoma as well as for sarcomatoid carcinoma [14]. Our study showed similar results with all these factors. Additionally, tobacco chewing (60.86%) was more commonly observed than smoking (26.08%) in our study, similar to the reported figures of 77% and 42% from this part of the world [15, 16]. The clinical picture varies from an exophytic growth, pedunculated or sessile, a polypoid mass with surface ulceration to a frankly infiltrative or endophytic ulcer [13]. (Fig. 2a, b and c)No study definitely points to the role of neo adjuvant chemotherapy in advanced cases of sarcomatoid carcinoma of the oral cavity. In view of advanced disease, 4 patients in our study received NACT prior to surgery. However, in 100% of the patients response to chemotherapy was nil (CRS 1) Our study indicates that instead of using NACT in an attempt to downstage the tumour upfront surgery or definitive radiation should be used as the primary mode of treatment. Overall nodal

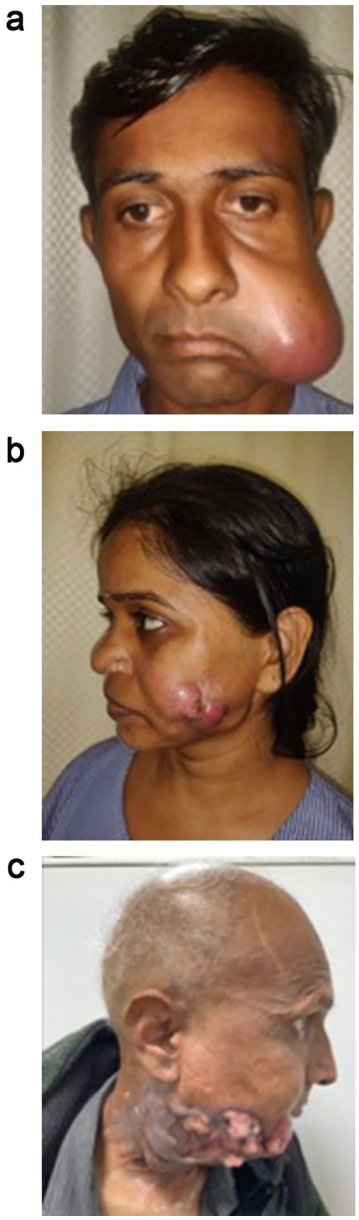

Fig. 2 **a** Extra-oral swelling without any frank ulceration. **b** Extra-oral swelling with ulceration. **c** Extensive ulcero-proliferative growth

metastasis is typically uncommon in sarcomatoid carcinoma of the oral cavity. Gamez et al. [17] reported that positive neck nodes were present in only 5% of the cases in patients of sarcomatoid carcinoma of Carcinoma Larynx. In another study by Niu et al. [18], reported that 20% patients had pathologic node metastasis in patients who underwent neck dissection. However, in our study, it was noted that 7 (30.43%) patients had neck metastatic disease which is more than that of the other reported studies. This discrepancy may be due to the fact that our study focusses on sarcomatoid carcinoma of the oral cavity where nodal metastasis is more common than that of laryngeal carcinomas. Out of these 7 patients, 4 patients developed nodal recurrence of the opposite neck during the said follow up period. Hence, in cases where neck nodes are positive in the post-operative histopathology report, we recommend addressing the opposite neck at that time to prevent nodal recurrence. Chang et al. [19] in their study of 78 patients, reported 64% (n = 50) to be having T3 or T4 tumours at the time of diagnosis. Our study showed a slightly higher incidence of 82.60% of the patients reportedly having T3 or T4 tumours at the time of initial diagnosis. Most patients had two or more poor prognostic factors present which suggested a dimal outcome for these patients. Lymphovascular invasion was present in 43.47% of the patients, perineural invasion in 65.21% of patients, WOPI of 4 and 5 were present in 100% of the patients and depth of invasion greater than 1 cm was seen in 60.86% of the patients. Effectiveness of adjuvant radiotherapy and chemotherapy for local and distant control of conventional squamous carcinoma is known and widely accepted but little is known about the effectiveness of the same for sarcomatoid carcinoma. Chang et al. [19] in his study found that in 64.1% of the patients who received radiotherapy, no apparent survival benefit was present. Another paper demonstrated sarcomatoid carcinoma of the larynx [20] the authors reported that compared to a 57.1% disease specific survival rate with nonsurgical treatment, surgery led to a 5-year DSS rate of 84.1%, and adjuvant radiotherapy was not advised. In out case series 100% of the patients received adjuvant radiation and 7 patients (30.43%) received additional chemotherapy along with radiation therapy. No survival benefit or improvement in disease free survival was found. However, for the patients who underwent a recurrent disease, oral metronomic therapy consisting of methotrexate (9 mg/m2), Celecoxib (200 mg twice a day), Gefitinib (250 mg once a day) were started and 4 patients had a significantly increased overall survival with a mean of 18 months and 2 patients are alive till date. Disease progression in sarcomatoid carcinomas is reported to be characterized by disease recurrences and distant metastases [14]. This was found in 13 (56.52%) of the patients in our study. Local recurrence was seen in 8 patients (34.78%), similar to the figures of reported literature between 16 and 32% [14]. Thompson et al. [21] reported lungs to be the most frequent site for distant metastasis. In our study pulmonary metastasis was seen in 4(17.39%) of the patients. The prognosis of patients with sarcomatoid carcinoma of the head and neck is found to be typically dismal. Berthelet et al. [22] reported a total of 17 patients in his study and the authors found that the median survival time was 32 months, with an actual survival of 72% and 42% at 2 and 5 years, respectively. Mean disease-free survival was 12.4 months ranging from 1 month to 36 months. Death due to disease was documented in 11 (47.82%) patients. In these

patients, mean overall survival was documented to be 8.72 months (ranging from 2 to 18 months). However, no definite conclusions on survival could be made because rest of the patients were lost to follow up. In patients with stage IV disease but histologically proven squamous cell carcinoma, the mean DFS was found to be 19.56 months ranging from 6 months to 33 months which is significantly higher than the group of patients suffering from sarcomatoid carcinoma. Only 4 patients succumbed to the disease in a follow up period of minimum 1.5 years with a maximal follow up of 4 years with a mean overall survival of 24.25 years. The comparison (Table 1) proves that even though patients with stage IV conventional squamous cell carcinoma present with poorer prognostic factors, the DFS and overall survival is better than the group of patients of sarcomatoid carcinoma.

Because sarcomatoid carcinoma is rare, there is no absolute consensus on the optimal treatment for sarcomatoid carcinoma. Literature suggests that surgery with radiotherapy and/or chemotherapy are used to manage such tumours. The effectiveness of radiotherapy with respect to survival is controversial, and the optimal cytotoxic chemotherapy regime remains unclear. Total treatment efficacy is lower than that of conventional squamous cell carcinoma and the prognosis is sombre. Toripalimab is a novel humanized IgG4 monoclonal antibody directed against PD-1 that differs from other monoclonal antibodies pembrolizumab and nivolumab. A paper from China presented a case report, where taking into account the rarity of sarcomatoid carcinoma and the patient's PD- L1 overexpression they opted for treatment with toripalimab combined with cisplatin and liposomal doxorubicin, which achieved a substantial partial response [23]. Though larger study population is required, this may be a promising treatment option in similar patients in the future.

Thus, to conclude, Sarcomatoid carcinoma of the oral cavity is an extremely rare but aggressive variant of conventional squamous cell carcinoma. We have to systematically understand their clinical, morphological and immunohistochemical features which is critical for their accurate diagnosis which aids in correct patient management. After radical surgery and adjuvant radiation therapy, strict follow up for development of recurrence and distant metastasis should be done. If nodal disease is positive, opposite neck dissection should be considered to prevent opposite neck nodal recurrence during follow up. The role and advantage of using oral metronomic therapy in these patients should also be evaluated in the long run. The utility of novel agent Toripalimab in these patients should also explored for these patients.

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