International Journal of Research in Medical Sciences
Qayoom S et al. Int J Res Med Sci. 2019 Feb;7(2):561-567
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190088

Original Research Article

Clinicopathological and immunohistochemical analysis of Sarcomatoid carcinoma of head and neck mucosal region: a retrospective analysis

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Received: 25 December 2018
Revised: 12 January 2019
Accepted: 15 January 2019

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ABSTRACT

Background: Sarcomatoid carcinoma is a biphasic tumour comprising both of malignant epithelial and mesenchymal elements derived monoclonally from same stem cells. These are unusual variants of squamous cell carcinoma and constitute less than 1% of the head and neck mucosal tumors. Only few studies have been published and needs more understanding to establish treatment guidelines. The aim of this study was to review the cases of carcinosarcoma arising from mucosal sites of head and neck and study their clinical, histological and Immunohistochemical features.
Methods: Retrospective data and slides of histologically proven sarcomatoid carcinoma over a period of thirty -four months between January 2016 - October 2018 were retrieved and evaluated for various clinical and histopathological parameters.
Results: Total of 22 cases were included in the study and the mean age of presentation was 58years with male: female ration 2:1. Most of the patients (81.8%) presented with a mass lesion of less than 6 months duration. The most common site was oral cavity (68.1%) followed by larynx (22.7%). Clinical stage was known in eleven cases. One case presented with pulmonary metastasis. Histopathologically, epithelial differentiation was identified in nine cases (41%) on morphology and in thirteen cases could be highlighted by cytokeratin positivity. The Mesenchymal component was arranged in sheets (63.7%) and fascicles (31.8%). Marked anaplasia and brisk mitosis wereseen in 54.5% and 19.3% respectively. On immunohistochemistry all 22 cases were positive for Vimentin, twenty cases were positive for cytokeratin/EMA and aberrant mesenchymal markers were expressed in 10% of cases. Follow up was available in eighteen cases out of which fourteen cases died within one year of diagnosis.
Conclusions: Diagnosis of sarcomatoid carcinoma is challenging especially on small biopsy because of overlapping features with other spindle cell tumors. Understanding the clinicopathological features facilitates their diagnosis and effective clinical management.

Keywords: Head and neck, Immunohistochemical, Mucosal, Sarcomatoid carcinoma

INTRODUCTION

Sarcomatoid carcinoma is a biphasic tumor comprising both of malignant epithelial and mesenchymal elements derived from the same stem cells. These are unusual variants of squamous cell carcinoma and constitute less than 1% of the head and neck mucosal tumors. The most common reported sites are larynx followed by gingiva, tongue, hypopharynx and nasal cavity.[1] Even though these tumors are biphasic, both the components have been proven to have a common origin.[2] These lesions pose a diagnostic difficulty especially on small biopsy as they closely resemble other benign and malignant spindle cell tumors. However, their correct diagnosis is essential as they differ in clinical management and outcome.[3] The aim of this study was to review the cases of

carcinosarcoma arising from mucosal sites of head and neck and study their clinical, histological and immunohistochemical features.

METHODS

This was a retrospective study of all consecutive cases of sarcomatoid carcinoma in head and neck mucosal region diagnosed over a period of thirty four months between January 2016-October 2018. The study was conducted in a tertiary care centre which receives the large burden of oral cavity cancers constituting approximately 35% of total cancer cases. Clinical details comprising of demographic profile, history of tobacco or alcohol intake, symptoms and duration of illness were available in all cases and retrieved from hospital records. Follow up details were available in eighteen cases.

Histopathological evaluation

Hematoxylin and eosin stained slides were examined for reviewing the diagnosis and evaluating other histopathological parameters like presence or absence of overlying epithelium, dysplasia in overlying epithelium, presence or absence of squamous differentiation, pattern of arrangement of the tumour cells, presence or absence of necrosis, tumour giant cells, nucleoli, nuclear anaplasia which was graded as mild , moderate and severe, mitotic figures counted as number of mitotic figures per ten high power field, retraction clefts in invasive epithelial component, lymphovascular and perineural invasion. For the cases where a resection specimen were available status of the lymph node and underlying bone was also evaluated along with the pathological stages.

Immunohistochemical evaluation

IHC markers were used depending upon the morphological evidence of squamous cell differentiation as and when required. The details of the panel of antibodies used is given in Table 1.

Table 1: Immunohistochemistry antibodies and their clones.

Antibody	Clone	Company
Cytokeratin	AE1/AE3	Dako
Epithelial membrane antigen	E29	Dako
Vimentin	V9	Dako
CK5/6	D5/16B4	Dako
CD10	56C6	Dako
CD56	123C3	Dako
P63	P63	Dako
S-100	Poly	Dako
Smooth Muscle Actin (SMA)	1A4	Dako
CD31	JC70A	Dako
CD34	QBEnd10	Dako
BCL2	124	Dako
Melanosome	HMB45	Dako

RESULTS

A total of twenty two cases of sarcomatoid carcinoma were diagnosed over the study period. Thirteen cases were small biopsies where resection specimen was not available. These were from those patients who did not opt for surgical resection, were given palliative chemoradiotherapy due to inoperable stage or died before surgery could be done.The median age at presentation was 58 years (range- 30 to 72 years) with a male: female ratio of 2:1. The most common site was oral cavity constituting fifteen cases (68.1%) followed by larynx involved in five (22.7%) cases, nasal cavity involved in two cases (9.1%). In oral cavity the most common site involved was upper or lower alveolus followed by gingiva, buccal sulcus and tongue. The clinical information of the patients is summarized in Table 2.

Table 2: Clinical and demographic details of patients.

clinical feature	No of cases (%)
Gender	
Females	07
Males	15
Age at Presentation (yrs)	
Average	58
Range	30-72
Tobacco chewing	
Yes	16 (73%)
No	06 (27%)
Bidi Smoking	
Yes	05 (23%)
No	17 (77%)
History of radiation head and neck	
Yes	None
No	22
Presenting Complaint	
Rapidly growing Mass	11(50%)
Ulcer	04 (18.1%)
Pain	10(45.5%)
Difficulty in swallowing	02(9%)
Change in voice	02(9%)
Hemoptysis	02(9%)
Duration of symptoms	
Less than six months	18 (82%)
More than six months	04 (17.6%)
Site involved	
Oral Cavity	15(68%)
Larynx	05(22.7%)
Nasal Cavity	02(9%)
Clinical stage (known in eleven patients)	
cT1	01(9.0%)
cT2	05(45%)
cT3	02(18%)
cT4	03(27%)
Distant metastasis	01(9.0%)

Predisposing factors

History of tobacco chewing was present in sixteen cases (73%), bidi smoking in five cases (23%) and no history of either tobacco chewing or smoking in one patient.

Clinical details

The most common presenting symptom in cases with oral cavity lesion was ulcero-proliferative growth. The cases with lesion in larynx presented with difficulty in deglutition and change in voice. Both the cases with nasal cavity lesion presented with bleeding and nasal block. History of pain was seen in ten patients (45.5%). The duration of symptoms ranged from twenty days to one year, and in almost 80% cases it was less than 6 months. Tumor size was available in nine cases and ranged from 1.9cm to 9cm on clinical examination**.** Gross appearance was polypoidal or ulceroproliferative in twenty cases (91%) (Figure 1) and ulceroinfiltrative in two cases (9%). Clinical stage was known in eleven cases in which one case was T1, five cases were T2, two cases were T3 and three cases were T4. Out of these eleven cases lymph node metastasis was present in eight cases. Pulmonary metastasis was seen in one patient.

Gross examination

Nine resection specimens showed polypoidal or proliferative growth with ulcerated overlying mucosa (Figure 2).

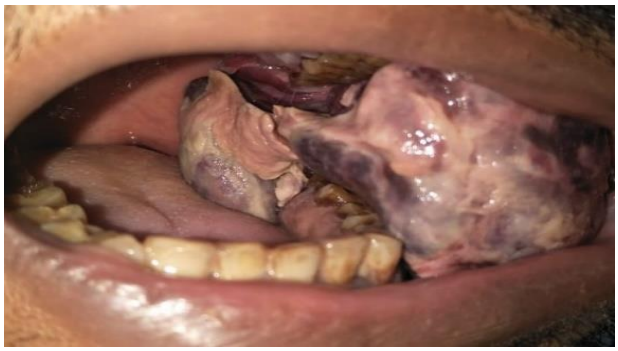

Figure 1: Polypoidal ulceroproliferative mass.

Figure 2: Gross specimen showing a polypoidal growth.

Table 3: Microscopic features of sarcomatoid carcinoma.

Microscopic features (H & E)		No of cases found / No of cases evaluated (%)
Overlying epithelium		
Present		11/22 (50%
Hyperplastic		5/11 (45.5%)
Dysplastic		4/11 (36.4%)
Atrophic		2/11(18.2%)
Evidence of squamous differentiation on H&E		9/22 (41%)
Arrangement of mesenchymal component		
Fascicles		7/22 (31.8%)
Sheets		14/22 (63.7%)
Perivascular		1/22 (4.5%)
Cellular feature of mesenchymal component		
Spindle shaped		19/22 (86.4%)
Epithelioid		2/22 (9.1%
Round to oval		1/22 (4.5%)
Degree of nuclear anaplasia		
Marked		12/22 (54.5%)
Moderate		6/22 (27.2%)
Mild		4/22 (19.3%)
Nucleoli		
Prominent		10/22 (45.5%)
Conspicuous		6/22 (27.2%)
Inconspicuous		6/22 (27.2%)
Mitosis		
Significant mitosis		16/22 (72.7%)
Brisk mitosis (>30/10 hpf)		4/22 (19.3%)
Atypical mitosis		5/22 (22.7%)
Other Features		
Necrosis		10/22 (45.5%)
Extensive necrosis (>50% area)		3/22 (13.7%)
Tumor giant cells		5/22 (27.8%)
Tumor infiltrating lymphocytes	Mild	8/22 (36.4%)
	Moderate	4/22 (19.3%)
Lymphovascular invasion		2/22 (9.1%)
Perineural invasion		2/22 (9.1%)
Retraction clefts (cases with invasive squamous components)		5/5 (100%)
Lymph node involvement (resection specimen)		4/9 (44.4%)
Immunohistochemical features		
CK/EMA		20/22 (91.1%)
P 63		8/12 (66.6%)
CK5/6		2/7 (28.6%)
Vimentin		22/22 (100%)
S-100		1/20 (5%)
CD56		1/20 (5%)
SMA, CD31, CD34, BCL2, HMB45		0/9 (0%), 0/6 (0%), 0/7 (0%), 0/13 (0%), 0/5 (0%)

Microscopy

The microscopic features of these cases are presented in Table 3 and represented in Figure 3. The overlying epithelium was present in eleven cases (50%) which was hyperplastic in five, dysplastic in four cases and atrophic in two cases, respectively (Figure 3). On morphological examination of H & E sections, squamous differentiation could be identified in nine cases only (41%) (Figure 4). The squamous differentiation was seen as nests and sheets of invasive squamous cell carcinoma cells in five cases (22.7%) and dysplastic overlying epithelium in four (18.2%) cases. In remaining thirteen cases epithelial differentiation was highlighted by the positivity of cytokeratin/Epithelial membrane antigen (EMA).

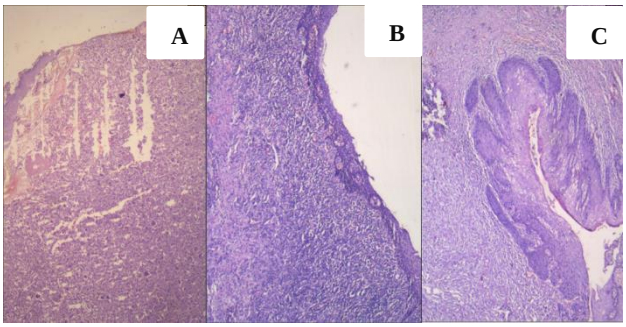

Figure 3: Polypoidal configuration of tumor with focal ulceration of overlying epithelium. (A), tumor with atrophic epithelium, (B) hyperplastic overlying epithelium, (C) (H&E x40).

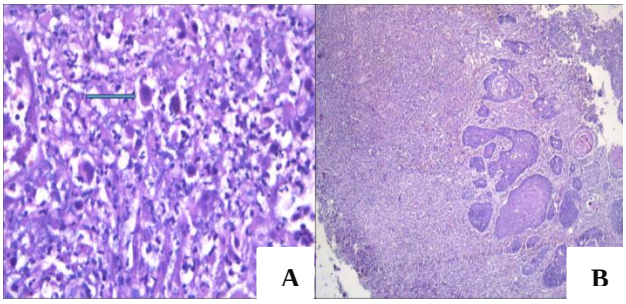

Figure 4: Singly lying dysplastic squamous cells. (A) H&EX 200X) and frank squamous differentiation, (B) H&EX 200X).

The mesenchymal component was resembling conventional soft tissue sarcoma and showed significant anaplasia in most of the cases (Figure 5). Nuclear anaplasia was graded as mild, moderate and marked (Figure 6). Mitotic activity was significant in sixteen cases out of which four cases showed brisk mitosis more than 30/10hpf (Figure 7). The tumor cell displayed moderate to abundant amount of dense eosinophilic cytoplasm, serving a clue for epithelial neoplasm (Figure 7). There was no metaplastic mesenchymal element in any of our case. Necrosis was seen in ten cases out of which 3 cases showed extensive necrosis more than 50% of the tumor area; while seven showed focal necrosis. Tumor giant cells were seen in five cases only (Figure 8). Tumor infiltrating lymphocytes (TILs) were noted in all the cases and were mild in 18 and moderate in 4 cases. None of the cases had intense TILs. Retraction clefts were observed in 4 out of 5 cases having invasive squamous component.

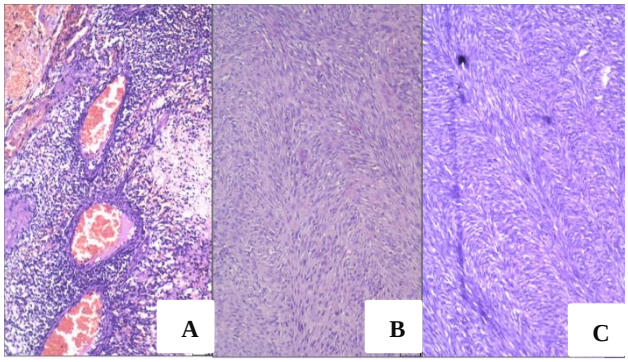

Figure 5: (A) Mesenchymal element with perivascular arrangement, (B) short fascicles, (C) herring bone pattern (H&E X100X).

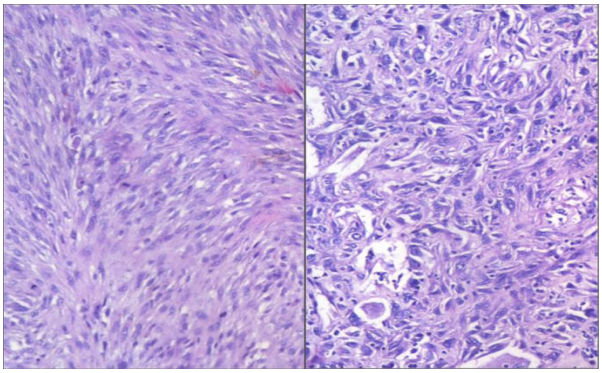

Figure 6: Mesenchymal cells with marked and moderate nuclear anaplasia (H&E X 400X).

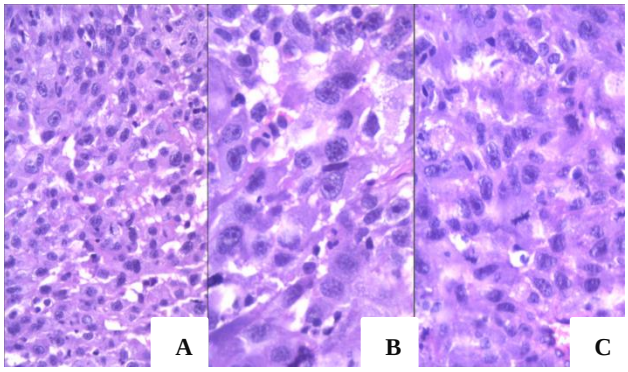

Figure 7: (A) Cells with abundant cytoplasm with Epithelioid appearance. (H& Ex 400X), (B) Cells with vesicular nucleus and prominent nucleolus. (H& Ex 400x), (C) Brisk mitosis (H&E. 600X).

Lymphovascular invasion and perineural invasion was observed in two patients each. Underlying bone was not

involved in any of resection cases. Lymph nodes were involved in 4 resection cases.

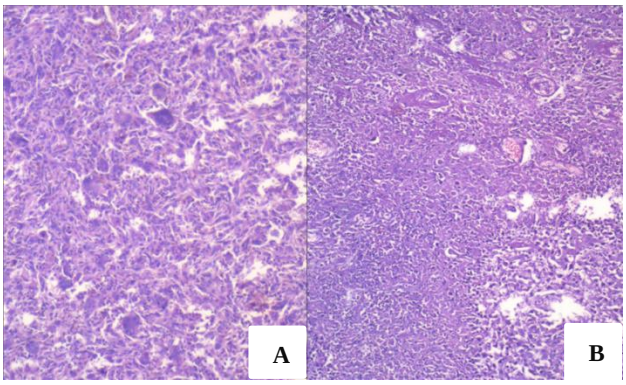

Figure 8: (A) Many tumor giant cells (H&E X 200X), (B) areas of necrosis (H&E X 100X).

Immunohistochemistry for epithelial differentiation was subjected in all the cases (n=13) where squamous differentiation was not evident on histomorphology. A panel of antibodies was used as and when required in selective cases. A detailed overview of IHC is represented in Table 3 and Table 4.

Cytokeratin was diffusely positive in eight cases, focally positive in three cases and negative in 2 cases. EMA was positive in one of the cytokeratin negative cases. P63 was positive in ten cases out of thirteen and ck5/6 was positive in 2 of the three p63 negative cases. Out of these thirteen cases, marked pleomorphism was seen in nine cases which favored the diagnosis of sarcomatoid carcinoma over myoepithelial carcinoma.

In remaining five cases CD10 staining was performed which was negative hence leading to the diagnosis of sarcomatoid carcinoma. Vimentin was diffuse strong positive in all twenty cases (100%). S-100 and CD56 expression were seen in one case each however the expression was focal or weak. None of the cases was positive for SMA (0/9) CD31 (0/6), CD34 (0/7), BCL2 (0/13) and HMB45 (0/5) in which these markers were done (Table 3) (Figure 9).

Table 4: Immunohistochemical features of the 13 cases where the evidence of squamous differentiation was not evident on histomorphology along with presence or absence of significant pleomorphism.

	CK	EMA	P63	CK5/6	CD10	Significant pleomorphism
Case 1	P	P	ND	ND	ND	P
Case 2	P	ND	P	ND	ND	P
Case 3	N	P	P	N	ND	P
Case 4	P	P	P	ND	N	N
Case 5	P	P	N	P	ND	P
Case 6	P	P	P	N	ND	P
Case 7	P	P	N	P	ND	P
Case 8	P	P	P	ND	ND	P
Case 9	P	P	P	N	ND	P
Case 10	P	N	P	N	N	N
Case 11	N	N	P	ND	N	N
Case 12	P	P	P	N	ND	P
Case 13	P	N	P	ND	N	N

P: Positive, N: Negative, ND: Not done

Follow up

Follow up details were available in eighteen cases of which two expired within three months after refusing surgery and opting for chemotherapy/radiotherapy (CT/RT) only. Six patients died within six months of curative surgery, two died within six months after palliative CT/RT; while three expired within one year. Five patients were alive and the longest follow- up period among these patients was 13 months. Distant metastasis in the form of pulmonary metastasis was seen in one patient who survival period was two months after the diagnosis.

DISCUSSION

Sarcomatoid carcinomas are unusual variants of squamous cell carcinoma that constitutes approximately 3% of all the squamous cell carcinomas of head and neck region and 1% of all tumors in the oral cavity.[3-5] It has been now established that sarcomatoid component is the dedifferentiated form of epithelial component both arising from same stem cells.[6,7] Our study consists of 22 cases reported in a span of 3 years comprising of thirteen biopsy specimens and nine resection cases. This study consists of a second highest number of cases from India after the largest study by Viswanathan S et al.[1] We observed the median age of diagnosis as 58 years which

is similar to other reports published.[3,8] Similar to previous studies, we also noted a male preponderance with an M:E ratio of 2:1.[9] The most common predisposing factor for oral squamous cell carcinoma seen in our study was tobacco chewing (73%) followed by smoking (21%) as was also reported by the largest study from southeast Asia.[1] On the contrary, studies from the western world have reported smoking as the most common predisposing factor.[10] This could explain the most common site involved being buccal mucosa in our study and compared to larynx in western studies. There was no history of radiation in any of our cases. The duration of symptoms was very short and in most of the cases less than six months. A feature reported by previous studies as well.[1,3]

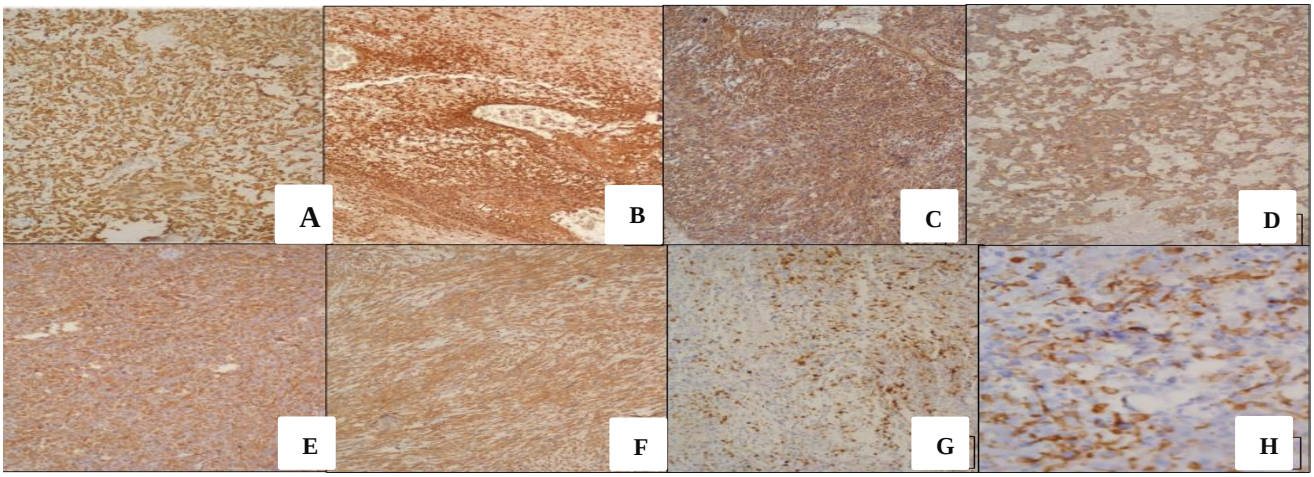

Figure 9: (A) Diffuse cytokeratin positivity, (B) Diffuse cytokeratin postivity in case with unusual perivascular arrangement, (C) EMA Positivity, (D) CK5/6 positivity, (E) strong vimentin positivity in epitheloid looking cells, (F)Vimentin in spindle cells, (G) Aberrant focal expression of S-100, (H) Aberrant weak expression of CD56 (100X).

Gross appearance of a polypoid lesion was noted in all the nine resected specimen, a feature which is often considered characteristic of this type of tumor.[1,3]

Features of epithelial differentiation can be ascertained either by light microscopy or by the immunohistochemical expression of epithelial markers. Light microscopic features of epithelial differentiation are often variable in sarcomatoid carcinoma, which ranges from dysplasia in overlying epithelium/carcinoma in situ to foci of invasive carcinoma as noted in the present study as well.[4] In some of the cases, immunohistochemistry is required to confirm the epithelial nature of the tumor, the degree and intensity of which has been noted to vary.[11,1,3] In this study, immunohistochemistry either for cytokeratin(CK) or epithelial membrane antigen (EMA) was performed in thirteen cases in which epithelial differentiation was not appreciated on morphology. Either of these was positive in 92.3% of our cases. The expression pattern was variable, with 61.5% of cases having an intense positivity, while 30.7% cases expressed CK only focally and weakly. Small biopsies, which have limited tissue can increase the chances of negative expression of these epithelial markers. Additionally, as the degree of epithelial differentiation decreases, the epithelial marker expression can be lost in entirety, in some of the cases of sarcomatoid carcinoma.[3] Hence, a negative result for expression of epithelial markers does not rule out the diagnosis of sarcomatoid carcinoma.

Sarcomatoid carcinoma has been found to be a result of phenotypic plasticity of epithelial cells. This inter-conversion of the epithelium to the mesenchymal element is characterized by loss of epithelial features like intercellular connections, loss of polarity, keratin expression, basement membrane and gaining the mesenchymal features like metamorphosis to spindle shape, expression of Vimentin, production of the mesenchymal matrix, collagen and even cartilage and bone.[3,12,13] Presence of these features include all the malignant spindle cell lesions in the differential diagnosis of sarcomatoid carcinoma. This includes myoepithelial carcinoma, mucosal spindle cell melanoma,leoimyosarcoma and sometimes odontogenic tumors and osteosarcoma invading the mucosa. Radiological features show bone as the epicenter in tumors like osteosarcoma and odontogenic tumors. However, in other tumors, the epicenter is soft tissue based. IHC helps in differentiating the mesenchymal tumors. Strong expression of SMA and Desmin favors leimyosarcoma; while S-100, HMB45 and Melan A positivity helps in making a diagnosis of melanoma. Although uncommon, rare expression of these markers can be seen in sarcomatoid carcinoma.[1,3] But, the intensity is usually weak and is noted focally.

Sarcomatoid carcinoma and myoepithelioma share common light microscopic and IHC features, like the expression of CK, EMA, P63. However, the presence of anaplastic features and absence of CD10 expression favors a sarcomatoid carcinoma over myoepithelial carcinoma. Of the 13 cases in this study, where light microscopic feature of squamous cell carcinoma was not seen, nine cases showed marked anaplasia. Remaining four cases were positive for CK/EMA/p63 and/or CK5/6; while negative for CD10, hence favoring a diagnosis of sarcomatoid carcinoma over a myoepithelial carcinoma.

In this study, lymph node involvement was seen in 44.4% of resection specimens which was much lower than reported in K Tarun et al but Bataskis reported lymph node metastasis only in 24%.[14,15]

Sarcomatoid carcinoma overall carries worse prognosis as compared to squamous cell carcinoma and is characterized by frequent recurrences, metastasis and early deaths.[15] Similar findings were observed in our studies where 13/18 (72.2%) died within a year of diagnosis. Out of all mortalities, 55% was within 6 months of diagnosis.

CONCLUSION

To summarize, sarcomatoid carcinoma is an aggressive tumor despite being just a variant squamous cell carcinoma with much higher mortality and aggressive behavior than conventional squamous cell carcinoma. Morphological features masquerade other spindle cell lesion of head and neck region. A careful morphological examination along with Immunohistochemical findings, help in making a correct diagnosis which is useful for appropriate treatment and prognostication of these patients.

ACKNOWLEDGEMENTS

Authors would like to thank Ms Pooja, Ms. Nidhi and Mr Kamlesh for the technical support and retrieval of diagnostic material from filing.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Qayoom S, Akhtar N, Kumar M, Agarwal P, Maurya MK, Raghuvanshi S, et al. Clinicopathological and immunohistochemical analysis of Sarcomatoid carcinoma of head and neck mucosal region: a retrospective analysis. Int J Res Med Sci 2019;7:561-7.