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Review Article

Diagnostic Enigma of Spindle Cell Carcinoma of the Oral Cavity- Review of Literature

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Abstract

Spindle cell carcinoma is a variant of squamous cell carcinoma which has been reported in oral cavity with different demographic data. Spindle cell carcinoma has been addressed with various terminologies including, "sarcomatoid carcinoma", "collision tumor", "pseudocarcinoma" owing to its varied proposed histogenesis. Spindle cell carcinoma is important to understand due to its perplexing pathological diagnosis. The "dedifferentiating" epithelial population into spindle cell morphology leads to overlapping features with other sarcomatous tumors. It is essential to evaluate the lesion and attain a proper diagnosis for better treatment and clinical outcomes. Thus, in this review published literature and reported cases has been presented to understand such aggressive lesion with importance of using diagnostic techniques such as immunohistochemistry to understand the pathogenesis.

Keywords: Squamous Cell Carcinoma; Oral Cancer; Sarcomatoid; Spindle Cells; Immunohistochemistry

Introduction

Spindle cell carcinoma (SpCC), also called sarcomatoid carcinoma or pseudosarcoma or pleomorphic carcinoma or polypoid carcinoma or carcinosarcoma is a relatively an rare tumor [1]. The W.H.O. classification of tumors of the oral cavity and oropharynx has placed this disease entity under malignant epithelial tumors of Squamous Cell Carcinoma (SCC) and labeled it "Spindle cell carcinoma" (SpCC). It is an unusual form of poorly differentiated squamous cell carcinoma (SCC) which has spindled or pleomorphic tumor cells [2]. SpCC is a biphasic tumor with divergent differentiation composed of a SCC, either *in situ* and/or invasive, with a malignant spindle cell component. It is a malignancy of epithelial origin often mimicking its mesenchymal counterpart [3].

These tumors pose a significant diagnostic challenge to the clinician with remarkable morphological, histopathological and immunohistochemical overlap resembling other benign and malignant spindle cell tumors [4,5]. There has been confusion over the basic nature of the sarcomatoid element, whether it is benign or malignant, and mesenchymal or epithelial in origin or a biphasic derivative of pseudosarcoma or a collision tumor [6]. An accurate diagnosis of these tumors is essential for proper management. This review is being carried out to provide a brief overview of the prevalence, clinical features, histopathological variants, site specificity, management and outcomes in the oral cavity based on the cases reported in literature.

Prevalence and incidence

Spindle cell carcinomas are atypical variants of squamous carcinoma accounting for 3% of all squamous carcinomas of the head and neck region [7]. These tumors are relatively uncommon in the oral cavity; reportedly accounting for less than 1% of all tumors

of oral regions [8]. The incidence rate of spindle cell carcinoma is about 0.59 percent of all upper aerodigestive tract neoplasms.

Age and sexual predilection

Leventon., *et al*. reported age -range of 47 years to 88 years with a mean age of 65.7 at the time of diagnosis and a greater predilection in male patients [6]. Vishwanathan., *et al*. reported age-ranges from 22 - 90 years (median 53 years), and male:female ratio of 3.7:1 [9]. Feng., *et al*. reported that SpCC occurs in the seventh decade of life and the male-to-female ratio is almost 1:1 without predominance in any gender [10].

Spindle cell carcinoma of the oral cavity presents with a profound male to female predilection (11:1) and the mean age of occurrence is 57 years; although it can be diagnosed in a younger age group and very old age group (range 29 - 93 years) [11,12].

Site specificity of the oral and maxillofacial region

SpCC is a rare variant of squamous cell carcinoma and most frequently occurs in the larynx, with infrequent occurrence in various other organs like upper aerodigestive tract [1,13,14] including hypopharynx and nasal cavity, esophagus, skin and breast [2]. It also show predilection for the lower lip, tongue and alveolar ridge or gingiva [11,12]. In order to review a summary of the cases and the site specificity in the oral cavity data have been tabulated. Table 1 presents the cases reported in the literature.

Author	Year	Site of lesion
Munakata., *et al*. [15]	1998	Gingiva (retromolar area)
Katase., *et al*. [16]	2008	Posterior mandibular gingiva
Kwon., *et al*. [17]	2010	Mandible
Parikh., *et al*. [18]	2011	Maxillary alveolar ridge
Ravindran., *et al*. [19]	2013	Maxilla
Shen., *et al*. [20]	2014	Mandibular gingiva
Shetty., *et al*. [21]	2015	Anterior maxilla
Mahajan., *et al*. [22]	2017	Mandible alveolar ridge
Patnakar., *et al*. [23]	2018	Anterior mandibular gingiva
Mathew., *et al*. [24]	2019	Maxillary alveolus
Palla B., *et al*. [25]	2020	Anterior Maxilla
Ono S., *et al*. [26]	2021	Tongue

Table 1: List of spindle cell carcinoma cases published.

Pre-disposing factors

Cancer of oral cavity has been reported to have various risk factors, including tobacco, alcohol dietary and nutritional habits as well as daily intake of macro as well as micro nutrients [27]. In spindle cell carcinoma, 4 factors are considered to be possibly associated with this disease: tobacco abuse and smoking, alcohol abuse, poor oral hygiene, and previous irradiation to the area of tumor [18,23]. Viswanathan., *et al*. in a clinicopathologic review of 103 cases of sarcomatoid carcinoma of the head and neck reported that tobacco chewing (63.8%) was more frequently observed than smoking (21.3%) in patients without any past history of radiation exposure. Where smoking tobacco is a predominant habit, the maximum number of cases were reported in the larynx [9]. Table 2 represents the commonly associated predisposing factors in the cases reported in the literature.

Author	Year	Pre-disposing factor
Munakata., *et al*. [15]	1998	Not known
Katase., *et al*. [16]	2008	Not mentioned
Kwon., *et al*. [17]	2010	Non smoker
Parikh., *et al*. [18]	2011	Smoking
Ravindran., *et al*. [19]	2013	Paan chewing
Shen., *et al*. [20]	2014	Not mentioned
Shetty., *et al*. [21]	2015	Not mentioned
Mahajan., *et al*. [22]	2017	No history of smoking and alcohol
Patnakar., *et al*. [23]	2018	Tobacco quid placement
Mathew., *et al*. [24]	2019	No history of smoking and alcohol
Palla B., *et al*. [25]	2020	Smoking
Ono S., *et al*. [26][26]	2021	No history of smoking and alcohol

Table 2: Predisposing factors for Spindle cell carcinoma of oral cavity.

Onset of the disease/symptomology

Most of the patients present a short duration of onset of less than 1 year [5]. Viswanathan., *et al*. reported that the duration of symptoms ranged from 20 days to 2 years with less than 1 year in 95% of patients [9]. Majority of the patients present with a hard, indurated, non-mobile, painful or painless swelling, sometimes an echymotic or non-healing ulcer which showed a rapid increase in

size in a very short duration of time. Although swelling was a consistent finding symptoms such as regional lymphadenopathy, inability to eat properly paresthesia or numbness, inability to open the mouth, tooth mobility with angular bone less, hyperplastic gingiva or root resorption are found associated depending on the site of the lesion. Tumors in the maxilla or nasal cavity sometimes can present with excessive tearing from the eye, mass lesion, nasal blockade and bleeding [17,18,22]. Table 3 presents the symptomology of the reported cases.

Author	Year	Duration of onset	Lymphadenopathy	Paresthesia/tenderness	Invasion or metastasis
Munakata., *et al*. [15]	1998	3 weeks	Present	Not present	Seen in the lungs
Katase., *et al*. [16]	2008	Not mentioned	Absent	-	Not seen
Kwon., *et al*. [17]	2010	2 weeks	Present	Not present	Seen in the lungs and stomach
Parikh., *et al*. [18]	2011	3 weeks	Absent	Not present	Not seen
Ravindran., *et al*. [19]	2013	4 - 5 months	Present	Tenderness	Local invasion into the maxilla and sinus
Shen., *et al*. [20]	2014	2 months	Absent	Paresthesia	
Shetty., *et al*. [21]	2015	4 months	Absent	Tenderness	Not seen
Mahajan., *et al*. [22]	2017	15 days	Present	Tenderness	Not seen
Patnakar., *et al*. [23]	2018	2 months	Absent	Tenderness	Not seen
Mathew., *et al*. [24]	2019	3 months	Present	Not present	Local invasion
Palla B., *et al*. [25]	2020	6 months	Present	-	Present
Ono S., *et al*. [26]	2020		Absent	-	Absent

Table 3: Symptoms reported in published literature.

Clinical presentation

The tumor usually represents as large exophytic, polypoid growth of variable size (2 - 6 cm) with rough irregular ulcerated surface covered with brown necrotic tissue or with erythematous patches [9]. These ulcerative and necrotic areas are often associated with pain [25]. Although, sessile, pedunculated nodular or endophytic presentations have also been described in the literature [9].

Radiographic apprearance

Panoramic and intra-oral radiographs present a variable picture depending on the site of the tumor. An irregular radiolucency or radio-opacity with ill-defined margins, localized or diffuse bone loss with or without sclerotic margins with cortical bone invasion and destruction can be seen in the posterior mandibular lesions. The anterior mandibular lesions may reveal severe vertical bone loss with destruction of trabecular pattern, widening of periodontal space and break in the continuity of lamina dura of the incisors. Root resorption or displacement of the teeth can also be seen in some cases. The lesions of the gingiva may not present with any radiographic alteration. A CT scan or MRI might be required to delineate the exact dimensions, extent and invasion into the surrounding areas and to preclude any soft tissue involvement [15,20].

The differential diagnosis includes osteomyelitis, pyogenic granuloma, osteonecrosis, odontogenic tumor or any metastatic tumor on the basis on radiographic presentation**.** Thus, a biopsy is required to confirm the provisional diagnosis [20].

Gross examination

The overlying mucosa may appear polypoidal or ulcerated while submucosa gives a firm fibrous appearance. The ulcerated areas are covered by fibrinoid material and slough [9]. Similarly, Parikh., *et al*. reported a case having gross polypoid growth. Cut surface was grey white in color and firm in consistency [18].

Microscopy

Microscopically the spindle cell carcinoma presents two components - epithelial component and sarcomatoid component. The

proportion of these components varies in every case. Usually, the epithelial component is less than the sarcomatoid. It is believed that despite the epithelial and spindle components shows phenotypic divergence, but have similar tumorigenic pathway [18].

Epithelial squamous component: (Carcinomatous/SCC)

The squamous component has been reported to appear in form of dysplasia, conventional squamous carcinoma nests, squamoid differentiation, Carcinoma-*in situ*. Sarcomatoid and squamous component seen in complex fashion. Sometimes it is difficult to indistinct the overlying epithelium origin as the basal cells show elongating and spindling into the stromal areas [9,18].

Sarcomatoid spindle component (Dysplastic spindle cells)

This component arises when the epithelial component undergoes phenotypic changes and converts into a spindle cell. These cells acquire Mesenchymal expression [18].

Sarcomatoid component can be divided based on degree of anaplasia- mild, moderate and severe anaplasia [9].

Sarcomatoid areas in spindle cell carcinomas shows varied patterns which resembles Mesenchymal malignancies histopathologically and show similar immune-expression. Tumor cells can be seen organized in fascicles, storiform pattern, areas of severe inflammation as well as granulation tissue resembling inflamed myofibroblastic tumors. Cases may show epithelioid appearing tumors cells [9]. Few authors also stated that these patterns might have a link with tumor invasion and metastasis [2].

Parikh., *et al*. reported a case spindle cells histologically appeared bizarre, basophilic in nature, hyperchromatic and pleomorphic (malignant histiosarcoma like) [18]. While the invading spindle cells with prominent mitotic figure, atypical mitosis were laid into fascicle pattern, resembling fibrosarcoma. These spindle cells have been reported to undergo alterations leading the keratin loss. While areas may show true metaplasia of epithelial cells into fibroblast like cells, having acquired both morphological and functional properties of a Mesenchymal cell. These metaplastic altered spindle cells results in vimentin positive [18].

Tumor matrix

The intervening stroma demonstrates presence of collagen, marked myxoid component. This matrix in different proportions along with the tumor cells forms numerous patterns [9]. Presence of areas showing adipose tissue, myxoid and necrosis has also been reported. Tumor stroma may also show evidence of other cell population such as acute and chronic inflammatory cells [25], tumor giant cells [9].

Lymph node metastasis

Morphologically it presents squamous carcinoma or mixed epithelial and spindle appearance or spindle component purely [9]. Viswanathan., *et al*. studies the cases by dividing then into three groups: Group I- Frank epithelial differentiation, Group II- Epithelial differentiation at IHC level only, Group III - lack of epithelial differentiation [9].

Metaplastic changes

Degree of metaplastic changes occurring in a tumor varies. Few theories have been put forward for these metaplastic changes 1) Due to stromal activation linked to human-host interface, 2) Due to radiotherapy, although it is still unclear. Along with this, it has been seen that its affection on clinical findings and prognosis metaplastic is not found [16]. Apart from this, few cases with foci of osteoid, cartilage and bone formation has been reported giving osteosarcomatous appearance [9,26].

Need for IHC

To establish a diagnosis of epithelial origin especially in cases with no evidence of squamous differentiation, Immune-expression of epithelial markers plays important role. The percentage and intensity of the markers varied in different studies ranging from weak focal to diffuse and intensely positive [9].

It was noted that occasionally the Mesenchymal markers expressed aberrantly leading to diagnostic confusion. It should be noted that cases where the both epithelial differentiation epithelial markers expression is absent, diagnosis can be reached by exclusion [9]. Absence of immune-staining can be due to different factors such as improper sampling, poor fixation, sensitive IHC technique, intra-observer subjectivity less epithelial component present or only a part of biopsy is available for assessment [9].

Another point to be kept in mind is that the epithelial markers have been reported to decrease in expression and even lost completely within the tumor. This does not excludes the diagnosis of sarcomatoid carcinoma [9].

Most sensitive and consistent epithelial markers to confirm epithelial phenotype are keratin (AE1/AE3) and EMA (epithelial membrane antigen). Spindle cell component showing positive expression for these two markers can be helpful in the differential diagnosis of Sarcomatoid carcinoma with other sarcomatous lesions. Another important point states that in spindle cell carcinoma a positive response for vimentin in sarcomatoid cells should not be ruled out of the differential diagnosis [21].

Addition to it, a panel of anti-keratin antibodies should be used. Mere, absence of keratin staining in sarcomatoid tumor cells does not always exclude Spindle cell carcinoma as it may come positive for only some anti-keratin antibodies. Different kinds of anti-keratin antibodies should be applied in the differential diagnosis. To include wide range of cytokeratins, PAN-CK can be used [21].

Taken into account, the bizarre fibroblastic population, the spindle cells with true mesenchymal features (both morphological and functional), these show vimentin positivity. P63 is another marker used for the diagnosis [21].

A study by Ramamurti., *et al*. enlightened the use of IHC marker for evaluating the invasive potential in such neoplasms. For this purpose they used podoplanin, mucin like glycoprotein which is important for lymphangiogenesis. Noted that it is not a diagnostic marker but can be used to assess the potential of a tumor to spread [8,23]. Table 4 enlists the important antibodies that can aid in diagnosis of spindle cell carcinoma of oral cavity.

Immunomarkers	Immunoreaction	
	Spindle cells population	Epithelial cell population
Cytokeratins		
AE1/AE3	+	+
8	+/-	+
19	+/-	+
Cam5.2	-	+/-
Vimentin	+	-
S-100	-	-
CD 68 (KP1, PGM1)	-	-
Pan-actin (HHF-35)	-	-
Lysozyme	-	-
A-Antitrypsin	+	-
Desmin	-	-
αSMA (alpha smooth muscle actin)	+/-	+/-
Osteopontin	-	-
BMP-2	-	-
BMP-4	-	-
Ki-67	> 40%	< 30%
p53	50%	50%

Table 4: Summarizing expression of immunomarkers for different tumor population [11,21,25].

BMP: Bone Morphogenetic Protein; +: Positive, +/-: Focally Positive, -: Negative.

Electron microscopy

Studies have demonstrated presence of desmosomes and tonofilaments which strongly supports the epithelial origin of spindle cell component [18]. Ultrastructurally, transitional zone exists between the carcinomatous and sarcomatous components, the latter generally accounting for > 50% of the lesion [20].

Differential diagnosis

Differential diagnosis of sarcomatoid carcinoma may include other benign lesions and mesenchymal malignancies- Squamous cell carcinoma [9] mucosal spindle cell melanoma, leiomyosarcoma, myoepithelial carcinoma [17], malignant fibrous histiocytoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, osteosarcoma, mesenchymal chondrosarcoma, malignant melanoma, fibromatosis, leiomyoma, nodular fasciitis, reactive epithelial proliferations [9]. Literature also states that sometimes may resemble bony lesions such as osteosarcoma extending to mucosa causing diagnostic dilemma. In such cases radiographic picture should be taken into consideration [17]. Patankar., *et al*. also states that they should be differentiated from fibrosarcoma and true superficial sarcomas [23].

Treatment

Treatment of choice involves surgical resection of the tumor along with neck dissection [23].

Su., *et al*. observed in their study that surgical margins were negative in local recurrence cases and thus suggested wider safe margin > 2 cm. Further, a close post-operative follow up may help to detect early recurrence [8].

Additionally, radiotherapy or chemotherapy also play a part in treatment but varies from case to case. Mostly, radiotherapy and chemotherapy is given post-surgery. This is because of adverse prognostic factors including unconfirmed surgical margins, poor differentiation pathologically and advanced tumor stage etc [10]. Adjuvant radiotherapy has also been reported to be of some help in improving local control in with positive surgical margins but cannot be relied on. Chemotherapy will still holds its benefit in the future, with distant recurrence cases. Cases with high angiogenic response and > T2 tumor staging may need chemotherapy to reduce risk of metastasis [2].

Prognosis

The biological behavior of each tumor differs. Kwon GY., *et al*. states that the prognosis depends on location, size of tumor, depth of invasion, stage along with presence of any keratin immune-staining in the spindle cells. The presence of such neoplasm in oral cavity or oropharynx may show aggressive behavior and reoccur often easily [17]. Spindle cell carcinoma cases show location specific prognosis [10].

Deep invasive tumors show poor prognosis while early stage cases have excellent prognosis. Some of the reliable prognostic features may include, distant metastasis, depth of tumor invasion and polypoid configuration [21]. Study by Su., *et al*. concluded that spindle cell carcinoma cases show 36.7 overall survival rate in one year and in early cases it was 100% 3 year survival [2]. Another study stated a 55% survival rate in 2 years and 36% metastases prevalence [15]. It is identified presence of inflammatory state can cause the epithelioid cell to change to spindle phenotype to support migration. Su., *et al*. also highlighted that oral and oro-pharyngeal spindle cell carcinoma has more aggressive behavior, where even early stage cases can show high recurrence rate and advance stage cases have high metastatic rate [2].

Cases with histopathological evidence of osteoid, cartilage or bone formation did not yield in poor prognosis when compared cases with absence of this feature [26].

Recent case report by Palla B., *et al*. highlights that a noticeable difference exists between spindle cell carcinoma when compared to SCC, when prognosis and overall survival is taken into consideration. They considered only 30% of 5 year survival in cases of oral spindle cell carcinoma [25].

Diagnostic criteria

Su HH., *et al*. in his study mentioned the diagnostic criteria which needs to be fulfilled for Spindle cell carcinoma. It included Identifying carcinoma with squamoid feature within or in some part of the tumor, Cytokeratin positive and vimentin negative spindle cells and presence of carcinoma *in situ* [2]. A diagnostic plan is explained in figure 1.

Figure 1: Diagnostic algorithm for spindle cell carcinoma of oral cavity.

Conclusion

Spindle cell carcinoma which still demands a systematic approach for an precise diagnosis and patient management. Taking into account the aggressive behavior of spindle cell carcinoma of oral and oro-pharyngeal region the treatment should be targeted to control local as well as distant recurrences. A planned management of such aggressive lesion is needed which includes clinical, radiographic evaluation but most essential is histopathological diagnosis aided with special stains and immunohistochemical staining for tumor cell population and stromal changes, that would give a better insight into the pathogenesis of spindle cell carcinoma. Prognostic indices may further help to reveal the prognostic significance for each case.

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Volume 5 Issue 7 July 2021