Clinico- Pathological Features of Spindle Cell Carcinoma of the Oral Cavity : A Systematic Review

ABSTRACT

Introduction: Oral Spindle Cell Carcinoma (OSCC) is a rare and aggressive form of oral squamous cell carcinoma (OSCC) that is characterized by the presence of spindle-shaped wcells within the tumor. It is often difficult to diagnose due to its histological similarity with other soft tissue tumors and malignancies, leading to challenges in clinical management. The limited number of cases reported in the literature necessitates a systemic review to understand its clinical behavior, diagnosis, treatment strategies, and prognosis.

Objective: This systematic review aims to collate, analyze, and extract existing data on oral spindle cell carcinoma, with a focus on its epidemiology, pathogenesis, clinical presentation, diagnostic modalities, histopathology, and prognostic factors.

Methods: A systematic search was conducted in multiple electronic databases to identify relevant studies published. Inclusion criteria included case reports, case series, and retrospective studies that documented cases of OSCC, focusing on clinical, histopathological, and treatment-related information. A qualitative analysis was performed to extract key findings, and data were organized into thematic categories.

Results: 20 case reports were included in the review. The oldest case on Spindle cell carcinoma in oral cavity was reported in 1976 by Someren et al. All the cases were reported in different parts of the world, eight in India, one in United states, three in Japan, two in Brazil, one in China, one in Italy, one in Taiwan, one in Malasiya and one in Turkey. Three studies with cross-sectional study design were included in which data was collected retrospectively. A total of 91 participants were included. The conclusion of studies indicated that median age at onset was 51 years (range, 32–76 years). Moreover, most common site were the tongue (28%) and buccal mucosa (22%) . Immunohistochemistry is helpful to know the histogenesis and nature of SpCC. Prognosis of the disease always poor and distant metastasis is always more then the conventional SCC.

Conclusions: Oral spindle cell carcinoma is a rare and aggressive malignancy that presents diagnostic challenges due to its histological overlap with other tumors. Early detection and prompt, multimodal treatment are critical for improving outcomes. Due to the scarcity of large-scale studies, more research is needed to better understand the molecular pathogenesis, refine diagnostic criteria, and optimize treatment strategies. Regular follow-up and surveillance are essential for early detection of recurrence and metastasis, given the poor prognosis associated with advanced disease stages.

Keywords: Oral Spindle Cell Carcinoma, Diagnosis, Treatment, Prognosis, Systematic Review, Squamous Cell Carcinoma, Oral Cancer.

INTRODUCTION

Oral cancer is the sixth most common cancer globally and it is estimated that 198,975 new cases in men and 101,398 cases in women occur each year. Squamous cell carcinomas account for up to 80–85% of oral malignancies, which include several variants like verrucous, basaloid, adenoid, spindle cell, adenosquamous, and undifferentiated carcinoma.3

Spindle cell carcinoma (SpCC) of the head and neck is a rare, biphasic neoplasm first described by Virchow in 1865.4 The World Health Organization (WHO) defines this tumor as a ‘‘carcinoma within which there are some elements resembling a squamous cell carcinoma that are associated with a spindle cell component’’.3 It accounts for 3% of all SCCs in the head and neck region . It is most commonly encountered in the upper aero digestive tract , the larynx (particularly the vocal cords) and hypo pharynx being the most common sites and rarely in the oral cavity.[4]

Spindle cell carcinoma (SpCC)—also known as carcinosarcoma, pseudosarcoma, sarcomatoid squamous cell carcinoma, and polypoid carcinoma—is an infrequent variant of squamous cell carcinoma and is confirmed by elongated and pleomorphic epithelial cells that resemble a sarcoma.[1] In this tumor keratinocytes infiltrate the connective tissue as single cells with elongated nuclei, not as cohesive nests or islands, and there are minimal or no signs of keratinization of conventional squamous cell carcinoma.

In a true spindle cell carcinoma, the malignant spindle-shaped cells should be demonstrably of epithelial origin and derived from the squamous cell component of the carcinoma. So this tumor is also termed as metaplastic carcinoma. This tumor must be distinguished from both a squamous cell carcinoma, which has provoked a reactive fibroblastic stromal proliferation, and a carcinosarcoma in which a squamous cell carcinoma is accompanied by a sarcoma of fibroblastic or other connective tissue cell type. Care should also be taken not to confuse a spindle cell carcinoma with a spindle cell malignant melanoma or with sarcomas of various types.

Clinically, the mean age of occurrence of the lesion was 57 years, with a range of 29–93 years. The lesions developed with the greatest frequency on the lower lip (42%), tongue (20%), and alveolar ridge or gingiva (19%) with the remainder scattered at other sites. The most common findings presented were swelling, pain, and the presence of a nonhealing ulcer.

The initial lesion appeared either with a polypoid, exophytic, or endophytic configuration. It known to have a history of prior therapeutic radiation to the region where the tumor subsequently developed. The time interval from radiation to diagnosis of the tumor ranged from 1.5 to 10 years with a mean of about 7 years.

It is a bimorphic or biphasic tumor, which, although almost always ulcerated, will show foci of surface epidermoid carcinoma or epithelial dysplasia of surface mucosa, usually just at the periphery and often quite limited. Proliferation and "dropping-off" of basal cells to spindle cell elements is a common phenomenon. The tissue patterns making up the bulk of the tumor have been categorized as fasciculated, myxomatous, or streaming.

The cells, particularly in the fasciculated form, are elongated with elliptical nuclei, although pleomorphic cells are also common .The number of mitoses may vary from few to many. Giant cells, both benign-appearing of the foreign body–type and the bizarre, pleomorphic, and atypical cells may be found. Finally, an inflammatory cell infiltrate is often present. Osteoid formation within the tumor component is sometimes seen. Microscopic invasion of subjacent structures is evident, as it is with most epidermoid carcinomas of the oral cavity.

Molecular evidence, however, has shown that SPCC is an epithelial neoplasm, with a divergent differentiation, and not a collision tumor, biphasic derivation or pseudosarcoma. Immunohistochemical findings showed tumor cells could express both epithelial and mesenchymal markers, and spindle cells could express vimentin and other mesenchymal filaments . It was also shown that the SCC component was more biologically active than the spindle cell component.

In addition, distant metastases and depth of tumor invasion into underlying structures were found to be reliable prognostic features, together with their polypoid configuration. Thus, metastases usually contain SCC or both SCC and spindle cell component, and rarely only just the spindle cell component . These reasons have proved that the polypoid type of SPCC has a longer survival rate than invasive SCC. 5

MATERIAL AND METHOD

The study protocol was registered on PROSPERO database.

The PROSPERO registration number for protocol for this study is CRD42023495089.

REVIEW QUESTION:

1. What are the clinical findings and histopathological features for the diagnosis of Spindle cell carcinoma in the oral cavity?
2. What are the trends of demographics , differential diagnosis and prognosis of Spindle cell carcinoma in the oral cavity?

ELIGIBILITY CRITERIA:

[A] Inclusion criteria:

i. Studies including patients diagnosed with Spindle cell carcinoma (histologically confirmed)
ii. Case reports, case series, retrospective studies were included

iii. Studies published until March 2024 were included

iv. Studies with full-text articles were included.

[B] Exclusion criteria:

i. Studies involving patients of spindle cell carcinoma of site other than oral cavity.

ii. Studies involving patients with other premalignant or malignant condition.

iii. Studies involving patients not providing informed consent.

iv. Pre-clinical studies, letters to the editor, commentaries and reviews were excluded.

v. Studies providing only abstract and not full text.

SELECTION OF STUDIES:

The title and the abstract of each study were reviewed and critically assessed by two independent reviewers. The methods used to apply the selection criteria were the following:

i. integration of the searched outcomes to delete duplicate entries

ii. examination of titles and abstracts to delete clearly irrelevant articles

iii. recovery of the full text of potentially relevant articles

iv. binding and gathering of multiple articles of the very same study

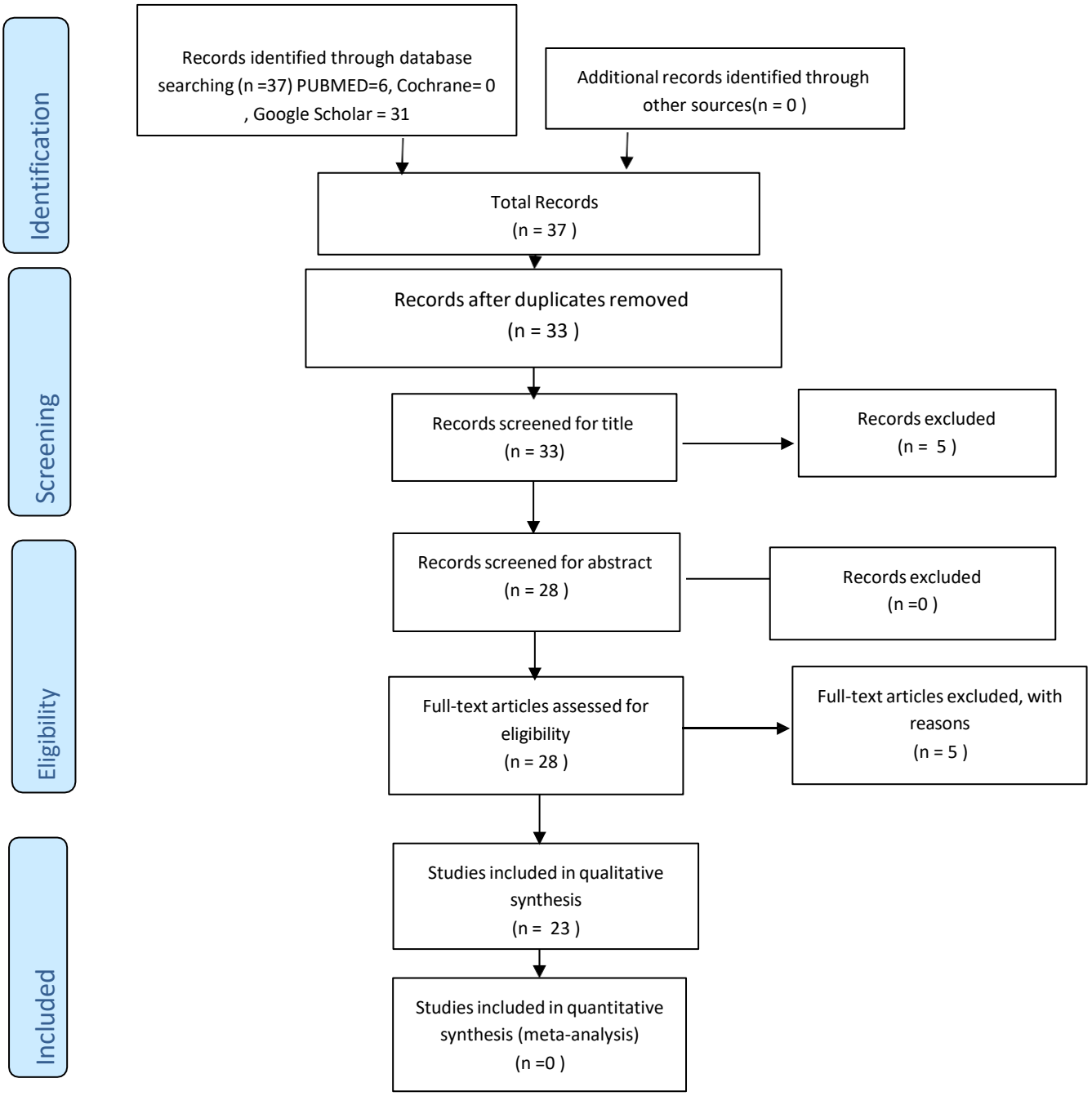
v. examination of the articles' full text to verify the degree of compliance that the studies had with the eligibility criteria

vi. establishing connection with researchers, if necessary, to clarify the study's eligibility

vii. Deciding about the study's inclusion and proceeding with data gathering.

RESULTS

PRISMA 2009 Flow Diagram



A list of the included studies as well as the excluded studies after full text evaluation with the reason for their exclusion has also been provided

Table 1: A List of Included studies.

Sr. No.	Author	Year	Title
CASE REPORTS			
1.	Someren et al	1976	Polypoid spindle-cell carcinoma (pleomorphic carcinoma)
2.	Munakata R et al	1997	Spindle cell carcinoma of the gingiva: report of an autopsy case
3.	Chen et al	1998	Spindle Cell Carcinoma of the Tongue: Case report and immunohistochemical study
4.	Rizzardi et al	2003	A Look at the Biology of Spindle Cell Squamous Carcinoma of the Oral Cavity: Report of a Case
5.	Fifita et al	2006	A Case of Spindle Cell Carcinoma of the Oral Cavity: With Special Reference to Cytopathological Features and Review of Literature
6.	Chou, Wu, Kao, et al	2007	Spindle Cell Carcinoma in the Oral Cavity
7.	Nilima Prakash et al	2010	Spindle Cell Carcinoma of the Oral Cavity: A Case Report of a Rare Entity and Review of Literature
8.	Neelampari Parikh et al	2011	Spindle Cell Carcinoma of the oral cavity: A case report of a rare entity and review of literature
9.	Murat Oktay et al	2011	Spindle Cell Carcinoma of the Tongue: A Rare Tumor in an Unusual Location
10.	Biradar et al	2014	Spindle cell carcinoma of the tongue: a rare variant of squamous cell carcinoma

11.	Ezulia et al.	2015	Spindle Cell Carcinoma of the Oral Cavity: A Case Report
12.	Haytham Al-Bayaty et al	2015	Spindle cell carcinoma of the mandible: Clinicopathological and immunohistochemical characteristics
13.	Ohba et al.	2015	Spindle cell carcinoma arising at the buccal mucosa: a case report and review of the literature
14.	Wadhawan, et al.	2018	Spindle Cell Tumor in Oral Cavity: A Rare Case Report
15.	M. Varshini et al	2019	Spindle cell carcinoma in the maxilla: A rare case and literature review
16.	Silva DF et al	2019	Clinicopathological and immunohistochemical analysis of spindle cell squamous cell carcinoma of the tongue: a rare case
17.	B. Palla et al.	2020	Spindle cell variant squamous cell carcinoma of the oral cavity: Case presentation and review of literature
18.	Donohue-Cornejo A et al	2020	Spindle cell carcinoma of the maxillary sinus with extension to the oral cavity
19.	James AR, et al.	2021	Spindle cell carcinoma of tongue
20.	Kini et al	2022	Spindle cell carcinoma masquerading as a benign polyp of the soft palate
CROSS-SECTIONAL STUDIES			
21.	Ellis and Corio et al	1980	Spindle cell carcinoma of the oral cavity

22.	Su et al	2006	Spindle Cell Carcinoma of the Oral Cavity and Oropharynx: Factors Affecting Outcome
23.	Sarma et al	2012	Spindle Cell Carcinoma of the Head and Neck: A Clinicopathological and Immunohistochemical Study of 40 Cases

Table 2: A list of excluded studies with reason for exclusion

Study	**Author**	**Year**	**Title**	**Reason for exclusion**
CASE REPORTS				
1.	Viswanathan et al	2010	Sarcomatoid (Spindle Cell) Carcinoma of the Head and Neck Mucosal Region: A Clinicopathologic Review of 103 Cases from a Tertiary Referral Cancer Centre	2,3
2.	Reyes et al	2015	Sarcomatoid (Spindle Cell) Carcinoma of Tongue: A Report of Two Cases	1
3.	Colney et al	2022	Second Primary Spindle Cell Carcinoma of the Tongue: A Rare Histology	4
CASE STUDY				
4.	Slootweg et al	1989	Spindle-Cell Carcinoma of the Oral Cavity and Larynx Immunohistochemical Aspects	1
5.	Iqbal et al	2015	Spindle cell carcinoma of the head and neck region: treatment and outcomes of 15 patient	5

REASON FOR EXCLUSION

1. Diagnosis not justified
2. Site other than oral cavity
3. Review article
4. Neoplasm other than Spindle cell carcinoma
5. Mentioned outcomes are not included in the study.

RESULTS

CASE REPORTS

20 case reports were included in the review. The oldest case on Spindle cell carcinoma in oral cavity was reported in 1976 by Someren et al. All the cases were reported in different parts of the world, eight in India, one in United states, three in Japan, two in Brazil, one in China, one in Italy, one in Taiwan, one in Malasiya and one in Turkey.

The age of cases ranged from 18 years to 84 years. Amongst the reported cases, twelve were male and eight were female. The clinical common to all cases were exophytic, irregular shaped, may be ulcerated on affected side, history of tobacco abuse in some cases.
Histopathologically, spindle-shaped cells, separated by delicate connective tissue strands can be seen. Cells are enlarged, round or polygonal, with oval nuclei and abundant cytoplasm. Nuclei of these spindle-shaped cells are variable in size and shape, vesicular, prominent nucleoli with abundant, finely granular, eosinophilic cytoplasm. Mitotic figures are evident.

Immunohistochemistry , special stain , electron microscopy ,serum analysis are few additional investigations conducted in these case reports. Six cases out of 20 cases succumbed to the disease.

CROSS-SECTIONAL STUDIES

Three studies with cross-sectional study design were included in which data was collected retrospectively. A total of 91 participants were included. The conclusions of studies indicated that median age at onset was 51 years (range, 32–76 years). Moreover, most common disease sites were the tongue (28%) and buccal mucosa (22%) . Immunohistochemistry is helpful to know the histogenesis and nature of SpCC. Prognosis of the disease always poor and distant metastasis is always more then the conventional SCC.

CASE REPORTS:

The maximum score that could be assigned to each study is 8. Out of 20 case reports, one showed high risk, seven showed unclear risk and twelve reports showed low risk of bias. In reports with high risk of bias, demographic characteristics of the patient, treatment procedures description and post intervention clinical condition were not mentioned. In cases with unclear risk, information about treatment procedures description was not mentioned.

RETROSPECTIVE STUDIES:

Newcastle Ottawa tool for cross-sectional studies was used. Among the three studies, one [Ellis and Corio et al (1980)] showed moderate risk of bias and two [Su et al (2006), Sarma et al (2012)] showed high risk. Sample size determination was not mentioned in any of the included studies.

DISCUSSION

Spindle cell carcinoma (SpCC) is atypical form of poorly differentiated squamous cell carcinoma. According to Biradar et al (2014),it accounts for 3% of all SCCs in the head and neck region.[6] It is most commonly encountered in the upper aero digestive tract, the larynx (particularly the vocal cords) and hypo pharynx being the most common sites and rarely in the oral cavity .

It forms less than 1% of all tumours of the oral regions .[2]The commonest site in this systematic review has been found to be tongue . In the summation of case reports , alveolar mucosa was second most common site while case studies have shown buccal mucosa to take that position after tongue. Additional locations within the oral cavity where SpCC can occur are retromolar area , floor of the mouth, palate ,maxilla and mandible.

The majority of SpCC cases occurs in men (85%), most frequently between the sixth and eighth decades of life.[6]Out of 20 case reports 12 were male and 8 were females .The median age at onset was 52 years ranging from 32 – 75 years.

It has been linked to cigarette smoking, alcohol abuse, and previous radiation exposure to the affected area .Potential risk factors include the history of tobacco use, poor oral hygiene, alcohol abuse, and previous ionizing irradiation of the area. In this systematic review, we found that five patients out of 20 case reports were heavy smokers and has been using tobacco for more than two decades. Two patients had history of previous irradiation . Inadequate habit history recording , could be the possibility for the negative outcome in in the remaining cases. Growth configuration is often exophytic polypoid, but a sessile, nodular, or endophytic configuration has also been described. We observed that growth was mostly exophytic and polypoid with ulcerated surface covered by brown to yellowish necrotic tissue. Firm nodular growth were predominantly painless while pain was a feature of extensively ulcerated lesions.

Diverse terms have been used, such as pseudo sarcoma, sarcomatoid carcinoma, collision tumor, carcinosarcoma, pleomorphic carcinoma, and polypoid carcinoma, highlighting the varied interpretations of the spindle cell component's histogenesis. Three primary theories have emerged regarding the histogenetic origin of spindle cells. The initial theory proposes that spindle cells and epithelial cells develop simultaneously from distinct stem cells, leading to the term "collision tumor." The second theory describes the spindle cell component as an abnormal reactive proliferation of the stroma, hence termed "pseudo sarcoma." Lastly, the monoclonal hypothesis suggests that both spindle and epithelial components stem from the same monoclonal origin, with dedifferentiation or transformation resulting in spindle cells. Currently, the monoclonal hypothesis is widely favored and is strongly backed by several studies.[6]

In these cases, a polypoidal mass covered in ulcerated stratified squamous epithelium was

histologically observed. The underlying tumor tissue exhibited a composition of pleomorphic spindle cells arranged in intersecting fascicles and whorls, characterized by a high nucleus-to-cytoplasm ratio, pleomorphic vesicular nuclei, prominent eosinophilic nucleoli, and scanty cytoplasm. Multiple cases also displayed numerous bizarre cells and multinucleated tumor giant cells. The stroma surrounding these tumors showed signs of hyalinization, desmoplasia, and chronic inflammatory infiltrate. Additionally, in a few cases, multiple areas of spindle cell proliferation with a myxoid background consisting of elongated, spindled fibroblasts in loosely arranged whorls were noted.

Various other investigations were also conducted in these case reports and studies ranging from use of special stains, immune-histochemistry(IHC), electron-microscopy, Flowcytometry ,DNA ploidy analysis to detection of carcinoembryonic antigen (CEA) in serum. Fifita et al (2006) using Papanicolaou-stained (PAP) smear identified two kinds of tumor cells population in biphasic tumors, sheets or single squamous, and spindle or polygonal cells.[7]Munakata R et al (1998) evaluated serum levels of carcinoembryonic antigen (CEA) were essentially within normal limits.[8] Numerous IHC markers such as AE1/AE3 ,Vimentin, S-100 , α-SMA, Desmin, p63, CD34 ,CD18 ,EMA ,Ki67,CK7 ,HMB-45 , CK14 ,CK 20, CK56 ,CK 5/6 , β-catenin were evaluated for diagnosing SpCC correctly.

As early as in 1989, Slootweg PJ et al ,concluded that spindle cells shows reactivity for Vimentin while the cytokeratin expression was variable in SpCC. [9] Rizzardi C et al (2003) in his panel of various IHC markers found that tumor cells were negative for CD68 (PG-M1 and KP1), lysozyme, smooth muscle actin, desmin, and S-100 protein. The squamous cell portion exhibited positivity for cytokeratin and epithelial membrane antigen (EMA), while the spindle cell portion lacked cytokeratin expression but displayed occasional positivity with the anti-EMA antibody. Additionally, the spindle cells strongly expressed vimentin, alpha-1-antitrypsin, and, in some areas, pan-actin (HHF35), whereas the carcinomatous element did not demonstrate these mesenchymal markers. Furthermore, the flow cytometric study revealed p53 protein accumulation in both tumor components, with a notable concentration in the regions of squamous cell carcinoma. DNA analysis was also conducted to determine the degree of aneuploidy, which was recognized as one parameter indicating the malignant potential of a neoplasm.[10]

Recently , Donohue-Cornejo A et al (2020) found positivity for antibodies targeting AE1/AE3, CK18, p63, vimentin, and EMA confirmed the presence of a biphasic tumor in their examination.

The varied presentation of this atypical tumour alludes the consideration of distinct entities as differential diagnosis. Spindle cell carcinoma can be differentiated from other sarcomas such as fibrosarcoma and leiomyosarcoma as these entities are rare in head and neck region , also intervening fibrous layer separate lesion from overlying epithelium. Similarly, Inflammatory myofibroblastic tumor can be distinguished by the absence of dysplastic carcinomatous epithelial component and lack of dropping off from overlying epithelium . Mucosal Malignant Melanoma are positive for S100 & HMB45 while inflammed granulation tissue resolves on its own with time. On contrary, SpCC are negative for S100 & HMB45 and

doesn’t heal with time.

The spindle cell lesion must also be distinguished from malignant fibrous histiocytoma (due to its cytologic pleomorphism and multinucleate giant cell), rhabdomyosarcoma (owing to the presence of tadpole or strap cells), synovial sarcomas (because of its age at presentation, location, and chromosomal translocation), and malignant peripheral nerve sheath tumors (demonstrating nerve coursing of tumor cells and herniation of tumor into blood vessels). [6] Nodular fasciitis can be differentiated as there is no cellular pleomorphism , normal mitotic figure, immature myofibroblast , zonal organisation of spindle cells and regional heterogeneity i.e alternate areas of fibroblastic cellular areas and loose myxoid areas . The absence of other markers such as S-100, HMB-45, smooth muscle actin (a-SMA), desmin, and CD34, aided in excluding sarcomas originating from melanocytic, neural, muscular, and vascular tissues. [11]

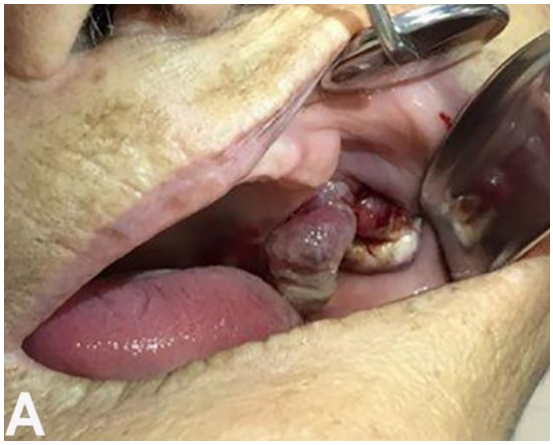
Spindle cell carcinoma (SpCC) typically exhibits a disease course marked by recurrent episodes and the spread of cancer cells to nearby regions (regional metastasis), which is more frequent than distant metastasis. Compared to the more common squamous cell carcinoma (SCC), SpCC is known for its heightened aggressiveness, leading to lower overall survival rates. Prognostic factors for SpCC include the depth of invasion, the growth pattern characterized by polypoid exophytic growth, prior history of radiotherapy, vascular invasion, and the presence of both regional and distant metastases.

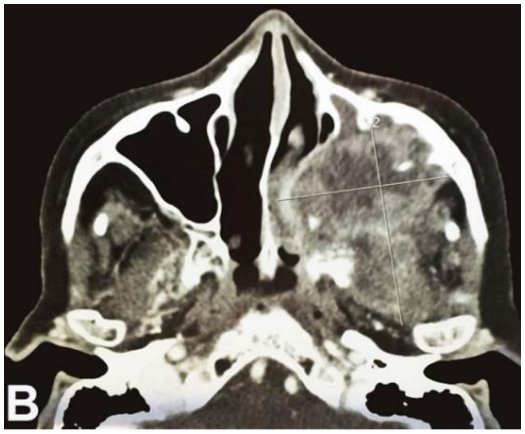
LIMITATIONS

Given the rarity of the disease, case report, case series and retrospective studies were included in this review, since these represent the only type of data available in the literature. This type of data is typically on the lower end of quality scales that have been developed for cohort and case-control studies and randomized control trials. Due to the same reason, meta- analysis couldn’t be performed. Also, there are concerns about combined data and higher risk of bias inherent to case reports and case series.
Geographical or temporal biases may have been introduced with this process.

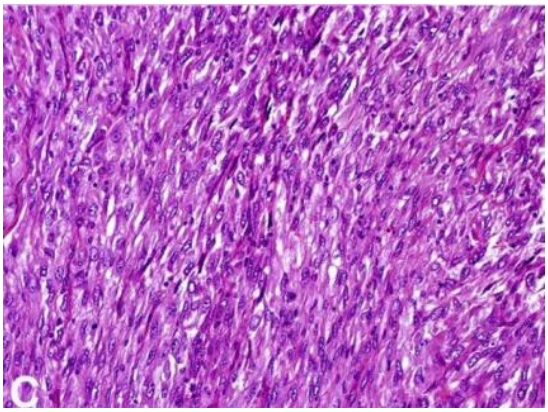
CONCLUSION

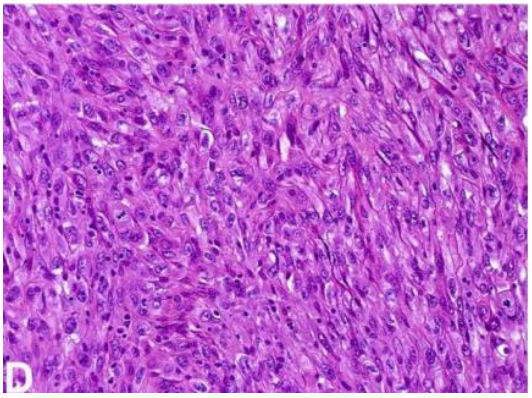
SpCC is a neoplasm of epithelial origin and considered to be a variant of SCC. It mimics other connective tissue sarcomas and spindle cell malignancies under light microscopy. Immunohistochemistry is helpful to know the histogenesis and nature of SpCC. Prognosis of the disease is always poor and distant metastasis is considerably more then the conventional SCC.





A-Intraoral examination showing an ulcerated mass; B – Axial computed tomography of the face showing a tumor mass involving the entire maxillary sinus and part of the nasal concha





C– Presence of pleomorphic fusiform cells with the sarcomatous appearance ; D- with a more epithelioid appearance, respectively

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