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ORIGINAL ARTICLE

Clinicopathologic Diagnostic and Prognostic Factors of Spindle Cell Carcinoma of Upper Airway

Amanda Bueno de Araújo[1] · Thiago Luís Infanger Serrano[1] · Maria Cláudia Mota Pedroso[1] · Fernanda Viviane Mariano[2] · Albina Altemani[2] · Flavio Mignone Gripp[1] · Agrício Nubiato Crespo[1] · Carlos Takahiro Chone[1]

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Abstract

Spindle cell carcinoma (SpCC) is a rare tumor, which occurs in upper respiratory tract, mainly in larynx. This study aimed to review the clinical and pathological characteristics for diagnosis and prognosis. Retrospective cohort study. All patients with SpCC in upper respiratory tract treated for curative intent was included. All patients were reviewed in search of epithelial component and immunohistochemistry when not found. It was evaluated rate of recurrence and disease-free survival with univariate and multivariate analysis with Kaplan Meier and Cox Regression model adjusted to propensity score indexes (PSI) according to age, gender, site of tumor, stage, surgical treatment, status of margins of surgical resection, lymphatic invasion. There were 16 cases of SpCC.31% were diagnosed with light microscopy and others with immunohistochemistry for epithelial marker. Disease-free survival was higher in early stage disease in univariate and multivariate analysis, as the main prognostic factor. Surgical treatment increases in 2.54 the rate of survival. The SpCC is a rare tumor considered a highly malignant variant of squamous cell carcinoma. It has male predominance and tobacco use as risk factors. Its treatment should follow the same recommendations for squamous cell carcinoma, with surgery as the maintain treatment. Immunohistochemistry is an adjuvant important tool for diagnosis of SpCC.

Keywords Spindle cell carcinoma · Sarcomatoid carcinoma · Head and neck cancer · Immunohistochemistry · Prognostic factors

Introduction

Spindle cell carcinoma (SpCC), also called sarcomatoid carcinoma, is a relatively uncommon cancer first described by Virchow in 1864 [1], although as a dual malignancy (carcinosarcoma), and then was definitively described by Figi in 1933. It has histologic, cytologic and molecular properties of both epithelial and mesenchymal tumors [, 2]. Thus, it presents heterogeneous pathologic features, clinical behavior and prognosis [2–9]. In the past, it was easily be misdiagnosed with pure mesenchymal tumors because of the unfamiliarity with this cancer. Nowadays, with larger series of patients and sophisticated pathologic molecular techniques has made the diagnosis of SpCC reliable. It could occur in any site of the body mainly in respiratory tract and is considered a variant of squamous cell carcinoma. Numerous terms have been used to describe these lesions: pseudosarcoma, carcinosarcoma, pleomorphic carcinoma, sarcomatoid carcinoma and pseudosarcomatous carcinoma [5].

These tumors have now been proved to be monoclonal, evolving from conventional squamous carcinoma with dedifferentiation associated with sarcomatoid transformation [7, 10]. They pose a significant diagnostic challenge to the pathologist with remarkable morphological and immunohistochemical overlap with other benign and malignant spindle cell tumors. An accurate diagnosis of these tumors is essential as they vary in their clinical management and outcome [10].

The differential diagnosis is done with fibrosarcoma, malignant fibrous histiocytoma, synovial cell sarcoma, giant cell tumor, leiomyossarcoma, rhabdomyosarcoma, osteosarcoma, mesenchymal chondrosarcoma, Kaposi sarcoma and

✉ Amanda Bueno de Araújo
mandibueno@hotmail.com

[1] Department of Otorhinolaryngology, Head Neck, University of Campinas, UNICAMP, PO BOX 6111, Campinas, São Paulo Postal Code: 13081-970, Brazil

[2] Department of Surgical Pathology, University of Campinas, UNICAMP, Campinas, São Paulo, Brazil

angiosarcoma [5–12]. Prognosis depends on a number of factors, including location, tumor (T) stage, presence of necrosis, prior radiation, and loss of immunoexpression of epithelial markers [4, 9, 11, 12]. The main treatment is surgery with adjuvant treatment in literature.

This article evaluates all cases treated in a tertiary hospital, observing clinicopathological features for contribution of evaluation of parameters for diagnosis and prognosis of SpCC of upper airway.

Materials and Methods

The study included patients with spindle cell carcinoma in upper respiratory tract followed in our institution during the period between january-1990 and december-2017. A chart review was performed, and data collected regarding gender, age, initial symptoms, site of tumor, stage, choice of treatment, pathological evaluation and the follow-up period of previously untreated patients. Stages were defined according to seventh edition of AJCC of 2010 [13].

All cases were re-submitted to anatomopathological re-evaluation with the following immunohistochemical markers when necessary: vimentin, EMA (epithelial membrane antigen), AE1 / AE3, 34BE12 and P63. All pathological evaluation was performed in a single center. When immunohistochemical markers were used all five markers were tested in all. Patients with positive surgical margins, perineural invasion, angiolymphatic embolus, multiple lymphatic metastases, extracapsular spread was referred to adjuvant treatment.

Due to the significant imbalance in baseline covariates between individuals with laryngeal vs non-laryngeal tumors, we used propensity score matching to assemble a balanced cohort of patients. We estimated propensity score indexes (PSI with the covariates: age, gender, tumor staging groups, surgical treatment, lymphatic invasion, prior carcinoma) for tumor localization for each of the 16 patients, using a non-parsimonious multivariable logistic regression model (c statistic = 0.71) and used that to match 6 pairs of patients with laryngeal vs non-laryngeal tumors. We assessed the effectiveness of matching and bias reduction by estimating standardized differences. Using the same risk equation used for matched pairs, we also estimated PSI of unmatched individuals.

Estimated Kaplan Meier curves with log-rank test and Cox proportional hazards ratio adjusted to PSI models were used to examine the association between tumor stages, surgical treatment, larynx vs non-larynx tumors, positive margins and lymphatic invasion for disease-free survival. Cox regressions were adjusted to PSI.

The models were defined based on the variables with p value less than 0.05 in comparisons among groups. A two-sided p value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Mac version 20.0 and R for Mac version 3.5.1 Patients with incomplete data and patients with different pathological result after reviewing the case were excluded.

This study was approved by the Ethics and Research Committee of UNICAMP on August 6, 2018, number of Certificate of Presentation for Ethical Consideration 90,786,018.5.0000.5404.

Results

During the period there were 16 cases of spindle cell carcinoma treated for curative intent. There was male predominance (13:3) and the mean age of diagnosis was 59 years-old (45 yo to 75 yo). The follow-up period ranged from 2 to 132 months, with an average of 54 months.

The sites of the tumor were oral cavity in three cases (18,7%), three cases in tongue base (18,7%) and larynx in ten cases (63%). The sites in larynx were supraglottic in three and seven in glottic area.

The diagnosis of sarcomatoid carcinoma was made with histopathological analysis with frank epithelial differentiation at light microscopic level (dysplasia/squamous carcinoma in situ/squamous nests/lymph node metastasis) in five and associated to immunohistochemical reactions in other eleven. The most common clinical presentation was an exophytic and polypoidal growth with broad base. In all cases the squamous cell carcinoma component was in base of polypoidal growth diagnosed without additional analysis **(**Fig. 1**).**

In eleven patients without epithelial component on light microscopy at least one epithelial immunohistochemical marker was positive and seven (64%) of these had also positivity to vimentin. 46% had multiple positive epithelial immunohistochemical markers. 54% (6) had only one positive epithelial marker being positive to EMA in 83% (5) of these and 83% was also positive to vimentin **(**Table 1**).** EMA was the most common positive epithelial

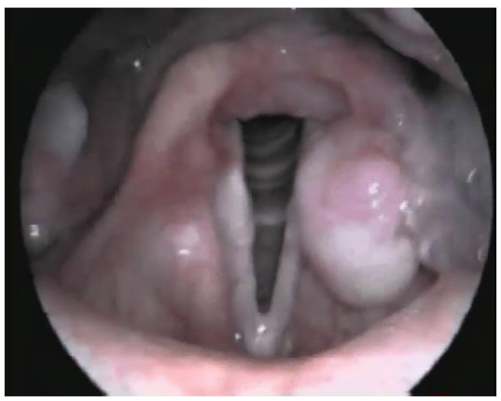

Fig. 1 Indirect laryngoscopy image demonstrating an exophytic and polypoid lesion in left aryepiglottic fold

Table 1 Immunohistochemistry panel for epithelial and mesenchymal markers in 11 patients

Patient	1	2	3	4	5	6	7	8	9	10	11
VIMENTIN	+	+	–	–	+	+	+	–	+	–	+
EMA	+	+	+	+	–	+	+	+	+	–	+
AE1/AE3	–	+	–	+	–	–	+	+	–	+	–
34BE12	–	–	–	+	–	–	+	+	–	+	–
P63	–	–	–	+	+	–	+	–	–	+	–

+, positive reaction to this marker on immunohistochemistry

-, negative reaction to this marker on immunohistochemistry

marker (82%), followed by AE1/AE3 and 34BE12 with 46% of positivity each and 36% to p63.

Most of cases (75%) were diagnosed in early local stages(T1/T2) without lymphatic metastasis (10) and two in base of tongue with lymphatic metastases, N1 and N2b. The most frequent choice of treatment was surgery in eleven with adjuvant concomitant chemoradiation in three of them. All patients were followed by an average period of five years (2 months to 11 years), with six recurrences. Three recurrences died, even after salvage treatment. Ten patients are alive without of disease free and three alive with disease. Age, gender, site of tumor, local stage, presence of lymphatic metastases and type of treatment was not related to recurrences in univariate analysis with Fisher exact Test **(**Table 2**).**

Estimated survival analysis using Kaplan-Meier with Log Rank test observed disease-free survival time of 8.82y (95% CI: 6.73–10.94y) in T1/ T2 subgroup and of 3.64y (95% CI 0.83–6.44y) in T3/T4, with a significant difference of $p = 0.042$ **(**Fig. 2**,** Table 3**).** Comparing mean disease-free survival time of laryngeal and non-laryngeal tumors the result was 7.55y (95% CI: 4.92 to 10.183) and 7.53 (95% CI: 3.68 to 11.39), respectively, without significant difference ($p = 0.97$). The multivariable cox logistic regression model, adjusted with propensity score indexes (PSI) observed a higher rate of tumor recurrence in T3/ T4 cases than early stage ones with an Odds ratio(OR) of 6.67**(**Fig. 3**),**with significance ($p = 0.046$) as also for non-surgical treatment OR = 2.54, despite absence of significance $p = 0.43$**(**Table 4**).**Test of equality of disease free survival distributions for the different levels of T Stage showed in Fig. 4, Log Rank = 0.08 with higher length of survival in early T stage lesions. Gender, age, site of primary tumor, type of treatment were not independent prognostic markers in univariate and multivariate analysis **(**Tables 3 and 4**).** Our estimated five-year disease-free survival was 62.5%. Age was not evaluated in univariate and multivariate analysis of survival because of small variation among patients. Gender was not evaluated in univariate analysis because due to small sample size.

Discussion

The diagnosis of spindle cell carcinoma (SpCC) requires histological demonstration of both the squamous cell component and the spindle shape cells with sarcomatous appearances. Sometimes monophasic spindle cell carcinoma can occur if the squamous element escapes detection. Electron microscopy or immunohistochemistry for keratin may provide evidence of epithelial differentiation of the spindle cell tumor portion in

Table 2 Clinico-pathologic features of 16 SpCC patients

Demographic and clinico-pathologic parameters		Status regarding recurrence of disease			
		Recurrence	Non recurrence	total	p value
Gender	M	3	10	13	0.2
	F	2	1	3	
Age	≥ 60	1	6	7	0.15
	< 60	4	5	9	
Location	Non larynx	1	4	5	0.21
	Larynx	4	7	11	
N stage	N+	1	1	2	0.46
	N0	4	10	14	
T stage	T1 T2	3	9	12	0.30
	T3 T4	2	2	4	
AJCC stage	I/II	2	8	10	0.21
	III/IV	3	3	6	
Treatment	Surgery	3	10	13	0.20
	Non surgery	2	1	3	

M male, *F* female, *AJCC* American Joint Committee on Cancer

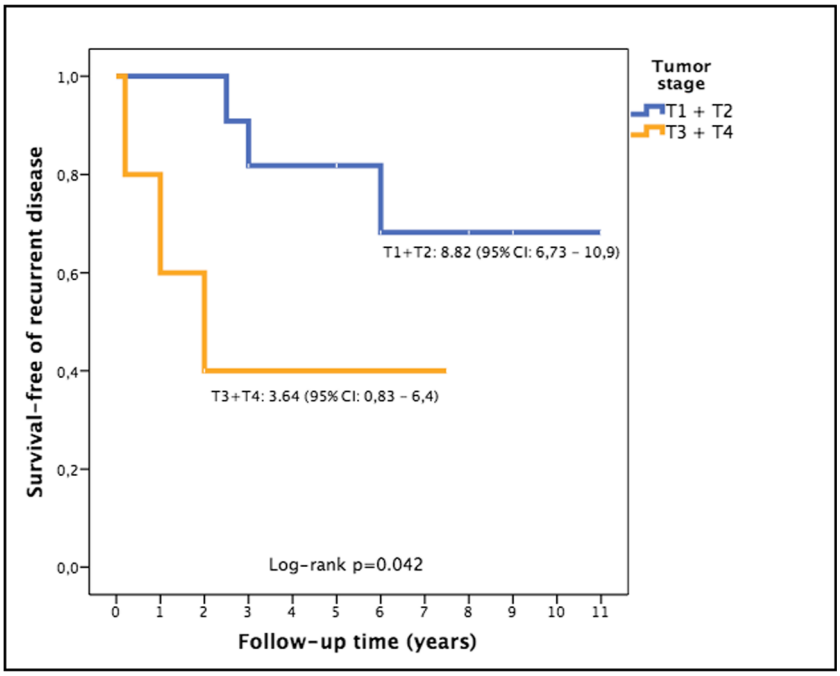

Fig. 2 Kaplan-Meier estimated disease-free survival time of the T1 + T2 subgroup was 8.818 (6.73–10.94) and the T3 + T4 subgroup was 3.64 (0.83–6, 44), with a significant $p = 0.042$

these cases [5]. **(**Fig. 5**).** It poses a challenge for clinician and pathology for diagnosis related to the uncommonness of this disease with an incidence of 0.023 cases per 100,000 inhabitants compared to 3.556 cases per 100,000 inhabitants for other laryngeal malignancies [12].

Molecular study with immunohistochemistry and genetic tests with DNA with PCR searching loss of heterozigozity and microsatellite analysis with markers observed an evolution and progression of conventional squamous cell carcinoma on sarcomatoid component with an aggressive feature [7].

The literature observes that the squamous areas are virtually always positive for AE1/AE3, while the spindle cell component has variable positivity. In cases of negative reaction for AE1/AE3, others epithelial markers may be added to the diagnosis. Recently it has been argued that the marker p63 increases epithelial differentiation detection in a rate of 30% compared to the other cytokeratin staining [5, 14]. In this series of eleven patients 16 cases were submitted to immunohistochemistry analysis. There was a 36% positivity for p63, followed by 46% 34BE12, 46% AE1AE3E, 82% for EMA and 64% for Vimentin. Mesenchymal markers in SpCC are often positive. On the other hand, these markers are most of the times negative in the squamous component [6]. Because of phenotypical appearance of mesenchymal cells in sarcomatous portion of SpCC of upper airway site when epithelial malignant component was not found it is important to test to multipaneled immunohistochemical epithelial markers when macroscopy of tumor is polypoid or pedunculated in a patient with previous tobacco habit even in positivity to vimentin

Table 3 Univariate Kaplan Meier estimated disease-free survival (Log Rank) analysis of clinical and pathological characteristics in years

		Years	95% CI	p value
Site	Non-laryngeal	7.53	3.68–11.39	0,967
	Laryngeal	7.55	4.92–10.18	
T stage	T1	9.33	6.67–12.00	0.08
	T2	8.25	5.13–11.36	
	T3	4.25	0–8.75	
	T4	1.4	0.04–2.76	
T stage(group)	T1/T2	8.81	6.73–10.90	**0.042**
	T3/T4	3.64	0.83–6.45	
Positive surgical	Negative	10	8.25–11.75	0.595
margin or Lymphatic invasion	Positive	8.75	4.93–12.57	

The bold characters represent statistically significant values, whose value of $p < 0.05$

Abbreviations: 95%CI, 95% confidence interval;

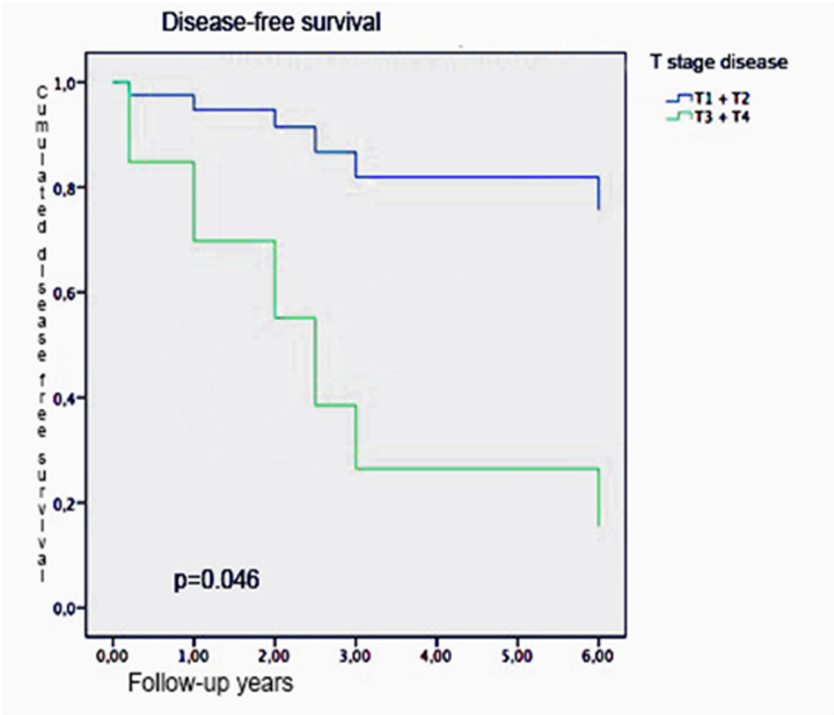

Fig. 3 Cox regression razard ratio model analysis adjusted to Propensity Score Index of disease-free survival according to stage T1/T2 versus T3/T4, with a significant p = 0.042

which is quite frequent and not confirmatory of sarcomatous tumor otherwise a squamous cell carcinoma variant.

The clinical behavior of SpCC is poorly understood, because of the small number of cases in literature compared to squamous cell carcinoma of head and neck but it seems the same of squamous cell carcinoma of upper airway so its treatment should follow it same rules respecting the site of origin

Table 4 Multivariate Cox regression analysis adjusted to Propensity Score Index(PSI) with Cox proportional hazards ratio adjusted to PSI models of disease free survival associated clinical and pathological characteristics

		Odds ratio	95% CI	p value
Gender	M	0.221	0.02–3.23	0.27
	F			
Site	Non-laryngeal	*	*	0.98
	Laryngeal			
T stage(group)	T1/T2	6.6	1.03–42.88	**0.046**
	T3/T4			
Treatment	Surgery	2.539	0.25–26.07	0.43
	Non surgery			
	T3/T4			
Positive surgical margin or Lymphatic invasion	Negative	*	*	0.58
	Positive			

The bold characters represent statistically significant values, whose value of $p < 0.05$

Abbreviations: 95%CI, 95% confidence interval; *Statistically not significant

in larger case series [4, 12]. But genetic and molecular study with microsatellite markers observed a higher aggressive feature of SpCC as basaloid carcinoma, or moderated or poorly differentiated conventional squamous carcinoma [8]. In a larger case series with 341 patients [4] with SpCC of upper aerodigestive tract the mean age at diagnosis was of 67 years, with a range of 24 to 94 years, similar to our cases (mean age of 62 years, ranging from 45 to 75 years-old). The male to female ratio ranged from 10:1 to 3:1 in the largest study published. In our report, there was found a ratio of 4.5:1. The main association appears to be tobacco use, found in all of our patients except one. Radiation therapy, seen in two cases, could be a risk factor too with better outcomes in larynx than oral cavity, maybe related to early diagnosis of larynx tumors than of the oral cavity ones.

The site of SpCC is more frequently at larynx, being about 70% in glottis, followed by oral cavity, the second most prevalent site, but could be found in esophagus, upper respiratory tract and uterus [4, 5]. Most of them are characterized as being polypoid or pedunculated tumors [4]. Then male patient with a polypoid or pedunculated tumor, with a history of tobacco use SpCC of upper airway must be ruled out. Biopsy must be made in it base of broad base searching epithelial neoplasm and immunohistochemical reactivity when it was not found.

Surgical therapy for curative intent with clear margins should be primary mode of treatment and conservative approaches should be performed when indicated, with neck dissections done primarily for hypopharyngeal, base of tongue, supraglottic, advanced glottic and transglottic tumors and infiltrative oral cavity lesions [5]. In recent

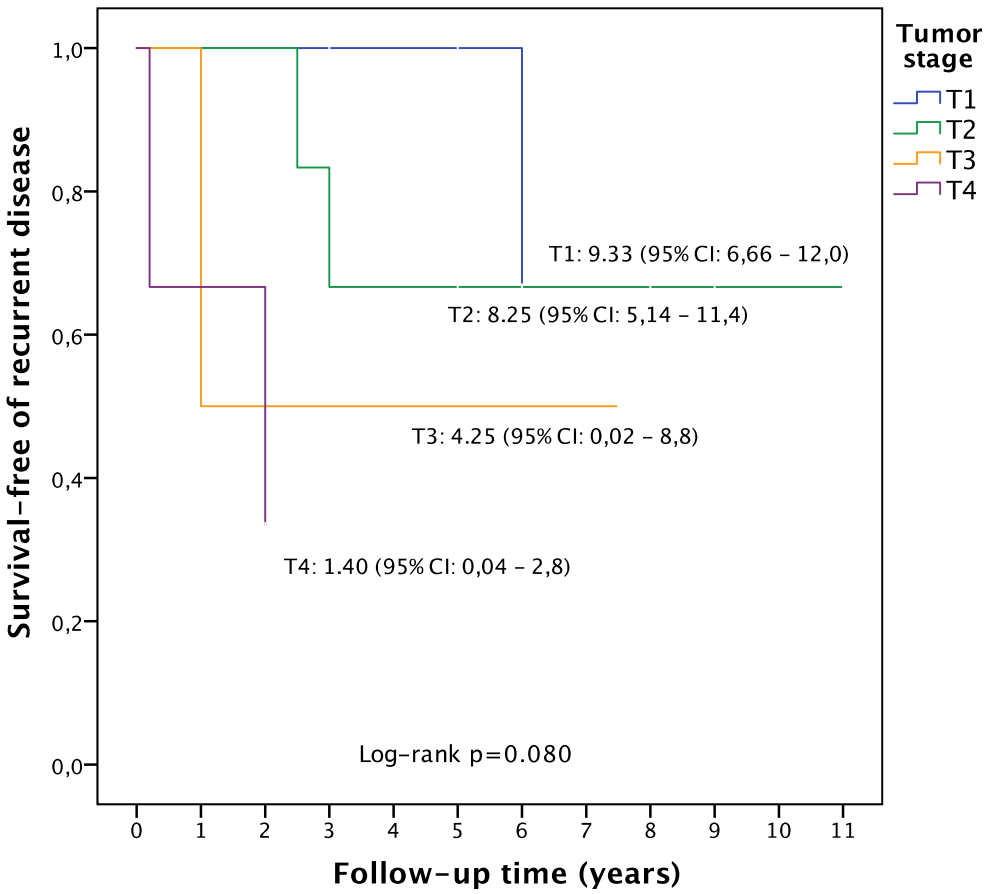

Fig. 4 Estimated disease-free survival on Kaplan Meir curves compared according to Test of equality of survival distributions for the different levels of T Stage, Log Rank = 0.08

literature, most patients with SpCC underwent combined treatment with surgery and radiation therapy or concomitant chemoradiation [5] as adjuvant treatment in microscopic positive margins, extracapsular extension of lymphatic metastasis, perineural or angiolymphatic invasion or multiple lymphatic metastases.

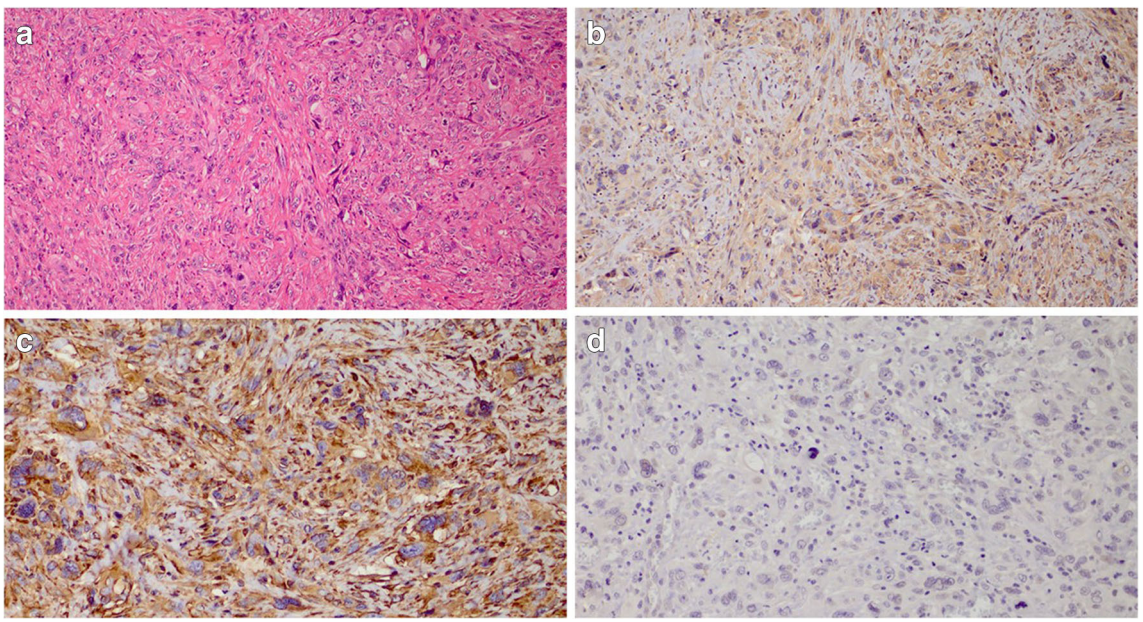

Fig. 5 Sarcomatoid carcinoma. **a** Histopathological view hematoxylin-eosin (10x) showing the epithelial and spindle cell component. Immunohistochemistry showing positive reaction in neoplastic cell to EMA **b** (10x) and Vimentin (C)(20x). This sarcomatoid carcinoma was positive in both areas for pancytokeratin p63 (D) (20x). All microscopic images were from the same patient

The prognosis of SpCC is controversial and seems to be like of the common SCC in a general view, including all sites and tumor stages [5]. Literature suggests metastasis in regional lymph nodes in 25% of patients and distant metastasis in 5% to15%, being mainly in lung, brain and subcutaneous tissue. In our cases, two neck metastases were identified (12,5%) in different patients. The five-year survival reported in literature is between 65% to 95%, with better prognosis in absence of previous irradiation. We observed better outcomes in early tumor stage with an OR of 6.67 in local recurrence in advanced stage independent of age, gender, site of tumor, type of treatment, positive surgical margins or presence of lymphatic metastasis. As observed in general squamous cell carcinoma of upper airway, early stage cancer had better survival. It seems that surgical treatment followed of adjuvant treatment increases the rate of disease-free survival with an OR of 2.54 independent of other clinical and pathological parameters in our results. When overall prognosis is given, the overall lethality of this cancer is 30 to 32%.

Conclusion

The SpCC is a rare tumor considered a variant of squamous cell carcinoma. It has male predominance and tobacco use as risk factors. Early stage disease is related to better disease-free survival. Its treatment should follow the same recommendations for squamous cell carcinoma, with the surgery as the first choice. Immunohistochemistry can be used as an auxiliary tool in the diagnosis of sarcomatoid carcinoma, but not as the only confirmatory method yet.

Author Contributions **Amanda Bueno de Araújo**, Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.; **Carlos Takahiro Chone**, Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published;agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Agrício Nubiato Crespo,** final approval of the version to be published;agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Maria Claúdia Mota Pedroso,** final approval of the version to be published;agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Flávio Mignone Gripp,** final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Thiago Luís Infanger Serrano**, final approval of the version to be published;agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Albina Altemani**, final approval of the version to be published;agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Fernanda Viviane Mariano** final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

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

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