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Spindle cell squamous carcinoma of the oral region

An immunohistochemical and ultrastructural study on the histogenesis and differential diagnosis with a clinicopathological analysis of six cases

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Summary. Six cases of spindle cell squamous carcinoma (SCSC) of the oral cavity were studied clinicopathologically, immunohistochemically and ultrastructurally to summarize the clinicopathological features of this rare neoplasm and to discuss the debatable histogenesis of the sarcomatoid component and the differential diagnosis of SCSC. The mean age of the patients was 72 years and the female to male ratio was 1:2. Four of them had a history of irradiation for pre-existing squamous cell carcinoma. One patient died of SCSC. While clinical and histological prognostic factors of SCSC could not be determined, it was shown that radical surgery resulted in good prognosis. The epithelial nature of the sarcomatoid component of SCSC was clearly revealed by a combination of immunohistochemical staining for keratins and electron microscopic demonstration of tonofilament-like filaments and/or desmosome-like structures. Together with electron microscopic evaluation of the tumour cells, immunohistochemical characterization of tumour cells using antibodies to keratin, vimentin, glial fibrillary acidic protein and S-100 protein is very helpful in differentiating SCSC from true spindle cell sarcoma, melanoma and malignant myoepithelioma. In the immunohistochemical differential diagnosis of SCSC, it is important to remember that SCSC should not be ruled out of the differential diagnosis by a positive reaction for vimentin in sarcomatoid tumour cells. Absence of staining for keratin in the sarcomatoid tumour cells does not always exclude SCSC, because some SCSCs show immunoreactivity of keratin in their sarcomatoid components only with some anti-keratin antibodies. Different kinds of anti-keratin antibodies should be applied in the differential diagnosis of SCSC.

Key words: Spindle cell squamous carcinoma – Immunohistochemistry – Keratin – Vimentin – Differential diagnosis

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Introduction

Spindle cell squamous carcinoma (SCSC) is a unique and rare biphasic tumour consisting of sarcomatoid proliferation of pleomorphic spindle-shaped cells and squamous cell carcinoma, either in situ or invasive. SCSC has been referred to by a variety of names, including pseudosarcoma (Lane 1957), carcinosarcoma (Minckler et al. 1970), pleomorphic carcinoma or spindle cell carcinoma (Ellis and Corio 1980; Zarbo et al. 1986; Ellis et al. 1987), which reflect the divergent interpretation of the sarcomatoid component as reactive or neoplastic, mesenchymal or epithelial. While it is generally accepted that the sarcomatoid cells are derived from squamous cells, this view is not still unanimous, and the clinicopathological features and the differential diagnosis of SCSC are still not fully described.

In the present study, we summarize the clinicopathological features of six SCSCs in the oral region and discuss the histogenesis of the sarcomatoid component of the tumours and the differential diagnosis of SCSC based on immunohistochemical and ultrastructural findings.

Materials and methods

Six cases of SCSC were drawn from the files of the Department of Oral Pathology, Hiroshima University School of Dentistry. The primary diagnosis of the tumours was made by haematoxylin-and-eosin-stained sections together with additional histochemical staining.

Immunostaining of intermediate filaments and S-100 protein was achieved on formalin-fixed and paraffin-embedded tissue sections by means of either the peroxidase anti-peroxidase method or the biotin streptavidin system, routinely. The antigenic structures studied and the antibodies applied are listed in Table 1.

Electron microscopic examination could be performed in all cases but one (case 5). Fresh material from three cases and formalin-fixed material from two cases were fixed with a 2.5% buffered glutaraldehyde solution and post-fixed in a 1% osmium tetroxide

Table 1. Antibodies employed, their specifications and sources

Antibody	Type	Specificity	Source
Anti-keratin, wide spectrum (WKer)	Polyclonal	48, 51, 52, 56, 58, 60 kDa CK	Dako, Santa Barbara, Calif.
KL1	Monoclonal	56 kDa CK	Cosmo Bio., Tokyo, Japan
PKK1	Monoclonal	44, 46, 52, 54 kDa CK	Labsystems, Helsinki, Finland
Anti-vimentin	Monoclonal	Vimentin	Lipshaw, Detroit, Mich.
Anti-S-100	Polyclonal	S-100 protein	Dakopatts, Glostrup, Denmark
Anti-GFAP	Polyclonal	GFAP	Dakopatts

CK, Cytokeratin; GFAP, glial fibrillary acidic protein

Table 2. Summary of clinical data of six spindle cell squamous carcinomas (SCSCs)

Case	Age	Sex	Location	Growth configuration	Present history	Therapy	Follow up[a]
1	50	M	Oropharynx	Endophytic, ulcerative	18 years ago: SCC (gingiva), RT and ST	RSE CT	Alive (at 8 years)
2	83	F	Cheek	Endophytic, ulcerative	15 years ago: VC (buccal mucosa), RT 5 years ago: SCC (buccal mucosa), RT	PSE RT, CT	Dead from tumour (at 10 months)
3	84	M	Tongue	Exophytic, ulcerative	Nothing particular	RSE CT	Alive (at 4.8 years)
4	70	M	Maxillary antrum	Repletion of maxillary antrum	Nothing particular	PSE	Dead from stomach cancer (at 9 months)
5	71	F	Gingiva	Polypoid	8 years ago: leukoplakia (tongue) 2 years ago: SCC (tongue), RT	RSE	Alive (at 3.5 years)
6	76	M	Tongue	Endophytic, ulcerative	11 years ago: SCC (gingiva and oral floor) RT and ST	RSE	Alive (at 1.2 years)

SCC, Squamous cell carcinoma; VC, verrucous carcinoma; RT, radiation therapy; ST, surgical therapy; RSE, radical surgical excision; PSE, palliative surgical excision; CT, chemotherapy

[a] Time of last follow-up from the diagnosis of SCSC

solution. The specimens were dehydrated and embedded in epoxy resin. Ultra-thin sections were double stained with uranyl acetate and lead citrate, and examined with a transmission electron microscope.

Results

The clinical findings of the six SCSCs are summarized in Table 2. The mean age of the patients was 72 years, and the female to male ratio was 1:2. Four of them had a history of pre-existing squamous cell carcinoma and of radiation therapy. Four patients treated by radical surgical excision with or without chemotherapy are alive, while one patient, who had undergone palliative surgical excision with irradiation and chemotherapy, died 10 months after the diagnosis of SCSC.

The histological findings of the SCSCs, including the histological type, infiltrative growth pattern, degree of cellular pleomorphism, number of mitotic figures and amount of inflammatory cell infiltration, are summarized in Table 3. Five cases were biphasic SCSCs consisting of sarcomatoid and carcinomatous components (Fig. 1). One case (case 1) was a monophasic SCSC devoid of a classic carcinomatous component. Carcinomatous nests were often well demarcated from sarcomatoid components, while some nests were poorly defined, appearing to blend in with sarcomatoid components (Fig. 1). All tumours but one polypoid superficial tumour (case 5) infiltrated adjacent muscle or bone. Severe inflammatory cell infiltration and/or a myxomatous change in sarcomatoid areas were observed in some cases.

The results of the immunohistochemical staining are summarized in Table 4. The sarcomatoid components of all the six SCSCs were positive for vimentin, and the carcinomatous components in the five biphasic SCSCs were positive for keratins. In five cases (not case 2), the sarcomatoid components showed positive staining with at least two of the three anti-keratin antibodies employed in this study (Fig. 2a). But the combination of the anti-keratin antibodies which showed the positive reaction was different among the cases. Tumour cells in the transitional zone between the carcinomatous and sarcomatoid components showed intermediate immun-

Table 3. Histological findings of six SCSCs

Case	Type	Infiltrative growth pattern	Carcinomatous component	Sarcomatoid component	Inflammatory cell infiltration
1	Monophasic	Infiltrative		Cellular spindle cell sarcoma-like (DP, high; MF, 3–4)	Severe
2	Biphasic	Infiltrative	Moderately diff. SCC (DP, moderate; MF, 1–2)	Fibrosarcoma-like (DP, high; MF, 3–4)	Moderate
3	Biphasic	Infiltrative	Moderately diff. SCC (DP, moderate; MF, 5)	Fibromyxosarcoma-like (DP, moderate; MF, 1–2)	Severe
4	Biphasic	Infiltrative	Poorly diff. SCC (DP, high; MF, 5)	Malignant fibrous histiocytoma-like (DP, high; MF, 1–2)	Moderate
5	Biphasic	Superficial	Highly diff. SCC (DP, moderate; MF, 1–2)	Cellular spindle cell sarcoma-like (DP, high; MF, 3–4)	Moderate
6	Biphasic	Infiltrative	Moderately diff. SCC (DP, moderate; MF, 1–2)	Cellular spindle cell sarcoma-like (DP, high; MF, 2–3)	Severe

SCC, Squamous cell carcinoma; HPF, high power field ×400; DP, degree of pleomorphism; MF, number of mitotic figures/HPF

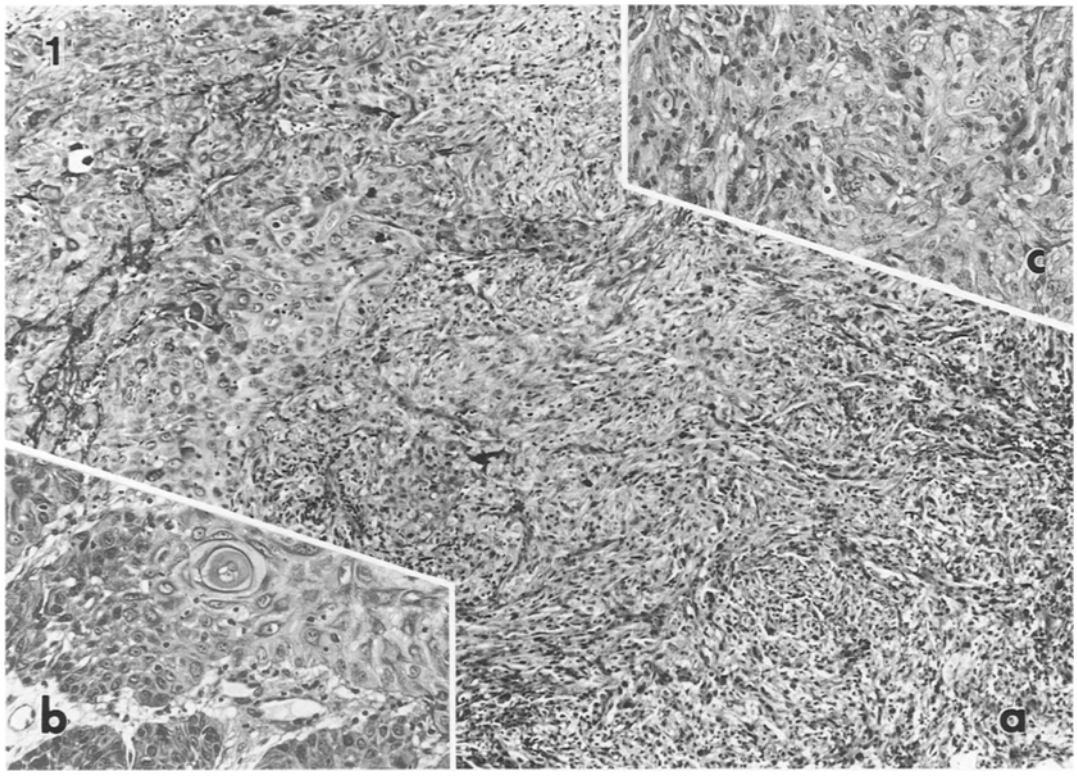

Fig. 1 a–c. Biphasic spindle cell squamous carcinoma consisting of a carcinomatous component and a sarcomatoid component. **a** The carcinomatous component (*left*) is poorly defined, appearing to blend in with the sarcomatoid component (*right*) H&E, ×100. **b**, **c** Higher magnification of the carcinomatous component and sarcomatoid component, respectively. H&E, ×300 (reduced to 85%)

oreactions between the carcinomatous and sarcomatoid components. Co-expression of keratin and vimentin in the sarcomatoid component was revealed by comparison of immunolocalization using serial sections (Fig. 2). S-100 protein and glial fibrillary acidic protein, which are usually positive in salivary myoepithelial tumours, were negative in both the carcinomatous and sarcomatoid components of all cases.

On electron microscopy, the sarcomatoid cells in the five cases studied showed bundles of tonofilament-like cytoplasmic filaments and/or desmosome-like structures (Fig. 3). These ultrastructural findings, suggesting an epithelial nature for the tumour cells, are listed in Table 4.

Discussion

SCSC has been reported as a mostly polypoid tumour with a predilection for occurrence in elder males (Barnes

Table 4. Summary of immunohistochemical and electron microscopic findings of six SCSCs

Case	Immunohistochemistry[a]												Electron microscopy of sarcomatoid cell
	Carcinomatous component				Transitional area				Sarcomatoid component				
	WKer	KL1	PKK1	Vim	WKer	KL1	PKK1	Vim	WKer	KL1	PKK1	Vim	
1	/	/	/	/	/	/	/	/	−	+	+	+	TF, DS
2	+	+	+	−	−	−	−	−	−	−	−	+	TF
3	+	+	+	+	+	+	+	+	−	+	+	+	DS
4	+	+	+	−	+	+	+	−	+	+	−	+	TF
5	+	+	+	−	+	+	+	+	+	−	+	+	ND
6	+	+	+	−	+	+	+	+	+	+	+	+	TF, DS

TF, Cytoplasmic tonofilament-like filaments; DS, desmosome-like structures; ND, not done
[a] S-100 protein and GFAP were not expressed in all tumour cells of the cases

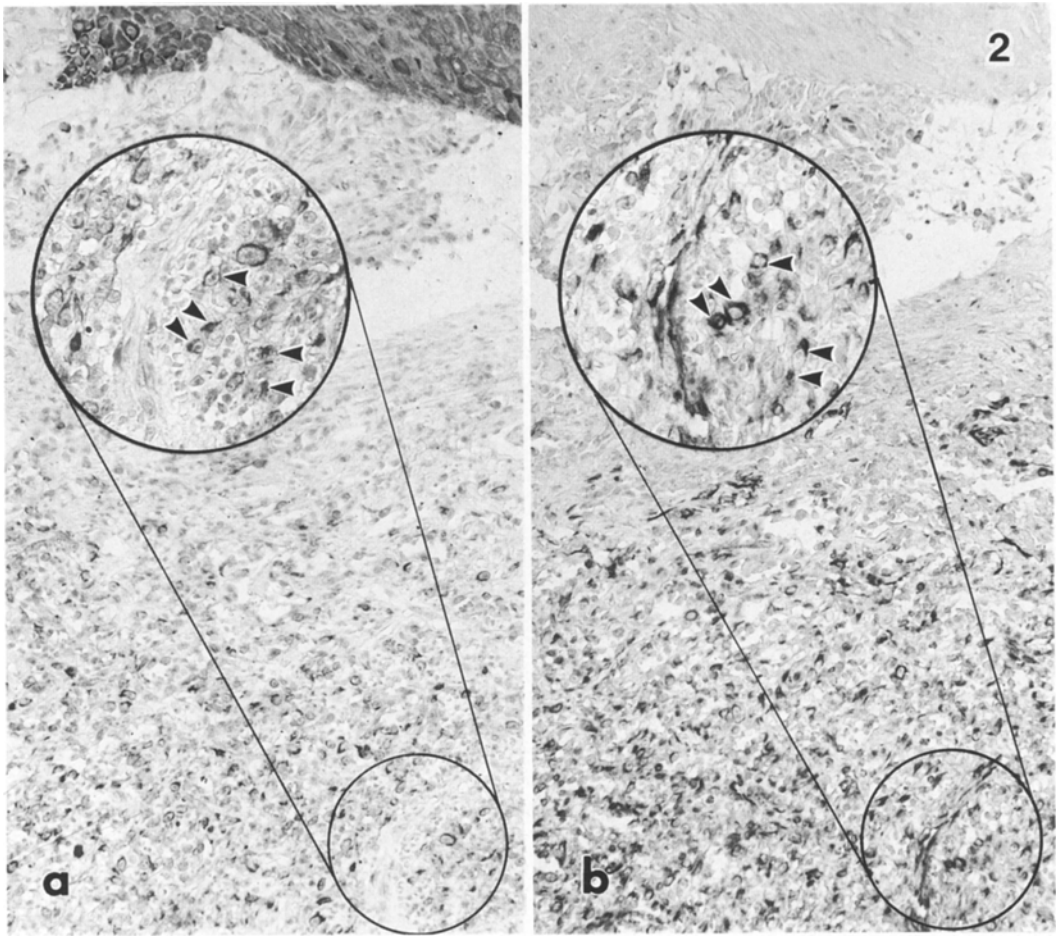

Fig. 2. Immunohistochemical demonstration of **a** keratin and **b** vimentin in a sarcomatoid component of a SCSC in serial section preparation. Sarcomatoid cells show positive reactions for keratin and vimentin. See stainability of the markers in covering epithelium (*top*) and vessels as controls. *Inset*: Co-expression of keratin and vimentin is observed in some tumour cells (*arrowheads*) **a** Immunoperoxidase staining using KL1, ×160; *inset*; ×300. **b** Immunoperoxidase staining using an anti-vimentin antibody, ×160; *inset*, ×300 (reduced to 85%)

and Gnepp 1985). In the present series, while a similar sex predilection was observed, only one case showed a polypoid configuration. The patients in this study were older than those of other reports, such as the study of Ellis and Corio (1980), where the mean age was 57 years. SCSC occurs mainly in the upper aerodigestive tract, especially in the vocal cord, oesophagus and oral cavity. In the oral cavity, lower lip is described as the most frequently involved site (Barnes and Gnepp 1985), but there was no lip tumour in the present series. Although

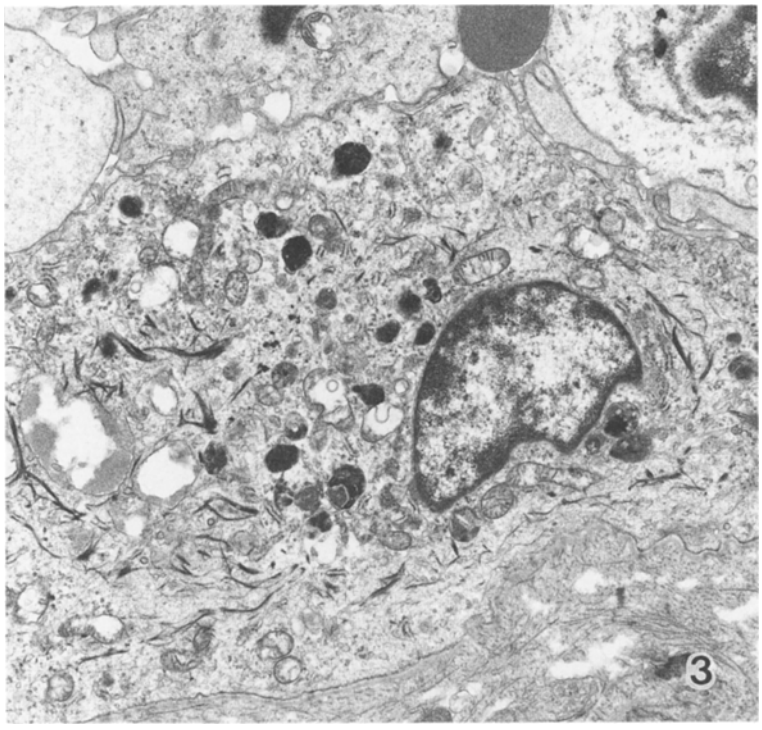

Fig. 3. Bundles of tonofilament-like filaments in the cytoplasm of a sarcomatoid cell. ×7000 (reduced to 85%)

the causative factors for SCSC are essentially unknown, a role for radiation or trauma has been emphasized by some authors (Green and Bernier 1959). Four of our six cases had a history of irradiation for pre-existing squamous cell carcinoma, but the aetiological significance of prior irradiation is not clear. The prognosis of SCSC has been reported to be poor and correlations with clinical and histological factors have been attempted. Leventon and Evans (1981) concluded that the major prognostic factor in mucosal SCSC was whether the tumour was superficial or invasive, but Ellis and Corio (1980) reported that no clinical or histomorphological characteristic other than distant metastasis was found to be a reliable prognostic indicator. Prognostic factors for SCSC were not determined in this study, but it was shown that radical surgery resulted in a good prognosis.

The epithelial nature of the sarcomatoid component was revealed by a combination of the immunohistochemical expression of keratins and the ultrastructural characteristics of epithelial cells, as Zarbo et al. (1986) demonstrated. We have concluded that the sarcomatoid component arose from metaplastic alteration of the malignant squamous component. Here, the finding that the sarcomatoid component of all six cases expressed vimentin seems to offer evidence against an epithelial origin for the sarcomatoid component. However, it has been widely accepted that vimentin can be expressed in epithelial cells in conditions such as tissue culture (Benze'eb 1984), and in neoplasia (Caselitz et al. 1981). It is suggested that expression of vimentin may be related to reduced cell-to-cell contact (Ben-ze'eb 1984). This concept of vimentin expression is consistent with the present results; increasing expression of vimentin is observed as neoplastic cells become spindle shaped and have reduced cell-to-cell contact. Keratin expression becomes less, in contrast to vimentin.

Using multiple tissue sections, SCSC can be diagnosed by appreciating the transition between the classic carcinomatous components and sarcomatoid components. However, tissue sections of a biphasic SCSC, including only sarcomatoid components, or of a monophasic SCSC, in which the carcinomatous component might be very focal or inconspicuous, provide difficulties in differential diagnosis. This must include spindle cell sarcomas such as fibrosarcoma and malignant fibrous histiocytoma or malignant melanoma. In the oral region, salivary gland tumours such as malignant myoepithelioma may be included in the differential diagnosis.

In the immunohistochemical differential diagnosis of SCSC, it should be kept in mind that SCSC should not be ruled out by the positive reaction for vimentin in sarcomatoid tumour cells. In addition, absence of staining for keratin in sarcomatoid tumour cells does not always exclude SCSC, because some SCSCs, as demonstrated in the present study, show positive immunoreactivity only for some keratin subunits. Conditions of tissue preparation such as fixation may also influence the reactivity. Therefore, different kinds of polyclonal and monoclonal anti-keratin antibodies should be applied in the differential diagnosis of SCSC.

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