SPINDLE CELL CARCINOMA OR CARCINOSARCOMA. A CASE REPORT

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Spindle cell carcinomas are rare malignant tumors composed of epithelial and mesenchymal elements. Malignant tumors with epithelial and mesenchymal elements are a controversial group of neoplasms with debatable histogenesis. Spindle cell carcinoma of the oral cavity is a rare phenomenon. Careful clinical, radiographic and histopathological examinations are needed in order to set the exact diagnosis. Radical surgical excision and neck dissection in the presence of positive nodes is the treatment of choice. Radiotherapy may be used as a palliative treatment in inoperable cases or as an adjunct to surgical treatment.

We present a case of spindle cell carcinoma of the oral cavity and discuss the histogenesis, incidence, clinical presentation, radiographic features, histological findings and management of patients with this disease. In the case presented, a broad-based, bilobular tumor on the left mandibular gingiva causing "mild pain and bleeding" were the presenting signs and symptoms, as seen with a wide variety of other benign or malignant tumoral oral lesions. The tumor did not involve the underlying bone and radical surgical excision combined with peripheral osteotomy resulted in a five-year disease-free period.

INTRODUCTION

Malignant tumors composed of epithelial and mesenchymal elements are rare. Those tumors have a debatable histogenesis, as evidenced by the multitude of names used for their description. Brodsky lists 17 synonyms, with the terms carcinosarcoma, pleomorphic carcinoma, pseudosarcoma and spindle cell carcinoma being the most frequently cited[1].

Malignant tumors with epithelial and mesenchymal components are usually found in the larynx and oral cavity, less frequently in the esophagus, pharynx and upper respiratory system, while they are unusual in other anatomic regions[2-7]. The tumors of the upper aerodigestive tracts show strong evidence of epithelial origin and are considered as a unique variant of squamous cell carcinoma[8-13]. They are usually referred as spindle cell carcinomas, sarcomatoid squamous cell carcinomas and polypoid squamous cell carcinomas[2, 14-16].

Spindle cell carcinoma usually affects 50 to 60 year-old men[2, 4-6, 8, 10]. The most common intraoral locations are the

lower lip, posterior and lateral tongue, and the gingiva[11]. Irradiation of a primary carcinoma and smoking are considered as possible primary etiologic factors[1-3, 17, 18]. Spindle cell carcinoma usually manifests as a fast-growing polypoid tumor with superficial necrosis or, less commonly, as a sessile tumor or ulceration[11]. Symptoms frequently reported are pain or paresthesia in the tumor region[11, 14].

Microscopically, spindle cell carcinoma shows an infiltrative squamous cell carcinoma (well-differentiated or veruccous) or carcinoma in situ, and sarcomatoid spindle cells[1, 3, 11, 19, 20]. When the surface is ulcerated, the carcinomatous element may have been lost and the tumor is sarcomatous (monophasic). In the presence of the carcinomatous element, the tumor is biphasic and the cells of the basal epithelial layer show transition with the spindle cell component; typical carcinomatous nests are unusual[5]. The sarcomatous component is composed of pleomorphic spindle cells arranged in interlacing or storiform bundles, or dispersed in the stroma, imitating a sarcoma or fibrosarcoma[3, 5, 11, 18]. Cell nuclei are large, irregular, pale staining with multiple nucleoli; mitoses are common and atypical forms are frequent. The intervening connective tissue is vascular, fibrous or edematous, infiltrated by inflammatory cells, mainly close to the ulceration. Multinucleated giant cells, osteoid, bone and cartilage have been described in irradiated tumors[3, 5, 11, 12, 18].

The case of a malignant spindle cell tumor with epithelial and mesenchymal features that developed on the mandibular ridge of a 62-year-old man is described. The histogenesis, differential diagnosis, prognosis and therapeutic management of those tumors are reviewed.

REPORT OF A CASE

A 62-year-old man was referred by his dentist for diagnosis and treatment of a

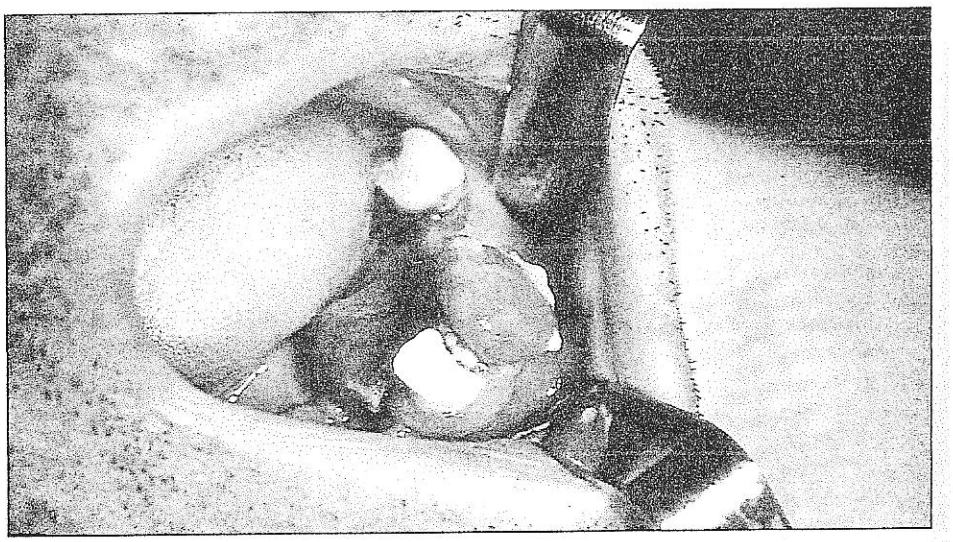

Fig. 1: Tumor on the lower left mandible.

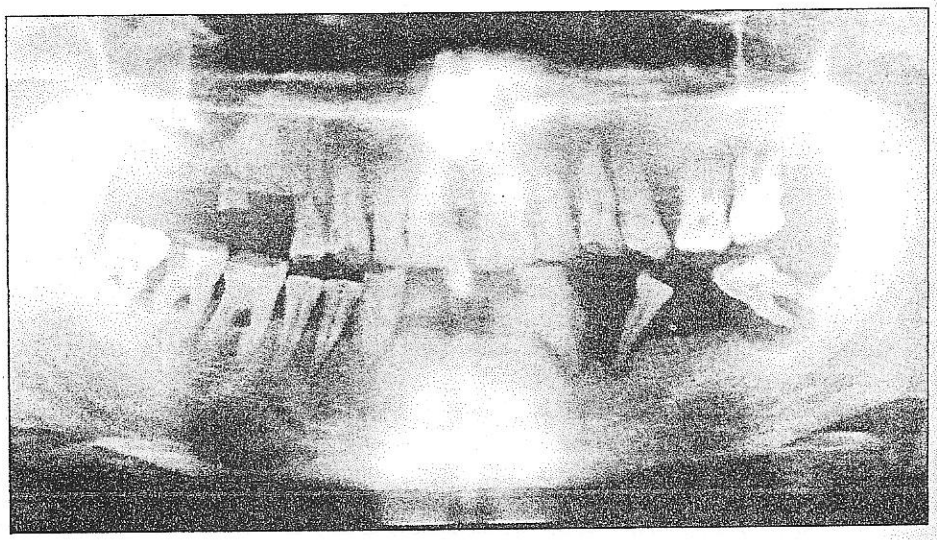

Fig. 2: Panoramic radiograph disclosing marginal bone loss of the involved teeth.

ximately a year before presentation and during the last two months it was causing "mild pain and bleeding". The patient's medical history was free of any local or systemic disease and medications. He had never smoked nor undergone therapeutic irradiation of the head and neck region.

Clinical examination showed a broad-based, bilobular tumor on the left mandibular gingiva, occupying the area between the canine and second molar teeth and expanding on the lingual and buccal aspect of the mandible (Fig. 1). The first premolar tooth was engulfed

Consistency was soft to rubbery without pain on palpation. The patient's oral hygiene and dental status were very poor. Extraoral examination did not locate any palpable lymph nodes in the head and neck area or abnormal neurological signs. A panoramic radiograph disclosed marginal bone loss of the involved teeth, consistent with periodontitis, but no intraosseous lesion (Fig. 2).

The clinical and radiographic signs were consistent with the diagnosis of a benign reactive gingival lesion, in particular peripheral giant cell granuloma.

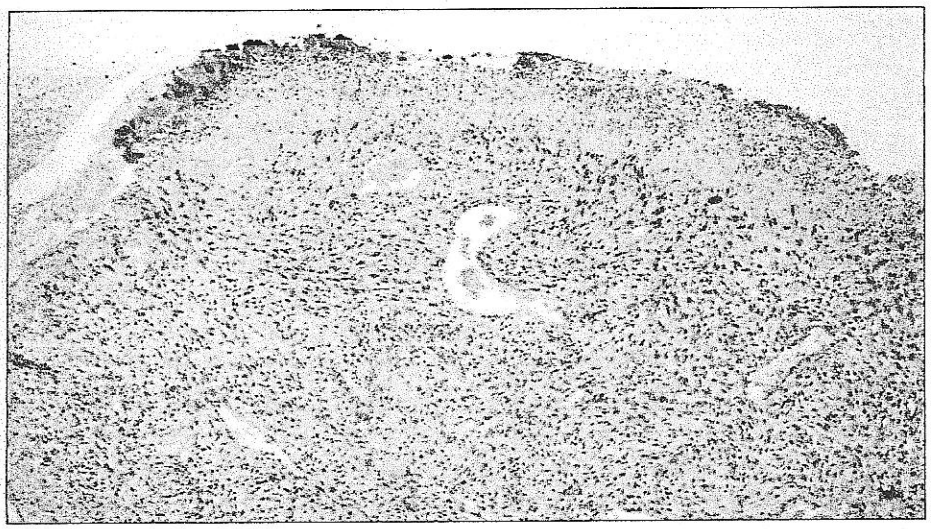

Fig. 3: Microscopic picture showing a cellular neoplasm covered by ulcerated squamous epithelium (hematoxylin-eosin stain, original magnification X40).

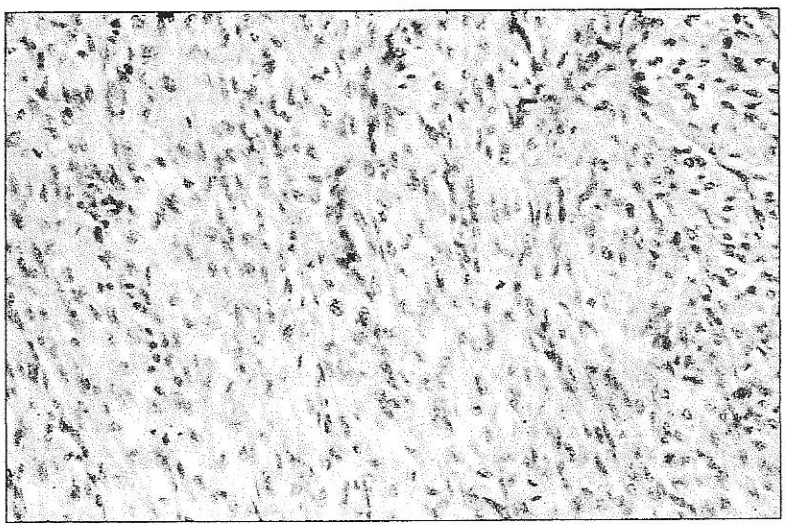

Fig. 4: Bundles of pleomorphic spindle cells with nuclear pleomorphism. Notice atypical mitosis (hematoxylin-eosin stain, original magnification X120).

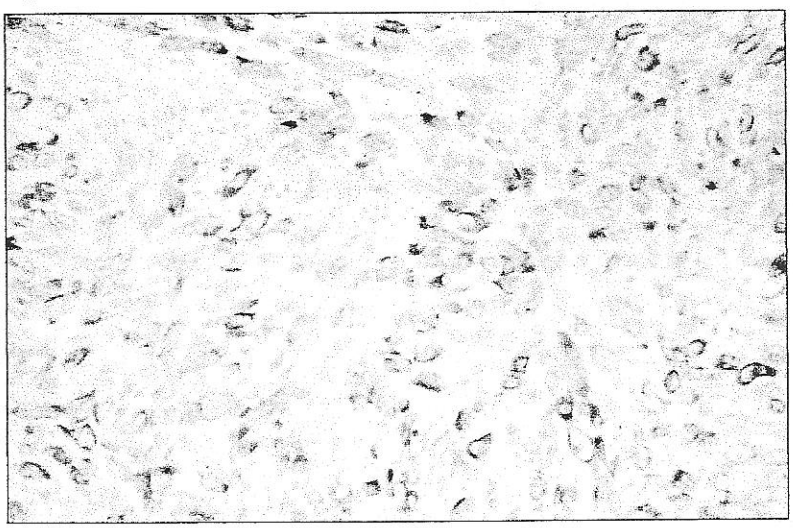

Fig. 5: Immunohistochemical stain for cytokeratin. Positive neoplasmatic spindle cells (ABC/DAB, original magnification X120).

anesthesia. The lesional tissue found to involve the tooth sockets was thoroughly removed en block with the main tumor on macroscopically healthy margins. Wound healing was uncomplicated.

Surgical specimens were fixed in 10% buffered formalin and embedded in paraffin. Five-micron thick tissue sections were stained with hematoxylin-eosin and PAS; immunohistochemical stains were performed with the avidin-biotin-peroxidase complex method, after microwave antigen retrieval. Antibodies used were polyconal anti-S-100 (Dako, Holmstrup, Denmark); and monoclonal against cytokeratin (CK1, Dako), vimentin (V9, Dako), desmin (D33, Dako), α-smooth muscle actin (CGA7, Dako), factor VIII related antigen (VIII-AG, Enzo Diagnostics, New York, NY, USA) and CD31 antigen (Dako). The reaction was visualized with 3', 3' diaminobenzidine tetrahydrochloride.

Microscopic examination showed a cellular neoplasm covered by ulcerated squamous epithelium (Fig. 3). The neoplastic cells were mainly arranged in interwoven bundles that were closely apposed to the overlying epithelium and showed continuity with it. The cells were mostly spindle-shaped (Fig. 4); they had a lightly eosinophilic or clear cytoplasm that reacted with PAS, and a large, pale-staining nucleus with discrete nucleoli. Many typical and atypical mitotic figures were seen. The neoplastic cells reacted for cytokeratin (Fig. 5) and vimentin (Fig. 6), but not for S-100 protein, desmin, α-smooth muscle actin, factor VIII related antigen and CD31 antigen. The histological and immunohistochemical features were consistent with a malignant spindle cell neoplasm, in particular a spindle cell carcinoma.

CT scan of the mandible and neck did not show istraosseous pathosis or metastatic lymph nodes. However, peripheral osteotomy was performed under general anesthesia in order to secure tumor-free margins. The duct of the submandibular gland was surgically prepared and an artificial opening was

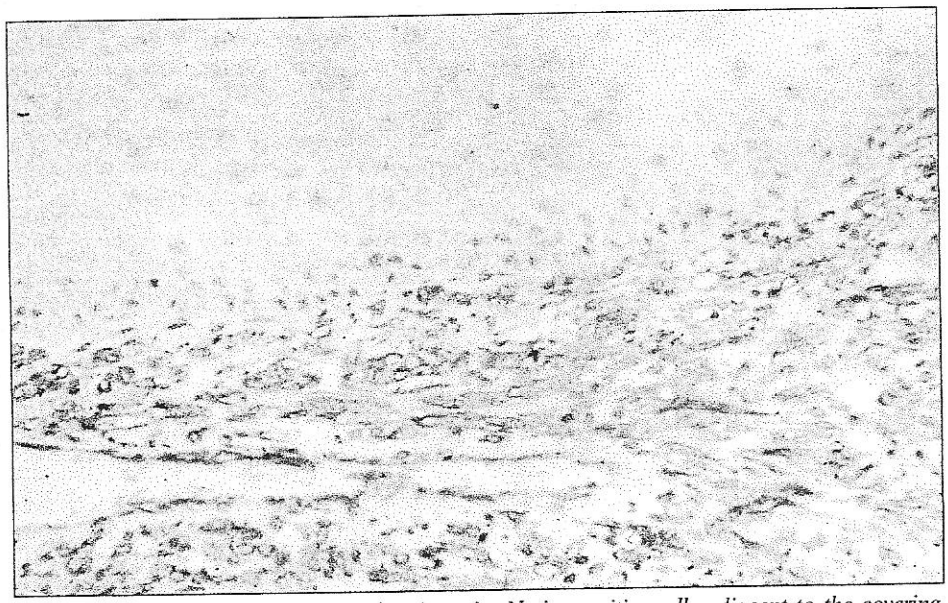

Fig. 6: Immunohistochemical stain for vimentin. Notice positive cells adjacent to the covering epithelium (ABC/DAB, original magnification X120).

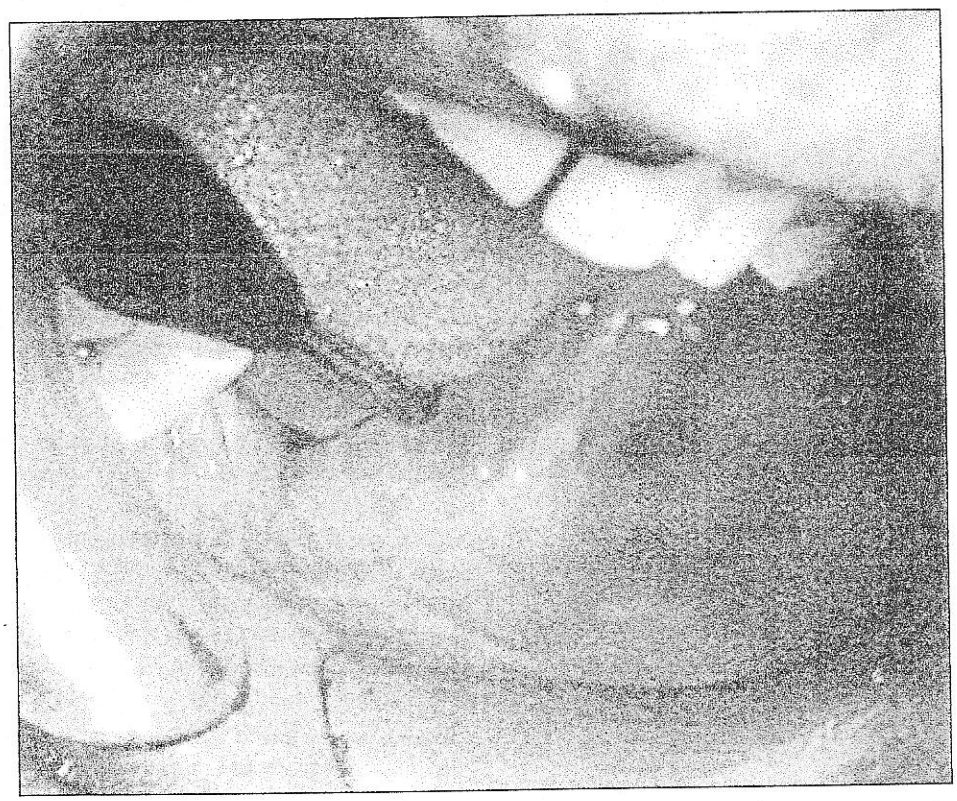

Fig. 7: Postoperative intraoral clinical appearance.

formed in a more distal position. Post surgical healing was uneventful, with satisfactory functional and esthetic restoration. The excised tissues were microscopically free of neoplastic infiltration.

During the five-year follow-up period the patient did not show any evidence of local or metastatic disease (Fig. 7).

DISCUSSION

Malignant tumors with epithelial and mesenchymal elements are a controversial group of neoplasms with debatable histogenesis[21]. Lane[22] suggested that the mesenchymal element represents an unusual and atypical non-neoplastic reaction of the stroma of a carcinoma, a view shared by Goellner et al[14]. However, the description of similar tumors metastasizing as sarcomas as well as the presence of aneuploid spindle cells indicate that the sarcomatoid element is malignant, at least in most cases[2, 10, 11, 17, 18, 23].

According to the multiclonal or convergence hypothesis, tumors combining carcinomatous and sarcomatous elements originate from the neoplastic transformation of at least two stem cells, an epithelial and a mesenchymal, respectively[24]. Variations of that theory are the synchronous neoplastic transformation of different stem cells under the influence of the same carcinogenic factor; the independent but synchronous development of a carcinoma and a sarcoma in the same region; and the development of a sarcoma (sarcomatous transformation) in the stroma of a carcinoma[1, 11, 12].

In malignant tumors with epithelial and mesenchymal components of the larynx, Lewis et al[18] found that the pattern of DNA ploidy in both components was similar, while in upper aerodigestive tract tumors, Ansari-Lari et al[6] showed that both components had the same pattern of p53 protein expression and identical point mutations in p53 gene. Furthermore, Thompson et al[24] and Torenbeek et al[25] reported a similar pattern of X chromosome inactivation in both components, that also tended to gather the same chromosomal lesions. Those findings support the monoclonal hypothesis, that is the common origin of both elements from a stem cell with epithelial, mesenchymal or mixed differentiation potential[21].

Many studies support the epithelial origin of the stem cell, that along the course of neoplastic transformation expresses a mesenchymal phenotype (mesenchymal metaplasia/anaplasia)[2, 5, 9-11, 13]. In particular, tumors of the upper aerodigestive tract combining carcinomatous and sarcomatous components show transitional zones between the two malignant components, while sarcomatoid cells react for keratins and show

ultrastructural features of epithelial differentiation, such as desmosomes and tonofilaments[1, 5, 7, 13, 23]. In addition, the biologic behavior of those tumor is similar to that of low-grade squamous cell carcinomas, while there are reports of biphasic tumors that recurred as sarcomatoid lesions, as well as monophasic sarcomatoid tumors that recurred as squamous cell carcinoma[8, 12, 21]. Thus, the epithelial origin of those tumors is favored and the terms spindle cell carcinoma or spindle cell squamous carcinoma are used in their description[16, 18, 19, 26-28].

Some authors prefer to separate tumors where the sarcomatous component does not show evidence of epithelial origin, where an epithelial origin cannot be proved, from spindle cell carcinoma[24, 27]. They designate those lesions as malignant mixed tumors or carcinosarcomas and suggest that they originate from a totipotent stem cell[21, 24, 27]. It should be noticed, however, that lack of evidence of epithelial derivation may be associated with the limitations of the currently available diagnostic techniques or "sarcomatoid metaplasia/anaplasia" of the carcinomatous cells[6, 12, 17, 21]. In addition, the terms carcinosarcoma and true malignant mixed tumor are used for the description of extremely rare adenocarcinomas of the salivary glands that combine a low-grade adenocarcinoma or undifferentiated carcinoma with sarcoma[29]. Thus, as far as there is no concise evidence for the separation of non-salivary carcinosarcomas from spindle cell carcinomas, debate on terminology remain of academic interest.

Spindle cell carcinoma usually presents as an exophytic tumor and a presumptive diagnosis of a benign reactive lesion, as in the case reported here, is common. Histological differential diagnosis from other spindle cell malignancies may be difficult and it is probable that different tumors histogenesis have been included in previously reported series of spindle cell carcinomas[3, 9, 12, 13, 16]. Monophasic tumors should be differentiated from sarcomas and spindle cell amelanotic melanoma, and biphasic tumors from non-neoplastic spindle cell proliferations in the stroma of irradiated carcinomas[19].

Extensive ulceration of the covering epithelium with complete loss of the carcinomatous component, as well as a non-representative biopsy may attenuate this problem. The study of multiple consecutive sections is mandatory for proper diagnosis[2, 6, 17]. Immunohistochemical detection of epithelial markers and ultrastructural demonstration of desmososmes and tonofilaments in sarcomatoid spindle cells are critical for the diagnosis of spindle cell carcinoma[2, 9, 17, 27]. Keratins are detected in 48% to 88% of biphasic tumors, but in less than 50% of monophasic[7, 12, 18]. Lack of positive reaction does not preclude a diagnosis of spindle cell carcinoma, as it may be associated with loss of epithelial antigens; focal keratin positivity has been described in non-epithelial tumors, such as sarcomas and pseudosarcomas[6, 9, 13, 17, 18]. Furthermore, there are differences in the expression of keratins among different spindle cell carcinomas, while in some cases keratin detection is not accompanied by the ultrastructural demonstration of epithelial origin[7, 12]. Increased expression of p53 protein is a strong indication of malignancy although it is not seen in every spindle cell carcinoma[19].

In the case presented, the identification of areas of continuity between the covering epithelium and the spindle cell component, and the co-expression of keratin and vimentin by the spindle cells, are consistent with an epithelial derivation of the spindle cell component. Epithelial dysplasia or frank carcinoma was not recognized, but this may be due to the extensive ulceration of the tumor and the concomitant loss of the epithelium. Vimentin expression has been reported in most cases of spindle cell carcinoma, frequently in keratin positive cells, and may be considered as an additional indication of the "mesenchymal metaplasia / anaplasia" of the carcinomatous cells[8-10, 12, 13, 17, 26].

Prognosis of spindle cell carcinoma is another point of debate. Early studies reported that sessile polypoid tumors have a better prognosis than ordinary squamous cell carcinoma, regardless of their particular histology[15]. However, Batsakis et al[3] showed that the biologic behavior of spindle cell carcinoma is more aggressive, as the tumor grows faster and has a tendency for earlier metastatic spread. Ellis and Corio[11] emphasized the depth of infiltration as an ominous diagnostic sign, but did not find any association with macroscopic appearance, size, thickness or differentiation of the carcinomatous element[2].

Radical surgical excision and neck dissection in the presence of positive nodes is the treatment of choice[11, 16]. Radiotherapy may be used as a palliative treatment in inoperable cases or as an adjunct to surgical treatment[4]. A 36% recurrence rate has been reported for oral spindle cell carcinomas, while two-year survival is 36-55% and five-year survival is approximately 50%, with most deaths ensuing during the first year[11, 16, 26]. For spindle cell carcinomas of the lower lip a tendency to spread along the course of peripheral nerves to the mental foramen and the skull base has been reported[5]. In the case presented, the tumor did not involve the underlying bone and radical surgical excision combined with peripheral osteotomy resulted in a five-year disease-free period.

CONCLUSION

Spindle cell carcinomas are rare malignant tumors composed of epithelial and mesenchymal elements. These lesions constitute a controversial group of neoplasms with debatable histogenesis. They usually present as exophytic tumors and a presumptive diagnosis of a benign reactive lesion is common. Careful clinical, radiographic and histopathological examinations are needed in order to set the exact diagnosis. Radical surgical excision and neck dissection in the presence of positive nodes is the treatment of

choice. Radiotherapy may be used as a palliative treatment in inoperable cases or as an adjunct to surgical treatment.

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