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CASE REPORT

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Reşit Doğan KÖSEOĞLU[1]
İbrahim ALADAĞ[2]
Engin SEZER[3]
Nilüfer ÖZKAN[4]

Primary mucosal desmoplastic melanoma of the gingiva

Abstract: Desmoplastic melanoma (DM) is a very rare variant of malignant melanoma. Mucosal involvement in DM is exceedingly rare and the differential diagnosis is problematic for surgical pathologists. To the best of our knowledge only 16 cases of DM originating from mucosal surfaces of the oral cavity have been described in the literature. Herein we describe a 59-year-old male with primary DM of the oral mucosa and discuss the status of p53, caspase-3, and FasL (Fas ligand) in the pathogenesis of this rare disease.

Key Words: Desmoplastic melanoma, oral mucosa, p53, FasL, caspase-3

[1] Department of Pathology, Faculty of Medicine, Gaziosmanpaşa University, Tokat - TURKEY
[2] Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Gaziosmanpaşa University, Tokat - TURKEY
[3] Department of Dermatology, Faculty of Medicine, Gaziosmanpaşa University, Tokat - TURKEY
[4] Department of Oral Health and Orthognathic Surgery, Faculty of Medicine, Gaziosmanpaşa University, Tokat - TURKEY

Jinjivanın primer mukozal desmoplastik melanomu

Özet: Desmoplastik melanoma (DM) malign melanomanın çok nadir bir alt tipidir. Bu alt tip mukozal yüzeylerde ileri derecede nadir olarak görülür ve ayırıcı tanısı cerrahi patologlar için güçlük arz etmektedir. Literatürde, oral kavitenin mukozal yüzeylerinden kaynaklanan sadece 16 DM olgusu saptayabildik. Bu raporda, oral mukozanın primer DM'lı 59 yaşındaki erkek hastamızı takdim ediyor ve bu nadir hastalığın patogenezinde p53, caspase-3 ve FasL'nin durumunu tartışıyoruz.

Anahtar Sözcükler: Desmoplastik melanoma, oral mukoza, p53, FasL, caspase-3

Introduction

Desmoplastic melanoma (DM) of the skin was first described in 1971 (1). DM constitutes 0.1% of all cutaneous melanomas (2). DM is characterized by amelanotic invasive spindled cell morphology and a histopathological appearance resembling soft tissue sarcomas, causing diagnostic confusion (3). Conley et al. (1), who first described DM, suggested that this rare malignant melanoma variant generally arises from chronically sun-damaged skin. In 1979 Batsakis et al. first described primary mucosal DM of the maxillary alveolus in the absence of sunlight exposure (4). Only 1 case of mucosal origin in a series of 45 DM cases with head and neck involvement was reported (5).

In the English language literature only 16 cases of DM originating from the oral mucosa have been reported (3,4,6-12). We report a 59-year-old male with primary DM of the oral mucosa, because of the extreme rarity of this melanoma variant and the diagnostic difficulties associated with it, and discuss the status of p53 and expression of 2 important markers (caspase-3 and FasL) in the alternative apoptosis pathway.

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Correspondence
Reşit Doğan KÖSEOĞLU
Department of Pathology, Faculty of Medicine, Gaziosmanpaşa University, Tokat - TURKEY

residdogan@hotmail.com

Case Report

A 59-year-old male patient with an ulcerated mass in the left-upper second premolar tooth region was admitted to hospital. His complaints had begun 5 years earlier and a punch biopsy performed at that time was not diagnostic. His complaints initiated with hemorrhagic mucosal pigmentation of the oral cavity. The patient's oral hygiene was very poor. An ulcerated nodular mass involving the left upper gingival alveolar arc at the level of the second premolar tooth and hard palate was detected on physical examination. There was no cervical lymphadenopathy or suspicious pigmented skin lesion. Incisional biopsy revealed hyperplastic squamous epithelium with prominent pigmented junctional activity resembling lentigo maligna in situ, and infiltration of predominantly spindle-shaped atypical cells in the submucosa and deeper tissues (Figure 1A, B). Atypical spindled and melanocytic cells were strongly positive for vimentin and S-100 (Figure 1C, D). The atypical cells were negative for homatropine methyl bromide antigen (HMB-45), low and high molecular weight cytokeratins (LMWCK and HMWCK), and leukocyte common antigen (LCA). The patient was diagnosed with primary mucosal malignant melanoma (MMM) of the oral cavity on the basis of histopathological and immunohistochemical findings.

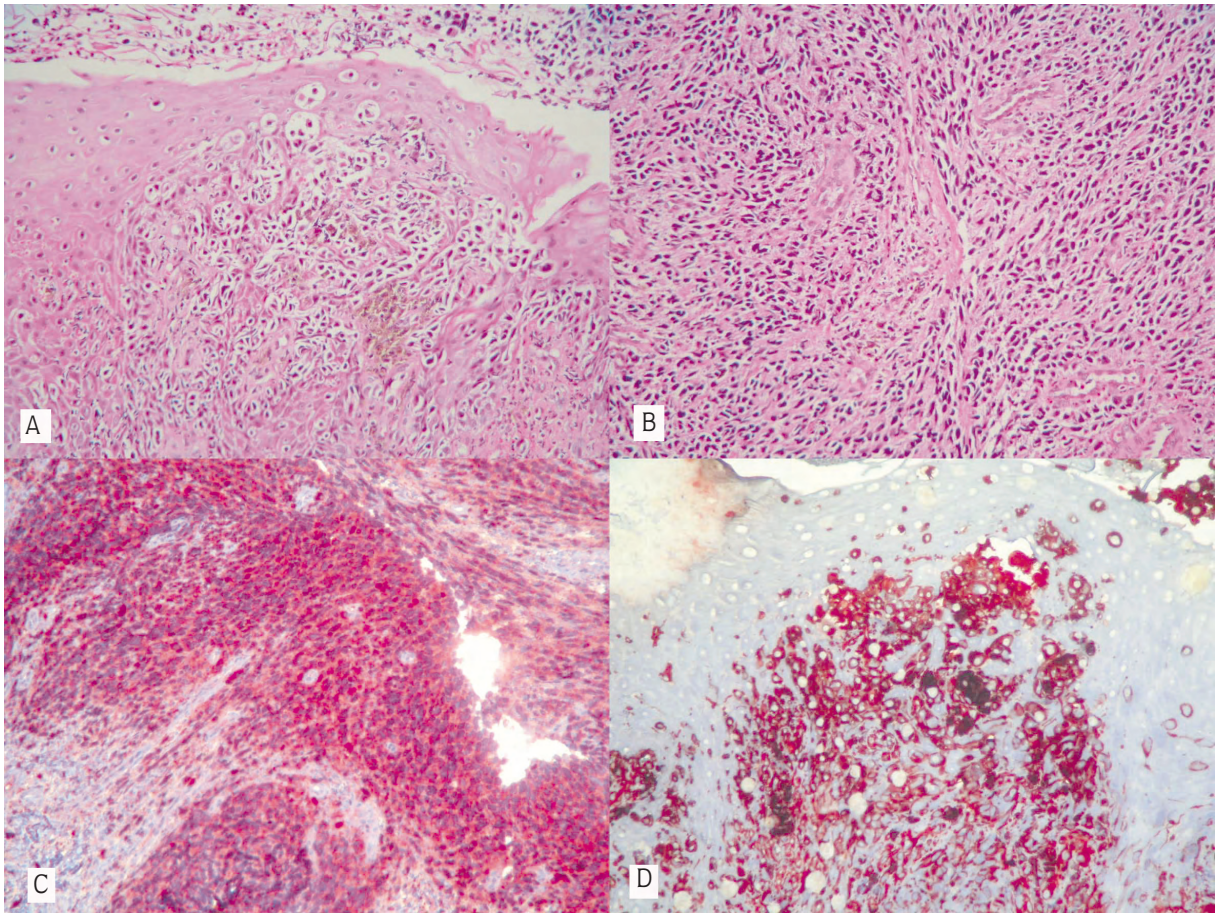

Figure 1. A. Extensive and pigmented junctional activity in mucosal squamous epithelium (HE, 10×).
B. Atypical, spindled cell infiltration in deeper areas of the mucosal tissue (HE, 20×)
C. Extensive and strong positivity for vimentin in tumoral cells (AEC, 15×).
D. Strong S-100 positivity in junctional activity and spindled cell infiltration beneath squamous epithelium (AEC, 15×).

Maxillary bone tomography revealed bone destruction in the alveolar processes and hard palate of the left maxillary bone, without involvement of the base of the maxillary sinus. Subtotal maxillary resection and reconstruction were performed. The tumoral lesion primarily involved the hard palate and also infiltrated gingival areas. The tumor consisted of a nodular mass with an ulcerated surface and elevated edges. At its widest point the tumor was 55 mm. The tumor had a solid gray-white cut surface with hemorrhagic foci and dark staining areas. Surgical margins were macroscopically free of the tumor. The tumor extensively infiltrated the maxillary bone. Microscopic examination showed a hyperplastic squamous epithelium layer with extensive junctional activity (Figure 2A, B) and extensive tumoral infiltration beneath the squamous epithelium (Figure 2A). The tumor consisted of spindled atypical cells, without pigmentation (Figure 2C). An extensive fascicular pattern, and focal whorled and nesting areas were also noted in the sections. Most areas of the tumor had prominent collagenous stroma between tumor cell fascicles (Figure 2D). The tumor cells had pleomorphic, hyperchromatic nuclei with some prominent nucleoli (Figure 2E). The degree of nuclear atypia was usually moderate, but marked pleomorphic areas were also present. Mitotic activity was 4-5/10 high power fields and areas of focal necrosis were present. The tumor cells with an epithelioid appearance were fewer (Figure 2F). Focal perineural infiltration areas were present (Figure 2G). Most of the fascicular pattern areas resembled fibrosarcoma and in some areas a malignant peripheral nerve sheath tumor.

HMB-45, desmin, caldesmon, calponin, alpha-1 antitrypsin, HMWCK, p53, caspase-3, and FasL antibodies in the tumor were analyzed. Several tumor cells reacted to HMB-45, both in spindled and epithelioid cell areas (Figure 2H). Both epithelioid and spindled cell areas were diffusely positive for FasL (Figure 2I). Focal expression (15%-20% tumor cells) for p53 was determined (Figure 2J). The tumor cells were negative for the other antibodies.

These histopathological and immunohisto-chemical findings in both the punch biopsy and resection material were consistent with a diagnosis of primary MMM of the oral cavity. The findings of prominent collagenous stroma, a fascicular pattern, absence of melanin pigment, and atypical melanocytic proliferation areas in the basal layer of squamous epithelium, supported the diagnosis of primary mucosal DM. Local recurrence in the left buccal region (previous area of the surgery) and lymph node metastasis in the left neck occurred in the ninth month following surgery. Aspiration cytology revealed atypical epithelioid and spindled cells, and stromal fragments. Cell nuclei were round and oval with coarse chromatin, and devoid of nucleoli. Aspiration biopsies from both lesions confirmed the recurrence and metastasis of malignant melanoma (Figure 3). At the time of writing, the patient is being treated with radiotherapy, chemotherapy, and meticulous follow-up examinations.

Discussion

The desmoplastic variant of melanoma is very rare and primary DM of the oral mucosa is exceedingly rare. DM may be frequently confused with non-melanocytic spindle cell tumors. We suggest that the disease may be underreported because of the difficulty in histopathological diagnosis. The Table shows the distribution of reported cases of primary mucosal DM of the oral cavity, according to compartments of the oral cavity. Maxillary gingival location was the most common origination site. In the presented case left maxillary gingival mucosa, hard palate, and left maxillary bone involvement were observed. A male predominance, with a male/female ratio of 3:1, was noted. The age range of diagnosed cases was 23-75 years. DM tends to occur in middle- and older-aged males.

DM has various microscopic morphologies and often resembles mesenchymal tumors, such as fibrosarcoma, malignant peripheral nerve sheath tumor, leiomyoma, or sarcomatous squamous cell carcinoma. The histology of DM is characterized by spindled cell proliferation, with variable cellularity (1,5,13-15). The cellular arrangement usually consists of interlacing fascicles and whorls. DM exhibits nuclear/cellular pleomorphism, varying in

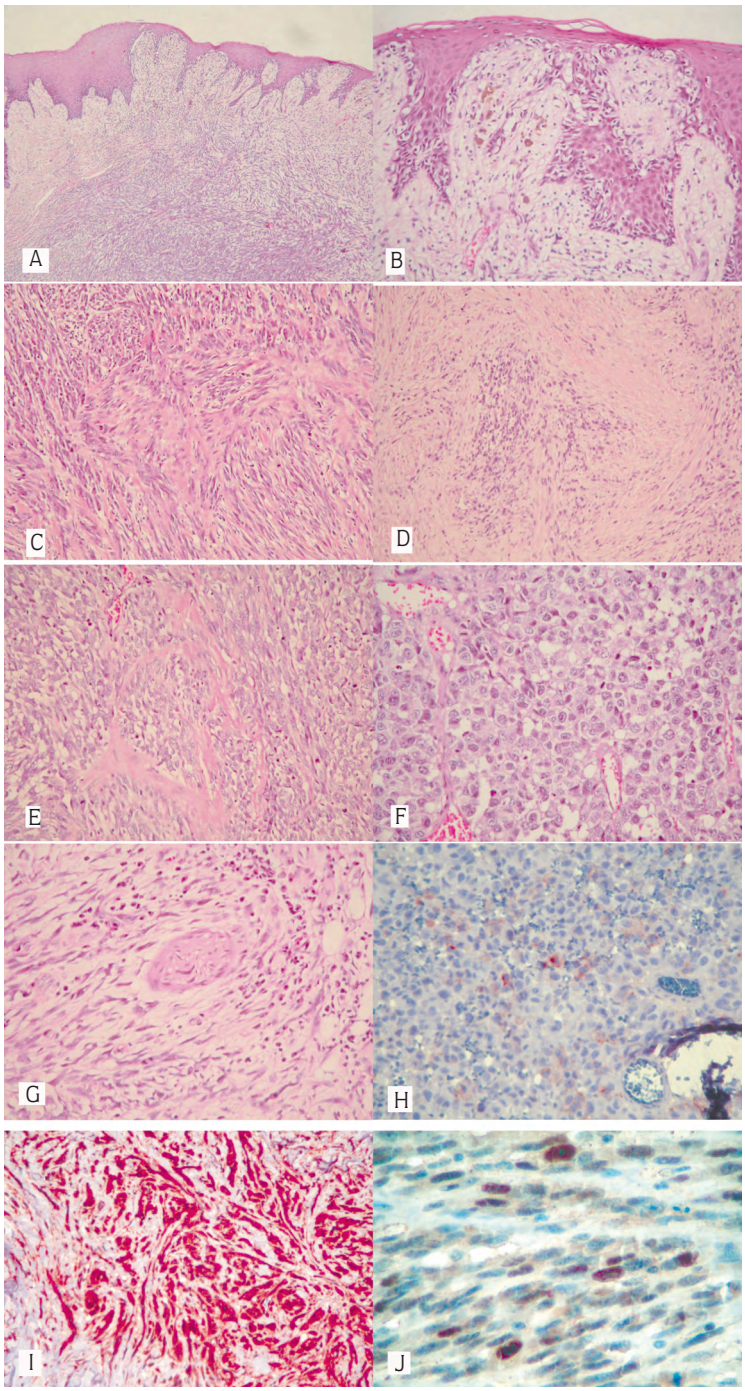

Figure 2. A. Extensive spindle-shaped cell infiltration beneath hyperplastic squamous epithelium (HE, 6×).
B. Extensive junctional activity in the basal layer of squamous epithelium (HE, 16×).
C. Fascicular pattern of spindled cells in the tumor (HE, 20×).
D. Extensive desmoplastic stromal areas in the tumor (HE, 10×).
E. Atypical spindled cells, with vesicular nuclei and prominent nucleoli. Mitotic figures were frequently noted (HE, 30×).
F. Atypical cells with epithelioid appearance in the tumor (HE, 40×).
G. Perineural invasion in the tumor (HE, 30×).
H. Rare focal cytoplasmic positivity for HMB-45 (AEC, 40×).
I. Diffuse, strong cytoplasmic positivity for FasL in the tumor (AEC, 20×).
J. Focal nuclear p53 positivity in the tumor (AEC, 60×).

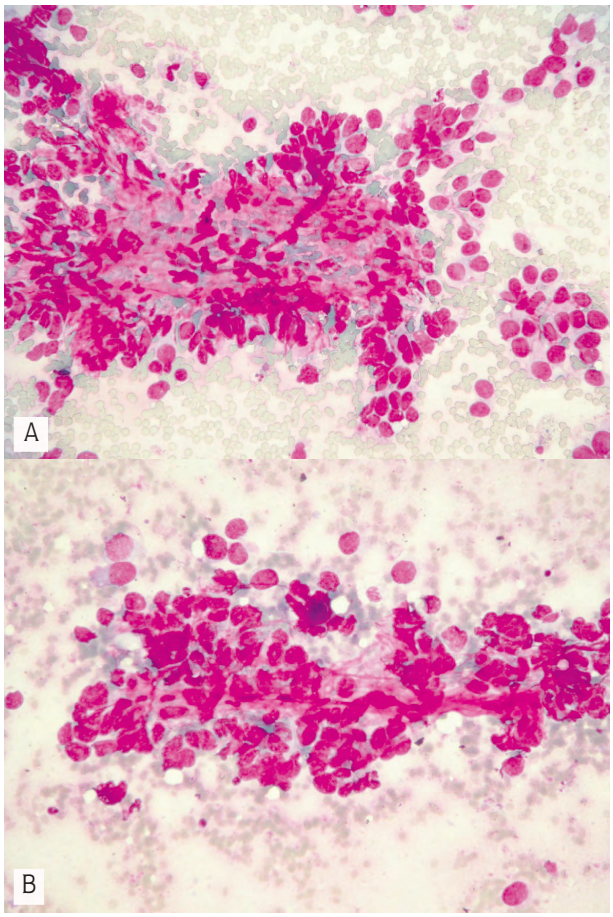

Figure 3. A. Epithelioid and spindled cells around and within the stromal component in an aspiration smear (MGG, 30×). B. The cell groups consisted of pleomorphic and hyperchromatic nuclei, devoid of nucleoli. Pigment accumulation was not observed in any areas (MGG, 30×).

Abbreviations; HE; Hematoxylin-eosin; AEC; amino-ethyl-carbozole; MGG; May Grünwald giemsa.

degree from mild to severe. Whereas nuclear enlargement, a coarse chromatin pattern, and irregular nuclear membranes are common cytological features, large nucleoli are rare. The absence of melanin pigment is another characteristic feature. The lack of macro-nucleoli and melanin pigment are 2 factors that make the diagnosis of DM difficult.

The most important clue for diagnosis may be squamous epithelium of the oral mucosa, especially in the basal cell layer, with atypical melanocytic proliferation in the form of junctional activity or pagetoid infiltration. Mucosal surfaces may have foci of lentigo maligna melanoma in situ. Collagenous stroma is invariably present and collagenous content may be very high. Because of the desmoplastic stromal response, atypical spindle cells may have a relatively bland cytological appearance and may be mistakenly considered benign. High cellular areas may resemble soft tissue tumors. The differential diagnosis includes benign soft tissue tumors and tumor-like processes, such as dermatofibroma, schwannoma, neurofibroma, leiomyoma, fibromatosis, and reparative processes. High cellularity, evident nuclear atypia, high mitotic rate, and necrosis indicate the diagnosis of DM. Fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma, as well as sarcomatous variant squamous cell carcinoma should also be considered in the differential diagnosis of DM (5,15,16). Lack of cytoplasmic melanin pigment, loss of melanoma in situ focus in ulcerated mucosa areas, and lack of other specific histological characteristics of DM may result in difficulty diagnosing DM. In situ carcinoma or invasive squamous cell carcinoma foci may help in the diagnosis of the sarcomatous variant of squamous cell carcinoma. Ancillary methods may also aid diagnosis.

A panel of immunohistochemical markers may serve to discriminate DM from other amelanotic spindled cell tumors. Vimentin and S-100 are invariably positive in DM. HMB-45, a specific marker for melanoma, is usually negative in DM. On the other hand, epitheloid areas of DM may show mild to moderate positivity. Alpha-1 antitrypsin is a specific marker for malignant fibrous histiocytoma, whereas caldesmon and calponin may be useful in the diagnoses of leiomyosarcoma and fibrosarcoma, respectively. The sarcomatous variant of squamous cell carcinoma may be identified by cytokeratin positivity. The differentiation of DM from MPNST may be very difficult or even impossible, because both tumors have many overlapping features. DM exhibits evidence of Schwannian differentiation, both at ultrastructural and light microscopic levels (5,13,17,18). Both tumors are positive for S-100 and negative for HMB-45 (5,19). Clinical data, such as a previous history of a pigmented mucosal lesion, the

Table. The cases of primary mucosal desmoplastic melanoma of the oral cavity reported in the literature.

Case	Age	Gender	Localization	Report date/author	Ref.
1.	60	M	Maxillary alveolar mucosa	1979/Batsakis et al .	4
2.	59	F	Palatal mucosa, gingiva	1983/Saku et al.	6
3.	24	M	Palatal mucosa	1989/Chen et al.	7
4.	58	M	Maxillary gingival mucosa	1992/Kurihara et al.	8
5.	66	F	Maxillary gingival mucosa	1996/Ueta et al.	9
6.	42	M	Maxillary mucosa	1996/Kilpatrick et al.	10
7.	64	M	Maxillary mucosa	1996/Kilpatrick et al.	10
8.	75	M	Lower lip mucosa	1996/Kilpatrick et al.	10
9.	60	M	Lower lip mucosa	1998/Madrigal et al.	11
10.	53	F	Palatal alveolar mucosa	2000/Kavanagh et al.	12
11.	74	M	Buccal mucosa	2004/Prasad et al.	3
12.	34	M	Maxillary gingival mucosa	2004/Prasad et al.	3
13.	23	F	Lower (mandible) gingival mucosa	2004/Prasad et al.	3
14.	61	M	Lower lip mucosa	2004/Prasad et al.	3
15.	73	M	Lower (mandible) gingival mucosa	2004/Prasad et al.	3
16.	54	M	Lower lip mucosa	2004/Prasad et al.	3
17.	59	M	Maxillary gingival mucosa	Present case	

Abbreviations; M; Male; F; female; Ref; references.

presence of lymph node metastasis, and a history of neurofibromatosis, may facilitate their differentiation (16,20,21). As both entities are of neural crest origin and are aggressive, some researchers suggest that differentiating these 2 entities is unnecessary (16,20).

The presented case also had similar areas of MPNST, especially in the deep portions of the tumor, and these foci alternated as hypocellular and hypercellular areas. The lack of nuclear palisading and clinical history/findings in our patient excluded the diagnosis of MPNST. Areas of reminiscent fibrosarcoma, MFH, and leiomyosarcoma were also present in our case, but prominent storiform, herringbone patterns, and extensive necrotic areas were not observed. In addition, areas resembling malignant mesenchymal tumors were also negative for calponin, caldesmon, desmin, and alpha-1 antitrypsin. In the presented case S-100 and vimentin were diffusely positive, while HMB-45 was focally positive. These immunohistochemical findings and histological features (melanoma in situ foci, amelanotic spindled cells with mostly bland cytological features, desmoplastic stromal response, and neurotropism) were indicative of the diagnosis of primary mucosal DM.

The literature contains only 2 reports describing the cytological features of DM (22,23). Nance et al. (22) emphasized the presence of microtissue fragments of spindle cells with hyperchromatic nuclei and prominent nucleoli in aspiration smears. Chhieng et al. (23) reported predominantly isolated spindle cells with a bland nuclear appearance in the smears. The same authors reported that some spindle cells had moderate nuclear atypia based on retrospective examination of the same smears (23). Intracytoplasmic pigmentation and intranuclear inclusion were absent in both cases (22,23). Aspiration material from a recurrent mass in the buccal region of the presented case at the ninth postoperative month follow-up showed cytological findings similar to 2 previously reported cases. Aspiration smears were strongly cellular, and atypical spindled and epithelioid cells with pleomorphic nuclei without nucleoli were observed.

Surgery, especially complete resection of mucosal DM of oral cavity, is very difficult because of the complex anatomy and the great propensity for neurotropism (3). Neurotropism predisposes to recurrence. A recurrence rate of 100% was reported in patients with primary DM of the oral cavity by Prasad et al. (3), who reported the largest series of

primary mucosal DM of the oral cavity in the literature. This rate was higher than in cutaneous DM, which has a recurrence rate of about 33% (24). Regional and distant metastases may be seen in DM of the oral cavity. In the series by Prasad et al. (3) 3 cases had regional and/or distant metastases. Smithers et al. (24) reported that the distant metastasis rate was 19% in cutaneous DM. Similarly, Prasad et al. (3) reported that patients with cutaneous DM may have a better prognosis than those with conventional mucosal melanoma. The 5-year disease-specific survival rate in their series was 57% (median: 8 years). This rate was reported as 42% (median: 2.4 years) in 2 previous studies by the same authors, which included all primary mucosal melanomas of the head and neck (25,26). Our patient had a 69-month history of primary mucosal DM, with recurrence and lymph node metastasis at the ninth month after resection.

The development of malignancies, and resistance to chemotherapy and radiotherapy are complicated processes in which apoptosis and apoptosis-related genes are of crucial importance. Mutations in the p53 gene have been observed in only a minority of cutaneous melanomas (17.6%) and primary mucosal melanomas (28.6%) (27). Expression of p53 was noted in 37% of primary non-desmoplastic mucosal melanomas (28). Prasad et al. (3) observed p53 expression in 6 cases (86%) out of 7 of DM. This rate was much higher than for those of non-desmoplastic cutaneous and mucosal melanomas. In the series by Prasad et al. (3), among 6 cases of p53 expression, 4 cases had intense expression (> 50% tumor cells), while focal p53 expression (6%-25% tumor cells) was detected in 2 cases. The presented case had focal p53 expression (15%-20% tumor cells).

Apoptosis occurs via 2 primary pathways. The first involves the extrinsic or cytoplasmic pathway. The extrinsic pathway is triggered by death receptors. The second apoptosis pathway involves intrinsic mitochondrial damage, the release of cytochrome c, and activation of caspase-9. Activation of caspase-3 is closely related to that of caspase-9 (29). The Fas/FasL system in the extrinsic pathway is a major pathway for the induction of apoptosis (30). In a study by Redondo et al. (30) Fas expression was highly variable in primary melanomas, but the absence of Fas expression in metastatic lesions was the most noteworthy finding. This finding is a phenomenon that has previously been reported, and it was suggested that reduced Fas expression may be related to a metastatic phenotype (31). Hahne et al. (31) reported that FasL is expressed by human melanoma cells. FasL is not expressed by normal melanocytes of the skin, indicating that FasL upregulation probably occurs during tumorigenesis (30). Most studies have reported intense FasL expression in metastatic foci of melanomas (31,32-35). In the presented case, FasL expression was widespread and strongly positive. Nonetheless, caspase-3 expression was not observed in the tumor. Extensive strong FasL expression in the tumor in the presented case might have been associated with the progressive prognosis of DM. This variant of malignant melanoma, with variable clinical and prognostic features, may have a different apoptosis pathway than other variants of malignant melanoma.

In conclusion, we presented primary mucosal DM of the oral cavity in a 59-year-old-male patient. The diagnosis was established on the basis of histopathological, immunohistochemical, and clinical findings. The differential diagnosis may be difficult because of the similarity of the morphological features of DM and other soft tissue tumors.

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