Liposarcoma of the Oral Cavity – Case Reports of the Pleomorphic and the Dedifferentiated Variants and a Review of the Literature

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Abstract. *Liposarcoma is one of the commonest soft-tissue sarcomas, but very rare in the oral cavity. We present two cases of liposarcoma of the oral cavity, together with the related clinical, histopathological and immunohistochemical findings: one affecting the cheek of a 62-year-old man and the other the gingival maxillary tuber of a 41-year-old woman. At histological examination a diagnosis of liposarcoma was made in both cases. In the first case, immunohistochemical analysis revealed intense positivity for p53, MIB-1, MDM2, and focal positivity for S100 protein and CD34, but was negative for alpha-smooth muscle actin, desmin and CD68. The second case it was intensely positive for p53, MIB-1, S-100, and focal positive for MDM2, but negative for alpha smooth muscle actin, CD34, CD68 and desmin. Histological examination and immunohistochemical profiles in the first case were consistent with pleomorphic liposarcoma, whilst that in the second case with dedifferentiated liposarcoma. Both patients were subjected to surgical treatment with wide surgical margins, without adjuvant radio- or chemotherapy. The first case was lost at follow-up one year after surgery, while the second case has not undergone relapse after seven years. We discuss differential diagnosis, examining the histopathological and immunohistochemical features that are potentially useful for distinguishing this tumor from other malignant adipose tissue tumors.*

While liposarcoma (LS) is considered to be the commonest soft-tissue sarcoma in adults (9.8%-16% of all cases) (1, 2), generally arising in the thighs, buttocks, or the retroperitoneum, intraoral liposarcomas are uncommon, accounting for only 0.3% of all liposarcomas (3-6). A review of the literature regarding liposarcomas with strictly intraoral location reveals fewer than 100 case reports (3).

Histologically, the World Health Organization (WHO) classification distinguishes 5 LS subtypes: well-differentiated with its variants, myxoid, round cell, pleomorphic and dedifferentiated (2). The commonest subtype is the myxoid variant, followed by the well-differentiated, round cell, dedifferentiated and pleomorphic variants, in that order. Of the pleomorphic variant only five cases primarily of the oral cavity have been reported in the English language literature (6-8) (Table I) and of the dedifferentiated variant in the oral cavity our case is the seventh report (3, 9-12) (Table II).

The peak incidence of all liposarcomas occurs between 40 and 60 years of age, with men more frequently affected than women (9). Of intraoral cases, the tongue is the primary site of incidence (9, 13), followed by the cheek and the floor of the mouth (9, 13, 14).

The gross appearance of liposarcoma may be well-circumscribed, encapsulated, or both, usually showing a multilobular pattern with occasional satellite nodules. The tumor may appear mucinous, gelatinous, or more fibrous, soft or firm in consistency. The color is pale yellow. Areas of necrosis or hemorrhage may be present, either superficially or at a depth, and are frequent in deep soft tissue. The morphology varies with histological type; in this report only the pleomorphic and the dedifferentiated variants were considered.

The pleomorphic (PL) variant is defined as a high-grade sarcoma, first recognized by Enzinger and Wislow (15), and is considered to be the least common variant of liposarcoma, accounting for approximately 5% of all liposarcomas (16). Clinically it is characterized by the tendency to occur in the limbs of older adults and, less frequently, in the trunk and retroperitoneum. Histologically, it shows multivacuolated lipoblasts (16) and is further subdivided into two forms, the malignant fibrous histocytoma-like form and the pleomorphic giant-cell-rich form. Recently, Miettinen and Enzinger have

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Table I. *Cases of pleomorphic liposarcoma of the oral cavity reported in the literature and the present case.*

Case reported (reference/years)	Age (years)/gender	Anatomic location	Size in cm	Histology
Adkins *et al.* (5)/1978	24/male	Right posterior maxillary gingiva	N/A	Pleomorphic
Eidinger *et al.* (6)/1990	80/male	Cheek	8x8x5cm	Pleomorphic
Mc Culloch *et al.* (7)/1992	N/A	Cheek	8x8x5cm	Pleomorphic
Friedman *et al.* (8)/1995	18/male	Pterymandybular space	8x7x4 cm	Pleomorphic
Ogawa *et al.* (9)/1996	29/male	Cheek	N/A	Pleomorphic
Angiero *et al.* (pc)/2006	41/female	Right posterior maxillary gingiva	1.0 cm	Pleomorphic

N/A, not available; pc: present case.

Table II *Cases of dedifferentiated liposarcoma of the oral cavity reported in the literature and the present case.*

Case reported (reference/years)	Age (years)/ gender	Anatomic location	Size in cm	Types of dedifferentiation	Follow-up (recurrence)
Diamond *et al.* (10) /2002	57/male	Cheek	8.0 cm	Spindle cell pattern with areas showing multinucleated giant cells	12 months without recurrence
Fanburg-Smith *et al.* (11)/2002	39/male	Tongue	6.0 cm	Bland spindle proliferation and scattered floret cells	6 years follow-up without recurrence
Fanburg-Smith *et al.* (11) /2002	56/male	Left buccal mucosa	5.0 cm	Spindled pleomorphic liposarcoma-like areas	26-year follow-up, six recurrences
Nascimento *et al.* (9) /2002	83/ female	Tongue	2.5 cm	Non lipogenic rounded tumors cells	N/A
Gustavo de la Roza *et al.* (12)/2004	61/ male	Cheek	5.0 cm	Non lipogenic spindle cells with focal rhabdomyoblastic differentiation	Lost to follow up Recurrence 5 month after surgery
Werneck da Cunha I *et al.* (3)/2005	42/women	Cheek	6.0 cm	Spindle cells with nuclear atypias arranged in sheets or forming rudimental vascular channels angiosarcomatous dedifferention	12 months without recurrence
Angiero F *et al.* (pc)/2006	62/male	Cheek	3.0 cm	Spindle cells with nuclear atypias arranged in sheets	7 years follow-up without recurrence

N/A, not available; pc, present case.

described 12 cases of a new variant of PL with an epithelioid morphology (17). These tumors exhibit focal adipocytic differentiation, but appear to be composed predominantly of sheets of epithelioid-like cells separated by a minimal amount of intercellular matrix.

The concept of dedifferentiated liposarcoma (DL) was introduced by Evans in 1979 (18) and is now widely recognized. The dedifferentiated liposarcomas were defined as tumors containing distinct areas of well-differentiated liposarcoma, and of non-lipogenic cells or pleomorphic sarcoma. This was simply a fresh work-up of the earlier description of dedifferentiation introduced by David Dhalin in 1977 in the context of the description of tumor progression in chondrosarcoma (19). The commonest site of DL is the retroperitoneum, followed by the limbs, accounting for approximately 10% of all liposarcoma (20, 21).

Histologically it is a biphasic neoplasm in which one component is an atypical lipomatous tumor or well-differentiated, and the other is a cellular, non-lipogenic sarcoma that constitutes the dedifferentiated component. This pattern may show a transition from a low-grade to a high-grade non-lipogenic morphology, within a well-differentiated liposarcoma; the transition generally occurs abruptly, but can be gradual or intermediate (2, 22). Recently, Nascimento *et al.* described a peculiar new variant of DL in which the formation of 'neural-like' or 'meningothelial-like' whorls of spindle cells is seen (23) often in association with metaplastic bone formation. Dedifferentiation in well-differentiated liposarcoma occurs more frequently in the primary tumor (90%) than in recurrences (10%) (24).

Cases

Case 1. A 62-year-old man was referred for evaluation of a swelling in the cheek, present for about 12 months. The swelling was asymptomatic and had increased in size. At extraoral examination there was an enlargement of the right cheek, which was of firm consistency. Intraorally, the lesion

Table III. *Immunohistochemical profile of current cases of liposarcoma.*

Antibody	Supplier	Dilution	Reactivity Case 1 (dedifferentiated)	Reactivity Case 2 (pleomorphic)
Mib-1	Dako	1: 200	++	++
Alfa-Smooth Muscle Actin (Sma)	Sigma	1: 400	–	–
Desmin	Dako	1: 200	–	–
S100	Dako	1: 200	+	++
Mdm2	Calbioch 5M	1: 25	+ +	+
Cd34	Novocastra	1: 50	+	–
Cd68	Dako	1: 500	–	–
p53	Novocastra	1:100	++	++

– (negative), no staining; + (positive), focally positive for a limited number of cells; and ++ (intensely positive), focally or diffusely positive for numerous cells.

appeared as a smooth, firm submucosal mass in the right cheek extending from the right buccal mucosa toward the zygomatic area, measuring 3.0 x 2 cm at its greatest dimension. The overlying mucosa was non-ulcerated and normal in color. The patient underwent incisional biopsy under local anesthesia and a diagnosis of liposarcoma was rendered; surgical treatment with wide surgical margins followed, without any adjuvant radio- or chemotherapy. There is no evidence of recurrence seven years after surgery.

Case 2. A 41-year-old woman presented with a history of a small painless mass of 1-year duration on the right maxillary gingiva. At extraoral examination there was an enlargement of the right maxillary gingiva. At intraoral examination, the submucosal lesion appeared firm, nodular, slightly tender, measuring approximately 1 cm in diameter. An incisional biopsy was performed and a diagnosis of liposarcoma was rendered. The patient underwent surgical treatment with wide surgical margins, without any adjuvant radio- or chemotherapy, but was lost at follow-up one year after surgery.

Materials and Methods

Excised biopsy specimens were fixed in 10% formalin-buffered and paraffin-embedded. Sections of 5-μ were stained with hematoxylin and eosin. For immunohistochemistry, the avidin-biotin complex (ABC) method was applied (25). A panel of monoclonal antibodies was used for the following markers (Table III): Desmin (1: 200, DAKO), Ki-67 antigen (MIB-1 1: 200, DAKO), p53 (1: 100, NOVOCASTRA) MDM2 (1: 25, CALBIOCH 5M), alpha-smooth muscle actin SMA (1: 400, SIGMA), S100 protein (1: 100, DAKO), CD34 (1: 100, NOVOCASTRA), CD68 (1: 500, DAKO). The immunohistochemical antibodies, their sources and dilutions, are listed in Table III. Appropriate controls were tested simultaneously. The immunohistochemical reactivity was evaluated and graded as follows: – (negative), no staining; + (positive), focally positive for a limited number of cells; and ++ (intensely or strong positive), focally or diffusely positive for numerous cells.

Results

Microscopic examination of Case 1 (Figure 1) revealed a pleomorphic adipose tissue neoplasm with areas of mature lipocytes and lipoblasts with atypical and hyperchromatic nuclei. Round cells were also present, and rare mitotic figures. The diagnosis was pleomorphic liposarcoma with rounded cells. Histological examination of Case 2 showed that the tumor was characterized by a solid non-lipogenic sheet and areas of well-differentiated lipoblasts arranged in lobules interspersed with dense fibrous bundles. Individual cells were vacuolated, containing varying numbers of lipid droplets, and displaying hyperchromatic, peripheral and pleomorphic nuclei. Small, scattered nests of multi-vacuolated lipoblasts were also visible. Signet-ring cells were present, filled with a single large lipid globule, and showing a lateral displacement of the nucleus; however, lipoblasts in several stages of differentiation were abundant. The dedifferentiated areas consisted mostly of spindle or stellate fibroblastic cells (Figure 2).

Immunohistochemical studies using the avidin-biotin-peroxidase technique were performed in both cases and are summarized in Table III.

Case 1. The tumor cells were intensely positive for p53, (Figure 3A), focal positive for S-100 (Figure 4A) and for CD34, strongly positive for MIB-1 and MDM2 (Figures 5A, 6A), and negative for desmin, alpha-smooth muscle actin and CD68.

Case 2. Intense positive reactivity was seen for p53, (Figure 3B), S-100 (Figure 4B), MIB-1 (Figure 5B) and focal positive for MDM2 (Figure 6B); the reaction was negative for alpha-smooth muscle actin SMA, CD34 and desmin.

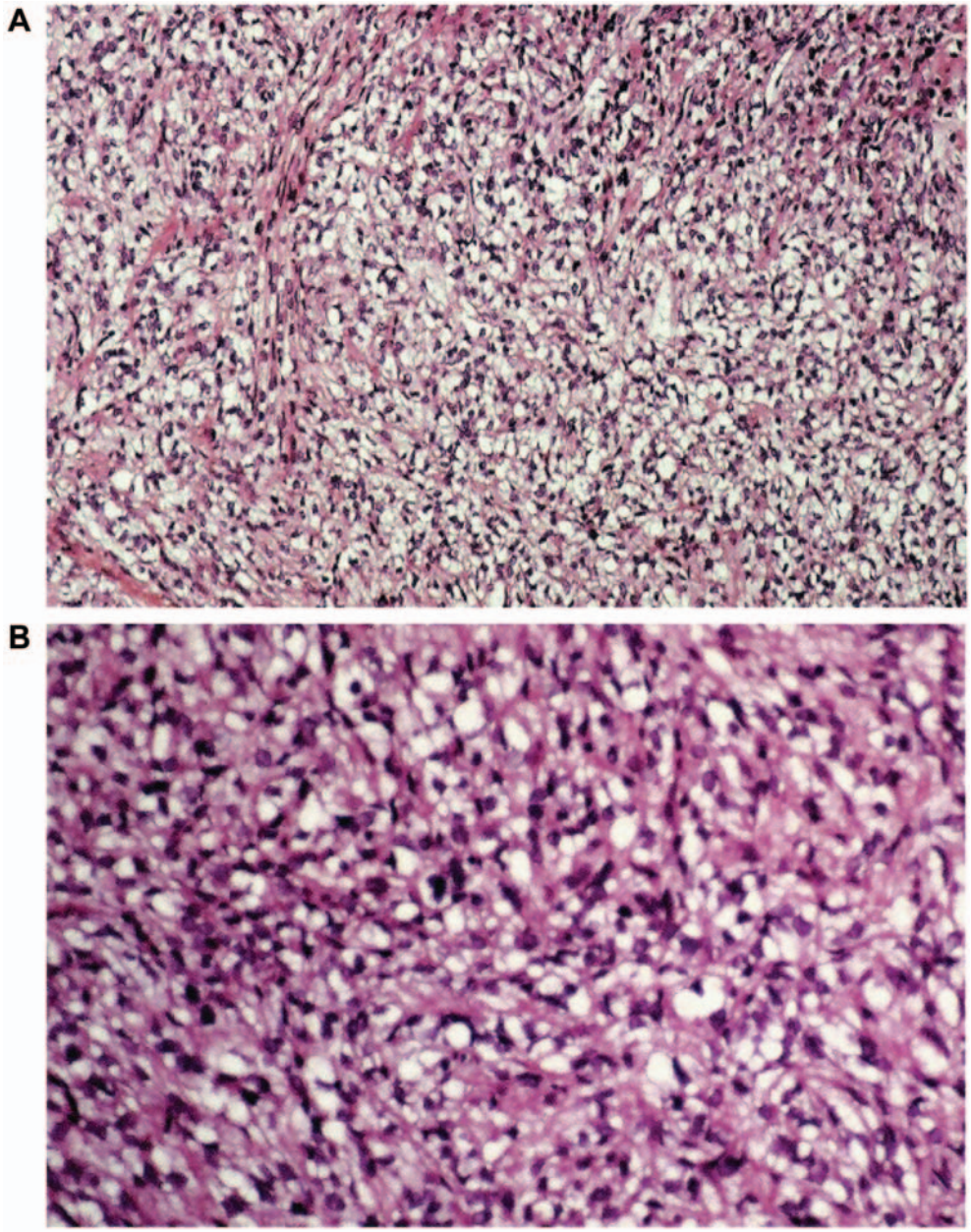

Figure 1. *A-B) Pleomorphic liposarcoma (Case 1). A) Low-power view, B) high-power view with pleomorphic lipoblasts and round cells. Histology disclosed hypercellular areas of neoplastic cells with ill-defined cytoplasm and round nuclei (hematoxylin and eosin staining; original magnification, A x150 and B x200).*

Discussion

The histopathological diagnosis of intraoral liposarcoma presents a challenge to the oral pathologist, because of the rarity of this tumor in the oral cavity. Differential diagnosis of dedifferentiated liposarcoma and pleomorphic liposarcoma in the oral cavity includes a vast panorama of malignant tumors. Malignant tumors that must be considered are, above all, those in which evidence of non-adipose cellular differentiation must be carefully evaluated; differential diagnosis includes high-grade variants of myxofibrosarcoma, malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma and rhabdomyosarcoma, and also towards some liposarcomas containing adipose differentiation, such as spindle cell liposarcoma and the well-differentiated sclerosing liposarcoma.

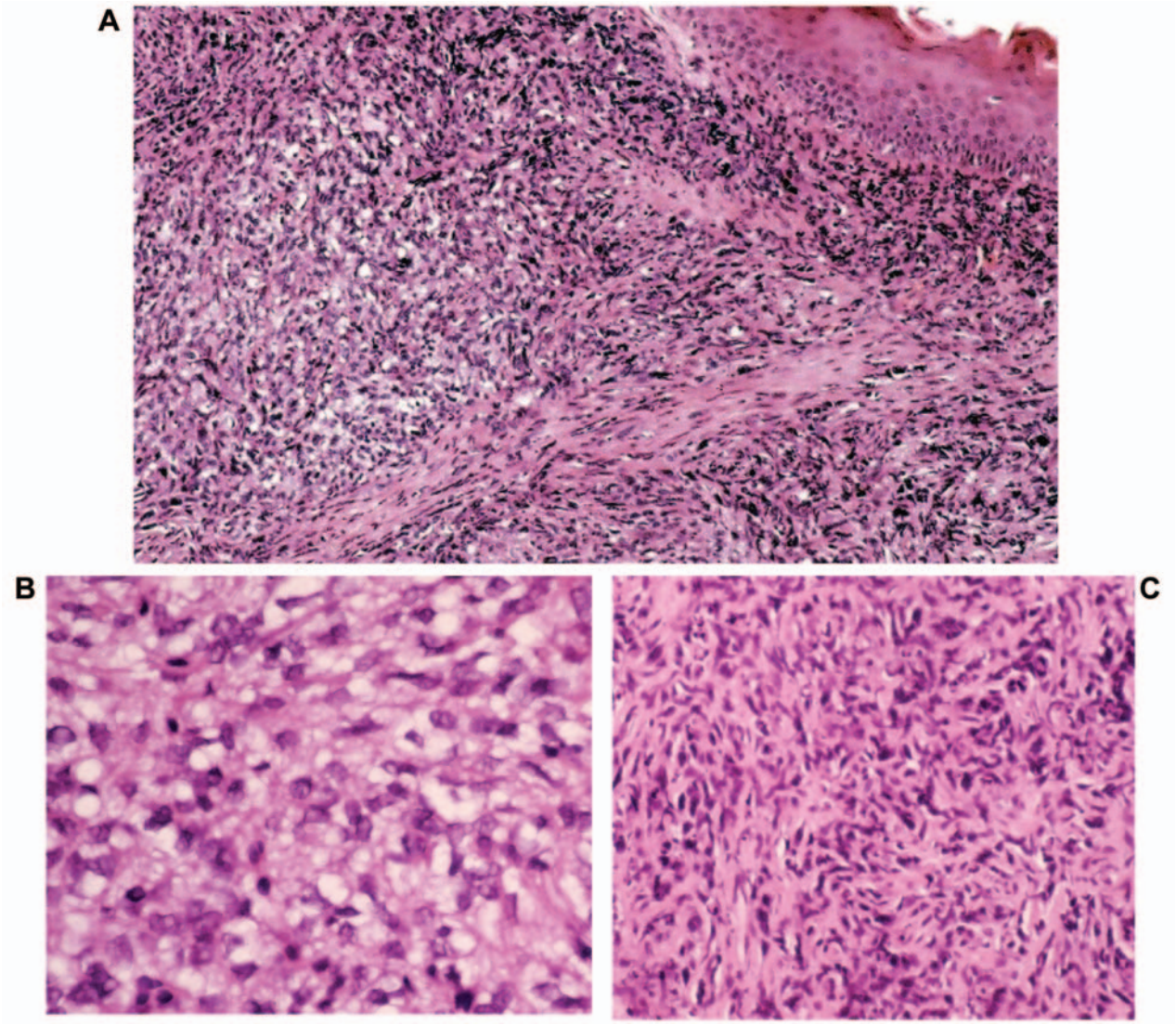

Figure 2. *Dedifferentiated liposarcoma (Case 2). A) Low-power view with both components, B) high-power view, with areas of well-differentiated lipoblasts, C) areas resembling a high-grade fibrosarcoma with storiform pattern (hematoxylin and eosin staining; original magnification, A x150 and B, C x200).*

In many cases, the histopathology of pleomorphic liposarcoma may be indistinguishable from that of dedifferentiated liposarcoma. Beyond that, it has been observed that the well-differentiated and high-grade components in the dedifferentiated variant may be intermingled (26). However, in that case the dedifferentiated component is non-lipogenic, in contrast to the pleomorphic form.

In a series of 155 cases of dedifferentiated liposarcoma reported by Henricks *et al.* (20), the majority displayed areas of high-grade dedifferentiation, resembling fibrosarcoma or pleomorphic sarcomas. It is, thus, clear that the presence of large dedifferentiated areas similar to that of fibrosarcoma or pleomorphic sarcoma may lead to incorrect interpretation and, thus, to an inaccurate diagnosis.

It has also been observed that about 5-10% of cases, the dedifferentiated component may exhibit heterologous differentiation, most often myogenic or osteo-chondrosarcomatous and more rarely angiosarcomatous (27), and may have either low-grade or high-grade differentiation. Such cases, thus, enter into differential diagnosis with the above-mentioned tumor types. Furthermore, from the morphological standpoint the dedifferentiated areas overlap with the storiform and pleomorphic variant of malignant fibrous histiocytoma, or less frequently with myxofibrosarcoma. A difficulty consists

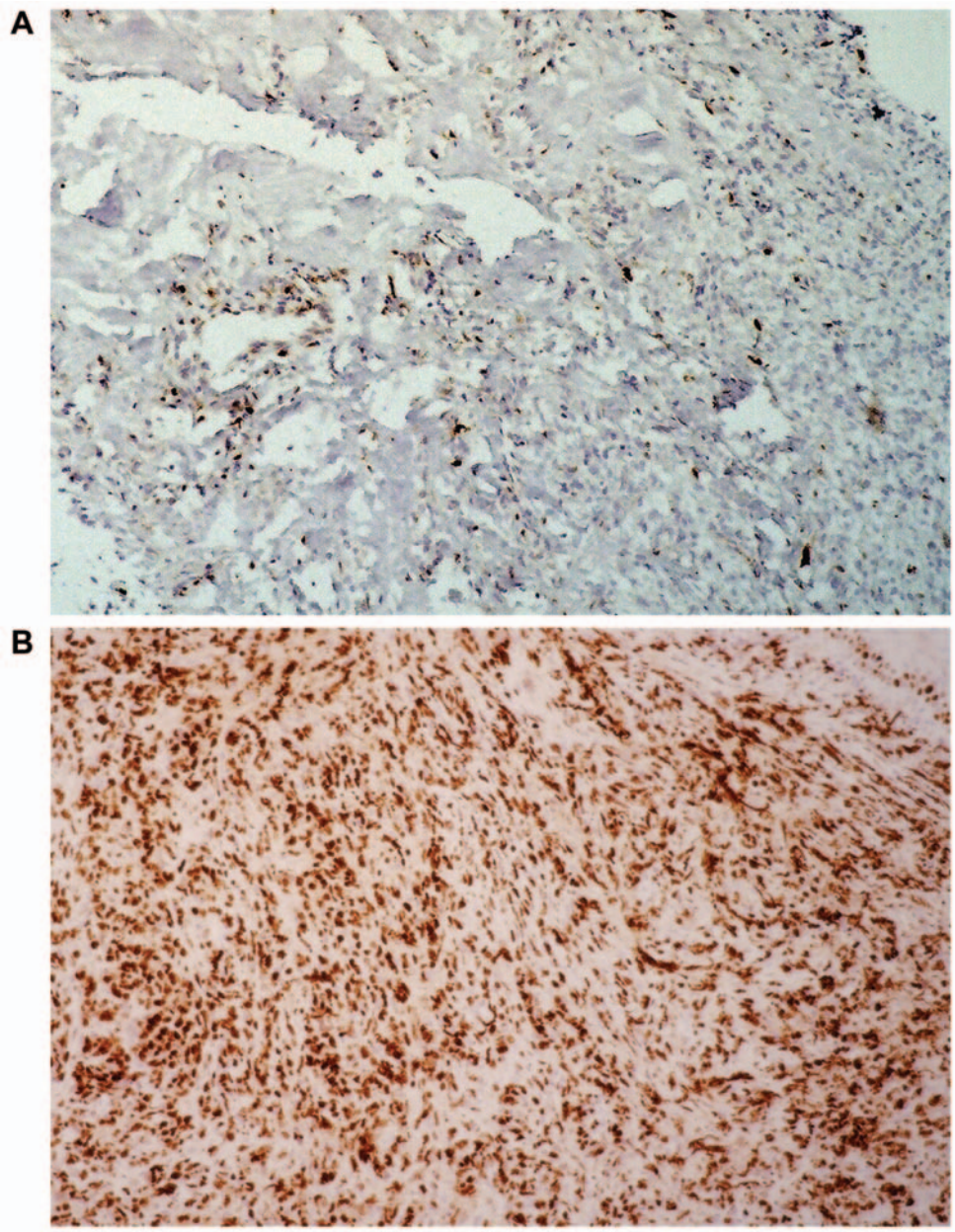

Figure 3. *p53 immunoreactivity can be seen in both components in (Case 1, A) and (Case 2, B) components (original magnification, x150).*

in differentiating between dedifferentiated liposarcoma and malignant fibrous histiocytoma, and it has been observed that some cases reported as the latter may in fact have been dedifferentiated liposarcomas (28).

Sometimes dedifferentiated liposarcoma exhibits the presence of fascicles of bland spindle cells with a cellularity intermediate between well-differentiated sclerosing liposarcoma and usual high-grade areas (29, 30). The term proposed to describe these areas is "low-grade dedifferentiation"; however, spindle cell liposarcoma is a lipogenic lesion, whereas both low- and high-grade dedifferentiated areas are generally non-lipogenic.

In PL, an acute inflammatory infiltrate may be present, though rarely, that may cause diagnostic confusion with well-differentiated inflammatory liposarcoma.

The histological pattern in the first of our cases, with the atypical population of bizarre and pleomorphic cells and the presence of round cells allowed the diagnosis of PL with

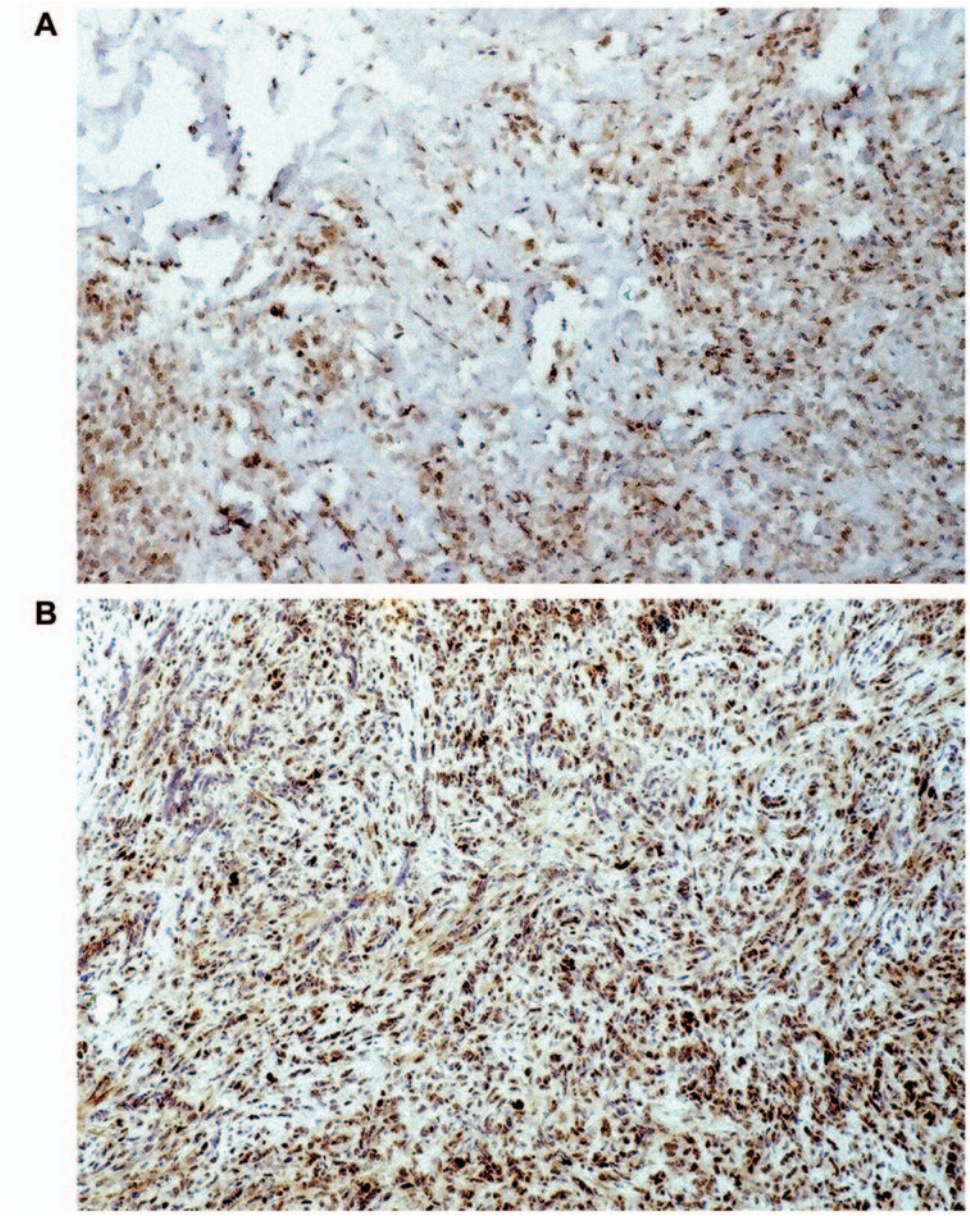

Figure 4. *Positive cytoplasmatic S-100 immunopositivity in both (Case 1, A) and (Case 2, B) (original magnification, x150).*

rounded cells. In the second case, the dedifferentiated areas consisted mostly of spindle or stellate fibroblastic cell in a storiform pattern intermingled with area of well-differentiated LS, and was indicative of a dedifferentiated liposarcoma.

Immunohistochemistry was carried out to achieve a correct diagnosis. From the immunohistochemical standpoint, adipocytes and lipoblasts are known to stain positively for S-100 and vimentin. Hashimoto *et al.* (31) suggested that S-100 protein positivity is useful for distinguishing liposarcoma from myxoid malignant fibrous histiocytoma, although it has been noted that poorly-differentiated liposarcomas may stain negatively for S-100 and vimentin (2).

Both of our cases stained positive for the S-100 protein, the dedifferentiated variant more markedly than the pleomorphic variant. In both variants, positivity for p53 and MDM2 (protein frequently expressed in several sarcoma types) was found (19, 20, 32); the concomitant positive expression for MDM2 protein and p53 is thought to indicate a form of tumor progression, suggesting a key

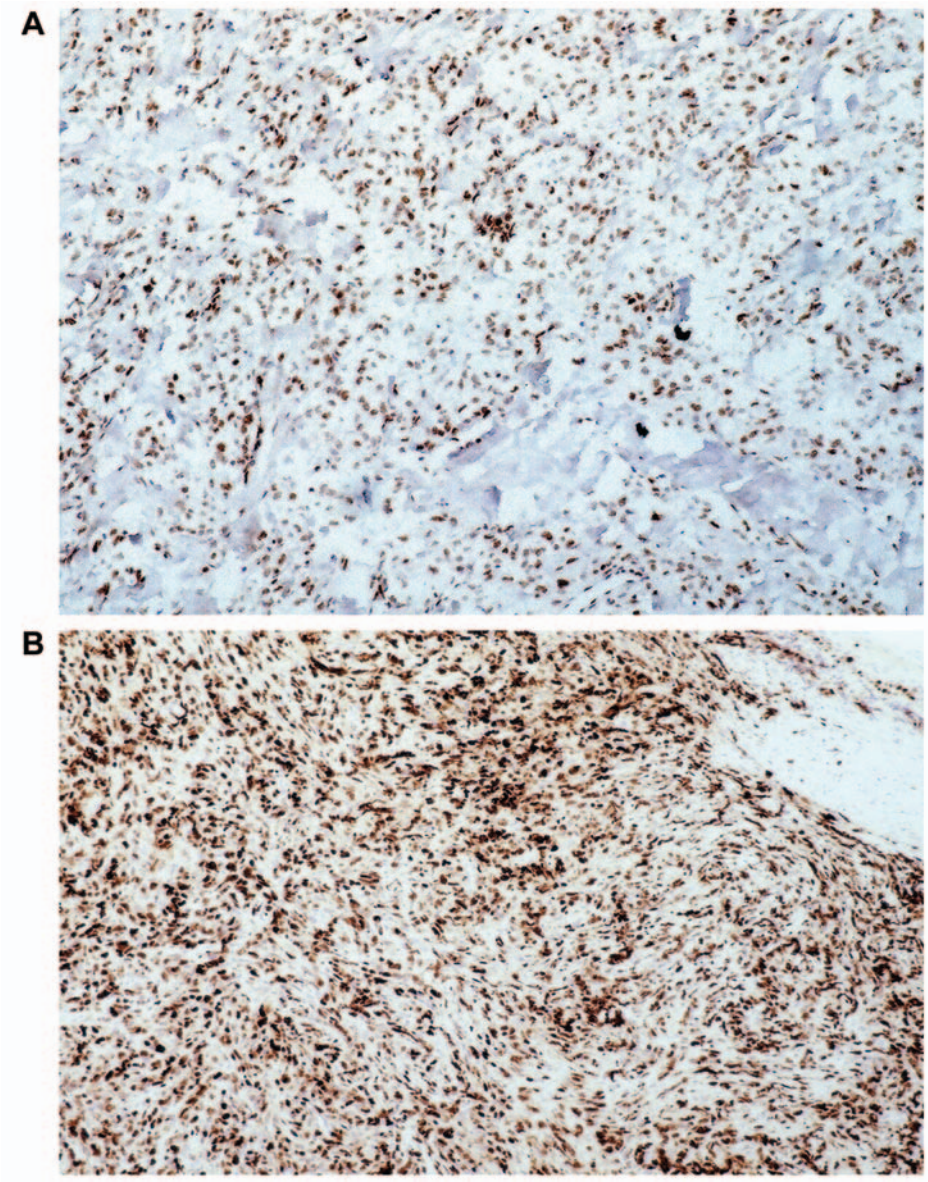

Figure 5. *The pleomorphic component showing a high MIB-1 immunopositivity (Case 1, A), the dedifferentiated component (Case 2, B) also shows a high MIB-1 immunopositivity (original magnification, x150).*

role for the *p53* gene, from well-differentiated liposarcoma to a high-grade neoplasm (29, 33). Moreover the pleomorphic variant was strongly positive for MIB-1, focal positive for CD34 and negative for CD 68, alpha-smooth-muscle actin and desmin; the dedifferentiated variant was strongly positive for MIB-1, but mostly negative for alpha-smooth-muscle actin and desmin. In the light of these results, the initial diagnosis was confirmed with H&E staining with the first case classified as pleomorphic liposarcoma with round cells, and the second case as dedifferentiated liposarcoma.

The prognosis of liposarcoma is influenced by several factors: histopathological variant, location, tumor size, adequacy of surgical treatment and distant metastases (7, 34). With regard to the histopathological variant of liposarcoma, it has been observed that the various subtypes identified by the WHO have a different biological behavior. Pleomorphic and dedifferentiated liposarcomas located outside the oral cavity are reported to have more aggressive biological behavior, and are associated with a significantly higher rate of mortality and metastasis than myxoid and well-differentiated liposarcomas (23, 35), and in some cases

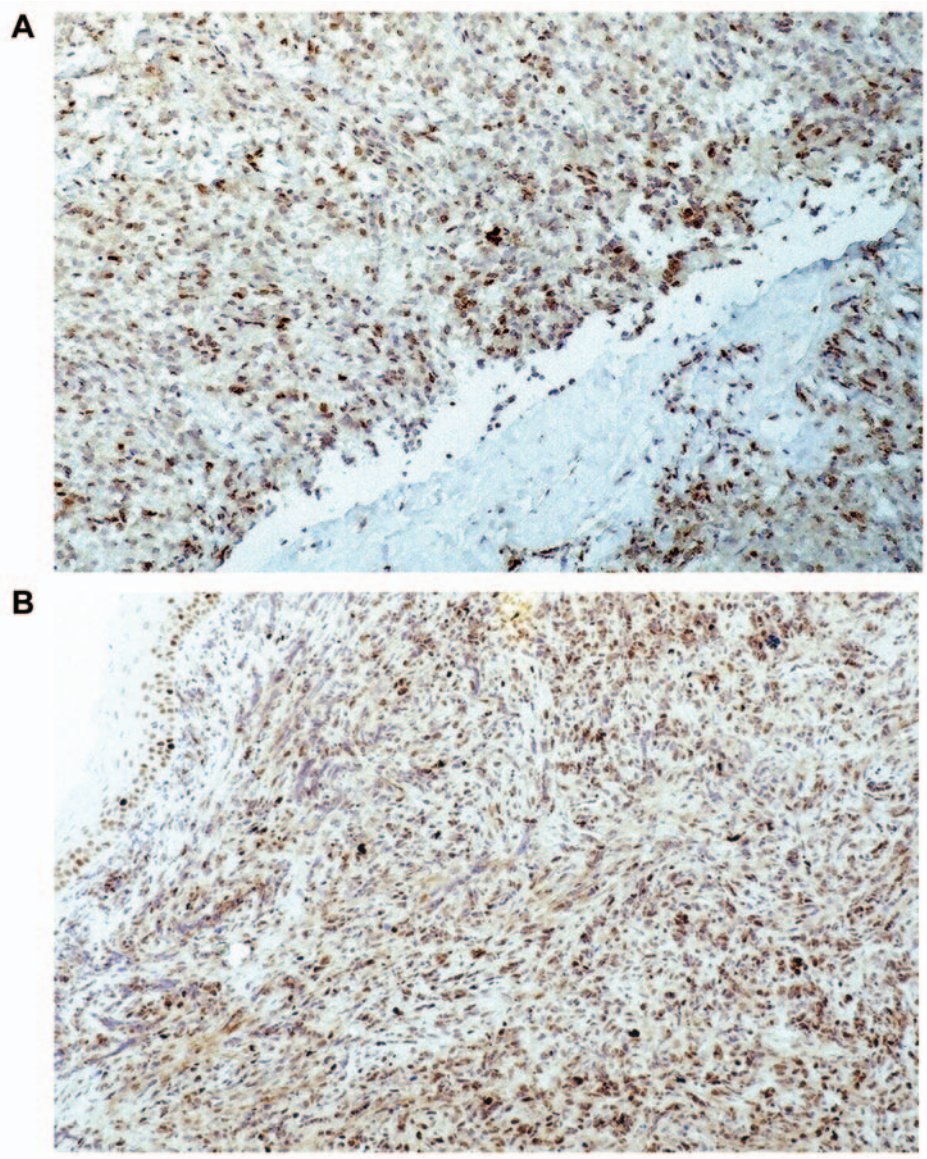

Figure 6. *Positive immunoreactivity for MDM2 (Case 1, A) and (Case 2, B) expression is strong whereas it is reduced in the dedifferentiated variant (original magnification, x150).*

a metastatic liposarcoma may be of a more aggressive histological type than the original tumor (3). The pleomorphic variant is reported to have a 30% metastasis rate and an overall mortality of at least 40% (36). Regarding the dedifferentiated variant, there are limited data available on the prognosis, but Mc Cormick *et al.* (37) have reported that they have a better prognosis than pleomorphic sarcomas, and are associated with a 15-20% metastatis rate.

As far as location concerned, malignant forms tend to be located in deep soft tissue, whereas less aggressive or benign forms tend to be observed in superficial adipose tissue; thus, as has also been reported by Enzinger and Wislow (15), different locations may correspond to different prognoses. In a recent study, Fanburg- Smith *et al.* (38) have reported patients with liposarcomas in the oral cavity appear to have a better prognosis than their soft-tissue counterparts, and that tumor size irrespective of the histological subtype may be the best predictor of recurrence.

In terms of adequacy of surgical treatment and distant metastases, in general, the treatment of choice for liposarcomas is surgical excision (38, 39) and the frequent presence of satellite nodules means that wide surgical excision is necessary for adequate removal of the tumor. It

has also been reported that non-surgical treatments have limited value, and the role of adjuvant chemotherapy or radiotherapy is controversial (40-42).

Cytogenetic and molecular analyses (not done in our cases) are considered very important prognostic factors; they are helpful in identifying the histological subtype, as well as in elucidating pathogenesis. Cytogenetic analysis is useful in that it provides accurate classification of types of liposarcoma and enables liposarcoma to be distinguished from benign adipose tumors. It has been observed that the dedifferentiated form frequently retains some of the cytogenetic changes present in well-differentiated liposarcoma, including ring and marker chromosomes composed of amplified material from 12q13-15 in about 50% of cases (43, 44). There are also gene abnormalities in MDM2 in over half of all cases.

In contrast, pleomorphic liposarcoma frequently has a highly abnormal and complex karyotype without specific abnormalities (45, 46) and does not appear to arise from a low-grade precursor. Recent microarray data using comparative genomic hybridization and expression profiling also suggest that the molecular signatures of dedifferentiated and pleomorphic liposarcomas are different (47, 48).

Conclusion

We have added two more cases of this rare tumor located in the oral cavity, one being the dedifferentiated and the other the pleomorphic variant. The first type, of which only six other cases have been reported in the literature, was located at the cheek. The second is the sixth case reported to date involving the gingival maxillary tuber.

Histological classification and differential diagnosis are indispensable not only in discriminating the variant, but also in predicting clinical behavior and prognosis: clinical course is directly related to aggressiveness, which can only be determined by histology. Immunohistochemistry helps in this, and provides the key to discriminate between the various forms. It is probable that the prognosis of the dedifferentiated form in the oral cavity is similar to that observed in other parts of the body, although the degree of aggressiveness has also been reported to depend on location. Case reports to date are very few for proper evaluation; in particular, the case of the pleomorphic form reported here, only the sixth such case to date, is now lost at follow-up and further data are not available.

It cannot be ruled out that, in the oral cavity, many more cases occur than are reported, due to the difficulty of diagnosis and the rarity of these tumors in this location. For this reason it is important to enhance diagnostic accuracy, by using, alongside with the routine histological tests, immunohistochemical exams, such as MDM2, MIB-1 and p53.

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