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ORIGINAL PAPER

Lipomas of the Oral Cavity: Utility of MDM2 and CDK4 in Avoiding Overdiagnosis as Atypical Lipomatous Tumor

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Abstract

Traumatized lipomas with degenerative change may demonstrate histopathologic features that mimic atypical lipomatous tumor (ALT). Previously reported series of ALT involving the oral cavity preceded routine use of MDM2 and CDK4 immunohistochemistry. Our aim is to evaluate MDM2 and CDK4 immunohistochemical expression in adipocytic tumors arising in this site, in conjunction with the histiocytic marker PU.1, to determine whether MDM2 and CDK4 impacts classification. 17 cases originally diagnosed as ALT were retrieved and immunohistochemical studies for MDM2, CDK4 and PU.1 were performed. FISH analysis for *MDM2* amplification was performed in select cases. For this study group, the male:female ratio was 9:8 and the median age was 62 (range 41–88). All 17 cases presented as well- or predominantly well-circumscribed proliferations of variably sized, mature adipocytes exhibiting uni- or multi-vacuolation with occasional scalloped nuclei and mild nuclear atypia. Variable amounts of fibrous stroma with focal myxoid change and bland spindle cells were identified in 14/17 cases. Lipoblasts or atypical hyperchromatic stromal cells were not identified in any cases. 14 of 17 cases were negative for MDM2 and CDK4 in tumor cells and 11 of these 14 showed weak nuclear positivity for MDM2 in histiocytes. 3 of 17 cases showed weak, multifocal immunohistochemical expression of MDM2 and CDK4. PU.1 highlighted histiocytes in all 17 cases. FISH analysis for *MDM2* amplification was negative in all 3 cases with weak MDM2/CDK4 expression. All cases were reclassified as lipoma with degenerative changes. ALT, in all likelihood, is less common than previously thought in this anatomic location and best diagnosed with ancillary studies. MDM2 expression in histiocytes is best interpreted in conjunction with CDK4 immunohistochemistry and confirmatory FISH for *MDM2* amplification.

Keywords Lipoma · Atypical lipomatous tumor · Liposarcoma · Well-differentiated liposarcoma · Immunohistochemistry · FISH

Introduction

Adipocytic tumors of the oral cavity most frequently represent lipoma or herniation of the buccal fat pad, analogous to herniation of orbital fat [1, 2]. Atypical lipomatous tumors (ALT) have also been reported, albeit less commonly, and other adipocytic neoplasms such as spindle cell lipoma or myxoid liposarcoma are uncommon [3–6]. ALT is the preferred nomenclature for well-differentiated liposarcoma (WDLPS) arising in surgically amenable sites such as the oral cavity, as it does not metastasize without first undergoing dedifferentiation and has an excellent prognosis with complete excision [7, 8].

Four histologic variants of ALT/WDLPS are recognized in the most recent WHO classification of soft tissue tumors, of which adipocytic (lipoma-like) is the most common in the oral cavity [3, 4, 9]. Adipocytic (lipoma-like) ALT/WDLPS

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can be definitively distinguished from lipoma when the characteristic microscopic features of adipocyte size variation and nuclear atypia of adipocytic or stromal cells are present, often in a neoplasm exhibiting lobular architecture with fibrous septae [10, 11]. Lipoblasts, characterized by one or more lipid cytoplasmic vacuoles and a scalloped, hyperchromatic nucleus, are a helpful diagnostic clue if present, although they are typically absent in the majority of ALTs.

Diagnostic difficulties arise in sites prone to trauma such as the oral cavity. Traumatized adipocytic tumors show characteristic degenerative features including variation in adipocyte size, reactive nuclear atypia, fibrosis, increased stromal histiocytes, and fat necrosis [1]. These changes may be mistaken for malignant adipocytic neoplasms, in particular ALT/WDLPS.

Immunohistochemistry for MDM2 and CDK4 expression are sensitive and specific confirmatory markers of ALT/WDLPS and an invaluable ancillary test in diagnostically challenging cases [12–14]. Nuclear overexpression of MDM2 and CDK4 in ALT/WDLPS is a result of 12q13-15 chromosomal amplification in ring or giant marker chromosomes [15, 16]. Benign lipoma may have various cytogenetic findings including 12q13-15 rearrangement targeting *HMGA2*, 13q deletion, or 6p21-23 rearrangement but does not overexpress MDM2/CDK4 [17, 18].

Previously reported series of ALT involving the oral cavity preceded routine use of MDM2 and CDK4 immunohistochemistry [3, 4]. The aim of this study is to re-evaluate a series of adipocytic tumors originally diagnosed as ALT to determine whether MDM2 and CDK4 impact diagnosis. The histiocytic marker PU.1 was utilized to identify histiocytes, which may express MDM2 in the setting of fat necrosis. Fluorescent in situ hybridization (FISH) for *MDM2* amplification was performed in select cases.

Materials and Methods

Cases originally diagnosed as ALT were identified in a 60-month period from February 2011 through January 2016 from the archives of StrataDX, the surgical pathology laboratory affiliated with the Harvard School of Dental Medicine in Boston, MA, USA. The original diagnosis of ALT was made based on the features of a mature adipocytic proliferation exhibiting variation in adipocyte size with nuclear atypia, multivacuolated adipocytes, and a cellular proliferation of stromal spindle cells.

Immunohistochemical analysis was performed on 4 µm whole-sections cut from formalin-fixed paraffin-embedded blocks using pressure cooker heat-induced epitope retrieval (0.01 M citrate buffer, pH 6.0), and the following antibodies: MDM2 (Calbiochem, San Diego, CA; clone 1F2; dilution 1:20), CDK4 (Cell Signaling Technology, Danvers, MA; clone D9G3E; dilution 1:250), and PU.1 (BD Pharmingen, San Jose, CA, clone G148-74 dilution 1:100). The Envision Plus detection system (Dako, Carpinteria, CA) was used. Appropriate positive and negative controls were used throughout. Nuclear staining was scored semi-quantitatively based on intensity of staining (negative, weak, moderate, or strong) and extent of staining (none; focal, < 0%; multifocal, 10–75%; diffuse, > 75%). Immunohistochemistry results were reviewed blinded to the morphologic findings, and the original hematoxylin and eosin (H&E) stained slides were also re-reviewed independently of MDM2 and CDK4 status.

FISH analysis for select cases was performed on 4 µm whole-sections cut from formalin-fixed paraffin-embedded blocks following standard protocols in our laboratory. The cases were examined with a commercially available probe kit for *MDM2* and CEP12 (Vysis LSI MDM2 SO and CEP12 SG, Abbott Molecular). *MDM2* amplification was defined as an average *MDM2*/CEP12 ratio > 2. One hundred interphase nuclei were evaluated in tumor cell-rich areas from each specimen.

Results

17 cases diagnosed as ALT were identified (Table 1). During the study time frame, there were 163 total adipocytic neoplasms in the oral cavity identified, including

Table 1 Clinical and histopathologic features

Clinical features	
Male	9/17 (52.9%)
Female	8/17 (47.1%)
Median age	62 years
Age range	41–88 years
Location	
Tongue	15/17 (88.2%)
Lip	1/17 (5.9%)
Alveolar mucosa	1/17 (5.9%)
Histopathologic features	
Greatest dimension (range)	0.2–1.2 cm (0.4 cm)
Circumscription	17/17 (100.0%)
Fibrous septae	2/17 (11.8%)
Adipocyte size variation	17/17 (100.0%)
Uni/multivacuolated cells with scalloped nuclei	17/17 (100.0%)
Lockhern cells	15/17 (88.2%)
Fibrous stroma with bland spindle cells	14/17 (82.4%)
Coarse/ropy collagen fibers	0/17 (0.0%)
Mast cells	13/17 (76.5%)
Lipoblasts	0/17 (0.0%)
Atypical hyperchromatic cells	0/17 (0.0%)
Mitoses ≥ 1/10 HPF	1/17 (5.9%)

139 conventional lipomas and 7 spindle cell lipomas. The male:female ratio was 9:8. The median age was 62 (range 41–88). 15 out of 17 cases involved the tongue. Tumor sizes ranged from 0.2 to 1.2 cm (median 0.4 cm). Microscopically, all 17 cases presented as well- or predominantly circumscribed proliferations of variably sized, mature adipocytes (Fig. 1a, b). Thin fibrous septae were noted in 2/17 cases. All 17 cases exhibited uni- or multivacuolated cells lacking nuclear enlargement, significant nuclear scalloping by cytoplasmic vacuoles, and hyperchromasia. Many of these cells were confirmed to be histiocytes (see below) (Fig. 1c, d). Lochkern cells were identified in 15/17 cases. There were variable amounts of fibrous stroma with focal myxoid degeneration, and often more cellular foci of bland spindle stromal cells in 14/17 cases. Coarse/ropey collagen fibers were consistently absent. Mast cells were identified in 13/17 cases. True lipoblasts and atypical cells with hyperchromatic were not identified in any cases. One case had a mitotic count of 1 per 10 high-power fields; no mitotic figures were identified in the remaining cases.

14 of 17 cases were negative for MDM2 and CDK4 by immunohistochemistry in tumor cells (Fig. 2) and 11 of these cases showed weak/multifocal nuclear MDM2 positivity in histiocytes (Fig. 3). 3 of 17 cases showed weak/focal immunohistochemical expression of MDM2 and CDK4 in tumor cells (Fig. 4). PU.1 highlighted histiocytes in all 17 cases, including those with multivacuolated cytoplasm (Fig. 2d). FISH analysis for *MDM2* amplification was negative in all 3 cases with weak MDM2/CDK4 expression (Fig. 4d). All cases were reclassified as lipoma with fat necrosis and reactive/degenerative changes.

Follow up data was available on 8 cases. Six patients had no further treatment and no evidence of disease at follow up ranging from 6 to 37 months (median 30 months); 4 of these 6 patients had positive margins at initial excision. One patient underwent re-excision at 1-month follow

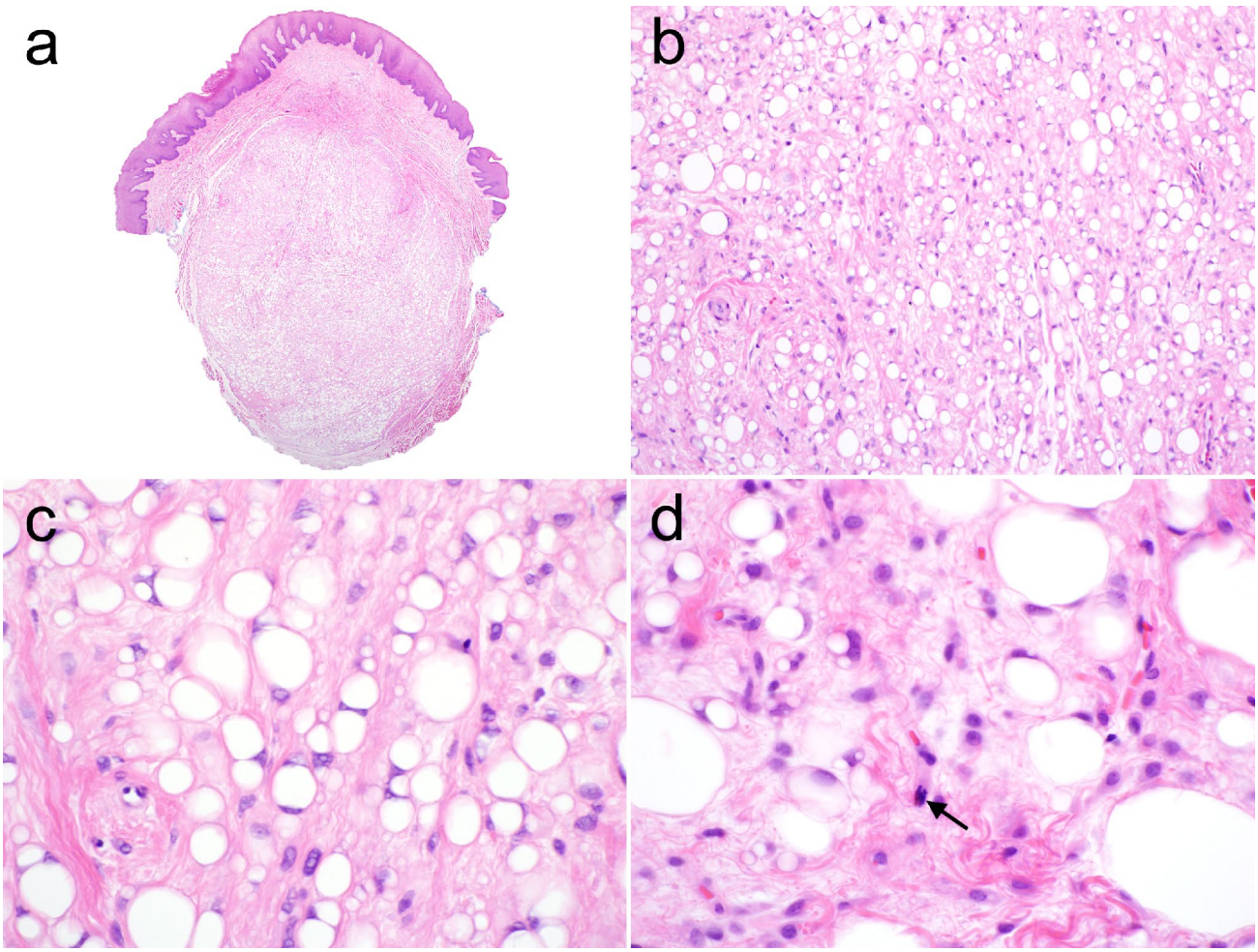

Fig. 1 **a** All cases presented as well-circumscribed proliferations of mature adipocytes (×20), **b** histiocytes and adipocytes exhibited size variation, multivacuolation and nuclear scalloping, mimicking lipoblasts (×200), **c** Multivacuolated histiocytes and adipocytes do not exhibit nuclear hyperchromasia (×600), **d** A solitary mitotic figure (arrow) was observed (×600)

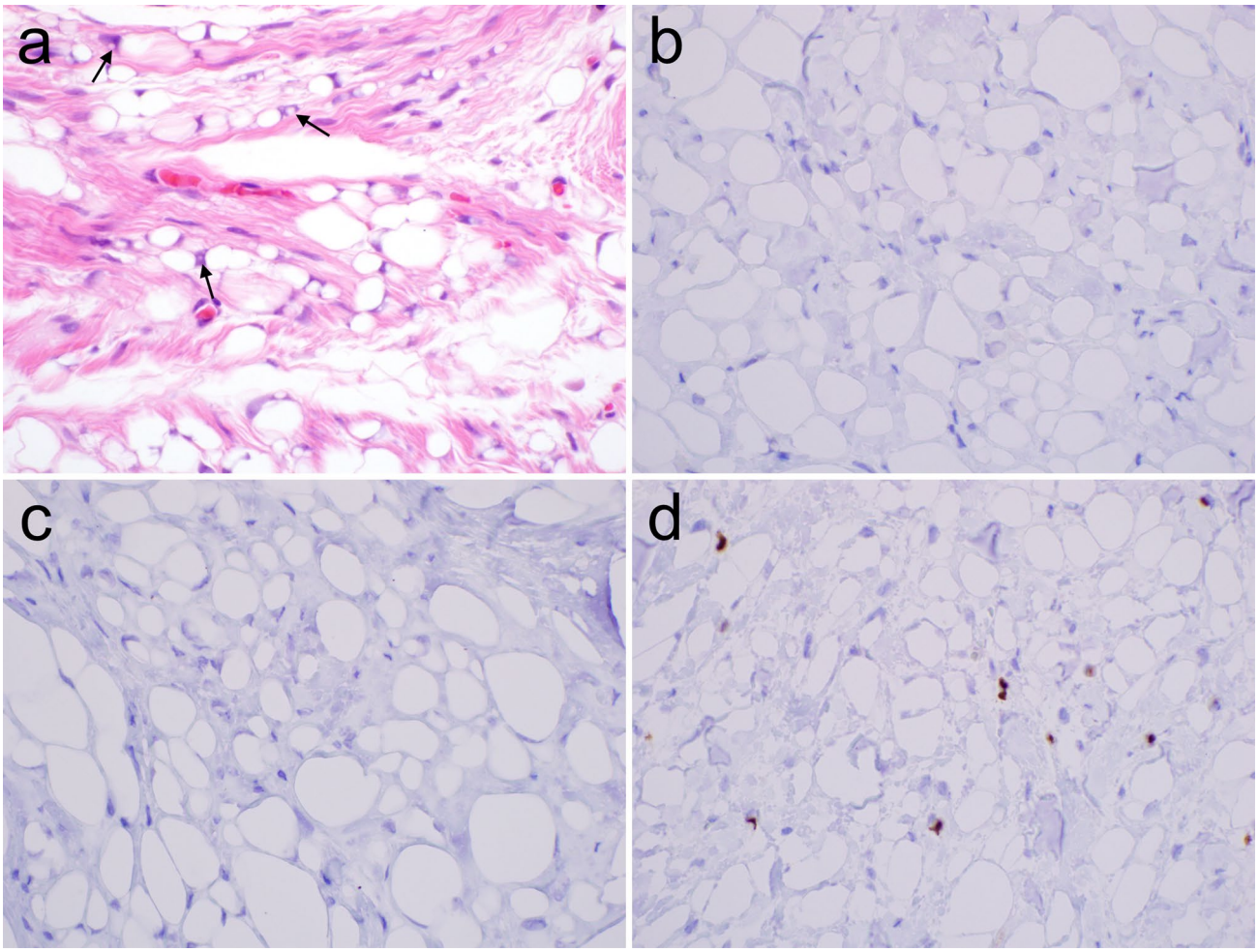

Fig. 2 **a** Lockhern cells (arrows) were frequently identified in the adipocytic proliferation (×mag), **b** MDM2 (×600) and **c** CDK4 (×600) were entirely negative while in this case, **d** PU.1 highlighted abundant stromal histiocytes (×600)

up with clear margins, and had no evidence of disease at 7-month follow up. One other patient underwent re-excision at 3 months with positive margins and was lost to follow up.

Discussion

This series of 17 cases of traumatized lipoma initially diagnosed as ALT highlights the spectrum of reactive changes in traumatized lipomas and the diagnostic pitfalls for adipocytic neoplasms. Lipoma with fat necrosis may show features suggestive of ALT. All cases in this series presented as a proliferation of variably sized adipocytes, with reactive changes mimicking mild atypia. Misleading features included vacuolated histiocytes mimicking lipoblasts, degenerated adipocytes, Lochkern cells (15/17 cases), and the presence of a bland spindle cell proliferation in a fibrous stroma with focal myxoid degeneration (14/17 cases). Notably, the short spindled-ovoid tumor cell morphology and coarse/ropy collagen fibers characteristic of spindle cell lipoma were not identified in any cases.

Uni- or multi-vacuolated histiocytes with scalloped nuclei, identified in all cases by PU.1, may be misinterpreted as lipoblasts and lead to a misdiagnosis of ALT. True lipoblasts have hyperchromatic and atypical nuclei scalloped by cytoplasmic vacuoles and should not be confused with vacuolated histiocytes or degenerated adipocytes. In all cases in this series, no true lipoblasts were identified. All multivacuolated cells with scalloped nuclei represented histiocytes or degenerated adipocytes, with no nuclear atypia or hyperchromasia. Another misleading feature of traumatized lipoma is the bland though somewhat cellular stromal spindle cell proliferation that should not be confused with the atypical stromal cells exhibiting enlarged, hyperchromatic nuclei characteristically seen in ALT/WDLPS. Similarly misleading features have been observed at other anatomic locations, in particular in cases of subcutaneous lipoma (median size 6–7 cm) with prominent adipocyte size

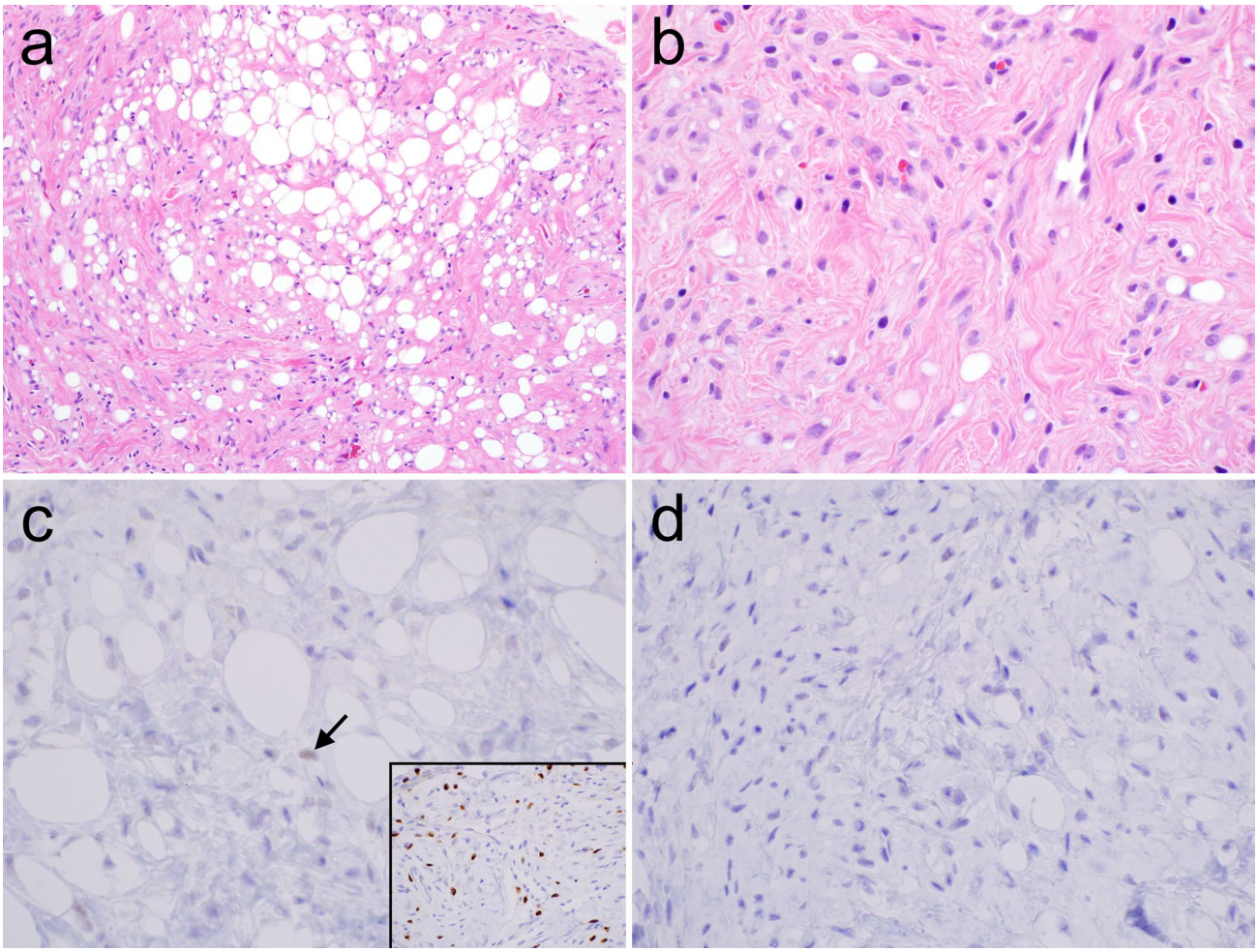

Fig. 3 **a** Mature adipocytic proliferation with fibrous stroma and admixed bland stromal cells (×200), **b** bland stromal cells imparting greater cellularity (×600), **c** MDM2 showed weak, multifocal nuclear positivity in this case (×600, inset: PU.1 highlighting stromal histiocytes), **d** while CDK4 was entirely negative (×600)

variation, minimal nuclear atypia and multivacuolated cells, which have been designated "anisometric cell lipoma" in two recent publications [19, 20].

Immunohistochemistry for MDM2 and CDK4 plays an important role in the differential diagnosis of lipoma with degenerative changes and ALT, especially as lipoblasts are typically absent in ALT/WDLPS and their presence is not required for its diagnosis [3]. However, MDM2/CDK4 immunohistochemistry is not without diagnostic pitfalls. MDM2 expression in histiocytes has been previously reported, and in this study we observed weak, multifocal MDM2 expression in histiocytes in 11/14 cases that were negative for CDK4 [21]. The diagnosis of ALT should be considered when tumor cells exhibit diffuse and strong MDM2 and CDK4 nuclear reactivity. 3 cases in our series showed weak/multifocal positivity for MDM2 and CDK4 and all three were negative for *MDM2* gene amplification by FISH. A recent study of MDM2/CDK4 immunohistochemistry in ALT/WDLPS and lipoma noted expression in < 50% in ALT/WDLPS and, additionally, MDM2 and CDK4 expression in 2/125 and 10/17 benign lipomatous tumors, respectively [22]. The frequent need for reflex FISH testing combined with a cost-benefit analysis led the authors to suggest that FISH for *MDM2* amplification should be employed routinely as first-line ancillary testing. While this approach may be prudent in anatomic sites for which ALT/WDLPS has a predilection, the relative infrequency of ALT compared to lipoma in the oral cavity supports that MDM2/CDK4 immunohistochemistry can be used to resolve the vast majority of differential diagnoses. In this anatomic site, FISH should be considered when immunohistochemistry is equivocal or with recurrence of a lipomatous tumor previously diagnosed as benign on the basis of negative MDM2/CDK4 immunohistochemistry.

A total of 70 cases of ALT/WDLPS have been previously reported in the oral cavity, most before the advent

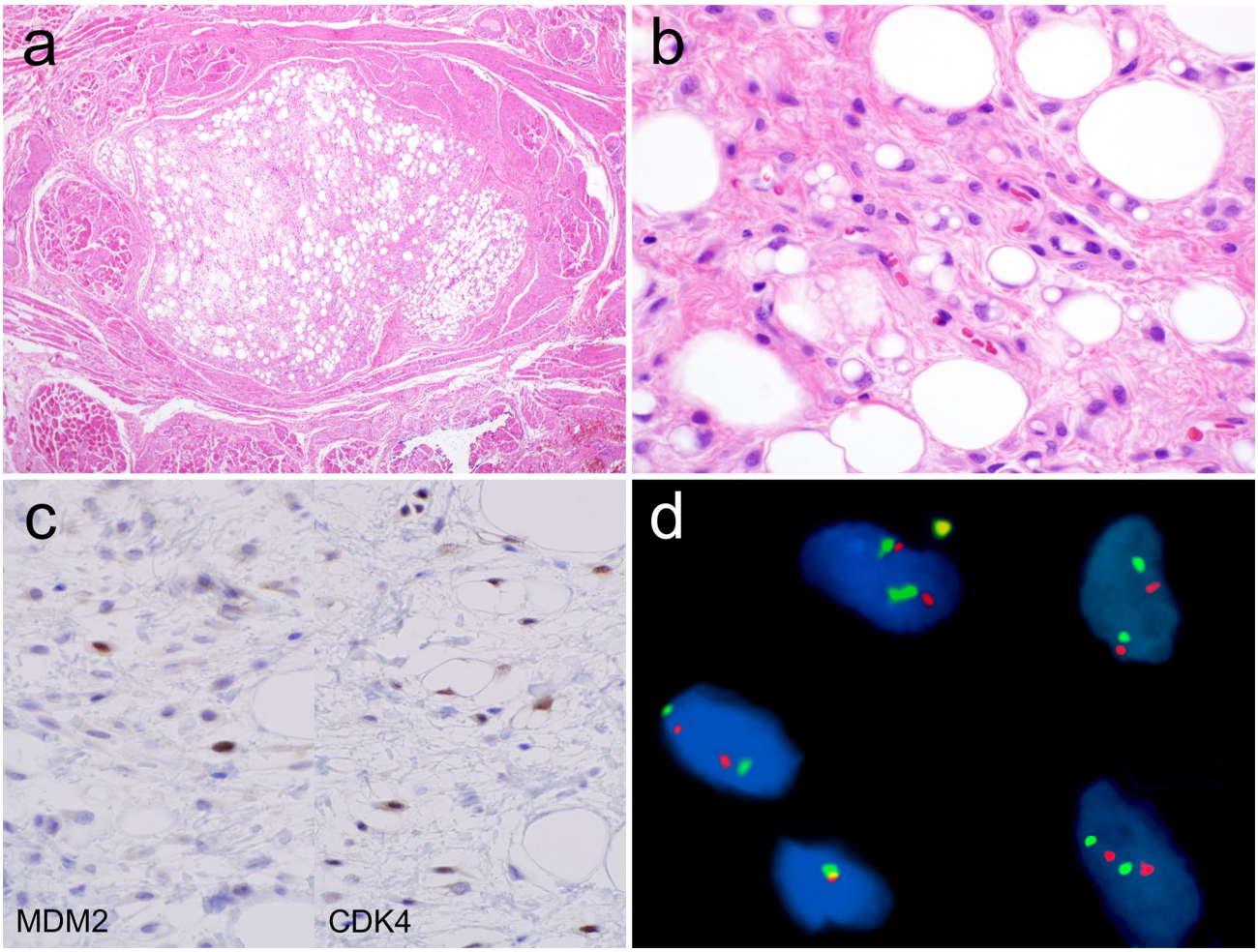

Fig. 4 Typical proliferation of variably sized, multivacuolated cells with minimal atypia (**a** ×40, **b** ×600), **c** this case exhibited weak, multifocal expression of MDM2 and CDK4, **d** composite image of *MDM2* FISH on interphase nuclei demonstrating two *MDM2* (red) and two CEP12 (green) signals, consistent with a diploid status of chromosome 12 and absence of *MDM2* amplification in tumor cells

of MDM2 and CDK4 immunohistochemistry [5, 23–25]. As in this series, the tongue has been the most common intraoral location (37 cases). 4 of these 70 cases reported MDM2/CDK4 expression by immunohistochemistry, with an additional case reporting isolated CDK4 expression and one other case reporting MDM2 expression alone [25–27]. The remaining 64 cases were diagnosed based only on histopathologic features, with many published photomicrographs bearing morphologic similarity to the traumatized lipomas in this series. Of the 70 cases reported as ALT/WDLPS, 8 exhibited one or more recurrences over a period of 9 months to 23 years, with no reported metastases or deaths. The 8 cases with recurrences comprised 2 (of 4) MDM2/CDK4 positive cases and 6 (of 64) cases diagnosed by H&E [3, 4, 23, 25, 27–29]. The remaining 61 cases exhibited no recurrences over follow-up periods ranging from 2 to 63 months, which may reflect misclassification of benign lipomas. Based on available follow-up data for 8 patients in this present series, no patients developed recurrence (median, 30 months) regardless of margin status.

In summary, traumatized lipomas in the oral cavity may show morphologic features that mimic ALT, with increased stromal cellularity and multivacuolated cells that superficially resemble lipoblasts but actually represent histiocytes. Distinguishing traumatized lipoma from ALT is important because the latter may recur or undergo dedifferentiation (thus acquiring metastatic potential). MDM2/CDK4 immunohistochemistry plays an important role in diagnostically challenging cases and helps exclude ALT in the majority of cases, bearing in mind the pitfall that MDM2 expression may occur in histiocytes, which may be identified with PU.1 expression. In cases with equivocal immunohistochemistry results, such as multifocal weak reactivity, FISH for *MDM2* amplification may be necessary for definitive classification. In the oral cavity, the

diagnosis of ALT is best confirmed with ancillary studies and, in all likelihood, may be less common than previously assumed.

Compliance with Ethical Standards

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

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was not obtained as this study consists of secondary research performed on excess tissue of specimens previously obtained for diagnostic purposes. Research was conducted using de-identified samples and private patient information was not accessed at any point during the design of the study, data collection/interpretation, or manuscript preparation.

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