

Lipomatous mixed tumor of the skin with cystic formation affecting the upper lip: A case report

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Abstract. Mixed tumor of the skin (MTS) is a rare neoplasm derived from the sweat glands with a reported frequency of 0.01-0.098% among all primary skin tumors. MTS often occurs in the head and neck region and is characterized by a mixture of epithelial, myoepithelial and stromal components. MTS also shows various morphological patterns, thus the presence of variants with rare components and its rarity make the clinical diagnosis even more difficult. A 47-year-old man was referred due to a painless, slowly growing, exophytic swelling intracutaneous mass of the upper lip. Magnetic resonance imaging revealed that the mass was a solid tumor with a fatty component in the proximal portion, while the distal portion was cystic and possibly contained highly viscous fluid. The mass was located between the skin and the orbicularis oris muscle in the upper lip. Excisional biopsy was performed and the lesion showed two intriguing features: A tumor with extensive lipomatous stroma and some large cysts. It was histopathologically diagnosed as lipomatous MTS with cystic formation in the upper lip. No evident signs of recurrence were observed during follow-up. The present report describes this case and includes a brief literature review of reported cases in the lip, since MTS can be confused with various skin lesions in clinical settings due to this rarity. Recognition by clinicians

of different variants of MTSs, including the present case, is important for preventing erroneous diagnosis and treatment.

Introduction

Mixed tumor of the skin (MTS), also termed 'chondroid syringoma,' is a small benign tumor arising from the sweat glands (1). This tumor is uncommon, with an incidence of 0.01-0.098% among all primary skin tumors, and demonstrates a predilection for males (2,3). MTS commonly involves in the head and neck areas; however, a very small number of cases of MTS of the lip have been reported (4-7). It presents as asymptomatic slow growing, firm subcutaneous or intradermal nodule (3,6). It is difficult for most clinicians to clinically differentiate MTS from other lesions because of its silent presentation and rarity (3,8,9).

Pathologically, MTS consists of epithelial and mesenchymal stromal components, and shows neoplastic proliferation of glandular cells embedded in a myxoid or chondroid stroma, findings occasionally include osteoid stroma or adipocytes (1,4,10). The histological features of these tumors are recognized as two variants: the eccrine cell type, which shows smaller lumens lined by a single row of cuboidal epithelial cells, and the apocrine cell type, which shows tubular and cystic branching lumina lined by double-layered epithelial cells, dual epithelial cells and myoepithelial cells (1,11). This tumor is considered as the cutaneous analog to pleomorphic adenoma of the salivary glands, and shares some features with pleomorphic adenomas (or salivary gland mixed tumors) (1,9). Therefore, its diagnosis is dependent on the tumor location, to exclude tumors originating in the salivary glands (12). Furthermore, the broad spectrum of metaplastic changes and differentiation can sometimes lead to its misdiagnosis as other adnexal or mesenchymal neoplasms (4).

In this report, we present a case of MTS with abundant adipose tissue and large cystic structures in the upper lip. This case is unique because of the clinical location of the mass and the rare histopathological features. Awareness of the various

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variants of MTS can contribute to making a correct diagnosis and the provision of appropriate treatment.

Case report

A 47-year-old Japanese man was referred to the Department of Oral and Maxillofacial Surgery at Kyushu University Hospital (Fukuoka, Japan) with a 6-year history of a painless mass in the right upper lip. Recently, the mass had been slowly growing (Fig. 1A). He had no clinical evidence of cervical lymphadenopathy and no medical history of any significant diseases. On extra- and intra-oral examination, he had 14x12x10 mm round, soft-elastic, less movable, intradermal nodule of the upper lip that appeared to be fixed to the skin. Both the overlying skin-a part showed bluish-and the underlying intraoral mucosa appeared normal. In addition, the patient was concerned about the postoperative functional and aesthetic consequences.

Magnetic resonance imaging (MRI) demonstrated a 10x11x7 mm area of delimited soft tissue without apparent attachment to the skin of the right upper lip. On T1-weighted imaging, the mass was partially hyperintense (Fig. 1B). It had an inhomogeneous and slightly high signal intensity on T2-weighted water-only imaging (Fig. 1C). An area of the high signal intensity was found in the proximal portion on T2-weighted fat-only imaging, which suggested the presence of a fatty component (Fig. 1D). A time intensity curve showed gradual enhancement in proximal portion and non-enhancement in distal portion (Fig. 1E). Taken together, the proximal portion was a solid tumor with fatty component, while the distal portion was cystic and possibly contained highly viscous fluid. Ultrasonography showed a well-circumscribed mass with two different components (Fig. 1F). The proximal solid portion was hyperechoic, and the distal portion was hypoechoic. It was close to the skin surface, but the direct contact was not clear. Based on these findings, the tumorous mass was clinically diagnosed as a non-malignant tumor.

An excisional biopsy was performed via an intraoral approach by extracapsular dissection of the lesion under local anesthesia for aesthetic reasons. The tumor was easily and bluntly dissected and totally removed from the adjacent tissues. The mass was well-encapsulated, and intracutaneously located between the orbicularis oris muscle and the skin, without invading the orbicularis oris muscle or skin. There was no obvious damage to the nerves or blood vessels. Gross examination of the specimen revealed a well-circumscribed tumor mass measuring of 12x14x10 mm in size. The specimen had a dark-red colored area with a central convex part and a yellowish white area. The cut surface showed a yellowish white solid area and cystic structures in which the viscous liquid content leaked out when the specimen was cut (Fig. 1G and H).

On histopathological examination, the lesion was encapsulated with thin fibrous tissue and consisted of a solid lesion and a few large cystic structures in the hematoxylin and eosin-stained section (Fig. 2A). The solid lesion showed a stromal component with abundant adipose tissue and epithelial structures with elongated branched ducts/tubules and sheet-like growth patterns. The stromal component showed myxoid, hyaline and fibrous changes, and abundant mature adipose tissue replaced stromal component, intermingled with the epithelial structures and was observed to account for approximately 40% of the

solid lesion (Fig. 2B). The ductal/tubular structures were lined by double-layered cells; the outer layer was composed of polygonal to flattened clear cells, and the inner layer was formed by cuboidal/columnar ductal epithelial type cells (Fig. 2C-K). A few large cystic lesions were lined by thin double-layered cuboidal and/or polygonal to flattened epithelial cells that were associated with the tumor cells (Fig. 2L-N). Serous and mucous acinar cells were not evident in the tumor. The following antibodies were used in immunohistochemical staining for this case: epithelial markers, AE1/3 and EMA; mesenchymal and myoepithelial markers, vimentin, S-100, α SMA, GFAP, CK14, p40 and p63; and a cell proliferation marker, Ki-67. Immunohistochemically, the epithelial tumor cells with elongated branched ducts/tubules and sheet-like growth patterns were positive for AE1/3 (Fig. 2J). The polygonal to flattened clear cells in the outer layer were positive for p63 (Fig. 2D and M), p40 (Fig. 2E) and CK14 (Fig. 2F), and the ductal epithelial type cells were positive for EMA (Fig. 2K and N). S100-positive cells were observed in the limited epithelial area, in the stromal component and in the lipomatous area (Fig. 2B inset, Fig. 2H). Ki-67-positive cells were scattered and the proliferative index was low (data not shown). GFAP-positive signals were observed in some epithelial cells of the outer layer (Fig. 2G). α SMA signals were almost negative in the epithelial areas (Fig. 2I). Based on the above-mentioned histopathological features and anatomical location of the lesion, the tumor was diagnosed as lipomatous MTS with large cystic formation affecting the upper lip. No local recurrence of the tumor was observed during 5 months of follow-up.

Discussion

MTS, also known as chondroid syringoma, is a rare benign skin appendageal tumor with an incidence of 0.01-0.098% among all primary skin tumors (1-3). This tumor presents as a slow growing, asymptomatic, intradermal or subcutaneous nodule, commonly affecting the middle-aged and elderly males, and generally involves the head and neck region (6). Stout and Gorman (6), Hirsch and Helwig (5), and Kazakov *et al* (4) reported that among cases of MTS, the frequency of MTS in the head and neck region was 67.9% (91/134 cases), 79.8% (150/188 cases), and 75.0% (183/244 cases) in MTS, respectively. We herein report a rare case of MTS with three unusual clinicopathological features.

The first feature of the present case is the location of the lesion. MTS most commonly occurs in the head and neck region. Among cases of MTS, the frequency of MTS of the lip reported by Stout and Gorman (6), Hirsch and Helwig (5), and Kazakov *et al* (4) was only 13.4% (18/134 cases), 12.8% (24/188 cases), and 16.0% (39/244 cases), respectively. The frequency among MTSSs in the head and neck region is similar to that in the nose and cheek skin regions (4-6). The frequency at which MTS occurs in the lip is considered to be very low in comparison to the frequency of all primary skin tumors (8). In our search of the relevant literatures, the number of cases of MTS of the lower lip was less than one-eighth the number of cases of MTS of the upper lip. In addition, the clinical diagnosis of MTS is quite difficult due to the lack of specificity of the clinical manifestations, therefore MTS is most often

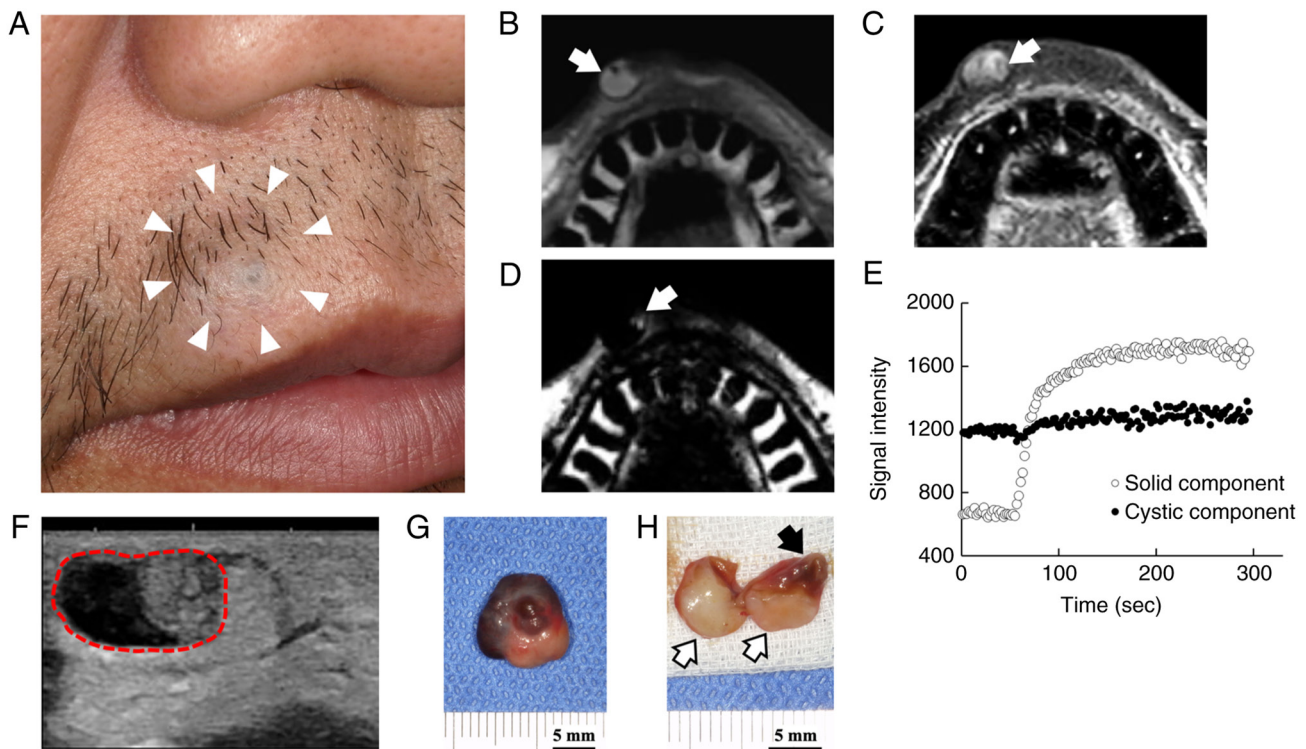


Figure 1. Macroscopic appearance of the lesion, preoperative MRI and US images and excisional biopsy of the tumor. (A) A macroscopic photo of the upper lip at the initial visit. The soft-elastic, less movable, intradermal nodule was overlaid with partially bluish skin. Arrowheads indicate the location of the tumor. (B) On T1-weighted MRI, the lesion was hyperintense (arrow) with the exception of the proximal portion of the lesion. (C) T2-weighted water-only MRI showed inhomogeneous and high signal intensity in the tumor and slightly low signal intensity in the proximal portion (arrow). (D) T2-weighted Dixon fat-only MRI showed an area of high signal intensity in the proximal portion of the lesion (arrow). (E) A time intensity curve was obtained by dynamic contrast enhanced MRI. The contrast agent was injected 30 sec after the start of data acquisition. The result showed gradual enhancement in the proximal portion (solid component; open circles) and non-enhancement in the distal portion (cystic component; black circles). (F) US showed a 13x12x6-mm well-circumscribed subcutaneous mass with the two components. The red dotted line indicates the tumor margin. (G) Excisional biopsy of the tumor revealed a round mass measuring 12x14x10 mm in size that was covered by a thin fibrous capsule. The surface had a dark-reddish area with a central bulge and a smooth whitish pink area. (H) Cut surface of the lesion showing a yellowish white solid mass (white arrows) and cystic structures (black arrow). US, ultrasonography.

overlooked or mistaken for other lesions, such as dermoid or sebaceous cysts or any other benign adnexal tumors (8,9). Therefore, a histopathological examination is considered very important for establishing a definitive diagnosis in MTS (8,9).

MTS shows various histological findings, but mainly exhibits as epithelial components embedded in a mucus-like, cartilage-like, and/or fibrous matrixes, and consists of varying proportions in each case. MTS can be mainly divided into two variants, apocrine and eccrine types, based on the pattern of the lumina observed in the MTS. The apocrine type is characterized by tubular and cystic branching lumina lined by double layers of epithelial cells of different types, whereas the rare eccrine type is characterized by small tubular lumina lined by a single layer of cuboidal epithelial cells (1,11). It is well known that the apocrine type may show a broad spectrum of differentiation and metaplastic changes (4). Sometimes these changes are so pronounced that they can cause the clinicians to misdiagnose MTS as other adnexal or mesenchymal neoplasms (4). Based on the findings mentioned above, the present case was diagnosed as apocrine MTS with two unusual histological features.

The second feature is that the fatty component was prominent and constituted approximately 40% of the solid lesion. Although lipomatous metaplasia is a frequent finding, being found in 44% of apocrine MTSs, it is usually observed

multifocally with clusters of mature lipocytes (4). MTSs with predominant and extensive lipomatous metaplasia are rare and were found in only 3 cases of 244 apocrine MTS cases (1%) (4). Only a few cases showing a prominent adipocytic growth pattern has been reported. In those cases, the proportion of the MTS that was filled with adipose tissue ranged from 40% to more than 90% (13-18). To date, there are no reported cases of MTS with extensive lipomatous metaplasia occurring in the lip. MTS shares some features with pleomorphic adenoma of the salivary gland (1,9). To the best of our knowledge, 16 cases of pleomorphic adenoma with predominant adipocytes in the salivary gland has been reported, and the proportion of the tumor that was occupied by adipose tissue ranged from 25% to more than 95% (19-21). Thus a prominent adipocytic metaplastic pattern is rare in both MTS and pleomorphic adenoma. Abundant mature adipose tissue prominently replaced the stromal component and was intermingled with epithelial structures, and could be confused with various other lesions. The histopathological differential diagnosis included lipoma, atypical and spindle cell lipoma, adenolipoma of the skin, eccrine angiomatous hamartoma, eccrine and apocrine hidrocystoma, fibroadenoma, hidradenoma, mucinous adenocarcinoma, and adenoid cystic carcinoma (11,17,22). In our case, cellular atypia and pleomorphism were not observed and its histomorphological features differentiated it from

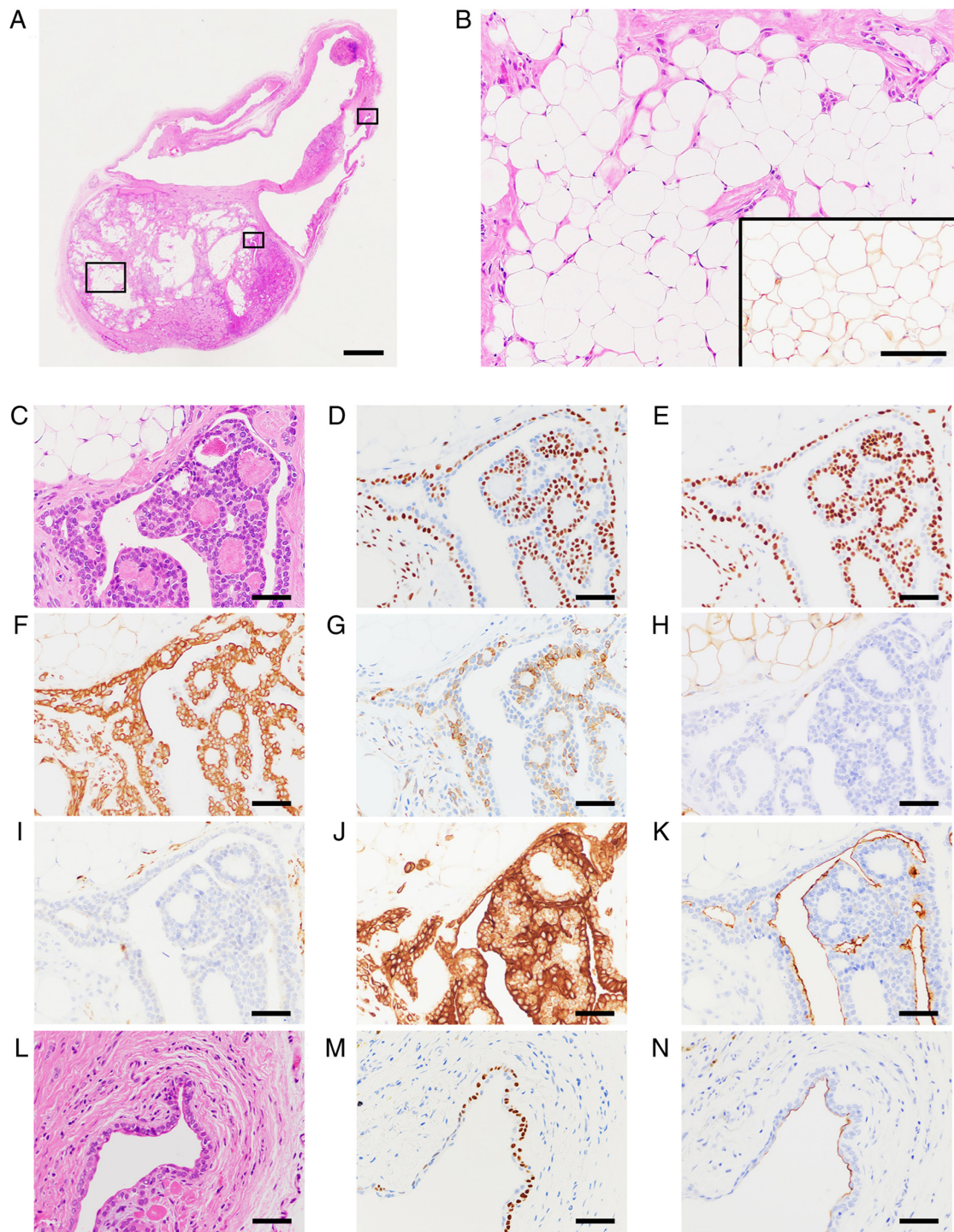


Figure 2. Histological and immunohistochemical features of the biopsy specimen. (A) A magnifying glass view showing the tumor encapsulated with thin fibrous tissue, which was composed of a solid lesion with abundant adipose tissue and large cystic structures (magnification, x7.5; scale bar, 1 mm). (B) A magnified image of the left square area in (A) shows abundant adipose tissue. S100-positive adipocytes are indicated in the inset (magnification, x122; scale bar, 100 μ m). (C) A magnified image of the middle square area in (A) shows ductal/tubular structures with hematoxylin and eosin staining. These structures were composed of double-layered cells. Immunohistochemical images of this tumor lesion are present in the following panels. (D) Cells in the outer layer were positive for p63. (E) These cells were positive for p40. (F) These cells were positive for cytokeratin 14. (G) Some cells in the outer layer were positive for glial fibrillary acidic protein. (H) S100-positive cells were observed in the lipomatous area. (I) α -Smooth muscle actin signals were almost negative in the epithelial areas. (J) Epithelial cells were positive for AE1/3. (K) The inner layers were positive for EMA. (L) A magnified image of the right square area in (A) shows large cystic structures with hematoxylin and eosin staining. These structures were composed of double-layered cells. Immunohistochemical images of the tumor are shown in the following panels. (M) Cells in the outer layer were positive for p63. (N) Inner layers were positive for EMA. (C-N) Magnification, x145; scale bars, 50 μ m. EMA, epithelial membrane antigen.

malignant tumors. These differential diagnoses were ruled out mostly based on clinical findings and/or histopathological findings (11,17,22).

The third feature was that the lesion included large cystic components. As mentioned above, ultrasonography showed the cystic structure as a hypoechoic region located at the

distal portion in the well-circumscribed mass. The region that appeared hypoechoic on ultrasonography showed hyperintensity on T1-weighted imaging, showed inhomogeneous and slightly high signal intensity on T2-weighted water-only imaging, and was not enhanced by contrast agent, which suggested that the cystic structure contained a protein-rich fluid with high viscosity. The mass appeared to be located anterior to the orbicularis oris muscle and close to the skin; thus, cystic lesions and benign adnexal or mesenchymal neoplasms on the skin would be included in the differential diagnosis of this case. Although the clinical differential diagnosis included dermal cyst, epidermoid cyst, sebaceous cyst, trichilemmal cyst and benign adnexal or mesenchymal neoplasms, it was possible to exclude these lesions because in the present case both the hyperechoic and echo-free regions was observed in a single capsule. The mechanism of cyst formation in MTS has been published in the relevant literature. To consider the origin of cyst formation, it may be helpful to refer to cases of pleomorphic adenoma with large cystic formation (23,24). The large cyst formation may originate from the followings: squamous metaplasia of tumor cells; enlargement of ductal-like structures by secretions from tumor cells or salivary gland tissue; hemorrhagic infarction; and necrosis in the tumor (23,24). In our case, the thin double-layered ductal epithelial cells and polygonal to flattened cleat cells lining the large cystic structures were immunohistochemically positive for EMA and p63, respectively. Therefore, the large cyst formation in our case may have originated from enlargement of ductal-like structures by secretions from tumor cells.

The immunoprofile in our case demonstrated that the polygonal to flattened clear cells in the outer layer were positive for p63, p40 and CK14, and S100-/GFAP-positive cells were observed in the limited epithelial area, but α SMA signals were almost negative. The results suggest that the degree of myoepithelial differentiation in this case was lower. Wan *et al* (9) reported that the outer epithelium and epithelial nests of MTS express epithelial and mesenchymal markers, and showed the high expressions of S-100, GFAP, α SMA, and p63, verifying that myoepithelial differentiation was present, but that the tumor was almost negative for desmin and actin. MTS is considered to be the cutaneous analog to pleomorphic adenoma of the salivary glands (1,4). Because neoplastic myoepithelial cells in the tumors can show diverse morphological and cytological features (spindle, polygonal, plasmacytoid, etc) (1,4,9), it is possible that the neoplastic myoepithelial cells can exhibit various steps in the combined epithelial and smooth muscle immunoprofiles. These immunostaining results may be due to the metaplastic features in the MTS, which can be caused by the transformation of myoepithelial cells into stromal components, including adipocytes.

The histopathological examination of the skin lesions could establish a definitive diagnosis of the lesion as MTS; however, there are histological similarities between MTS and pleomorphic adenoma of the salivary glands. Consequently, the points for the differential diagnosis between skin lesions of salivary gland origin or skin origin should be considered. In the report of Reddy *et al* (8), histological features of MTS and pleomorphic adenoma were compared and some contrasting features were listed, as follows. In MTS, the tumor epithelial cells show differentiation towards adnexal structures (i.e., hair

follicle, sebaceous gland, apocrine sweat gland and eccrine sweat gland). Epithelial cells arrange in tubulocystic structures lined by single or double rows. Merkel cells may be involved in differentiation towards adnexal structures (25). Meanwhile, in pleomorphic adenoma, serous and mucous acinar cells are evident. In this case, the tumor epithelial structures mainly showed elongated branched ducts/tubules lined by double rows and only a little sheet-like growth pattern, and serous and mucous acinar cells were not evident. These findings in the present case were suggestive of MTS; however, differentiation towards adnexal structures and involvement of Merkel cells were not apparent in the tumor. Although Merkel cells may be an integral constituent of follicles in apocrine MTSs with follicular differentiation, only 14% of apocrine MTSs were reported to be associated with Merkel cells (25). Therefore, even if Merkel cells were not found in the tumor tissue, it would not be considered a reason to deny the diagnosis of MTS in this case. The differentiation into adnexal structures that was found within the tumor would be considered to be an important finding in differentiation between MTS and pleomorphic adenoma of the salivary glands.

In addition, the genetic profile could be considered as a means of differentiating MTS from pleomorphic adenoma of the salivary glands; however, the difference in the genetic and protein expression profiles of these two tumors has not yet been completely revealed (7). For example, PLAG1 fusion gene is detected in approximately 58% of pleomorphic adenomas (ranged 24-85%) (26). On the other hand, according to the most recent report published in 2022, PLAG1 fusion genes are found in approximately 33% of MTSs (27). There have also been reports concerning other genes other than PLAG1, but no genes have been found to be useful for differentiating between the two tumors, and further research is warranted (28,29).

In the differential diagnosis, the anatomical location of the tumor is one of the most important things to be considered. Based on the clinical findings-including MRI and ultrasonographic images-as well as the operative findings in this case, this mass was well-encapsulated, existing intracutaneously between the skin of the upper lip and the orbicularis oris muscle, without invading into the adjacent structures. The sweat glands on the facial skin comprise both eccrine and apocrine glands and the apocrine glands are mainly distributed on the alae nasi, nasal vestibule and ear canal (7). Hence, the lesion was determined to be of skin origin.

In general, fine-needle aspiration cytology (FNAC), a type of biopsy, is frequently performed to check abnormal area, lump or swelling for the diagnosis of various diseases, including cancers. For example in the thyroid, breast or lymph nodes, FNAC can be used when the lesion is felt or touched as a palpable lump or swelling and/or found as an abnormal growth or area by imaging tests. FNAC also has great value in the diagnosis of lesions of the head and neck region (30,31). Even if MTS is considered a rare differential diagnosis of a lump or swelling in the head and neck region, the diagnosis can be confirmed or ruled out by means of FNAC when the histomorphological and cytomorphological features of MTS are well understood by the cytologist (30,31). Although FNAC was not performed in our case, further attention should be required when diagnosing lesions (like the present case)

in which the imaging analysis reveals predominant fatty components and large cystic structures. Therefore, it would be necessary to make the diagnosis in FNAC based on the anatomical location and clinical presentation of the lesion, histomorphological features (1,4,6,9) and previously reported cases (30,31), together with consideration of the cytological features of rare variant pleomorphic adenoma, cystic (24) and lipomatous pleomorphic adenoma (32), as a reference.

There is little information concerning the variants of MTS where more uncommon features predominate, which makes the diagnosis and treatment more challenging. In this case, although the predominance of adipocytes and cystic structures were notable findings, the tubular/ductal structures in a fibromyxoid background did not readily evoke the diagnosis of an MTS variant with distinct features. However, these findings of the lesion led us to diagnose this neoplasm as a unique, rare variant of a lipomatous MTS with large cystic formation. To the best of our knowledge, this is the first report of lipomatous MTS with cystic formation in the lip.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RN contributed to conception of the study and acquisition of the literature related to the study, drafted the initial manuscript, performed the histopathological analysis, and provided the associated images. TK contributed to conception and design of the study, analysis and interpretation of data, made the final histopathological diagnosis, performed the histopathological and anatomical analyses, provided the associated images, reviewed the literature, and drafted, reviewed and edited the manuscript. MMK, YM, MM, SN, TC and KY made substantial contributions in the acquisition of clinical and imaging data. MMK and MM performed the clinical diagnosis, treatment and follow-up of the patient. SF and HW made the histopathological diagnosis, performed pathological examinations, analyzed the data and interpreted the data. TK, SF, MM and TC confirmed the authenticity of all the raw data and contributed to critical revisions of the intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Kyushu University (approval no. 29-392;

Fukuoka, Japan). Written informed consent was obtained from the patient.

Patient consent for publication

The patient provided written informed consent for the publication of the case and any associated images.

Competing interests

The authors declare that they have no competing interests.

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