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CORRESPONDENCE

Adenoid cystic carcinoma with lipometaplasia: a case report with morphoproteomic analysis of lipogenesis

Sir,

Adenoid cystic carcinoma is composed of neoplastic two-cell epithelial components consisting of dominant myoepithelial cells and ductal cells with a tubular, cribriform, or solid pattern, akin to cylindroma of the skin. This tumour is generally infiltrative with perineural invasion, but can be well-circumscribed on rare occasions. Lipomatous tumours of the salivary glands are not frequent and have been recognised mainly as benign lesions, especially those that are well-capsulated and circumscribed. Lipometaplasia mostly occurs in pleomorphic adenoma and myoepthelioma and has not yet been reported in adenoid cystic carcinoma. The pathogenic mechanism of lipogenesis plays an important role in the clinical prognosis of some types of tumours,[1] but its aetiology remains unclear. The most plausible hypothesis is the generation of a lipometaplasia of myoepthelial cells or undifferentiated mesenchymal stromal cells in a certain environment.[2] We encountered a well-circumscribed, fat-containing, submandibular, malignant tumour masquerading as a benign lesion. This lesion was diagnosed as adenoid cystic carcinoma with lipometaplasia. The present case is the first description of lipometaplasia arising in adenoid cystic carcinoma. Here, we focus on a rare case of adenoid cystic carcinoma with lipometaplasia and validate the pathogenesis of lipogenesis through morphoproteomic analysis and a review of the appropriate literature.

An 84-year-old woman was admitted to the Department of Oral and Maxillofacial Surgery with xerostomia and left submandibular palpable masses without tenderness. The patient was taking oral medication for hyperlipidaemia and hypertension in addition to a preceding cerebral infarction. She had undergone ureteroscopic removal of ureteral stones and endoscopic submucosal dissection due to stomach cancer 2 years and 9 months prior to admission, respectively. There was no specific family history. Laboratory tests were within the normal range except for positive rapid plasma reagin (RPR) and *Treponema pallidum* haemagglutination assays (TPHA). The sagittal view of a neck computed tomography (CT) scan revealed two well-demarcated and fat-containing masses originating from the left submandibular space. Small lymph nodes in both submandibular spaces and along both upper internal jugular chains alluded to a reactive lesion (Fig. 1A). Clinical tentative diagnoses were suggestive of a benign lesion such as pleomorphomic adenoma or an unusually shaped epidermal cyst. The patient underwent minimally invasive surgery on only these masses.

Gross examination (Fig. 1B) revealed a well-circumscribed, yellow-brown, solid lesion containing fatty tissue (arrow) on the cut surface. The two masses were measured as 3.0 × 2.5 × 2.5 cm and 1.5 × 1.5 × 1.0 cm, respectively.

Upon microscopic analysis, these masses showed a well-demarcated lesion intermingled with varied clusters of adipocytes (Fig. 1C). Focal capsular penetration of tumour cells (arrowhead) was identified with perineural invasion (inset). Glandular tumour cells with a tubular structure were admixed with clusters of proliferative adipocytes of various sizes and rigidity (Fig. 1D). These glandular tumour cells with dual differentiation consisted of eosinophilic cuboidal ductal cells and surrounding myoepithelial cells with clear cytoplasm and basophilic angular- and irregular-nuclei. In areas with numerous adipocytic clusters, myoepithelial cells had more severe basal vacuolar changes (Fig. 1E). Lipoblast-like cells (Fig. 1E, arrow; inset) were frequently noted in the stroma and periphery of adipocyte clusters. Typical cribriform-patterned tumour cells also indicated dual differentiation with focal ductal cells (arrow) enclosed by predominantly myoepithelial cells. Dense hyalinised basal lamina and pseudocystic spaces containing basophilic accumulation corralled by tumour cells were demonstrated (Fig. 1F). A chondromyxoid stroma indicative of pleomorphic adenoma was not identified. The myoepithelial tumour components, stromal cells, and adipocytes were all immunoreactive for smooth muscle myosin heavy chain (SMMHC) (Fig. 1G). All tumour cells were negative for glial fibrillary acidic protein (GFAP), and Ki-67 expression was approximately 10%. On the basis of these morphological and immunohistochemical (IHC) results, the diagnosis was consistent with adenoid cystic carcinoma with lipometaplasia. After 5 months of follow-up, the patient remains free of local recurrence or distant metastasis, and will be managed according to the pathological results.

Lipogenesis (including adipogenesis or lipometaplasia) in tumours is uncommon, although adipocytic differentiation in benign salivary tumours such as pleomorphic adenoma or myoepithelioma has been well described. Lipogenesis (lipometaplasia) occurring in adenoid cystic carcinoma has not been described in the English medical literature, and little is known about its pathogenesis. For this reason, we reviewed the relevant literature and performed fluorescence *in situ* hybridisation (FISH) analysis of the *mouse double minute 2 (MDM2)* gene using a dual-colour Vysis MDM2/CEP 12 probe kit (Abbott, USA) and IHC analyses of MDM2, bone morphogenetic protein 9 (BMP9), epidermal growth factor receptor (EGFR), c-Kit, and β-catenin. All IHC results were compared to those of a normal salivary gland or adenoid cystic carcinoma without lipometaplasia (control).

FISH revealed no amplification of the *MDM2* gene (red signal) compared to CEP12 (green signal) (Fig. 2A). MDM2 was strongly immunoreactive in the nuclei of tumour cells, stromal cell, and adipocytes (Fig. 2B), all of which also demonstrated strong immunoreactivity for BMP9 (Fig. 2C). EGFR (Fig. 2D) and c-Kit (Fig. 2E) were positive in the cytoplasm of only tumour cells. β-catenin was immunohistochemically expressed in the cytoplasmic and membranous areas but not the nuclear area of neoplastic cells, stromal cells, or adipocytes (Fig. 2F), which was interpreted as negative. The present case revealed more intense expression for BMP9 and MDM2 and similar expression for EGFR, c-Kit, and β-catenin compared with adenoid cystic carcinoma without lipometaplasia. The normal salivary

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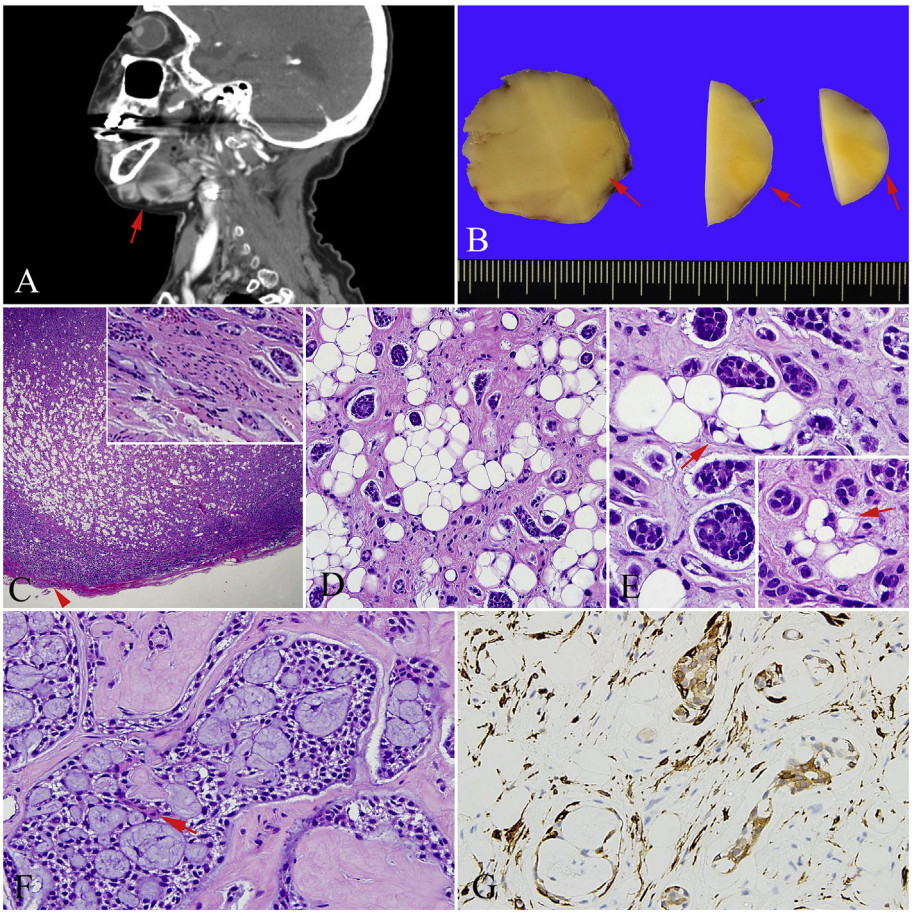

Fig. 1 Radiological, gross, and pathological findings. (A) The sagittal view of a neck computed tomography (CT) scan reveals two well-demarcated and fat-containing masses originating from the left submandibular space. (B) Gross examination illustrates well-circumscribed, yellow-brown, solid lesion containing fatty tissue (arrow) on the cut surface. These two masses measured as 3.0 × 2.5 × 2.5 cm, 1.5 × 1.5 × 1.0 cm, respectively. (C) This mass shows a well-demarcated lesion intermingled with varied clusters of adipocytes. Focal capsular penetration of tumour cells (arrowhead) is identified with perineural invasion (inset). (D) Glandular tumour cells with tubular structure are admixed with clusters of proliferative adipocytes of various sizes and rigidity. These glandular tumour cells with dual differentiation consisted of eosinophilic cuboidal ductal cells and surrounding myoepithelial cells with clear cytoplasm and basophilic angular- and irregular-nuclei. (E) In areas with numerous proliferative adipocytic clusters, myoepithelial cells showed more severe basal vacuolar changes. Lipoblast-like cells (arrow; inset) are frequently noted in the stroma and periphery of adipocyte clusters. (F) Typical cribriform-patterned tumour cells also indicate dual differentiation with focal ductal cells (arrow) enclosed by predominant myoepithelial cells. Dense hyalinised basal lamina and pseudocystic spaces containing basophilic accumulation encompassed by tumour cells are demonstrated. (G) The myoepithelial tumour components, stromal cells, and adipocytes were all immunoreactive for smooth muscle myosin heavy chain (SMMHC).

ducts and adipocytes (control) showed trace expression of BMP9 and MDM2 and no expression of EGFR, c-Kit, or β-catenin.

Adipocytic differentiation is mainly determined by peroxisome proliferator-activated receptor gamma (PPARɣ) and CCAAT/enhancer-binding protein alpha (C/EBPα), which enhance the expression of one another and promote lipogenetic genes.[3] BMPs, low-molecular weight glycoproteins, are principally synthesised by osteoprogenitor cells, osteoblasts, and chondrocytes, but the expression of BMPs is not confined to bone tissue and has been demonstrated in diverse neoplastic cells.[4,5] BMP9 is one of the most potent osteogenetic BMPs. BMPs play a dual role in early mesenchymal stem cell (MSC) differentiation both toward osteogenesis via Runx2 upregulation and toward lipogenesis via PPARɣ overexpression.[6] Determination of whether BMPs have an effect on MSC commitment to osteoblastic or adipocytic lineage relies on nuclear translocation of β-catenin (activated β-catenin), chiefly induced by Wnt signalling. Activated β-catenin upregulates Runx2 and downregulates PPARɣ and strengthens the osteoblastic tendency of BMPs, indicating that BMP signalling changes to promote osteogenesis by activated β-catenin. In the case of cytoplasmic localisation of β-catenin (inactivated β-catenin), the reverse is true, and MSC are inclined to lipogenesis.[7,8] MDM2, a proto-oncogene, has the capability to degrade p53 through directly binding to and ubiquitinising p53. MDM2 is overexpressed by Akt (protein kinase B) involving signalling from diverse growth factors such as EGFR, c-Kit, and HER2. MDM2 encourages recruitment of cAMP regulatory element-binding protein (CREB) coactivator to the CCAAT/enhance-binding protein δ (C/EBPδ) promoter. C/EBPδ promotes lipogenesis through upregulation of PPARɣ and C/EBPα.[9] In the present case, MDM2 is thought to be upregulated via Akt activation due to overexpression of c-Kit and EGFR, although we saw no amplification of the *MDM2* gene on FISH.

It has been recognised that adipocytes originate from MSC or uncommitted stromal cells. Mesenchymal stromal cells can be derived from transformed myoepithelial cells, which have

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