Case Report
Mucinous myoepithelial carcinoma of the parotid gland: report of a new histological variant

Shaodong Yang[1,2], Ming Zeng[1], Jiangli Zhang[2], Xinming Chen[2]

[1]The State Key Laboratory Breeding Base of Basic Science of Stomatology, (Hubei-MOST) & Key Laboratory of Oral Biomedicine Ministry of Education, School and Hospital of Stomatology, Wuhan University, Wuhan, Hubei, China; [2]Department of Pathology, School and Hospital of Stomatology, Wuhan University, Wuhan, Hubei, China

Abstract: Mucinous myoepithelial carcinoma (MMC) is a newly recognized histologic variant of myoepithelial carcinoma, and only 14 cases have been reported in the English literature. The authors herein report an additional case of MMC of the parotid gland. A 72-year-old man presented with a right-sided facial mass. Computed tomography demonstrated a 5.6×4.3×2.9 cm soft tissue mass in the right parotid, with peripheral enhancement and internal low-density. Total excision of the right parotid gland was performed. Histologically, the tumor was characterized by proliferation of predominantly mucin-containing signet-ring cells. Many polygonal to plasmacytoid cells with abundant eosinophilic, faintly granular cytoplasm were intermixed with the signet ring cells. Immunohistochemically, the tumor was diffuse positive for CK AE1/AE3, CK7, CK18, S100, and mammaglobin, but negative for CK14, CK20, vimentin, p63, p40, HHF-35, smooth muscle actin, calponin, DOG-1, Sox10, and Wilms' tumor 1 gene protein. The patient's postoperative course was uneventful and he was then lost to follow up.

Keywords: Myoepithelial carcinoma, myoepithelioma, mucinous, signet-ring cell adenocarcinoma, signet-ring cell, parotid gland

Introduction

Myoepithelial neoplasms are tumors composed almost exclusively of cells with myoepithelial differentiation. Most behave in a benign fashion and are designated myoepithelioma. Myoepithelial carcinoma (MC), also known as malignant myoepithelioma, is the malignant counterpart of benign myoepitheliom, and is distinguished from benign myoepithelioma by its infiltrative, destructive growth [1]. Myoepithelial neoplasms account for about 1.5% of all salivary tumors, and MC is even rarer, representing about 10% of myoepitheliomas [1-3]. However, myoepitheliomas show a wide spectrum of morphologic and immunophenotypic variation, resulting in difficulties in their diagnosis. They remain underrecognized and might not be as rare as has been reported. The tumor cells of myoepitheliomas can be quite diverse, including spindled, stellate, epithelioid, plasmacytoid, basaloid, oncocytic, or clear cells [1-3]. In 2012, Esteva et al. reported 2 cases of unrecognized subtype of myoepithelial tumors that contained abundant intracellular mucin material, which they termed mucinous myoepithelioma [4]. Bastaki et al. described the clinicopathologic, ultrastructural, immunophenotypic and molecular features of four cases of primary signet ring cell adenocarcinoma, and designated them as secretory MC [5, 6]. According to the review by Gnepp, only 17 cases of mucinous myopitheliomas have been reported in the English literature; Four have been classified as benign, and 13 as malignant neoplasms [7]. The authors herein report an additional case of mucinous myoepithelial carcinoma (MMC) of the parotid gland in a 72-year-old man, and discuss its clinicopathologic and immunohistochemical features.

Case report

A 72-year-old man presented with a right-sided facial mass. He had first noticed a mass in the right parotid region 3 years earlier but left it

Figure 1. Axial (A) and coronal (B) computed tomography images show a large lesion with peripheral enhancement and internal low-density, located in the right parotid gland.

untreated, and the mass had gradually enlarged. The lesion had recently increased in size and associated with pain for the last 3 months. The patient reported a 30-year history of smoking (2 packs per day) and alcohol consumption (250 ml per day). The patient's past medical history included hypertension and hyperlipemia. His family history was unremarkable. Physical examination revealed a 6-cm, firm, and nodular mass in the right parotid region. The swelling was vaguely palpable perorally, with a normal overlying mucosa. No skin abnormalities were noted. There was no facial palsy or palpable lymphadenopathy. Routine hematologic and biochemical examination, chest radiograph, and abdomen ultrasound appeared normal. Computed tomography (CT) with contrast demonstrated a 5.6×4.3×2.9 cm, ill-defined soft tissue mass in the right parotid, with peripheral enhancement and internal low-density (**Figure 1**). No abnormal lymphadenopathy was noted in the neck. Total excision of the right parotid gland was performed under a diagnosis of a malignant parotid tumor, probably a carcinoma ex pleomorphic adenoma. Frozen section histopathological evaluation showed a malignant tumor with features suggestive of acinic cell carcinoma. The patient's postoperative course was uneventful. He was then lost to follow up.

Gross examination of the surgical specimen demonstrated an ill-defined mass involving the entire parotid gland; the cut section was grayish white and gelatinous. Microscopic examination revealed an unencapsulated neoplasm with infiltrative margins. Variably sized mucin lakes were divided into compartments by the fibrous bands and accounted for approximately two-thirds of the total tumor area, especially in the center (**Figure 2A**). Tumor cells nests and single tumor cells were floating within the mucinous material, resembling mucinous (colloid) adenocarcinoma (**Figure 2B**). In other areas, the tumor was composed primarily of solid nests of pleomorphic cells separated by intervening fibrous stroma, which often had a multinodular architecture with hypercellular peripheral rims and myxoid and necrotic central zones (**Figure 2C**). Most of the tumor cells were signet-ring cells, which demonstrated mucin-filled cytoplasmic vacuoles and displaced indented nuclei (**Figure 2D**). Both intracellular and extracellular mucins were strongly positive for mucicarmine and periodic acid Schiff after diastase staining. In addition, many polygonal tumor cells with abundant eosinophilic, faintly granular cytoplasm were intermixed with the signet ring cells (**Figure 2E**). Some of these tumor cells exhibited a plasmacytoid appearance, with eccentric nuclei and abundant eosinophilic cytoplasm. Tumor cells showed moderate to focally marked cellular pleomorphism with nuclear enlargement, vesicular or coarse chromatin, and variably prominent nucleoli (**Figure 2F**). Mitotic figures were frequently noted (24 mito-
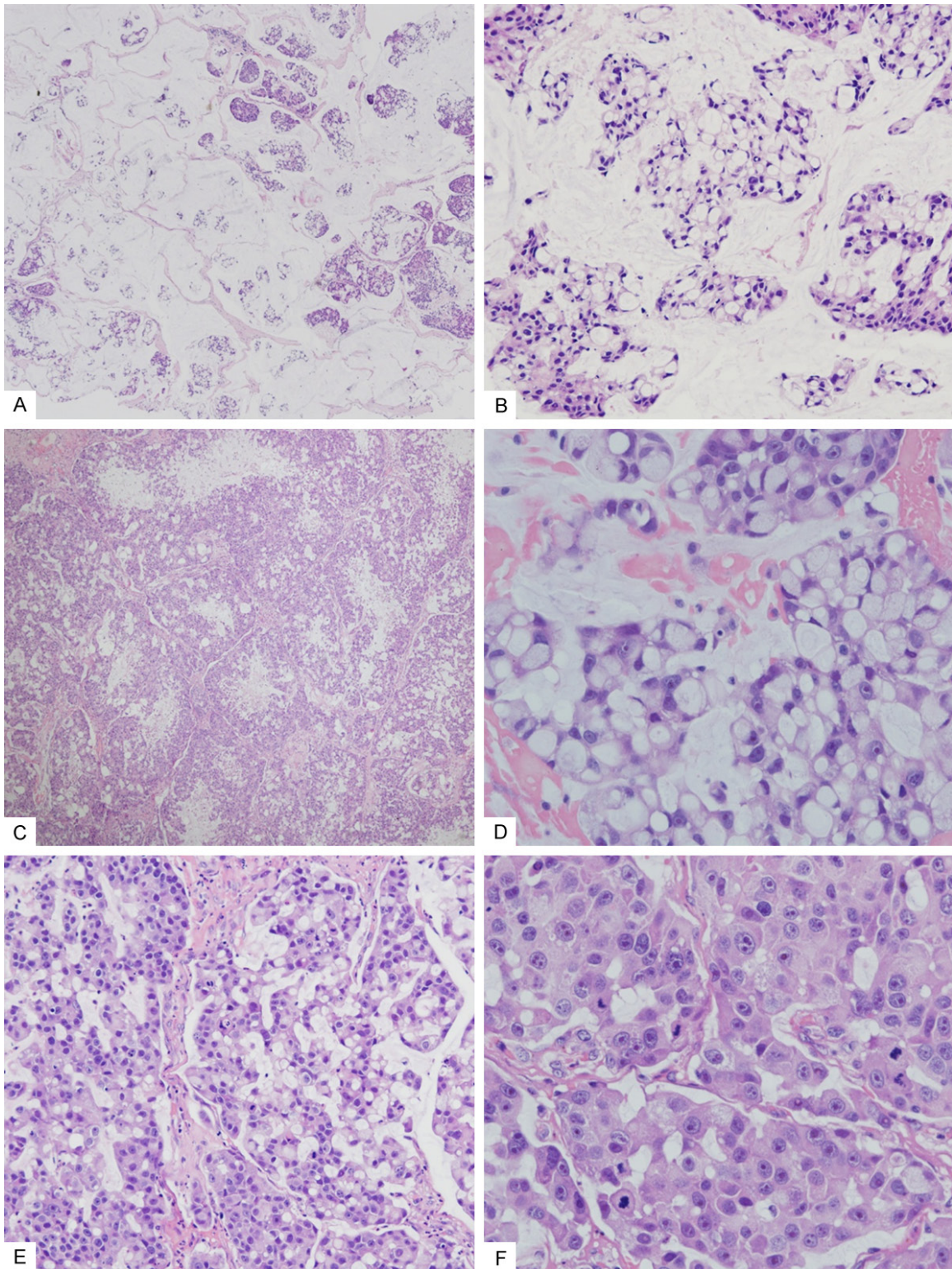
Figure 2. Histopathological findings. A. Mucinous area comprising pools of mucus separated into compartments by fibrous bands. Clusters of tumor cells appear to float within the mucus (hematoxylin-eosin, ×40); B. Cancer cells floated in the pools of mucin, a pattern that mimicked that of mucinous adenocarcinoma (colloid carcinoma). Most of the tumor cells exhibited signet ring morphology (hematoxylin-eosin, ×200); C. Low magnification shows a multi-nodular architecture with hypercellular peripheral rims and myxoid and necrotic central zones (hematoxylin-eosin, ×40); D. High magnification shows typical signet ring cells with intracytoplasmic mucin vacuoles and displaced indented nuclei. (hematoxylin-eosin, ×400); E. Tumor cells with abundant eosinophilic cytoplasm often seen admixed with the signet-ring cells (hematoxylin-eosin, ×200). F. High magnification shows tumors cells with prominent nucleoli and high mitotic index (hematoxylin-eosin, ×400).
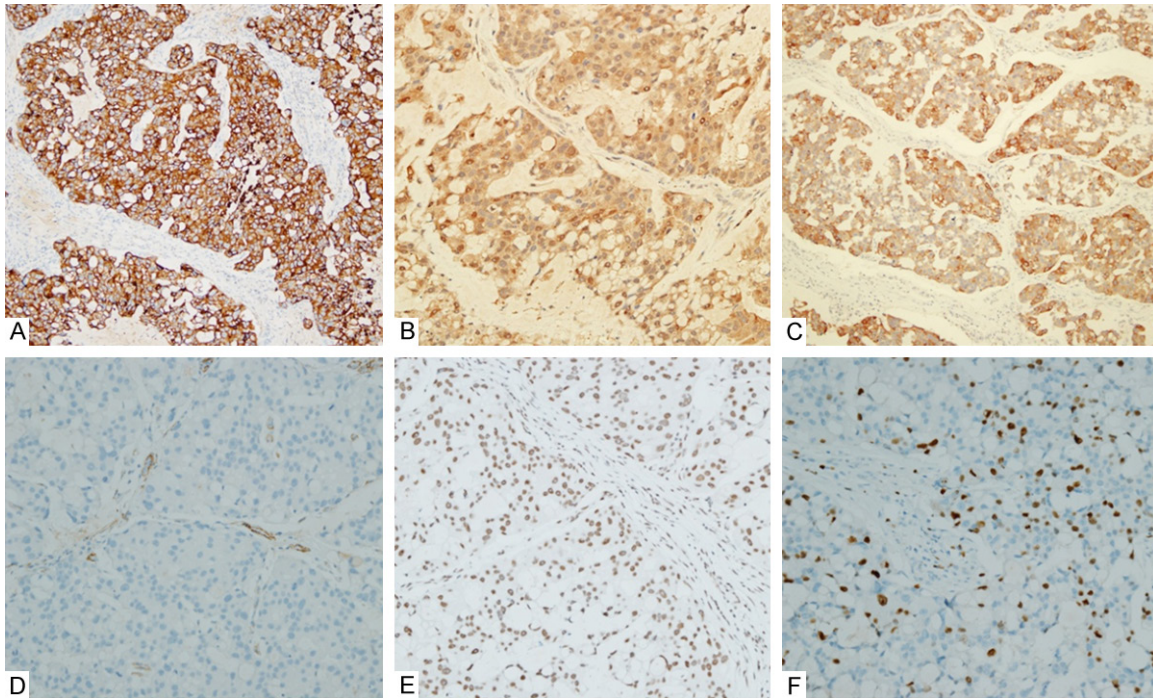
Figure 3. Immunohistochemical findings. A. The tumor cells were diffusely immunoreactivity for CK7 (×100). B. The tumor cells were diffusely immunoreactivity for S100 (×200); C. The tumor cells were diffusely immunoreactivity for mammaglobin (×100); D. The tumor cells were negative for smooth muscle actin (×200). E. The tumor cells showed intact expression of SMARCB1/INI1 (×200). F. Immunoreactivity for Ki-67 was observed in 20% of the tumor cells (×100).

ses/10 high-power fields), and perineural invasion was observed. Focal tubule formation was noted. Immunohistochemically, the tumor cells showed diffuse reactivity for cytokeratin (CK) AE1/AE3, CK7 (**Figure 3A**), CK18, S100 (**Figure 3B**), and mammaglobin (**Figure 3C**), and focal positivity for CK5/6 and CK 34βE12. CK14, CK20, vimentin, p63, p40, HHF-35, smooth muscle actin (**Figure 3D**), calponin, DOG-1, Sox10, and Wilms' tumor 1 gene (WT1) protein were all negative. The tumor cells showed intact expression of SMARCB1/INI1 (**Figure 3E**). The proliferative index (Ki-67) was up to 20% in some tumor regions (**Figure 3F**).

Discussion

Signet-ring cells are characterized by round spaces, inclusions, or substance accumulations occupying the cytoplasms and compressing the nuclei toward the cellular borders. The signet-ring cell appearance can result from different mechanisms, and the content of the vacuoles is variable (e.g. mucin, lipid, or glycogen) [8]. Signet-ring cells are characteristically found in carcinomas of high malignant poten-

tial. The gastrointestinal tract, breast, and lungs are the most common primary sites. Although much less frequently, signet-ring cells have also been reported in single cases of primary salivary gland neoplasms, such as oncocytic cystadenoma, mucinous (colloid) carcinoma, mucinous cystadenocarcinoma, mucin-rich salivary duct carcinoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma [8-11]. Moreover, salivary glands tumors described by name containing signet-ring cells have also rarely been reported. In 2004, Ghannoum and Freedman reported seven cases of a hitherto unknown salivary malignant neoplasm characterized by marked presence of mucin-containing signet ring cells, which they termed signet ring cell (mucin producing) adenocarcinomas of minor salivary glands [12]. Interestingly, a myoepithelial phenotype was implied by immunohistochemistry. Since then, a few similar cases, also including benign signet-ring cell tumors have been reported [5, 13-15]. Recently, these tumors were considered to be a unique subtype of myoepitheliomas, and the term mucinous myoepitheliomas and secretory MCs has been

proposed by Esteva et al. [4] and Bastaki et al. [6], respectively.

To date only 15 cases of MMC, including the present case, have been reported [6, 7, 12-14]. The male to female ratio is 7:8, and the mean age is 58.3 years ranging from 18 to 81 years. 11 cases arose in the minor salivary glands and 4 in the parotid. Tumors ranged in size from 1 to 5.6 cm. Most tumors were treated with surgical excision alone with negative margins. One patient presented with neck metastasis at the time of initial presentation. Seven patients available for follow-up had no evidence of disease with an average follow-up of 33 months.

Histologically, MMC is composed mainly of large mucin containing cells, arranged in solid nests, sheets, cords and trabeculae and embedded in a myxoid stroma. The mucin containing cells often have a signet ring cell appearance with abundant vacuolated clear cytoplasm and displaced indented nuclei. The intracellular mucin can be confirmed by mucicarmine, alcian blue and periodic acid schiff after diastase staining. A mixture of other cell types, including epithelioid or plasmacytoid cells, have been identified [6, 7, 12-14]. The epithelioid cells are polygonal, characterized by eosinophilic cytoplasm and ovoid nuclei. The plasmacytoid cells contain abundant brightly eosinophilic cytoplasm and eccentric nuclei. The tumor cells usually have minimal to moderate cytologic atypia. At present, the histological criteria for discriminating between benign and malignant mucinous myoepitheliomas are not clearly defined. Gnepp proposed that the same histological criteria should be used to evaluate for malignancy as any other myoepithelioma [7].

Immunohistochemistry is almost essential to identify myoepithelial cells and reactivity for CKs and at least one of the other myoepithelial markers, including S100, vimentin, calponin, p63, glial fibrillary acidic protein, CD10, smooth muscle actin, and smooth muscle myosin heavy chains, is required for diagnosis [1]. The immunophenotype of individual cases is highly variable. Therefore, a broad panel of markers typical of the myoepithelial immunoprofile should be used. Of the 15 reported cases of MMC, all stained with cytokeratins (8/8 for pancytokeratin, 11/11 for CAM5.2, and 6/6 for CK7). CK5/6 was focally positive in 3 of 5 tumors, and CK20

was negative for all 6 tumors that were examined. 10 of 12 showed nuclear labeling for p63 (diffuse positive in 8 cases while sparse in 2 cases). 10 of 15 tumors showed positivty for S100 and 5 of 9 tumors showed positivty for glial fibrillary acidic protein. 9 of 14 tumors showed positivty for smooth muscle actin, 7 of 12 tumors showed positivty for HHF-35, and 3 of 12 tumors showed positivty for calponin. Of note, one case reported by Bastaki et al., was negative for all myoepithelial markers tested by immunohistochemistry, but it showed evidence of myoepithelial differentiation on ultrastructural analysis [6].

In terms of frequency, the finding of signet-ring cells in a salivary neoplasm requires always to rule out metastatic adenocarcinoma. A full evaluation failed to identify any concomitant malignancy in our patient. The immunohistochemical study with CK7 and CK20 antibodies is sometimes advocated for the differential diagnosis. Salivary gland neoplasms often show the typical CK7+/CK20- immunophenotype, whereas a conjointly CK7-/CK20+ profile may serve as a clue to an intestinal origin [16, 17]. Histopathological differential diagnosis of MMC also includes those primary mucin-rich adenocarcinomas of salivary glands that may contain signet-ring cells, such as mucinous cystadenocarcinoma, mucin-rich mucoepidermoid carcinoma, mucin-rich salivary duct carcinoma and mucinous (colloid) adenocarcinoma [6, 7, 10, 17]. Mucinous cystadenocarcinoma has characteristic histological features with a mucus-filled cystic space lined by malignant epithelial cells. It is typically more cystic and papillary than MMC and do not stain with myoepithelial markers. Occasionally, mucoepidermoid carcinoma may be associated with prominent pools of acellular or paucicellular mucin and may also contain signet ring cells. However, mucoepidermoid carcinoma is characterized by the presence of squamoid cells, mucinous cells, and intermediate cells. The mucin-rich salivary duct carcinoma is characterized by the presence of a mucinous component that comprises prominent mucinous lakes or pools divided into small compartments by fibrous tissue bands. These mucinous lakes and pools contain floating cancer nests. Thorough histological sampling will reveal areas with the histological appearance of a typical salivary duct carcinoma. Mucinous (colloid) adenocarcinoma is the most likely can-

didate in the differential diagnosis of our case because approximately two-thirds of the tumor consisted of a mucinous area with floating cancer nests. However, the cells in mucinous (colloid) adenocarcinoma are epithelial and present as single cells, cells forming ductlike structures, or solid strands or clusters of cells. Moreover, mucinous (colloid) adenocarcinoma lacks the expression of S100 and other myoepithelial markers. Mammary analogue secretory carcinoma is a recently described new distinctive salivary gland tumor composed of uniform cells with bland-looking vesicular nuclei and eosinophilic vacuolated cytoplasm, arranged in tubular, microcystic and solid growth patterns. Immunohistochemically, mammary analogue secretory carcinomas show diffuse and strong expression of CK7, CK8, CK18, S-100, vimentin, and mammaglobin [18]. The tumor in our case contained abundant signet-ring cells, which are not seen in mammary analogue secretory carcinoma.

In summary, we presented a rare case of MMC of the parotid gland. For pathologists, it is important to recognize this unusual variant of salivary gland-type neoplasm and to avoid confusing it with other primary and metastatic mucin-producing tumors, which require alternative management and have a correspondingly different natural history.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xinming Chen, Department of Pathology, School and Hospital of Stomatology, Wuhan University, 237 Luoyu Road, Wuhan 430079, Hubei, China. Tel: +86-27-87686229; Fax: +86-27-87686375; E-mail: xmchen3011@126.com

References

[1]   Barnes L, Eveson JW, Reichart P. World Health Organization classification of tumors: pathology and genetics of the head and neck tumours. Lyon: IARC Press; 2005.

[2]   Savera AT, Sloman A, Huvos AG and Klimstra DS. Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 patients. Am J Surg Pathol 2000; 24: 761-774.

[3]   Yang S, Li L, Zeng M, Zhu X, Zhang J and Chen X. Myoepithelial carcinoma of intraoral minor salivary glands: a clinicopathological study of 7 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: 85-93.

[4]   Esteva CJ, Slater LJ and Gnepp DR. Mucinous Myoepithelioma, a Previously Unrecognized Variant. Modern Pathology 2012; 25: 308A-308A.

[5]   Bastaki JM, Purgina BM, Dacic S and Seethala RR. Primary Signet-Ring Cell (Mucin-Producing) Adenocarcinoma of Minor Salivary Glands: A Clinicopathologic, Immunohistochemical and Molecular Survey. Modern Pathology 2012; 25: 304A-305A.

[6]   Bastaki JM, Purgina BM, Dacic S and Seethala RR. Secretory myoepithelial carcinoma: a histologic and molecular survey and a proposed nomenclature for mucin producing signet ring tumors. Head Neck Pathol 2014; 8: 250-260.

[7]   Gnepp DR. Mucinous myoepithelioma, a recently described new myoepithelioma variant. Head Neck Pathol 2013; 7 Suppl 1: S85-89.

[8]   Altemani A, Costa AF, Montalli VA, Mosqueda-Taylor A, Paes de Almeida O, Leon JE and Hermsen M. Signet-ring cell change in adenoid cystic carcinoma: a clinicopathological and immunohistochemical study of four cases. Histopathology 2013; 62: 531-542.

[9]   Michal M, Hrabal P and Skalova A. Oncocytic cystadenoma of the parotid gland with prominent signet-ring cell features. Pathol Int 1998; 48: 629-633.

[10]   Yakirevich E, Sabo E, Klorin G, Alos L, Cardesa A, Ellis GL, Shumway BS and Gnepp DR. Primary mucin-producing tumours of the salivary glands: a clinicopathological and morphometric study. Histopathology 2013; 57: 395-409.

[11]   Kusafuka K, Maeda M, Honda M and Nakajima T. Mucin-rich salivary duct carcinoma with signet-ring cell feature ex pleomorphic adenoma of the submandibular gland: a case report of an unusual histology with immunohistochemical analysis and review of the literature. Med Mol Morphol 2012; 45: 45-52.

[12]   Ghannoum JE and Freedman PD. Signet-ring cell (mucin-producing) adenocarcinomas of minor salivary glands. Am J Surg Pathol 2004; 28: 89-93.

[13]   Bastaki J and Summersgill K. Signet-ring cell (mucin-producing) adenocarcinoma of minor salivary glands: report of a case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: e33-36.

[14]   Singh M, Khurana N, Wadhwa R and Gulati A. Signet ring carcinoma parotid gland: a case report. Head Neck 2011; 33: 1656-1659.

[15]   Foschini MP, Baldovini C, Pennesi MG, Cocchi R and Simpson RH. Signet ring cell tumor of the minor salivary gland exhibiting benign behavior. Hum Pathol 2012; 43: 303-306.

[16] Meer S and Altini M. CK7+/CK20- immunoexpression profile is typical of salivary gland neoplasia. Histopathology 2007; 51: 26-32.

[17] Ide F, Mishima K, Tanaka A, Saito I and Kusama K. Mucinous adenocarcinoma of minor salivary glands: a high-grade malignancy prone to lymph node metastasis. Virchows Arch 2009; 454: 55-60.

[18] Bishop JA. Unmasking MASC: bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head Neck Pathol 2013; 7: 35-39.