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Case Report

A Cribriform Cancer Metastatic to Liver: Case Report and Literature Review

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Keywords
Liver metastasis · Malignancy · Mammary analogue secretory carcinoma · Parotid gland tumor · Tyrosine-kinase inhibitor

Abstract
Metastasis from salivary gland tumors to liver is exceedingly uncommon. Reported is the first case of a mammary analog secretory carcinoma (MASC) of salivary gland origin metastasized to the liver, even after complete surgical resection. A 76 year old female, with past history of a completely extirpated right parotid gland MASC, presented 2 years after right superficial parotidectomy and right neck dissection, with back and flank pain. Subsequent abdominal and pelvic CT revealed multiple small hepatic lesions. Biopsy of the largest hepatic lesion confirmed metastatic MASC of primary parotid gland origin. Both the parotid primary and the hepatic metastases had the confirmatory ETV6 rearrangement by fluorescence in situ hybridization. Although high-grade malignancy and distant metastases of MASC of salivary gland origin to liver is rare, recognizing metastatic MASC potentially alters prognosis and determines therapeutic options.

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Introduction

Mammary analog secretory carcinoma (MASC) is a rare primary salivary gland tumor, first described in 2010. MASC exhibits analogous features to secretory carcinoma of the breast, including the presence of a t(12;15) translocation resulting in the *ETV6-NTRK3* gene fusion. MASC is a low grade malignancy and infrequently reoccurs or metastasizes after complete surgical removal. To our knowledge, this is the first case of MASC of salivary gland metastasized to the liver, even after complete surgical resection of the primary tumor.

Case Report/Case Presentation

76-year-old Caucasian female presented with a right parotid tumor that had grown significantly in last 5 years. She was otherwise in good health with no significant complaints. She underwent a CT scan and fine needle aspiration which showed low grade carcinoma with tubular and cribriform pattern and eosinophilic colloid-like material. Right superficial parotidectomy with right neck dissection was performed. The resected primary tumor showed mammaglobin and S100 protein positivity as well as ETV6 rearrangement by fluorescence in situ hybridization consistent with right parotid mammary analogue secretory carcinoma (Fig. 1). Margins were negative, no lympho-vascular invasion was found and there was no nodal metastasis.

She was doing well after surgery for about 2 years, when she developed back and left flank pain. For further evaluation, she had a CT of the abdomen and pelvis which revealed multiple small hepatic lesions especially in the left lobe with largest measuring about 5.4 cm (Fig. 2). Needle biopsy of the largest hepatic lesion was performed. Histopathology confirmed an identical appearing carcinoma to that of the right parotid gland (Fig. 3), including a cribriform pattern with eosinophilic proteinaceous secretions or colloid-like material in the center of cystic spaces. The metastatic carcinoma was also mammaglobin and S100 protein positive (Fig. 4, 5) and FISH positive for the ETV6 rearrangement. Additional ancillary immunohistochemical stains showed focal positivity for ER, HBME1, BRST2 (gross cystic disease fluid protein), and TTF1 was negative, helping to further confirm the diagnosis of metastatic mammary analogue secretory carcinoma of liver from the parotid gland.

Discussion/Conclusion

Mammary analog secretory carcinoma (MASC) of salivary glands has been accepted in the recent literature as a new neoplastic entity. It is a rare salivary gland tumor that recapitulates the cytomorphology, immunophenotype and genetics of an equally rare malignancy of the breast known as secretory carcinoma [1]. It is a distinctive low- grade malignant salivary cancer that harbors a characteristic chromosomal translocation, t(12;15) (p13; q25) resulting in an *ETV6–NTRK3* fusion [2]. The fusion gene encodes a chimeric tyrosine kinase, which has potential transformation activity, and plays a major role in carcinogenesis. It was first reported by Skalova et al in 2010. They reviewed the pathology of 16 salivary gland tumor cases previously classified as either acinar cell carcinoma (AciCC) or adenocarcinoma, not otherwise specified (ADC-NOS). It was noted that histological features-in particular the absence of zymogen granules, strong staining for mammaglobin, and the presence of abundant extracellular colloid-like material prevented easy classification by the existing pathological definitions

of known salivary gland tumors. After noting features similar to SC of the breast, the *ETV6-NTRK3* translocation was detected in 15 of these cases by fluorescence in situ hybridization [3].

Recently, primary cutaneous tumors resembling secretory carcinoma of salivary gland and breast have been described [4]. One study has shown MASA in lung which presented with advanced-stage disease that included visceral pleural invasion and lymph node metastasis [5]. About 8 cases of MSAC like features in thyroid gland have been reported [6]. A case of MASC presenting as a cervical lymph node metastasis of unknown primary site together is reported [7]. To our knowledge, this is the first case of salivary gland MSAC with metastases to the liver reported so far in the English literature.

Most cases of MASC that has been described are low-grade carcinoma with overall favorable prognosis. In rare cases, however, MASC with high-grade transformation have the potential for regional and distant metastasis [2]. The clinical behavior of MASC ranges from slowly growing tumors that infrequently recur after surgical resection, to aggressive tumors that cause widespread metastasis and death. According to a review by Sethi et al., of the 91 reported cases of MASC, only 4 cases of death from disease have been reported, although survival data were variably reported and follow-up was minimal [8].

The differential diagnosis of MASC includes AciCC and ADC-NOS. There are considerable overlapping histological features between AciCC and MASC, as both exhibit acinar differentiation and intercalated duct-type cells, but MASA show a multivacuolated eosinophilic cytoplasm, often with luminal and intracytoplasmic mucin. A major point of distinction is the presence of PAS-positive cytoplasmic zymogen granules, which are observed in AciCC. Both secretory carcinoma and acinic cell carcinoma may show PAS positivity after diastase digestion, but the pattern in secretory carcinoma is globular (indicative of mucin) while that in acinic cell carcinoma is granular. In addition, MASC characteristically shows positive staining for S100 protein and mammaglobin whereas DOG1 stain is positive in the majority of cases of AciCC [1]. MASC may also express GATA3, pancytokeratin, CK7, CK8, CK18, CK19, epithelial membrane antigen, vimentin, MUC1, MUC4, STAT5a, GCDFP15, and adipophilin. MASC is typically negative for high-molecular-weight keratin and basal cell/myoepithelial markers, such as calponin, SMA, CK5, CK6, CK14, and p63. The defining cytogenetic characteristic of MASC is the presence of the t(12;15)(q13;q25) *ETV6-NTRK3* translocation, demonstrated by either FISH or PCR [9].

Although high-grade malignancy and distant metastases were rarely reported, careful attention should be paid both to the nature of this tumor, and to the indicated close follow-up of such cases, especially when necrosis, increased mitotic activity, and other classic caveats are conspicuous. In the review by Sethi et al., the treatment modalities mentioned in the literature included details for 86 patients: 26% of the patients underwent neck dissections, and 20% were given postoperative radiotherapy (PORT), while 2% received PORT with chemotherapy [8]. In the case of MASC presenting as a cervical lymph node metastasis of unknown primary, a complete resection was performed with no adjuvant therapy, and no local recurrence or metastatic disease was detected during a follow-up period of 9 months [7]. Entrectinib, a potent oral inhibitor of the tyrosine kinases (TKI) was evaluated in two Phase trial. A response was noted in patients with mammary analog secretory carcinoma, as early as 4 weeks after starting treatment and lasting as long as >2 year. In one of the case reports, a mutation was identified in the M2b tumor, correlating to the development of entrectinib resistance [10]. Our patient has been enrolled in a clinical trial with Larotrectinib – a new TKI targeted drug. Hence, MASC has a capacity for an aggressive course, and the *ETV6-NTRK3* translocation might

provide a potential therapeutic target. Further investigation is needed to translate targeted molecular therapies into therapeutic options for salivary grand malignancies including MASC.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The patient passed away, so consent could not be obtained.

Disclosure Statement

We declare that there is no conflict of interests. The authors have no personal or financial disclosure.

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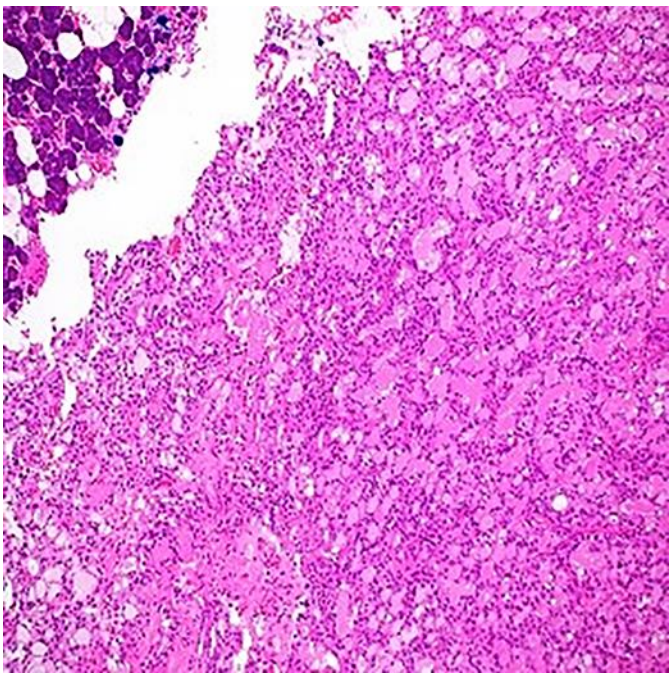

Fig. 1. Primary parotid MASC showing a cribriform architecture with eosinophilic luminal secretions, center and right, with normal parotid gland in the upper left at 40 magnification (H&E 40×).

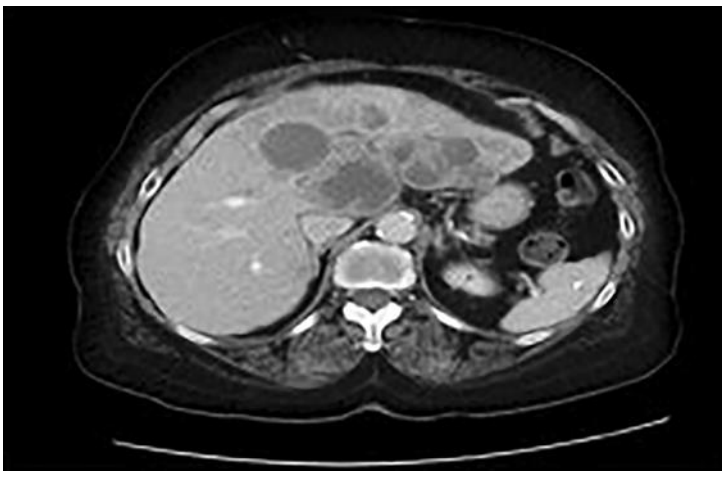

Fig. 2. Abdominal CT showing multiple hepatic lesions.

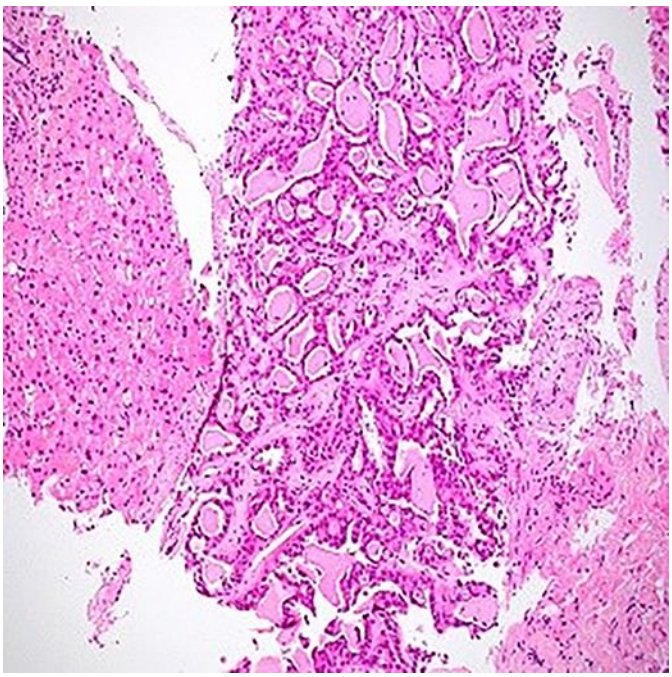

Fig. 3. Fragmented needle core liver biopsy showing metastatic MASC identical to parotid primary at 100 magnification (H&E 10×).

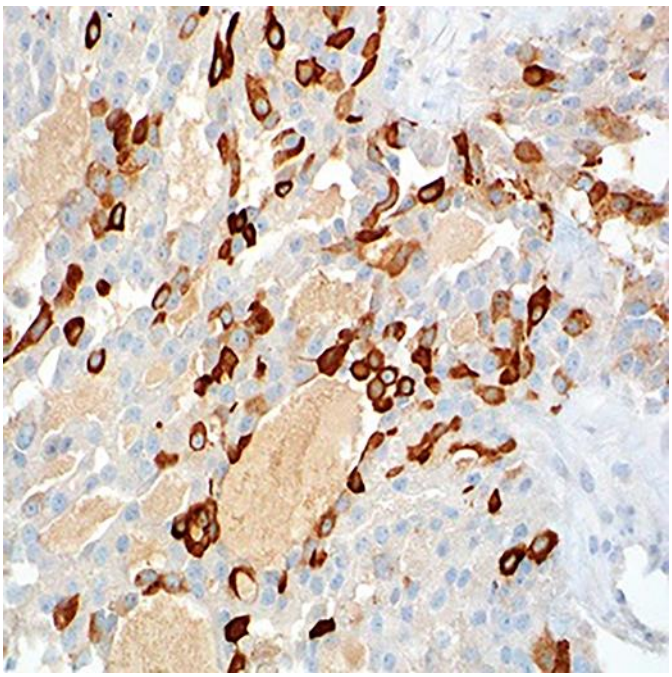

Fig. 4. Metastatic MASC to liver with mammaglobin positivity at 400 magnification (40×).

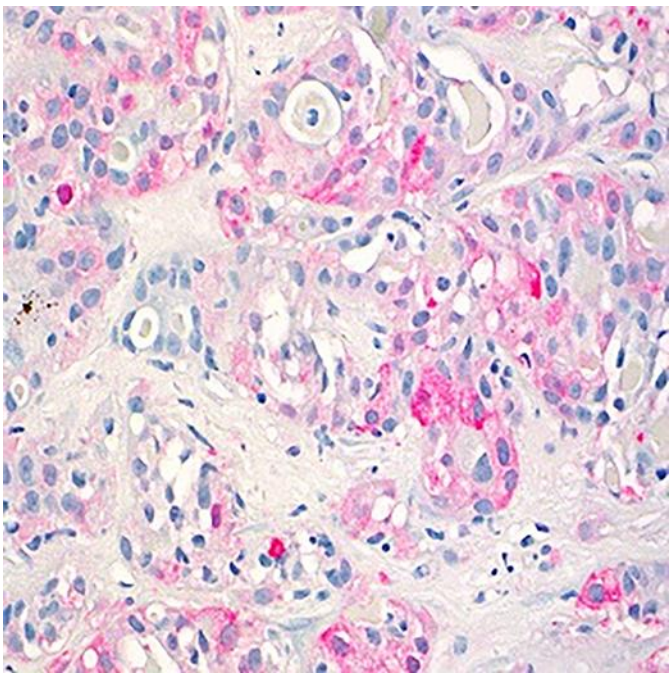

Fig. 5. Metastatic MASC to liver with S100 protein positivity at 400 magnification (40×).