

Case Report

Mammary Analogue Secretory Carcinoma Presenting as a Cervical Lymph Node Metastasis of Unknown Primary Site: A Case Report

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Keywords

Salivary gland carcinoma · Mammary analogue secretory carcinoma · Cervical lymph node metastasis · Unknown primary site

Abstract

Background: Mammary analogue secretory carcinoma (MASC) is a pathological entity arising in the salivary glands first described by Skalova et al. [Am J Surg Pathol 2010;34:599–608]. Here, we report the first case of MASC presenting as a cervical lymph node metastasis of unknown primary site together with a brief review of the literature. **Case Report:** We present a 74-year-old male with a painless lump in his left neck. Based on the fine-needle aspiration cytological findings, a possible malignant tumor was suspected. No evidence of a primary lesion was observed using imaging modalities including positron emission tomography/computed tomography. The patient underwent an ipsilateral modified radical neck dissection. Immunohistochemical staining showed that the neoplastic cells were positive for S100 protein and GATA3. A rearrangement of the ETV6 gene was noted during fluorescence in situ hybridization, and the final histopathological diagnosis was MASC. **Conclusion:** We encountered a MASC presenting as a cervical lymph node metastasis of unknown primary site. No adjuvant therapy was administered, and no local recurrence or metastatic disease

has been detected during a follow-up period of 9 months. This is the first case report of MASC presenting as a cervical lymph node metastasis of unknown primary site and suggests the new properties of MASC.

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Introduction

Mammary analogue secretory carcinoma (MASC) is a recently described pathological entity arising in the salivary glands. In 2010, Skalova et al. [1] reported a case series comprising 16 cases of this salivary gland tumor showing identical histological as well as molecular features to breast secretory carcinoma. MASC harbors the recurrent translocation t(12;15)(p13;q25) resulting in ETV6-NTRK3 gene fusion. The fusion gene encodes a chimeric tyrosine kinase, which has potential transformation activity and plays a major role in carcinogenesis [2, 3].

Histopathologically, MASC is a distinctive entity, and histology in combination with appropriate immunohistochemical analysis is sufficient for a diagnosis in most cases. However, several histopathological features of MASC overlap with those of other salivary gland tumors, such as acinic cell carcinoma (AcicC), adenocarcinoma not otherwise specified (ADC-NOS), and low-grade mucoepidermoid carcinoma [1, 2, 4].

In the first reported case series by Skalova et al. [1], most tumors (13/16 cases) arose in the parotid gland with 3 cases originating in the minor salivary glands. Since that seminal paper, some retrospective studies and case reports have been published [5–8]. MASC arose in the parotid gland in the majority of cases, followed by the submandibular gland and the oral cavity (soft palate, buccal mucosa, and lip) [2, 8–10]. In this paper, we present the first reported case of MASC presenting as a cervical lymph node metastasis of unknown primary site together with a brief review of the literature and discussion of possible appropriate treatments.

Case Presentation

A 74-year-old male presented with a 2-month history of a painless lump in the left neck. He had no other associated symptoms. He had a past medical history of hypertension, and his family history was not significant. On physical examination there was a 2 × 2 cm firm swelling present in the left upper neck, the mobility of which was slightly restricted. There was no identifiable primary lesion. Sonograms showed that the mass was hypoechoic, 16 × 14 × 20 mm in size, and with a relatively regular border. Back echoes were enhanced, and internal echoes were dissimilar (Fig. 1a, b). Computed tomography showed an enhanced lesion in the left upper neck in contact with the carotid bifurcation and the jugular vein (Fig. 1c). Based on the fine needle aspiration cytological findings, a possible malignant tumor, such as epithelial-myoeplithelial carcinoma or basal cell adenocarcinoma, was suspected, but no definitive diagnosis was given. Positron emission tomography/computed tomography (PET-CT) revealed FDG avidity in the left-sided neck at a level II lymph node, the size of which was 21 × 16 mm. There was no evidence of a primary lesion, including the parotid and submandibular glands, on PET-CT (Fig. 1d). Further, no tumorous lesions were detected in the mammary gland on PET-CT. Therefore, with a provisional diagnosis of suspected cancer of unknown primary site, he underwent left modified radical neck dissection. Intraoperatively, the level II lymph node invaded the internal jugular vein and superior thyroid artery, and

these vessels were sacrificed. The parotid and submandibular glands were not involved. Poorly differentiated adenocarcinoma was suspected on the basis of an intraoperative frozen section. No random biopsy was performed as there was no possibility that it was a squamous cell carcinoma.

The gross resected specimen was yellow-white in color and formed lobular nodules (Fig. 2a). Histopathological examination revealed a metastatic tumor in the left-sided neck at a level II lymph node. The tumor consisted of tubular structures containing secretion, papillary-cystic structures, and a solid proliferative component (Fig. 2b). The papillary-cystic lesion showed many microcystic structures in the component cells (Fig. 2c). These morphologic findings suggested AcicC or MASC. Immunohistochemical staining showed that the neoplastic cells were negative for p63 and DOG1 (Fig. 3a) but were positive for S100 protein (Fig. 3b) and GATA3 (Fig. 3c). A fluorescence in situ hybridization (FISH) study with an ETV6 (12p13) break apart probe revealed split signals in 95% of the nuclei (Fig. 3d). The final histopathological diagnosis was MASC. No other pathologically positive nodes were detected at other levels in the neck, and there was no tumor in the submandibular gland. We, therefore, made the final diagnosis of a cervical lymph node metastasis of MASC from an unknown primary site. No adjuvant therapy was administered as our case showed solitary lymph node metastasis and complete resection was achieved. No local recurrence or metastatic disease has been detected during a follow-up of 9 months.

Discussion

From the literature, MASC involves the parotid gland in about 70% of cases, the submandibular gland in about 7% of cases, and other sites, such as the soft palate, buccal mucosa, base of the tongue, and lip, less commonly [2, 8–10]. The tumor presented herein is the first documented case of MASC presenting as a cervical lymph node metastasis of unknown primary site.

The salient histologic features of MASC include solid, microcystic, tubular, and papillary-cystic patterns in varying proportions [8, 10–12], and these findings were displayed by the tumor presented herein. In addition, intraluminal and/or intracellular colloid-like secretions that react positively with periodic acid-Schiff (PAS) are often observed histologically in MASC [6, 8, 13]. Immunohistochemically, MASC characteristically shows positive staining for S100 protein and mammaglobin [1, 10]. MASC may also express GATA3, pancytokeratin, CK7, CK8, CK18, CK19, epithelial membrane antigen, vimentin, MUC1, MUC4, STAT5a, GCDPF15, and adipophilin [1, 10]. MASC is typically negative for high-molecular-weight keratin and basal cell/myoepithelial markers, such as calponin, SMA, CK5, CK6, CK14, and p63 [4, 10].

The differential diagnosis of MASC includes AcicC and ADC-NOS. Chiosea et al. [12] reviewed 337 cases of salivary gland malignancy diagnosed at their institution. The most common malignancy reclassified as MASC was ADC-NOS (14/37), followed by AcicC (11/89) [12]. There are considerable overlapping histological features between AcicC and MASC, as both exhibit acinar differentiation and intercalated duct-type cells. A major point of distinction is the presence of PAS-positive cytoplasmic zymogen granules, which are observed in AcicC [8, 12]. In addition, MASC stains more reliably for S100 protein, and AcicC is not positive for mammaglobin [8], whereas DOG1 stain is positive in the majority of cases of AcicC [6, 10]. Similar to those in previous reports, our case displayed positive staining for S100 protein and GATA3 but negative staining for p63 and DOG1.

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 [1, 8, 11]. We performed a FISH study with an ETV6 break apart probe for molecular genetic analysis and revealed split signals in 95% of the nuclei. In the study by Skalova et al. [1], all but one of the examined cases (13/14) were positive for the t(12;15) (ETV6-NTRK3) fusion transcript, and all examined cases (11/11) were positive for ETV6 gene rearrangement on FISH. Recently, Skalova et al. [14] reported that, in some cases of MASC whose profile was NTRK3 split-negative and ETV6 split-positive, unknown (non-NTRK) genes appeared to fuse with ETV6 (ETV6-X fusion).

According to the review by Sethi et al. [8], 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. MASC is currently treated as a low-grade carcinoma with an overall favorable prognosis. However, some cases of MASC have the potential for regional and distant metastasis [2]. Some authors reported that the risk for regional lymph node metastasis at diagnosis may also be higher in patients with MASC than in patients with AcicC [2, 8].

To date, there is no conclusive evidence that MASC should be treated any differently to other low-grade malignant salivary gland cancers [8]. In the review by Sethi et al. [8], 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. As our case showed a solitary regional metastasis without a detectable primary lesion and complete resection was achieved, we did not choose PORT and adjuvant chemotherapy. Fortunately, the patient presented herein has been free from disease for 9 months.

To our knowledge, this is the first case report of MASC presenting as a cervical lymph node metastasis of unknown primary site and suggests new properties of MASC. As previously described, MASC has a capacity for an aggressive course, and the ETV6-NTRK3 translocation might provide a potential therapeutic target [2, 15]. Further investigation is needed to translate targeted molecular therapies into therapeutic options for salivary gland malignancies including MASC.

Conclusions

We encountered the first case of MASC presenting as a cervical lymph node metastasis of unknown primary site. No adjuvant radiotherapy was administered, and no local recurrence or metastatic disease has been detected during the 9-month follow-up period. MASC has the potential for metastasis; therefore, careful observation is important.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure Statement

None of the authors have any conflicts of interest to declare in association with this study.

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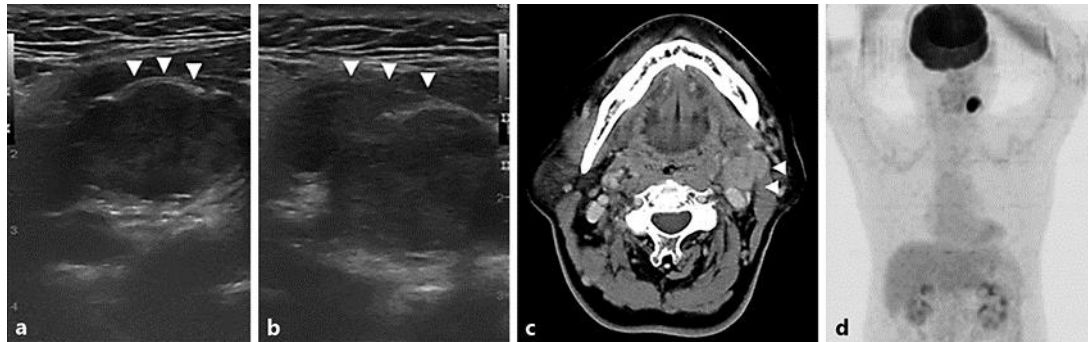


Fig. 1. Sonograms of the left neck in the transversal (**a**) and longitudinal (**b**) planes showing a hypoechoic mass. The mass (arrowheads) showed a relatively regular border, enhanced back echoes, and dissimilar internal echoes. **c** Computed tomography showing an enhanced lesion (arrowheads) in the left upper neck in contact with the carotid bifurcation and the jugular vein. **d** Positron emission tomography/computed tomography (PET-CT) revealed FDG avidity in the left-sided neck at a level II lymph node. There was no evidence of a primary lesion including the parotid and submandibular glands on PET-CT.

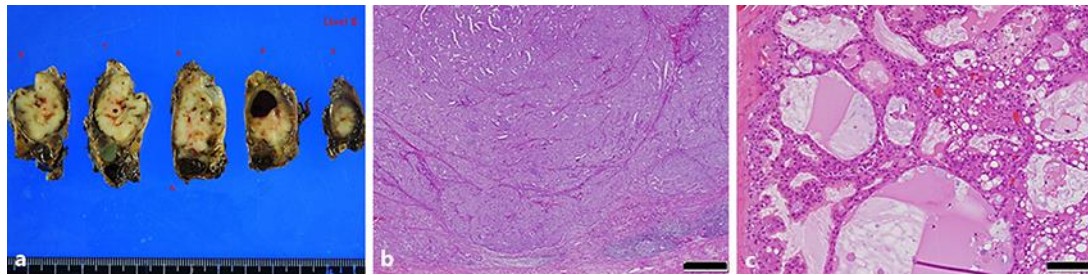


Fig. 2. **a** The gross resected specimen was yellow-white in color and formed lobular nodules involving a level II lymph node in the left-sided neck. **b, c** HE staining of the tumor revealed various cell populations, including a solid proliferative component (**b**) and tubular and papillary-cystic structures (**c**). The papillary-cystic lesion (**c**) included many microcystic structures in the component cells. Scale bars, 500 μ m (**b**); 100 μ m (**c**).

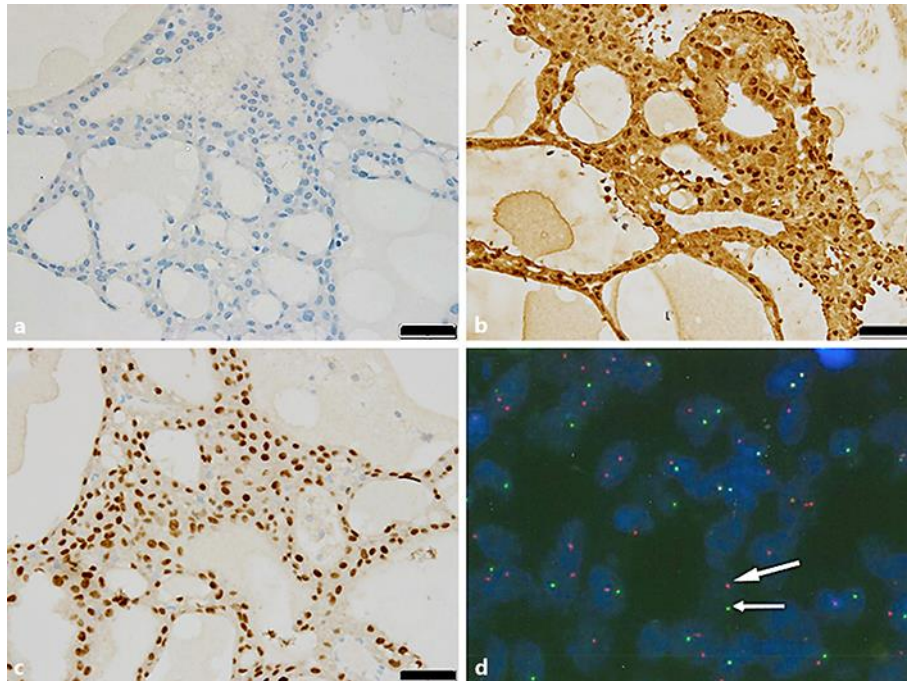


Fig. 3. **a–c** Immunohistochemical staining showed that the neoplastic cells were negative for DOG1 (**a**) but positive for S100 protein (**b**) and GATA3 (**c**). Scale bars, 50 μ m (**a–c**). **d** A fluorescence in situ hybridization study with an ETV6 (12p13) break apart probe revealed green (small arrow) and red split signals (large arrow), indicating a break in the ETV6 gene.