Case report

Mammary analogue secretory carcinoma presenting with cervical lymphadenopathy: A rare case report with review of the literature

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ABSTRACT

Introduction: Mammary analogue secretory carcinoma is a rare malignant tumor of the salivary glands that typically involves the major glands. The aim of the current study is to report a rare case of mammary analogue secretory carcinoma that presented with left cervical lymphadenopathy.

Case report: A 59-year-old lady presented with left cervical lymphadenopathy. Tissue biopsy and immunohistochemistry revealed metastatic carcinoma, favoring ovarian origin. Staging workup was performed and, ultimately, the patient was treated as having a carcinoma of unknown primary. After showing partial response to therapy, left side neck dissection was performed. Based on better assessment of the histologic picture and a broader panel of immunohistochemistry performed on the excision specimen, the final diagnosis was that of mammary analogue secretory carcinoma.

Discussion: Mammary analogue secretory carcinoma is usually an indolent salivary gland carcinoma, with the majority of patients presenting with a slow-growing, painless mass measuring approximately 2 cm in size, and a reported duration ranging from 2 months to several years. In certain cases, pain and facial paralysis have been reported. It could also be found incidentally during radiologic assessment for thyroid illness or routine dental screening.

Conclusion: Diagnosing mammary analogue secretory carcinoma is challenging, and this should be in the differential diagnosis list of metastatic carcinomas to cervical lymph nodes.

1. Introduction

Mammary analogue secretory carcinoma (MASC) is a rare malignant salivary gland neoplasm that predominantly affects the parotid gland, followed in frequency by the submandibular gland and other minor salivary glands [1]. MASC was first reported in 2010 by Skalova et al. After reassessing 16 salivary gland tumors with these features, it was discovered that they had similar histological and molecular characteristics to secretory carcinoma of the breast [2]. The repeated balanced chromosomal translocation t(12;15)(p13;q25), which results from fusion of the ETS Variant Transcription Factor 6 (ETV6) gene on chromosome 12 and the Neurotrophic Receptor Tyrosine Kinase 3 (NTRK3) gene on chromosome 15, has been associated with both MASC and secretory breast carcinomas. The fusion gene creates a chimeric tyrosine kinase which has potential transformation activity and plays a role in carcinogenesis [3]. MASC has been included in the World Health Organization’s (WHO) Classification of Head and Neck Tumors since 2017 [4]. MASC is a very rare subtype of salivary gland malignancy. Major salivary glands, primarily the parotid gland, are involved in 70% of cases of MASC, while small salivary glands account are involved in less than a quarter of cases [3].

The aim of the current study is to report a rare case of MASC that presented with left cervical adenopathy. The report has been written in line with SCARE 2020 guidelines [5].

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2. Case report

2.1. Patient's information

A 59-year-old lady presented with a painless, slowly enlarging left-sided neck mass for a duration of 6 months. She had history of hypertension and thyroid disease. Past surgical history was negative.

2.2. Clinical examination

There was an ill-defined non tender swelling in the left side of the neck near the tail of parotid gland. The thyroid gland was found to be mildly enlarged.

2.3. Diagnostic assessment

Ultrasound (US), computed tomography (CT) scan, magnetic resonance imaging (MRI), and \(^{18}\)F-fluorodeoxyglucose (FDG) PET/CT were performed. The PET/CT showed two FDG-avid lymph nodes in the superficial part of the left parotid gland with a maximum standardized uptake value (SUVmax) of 5.44, with the larger node having a maximum diameter of 1.0 cm. There were also multiple FDG-avid lymph nodes in the left side of the neck involving level IB, level II, level III, and level IV, extending up to the thoracic inlet, with maximum SUVs ranging up to 16.5 and maximum diameters of up to 2.1 cm. Multinodular thyroid gland was also seen (TIRAD III); however, on biopsy this proved to be thyroiditis. There was no other FDG-avid lesion in the rest of the body to suggest a primary neoplastic lesion of origin.

A core needle biopsy from the neck mass was taken. The histologic picture was consistent with a poorly differentiated metastatic carcinoma (Fig. 1). Immunohistochemistry (IHC) revealed strong reactivity of the malignant cells for cytokeratin 7 and CA 125 (Fig. 2) as well as focal reactivity for CA 19-9. The tumor cells were negative for p40, cytokeratin 20, napsin A, TTF-1, and thyroglobulin. The patient was diagnosed with metastatic carcinoma, poorly differentiated (high-grade), most likely from an ovarian primary. Serum tumor marker levels showed an elevated level of CA-125 at 172 while the other markers (carcinoembryonic antigen (CEA), CA-15-3, CA-19-9, thyroglobulin, and antithyroglobulin antibody) were all within normal limits.

Subsequently, bilateral breast mammograms, pelvic MRI, and upper aerodigestive tract endoscopy were performed, and all were negative. The patient was then discussed at an oncology board, and based on the result of the pathology report, immune findings, and tumor markers, it was decided that the patient should be treated as a case of carcinoma of unknown primary (CUP). She received 4 cycles of carboplatin and paclitaxel. After the 4th cycle, a follow-up CT scan was performed and this showed partial response to systemic therapy. The patient developed coronavirus disease 2019 (COVID-19) and was lost to follow-up for 2 months. When she returned to the clinic, she received 4 additional cycles of carboplatin and paclitaxel. About 3 weeks post-chemotherapy, a new PET/CT was performed. This redemonstrated FDG-avid lymph nodes at levels IB, II, III, IV, and V which extended into the thoracic inlet, with SUVs ranging from 5.8 to 16.5. The size of the largest lymph node had decreased from 2.1 cm to 1.4 cm in the largest (AP) dimension. There were again two avid areas in the left parotid gland, with a reduced SUV of 3.94 compared to the previous value of 5.44. No other FDG-avid lesions were seen in the neck or the rest of the body to suggest a primary neoplastic lesion.

2.4. Therapeutic intervention

After further discussion at the multidisciplinary oncology board, the patient was treated with a left parotidectomy in addition to unilateral left neck lymph node dissection (the procedure was performed by the last author). The lymph node dissection included levels I-IV with a yield of 52 lymph nodes, with level I, II-III, and IV containing 4, 33, and 15 lymph nodes, respectively. The largest lymph node measured 31 mm in largest dimension. All the lymph nodes were involved by metastatic high-grade carcinoma, with extracapsular extension being present in nearly all of them. Microscopic examination of the left parotidectomy specimen showed normal salivary gland architecture with multiple malignant foci (Fig. 3), the largest measuring 9 mm (Fig. 4) and the other two each measuring 1 mm in greatest dimension. Two out of three intra-parotid lymph nodes showed metastatic carcinoma. The tumor cells exhibited large, pleomorphic, vesicular nuclei; prominent, eosinophilic nucleoli; and abundant cytoplasm that was eosinophilic rather than clear or vacuolated in the majority of the cells. The tumor cells were arranged in solid sheets with occasional pseudocircular arrangement. There were many multinucleated tumor giant cells, atypical mitotic figures and multifocal extensive necrosis. A broader panel of IHC staining was performed which showed strong reactivity for S100 protein as well as CK7, mammaglobin and GATA3 (Fig. 5). Cytokeratin 20, CD56, PAX8, synaptophysin, estrogen receptor, and HER2 staining were all negative. Based on these findings, it was deemed that the features were compatible with secretory carcinoma of the primary parotid gland, also known as MASC. The pathological stage was IVB (T1, N3b, M0).

2.5. Follow up

Weekly radiation and chemotherapy (cisplatin) were administered to the patient. She has developed high tolerance to the drug. The patient is doing well four months after therapy and is disease-free.

3. Discussion

Mammary analogue secretory carcinoma (MASC) is a novel entity in the differential diagnosis of salivary gland malignancies [6]. MASC is found almost equally in both sexes [6]. However, Sethi et al. reported a
higher frequency in males compared to females [7]. Patients with MASC often present in their fourth or fifth decade of life. Although the tumor is exceedingly rare in children and teens, a few cases have been reported in these age groups [8,9].

MASC is usually an indolent salivary gland carcinoma, with the majority of patients presenting with a slow-growing, painless mass measuring approximately 2 cm in size and a reported duration ranging from 2 months to several years. In certain cases, pain and facial paralysis have been reported [7]. MASC could also be found incidentally during radiologic assessment for thyroid illness or routine dental screening.

Fig. 2. Immunohistochemistry showing positive staining for CK7 (left) and CA-125 (right).

Fig. 3. Two malignant foci, each measuring 1 mm in greatest dimension, in the left parotid gland specimen.

Fig. 4. A 9-mm focus of malignancy in the left parotid gland specimen.
The current case presented with a painless, slowly enlarging left-sided neck mass of 6 months' duration. Although it is most commonly found in the salivary glands, it can also be found in the soft palate, buccal mucosa, base of the tongue, and lip [11]. Various imaging modalities, including US, CT, and MRI, have been utilized in numerous case reports. MASC is hypoechoic on US but hyperintense on T1 phase MRI [6]. The PET/CT of the current case revealed two FDG-avid lymph nodes in the superficial area of the left parotid gland with an SUVmax of 5.44 and a maximum diameter of 1.0 cm. There were also several FDG-avid lymph nodes in the left side of the neck involving levels IB, II, III, and IV and extending up to the thoracic inlet with maximal SUVs ranging up to 16.5 and maximum diameters of up to 2.1 cm.

A definitive preoperative diagnosis of MASC is difficult due to the uncertain pathophysiology and a lack of distinct clinical and/or imaging characteristics [12]. MASC is a lipid-rich tumor containing large lipid droplets enclosed by adipophilin or adipocyte differentiation-related protein, suggesting that MASC may have lactation-like properties [13]. Cytologic features are similar to the histologic findings and include moderately cellular sheets of S100-positive cells arranged in papillary, cystic, tubular, and solid growth configurations [3,14,15]. Several histologic features of MASC are shared with those of other salivary gland malignancies, such as acinic cell carcinoma, adenocarcinoma not otherwise defined, and low-grade mucoepidermoid carcinoma [12]. As a result, accurate and comprehensive immunohistochemistry (IHC) will assist in distinguishing MASC from other primary salivary gland malignancies. According to Khurram et al., the IHC technique may properly detect MASC tumors and differentiate them from acinic cell carcinomas, which closely resemble MASC [16]. MASC is immunoreactive for S100 (70% of the time) and these markers are rarely positive in acinic cell carcinoma [7]. In contrast, DOG-1 is usually positive in acinic cell carcinoma while it is predominantly negative in MASC [17].

The diagnosis of CUP of cervical lymph nodes makes up 3-9% of all head and neck malignancies [18,19]. The most prevalent histologic subtypes of metastatic carcinomas to cervical lymph nodes include squamous cell carcinoma, which accounts for 75% of the cases, followed by adenocarcinoma, undifferentiated carcinoma, and other cancers, for example, lymphoma and melanoma [20]. Lung and breast cancers are the most frequent non-head and neck cancers that metastasize to cervical lymph nodes in retrospective studies [21]. Based on these findings, primaries of the head and neck, including MASC, lung, and breast carcinomas, should be considered first in patients with CUP to cervical lymph nodes before searching for other uncommon carcinomas that can metastasize to cervical lymph nodes, such as ovarian carcinoma. Judicious selection of IHC markers is crucial in directing us to the main site of metastatic malignant cells. Although IHC is neither completely sensitive nor specific, it is a good starting point [22]. In the current study, a tissue biopsy from the neck mass was consistent with poorly differentiated metastatic carcinoma. Immunohistochemistry (IHC) examination revealed strong reactivity of the malignant cells for S100 protein, CK7, mammaglobin and GATA3, while the cells were negative for cytokeratin 20, CD56, PAX8, synaptophysin, estrogen receptor, and HER2/neu.

The gold standard for establishing a definite diagnosis of MASC is fluorescence in situ hybridization (FISH) test for the ETV6-NTRK3 fusion which is present in nearly 99% of MASC tumors while NTRK gene fusions are rare in other cancer subtypes (less than 1%) [23,24]. The biological importance of this translocation is the presence of a fusion oncogene which promotes cell proliferation and survival [25]. If IHC can facilitate the diagnosis of MASC, the use of cytogenetics to diagnose MASC may be minimized or avoided [26]. This is especially important for people living in low- and middle-income countries, where resources for genetic studies are few [23].

This fusion gene has important clinical implications because pan-Trk inhibitors such as entrectinib and larotrectinib have been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of tumors with an NTRK gene fusion in both pediatric and adult age groups [27,28]. Because MASC has the highest rate of ETV6-NTRK3 fusions among all other human cancers, practically all the cases will be positive for this fusion gene [23]. It is still critical to screen these tumors for the ETV6-NTRK3 fusion before initiating therapy with any TRK inhibitors, as there are still cases of metastatic MASC detected on IHC that do not show an ETV6-NTRK3 fusion gene [29,30].

In conclusion, although MASC frequently runs an indolent course, it can metastasize to cervical lymph nodes, similar to other subtypes of primary head and neck salivary carcinomas, and it can be locoregionally aggressive. Having a systematic approach is crucial to finding the primary origin in instances of metastatic carcinoma to cervical lymph nodes, and MASC needs to be in the differential diagnosis of these cases.

Ethical approval

Approval is not necessary for case report (till 3 cases in single report) in our locality.

The family gave consent for the publication of the report.

Research registration unique identifying number (UIN)

Not applicable.

Trial registry number–ISRCTN

Not applicable.

Guarantor

Fahmi Hussein Kakamad

Consent

Written informed consent was obtained from the patient’s family for publication of this case report and accompanying images. A copy of the
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Sami S. Omar: major contribution of the idea, literature review, final approval of the manuscript.
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Declaration of competing interest
None to be declared.

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