

Breast cancer metastatic to the submandibular gland. Case report

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SUMMARY: Breast cancer metastatic to the submandibular gland. Case report.

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Metastatic disease in the major salivary glands is rare and the parotid gland is most frequently involved. Secondary deposits in the submandibular gland are very uncommon. We report a case of a 50-year-old woman who developed a metastasis from breast cancer in the right submandibular gland, 9 years after primary surgery for G3 T1c N0 ipsilateral breast carcinoma. The peculiarity of the case was the unusual site of the metastatic disease and the difficulty in differential diagnosis with primitive ductal salivary carcinoma.

RIASSUNTO: Tumore mammario metastatico alla ghiandola sottomandibolare. Descrizione di un caso.

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La malattia metastatica alle ghiandole salivari maggiori è un evento raro e la ghiandola parotide è la più frequentemente coinvolta. Le localizzazioni secondarie alla ghiandola sottomandibolare sono poco comuni. Riportiamo il caso di una paziente di 50 anni che ha sviluppato una metastasi da carcinoma mammario nella ghiandola sottomandibolare destra, nove anni dopo l'intervento per tumore alla mammella ipsilaterale G3 T1c N0. La peculiarità del caso è data dall'inusuale sito per la malattia metastatica e dalla difficoltà nella diagnosi differenziale con un carcinoma primitivo duttale delle ghiandole salivari.

KEY WORDS: Submandibular gland - Metastatic breast cancer.
Ghiandola sottomandibolare - Tumore mammario metastatico.

Introduction

Metastatic neoplasia of major salivary glands constitutes about 10 percent of malignancy in these districts (data from the Armed Forces Institute of Pathology) (1). Approximately 80% of metastases involve the parotid gland, arising from primary tumors of head and neck, above all squamous cutaneous or mucosal carcinomas and melanomas (2-5). Only 10-15 percent of metastatic neoplasia involves submandibular gland, and the most of reported cases have documented primitivity in infraclavicular region, in particular lung and kidney in men, breast

in women (6-17). Metastatic tumors have not been described in sublingual salivary glands (13). We report a case of breast cancer metastasis to the submandibular gland in a 50 year-old woman with a past history of ductal G3 T1c N0 ipsilateral breast carcinoma.

Case report

A 50-year-old female patient with a past history of G3 T1c N0 breast carcinoma, presented to our cytohistological department for a light swelling of the right submandibular gland, ultrasonographically corresponding to solid intraparenchymal nodular lesion, 1 cm in maximum diameter. Fine-needle aspiration cytology was performed and the material obtained was fixed in alcoholic solution for ThinPrep Papanicolaou Test slides; some of the smear was prepared for conventional cytology, dry fixed and coloured with May-Grunwald Giemsa method. Microscopic evaluation of the cytological slides revealed the presence of epithelioid atypical and hyperchromatic cells of great dimension disposed in irregular aggregates or sometimes isolated (Figs. 1, 2). This report was suspected for localization of undifferentiated carcinoma. The morphology of the neoplastic elements and the previous history of the patient in-

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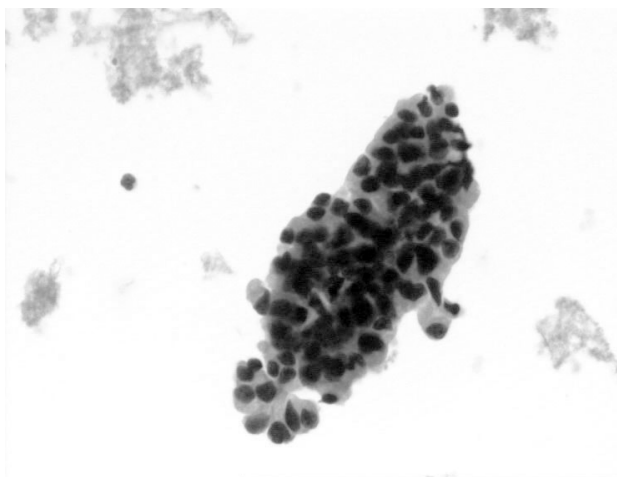


Fig. 1 - Papanicolaou stain of Thin Prep slide obtained from fine-needle aspiration material (40x).

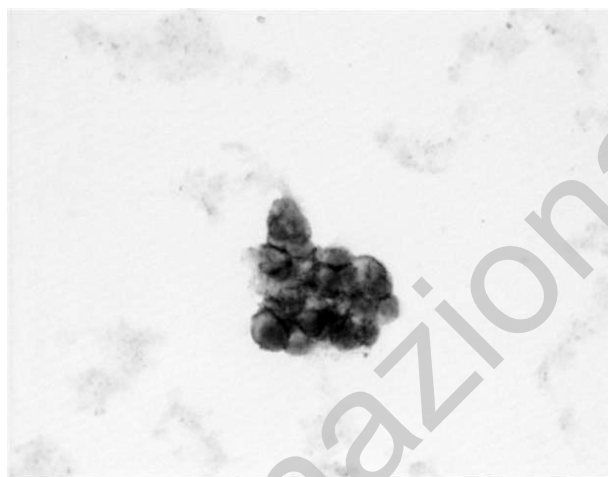


Fig. 3 - Immunocytochemical staining with anti-E-cadherin monoclonal antibodies (40x).

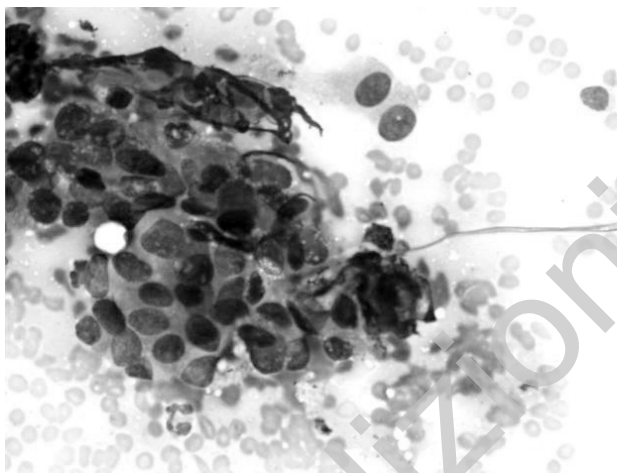


Fig. 2 - May-Grunwald Giemsa stain of cytological smear, with evidence of atypical aggregated and dispersed cells (40x).

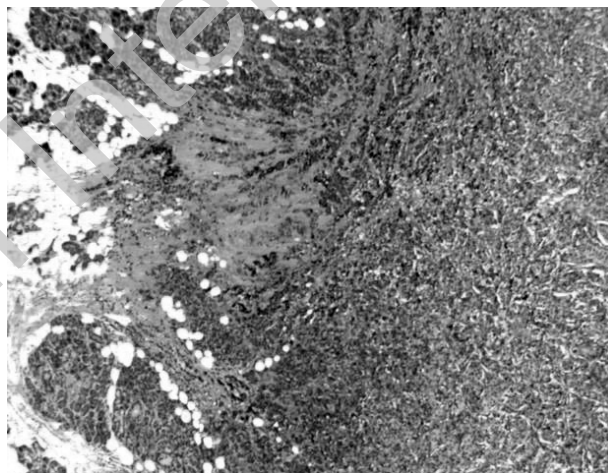


Fig. 4 - Hematoxylin-eosin stain of histological sample, with evidence of neoplastic nodule infiltrating salivary parenchyma (4x).

duced the pathologist to detect E-cadherin monoclonal antibody (NCH-38, 1:200 dilution) on these cells through immunocytochemical analysis on Thin Prep *de novo* slide obtained from FNA material. Positive immunostaining of the neoplastic cells for E-cadherin (Fig. 3) induced to conclude that submandibular lesion was consistent with ductal carcinoma, with uncertain primitivity, but suggestive for breast cancer. Patient underwent surgical removal of the salivary gland. The specimen measured 3x2,5x2 cm and presented intraparenchymal whitish solid and firm nodule of 1,5 cm in maximum diameter.

Histologically the tumor was composed of solid nests of atypical great epithelial cells infiltrating glandular parenchyma (Figs. 4, 5), in absence of detection of lymphoid tissue and of images of ductal *in situ* carcinoma. Immunostaining of the neoplasia confirmed breast primitivity of the lesion. In fact positivity was obtained for monoclonal E-cadherin (Fig. 6), for monoclonal (Dako clone 1D5) estrogen receptor in 70 percent of cells (Fig. 7), and for monoclonal (Dako clone PgR 636) progesterone-receptor in 20 percent of cells. Glandular acinar and ductal elements did not react for estrogenic receptors, with a moderate immunopositivity for E-cadherin. HercepTest score on the surgical specimen was 2+, with negativity of the fluo-

rescence *in situ* hybridization (FISH) analysis (Fig. 8). Comparison was made between the submandibular right lesion and ipsilateral ductal breast carcinoma observed in our hospital 9 years before. Neoplastic elements had very similar morphological and immunophenotypical aspects in the primitive and metastatic tumor. At six months from last surgery, the oncologic staging computed tomography detected the presence of mediastinic lymph nodes metastases. After 8 months from operation the patient is still alive and she has been started on chemotherapy.

Discussion

Metastatic disease of salivary glands is rare, accounting for about 10 percent of malignant tumors of this district. Secondary neoplasias have been described only in parotid and submandibular glands. Pathogenesis of metastasis can be divided into three different pathways of progression of the primitive tumor (1):

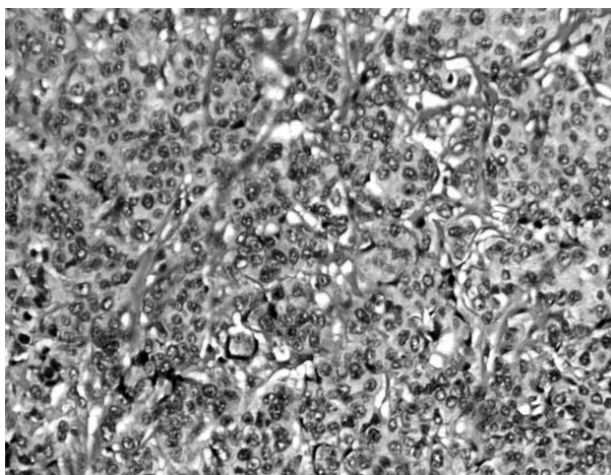


Fig. 5 - Hematoxylin-eosin stain of an histological aspect of ductal neoplasia (20x).

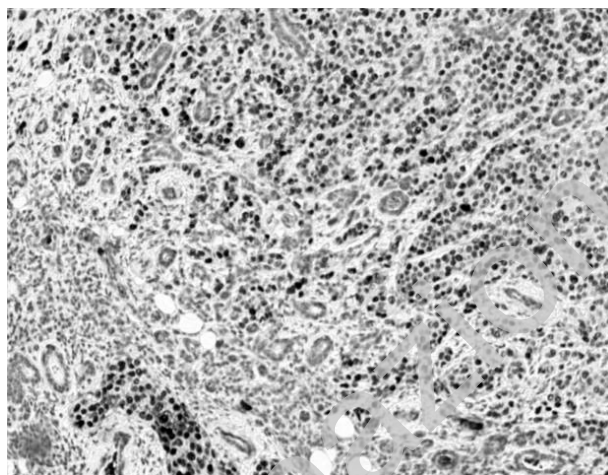


Fig. 7 - Estrogen receptor-immunostaining of the tumor, with negativity of adjacent salivary glandular parenchyma (10x).

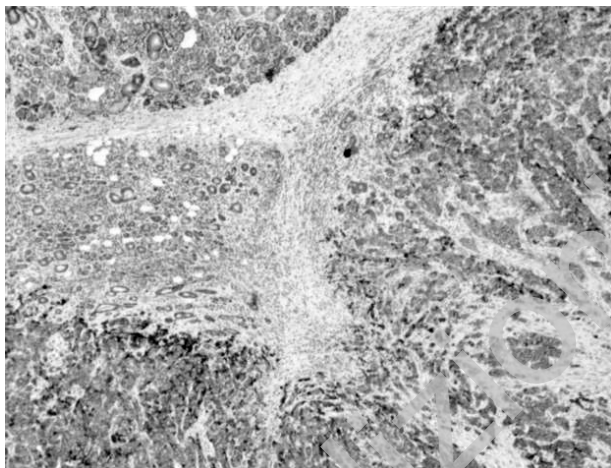


Fig. 6 - E-cadherin immunostaining of histological slide of the tumor (4x).

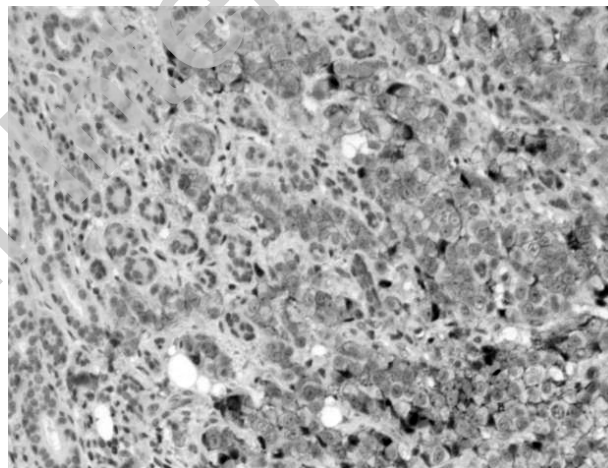


Fig. 8 - Hercep Test score (20x).

1. direct invasion from neoplastic adjacent tissue. In this case there is histological evidence of direct tissutal invasion from adjacent malignancy;
2. lymphatic invasion from regional neoplasia. Lymphatic neoplastic dissemination is frequently observed in locoregional tumors, in particular from cutaneous district (squamous carcinomas and melanomas) (2-5,18-22), and from thyroid carcinoma (23-27). The invasion is characteristically present not only in glandular parenchyma, but also in adjacent and intraparenchymal lymphoid tissue. The parotid gland is much more frequently involved than the submandibular gland;
3. hematogenous metastases from distant primary tumors. This is the favourite metastatic route of intraclavicular primary tumors. The most frequent primary tumors involve lung, kidney and breast (6-17).

The origin from gastric, pancreatic and prostatic cancer, and from soft tissue sarcomas has been also described (28-32). A higher percentage of hematogenous metastases are observed in the ipsilateral submandibular gland. The peculiarity of dissemination is related to the vascularization of the region. Histologically, secondary tumors of submandibular gland do not present lymphonodal involvement, while capillary venous and arterious neoplastic embolic cells have to be detected on serial sections (1).

Differential diagnosis between metastatic neoplasm and primary salivary gland tumor can be difficult if based on morphological and immunophenotypical aspect alone. In the majority of cases, clinical history is the most important and helpful factor in establishing the diagnosis of metastatic disease.

In our case, the 50 year-old female patient with right submandibular gland nodule had a previous history of breast ipsilateral ductal carcinoma. In 1999 the patient underwent right mastectomy and axillary lymphadenectomy for a 1,8 cm nodule of the central quadrant. Histologic examination revealed a G3 T1c N0 pathologic stage, without evidence of neoplastic involvement of peritumoral lymph vessels. The patient was well and free of disease for nine years. The first evidence of metastatic tumor was the submandibular ipsilateral localization described in the present report. Six months later the patient developed mediastinal metastatic adenopathy described on computed tomography. She will undergo restaging of the disease at the end of chemotherapy.

In our case the differential diagnosis was between primitive and metastatic ductal carcinoma. Primitive ductal carcinoma of salivary gland account for about 1 percent of malignancies in this district, with the absence of a complete report of all the cases observed (13,33). This evidence is linked to the rarity of the pure lesion, almost always associated to adenocarcinoma with oncocytic aspect, adenoid cystic carcinoma, mucoepidermoid carcinoma. On the other hand, the lack of a uniform terminology for the classification of this neoplastic entity has induced to lose many cases of primitive ductal salivary carcinoma. The existence of this specific neoplastic entity has been accepted, in fact, only through the WHO classification in 1991 (33), even if the first ductal primitive carcinoma has been described in 1968 by Kleinsasser (34). For twenty years this carcinoma has been referred in several ways (epithelial-myoepithelial carcinoma, cribriform salivary carcinoma, intraductal salivary carcinoma) with confusion in the international literature

and many cases of misdiagnosis.

Histologically, primitive ductal carcinoma of salivary glands characteristically presents a high percentage of in situ cribriform and comedonic aspects, while metastatic ductal carcinoma has infiltrating aspect in quite total absence of intraductal areas (13,35). The cytological aspect of primitive ductal salivary carcinoma remarks the malignancy of this neoplasia, with irregular and pleomorphic nuclei and high mitotic index. Immunoprofile of ductal carcinoma is very similar both in primitive and metastatic entities (positivity for cytokeratins, including CK 19, and monoclonal E-cadherin). Anyway, the absence of expression of estroprogestinic receptors in primitive ductal malignancy (or the very low number of cells staining positively compared to breast cancer) can be helpful in differential diagnosis with a metastasis from breast ductal neoplasia (36-42).

Similarly to our case, due to the lack of univocal morphological and immunophenotypical characteristics, all malignant tumors of salivary glands need a precise clinical and instrumental profile, in order to obtain a correct histopathological diagnosis.

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