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Case Report

Primary Breast Carcinoma Arising from Ectopic Breast Tissue in the Groin of a Male Patient

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Abstract

Introduction: Breast carcinoma originating from ectopic breast tissue (EBT) in men is a rare event. It may occur anywhere in the so-called milk line, with preference to the axilla, followed by the area immediately inferior to the normal breast. Additionally, it is presumed that EBT has an increased rate of malignant progression, when compared with normal breast tissue. In fact, benign and malignant tumors, such as epithelial, stromal or fibro-epithelial neoplasms, may arise from EBT.

Presentation of Case: Here we describe a case of a 45-year old male who presented with a erythematous-brownish skin plaque located at his left groin. An incisional biopsy followed by a routine hematoxylin-eosin study revealed invasive neoplastic epithelial proliferation with obvious glandular differentiation extending from deep subcutaneous tissue to the superficial dermis. Lymphatic invasion was easily observed and the mitotic count was low (1 mitotic figure per square mm). Immunohistochemical staining showed neoplastic cells positive for estrogen receptor, progesterone receptor, gross cystic disease fluid protein 15 (GCDFP15) and mammaglobin, conforming a low-grade ductal infiltrating carcinoma (invasive mammary carcinoma of no special type).

Conclusion: To our knowledge, this is the first report in the literature of a breast carcinoma originating from EBT in a male patient outside the thoracic region. Clinicians must be aware of EBT tumors to any lesion occurring in the milk line.

Keywords: Ectopic breast tissue; Milk-line breast cancer; Male breast cancer

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Introduction

Ectopic breast tissue (EBT) is presumed to result from incomplete regression of the mammary ridges[1]. Moreover, EBT is not a common finding, with an incidence rate of 2.4% in neonates [2]. It may occur anywhere in the so-called milk line, with preference to the axilla, followed by the area immediately inferior to the normal breast. Comparing with orthotopic breast tissue, EBT usually responds to physiological stresses and hormonal stimulation in a similar way. Furthermore, benign and malignant tumors, such as epithelial, stromal or fibro-epithelial neoplasms, may arise from EBT [3-9].

Breast carcinoma originating from EBT is an even rarer event. Although its true incidence is not clear[10], it is presumed to occur in 3.8% of EBT [11]. Some authors assume that EBT has an increased rate of malignant progression, when compared with normal breast tissue [10]. Here we describe a case of a low-grade ductal infiltrating carcinoma (invasive mammary carcinoma of no special type), arising from EBT located in the groin of a male patient.

Case Presentation

A 45-year-old male presented to a dermatologic consultation complaining of a 10-year history skin lesion located at the left iliac fossa. It started as a small papule and then progressed in the last year, when the patient noted erythema and induration of the lesion. No previous comorbidity was reported. On physical exam, an erythematous-brownish plaque measuring 2.0 x 3.0 cm was noted in the skin of his left groin. The lesion was irregular, with indistinct borders, central papillary projections and peripheral desquamation (Figure 1).

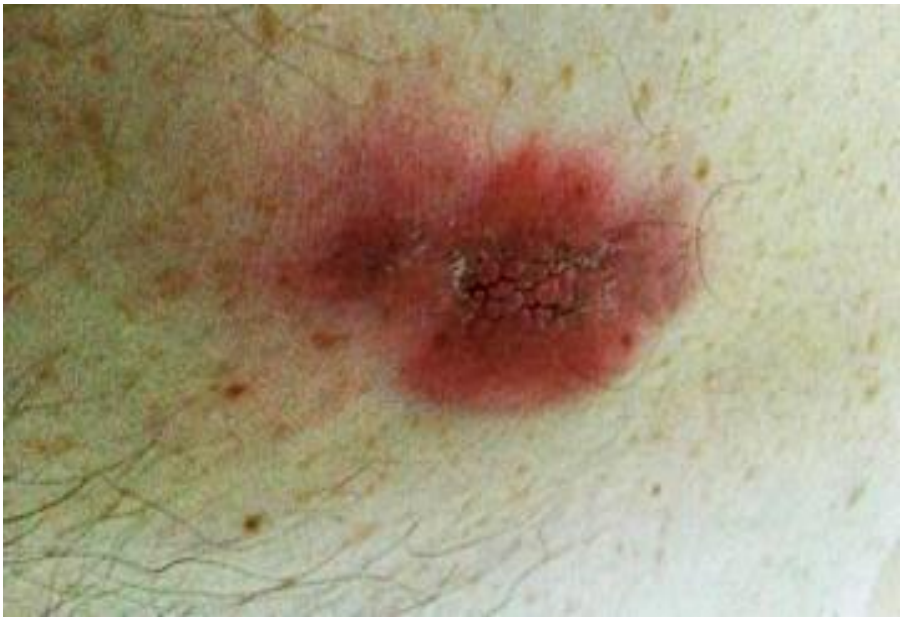

Figure 1 Lesion as seen in physical exam: erythematous-brownish plaque, measuring 2,0 x 3,0 cm, with central papillary projections.

Following the dermatologic consultation, an incisional biopsy was taken as the lesion was suspected to be neoplastic. Upon histologic evaluation of routine hematoxylin-eosin sections, an invasive neoplastic epithelial proliferation with obvious glandular differentiation was observed

extending from deep subcutaneous tissue to the superficial dermis. The proliferation consisted of haphazard arranged nests with solid, cribriform and acinar architecture with infiltrative borders (Figure 2). On high power examination, neoplastic cells were monomorphic with pale cytoplasm and basally oriented regular nuclei with micronucleoli. The epidermis had an irregular papillary acanthosis correlated to the central papillary projections seen on physical exam. After examination of serial sections, a focus of invasion of the epidermis was identified (Figure 3). Lymphatic invasion was easily observed. The mitotic count was low (1 mitotic figure per square mm).

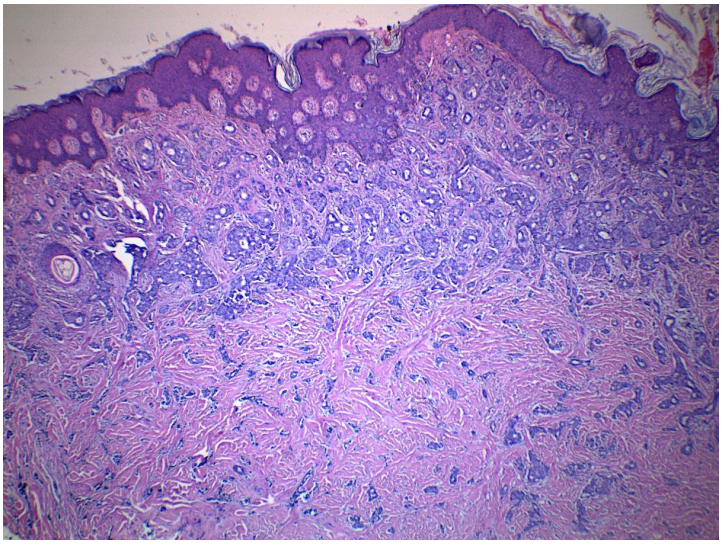

Figure 2 Low magnification light microscopy (40x) showing haphazard glandular proliferation in dermis.

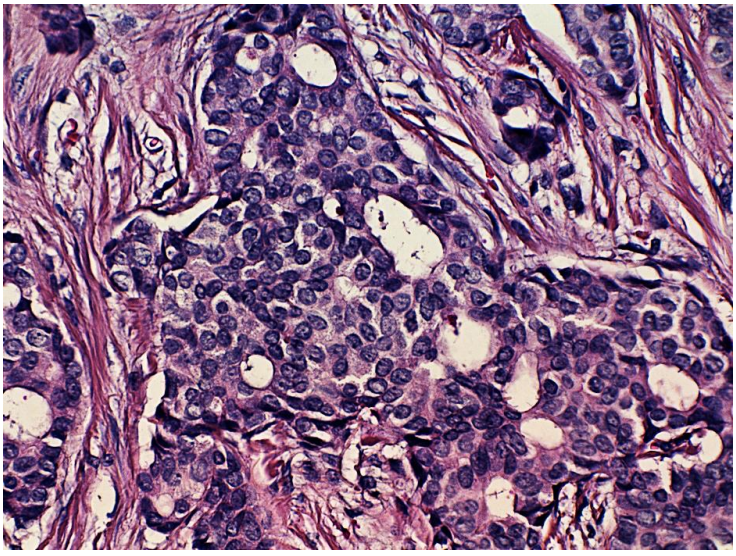

Figure 3 High magnification light microscopy (400x) showing cribriform glandular proliferation with low-grade nuclei.

Immunohistochemical staining showed neoplastic cells positive for estrogen receptor (ER), progesterone receptor (PR), gross cystic disease fluid protein 15 (GCDFP15) and mammaglobin (Figure 4). Of note, cells were negative for HER2/neu, p63 and CK5. Pathology report of the incisional biopsy mentioned three hypotheses: (1) Primary breast carcinoma originating in EBT; (2) Metastatic breast carcinoma with primary site in orthotopic breast; (3) Primary skin adenocarcinoma.

An extensive clinical and radiologic breast workup for primary tumors, including ultrasonography and magnetic resonance, was conducted and no tumor was found. An abdominal

computed tomography shown no sign of metastatic visceral disease. A positron emission tomography computed tomography (PET-CT) showed a hipercaptant sign in the inguinal location of the lesion, associated with hypermetabolic inguinal left lymph node. Plasmatic tumor markers (CA15-3, CA19-9, and CEA) were within normal limits.

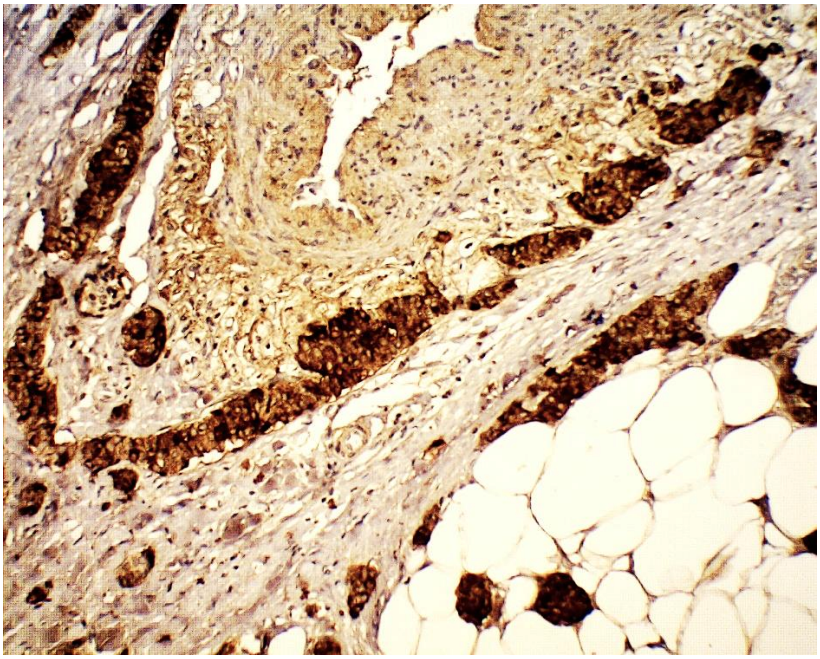

Figure 4 Diffuse and strong positivity for mammaglobin (immunohistochemistry, 100X)

A loco-regional surgery (R0 local excision with lymphadenectomy) was indicated. Surgical procedure was performed with no complications. Histopathologic examination demonstrated a residual tumor with similar morphologic and immunohistochemical features of the incisional biopsy. Surgical margins were free of tumor. Another skin lesion, located in left leg was also biopsied and reported as an unspecific dermatitis with lichenoid pattern. Resected inguinal lymph node showed a macrometastasis with involvement of perinodal soft tissue. Final histopathologic interpretation was of a ductal mammary carcinoma, histologic grade 1 (according to Nottingham classification), with lymph node metastasis and invasion of lymphatic and perineural spaces.

After a multidisciplinary tumor board conference, an adjuvant chemotherapy regimen based on anthracycline and taxane was proposed. The patient received four cycles of AC (doxorubicin 60 mg/m2, cyclophosphamide 600 mg/m2) followed by weekly paclitaxel (80 mg/m2) for 12 weeks. Considering the lymph draining areas were treated with lymphadenectomy, the patient was spared from radiation therapy, as it would increase rates of comorbidity, including lymphedema. Additionally, endocrine therapy with tamoxifen for five, up to 10 years, was also implemented. He is now in follow-up without evidence of disease recurrence.

Discussion

The exquisite final diagnosis of this case, initially presented as a skin tumor located in the groin of a male patient prompted the authors to write this brief manuscript. To our knowledge, this is the first report in the literature of a breast carcinoma originating from EBT in a male patient outside the thoracic region. Clinicians must be aware of EBT tumors to any lesion occurring in the milk line. Once identified, the ectopic tissue must be object of active surveillance in order to detect early neoplastic

alterations.

Our case presents two clinicopathologic dilemmas: (1) to define whether the tumor is metastatic to, or, primary from the skin in the groin region; (2) to define if the lesion is originated from cutaneous appendages or from EBT. Patient's ortotopic breasts were submitted to clinical and radiological examination, and no tumor was found. In addition, an uneventful follow-up (regarding eutopic breasts) makes the hypothesis of metastatic breast cancer an extremely remote possibility.

In milk-line arising lesions, it has been much more difficult to define if the tumor is originated on breast tissue or cutaneous appendages, specially sweat glands. Breast and sweat glands share embryological, structural and functional features resulting in a striking resemblance to one another [12]. Both of them derive from ectodermal appendages, and although the mammary ducts arise from specialized mammary ridges, they are essentially comparable to modified sweat glands. Moreover, correlation of clinical, histologic and immunohistochemical features is required to make a precise definition whether a lesion is a breast carcinoma (BC) or a sweat gland carcinoma (SGC), such as cutaneous apocrine adenocarcinoma[13], hidradenocarcinoma, and eccrine porocarcinoma[3]. Furthermore, location and number of the neoplastic foci, history of malignancy, and duration of skin tumor have been stressed as important clinical diagnostic determinants[12]. The presence of normal breast tissue surrounding the tumor or compromised by carcinoma "in situ"[3] is a morphological evidence supporting the hypothesis of carcinoma arising from EBT[10]. In contrast, the presence of an epidermal connection would argue in favor of a primary adnexal neoplasm[14].

Immunohistochemical assays have been used in a vast number of studies in order to differentiate BC from SGC [12, 14-17]. Essentially, these studies are underpowered because of the limited sample availability. This issue is even further complicated by the fact that BC and SGC are generic terms that cover a vast number of different tumors under the same name.

Generally, SGCs lesions are positive for basal cell markers (p63 and CK5/6). In contrast, BCs should be negative for them. Mentrikoski et al. demonstrated that the sensitivity and specificity for p63 in distinguishing BC from SGC is 81% and 94%, respectively [12]. However, not all BC will be negative for basal markers. The well-known basal-like breast cancers are known to express basal cytokeratin and p63. Fortunelly, basal-like breast cancers are either of a special histologic subtype or have a high grade sarcomatoid phenotype, and should not be confused with the low grade, ductal phenotype of SGC. In our case, the low-grade ductal morphology, in association with lack of expression of basal cytokeratin and p63, is a strong evidence of mammary differentiation. Also, GCDFP15 and mammaglobin are used to identify breast origin of carcinomas in metastatic setting[18]. Unfortunelly sensitivity and specificity of GCDFP15 in sorting BC from SGC have been low in some observations[17, 19, 20]. On the order hand, mammaglobin has been expressed in two-thirds of BC and has been negative in SGS, as reported by Rollins-Raval et al.[17]. In another series, mammaglobin was observed in one case of SGC, and the sensibility and specificity was 45% and 95%, respectively [12]. The expression of mammaglobin in the case presented here was interpreted as another strong evidence to support the breast differentiation for the neoplasia.

Hormonal receptors are routinely used for the identification of breast carcinoma in metastatic setting, as the majority of BCs express ER and PR. However, SGC also express these proteins [20-22]. Therefore, they are not helpful in differentiating BC and SGC as both lesions express hormonal receptors. Moreover, GATA3, a transcription factor involved in embryologic development of the mammary glands, is also of no use in this clinical setting[12].

Embriologically, breast tissue derives from the mammary ridges, which undergo septation to form mammary buds, the precursors of mature breasts. A theory, once universally accepted, states that

mammary ridges extend from the axilla to the inguinal regions (the so-called milk line), and that the incomplete regression of mammary ridges may be the origin of EBT. This concept is influenced by a blend of phylogenetic and ontogenetic embryological theories. In fact, human breast development, in early literature, was compared with cetaceans (e.g. whales and dolphins) breast development, which have breasts localized to the caudal perigenital region[23]. Regarding specifically breast-like tissue in anogenital regions, van der Putte[24] challenged this theory since it has not been supported by observations in human embryos, which show that primordia of the mammary glands do not extend beyond the axillary-pectoral area. The phenomenon of breast-like tissue and lesions in anogenital regions was then reevaluated, and resulted in the proposal of mammary-like anogenital glands (MLG) theory. These glands were assumed being a normal constituent of the vulva, and are a distinct type of cutaneous glandular unit present in the anogenital region, sharing features of eccrine, apocrine and mammary glands. Later, van der Putte postulated that mammary-type lesions of the vulva and perineum arise from these structures rather than from ectopic breast tissue[24]. This theory was subsequently accepted and served as basis for nomenclature in vulvar mammary-like lesions[3-9, 23-25].

It is beyond the scope of this brief report to elucidate the subject whether the mammary line theory or the MLG give rise to breast tissue outside the axillary-pectoral area. However, the occurrence of a mammary-like carcinoma occurring in the groin of a male patient as described herein should put both theories in debate again.

Conclusion

In summary, we report a case of a low-grade infiltrating carcinoma with ductal phenotype, expressing mammaglobin and lacking the expression of p63 and basal cytokeratins, thus interpreted as a breast carcinoma arising from EBT in the groin of a male patient. Lesions occurring underneath the mammary line should raise suspicion for dermatologists and pathologists, as they might be related to breast tissue development.

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