Clinical-Pathological Features of an Occult Mixed Mucinous Male Breast Cancer: A Case Report
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Abstract
Mucinous carcinoma of the male breast is an uncommon malignant breast neoplasm and its diagnoses remain difficult. It is probably due to such a low rate of breast cancer cases that men tend to be diagnosed at an older age than women and with a later stage of the disease. We describe a case of a 69-year-old male who displayed a palpable lump in his right axilla several years ago, showing signs of cutaneous adnexal mucinous adenocarcinoma after biopsy. After six years and several clinical examination and systemic investigation without results, the patient underwent to fine needle aspiration cytology and subsequently a biopsy of a mass with irregular margins in the retroareolar region of his right breast. The final diagnosis was of a mixed mucinous breast cancer with neuroendocrine differentiation. The tumor cells phenotype showed Synaptophisin (+), CEA (+/-), CK-20 (-), CK-7 (+), TTF-1 (-), estrogen receptor (-), progesterone (-) and HER 2 (++). These results were unusual for a mucinous male breast carcinoma. In the presence of a lesion in the axillary area with no specific primary origin, breast cancer should never be ruled out, even in the absence of clinical evidence and with an immunohistochemical pattern not indicative of mammary origin.

Keywords: Male breast cancer; Mixed mucinous cancer; Occult primary neoplasms

Introduction
Male breast cancer (MBC) is infrequently observed in clinical practice and, therefore, unusual cases are not completely characterized and described. Male patients and physicians are less suspicious of such a disease and this may sometimes cause a diagnostic delay [1]. Only 48% of mucinous breast cancer is diagnosed at stage I/II of the disease so, in comparison with women, men tend to be diagnosed at a later stage of the disease. Therefore, its prognosis has not been significantly improved over the past 25 years [2]. Data from surveillance, epidemiology and end results (https://seer.cancer.gov) show that 93.7% of MBCs are ductal or unclassified carcinomas, and only 1.5% are lobular. Other tumor types include papillary (2.6%) and mucinous (1.8%) lesions [3]. Its incidence shows an increasing tendency and accounts for significant morbidity and mortality, showing a peak of incidence at around 60 years [4]. In addition to the better elucidation of the role of BRCA2, an increasing incidence of MBC has renewed interest in the pathogenesis and morphological features, clarifying specific differences between male and female breast cancer. Significant differences between male and female breast cancer have been reported. These regard the expression of a variety of biological parameters including hormone receptors such as estrogen and progesterone and c-erbB-2 receptors [5-7]. While male ductal intraepithelial neoplasia compared to similar lesions in females show a distinct histological profile, lesions are morphologically indistinguishable in invasive carcinomas [8,9]. There are 12 different types of breast cancer, of which infiltrating duct carcinoma is the most common. Mucinous carcinoma of the breast accounts for about 2% of breast carcinomas. Since male breast cancer is about 100 times less common than female breast cancer, mucinous carcinoma of the male breast is very rare [10]. It is probably due to such a low rate of breast cancer cases that men tend to be diagnosed at an older age than women and with a later stage of the disease [11]. Regarding the histological features, mucinous carcinomas are classified into pure and mixed types. The pure type shows >90% of a mucinous component and is also classified into hypo cellular and hyper cellular types. It is associated with lower rates of recurrence and indolent behavior. The mixed type behaves as aggressively as the isolated, invasive, solid component [12,13]. The Authors present a mucinous mixed type of the male breast, which was initially diagnosed as a mucinous carcinoma of the skin, reporting its clinical and pathological features.

Case Report
In February 2017, a 69-year-old male presented at Sant’Andrea Hospital, Rome, with an enlarged lump in the right breast and a palpable lesion in his right axilla. In December 2011, the patient had noticed thickening of the skin in the armpit area. During the examination, ultrasonography (US) revealed a hypoechoic, dishomogeneous area in the right axilla of 2 cm in diameter. Doppler US showed that the mass had internal vascularity. An x-ray of the thorax was negative. US confirmed the presence of a palpable lesion of the axilla but did not show any lesions in the breast. Other clinical examinations and systemic investigations including chest, abdominal and pelvis computed tomographies, and thyroid, breast and genitourinary tract ultrason failed to detect any primary lesion elsewhere. BRCA analysis was negative and no family history of carcinomas was reported. The patient underwent incisional surgery and histopathology diagnosed a mucinous carcinoma. The immunohistochemical evaluation, performed according to the standard procedure, showed that tumor cells were positive for cytokeratin 20 (Clone Ks20.8 Dako), weakly positive for CEA (Dako) and cytokeratin 7 (clone OV-TL 12/30, Dako) but negative for ER (clone EP1, Dako), PgR (clone PgR636, Dako), TTF1 (clone 8G7G1/1 Dako) and Ki67 was
30%. On the basis of these results, the hypothesis of a cutaneous adnexal mucinous adenocarcinoma was suggested. In 2013, ultrasonography (US) revealed two hypoechoic solid masses in the right axillary cavity. Fine-needle-aspiration cytology (FNAC) confirmed the neoplasia in the right axillary cavity and a histopathological examination revealed a mucin-producing adenocarcinoma in all the lymph nodes examined. As a result, the patient received adjuvant radiation therapy for 1 month, followed by chemotherapy. In 2016, the clinical examination, US and PET/CT confirmed the presence of multiple metastatic lateral cervical, axillary and right mammary lymph node chains. An increased uptake was evident in the right mammary gland. The patient began consolidation chemotherapy with taxol from 02/2016 until 01/2017 with a good response (partial response). Other clinical examinations and systemic investigations, including breast ultrasound were requested.

In 2017 US revealed a hypoechoic solid mass with irregular margins in the retroareolar region of the right breast and two lymph nodes with irregular margins in the right axillary cavity (Figure 1). A FNAC, supported by Rapid On-Site Evaluation (ROSE), of the breast lesion was performed. The cytological evaluation showed, in all smears, the presence of blood and mucus in the background, higher cellularity sometimes with nuclear atypia, overlapping, crowding and three-dimensional clusters (Figure 2) supporting the hypothesis of a primary breast tumor. In the same session, a core biopsy was performed. Histopathology revealed infiltrating ductal structures characterized by evident nuclear atypia, anisonucleosis, prominent nucleoli and mitotic activity in an extensive mucinous background. The immunohistochemical pattern showed that ER and PgR were both negative, p53 positive (24%), and c-erbB 2/neu very positive (continuous and strong membrane reactivity in more than 50% of the cells) and the MIB-1 (clone MIB-1, Dako) clone was 30-40%. Fluorescence in situ hybridization (FISH) assay for HER2 was amplified confirming the immunoreactivity (Figure 3). The lesion was also synaptophysin (Clone Synap, Dako) positive (Figure 4), confirming that the mucinous carcinoma is commonly associated with neuroendocrine differentiation [4]. The histopathology diagnosis was a mixed mucinous and infiltrating carcinoma of the male breast. The patient received cycles of molecular target therapy and neoadjuvant chemotherapy. Then, in November 2017, the patient underwent a radical mastectomy.

**Discussion**

We presented a case of mucinous carcinoma initially diagnosed as a mucinous carcinoma of the skin. Seven years later, after excision at the primary site, it was classified as a mixed mucinous and infiltrating carcinoma of the breast. According to the literature, differential diagnosis between these tumors remains difficult. Three quarters of cases of mucinous carcinoma of the skin were found on the head while only 2% of mucinous carcinomas occurred on the chest [14]. Furthermore, mucinous carcinomas are classified into pure and mixed type, where the pure type shows the mucinous component in more than 90% of the tumor; on the contrary, the mixed type shows mucinous and solid components formed by a ductal in situ, intraductal (IDC) or neuroendocrine differentiation carcinoma. The pure mucinous type is further sub-classified into hypocellular (A) and hypercellular

![Figure 1](image1.png)

**Figure 1:** Right breast ultrasonography revealed a hypoechoic solid mass with irregular margins approximately 1 cm in maximum size in the retro areolar region.

![Figure 2](image2.png)

**Figure 2:** FNAC. Mucinous carcinoma showing pools of mucus and ductal cells. Nuclear atypia, overlapping and crowding is observed in cases of mixed mucinous and ductal carcinoma (Papanicolaou x200).

![Figure 3](image3.png)

**Figure 3:** Fluorescence in situ hybridization (FISH) assay for HER2. This image shows the appearance of the dual-colored FISH assay (HER-2/neu DNA Probe Kit 17q 11.2-q12 Chromosome 17 satellite alla 17p11.1-q11.1, CEP17; Kreatech, Resnova, Italy), x1000 original magnification). Invasive tumor cell nuclei are highlighted by the blue fluorescent counter stain (4'-diamidino-2- phenylindole [DAPI]). Figure shows HER2-amplified breast cancer with an increased number of HER2 gene signals (red signals) relative to CEP17 (green signals) resulting in a calculated HER2/CEP17 ratio of greater than 2.

![Figure 4](image4.png)

**Figure 4:** Synaptophysin (Clone Synap, Dako) positive in the mucinous carcinoma.
Cancers have high rates of hormone-receptor expression. Giordano et al detected that approximately 90% of male breast cancers express the estrogen receptor, and 81% express the progesterone receptor [11]. In contrast, the her2-neu proto-oncogene is less likely to be overexpressed in cancers of the male breast. In a large series of studies, human epidermal growth factor receptor-2 (HER-2) was observed in only one tumor out of 58 male breast cancers showing overexpression without amplification, compared with 26% of female breast cancer tumors showing overexpression and 27% manifesting amplification [3]. At present, there are no reports in the literature of MBC cases showing a mucinous carcinoma which is negative for ER/PgR and Her2neu amplified. This pattern is extremely uncommon in MBC. In fact, the literature reports that the immunoprofiles of mucinous carcinoma in males and females show fundamentally the same patterns [7,12]. Nevertheless, Ha et al reported a case of invasive mucinous breast carcinoma in a woman in which the lesion was estrogen and progesterone receptor negative and HER-2 positive [19]. Studies have revealed that there is a subset of patients with mucinous carcinoma showing mammographically occult neoplasms and/or multicentric multifocal disease. Some of these patients demonstrated metastases at presentation as well as ER/PR negative and HER-2 positive [20,21].

Conclusion

In these cases, immunohistochemistry was misleading. The presence of both negative hormonal receptors gave information that confused the diagnosis. Moreover, the histological pattern of a colloid carcinoma supported the hypothesis of a rare skin mucinous adenocarcinoma of the axilla, by ruling out other primary cancers. In conclusion, from our experience, in the presence of a lesion in the axillary area with no specific primary origin, breast cancer should never be ruled out, even in the absence of clinical evidence and with an immunohistochemical pattern not indicative of mammary origin. In this unusual case, it is probable that FNAC contributed significantly to the diagnosis and that the collaboration between the clinician and the pathologist led to a correct evaluation. The presence of the classic pattern of breast colloid carcinoma, found by breast FNAC, made the diagnosis evident. In this case, the cytopathology evaluations suggest a new hypothesis on the primary origin of the lesion, which was later supported by the histological examination.

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