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Case Report

Metastatic Small Cell Carcinoma of a Male Breast: A Case Report and Review of the Literature

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Abstract: Neuroendocrine breast cancers are rare tumors that were recognized as a distinct entity by WHO classification in 2003. It is much rarer in male breast cancer. Diagnosis is based on immunochemical analysis in which the expression of at least one neuroendocrine marker is required, associated with the exclusion of another primary site of the tumor. These tumors have a worse long–term outcome compared to other breast cancers. Small cell carcinoma of the breast is a high–grade subtype, presents with more advanced disease, and has a poorer prognosis compared with other neuroendocrine breast subtypes. A proper therapeutic strategy is still not well established. In the herein reported case, a 62–year–old male patient was diagnosed with small cell neuroendocrine carcinoma of the breast, metastatic to the liver, lung, bone and lymph node, and was treated with a first–line Platinum–Etoposide chemotherapy combination with a good clinical and radiological response. Only four previous cases of male small cell breast carcinoma were reported.

Keywords: Neuroendocrine Breast Carcinoma, Small Cell Carcinoma, Diagnosis, Prognosis, Treatment.

Introduction

Primary Neuroendocrine Breast Cancers (NEBCs) are a rare histological subtype that represents less than 1% of all breast carcinomas[1]. They are more rare in the male breast where the incidence of breast cancer (BC) is less than 1% of all BCs[2]. This rare entity was first described by Feyrter and Hartmann in 1963[3]. It wasn't until 2003 when World Health Organization (WHO) first recognized it as a distinct entity[4]; for that, it was poorly defined in the literature. Here we report a case of a male patient diagnosed with neuroendocrine Small Cell Carcinoma of the breast, metastatic to the liver, lung, bone, and lymph nodes. Based on a PubMed research, primary Small Cell Carcinoma of a male breast appears to be very uncommon with only 4 reported cases.

Case Presentation:

In September 2020, A 62–year–old male patient with no medical history presented in our referral hospital with a 1–month history of a left breast palpable mass and mastodynia. On physical examination, a 3 cm mobile peri–areolar nodule of the left breast was located, with no inflammatory signs and no palpable axillary lymph nodes (Fig.1). Abdominal palpation found a hard and painful hepatomegaly of more than 3 finger breadths. The rest of the physical examination was normal.

Mammography and a Breast Ultrasound (US) showed a suspicious well–defined 3x2 cm hypoechoic peri areolar mass.

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A biopsy of the nodule disclosed the diagnosis of a malignant round cell tumor with extensive infiltration of the underlying fibrous tissue. Immunohistochemical staining (IHC) objectified a morphological and IHC aspect of a mammary localization of a Small Cell Neuroendocrine Carcinoma with the expression of Chromogranin, Synaptophysin and CD56 in tumor cells. The tumor was negative for TTF–1 and GATA3. Hormonal receptors (HR) were not expressed, human epidermal growth factor receptor 2 (Her2 / Neu) was negative, and the Ki–67 proliferation index was 85%.

A thoraco–abdominopelvic computed tomography (CT) scan was performed and showed, in addition to breast nodule, multiple bilateral pulmonary nodules,

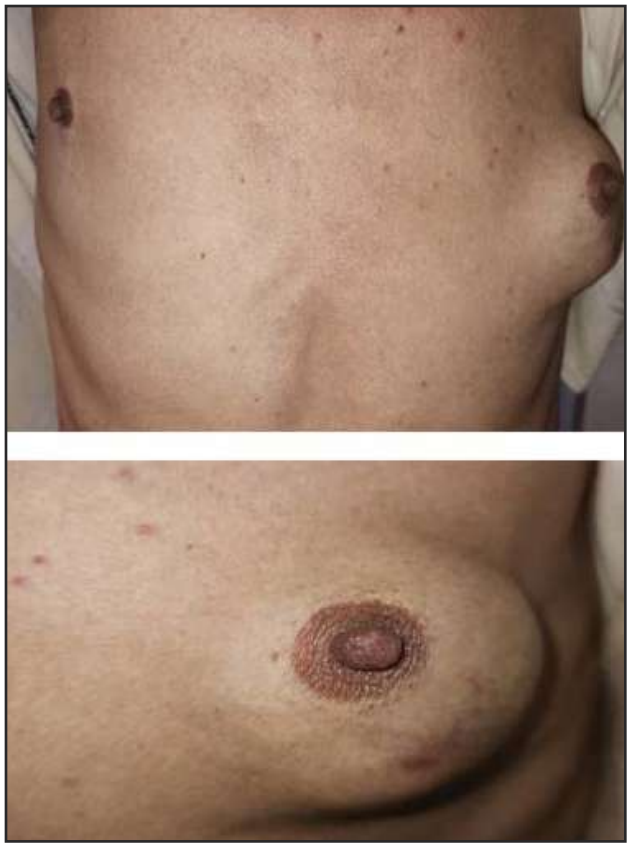

Figure 1: A 3 cm peri–areolar nodule of the left breast.

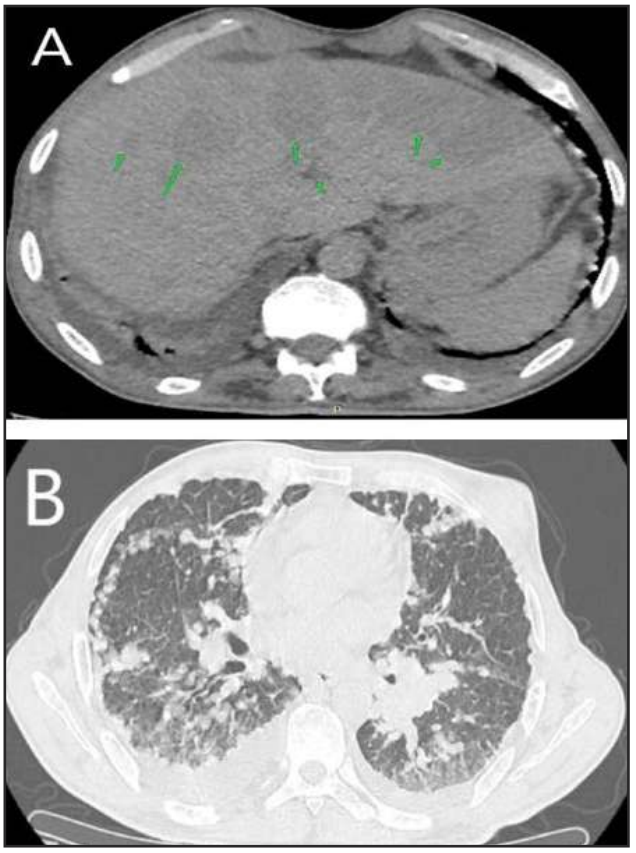

Figure 2: CT scan showing: Multi–nodular hepatomegaly (A), multiple bilateral pulmonary nodules, and lymphadenopathy (B).

lymphadenopathy, multi–nodular hepatomegaly and diffuse bone metastases (Fig.2).

Final diagnosis of primary small cell NE Carcinoma of the breast with liver, lung, bone, and lymph nodes metastases was made. Following which, the patient received a first–line metastatic chemotherapy of Cisplatin 40 mg/m2/day x 2 days (days 2 to 3) and Etoposide 100 mg/m2/day x 3 days (days 1 to 3). With the addition of Zoledronic Acid 6 weeks after the completion of dental care.

After 3 cycles of treatment, clinical examination showed complete resolution of the breast nodule. CT scan was in favor of a partial therapeutic response. Given the good tolerance of the treatment, we decided to continue with the

	Age (y)	Laterality	Size(cm)	Node	Stage	Primary therapy	chemotherapy protocol	Outcome
Case 1(17)	52	Right		Positive Ipsilateral Node	IV	Irradiation, and Chemotherapy	Associate degree	Dead 14 months after the appearance of the first symptoms.
Case 2(18)	61	Right	3	Clinically Negative		Concurrent Chemoradiotherapy	Etoposide combined with Carboplatin	Was free of breast disease, Alive with NSCLC
Case 3(19)	79	Right	2	Clinically Negative		Mastectomy followed 20 months later by chemotherapy after relapse	irinotecan combined with carboplatin	Dead 27 months after surgery
Case 4(20)	55	Right	3	Clinically Negative	27	Mastectomy, Chemotherapy, and Irradiation		Was Free of disease

Table1: Review of the literature of previously reported cases of male small cell breast carcinoma based on a PubMed research.

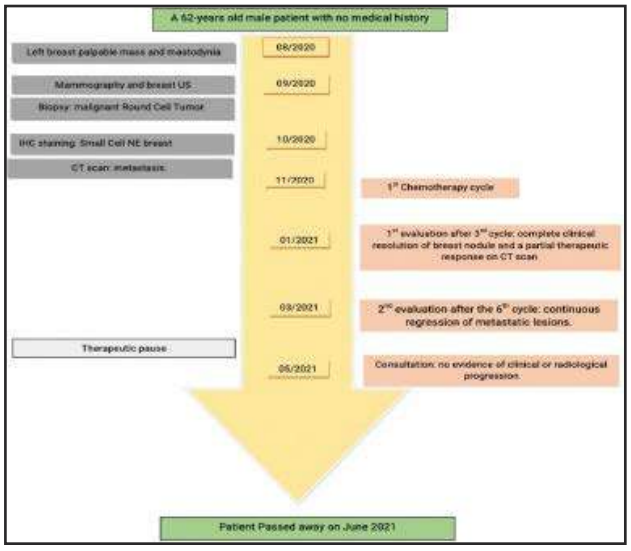

Figure 2: Timeline of the case report

same protocol for 3 additional cycles. After the sixth cycle, radiological evaluation showed continuous regression of metastatic lesions. A therapeutic pause was decided. After 2 months of follow–up, there was no evidence of clinical or radiological progression. The patient was then lost of sight. We contacted the patient's family who informed us that the patient had passed away in June 2021 (Fig.3).

Discussion and Conclusion:

Primary Neuroendocrine Breast Cancer (NEBC) is a rare histological subtype that was described many years ago. In 2001, Sapino et al. proposed the first diagnostic criteria[5]. These same criteria were later adopted in 2003 when the WHO classification of breast tumors recognized NEBC as a separate unique entity. It was defined as a neoplasm expressing at least one neuroendocrine marker in more than 50% of the tumor cell population[4]. However, in 2012 the classification was revised and the 50% threshold was removed, including in this group all NEBCs regardless of markers expression levels(6). The tumor in the present case was diagnosed as NEBC based on the 2012 revised criteria.

The 2019 WHO classification of Breast Tumors classifies NE Neoplasms into two categories. The "Neuroendocrine Tumor" category includes Well–differentiated Neuroendocrine Tumors and Invasive Carcinomas with Neuroendocrine differentiation. And the "Neuroendocrine carcinoma" category includes Small Cell Carcinoma and Large Cell Neuroendocrine Carcinoma which are morphologically identical to their pulmonary counterparts(1). Our patient was diagnosed with Small Cell Neuroendocrine Carcinoma of the breast.

NEBCs are often diagnosed in elderly women in the sixth and seventh decades of life[7]. Only a few cases in male patients have been reported[8]. Yet, the SEER data showed that the proportion of NEBC in men is higher than Invasive mammary Carcinoma of no special type[9]. Our patient was a 62–year–old male.

Clinical presentation of NEBC does not differ from other types of BC with breast lump being the most common presentation[1]. It also tends to present with more frequent regional lymph node metastasis[9], especially in the case of Small Cell Carcinoma[1]. Regarding imaging presentation, some have reported that NEBC may appears on mammography as an oval or lobular hyperdense mass with nonspiculated margins, and as an indistinct irregular hypoechoic, hypervascular mass with posterior enhancement on sonography[10]. In the present case, mammography and US showed a well–defined hypoechoic mass without posterior enhancement.

Diagnosis of NEBC is confirmed when neoplastic cells express at least one of the NE markers, these include Synaptophysin, Chromogranin, and CD56[1]. The presence of an intraductal component is a valid proof of the primary mammary nature of the tumor. Clinical, radiological, and IHC analysis permit to exclude metastasis from other primary sites, especially in the case of Small Cell Breast Carcinoma[11]. Most of NEBCs are HR positive and Her2 / neu negative[7], with the exception of Small Cell breast carcinoma where HRs are less frequently expressed[12]. In the present case, tumor cells expressed all three NE markers. HRs were not expressed, Her2 / neu was negative.

Due to the limited number of reported studies and the lack of uniformity in the definition and classification, conflicting results of NEBC prognosis have been reported. However, most recent studies found it to be associated with a worse long–term outcome[7]. Small Cell breast Carcinomas revealed that they have a very poor prognosis compared to other breast NE tumors, and a more favorable prognosis compared to their lung counterpart[13]. In a PubMed research, only 4 cases of primary Small Cell Carcinoma of a male breast were reported (Table1).

The management of this rare histological subtype poses a real challenge in daily clinical practice due to the absence of a standard protocol. Meanwhile, it is suggested that these neoplasms should be treated similarly to other types of invasive breast cancer.

Hence, in early NEBC, surgical treatment with radical mastectomy in male patients is recommended[2,7], preceded or followed by chemotherapy. Adjuvant radiotherapy follows the same recommendations applied in different kinds of invasive breast cancer. Although, some have reported that no survival improvement from radiation therapy was observed in small cell carcinoma[14]. Patients with positive HR are candidates to receive adjuvant Endocrine Therapy

(ET), with Tamoxifen as the choice in male BC[2,15].

In metastatic disease, systemic treatment represents the main choice. The effectiveness of ET has also been reported in metastatic settings both in Small and Non–small Cell NEBCs with positive HR[16]. Chemotherapy regimens administered for local or metastatic NEBCs are the same as those used in any Invasive Breast Cancer[12]. However, in Small Cell breast Carcinoma, chemotherapy used in Small Cell lung cancer, including combinations of Platinum compounds and Etoposide/ Irinotecan, appears to carry the best chance of survival and thus considered to be the best choice[15]. Our patient presented with a metastatic disease and was treated with first–line Platinum–Etoposide combination with a good clinical and radiological response.

In conclusion, primary neuroendocrine carcinoma of the breast is a rare and distinct entity that is known to have a worse prognosis than other breast cancers, especially in the case of small cell carcinoma. More studies with large series are needed to better understand the clinical and biological behavior of these tumors and ultimately adapt the best therapeutic strategies.

Funding and Conflict of Interest

The authors declare that they have no conflict of interests.

Consent for publication:

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

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