Case report

Primary neuroendocrine tumors of the breast: About a case and of the review of the literature

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ABSTRACT

Primary neuroendocrine carcinomas of the breast represent a minority and are currently included in the latest WHO classification of breast tumors. Their morphological and immunohistochemical features (chromogranin and synaptophysin expression) allow the retain the diagnosis. We report a case of primary neuroendocrine carcinoma of the breast in 50 years old Moroccan women who presented nodule 4,2 cm palpable and mobile of the left breast. Lumpectomy axillary lymph node resection was performed. A histopathological examination disclosed the diagnosis of primary breast neuroendocrine tumors with negative surgical margins and positive lymph nodes (13 N+/19 N). The tumor cells were positive for neuroendocrine markers, a high Ki67 proliferation index and the membrane expression of the invasive tumor cells to the anti-HER2 antibody was 2, a FISH done which was equivocal. Our patient received 6 courses of chemotherapy radiotherapy; currently she received adjuvant hormonal treatment with Tamoxifen.

1. Background

Neuroendocrine carcinomas mainly affect the bronchopulmonary and the gastro-intestinal systems. Breast localizations are very rare. They represent less than 0.1 % of all breast cancers [1,2]. A definitive diagnosis relies on histological and immunohistochemical examinations. The work has been reported with respect to the SCARE 2020 criteria [3].

2. Case presentation

We report a case of a 50-year-old woman, no menopausal, three gestations and three parities (vaginal delivery). with history family: her mother died of oropharyngeal cancer.

She had presented since November 2020, a nodule in the left breast, that gradually increased size during six months ago.

Mammography [Fig. 1], and breast ultrasound had shown a large nodular formation in the left upper-external quadrant measuring 32 × 25 mm, with irregular hypoechoic contours, assessed as Breast Imaging Reporting and Data System (BI-RADS) 5.

A biopsy of the nodule was performed and showed: a nonspecific, poorly differentiated, graded as Scarff-Bloom–Richardson (SBR) II, infiltrating breast carcinoma, with the presence of vascular emboli.

A surgical, tumorectomy with a homolateral axillary dissection, was performed.

Anatomopathological study showed a malignant infiltrating neoplastic process of 4,2 cm suggesting a large cell neuroendocrine differentiation carcinoma, graded SBRIII, with intra-tumoral lymphocytes estimated at 5 %, with thirteen positive lymph node metastases out of nineteen lymph nodes (13 N+/19 N). The edges of surgical excision were healthy. We stadified our patient pT2N3.

Immunohistochemical study showed that the tumor cells expressed diffusely and intensely Chromogranin A [Fig. 2] (polyclonal antibody), and focally Synaptophysin [Fig. 3] (DAK-SYNAP clone) with low intensity.

Hormone receptors were highly expressed (Estrogen receptor = 90 % [Fig. 4], Progesterone receptor = 60 % [Fig. 5]). The Ki67 proliferation index was expressed at 70 %. The membrane expression of invasive tumor cells to the anti-HER2 anti body was 2, a FISH done which was equivocal. The diagnosis retained was a large cell neuroendocrine carcinoma [Fig. 6].

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In order to rule out a secondary origin, a thoracic-abdominal-pelvic CT scan and a bone scan were requested, they were unremarkable and the primary breast origin was retained. The therapeutic decision was to perform sequential adjuvant chemotherapy: 3 courses of anthracyclines such as Epirubicin and 3 courses of taxanes such as Paclitaxel, without anti-Her2 treatment, followed by external radiotherapy and hormone therapy.

Currently, the patient had received six courses of chemotherapy, followed by fifteen sessions of radiotherapy on the tumor and lymph node areas with Boost, and put on Tamoxifen 20 mg/day in adjuvant, it has been six months.

3. Discussion

Neuroendocrine carcinomas are rare, the first description of primary neuroendocrine breast tumor was done by Wade and al. in 1983 [4,5]. Epidemiologically, these tumors are predominantly found in women around the seventh decade of age, but our patient is younger. Without excluding, cases reported in men.

These tumors are classified into 4 types: Solid neuroendocrine carcinomas, atypical carcinoids, small cell carcinomas, and large cell carcinomas [6,7]. The diagnosis of primary neuroendocrine tumors was retained in front of the expression by the cancer cell of neuroendocrine marker (Chromogranin and or synaptopysin), and after a detailed paraclinical examination made of an octreoscanner or thoraco-abdominopelvic scan with bone scintigraphy [8,9]. In our observation, it was a large cell neuroendocrine carcinoma.

Radiologically, stellate or spiculated opacities on mammography are rare [11]. These tumors present on mammography as a dense mass with irregular or multilobulated contours, hypoechogenic and homogeneous on ultrasound [6], this echo-mammographic appearance is strongly suggestive of a neuroendocrine tumor for some authors. A clinico-mammographic character similar to adenocarcinoma is noted [10].

Anatomically, primary neuroendocrine tumors of the breast are round or poly-lobed, whitish- yellow in color, firm in consistency, or rarely gelatinous in case of an associated mucinous component [6,7]. Thus, the origin of neuroendocrine tumors is confirmed by the expression of neuroendocrine markers, particularly Chromogranin A, CD56 and Synaptophysin [6,12]. Furthermore, the certainty of the mammary origin of these tumors is essentially based on the demonstration of an in situ contingent; the immunohistochemical expression of hormone receptors by the tumor cells also points to the “mammary” primitive nature of the tumor [6,13]. On the other hand, hormone receptors are expressed by neuroendocrine carcinomas of the breast and are related to

![Fig. 1. Mammographic showing a left breast of C density; deep rounded EQ opacity with irregular spiculated contours with macrocalcifications of the IQs.](image1)

![Fig. 2. Immunohistochemical aspect showing expression at chromogranin.](image2)

![Fig. 3. Immunohistochemical aspect showing Expression at synaptophysin.](image3)

![Fig. 4. Immunohistochemical aspect showing an expression of estrogen receptors (× 10).](image4)

Abbreviations

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| BIRADS       | Breast Imaging Reporting and Data System         |
| SBR          | Scarff–Bloom–Richardson                          |
| WHO          | World Health Organization                        |
Primary neuroendocrine tumors of the breast, the therapeutic course

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ductal breast carcinoma.

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In this series, anthracycline-based chemotherapy was given to patients

originally developed for gastrointestinal neuroendocrine tumors [24].

Ki67 proliferation index, according to a modified treatment algorithm

include: fluorouracil/epirubicin/cyclophosphamide followed by docetaxel; doctetaxel/epirubicin/cyclophosphamide; cyclophosphamide and
doxorubicin; cyclophosphamide/methotrexate/fluorouracil; paclitaxel
alone; carboplatin/paclitaxel; carboplatin or cisplatin and etoposide;
and cisplatin and irinotecan [22,23].

In a small series, the type of chemotherapy chosen was based on the
Ki67 proliferation index, according to a modified treatment algorithm
originally developed for gastrointestinal neuroendocrine tumors [24].
In this series, anthracycline-based chemotherapy was given to patients
with a Ki67 index of 15%, and cisplatin/etoposide to patients with a
Ki67 greater than 15% [25]. However, the lack of solid data on the role
of platinum and etoposide compounds in the adjuvant treatment of
primary neuroendocrine tumors of the breast, the therapeutic course
adopted is that of ductal breast carcinoma.

The neuroendocrine component usually escapes within a few months
but can be controlled by anthracycline-based chemotherapy [4]. Hormone
therapy was indicated in patients with hormone receptor

expression [22].

The prognosis of neuroendocrine differentiation in breast cancer is
still debated, as several studies were published with mixed results
[18–21]. These conflicting results can be explained by the limited
number of cases reported in each series, by the different inclusion
criteria according to the 2003 or 2012 World Health Organization
(WHO) definitions, as well as by the analysis performed considering
primary neuroendocrine tumors of the breast as a whole, without
analyzing the results according to the different histological subtypes.

The prognosis of primary neuroendocrine carcinomas of the breast
depends mainly on the histological grade and the anatomicoclinical stage
[6,8,13]. The evolution of endocrine tumors of the breast is slow. These
tumors are graded histologically like their counterparts in other sites
[6,7]. On the other hand, neuroendocrine carcinomas with atypical and
solid carcinoid variants have a better prognosis than small cell neuro-
endocrine carcinomas and poorly differentiated large cell carcinomas.
The presence of an associated mucinous contingent would be a good
prognostic factor [6,12].

The five-year survival rate exceeds 80% for all forms. On the other
hand, the latest studies speak of the frequency of locoregional recur-
rence and metastasis, which makes the prognosis dreadful overall
[12,15,16]. The accepted prognostic factors are represented by age,
terrain, tumor secretory power, tumor size and the existence or not of
metastases [15,16].

In our observation, we note histological factors of bad prognosis such
as large cell variant, tumor size of 4.2 cm; the presence of several lymph
node metastases and SBR grade III, on the other hand the only factor of
good prognosis was the expression of hormone receptors.

4. Conclusion

Neuroendocrine tumors of the breast are rare and can be primary or
secondary. The diagnosis of certainty is based on the histological study
and more particularly on the immunohistochemical study. The study of
larger series will allow a better understanding of their histogenesis as
well as their evolutionary profile.

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Consent for publication

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CRediT authorship contribution statement

KF wrote the article; MB, ZB, NB, HJ, NT, AB, and SS made critical
assessment of the article; MB supervised the work. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare having no conflicts of interest for this article.

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