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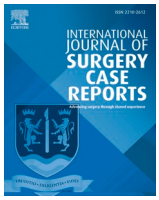

Case report

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 highKi67 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 chemotherapythen radiotherapy; currently she received adjuvant hormonal treatment with Tamoxifene.

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 immuno-histochemicalexaminations. 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 (BIRADS) 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.

Anatomo-pathological study showed a malignant infiltrating neoplaisc 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.

Immuno-histochemical 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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Abbreviations

BIRADS	Breast Imaging Reporting and Data System
SBR	Scarff–Bloom–Richardson
WHO	World Health Organization

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

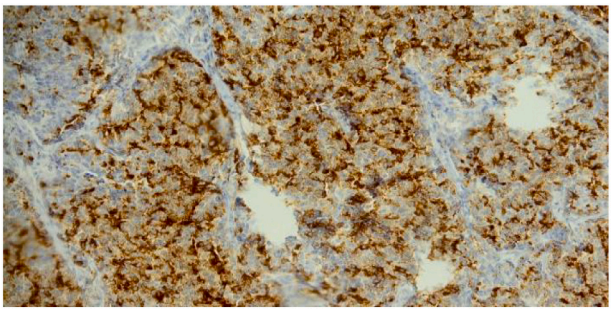

Fig. 2. Immunohistochemical aspect showing expression at chromogranin.

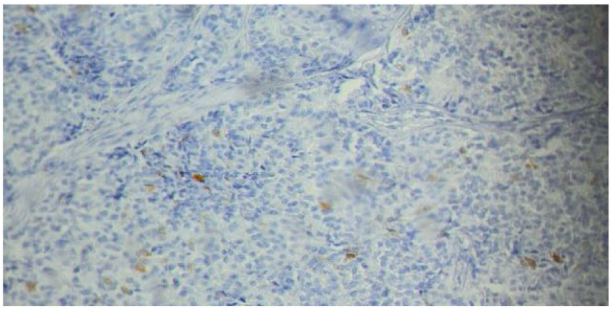

Fig. 3. Immunohistochemical aspect showing Expression at synaptophysin.

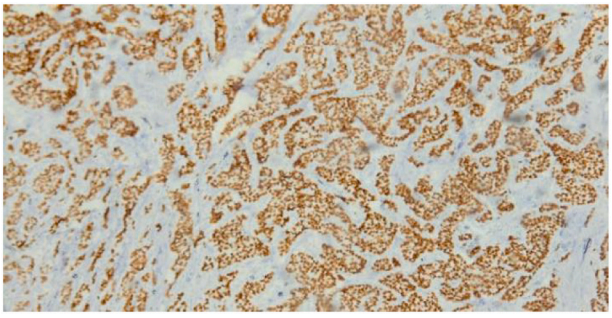

Fig. 4. Immunohistochemical aspect showing an expression of estrogen receptors (× 10).

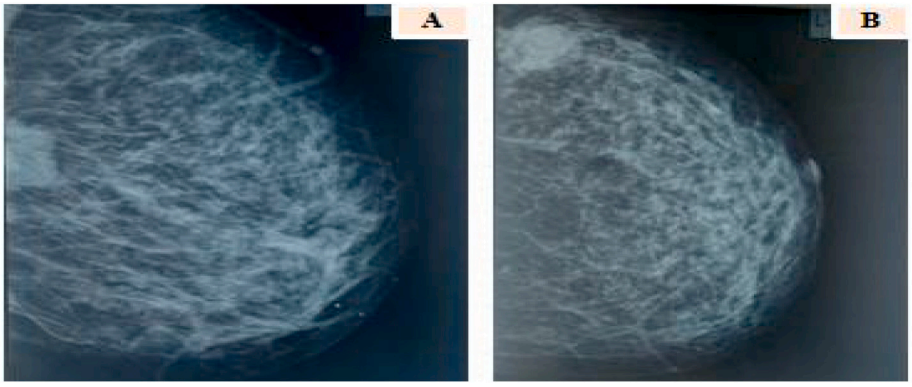

Fig. 1. Mammographic showing a left breast of C density; deep rounded EQ opacity with irregular spiculated contours with macrocalcifications of the IQs.

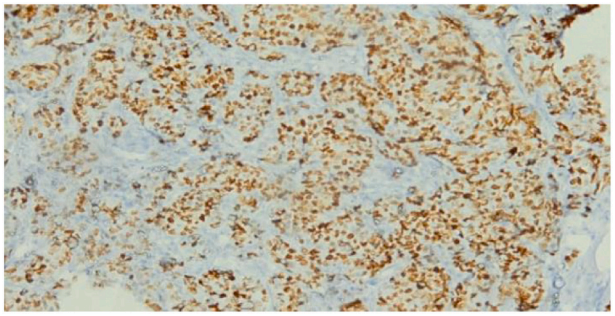

Fig. 5. Immunohistochemical aspect showing an expression of progesteron receptors (G× 10).

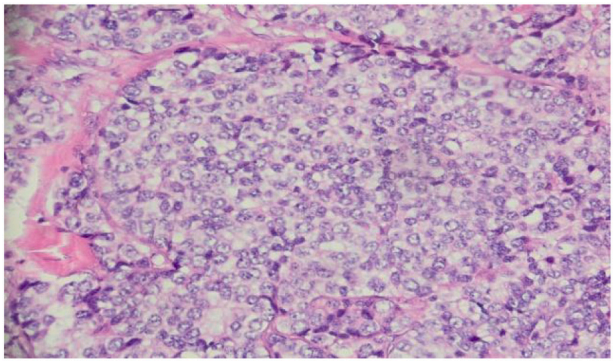

Fig. 6. Neuroendocrine tumor (Gx40).

a more favorable prognosis of the tumor, whereas HER2 is almost always negative. Accordingly, gene expression profile analysis had revealed that primary neuroendorine tumors of the breast belonged to the luminal subtype [17].

In our case, hormone receptors were highly expressed. However, the expression of estrogen and progesterone receptors in large cell neuroendocrine carcinomas of the lung andthose of other sites was cited. Thus, in this case, one cannot rely solely on their expression to maintain breast origin [14].

Surgical treatment (mastectomy with axillary dissection and metastasectomy), remains the first line treatment in neuroendocrine tumors.

The indications for chemotherapy and radiotherapy are the same as for other breast cancers. Given the rarity of this entity, the chemotherapy protocol is not standardized: neuroendocrine carcinomas of the breast are treated by some as an adenocarcinoma of the breast and by others as neuroendocrine carcinoma of the lung [10].

Some examples of chemotherapy regimens reported in the literature include: fluorouracil/epirubicin/cyclophosphamide followed by docetaxel; docetaxel/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 gastro intestinal 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 neuroendorine 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 neuroendorine 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 anatomoclinical 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 neuroendocrine 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 recurrence 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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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approvals and consent to participate

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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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References

[1] S. Singh, G. Aggarwal, et al., Primary neuroendocrine carcinoma of breast, J.Cytol. 28 (2) (2011) 91–92.
[2] Y. Fujimoto, R. Yagyu, K. Murase, et al., A case of solid neuroendocrine carcinoma of the breast in a 40-year-old woman, Breast Cancer 14 (2007) 250–253.
[3] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, pour le groupe SCARE, La ligne directrice SCARE 2020: mise à jour des lignes directrices du SCARE (Consensus Surgical CAse Report), Int. J. Surg. 84 (2020), 226-23.
[4] B. Potier, D. Arnaud, N. Paillocher, D. Darsonval, P. Rousseau, Primitive neuroendocrine cancer of the breast - post- traumatic discovery of a man, Ann. Chir. Plast. Esthet. 57 (6) (2012 Dec) 630–633.
[5] P.M. Wade Jr., S.E. Mills, M. Read, W. Cloud, et al., Small cell neuroendocrine (oat cell) carcinoma of the breast, Cancer 52 (1) (1983 Jul 1) 121.
[6] A. Trabelsi, S. Benabdelkrim, W. Stita, O. Gharbi, L. Jaidane, S. Hmissa, et al., Carcinome neuroendocrine primitif du sein, Imagerie de la femme 18 (3) (2008) 184–186.
[7] I.O. Ellis, S.J. Schnitt, X. Sastre-Garau, et al., Tumors of the breast, neuroendocrine tumours, in: F.A. Tavassooli, P. Devilee (Eds.), World Health Organization Classification of Tumours, Pathology And Genetics of Tumours of the Breast And Female Genital Organs, IARC, Lyon, 2003, p. 3264.
[8] Y. Fujimoto, R. Yagyu, K. Murase, H. Kawajiri, H. Ohtani, Y. Arimoto, et al., A case of solide neuroendocrine carcinoma of the breast in a 40-year-old, Breast Cancer 14 (2) (2007) 250–253.
[9] G. Scaramuzzi, R.M. Murgo, A. Cuttitta, L. Ciuffreda, Neuroendocrine carcinoma of the breast - our experience and a proposal of a therapeutic algorithm for a rare tumor, G Chir. 29 (5) (2008 May) 203–206.
[10] Wen-Chiuan Tsai, Jyh-Cherng Yu PhD, Chih-Kung Lin, Cheng-Ta Hsieh, Primary alveolar-type large cell neuroendocrine carcinoma of the breast, Breast J. 11 (6) (2005 Nov- Dec) 487.
[11] A. Amiraslanov, H. Muradov, H. Veliyeva, Brest endocrine cancer, Georgian Med. News 167 (2009 Feb) 36–39.
[12] A. Sapino, L. Righi, P. Cassoni, M. Papotti, F. Pietribiasi, G. Bussolati, Expression of the neuroendocrine phenotype in carcinomas of the breast, Semin. Diagn. Pathol. 17 (2) (2000 May) 127–137.
[13] M. Intire Mc, K. Siziopikou, J. Patil, P. Gattuso, Synchronous metastases to the liver and pancreas from a primary neuroendocrinecarcinoma of the breast diagnosed by fine- needle aspiration, Diagn. Cytopathol. 36 (1) (2008 Jan) 54–57.
[14] H. Ogawa, A. Nishio, H. Satake, S. Naganawa, et al., Neuroendocrine tumor in the breast, Radiat. Med. 26 (1) (2008 Jan) 28–32.
[15] H. Boufettal, M. Noun, S. Mahdaoui, S. Hermas, N. Samouh, Une tumeur du seininhabituelle: le carcinome endocrine mammaire primitif, Imagerie de la Femme 21 (1) (2011) 35–38.
[16] Z. Bourhaleb, N. Uri, H. Haddad, S. Azzouzi, S. Zamiati, N. Benchakroun, et al., Carcinome neuroendocrine à grandes cellules du sein: à propos d'un cas et revue de la littérature, Cancer/radiothérapie 13 (8) (2009) 775–777.
[17] B. Weigelt, H.M. Horlings, B. Kreike, et al., Re-finement of breast cancer classification bymolecular characterization of histological special types, J.Pathol. 216 (2008) 141–150.
[18] J. Wang, B. Wei, C.T. Albarracin, et al., Invasiveneuroendocrine carcinoma of the breast: a population-based study from thesurveillance, epidemiology and end results (SEER) data base, BMC Cancer 14 (2014) 147–156.
[19] . G Ogina E Munari M Brunelli et alNeuroendocrine differentiation in breast carcinoma: Clinicopathological.
[20] E. Lopez-Bonet, M. Alonso-Ruano, G. Barraza, et al., Solid neuroendocrine breast carcinomas:Incidence, clinic pathological features andimmunohistochemical profiling, Oncol. Rep. 20 (2008) 1369–1374.
[21] S.Y. Kwon, Y.K. Bae, M.J. Gu, et al., Neuroendocrine differentiation correlates with hormone receptorexpression and decreased survival in patients with invasive breast carcinoma, Histopathology 64 (2014) 647–659.
[22] F.A. Angarita, J.L. Rodríguez, E. Meek, et al., Locally-advanced primary neuroendocrine carcinoma of the breast: case report and review of theliterature. World J. Surg. Oncol. 11 (2013) 128–138.
[23] X. Wei, C. Chen, D. Xi, et al., A case of primary neuroendocrin breastcarcinoma that responded to neo-adjuvant chemotherapy, Front. Med. 9 (2015) 112–116.
[24] K. Oberg, Management of neuroendocrine tumors, Ann. Oncol. 15 (suppl 4) (2004) iv293–iv298.
[25] Y. Yildirim, S. Elagoz, A. Koyuncu, et al., Management of neuroendocrine carcinomas of the breast: a rare entity, Oncol. Lett. 2 (2011) 887–890.