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Original Research Paper

Pathology

PRIMARY NEUROENDOCRINE TUMORS OF THE BREAST: CASE REPORTS AND REVIEW OF THE LITERATURE

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ABSTRACT Neuroendocrine carcinomas mainly affect the bronchopulmonary and the gastrointestinal systems. Breast localizations are very rare. They represent less than 0.1% of all breast cancers. A definitive diagnosis relies on histological and immunohistochemical examinations. Primary neuroendocrine carcinoma of the breast (NECB) as defined by the World Health Organization (WHO) in 2012 is a rare, but possibly under-diagnosed entity. It is heterogeneous as it entails a wide spectrum of diseases comprising both well-differentiated neuroendocrine tumors of the breast as well as highly aggressive small cell carcinomas A 40-year-old woman consulted for a right breast lump. USG finding showed a lump at 3 O clock position with irregular marginated hypoechoic mass of approximately 1.4x1.1x1.2cm size. Overall features are suggestive of BIRADS –V, She underwent lumpectomy with. A histological and immunohistochemical examination of a mammary biopsy was consistent with a Primary neuroendocrine tumor Breast.Due to the rarity of primary breast neuroendocrine tumors, no standard therapy exists and the prognosis remains difficult to determine. Studies, including larger series, are needed in order to understand the biological behavior of these tumors.

KEYWORDS : Breast carcinoma, Immunohistochemistry, Neuroendocrine tumour

BACKGROUND

Primary breast neuroendocrine tumors are a rare histological type representing less than 0.1% of all breast cancers [1, 2]. These tumors were initially described by Cubilla *et al.* [3] in 1977; since then, additional cases have been reported. Primary neuroendocrine carcinomas of the breast are currently included in the latest World Health Organization (WHO) classification of breast tumors [4]. We report a cases of primary breast neuroendocrine tumors, with a literature review.

Case presentation

Case 1

A 40-year-old woman with unremarkable medical history presented with progressively enlarging nodule of 2 years' duration. A mammography showed an opaque heterogeneous mass with irregular contours between the right breast lower quadrants measuring 23mm.

Ultrasound scanning showed a hypoechoic solid formation, with irregular contours, measuring 21×16 mm, enclosing a rich Doppler signal, very suspicious of malignancy, graded as BIRADS V.

Biopsy of the right breast nodule was performed. Histo pathological analysis shows Well differentiated neuroendocrine pattern,Monotonous regular cells with round or oval nuclei with salt and pepper chromatin and moderate eosinophilic granular cytopla, tumor cells arranged in nests pattern(fig1,2,3,4)

So Morphological features are suggestive of Primary neuroendocrine carcinoma of the right breast, with a significant positive immunostaining for

IHC MARKER	% CELLS	INTENSITY	INTRINSIC CONTROL	INTERPRETATION
Estrogen Receptor (ER)	95	Strong	Present, stained	Positive
Progesterone receptor	20	Intermediate	Present, stained	Positive

IHC MARKER	Score	Interpretation
Her 2neu	00	Negative
Ki 67	43%	High
Chromogranin	2+	Positive
Synaptophysin	00	Negative

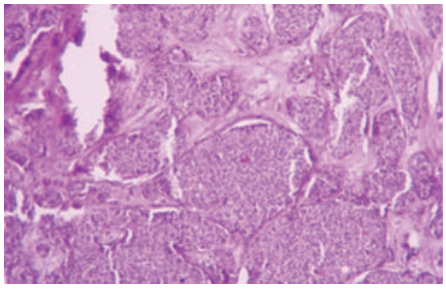

Fig1

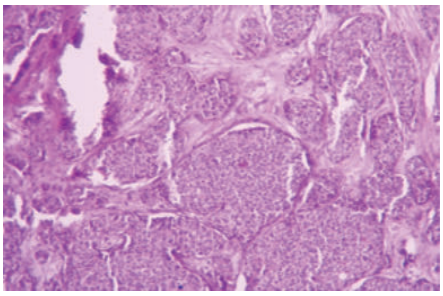

Fig.2

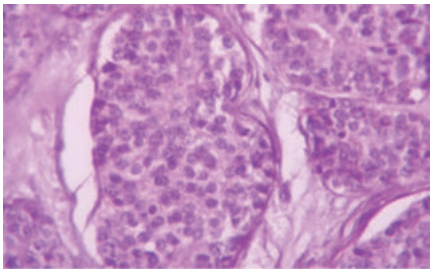

Fig.3

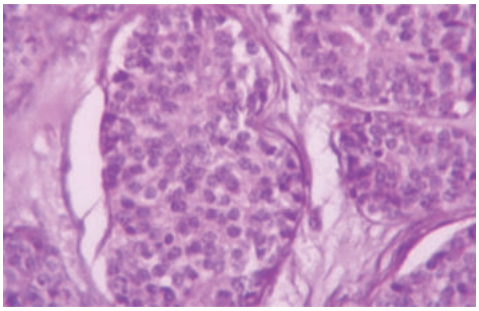

Fig.4
A surgical lumpectomy were performed. Macroscopic examination of the resected specimen showed a 1.5x1.2×1.2 cm whitish nodular tumor with a hard consistency. On microscopic examination, it was a breast neoplasm suggesting neuroendocrine carcinoma, Negative vascular, lymphatic invasion, negative perineural invasion and negative surgical margins.

DISCUSSION

Neuroendocrine carcinomas of the breast are very uncommon; they are little-known tumors, representing less than 0.1% of all breast cancers and less than 1% of neuroendocrine tumors [1]. Classically described in the pulmonary and digestive systems, they can also be seen in other extrapulmonary and extradigestive locations. Primary mammary gland localization is very rare [1]. Neuroendocrine tumors are mainly observed in white women aged from 60 to 70years [1], but younger patients have been reported in the literature. Men can also be affected by these tumors [5, 6].

Primary neuroendocrine tumor of the breast is a diagnosis of exclusion. An Octreoscan and a positron emission tomography (PET) scan should rule out primary sites: ears, nose, and throat (ENT), lungs, digestive, and cutaneous [2, 7]. No clinical signs are specific to these tumors [8, 9]. These tumors are characterized by a slow evolution and the most frequent reason for consultation is an isolated breast nodule or a breast nodule associated with other signs [8]. Our cases illustrate these features that are reported in the literature. Sometimes these tumors present as a well-limited erythematous and purplish cutaneous lesion [8].

The 2003 WHO classification of breast tumors recognizes neuroendocrine carcinoma as a distinct histological entity, with the same morphological characteristics as neuroendocrine tumors of the gastrointestinal tract, pancreas, and lung, with more than 50% positive immunostaining of tumor cells by a neuroendocrine marker such as chromogranin or synaptophysin [4].. Four groups are described: solid neuroendocrine carcinomas, atypical carcinoids, small cell carcinomas, and large cell neuroendocrine carcinomas [4]. This classification excludes mammary carcinomas with focal neuroendocrine differentiation defined as scattered tumor cells that stain positive with neuroendocrine markers [10, 11]. Focal neuroendocrine differentiation is reported in approximately 2–5% of breast cancers [12]. Sapino *et al*. proposed a classification of breast endocrine tumors into five types: the cohesive solid variant; the alveolar form; the small cell form; the papillary solid variant; and mucinous carcinoma [13, 14]. These last two forms are characterized by the production of mucus and the frequent association with an *in situ* component with endocrine differentiation [14].

There is no specific clinical or radiological sign to diagnose a neuroendocrine carcinoma; a histological examination is the only way to confirm the diagnosis of this tumor [8, 9]. On macroscopic examination, primary neuroendocrine carcinomas of the breast are round or multilobulated, yellowish-colored, and have a firm consistency, or, rarely, they are gelatinous if associated with a mucinous component [4, 13]. At histological examination, a diagnosis of the neuroendocrine differentiation of these tumors can be suspected morphologically and should always be confirmed after immunohistochemical analysis by showing positive staining with neuroendocrine markers by at least 50% of the tumor cells. Chromogranin and synaptophysin are the most sensitive and specific neuroendocrine markers [14, 15]. In our cases, the two markers were expressed. Other less specific markers can also be expressed: NSE, neuron cell adhesion molecules (NCAM), neurofilament, and bombesin. High molecular weight cytokeratins are negative. The expression of Her2 is generally absent whereas the estrogenic and progesterone receptors are strongly expressed as in our patients [16, 17]. Strict histological criteria have been defined for the diagnosis of primary breast neuroendocrine carcinoma: the presence of an *in situ* component and/or the absence of extramammary localization [1].

According to Günhan-Bilgen et al., the diagnosis of a primary endocrine tumor of the breast in imaging can be suggested if a patient presents with a dense mammary mass, with microlobulated or spiculated contours on mammography, and with a hypoechoic and homogeneous appearance on ultrasound [18]. However, these imaging features are not specific as a hypoechoic and homogeneous appearance on ultrasound can be seen in other malignant tumors (such as grade 3 infiltrating carcinoma or mucinous carcinoma). Neuroendocrine tumors of other organs may metastasize in the breast; their appearance in this case differs from primary breast neuroendocrine tumors.

Secondary mammary neuroendocrine tumors have the same imaging appearance as other breast metastases, they present as well-circumscribed nodules without spicules or calcification. In the 2012 WHO Classification of the Tumors of the Breast these entities were collected in another chapter, among the special sub-types: Carcinomas with neuroendocrine features, which encompass the categories of Neuroendocrine tumors which are well differentiated, Neuroendocrine carcinoma which is a poorly differentiated/ small cell carcinoma and Invasive breast carcinoma with neuroendocrine differentiation.

The treatment of neuroendocrine tumors of the breast is mostly surgical. It combines: mastectomy, axillary dissection, and metastasectomy. The indications for chemotherapy and radiotherapy are the same as for other breast cancers. The combination of an anti-aromatase acts on the mammary component. The neuroendocrine component usually escapes within a few months but can be controlled by anthracycline-based chemotherapy [19]. The indications for hormonotherapy and immunotherapy are not codified because their effects remain uncertain [18].

The evolution of neuroendocrine tumors of the breast is slow. Their prognosis depends mainly on the histological grade and the anatomoclinical stage [13, 20, 21]. These tumors are histologically graded as their counterparts in other sites [4, 13].

Thus, the solid variant of neuroendocrine carcinomas and atypical carcinoids have better prognoses than small cell neuroendocrine carcinomas and undifferentiated large cell carcinomas. The presence of an associated mucinous component would be a factor of a good prognosis [13, 14].

The 5-year survival of breast primary neuroendocrine tumors exceeds 80% in all combined tumor subtypes. However, recent studies specified the frequency of locoregional recurrences and metastases, making the prognosis better in general [8, 14,

22]. The main prognostic factors are the age, the field, the capacity of tumor secretion, the tumor size, and the existence or not of distant metastases [8, 22].

CONCLUSION

Neuroendocrine tumors of the breast are rare tumors; they can be primary or secondary. Histopathological analysis is the only way to achieve their correct diagnosis by using appropriate immunohistochemical staining. Studies including larger series are needed in order to understand the biological behavior of breast neuroendocrine tumors.

Availability of data and materials

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

Abbreviations

BIRADS: Breast Imaging Reporting and Data System

CT: Computed tomography

ENT: Ears, nose, and throat

NCAM: Neuron cell adhesion molecules

NSE: Neuron-specific enolase

PET:Positron emission tomography

SBR: Scarff–Bloom–Richardson

WHO: World Health Organization

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