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Full Length Research Paper

Primary neuroendocrine carcinoma of the breast: A rare and distinct entity

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Neuroendocrine tumor of the breast is a rare tumor that is under diagnosed and treated. This is a retrospective study over three years of neuroendocrine breast carcinoma cases seen at the National Institute of Oncology in Morocco between May 2007 and 2010. We analyzed various characteristics: Patient demographics, histological diagnosis, disease stage, treatment effects and outcome, in 7 non-metastatic neuroendocrine breast carcinoma. One patient had relapsed five weeks after radical mastectomy and neoadjuvant chemotherapy. The site of relapse was local and pleural at the liver. All the remaining patients are in a good control. Of note, at median follow up of 28 months, the disease free survival for the entire group was 85%, all the patients are still alive. In conclusion, neuroendocrine carcinoma is a subtype of mammary carcinoma with several distinctive features. They appear more likely to be estrogen/progesterone receptor (positive) and human epidermal growth factor receptor 2 (negative). To date, the optimal treatment for neuroendocrine carcinoma of breast is not clear. Radical mastectomy with neoadjuvant or adjuvant chemotherapy, adjuvant radiotherapy and hormonal therapy appears as a viable option.

Key words: Neuroendocrine carcinoma, breast carcinoma, chemotherapy, surgery, radiotherapy.

INTRODUCTION

Primary neuroendocrine carcinoma (NEC) of the breast is a rare tumor, which was first recognized in 1963, (Feyrter and Hartmann, 1963) and sporadically reported in the literature since then (Cubilla and Woodruff, 1977; Sapino et al., 2001). It accounts for less than 5% of all cancers arising from the breast (Tavassoli and Devilee, 2003). However, formal criteria for mammary NEC were not established until 2003, when the World Health Organization (WHO) classification of tumors (Tavassoli and Devilee, 2003) has clarified the interpretation of the phenomenon of neuroendocrine (NE) differentiation in breast cancer (BC) and defined NEC of the breast as having >50% neoplastic cells expressing NE markers. Because many of the previous studies used varying diagnostic criteria, it is difficult to compare the clinicopathological features and outcome data across these studies.

The WHO estimates that this uncommon and understudied malignancy represents approximately 2 to 5% of breast carcinomas (Tavassoli and Devilee, 2003). Unlike other special types of breast carcinoma such as tubular carcinoma (2% of invasive breast carcinomas), invasive cribriform carcinoma (0.5 to 3.5%), medullary carcinoma (1 to 7%), and mucinous carcinoma (2%) the biological behavior of NEC of the breast and its treatment have not been well studied. There are only 5 small series reported using the current WHO criteria, the largest series with follow-up data in only 35 patients (Sapino et al., 2001; Zekioglu et al., 2003; Lopez-Bonet et al., (2008). Because of the rarity of the disease, no standard treatment has yet been proposed. As a result, the issue of whether NEC of the breast behaves similarly to invasive ductal carcinoma (IDC) and can be treated as IDC remains in question. We conducted a retrospective study of all cases of NE non-metastatic breast cancinoma treated at the National institute of Oncology Morocco Cancer Centre over 3-year period.

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Table 1. Summary of the characteristics and treatment modality of neuroendocrine carcinoma of the breast in our patients.

Age	Anatpath type	Receptor (%)	Her-2	CT neoad	Surgery	Characteristics	LD	CT adj	RT adj	HT	Follow-up (months)
56	NEC Solid	O : 30 P : 10	Neg	No	Radical	SBR2 EV+	2N+/12	Cisp Etoposid	Yes	Tam	33
82	NEC Large cells	O : 70 P : 70	Neg	No	Radical	SBR3 EV+	12N-/12	Non	Yes	AI	37
51	NEC Solid	O : 90 P : 90	Neg	No	Radical	SBR3 EV+	1N+ /17	Cisp+ Etoposid	Yes	Tam	28
69	NEC Solid	O : 0 P : 0	Neg	No	Conservative	SBR2 EV+	2N+/18	Adriam+ Cycloph	Yes	No	27
56	NEC Solid	O : 90 P : 90	Neg	Adriam+ cycloph	Radical	SBR2 EV+	3N+ /12		Yes	Tam	10
50	NEC Solid	O :100 P :100	Neg	No	Conservative	SBR2 EV-	31N-/31	Adriam+ Cycloph	Yes	Tam	10
64	NEC Solid	O :100 P :100	Neg	Cisp+ etoposid	Radical	SBR3 EV-	16N+ /23N	No	No	No	Relapse 5 weeks 38

O: oestrogenic, P: progesteronic, Neg=negative, CT: chemotherapy, RT: radiotherapy, HT: hormonal therapy, AI: anti aromatases, tam: tamoxifene, LD: lymphadenopathy dissection, EV: vascular invasion embol.

MATERIALS AND METHODS

We retrospectively searched the files of all patients with carcinoma of the breast treated in the national institute of oncology of Rabat between May 2007 and 2010 to identify patients with NE carcinoma of breast. Patients were considered to have NE carcinoma of breast if pathological examination of their tumors revealed the presence of >50% of invasive tumor cells with cytoplasmic immunoreaction for synaptophysin, chromogranin or CD56. Immunohistochemical markers included synapthopyisin, chromogranin, estrogen receptor (ER), progesterone receptor (PR), HER2 (erbB-2), (Table 1). ER and PR were considered positive if >10% of nuclear invasive carcinoma cell staining was observed.

RESULTS

Incidence of NEBC

Seven tumors fully satisfied the NEBC criteria established by the WHO (the presence of >50% tumor immunoreactivity for one of NE markers including chromogranin, synaptophysin) were collected over a period of 4 years.

Clinical features of NEBC

All patients were female, menopausal, and they used oral contraceptive. Clinical data from NEBC patients are listed in Table 1. The age of NEBC patients ranged from 50 to 82 (median 56). Four patients had clinical t2, three patients had locally advanced disease with no distant metastasis at initial staging and one patient was classified t3. Surgical treatment was performed in all the patients. Radical mastectomy in 5/7 cases (71%) and conservative surgery in 2/7 (28.5%). A retroareolar localization of the tumor was identified in one case. Tumor size ranged from 1.4 to 13 cm (median 4 cm). Radical dissection of axillary nodes but not selective dissection of

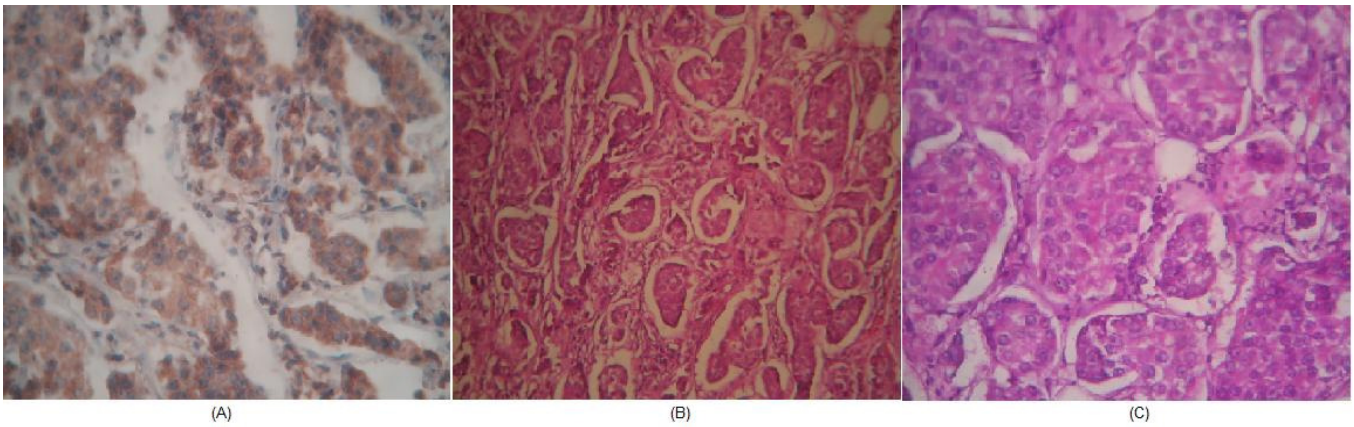

Figure 1. (A) Chromogranin A immunostaining in solid neuroendocrine carcinoma (x20), (B) Tumoral proliferation organized in solid and trabecular arrangements (x 20), (C) Atypical cells relatively monomorph and homogeneous organized in solid and trabecular arrangements, with fine granular eosinophil cytoplasm and hyperchromatic nuclei (x40).

sentinel node was performed in 7 cases. The number of dissected axillary lymph nodes oscillated from 12 to 31 (mean 18; median 17) with no node metastasis in 2 cases, one node metastasis in one case and more than 2 metastatic nodes in the four remaining cases (2,2,3 and 16 metastatic nodes, respectively).

Pathological features of NEBC

Six tumors were classified as solid NEBC (Figure 1), one as larges cells (Figure 2).

Immunohistochemical profiling of NEBC

6/7 cases (85%) were positive for ER and PR immunoreactivity. All the 7 selected NEBC cases (100%) were positive for synaptophysin or chromogranin in >50% of tumor cells (Figure 1a).

Treatment and prognosis of NEBC patients

Treatment schedules and follow-up of NEBC patients are listed in Table 1, four patients received adjuvant therapy (adriamycin and cyclophosphamide, or etoposide and cisplatine). Neoadjuvant chemotherapy (adriamycin and cyclophosphamide, or etoposide and cisplatine) was given in two patients. 6/7 cases (85%) received radiotherapy and hormonal therapy with tamoxifen. All the patients bearing NEBC were alive in the last clinical control with a mean follow-up of 28 months (range 10-38).

DISCUSSION

NEBC are defined by the diffuse expression of NE markers (chromogranin and/or synaptophysin) in ≥50% of cells. It distinguishes NEC of the breast from other mammary carcinomas that show only NE morphological features or focal (that is <50%) NE. This definition includes lesions with pure NE phenotype as well as variants which may co-express mucinous and/or apocrine phenotype. The existence of primary breast carcinoid tumors is still controversial and, if accepted, it would account for less than 1% of primary BCs (Feyrter, and Hartmann, 1963).

NE tumors of the breast are a rare malignancy in general; their prevalence is about 0.5% in a series of 1368 histopathologically proven BCs (Lopez-Bonet et al., 2008). Although NEC of the breast was recognized >40 years ago, this entity was first clearly defined in the most recent WHO classification of tumors in 2003.

Some authors suggest that NEC is usually seen in elderly woman. In our study, only one patient was over 70 and four patients were under 60 years old, the median age was 56 years. NEBC do not significantly differ from other breast carcinomas in terms of general clinical features. The radiological finding of NEC of breast mimics those of breast carcinomas in many ways without any specificity (Fujimoto et al., (2007).

The biological behavior and its treatment has not been well studied. With the exception of the recently published retrospective M. D. Anderson Cancer Center trial (Wei et al., 2010) in the literature there are only five small series reported using the current WHO criteria and none of them was case controlled, all had relatively small numbers of patients, the latter often lacking any follow-up information, and also there are few cases reported in the literature that describe therapeutic response to treatment, but most of them are about small-cell carcinomas (Nicoletti et al., 2010; Latif et al., 2010).

Three studies with 13, 12, and 7 patients, respectively, showed better prognosis in NEC (Zekioglu et al., 2003; Rovera et al., 2008; Lopez-Bonet et al., 2008) two studies with 35 and 10 patients showed no prognostic significance

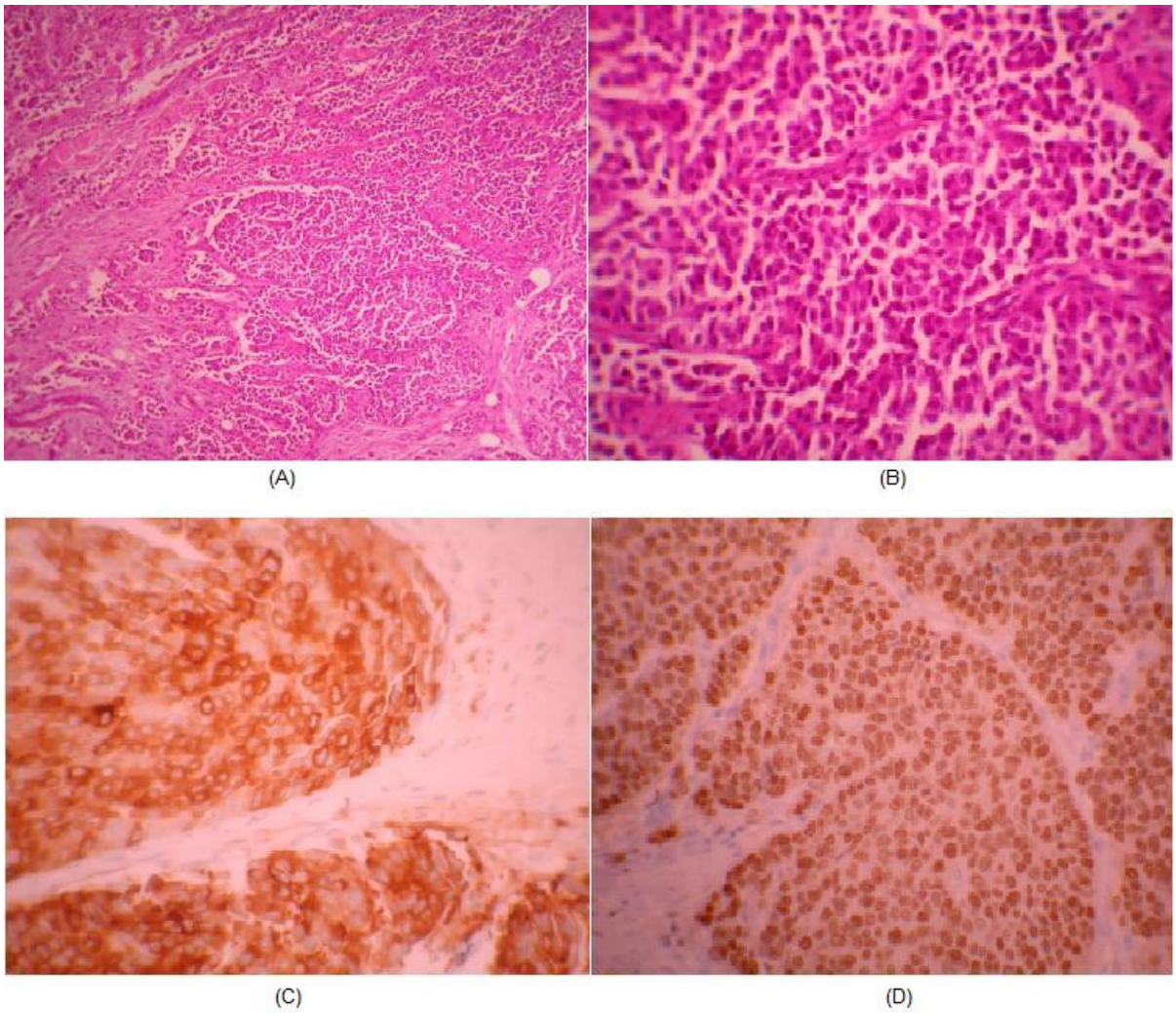

Figure 2. (A) Tumoral cells of big size organized in clumps and cords (Hématéine éosine x100), (B) Tumoral proliferation at the height enlargement (Hématéine éosine x400), (C) Intense expression of the synaptophysin by the tumoral cells (x 200), (D) Eostrogen receptor positivity in neuroendocrine larg cells carcinoma.

(Sapino et al., 2001; Surveillance, Epidemiology, and End Results, 2009; Tavassoli and Devilee, 2003; Zekioglu et al., 2003; Lopez-Bonet et al., 2008; Makretsov et al., 2003; Sawaki et al., 2010; Wei et al., 2010; Nicoletti et al., 2010; Latif et al., 2010; Rovera et al., 2008; Makretsov et al.,(2003). In agreement with earlier studies, all the NEBC in our series were classified as grade 2 or 3 (moderately differentiated) when the histological grade was classified according to modified Scarff-Bloom Richardson histological grading criteria. Two prognostic factors identified in a retrospective study are Regional lymph node metastasis and high nuclear grade. Of the five cases with node axillary metastases at the time of diagnosis reported in our study, four remained free of tumor disease after a follow-up of 27, 10, 33 and 28 months respectively.

NEC has a more aggressive course than ductal carcinoma, with a higher propensity for local and distant recurrence and poorer OS. In our study, one patient relapsed only 5 weeks after the mastectomy, at the median follow up of 28 months, the FDS is 85%, and all the NEBC cases are still alive. NEC is significantly more likely to be ER/PR positive and HER-2 negative. All the NEBC described in our study showed a positive status for estrogen and progesterone receptors except in one case, and a negative status for HER-2 consistent with the literature data. One case of large cell NEC of breast is reported in our study for 82 years old woman, The large cell NEC were initially described in the lung as poorly differentiated NE tumors and high grade of malignancy (Saint André et al., 2003).

They have been described in other organs like the thymus, stomatch, cevix, colon and rectum, urinary tract, ovary, the ampulla, salivary glands and uterus. To our knowledge, three cases have been reported in breast in the literature data (Kim et al., 2008; Tsai et al., 2005; Bourhaleb et al., 2009) and this is the fourth case. At the morphological level (Figure 2), it is a border

between atypical carcinoid and small cell NEC. The morphological appearance is similar to that observed in lung NE morphology with a high mitotic and necrotic power. The cells are large with moderate to abundant cytoplasm. The synaptophysin was expressed by >50% of cells. The hormonal receptors are positives (Figure 2d). Their expression in the breast does not suggest the evidence of mammary origin, the diagnosis is made if non mammary sites are confidently excluded or if an *in situ* component can be found (Tsai et al., 2005). Because NEBC is rare, and in the absence of randomized controlled trials, there is no standard treatment. NEBC tends to behave aggressively, 15% risk for local recurrence by 5 years, 34% risk for distant recurrence within 5 years, with up to 25% of patients presenting metastatic disease and up to two-thirds developing distant recurrence (Wei et al., 2010).

Most patients are treated like adenocarcinoma of the breast (Wei et al., 2010), there is no standard treatment protocol with various regimens has been used in different centers without defined conclusions on efficacy. Systemic therapy principles have been derived from small retrospective case reviews of primary neuroendocrine breast carcinomas and extrapolated from studies of non breast neuroendocrine carcinomas, since the clinical behavior and histology are similar. There is no consensus on the optimal adjuvant chemotherapeutic regimen in breast NEC. Multiple chemotherapeutic regimens have been used. The trials are difficult to evaluate due to small numbers of patients, multiple treatment regimens, and occasional use of radiation therapy. The chemotherapeutic regimens most commonly used can be simplified into cisplatine and etoposid or adriamycine and cyclophosphamid or 5 fluorouracil, epirubicin and cyclophosphamide. Wei et al. (2010) reported in a retrospective study of NEC of breast of 74 patients with NECB that hormonal therapy, chemotherapy and radiation therapy have not demonstrate an advantage in overall survival in comparison to ductal carcinoma.

In summary, NEC is a subtype of mammary carcinoma with several distinctive features. NEBC are more likely to be ER/PR positive and HER-2 negative. They have a more aggressive course than ductal carcinoma, with a higher propensity for local and distant recurrence and poorer OS. Studies with longer follow-up and greater case numbers will be needed to address this issue. The novel therapeutic used in the other sites should be explored like streptozotocine or cetuximab.

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