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Neuroendocrine carcinomas of the breast

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ABSTRACT

Introduction: Neuroendocrine (NE) breast cancers encompass a heterogeneous group of tumours showing morphological features similar to those of NE neoplasms of the gut and lung and expressing one or more neuroendocrine markers (neuron specific enolase, chromogranins synaptophysin) in at least 50% of tumour cells. They are rare lesions representing about 2–3% of all breast cancers and affecting more frequently elderly patients.

Aim: Prospective observational study is to analyse the clinico-pathological aspects of NE carcinomas of the breast undergone surgical resection compared to breast carcinomas with a minor neuroendocrine component and to conventional invasive ductal or lobular cancers.

Material and method: Thirty-five consecutive breast carcinomas showing morphological features suggestive of an endocrine differentiation were selected among breast cancers undergone surgical treatment during the period of January 1979–December 2004.

Results: The 35 patients were divided into two categories: 13 neuroendocrine carcinomas (NECs) and 22 ductal carcinomas with a minor neuroendocrine component (DC-NE). The average follow-up was 60 months. The patients with CNE developed breast cancer in an advanced age compared to the patients with infiltrating ductal carcinoma NAS or infiltrating lobular carcinoma. We did not find recurrent disease in the NEC group, while it was observed in 2 patients (9%) with DC-NE, in 6 cases (17%) with infiltrating ductal carcinoma NAS and in 7 cases (20%) with infiltrating lobular carcinoma.

Discussion: The CNE compared with the infiltrating ductal and lobular carcinoma are statistically different in relation to the expression of the receptor of c-erb-B2, p53, progesterone, for the lymph node state at diagnosis and the risk of reappearance of breast tumour. Our study confirms the choice to consider the neuroendocrine carcinoma of the breast as a separate histological group and seems to suggest a less aggressiveness of this type of tumour.

1. Introduction

Neuroendocrine (NE) breast cancers encompass a heterogeneous group of tumours showing morphological features similar to those of NE neoplasms of the gut and lung and expressing one or more neuroendocrine markers (neuron specific enolase, chromogranins synaptophysin) in at least 50% of tumour cells. They are rare lesions representing about 2–3% of all breast cancers and affecting more frequently elderly patients (WHO 2003). Although in the majority of cases NE carcinomas are endocrinologically silent, rare cases with symptoms correlated to ectopic secretion of ACTH, parathyroid hormone, calcitonin and norepinephrine have been described. Breast carcinomas showing focal endocrine differentiation, revealed by immunohistochemical expression of neuroendocrine markers in scattered tumour cells, are not included in this group.

Although the first description of two breast cancers showing morphological features resembling those of intestinal carcinoids was published in 1963,[1] the term "primary carcinoid tumour" of the breast was introduced by Cubilla and Woodruff in 1977 to characterize a group of tumours regarded as a new pathologic entity.[2] Since those descriptions, several attempts have been made to better characterize this particular tumour type, the existence of which and methods for recognizing have been a highly controversial issue over the past decade. It has been only recently definitively accepted as a separate entity, but the term "breast carcinoid" has been abandoned and the term "neuroendocrine carcinoma" is preferred (WHO, 2003).

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The pathogenesis of breast NE carcinomas is still controversial. Cubilla and Woodruff, although failed to detect argyrophilic granules in the normal breast epithelium, concluded that neuroendocrine neoplasms derived from argyrophilic cells of neural crest origin, presumably migrated to mammary ducts. However, this embryology-derived theory has not been definitively demonstrated. In 1985 Bussolati and co-workers identified, using immunohistochemistry, the presence of chromogranin positive neuroendocrine cells in normal ductal cells.[3] However, other authors[4] did not confirm this finding, so the presence of neuroendocrine cells in normal mammary ducts has to be definitively ascertained to date. An alternative hypothesis suggests that these tumors may originate from epithelial cells that, during the carcinogenesis process, acquire the ability to differentiate, focally or diffusely, toward an endocrine line.[5] This hypothesis could be indirectly confirmed by the fact that the existence of hyperplastic lesions or benign neuroendocrine tumours of the mammary gland has never been demonstrated in the breast, conversely to other system like the gastrointestinal tract.[6] Furthermore, the existence of a double exocrine–endocrine differentiation within neoplastic cells supports the hypothesis of a common origin from a stem mammary cell.[7]

As proposed in the last WHO classification of breast tumours (2003), NE carcinomas are divided in three categories: (1) solid neuroendocrine carcinoma, (2) small cells carcinoma, (3) large cells carcinoma.

2. Aim

The aim of this prospective observational study was to analyse the clinico-pathological aspects of NE carcinomas of the breast undergone surgical resection and to compare them with those of breast carcinomas with a minor neuroendocrine component and with those of conventional invasive ductal or lobular cancers.

3. Material and methods

Thirty-five consecutive breast carcinomas showing morphological features suggestive of an endocrine differentiation were selected, after morphological review, among breast cancers undergone surgical treatment at the Department of Surgical Sciences – University of Insubria in Varese during the period of January 1979–December 2004. Clinical data were registered in a computerized data-base. For comparison 35 consecutive cases of infiltrating ductal breast cancers NAS and 35 cases of infiltrating lobular carcinomas were also included in the study.

The selected cases of suspected NE carcinomas were immunohistochemically investigated to search for the expression of neuroendocrine markers, including neuron specific enolase, synaptophysin, chromogranin A, and CD56. In addition, all cases were studied for the expression of oestrogen and progesterone receptors, Ki67, p53 and c-erb-B2. The morphological study also included the evaluation of cytological grade, vascular and neural invasion, mitotic count, and morphological subtype according to Papotti et al.[8,9]

4. Results

On the basis of the immunohistochemical results, the 35 selected carcinomas presenting morphological characteristics suggestive for a neuroendocrine differentiation have been divided into two categories:

- 13 neuroendocrine carcinomas (NECs) showing the expression of at least one neuroendocrine marker in more than 50% of the tumour cells. According to the WHO classification all cases were classified as solid neuroendocrine carcinomas. The average age of patients was 79.8 years (range: 54–95 years). About 70% of these tumours were well differentiated (G1) and vascular invasion was demonstrated in 23% of cases.
- 22 ductal carcinomas with a minor neuroendocrine component (DC-NE), in which the expression of neuroendocrine markers was found in less than 50% of the tumour cells. The average age of patients was 79.4 years (range: 59–95 years) and vascular invasion was observed in 5 cases on 22 (22.7%).

The average follow-up was 60 months with an interval range between 24 and 120 months. Six patients (3 belonging to the NEC category and 3 to that of DC-NE) died for causes not directly related to the breast pathology; three patients were lost to follow-up as living in provinces far from Varese; one patient with DC-NE died for disease 33 months after surgery. Six patients (2 NECs and 4 DC-NEs) developed bone metastases diagnosed 34 and 58 months, respectively, after the diagnosis of breast cancer; in one patient (DC-NE) breast cancer was locally advanced with signs of skin infiltration (pT4b). We did not find a statistically significant different survival ($p = 0.06$) between patients with NECs and those with DC-NEs.

The expression of oestrogen receptors was observed in the majority of cells of all NECs (mean value of the cells expressing the receptor: 91.5%) and of all DC-NEs (mean value: 81.7%); in addition, the expression of the progesterone receptors was demonstrated in all cases of both categories with a mean value of 76.4% and 51%, respectively. Nuclear immunoreactivity for p53 was found in 2 of 13 NECs (15%) and 3 of 22 cases of CD-NE (13.6%). The Ki67 proliferation index ranged in both groups between 1 and 25% (mean value: 14%). The c-erb-B2 membrane receptor immunoreactivity was not found in any case.

Regarding the clinical aspects we observed that the patients with CNE developed breast cancer in an advanced age compared to the patients with infiltrating ductal carcinoma NAS or infiltrating lobular carcinoma. Ipsilateral axillary lymph node involvement (pN+) was observed in 2 patients (15%) with NEC, in 4 (18%) with DC-NE, in 10 (28.5%) with infiltrating ductal carcinoma NAS, and in 8 patients (23%) with infiltrating lobular carcinoma. This difference was statistically significant ($p = 0.01$). In addition, tumour resumption during the follow-up period was statistically significant when comparing the NEC group with the other histological types ($p = 0.009$). In details, we did not find recurrent disease in the NEC group, while it was observed in 2 patients (9%) with DC-NE, in 6 cases (17%) with infiltrating ductal carcinoma NAS and in 7 cases (20%) with infiltrating lobular carcinoma. Conversely, among various tumour groups there were not statistically significant differences in relation to diameter ($p = 1$), the expression of oestrogens receptors ($p = 0.58$) and Ki67proliferative index ($p = 0.86$).

5. Discussion

Although the existence of NECs of the breast and methods for recognizing have been a highly controversial issue over the past decade, the 2003 WHO classification of tumours of the breast legitimated this particular breast tumour type as a independent category. The diagnosis is based on a typical neuroendocrine morphology and on the expression of a neuroendocrine marker in more than 50% of cells.

Based on the results of our observational prospective study, the CNE compared with the infiltrating ductal and lobular carcinoma are statistically different in relation to the expression of the receptor of c-erb-B2, p53, progesterone, for the lymph node state at diagnosis and the risk of reappearance of breast tumour. These results confirm the choice to consider the neuroendocrine carcinoma of the breast as a separate histological group and seem to

suggest a less aggressiveness of the this type of tumour. The follow-up data show that patients with NEC of non-small cell type have a good survival. The overall survival of patients affected by NEC, in our study, has turned out to be better than that of patients affected by infiltrating ductal or lobular carcinoma. On the other hand, we did not observe a statistically significant difference between the survival rate of patients with NEC and those with DC-NE, although this data could be affected by the scarcity of the enrolled population.

Conflict of interest statement
The authors have no conflict of interest.

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Ethical approval
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