Clinical significance of neuroendocrine carcinoma of the breast

A. Sapino, M. Papotti, L. Righi, P. Cassoni, L. Chiusa & G. Bussolati
Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy

Summary

Background: Neuroendocrine (NE) carcinomas of the breast are defined by the diffuse expression of NE markers. This definition includes lesions with 'pure' NE phenotype as well as 'variants' which may co-express mucinous and/or apocrine phenotype. In the present work, the clinical significance of 'pure' NE differentiation in breast carcinoma and of its 'variants' will be analyzed.

Materials and methods: Forty-three NE breast carcinomas immunocytochemically positive for chromogranins and/or synaptophysin in ≥ 50% of cells were graded following the Elston and Ellis grading system for breast carcinomas. The production of mucin and the expression of the apocrine marker Gross Cystic Disease Fluid Protein-15 (GCDFP-15) were correlated with the grade and the hormonal receptor status. The clinical outcome of patients was also analyzed.

Results: The histological grade highly influenced the clinical evolution of NE breast carcinomas. We confirmed that mucinous differentiation is an important indicator of low biological aggressiveness. Estrogen and progesterone receptor expression was also correlated with a better prognosis. Presence of androgen was correlated with the expression of GCDFP-15 in NE tumors.

Conclusions: The histological grade overcomes the immunophenotype in determining the prognosis of NE differentiated carcinomas of the breast. Co-expression of exocrine products in such tumors is related to hormone dependency.

Key words: neuroendocrine carcinoma breast

Introduction

Reports on breast tumors showing features similar to carcinoids date back to 1963 [1]. Although in other non-endocrine organs, such as prostate [2] and lung [3], the neuroendocrine (NE) phenotype has been related to specific clinical features, evolution of NE breast cancer is still undefined. This may be the result of the fact that the term 'neuroendocrine' has been applied to a heterogeneous series of breast carcinomas, whereas in other organs this term defines tumors uniformly positive for NE markers. In addition, all the existing studies on the clinical evolution of NE breast carcinomas considered them as a single entity and did not take into consideration the histological grade [4]. Only the small-cell carcinomas are considered as the 'undifferentiated' variety of NE breast carcinomas [5].

A relatively common phenomenon of diagnostic interest, but of unknown clinical significance in NE breast carcinomas, is the presence of a 'divergent differentiation', which indicates the ability of a tumor to produce both exo- and endocrine substances. Mucin production is indeed a common feature in NE breast carcinomas and it has been correlated to a low aggressiveness of tumors.

We recently defined as 'NE differentiated breast carcinomas' a subset of tumors having specific morphological features and expressing NE markers in a relevant percentage (≥ 50%) of cells [6]. While studying these tumors we found that they could be associated to an apocrine differentiation based on the expression of GCDFP-15 (A. Sapino, personal communication). For these reasons we will, in the present work, subdivide lesions with 'pure' NE phenotype from 'variants' which may co-express mucinous and/or apocrine phenotype. In addition, we will analyze the influence of (a) the histological grade, (b) the 'divergent' differentiation and (c) the steroid hormone receptor status on the clinical features and evolution of breast carcinomas diffusely positive for NE markers.

Materials and methods

A series of 43 NE breast carcinomas which expressed at least one NE marker (namely Chromogranin A (CgA), or Chromogranin B (CgB), or Synaptophysin (Syn)) in ≥ 50% of their cells were graded using the Elston and Ellis grading system [7]. The production of the apocrine Gross Cystic Disease Fluid Protein (GCDFP-15) was evaluated using the immunocytochemical technique and a specific polyclonal antibody (kindly obtained by Dr D. Haagensen, Sacramento, California).

Immunohistochemical analysis of steroid receptors was performed on formalin fixed tissues using specific monoclonal antibodies anti estrogen receptor (ER) (1D5 mAb, Zymed, San Francisco, California), anti progesterone receptor (PR) (PgR-ICA mAb, Dakopatts, Copenhagen, Denmark) and anti androgen receptor (AR, F39.41 mAb, Biogenex San Ramon, California).

In 35 of 43 cases, the follow-up was available and correlated with the histological grade the immunophenotype and the steroid receptor status. Data were analyzed by one way analysis of variance (ANOVA).
apocrine cases had a longer survival after five years follow-up than pure NE carcinomas. The other important parameter was the expression of ER ($P < 0.0001$), followed by PR expression ($P = 0.02$). AR expression did not significantly change the prognosis ($P = 0.19$).

### Discussion

NE differentiation in breast carcinomas has been considered as a peculiar feature of minimal clinical significance. This paper stresses the biological and clinical interest of defining the spectrum of histological differentiation in 'pure' breast carcinomas as well as in variants where the exoNEcrine activity is co-expressed.

In a previous study we defined as NE differentiated carcinomas of the breast only those tumors expressing NE markers in at least 50% of their cells [6]. A clinical significance of such definition relies on the fact that a marked elevation of serum CgA has been detected in patients affected by small but intensely immunoreactive NE tumors [8].

All the existing studies on the clinical evolution of NE breast carcinomas considered them as a single entity and did not take into consideration the histological grade [9]. This led to some confusion on the clinical evolution of such tumors. In the present study we demonstrated that in analogy to the other non specified breast carcinomas [7], the histological grade is one of the most important parameters in the clinical evolution of the disease. Poorly differentiated (G3) NE carcinomas, which showed a high proliferative activity, were very aggressive. On the other hand well differentiated (G1) tumors with low proliferative activity could be considered as benign tumors, being all patients alive after more than 13 years of follow-up.

Another parameter correlated with the clinical follow-up was the tumor 'divergent differentiation' referred as the co-expression of NE and non-NE substances such as glycoproteins and apocrine protein in the same tumor. Such 'divergent differentiation' is frequently encountered in other organs [10, 11] and in NE breast carcinomas is maintained by cells of well differentiated tumors, whereas those of poorly differentiated carcinomas do not show this multi-differentiation capacity and express the NE phenotype only.

In agreement with other studies [12], we here demonstrated that the mucin production was correlated to a better prognosis; however, the grade overcame the importance of such differentiation on the clinical evolution. We previously demonstrated that patients with pure apocrine differentiated carcinoma had a better prognosis [13]. In the present study we could not find a significant improvement of prognosis in patients with NE-apocrine tumors in short-term follow-up. However five years after surgery, the association with apocrine differentiation seemed to improve long-term survival of patients with NE tumors.

The last important parameter in the prognosis of patients with NE breast carcinomas was the expression of ER, which highly correlated with a long overall survival. In addition the hormonal status influenced the
type of differentiation; in fact, in agreement with other authors [14], we here confirmed that the apocrine differentiation was correlated with a higher expression of AR and PR.

In conclusion, our results indicate that NE carcinomas of the breast, recognized as tumors producing high level of NE markers, are specific entity. The serum detection of the NE products may be useful in the clinical follow-up of patients. On the other hand, a potential role of GCDFP-15 as a marker of breast cancer micrometastasis has also been suggested [15]. Thus, the possibility to use these markers in the follow-up of these patients can justify the immunopheno-typing of NE tumors.

A major matter of concern stems from the impact on the patient's prognosis, when a diagnosis of NE carcinomas of the breast is made. Our results demonstrate that the pathologists should always specify the histological grade, which in these tumors is also an important parameter in the evolution of the disease.

References


Correspondence to:
Dr A. Sapino
Department of Biomedical Sciences and Human Oncology
University of Turin
Via Santena, 7
Torino
Italy
E-mail: anna.sapino@unito.it