Mixed neuroendocrine carcinoma consisting of small cell neuroendocrine carcinoma, metaplastic carcinoma, and invasive ductal carcinoma in the breast: A case report and review of the literature

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Case Report

Keywords: Breast, Mixed neuroendocrine carcinoma, Small cell neuroendocrine carcinoma, Metaplastic carcinoma

Posted Date: March 1st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2630697/v1

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Abstract

Introduction: Neuroendocrine carcinoma accounts for less than 0.1% of all breast cancers and is a rare clinical cancer with neuroendocrine morphology, immunophenotype, and high-grade cytologic features.

Case report: We report a case of a 54-year-old female patient with small cell neuroendocrine carcinoma of the right breast mixed with metaplastic carcinoma and invasive ductal carcinoma (non-specific type).

Discussion: No cases of mixed occurrence of the three types of carcinoma in the breast have been reported in the literature. In this case, we made the diagnosis based on morphological features and immunohistochemistry, discussing the histogenetic mechanism and therapy prognosis.

Conclusion: Due to the mixed occurrence of the three types of carcinoma, different morphological subtypes have different prognoses. Reporting the different components and their proportions becomes extremely important for clinical treatment and prognostic analysis in clinical work.

1. Introduction

Neuroendocrine carcinoma of the breast (NECB) is a rare clinical cancer with neuroendocrine morphology, immunophenotype, and high-grade cytological features, including small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC). NECB is characterized by heterogeneity, rarity, and poor differentiation\[1\]. To date, the mechanisms, molecular changes, clinicopathological features, and prognosis of NECB are not well understood. We report a case of small cell neuroendocrine carcinoma of the breast mixed with metaplastic carcinoma and invasive ductal carcinoma (non-specific type).

2. Case Report

The patient was a 54-year-old female with an abnormal hard mass in the right breast. X-ray showed an irregular dense mass in the right breast; MR showed a mass in the lateral quadrant with a dense DWIBS signal and abundant hematopoiesis; CT showed multiple enlarged lymph nodes in the right axilla(Fig. 1A). The patient underwent modified radical surgery for right breast cancer. The outer lower quadrant saw a grayish-white, hard mass with a volume of 4x2x1.5cm and poorly defined borders. 20 axillary lymph nodes were identified, including 2 cancer metastases.

Microscopically, the tumor composition showed small cell neuroendocrine carcinoma mixed with metaplastic carcinoma (including spindle cell carcinoma and osteoid metaplasia) and invasive ductal carcinoma (non-specific type) (Fig. 1B, C). Microscopically, small cell neuroendocrine carcinoma with diffuse growth, high N/C ratio, and blurred nucleoli with pepper-like cell areas were seen, which were consistent with small cell neuroendocrine carcinoma when combined with immunohistochemistry (Fig. 1D), accounting for approximately 60% of the cases. In addition, metaplastic carcinoma was seen, some areas were spindle cell carcinoma, and some areas were osteoid metaplasia (Fig. 1E), accounting for about 25% of the cases. Besides, the cancer cells showed trabecular growth areas with obvious
nuclear heterogeneity, which was consistent with invasive ductal carcinoma (Fig. 1F), accounting for about 15% of the cases. Immunohistochemistry of the masses showed that ER, PR, and Her-2 were negative (Fig. 1G). The tumors were highly proliferative, and the Ki-67 labeling index was 70% for all three types of cancer.

3. Discussion

Small cell neuroendocrine carcinoma of the breast mixed with metastatic carcinoma and invasive ductal carcinoma (non-specific type) has not been reported in the literature. In this case, the combination of microscopic morphologic features of neuroendocrine and small cell types, diffuse expression of neuroendocrine markers (Syn, CgA, INSM1) (Fig. 1H), and excluding other sources of neuroendocrine carcinoma is considered to be a primary small cell neuroendocrine carcinoma of the breast. Gregory R. Bean et al. found that dual allele inactivation of TP53 and RB1 is prevalent in SCNEC. This case verifies that RB deletion and P53 mutation are equally consistent with the findings by immunohistochemistry. For the diagnosis of metaplastic breast cancer (MpBC), Some areas were spindle cell carcinoma, some areas of tumor cells were osteoid metaplasia, and osteoblast-like giant cell reactive hyperplasia was visible. Immunohistochemical results support the diagnosis of metastatic carcinoma. The typical invasive histological presentation and immunohistochemical findings (membrane expression of P120, E-cad) support the diagnosis of invasive ductal carcinoma (non-specific type) (Fig. 1I).

The mechanism of NECB histogenesis is unknown. Some investigators suggest that NECB may be transformed by neuroendocrine cells present and/or proliferating in the breast. A more accepted theory is that NECB originates from epithelial and endocrine cell lines differentiated by tumor stem cells during early carcinogenesis. Regarding the rare pattern of coexistence of three types of cancer components, in this case, we have the following two views: one is that different types of tumors collide in the same mass, occurring independently and co-existing. In another view, since the histopathological subtype of metaplastic carcinoma is complex, it may differentiate into squamous cells, spindle cells, mesenchymal cells, and other lineages. It is our venture to speculate whether the development of neuroendocrine carcinoma components is related to metaplastic carcinoma and whether it is a specific type of metaplastic carcinoma that has not been reported. We consider whether this conjecture can be verified with the help of molecular assays and other methods, and it has been shown that a certain percentage of PIK3CA mutation rate exists in both NECB and MpBC.

In terms of treatment, there are no standardized guidelines for treating neuroendocrine carcinoma of the breast at home and abroad, and clinical staging and treatment are mostly similar to those for conventional breast cancer. Surgical procedures remain an important method for the treatment of early-stage NECB. In this case, the lack of ER, PR, and HER-2 receptors limited the options for endocrine and molecular targeted therapies. Berruti et al. showed that an anthracycline-based adjuvant chemotherapy regimen could benefit the survival of NECB patients. In addition to this, Vranic et al. suggested several potential targets for new therapies for NECB, including trophoblast surface antigen 2 (TROP-2), folate
receptor 1 (FOLR1), and H3K36Me3, which may help in the development of new NECB-targeted
therapeutics. The presence of neuroendocrine carcinoma and metaplastic carcinoma components often
suggests that patients are accompanied by higher aggressiveness and poorer prognosis. The prognosis
of this case will also be followed up continuously to provide better clinical information.

4. Conclusion

We report a new case of mixed neuroendocrine carcinoma of the breast. Since three types of carcinoma
occur in mixed form and different morphological subtypes have different prognoses, reporting the
different components and their proportion in clinical work becomes extremely important for clinical
treatment and prognostic analysis.

Declarations

Data availability statement

All datasets generated for this study are included in the article/Supplementary Material.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially
identifiable images or data included in this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial
relationships that could be construed as a potential conflict of interest.

Funding

This research was supported and funded by The National Natural Science Foundation of China(No.
81872163; No. 81672631).

Author contributions

Baogang Zhang conceived and designed the study. Qinpei Xiao and Kaixuan Sun contributed and
reviewed this case. Jianyu Cui was responsible for the technical performance of IHC. Zixin Pan wrote the
first draft, which was reviewed and approved by all co-authors.

References


**Figures**

**Figure 1**

Microscopic findings. **(A)** Mammographic CT and MR of the mass showed irregular borders. **(B)** The left side of this picture showed the small cell neuroendocrine carcinoma component with visible necrosis. The right side of the picture showed osteoid metaplasia with the reactive proliferation of osteoblast-like
giant cells. (C) Invasive ductal carcinoma and small cell neuroendocrine carcinoma were seen in this picture. (D) This picture showed a small cell neuroendocrine carcinoma component with a high N/C ratio and blurred nucleolus. (E) In this picture, mixed metaplastic carcinoma was observed (spindle cell carcinoma and osteoid metaplasia). (F) This picture displayed the component of typical invasive ductal carcinoma. (G) The results of immunohistochemistry showed negative for ER, PR, and Her-2. (H) Immunohistochemically, diffuse positive CgA in the region of small cell neuroendocrine carcinoma. (I) Diffuse positive CK in the area of invasive ductal carcinoma and mottled positive in the area of small cell neuroendocrine carcinoma.