Triple-Negative Mixed Neuroendocrine Carcinoma in the Breast: A Case Report and Review of the Literature

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Background: *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 (nonspecific type), and it's a rare case of triple-negative breast cancer.*

Discussion: *Herein, to the best of our knowledge, we present the first documented case of the mixed occurrence of the three types of breast cancer. In this case, we made the diagnosis based on morphological features and immunohistochemistry and discuss the histogenetic mechanism and therapy prognosis.*

Conclusion: *Reporting the different components and their proportions is extremely important for clinical treatment and prognostic analysis in clinical work. In this case, the unusual combination of components may provide a new pathologic basis for further study of the etiologic mechanisms and causation of the disease.*

BACKGROUND

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 SCNEC of the breast mixed with metaplastic carcinoma and invasive ductal carcinoma (nonspecific type).

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. Magnetic Resonance Imaging (MRI) showed a mass in the lateral quadrant with a dense Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) signal and abundant hematopoiesis. Computed Tomography (CT) showed multiple enlarged lymph nodes in the right axilla (Figure 1A-C). The patient underwent modified radical surgery for right breast cancer. The outer lower quadrant showed a grayish-white, hard mass with a volume of 4x2x1.5 cm and poorly defined borders. Twenty axillary lymph nodes were identified, including 2 cancer metastases. Microscopically, SCNEC with diffuse growth, a high N/C ratio, and blurred nucleoli with pepper-like cell areas were seen. These findings combined with the immunohistochemistry findings were consistent with SCNEC (Figure 2 D-F), which accounts for approximately 60% of the cases of

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Figure 1: Microscopic findings. Mammographic CT and MR of the mass showed irregular borders.

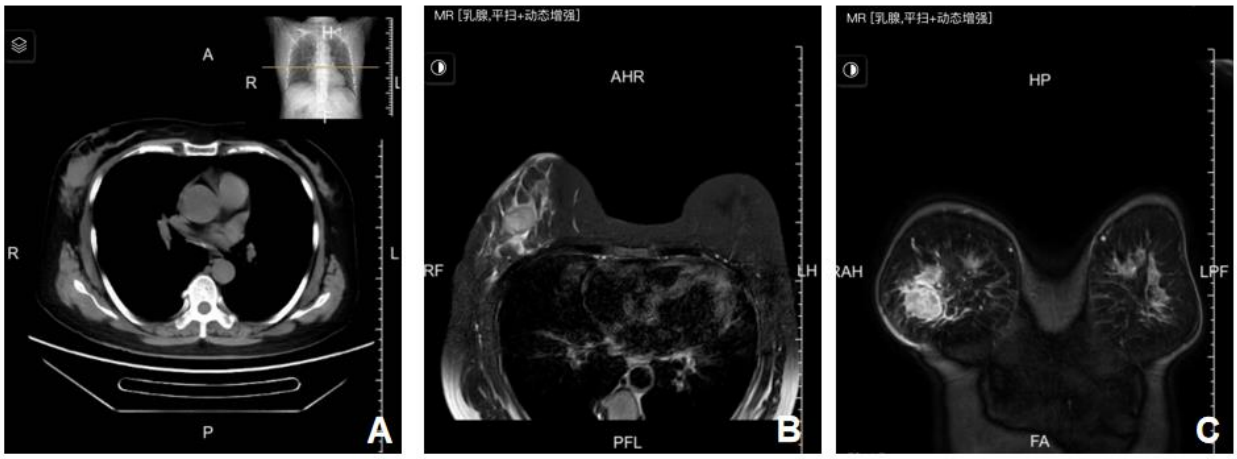
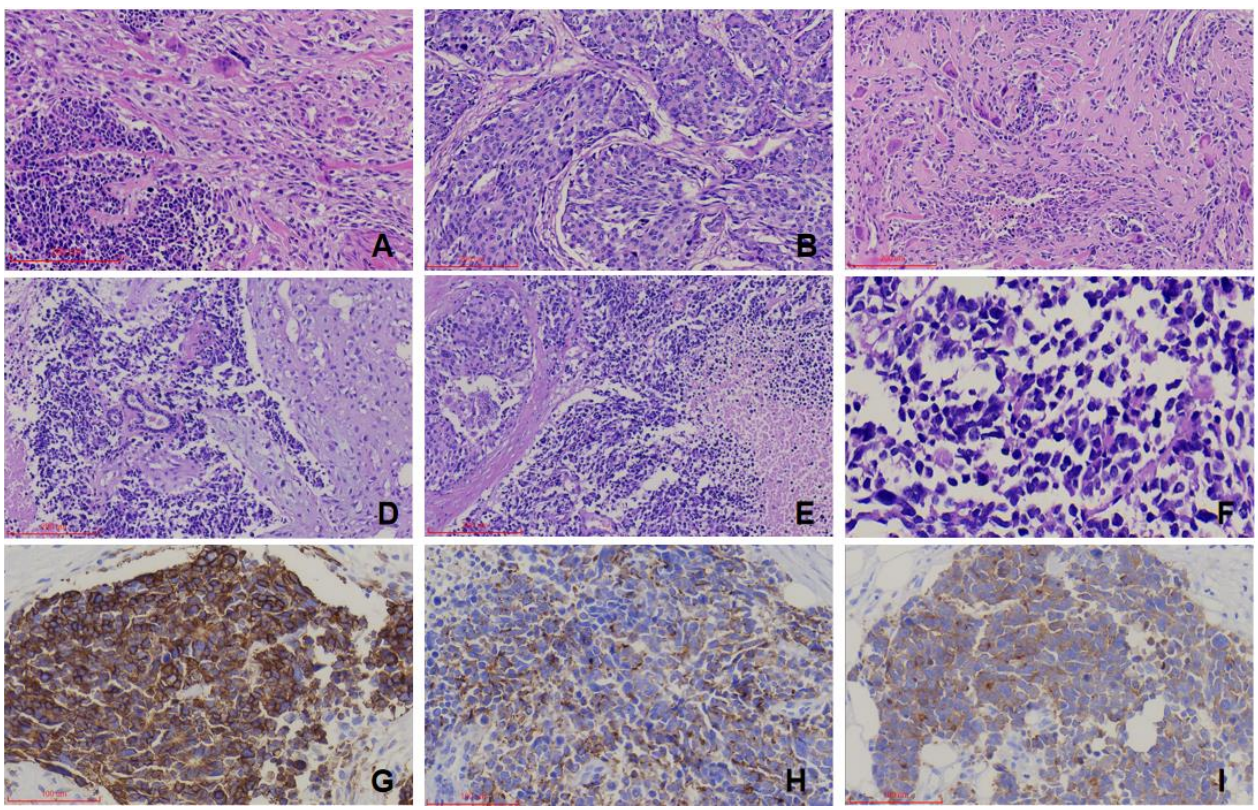


Figure 2: (A) Mixed occurrence of small cell neuroendocrine carcinoma and metaplastic carcinoma. (B) Typical invasive ductal carcinoma. (C) Osteoid metaplasia with the reactive proliferation of osteoblast-like giant cells. (D-F) Small cell neuroendocrine carcinoma component with visible necrosis. (G) Immunohistochemistry results of CD56. (H) Immunohistochemistry results of Syn. (I) Immunohistochemistry results of CgA.



the cases of carcinomas in this patient. In addition, metaplastic carcinoma was seen, and there were some areas of spindle cell carcinoma and some areas of osteoid metaplasia. These areas accounted for approximately 25% of the cases of carcinomas in this patient. Moreover, the cancer cells showed trabecular growth areas with obvious nuclear heterogeneity, which was consistent with invasive ductal carcinoma. These areas accounted for approximately 15% of the cases of carcinomas in this patient. Immunohistochemistry of the masses showed that ER, PR, and Her-2 were negative. The tumors were highly proliferative, and the Ki-67 labeling index was 70% for all three types of cancer.

DISCUSSION

SCNEC of the breast mixed with metastatic carcinoma and invasive ductal carcinoma (nonspecific type) has not been reported in the literature. In this case, the combination of microscopic morphologic features of neuroendocrine and small cell types, the diffuse expression of neuroendocrine markers (Syn, CgA, CD56) (Figure 2 G-I), and the exclusion of other sources of neuroendocrine carcinoma indicate primary SCNEC of the breast. Gregory R.[2] 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. The typical invasive histological presentation and immunohistochemical findings (membrane expression of P120, E-cad) support the diagnosis of invasive ductal carcinoma (nonspecific type).

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.[3] A more accepted theory is that NECB originates from epithelial and endocrine cell lines differentiated by tumor stem cells during early carcinogenesis.[4] Regarding the rare pattern of the coexistence of three types of cancer components in this case, we have two views. One is that different types of tumors collide in the same mass, occurring independently and coexisting. 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. Thus, we 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 PIK3CA mutation rate exists in both NECB and MpBC.[1,5] In terms of treatment, there are no standardized guidelines for treating NECB at home and abroad, and the 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.[6] anthracycline-based adjuvant chemotherapy regimen could benefit the survival of NECB patients. In addition,[7] 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 have higher tumor aggressiveness and poorer prognosis. The prognosis of this case will also be followed up continuously to provide better clinical information.

CONCLUSION

We report a new case of triple-negative 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 is extremely important for clinical treatment and prognostic analysis.

Data availability statement

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

Ethics statement

The manuscript is an original work of all authors. All authors made a significant contribution to this study. All authors have read and approved the final version of the manuscript.

Institutional Review Board Statement

The patient whose case is described in this review, freely agreed to participate in this case report as described, the publication of this case was approved by the IRB of Affiliated Hospital of Shandong Second Medical University.

Informed Consent Statement

Written informed consent has been obtained from the patient(s) to publish this paper.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

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

REFERENCES

1. Sun H, Dai S, Xu J. Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives. Front Oncol 2022;12: 848485.
2. Bean GR, Najjar S, Shin SJ, et al.Genetic and immunohistochemical profiling of small cell and large cell neuroendocrine carcinomas of the breast. Mod Pathol 2022;35: 1349-1361.
3. Kawasaki T, Mochizuki K, Yamauchi H, et al.Neuroendocrine cells associated with neuroendocrine carcinoma of the breast: nature and significance. J Clin Pathol 2012;65: 699-703.
4. Rosen LE, Gattuso P.Neuroendocrine Tumors of the Breast.Arch Pathol Lab Med 2017;141: 1577-1581.
5. Reddy TP, Rosato RR, Li X, et al. A comprehensive overview of metaplastic breast cancer: clinical features and molecular aberrations. Breast Cancer Res 2020;22:121.
6. Berruti A, Amoroso V, Fazio N.Endocrine and Neuroendocrine Tumors: A Special Issue. Cancers (Basel) 2022;14(20).
7. Vranic S, Palazzo J, Sanati S, et al.Potential Novel Therapy Targets in Neuroendocrine Carcinomas of the Breast. Clin Breast Cancer 2019;19:131-136.