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Original Research Paper

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UNVEILING A RARE ENTITY: MIXED MUCINOUS BREAST CARCINOMA WITH NEUROENDOCRINE DIFFERENTIATION

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ABSTRACT

Background: Mucinous carcinoma of the breast is a rare special histological subtype of invasive breast carcinoma, accounting for 1–7% of cases. It is subdivided into pure and mixed variants, the latter being less common and associated with a higher risk of lymph node metastasis and comparatively poorer prognosis. Neuroendocrine differentiation in breast carcinoma is an infrequent finding and has been reported in association with mucinous carcinomas, further adding to diagnostic complexity. **Case Presentation:** We report the case of a 60-year-old woman who presented with a progressively enlarging left breast lump of six months' duration. Imaging revealed a suspicious mass with microcalcifications in the lower outer quadrant. Tru-cut biopsy suggested invasive carcinoma with mucinous differentiation. The patient underwent modified radical mastectomy with axillary lymph node dissection. Histopathological examination showed an invasive carcinoma composed of abundant extracellular mucin lakes containing clusters and cords of tumor cells, along with a non-mucinous invasive component, consistent with mixed mucinous carcinoma. Immunohistochemistry demonstrated luminal A molecular subtype with a low proliferative index and strong expression of neuroendocrine markers synaptophysin and chromogranin, confirming neuroendocrine differentiation. **Conclusion:** Mixed mucinous carcinoma of the breast with neuroendocrine differentiation is a rare and underreported entity. Accurate diagnosis requires careful histomorphological assessment supported by appropriate immunohistochemical studies. Documentation of such cases is essential to improve understanding of their biological behavior, prognostic significance, and classification within the current WHO framework.

KEYWORDS : Mucinous Carcinoma, Breast, Neuroendocrine Differentiation, Rare.

INTRODUCTION

Breast carcinoma is the most frequently diagnosed cancer among women worldwide. According to recent global estimates, breast cancer accounts for approximately 2.3 million new cases annually, constituting nearly 11–12% of all newly diagnosed cancers, and is a leading cause of cancer-related mortality among women globally [1]. Despite advances in screening and therapy, breast carcinoma continues to pose a significant public health burden. The World Health Organization (WHO) Classification of Tumours of the Breast (5th edition) categorizes breast carcinomas based on distinct histomorphological and biological characteristics. Invasive breast carcinomas are broadly divided into invasive carcinoma of no special type (NST) and a group of special histological subtypes, which include tubular, cribriform, lobular, metaplastic, and mucinous carcinomas, among others [2]. These special subtypes account for approximately 25% of invasive breast cancers and exhibit varied prognostic and therapeutic implications.

Mucinous carcinoma of the breast is a rare special histological subtype characterized by clusters of neoplastic epithelial cells suspended in abundant extracellular mucin. It constitutes approximately 1–7% of all invasive breast carcinomas and is more commonly diagnosed in post-menopausal women [3,4]. Based on histological composition, mucinous carcinoma is further subclassified into pure mucinous carcinoma, in which mucinous components predominate, and mixed mucinous carcinoma, which contains both mucinous and conventional invasive carcinoma components [2].Among these, mixed mucinous carcinoma is particularly uncommon and clinically significant due to its association with a higher rate of lymph node metastasis and less favorable prognosis compared to the pure variant [5,6]. Owing to its rarity and overlapping histopathological features with other invasive carcinomas, mixed mucinous carcinoma remains under-reported. Even more intriguing is the occasional presence of neuroendocrine differentiation within such tumors, a feature that adds another layer of diagnostic complexity. This case report highlights one such uncommon presentation, where each step of evaluation gradually revealed a more intricate pathological identity.

Case Summary

A 60-year-old lady presented to the surgical outpatient department in October 2025 with a seemingly straightforward complaint—a left-sided breast lump that she had first noticed six months earlier. Initially managed with alternative medicine, the lesion continued to grow insidiously, prompting clinical consultation. On examination, a firm space-occupying lesion was palpable in the lower outer quadrant of the left breast. Imaging studies, including mammography, revealed a suspicious lesion at the 4 o'clock position, accompanied by microcalcifications—raising the first clinical suspicion of malignancy.

A tru-cut biopsy was performed, providing the first histological clue: invasive breast carcinoma with mucinous differentiation. The tumor was graded as histological grade 3 (tubular differentiation score 3, nuclear pleomorphism score 2, mitotic rate score 3). At this stage, the lesion appeared to fit within the spectrum of mucinous carcinoma, although the higher grade hinted at a potentially more complex biology. No DCIS, lymphovascular invasion, or microcalcifications were identified microscopically.

Immunohistochemistry further refined the picture, revealing a luminal type A breast carcinoma with a low proliferative

index—features typically associated with a relatively favorable prognosis. Yet, the story was far from complete.

The patient subsequently underwent a left-sided modified radical mastectomy with axillary lymph node dissection on 18.12.2025. Gross examination revealed a variegated soft-to-firm tumor measuring 5 × 4.5 × 3 cm, with the closest deep resection margin lying 0.4 cm away (Fig. 1). At this point, the lesion still appeared consistent with a mucinous carcinoma, but its heterogeneity invited closer scrutiny.

Microscopic examination unveiled the next layer of complexity. Extensive extracellular mucin lakes dominated the landscape, within which clusters, nests, cords, and scattered single tumor cells appeared to float. The tumor cells were relatively uniform, with round to oval nuclei, mild to moderate pleomorphism, finely dispersed chromatin, and inconspicuous nucleoli. The cytoplasm ranged from eosinophilic to amphophilic.

The mucin imparted a characteristic gelatinous appearance, traversed by delicate fibrovascular septae. Mitotic activity was low to moderate, and necrosis was absent. The surrounding stroma showed mild lymphocytic infiltration with variable fibrosis, while calcifications were sparse. Importantly, the mucinous component constituted between 10% and 90% of the tumor, confirming that this was not a pure mucinous carcinoma.

Then came a subtle but crucial observation—focal areas displaying an organoid architectural pattern (Fig. 2). This architectural shift raised the possibility of an additional line of differentiation, prompting further investigation.

Immunohistochemical analysis provided the decisive clue: strong positivity for synaptophysin and chromogranin (Fig. 3), confirming neuroendocrine differentiation. What initially appeared to be a conventional mucinous carcinoma had now evolved into a far rarer diagnosis.

The final diagnosis was established as 'mixed mucinous breast carcinoma with neuroendocrine differentiation'—a diagnosis that only became evident through careful, stepwise evaluation.

DISCUSSION

Neuroendocrine differentiation in breast carcinoma represents a distinctive but relatively uncommon phenomenon, defined by the expression of markers such as chromogranin A and synaptophysin. It has been reported across a spectrum of histological subtypes, including mucinous carcinoma, thereby expanding the morphological and biological diversity of these tumors [10–13].Mixed mucinous carcinoma of the breast is itself an uncommon histological variant, characterized by the coexistence of mucinous and conventional invasive carcinoma components. According to the WHO classification, it is defined by the presence of less than 90% mucinous elements in association with a non-mucinous invasive component [2]. The occurrence of neuroendocrine differentiation within this already rare subtype further adds to its diagnostic and biological complexity.

Only a limited number of case reports have documented this unusual combination. Anuradha and Lakshmi described a comparable case, highlighting its rarity and emphasizing the importance of immunohistochemical confirmation in establishing the diagnosis [7]. Additionally, prior studies have noted that hypercellular (mucinous B) variants may show morphological overlap with tumors exhibiting neuroendocrine differentiation, suggesting the possibility of a biological continuum rather than entirely distinct entities [8,9].

In the present case, the diagnostic progression reflects this morphological overlap. The initial biopsy suggested mucinous differentiation; however, subsequent histopathological evaluation revealed mixed features. The identification of organoid architecture, coupled with the application of neuroendocrine markers, ultimately led to the final diagnosis, underscoring the need for a high index of suspicion in such cases.

Immunohistochemistry remains the cornerstone for confirming neuroendocrine differentiation, with chromogranin A and synaptophysin being the most specific markers [13]. While some studies suggest an association between neuroendocrine differentiation and favorable prognostic indicators, such as hormone receptor positivity, its overall prognostic significance remains uncertain due to limited available data [6,7,12]. From a classification perspective, the WHO currently advocates for descriptive reporting of neuroendocrine differentiation rather than rigid categorization, acknowledging that both conventional and special types of breast carcinoma may exhibit such features [10].

Clinically, management aligns with standard treatment protocols for invasive breast carcinoma and is guided by established prognostic parameters. Nevertheless, recognition of this rare entity is important—not only for accurate diagnosis but also for its potential implications in future research and the development of targeted therapeutic strategies.

CONCLUSION

This case illustrates how a seemingly straightforward breast carcinoma can unfold into a diagnostically intricate entity upon deeper evaluation. Mixed mucinous carcinoma with neuroendocrine differentiation represents a rare intersection of two uncommon pathological features, demanding careful morphological assessment and judicious use of immunohistochemistry.

The stepwise emergence of diagnostic clues—from mucinous differentiation on biopsy to mixed histology and finally neuroendocrine marker positivity—highlights the importance of a meticulous and inquisitive approach in surgical pathology.

Within the current WHO framework, documenting neuroendocrine differentiation is essential, even in conventional or special histological subtypes. Although the prognostic implications remain unclear, continued reporting of such cases will enhance understanding, refine diagnostic criteria, and potentially influence future therapeutic strategies for this rare breast carcinoma subtype.

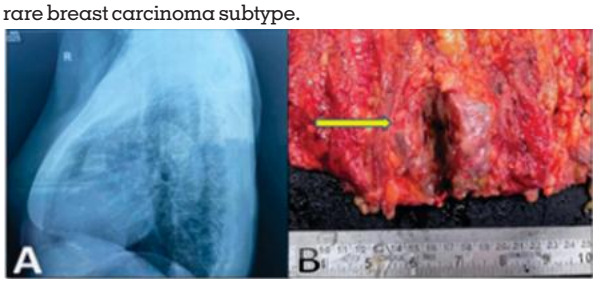

Figure 1. (A) Mammography of right brest showing a hyperdense SOL at lower-outer quadrant with microcalcification. (B) Photograph of gross specimen of right sided modified radical mastectomy showing a tumour at lower-outer quadrant having variegated cut surface comprising solid and mucinous areas.

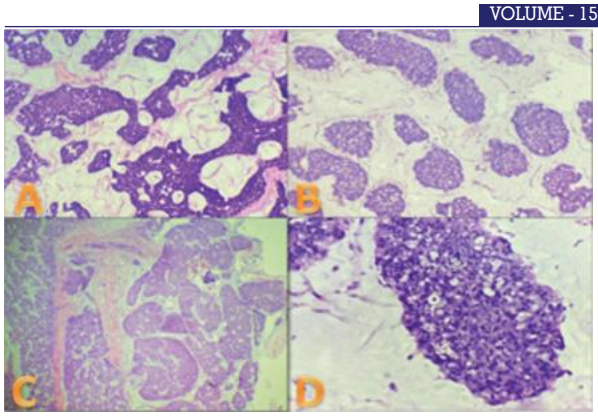

Figure 2. (A) H & E;400X- Clusters of neoplastic cells floating in extracellular mucin. (B) H& E;400x- Neoplasic cells arranged in organoid pattern. (C) H& E;200x- Neoplastic cells arranged in solid pattern. (D) H& E; Individual tumour cells are pleomorphic with marked cellular and nuclear pleomorphism, moderate to scant eosinophilic cytoplasm and vesicular to hyperchromatic nuclei.

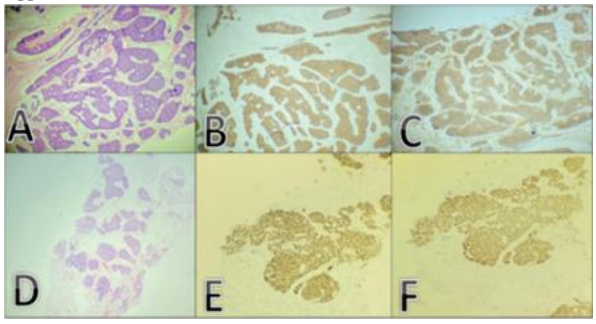

Figure 3. (A) H& E, 100X- showing clusters of neoplastic cell. (B) Strong Synaptophysin expression in tumour cells. (C)Strong Chromogranin expression of tumour cells. C. H& E, 100X; Showing tumour cells in a core biopsy specimen . (D) Estrogen receptor expression in tumour cells. (E) Progesterone receptor expression in tumour cells.

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