Estrogen and Progesterone Receptor Negativity and *HER-2* Positivity in a Pure Mucinous Breast Carcinoma

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Abstract

Introduction: Mucinous carcinomas may be pure or mixed, depending on the cellularity present. They are a slow growing neoplasm, are usually low grade, with rare axillary lymph node metastases. They have a better prognosis compared with other invasive carcinomas. Immunohistochemical studies of mucinous carcinomas regularly show Estrogen Receptor (ER) and Progesterone Receptor (PR) positivity and human epidermal growth factor receptor-2 (*HER-2*) negativity.

Case Summary: A 54-year-old female consulted due to a gradually enlarging mass on the upper outer quadrant of her right breast. Core needle biopsy of the mass revealed an invasive carcinoma with mucinous features. The patient underwent modified radical mastectomy, where the final histopathologic diagnosis for the submitted surgical resection specimen was mucinous carcinoma with signet ring cell features, Nottingham histologic grade II. Immunohistochemical staining of the core biopsy specimen and surgical resection specimen revealed negative estrogen and progesterone receptors and positive *HER2/neu* receptor (3+) in 100% of the tumor cells, which is different from the typical immunohistochemistry profile of mucinous breast carcinomas.

Discussion: Pure mucinous carcinoma or colloid carcinomas accounts for not more than 2% of invasive breast carcinomas and presents with large amounts of extracellular mucin. Between pure and mixed mucinous carcinoma, prognosis is better in pure types. Modified radical mastectomy remains the gold standard of treatment for breast tumors followed by post-operative endocrine therapy, which is indicated in estrogen and progesterone responsive tumors. *HER2/neu* expression in breast tumors along with the absence of hormone (estrogen and progesterone) receptors is associated with an aggressive phenotype. When *HER-2* is positive, treatment would be trastuzumab, although resistance for mucinous carcinomas has been reported.

Conclusion: Only few cases of pure mucinous carcinomas are positive for *HER2* receptors and negative for estrogen and progesterone receptors. It is important for physicians to know that cases of mucinous carcinoma positive for *HER2* and negative for estrogen and progesterone exist and to be aware of the clinical problems that they may present.

Keywords: Mucinous Carcinoma• Breast• Estrogen• Progesterone • *HER2*-neu • Treatment• Prognosis

Objectives

1. To discuss the characteristic features of mucinous breast carcinoma.
2. To correlate the prognostic implication of this tumor with the clinical, histopathologic and immunohistochemical features of mucinous breast carcinoma.
3. To understand the role of immunohistochemistry in managing patients with breast carcinoma.

Case Summary

Presented is a case of a 54-year-old postmenopausal woman admitted for a gradually enlarging breast mass. Two years prior to admission, the patient noted a palpable mass on the upper outer quadrant of her right breast, measuring about 2 × 2 cm in size with associated tenderness. No consult was done for the said mass, until one year prior to admission when the patient consulted at the out-patient department of Baguio General Hospital and Medical Center.

Targeted right breast ultrasound revealed a circumscribed, round, high echogenic mass measuring 4.4 × 4.8 × 5.9 cm (AP × T × CC) at the upper outer quadrant of the right breast with punctuate calcifications (Figure 1).

Core needle biopsy of the right breast mass tissue was submitted revealing infiltrating tumor cells seen in solid nests accompanied by extracellular mucin pools. The tumor cells exhibit enlarged hyperchromatic nuclei, some with irregular nuclear contours, prominent nucleoli and minimal cytoplasm (Figures 2 and 3). The pathologic diagnosis of the biopsy was consistent with an invasive carcinoma with mucinous features.

A. Low power view of ER Receptor Assay with negative staining in 100% of the neoplastic cells.

B. Low power view of PR Receptor Assay with negative staining in 100% of the neoplastic cells.

C. Low power view of *HER-2 neu* positive staining (3+) in 100% of the neoplastic cells.

The patient then underwent Modified Radical Mastectomy of her right breast. On gross examination, the specimen submitted consisted of the right breast and right axillary tail with cut sections

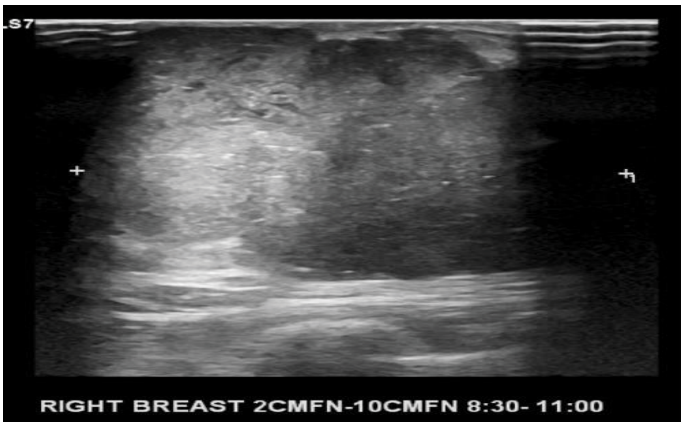

Figure 1. Targeted breast ultrasound showing a large echogenic mass (arrow) with angular borders and punctuate calcifications in the right breast at 8:30 to 11 o'clock position.

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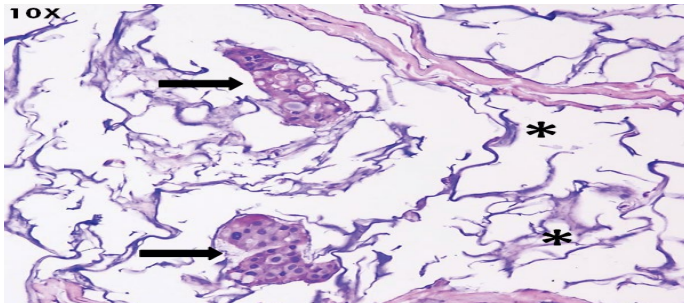

Figure 2. Low power view of the core needle biopsy showing irregular clusters of tumor cells (arrows) surrounded by extracellular mucin (*).

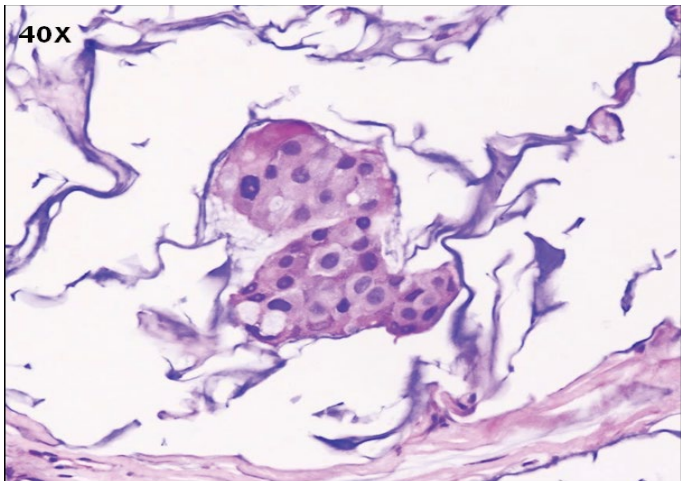

Figure 3. High power view of the core needle biopsy showing cells with enlarged, hyperchromatic nuclei, prominent nucleoli, and minimal cytoplasm.

revealing a well-circumscribed mass measuring 5.5 × 4.5 cm with moist and glistening surfaces. Several axillary lymph nodes were isolated.

Microscopic examination revealed a tumor composed of multiple clusters of neoplastic cells surrounded by variable amounts of extracellular mucin (Figure 5). These cells exhibit focal tubular and cribriform patterns, displaying moderate to marked nuclear atypia, some with intracellular mucin resembling signet rings, and accompanied by few mitotic figures (Figures 6 and 7). Lymphovascular invasion was observed (Figure 8). All isolated lymph nodes were devoid of tumor. ER/PR/*HER2* Testing was consistent with that of the core needle biopsy revealing ER-Negativity, PR-Negativity and *HER-2* Positivity (Figure 9). The final histopathologic diagnosis was Pure Mucinous Carcinoma with Signet Ring Cell Features, Nottingham Histologic Grade II. ER negative, PR negative, and *HER2* positive.

A. Low power view of ER Receptor Assay with negative staining in 100% of the neoplastic cells.

B. Low power view of PR Receptor Assay with negative staining in 100% of the neoplastic cells.

C. Low power view of *HER-2 neu* positive staining (3+) in 100% of the neoplastic cells.

Discussion

Pure mucinous breast carcinoma represents only 2% of all invasive breast cancer types [1,2]. It presents with a slower growth rate and better prognosis, with less involvement of axillary lymph nodes. The distinguishing histopathologic features of this type of tumor are the accumulation of abundant, extracellular mucin secretion around nests of cells [3]. Nuclear atypia is generally low in classic mucinous carcinoma, but in rare cases, as in the one presented, atypia and mitoses may prevail [4].

Numerous studies regarding the immunohistochemistry staining of mucinous breast carcinoma show that conventionally, almost all cases are positive for estrogen and progesterone hormone receptors, especially for ER, and more than 95% of the tumors usually do not express *HER2*. This justifies their good behavior and prognosis, with studies demonstrating a 10-year survival rate of 90% or more among women diagnosed with the tumor [5,6]. In this case, however, there was a difference in that the ER and PR immunohistochemical staining results were negative and the *HER2* staining results were strongly positive.

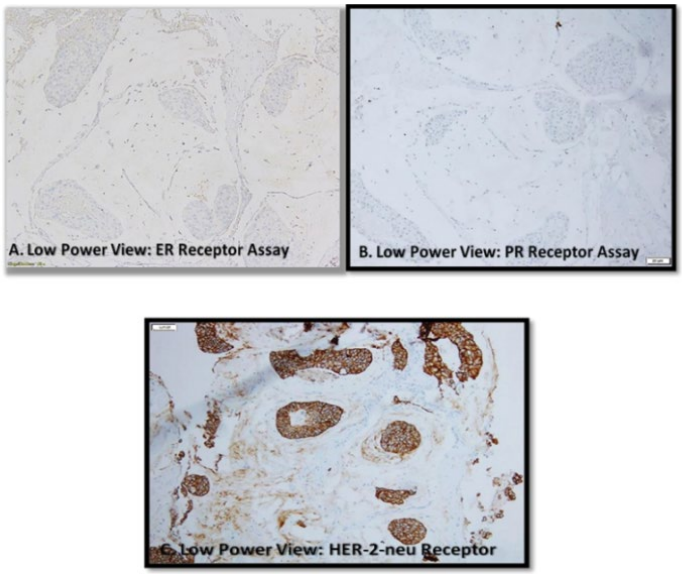

Figure 4. Core needle biopsy.

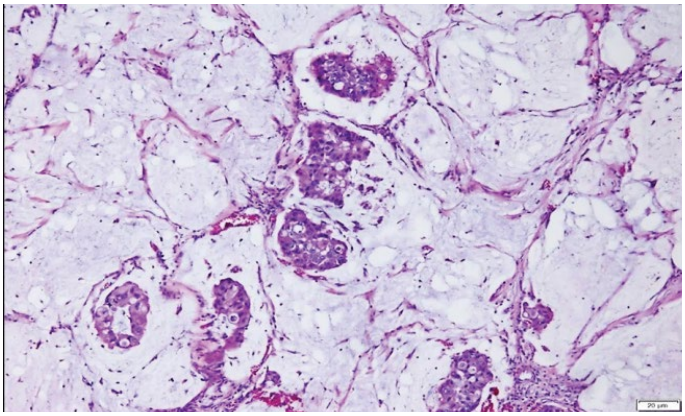

Figure 5. Multiple clusters of neoplastic cells surrounded by extracellular mucin. (10X magnification).

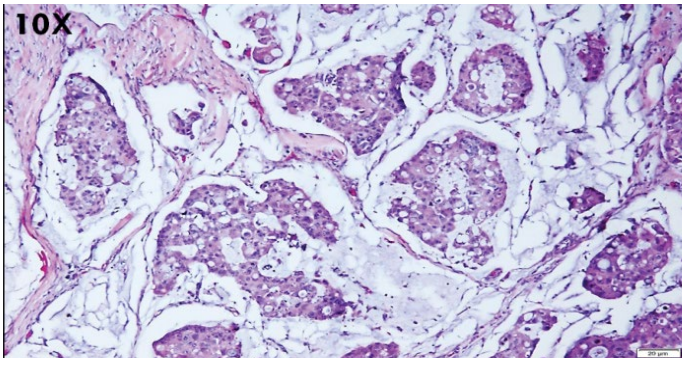

Figure 6. Tumor cells exhibiting tubular and cribriform patterns. (10X magnification).

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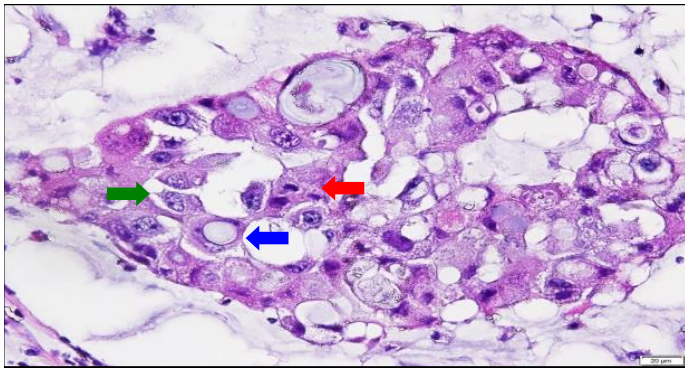

Figure 7. Tumor cell cluster showing cells with moderate to marked atypia (green), some resembling signet rings (blue), with few mitotic figures (red) (40X magnification).

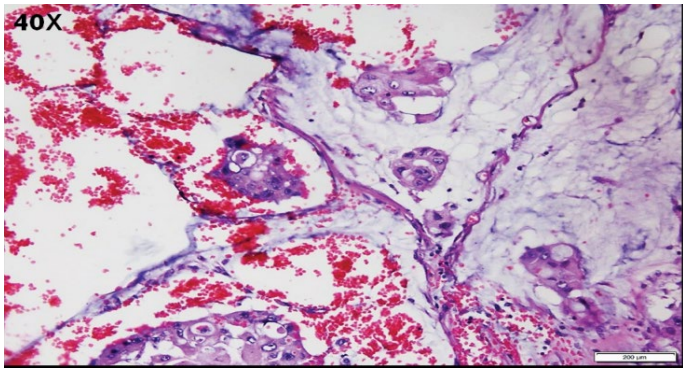

Figure 8. The tumor cells are seen invading vascular spaces (10X magnification).

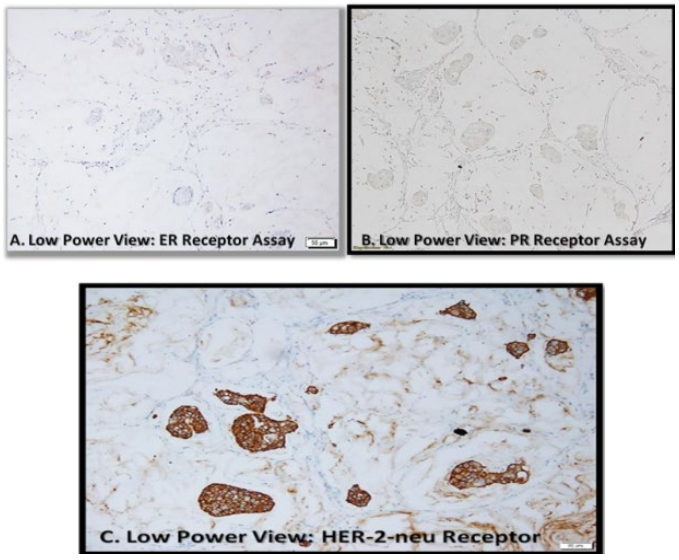

Figure 9. Surgical resection specimen.

For this case, additional immunostains showed a result of CK7 positive, CK20 negative, and CDX negative. Together with these findings and that clinically and radiologically there was no evidence of a mass from another organ, this suggests breast as the primary origin (Figure 10).

A. Low power view of CK7 positive staining in 100% of the neoplastic cells.

B. Low power view of CK20 with negative staining in 100% of the neoplastic cells.

C. Low power view of CDX2 with negative staining in 100% of the neoplastic cells.

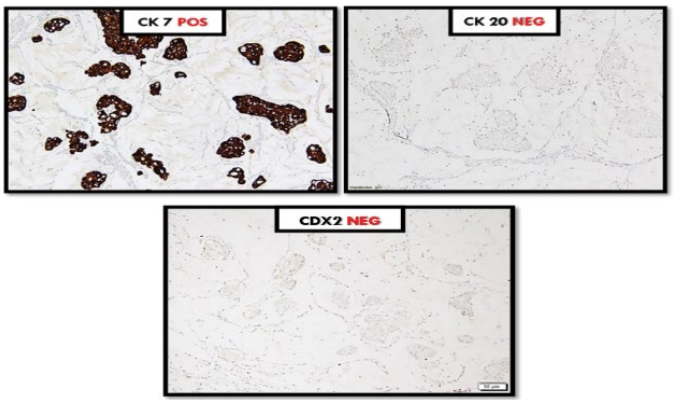

Figure 10. Other immunohistochemical markers.

Table 1. Major molecular subtypes of breast cancer determined by gene expression profiling.

Molecular Subtype				
Immunoprofile	**Luminal A**	**Luminal B**	***HER2* Enriched**	**Basal-Like**
ER, PR	ER+ and PR high+	ER+ and PR low or intermediate	ER-, PR-	ER-, PR-
HER2	*HER2-*	*HER2+* or *HER2-*	*HER2+*	*HER2-*
Treatment Response	Endocrine Therapy (Tamoxifen and Aromatase inhibitors)	Endocrine Therapy (Tamoxifen and Aromatase inhibitors)	Trastuzumab (Herceptin)	No response to endocrine therapy or trastuzumab
Outcome	Generally Good	Generally Good	Generally Poor	Generally Poor

On the basis of intrinsic molecular subtypes, the patient is classified under *HER2*-enriched, associated with a more aggressive tumor and a poorer prognosis [7]. In the case presented, even if pure mucinous carcinoma is associated with an excellent prognosis, the absence of estrogen and progesterone receptors and the presence of *HER2* expression may change the clinical evolution of this tumor. For the treatment, rather than using the usual tamoxifen used in mucinous breast carcinoma, trastuzumab would then be recommended (Table 1).

Conclusion

Only a few cases of pure mucinous carcinomas are positive for *HER2* and negative for ER and PR. It is imperative for physicians to know about this entity because there are no protocols or clinical practice guidelines regarding proper treatment in positive *HER-2* positive mucinous carcinomas, and although few, trastuzumab resistance have been reported. The patient must also be consistently evaluated due to high risk of tumor recurrence. This also reminds practitioners the importance of immunohistochemistry in the management of patients with breast carcinomas as not all tumors behave the same way.

With continued progress in our understanding of molecular alterations and tumor biology, it has come to a realization that breast cancer is a biologically diverse disease and varies according to morphology, biology and response to therapies. Profiling of carcinomas using Immunohistochemistry (IHC) has assumed an increasingly important role as prognostic and predictive markers in providing vital information the multidisciplinary team needs, to deliver the most appropriate treatment for each individual patient.

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