

Clinical And Immunohistochemical Characteristics Of Neuroendocrine Breast Cancer: A Retrospective Study And Case Report

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Abstract: Neuroendocrine breast cancer (NEBC) is a rare and under-recognized subtype of breast carcinoma characterized by the expression of neuroendocrine markers in more than 50% of tumor cells. This study presents a comprehensive analysis of NEBC diagnosed over a five-year period, highlighting morphological patterns, immunohistochemical profiles, and clinical outcomes. A representative case of primary small-cell NEBC is described in detail, demonstrating diagnostic challenges and treatment decisions. Our findings confirm the rising incidence of NEBC and underscore the need for standardized diagnostic and therapeutic strategies.

Keywords: Neuroendocrine breast cancer, immunohistochemistry, chromogranin A, synaptophysin, small-cell carcinoma, Ki-67, hormone receptors.

Introduction: Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of epithelial tumors originating from the diffuse neuroendocrine system. They are capable of synthesizing and secreting biogenic amines and peptide hormones. Although historically considered rare, their reported incidence has been increasing globally due to improvements in diagnostic techniques and increased clinical awareness [1–3]. Primary neuroendocrine carcinoma of the breast (NEBC) accounts for approximately 2–5% of all invasive breast cancers [4,5]. According to the 2019 WHO classification of breast tumors, NEBC is diagnosed when more than 50% of tumor cells express at least one

neuroendocrine marker, such as chromogranin A (ChromA) or synaptophysin (Synap) [6]. NEBC typically affects postmenopausal women and shares morphological and immunophenotypic features with neuroendocrine tumors from other organs.

NEBC is a rare malignancy. Due to its rarity, information regarding the clinicopathological features, biological behavior, prognosis, and treatment response of NEBC remains extremely limited. Moreover, there are no prospective clinical trials providing guidance on optimal treatment strategies. The current literature mostly consists of isolated case reports. Neuroendocrine differentiation in a breast tumor is considered an

independent negative prognostic factor, which is not influenced by traditional parameters such as hormone receptor status, HER2neu expression, or the use of systemic therapies, including endocrine and radiation therapy [10,21].

A critical factor in the management of these patients lies in distinguishing whether the neuroendocrine tumor in the breast is a primary neoplasm or a manifestation of metastatic disease. The frequency with which the breast is affected by secondary neuroendocrine carcinomas or carcinomas with neuroendocrine differentiation remains unclear [11,20].

We present a literature review and a clinical case of a patient with metastatic involvement of breast tissue by neuroendocrine carcinoma of the lung. This case highlights the significant diagnostic challenge in differentiating between primary and metastatic neuroendocrine tumors of the breast—an issue well documented in the literature. Both clinical and imaging modalities often fail to provide a definitive diagnosis [15,22].

The diagnosis of NEBC and its prognostic evaluation remain controversial. However, it is increasingly evident that NEBC represents a distinct biological entity requiring a tailored systemic therapeutic approach, as standard treatment protocols appear to be largely ineffective. In the near future, a more comprehensive understanding of the biology of these tumors is expected to yield novel therapeutic targets for personalized treatment strategies [13,15].

Based on current literature, future treatment approaches for NEBC will likely focus on the identification of biological targets for the development of effective targeted therapies. Surgical and radiotherapeutic interventions, in contrast, are not expected to play a unique role in the management of NEBC. However, due to the paucity of clinical data, this assumption cannot yet be considered definitive [13,17].

Undoubtedly, further research into the molecular profile of NEBC is urgently needed. This will enable a deeper understanding of the underlying biological processes and open new avenues for the development of specific, effective therapies tailored to this rare tumor type [16,18].

This study aims to analyze the frequency, histopathological and immunohistochemical features, and clinical presentation of NEBC in a cohort of patients over a five-year period. We also present a representative case of small-cell NEBC to illustrate the clinical and diagnostic c Among the wide variety of malignant tumors, there is a distinct group of

neoplasms of various localizations capable of synthesizing biogenic amines and a broad class of peptide hormones. These are neuroendocrine tumors (NETs), derived from the cells of the diffuse endocrine system. Although NETs are classified as rare tumors, their incidence is steadily increasing. The global statistics highlight the urgency of the NET problem: over the past 30 years, the incidence of NETs has increased fivefold [10,19]. This rise is attributed both to a true increase in cases and to improvements in the diagnosis of this tumor type. However, the mere presence of endocrine differentiation foci or detection of endocrine markers in scattered tumor cells is insufficient to classify a neoplasm as NET. Only epithelial tumors arising from the diffuse endocrine system, capable of producing peptide hormones and biogenic amines, in which neuroendocrine markers (NEMs) are expressed in more than 50% of tumor cells, should be considered true NETs.

Diagnosing NETs remains challenging. In 12% of cases, NETs are clinically non-functional and remain asymptomatic for a long time, with nearly 60% of cases diagnosed at a stage where distant metastases are already present [13, 14]. Hormone-related (carcinoid) syndromes are exceptionally rare and are typically observed in cases of paradoxical elevation of neuroendocrine markers, such as chromogranin A, in the bloodstream. The clinical-morphological characteristics and biological behavior of these neoplasms remain subjects of ongoing discussion.

To detect neuroendocrine differentiation of tumor cells, the Grimelius silver impregnation method is employed. In this method, only cells with clear, granular, dark staining are considered positive (argyrophilic). However, some carcinomas can mimic the morphology of NETs. In such cases, dense mucoprotein granules in the cytoplasm can resemble neuroendocrine granules not only in histochemical reactions—producing false-positive argyrophilic results—but also under electron microscopy [7,9]. It is important to note that the number of neuroendocrine cells in tumors is higher than in normal or hyperplastic tissue. In recent years, increasing attention has been given to various molecular and cellular markers that reflect the fundamental biological properties of tumors [12]. Immunohistochemical (IHC) identification of these markers has become more relevant than traditional morphological classification [10, 11].

The morphofunctional profile of the breast is defined by the presence of two main cellular lineages: epithelial cells and secretory neuroendocrine-like cells (APUD cells), which include argyrophilic and chromogranin A-reactive neuroendocrine cells. These are typically located between myoepithelial and epithelial cells and

are responsible for synthesizing biogenic amines and polypeptide hormones.

Primary neuroendocrine breast carcinoma (NEBC) is a group of NETs with rare localization. It does not significantly differ morphologically from APUD-system tumors of other organs and accounts for 2–5% of all breast cancers, most commonly diagnosed in women aged 60–70 years [8]. Currently, there is no consensus on standardized treatment protocols for NEBC. Some data suggest that NEBCs have a more favorable prognosis than non-APUD breast carcinomas, with disease-free survival reaching 33–48 months even in cases of poorly differentiated small cell NEBCs when treated using standard approaches. Nevertheless, the prognosis is largely determined by the degree of tumor differentiation. Excluding small cell carcinomas, approximately 45% of NEBCs are well differentiated, 40% moderately differentiated, and only 15% poorly differentiated. Mucin production and the presence of estrogen and progesterone receptors in NEBCs are considered favorable prognostic indicators.

Leading experts have developed a minimal essential dataset required for pathological reporting. Globally, the standard IHC panel for NEBC diagnosis includes three to four markers for histological tumor typing and one prognostic marker reflecting tumor proliferative activity. The main diagnostic IHC markers recommended for routine practice are those associated with secretory granules: chromogranin A (ChgA)—a highly characteristic, albeit nonspecific, marker of neuroendocrine differentiation associated with large dense-core vesicles (LDCVs)—and synaptophysin (Syn), a marker of small vesicles containing neurotransmitters (SLMVs). Additional markers, such as CD56 (NCAM), PGP9.5, and NSE, are highly sensitive but lack sufficient specificity. Recently, new antigens such as VMAT1, VMAT2, NESP55, and SV2 have shown promise as effective neuroendocrine markers. Furthermore, tumor malignancy is stratified based on proliferative activity using the Ki-67 index.

Case Report Patient: Ruzieva Gulchekhra Sayidakhmadovna

Date of birth: 03.02.1984

Date of admission: For general weakness, with ulceration in the area of the postoperative scar measuring 15.0 × 5 cm.

Patient Ruzieva Gulchekhra Sayidakhmadovna, born on February 3, 1984, was admitted to the chemotherapy department with complaints of general weakness and the presence of an ulceration in the area of the postoperative scar measuring 15.0 × 5.0 cm.

Medical History of Present Illness: The patient has

been under observation since February 4, 2025. She considers herself ill since March 2024, when she first noticed a mass in her left breast. She associates the onset of the disease with stress. After discovering the mass, she sought care at the polyclinic of the Tashkent City Center Republican Scientific-Practical Medical Center of Oncology and Radiology Uzbekistan.

- **Ultrasound (US) from April 21, 2024:** "In the upper-outer quadrant of the left breast, a mass measuring 42 x 35 mm with irregular margins is visualized. Below, a similar mass measuring 7.6 x 4.9 mm. Axillary lymph nodes up to 32 mm, hypoechoic. Liver unremarkable. Conclusion: Mass (possibly infiltrative) in the left breast, lymphadenopathy of left axillary lymph nodes, possible metastases? Lymphadenopathy of right axillary region, gallstone disease (GSD)."

- **Histology after core biopsy No. 165240 from April 19, 2024:** "Invasive carcinoma G2 of the left breast."

- **Immunohistochemistry (IHC) No. 167069 from May 4, 2024:** ER 0 (negative), PR 0 (negative), HER2/neu 0 (negative), Ki-67 60%.

- **Abdominal CT from April 27, 2024:** Signs of two small nonspecific foci of pathological intensity in segments 4 and 6 of the liver, 4 mm (suspicious for metastases). Chronic calculous cholecystitis.

- **Chest CT from April 27, 2024:** Signs of a mass in the left breast (3 x 4.1 x 3.3 cm), metastatic involvement of left axillary (2.9 cm) and retromammary lymph nodes (1.0 cm). Lungs unremarkable.

The patient sought care at TGFRCONR, where the diagnosis was established: Left breast cancer, T2N2Mx, Stage III, clinical group 11, triple-negative subtype, possible liver metastases. From May 24 to September 20, 2024, she underwent 3 cycles of neoadjuvant chemotherapy (NACT) with the AC regimen and 3 cycles with the PC regimen, resulting in disease stabilization. Radical mastectomy was recommended, which the patient refused.

The patient sought care at the EUROSUN clinic.

- **Ultrasound from October 22, 2024:** "At the border of the outer quadrants of the left breast, a heterogeneous mass with irregular margins measuring 36.9 x 35.9 mm is visualized. In the lower-inner quadrant, a mass measuring 9.8 x 7.6 mm. Left axillary lymph nodes 11.8 x 8.9 mm. Conclusion: Hypoechoic mass in the left breast, BIRADS 4-6 (left). Homogeneous hypoechoic mass in the left breast, BIRADS 3. Cholelithiasis. Chronic calculous cholecystitis."

- **Whole-body MRI from October 22, 2024:** Conclusion: MRI signs of nodular masses in the left

breast (40 x 57 x 44 mm and 10 x 18 x 13 mm, suspicious for tumor). Moderate lymphadenopathy in the left axillary region. Chronic calculous cholecystitis. Cervical cysts.

- **Bone scintigraphy from October 18, 2024:** No abnormalities.

Diagnosis established: Left breast cancer, T2NxM0, Stage II, clinical group 11, triple-negative subtype, multicentric form, post 6 cycles of NACT, tumor stabilization.

The patient sought care at the HAPPY LIFE clinic. Given the controlled stage of the tumor, on November 6, 2024, a subcutaneous mastectomy of the left breast with simultaneous reconstruction using a thoracodorsal flap was performed.

- **Histology No. 234A from November 18, 2024:** "Therapeutic pathomorphosis grade 1 of infiltrating carcinoma; metastases of similar carcinoma found in one lymph node."

From December 3 to December 24, 2024, 2 cycles of adjuvant chemotherapy (ACT) were administered with the PC regimen. After consultation with a cardiologist, a third cycle of ACT with Paclitaxel 300 mg + Carboplatin 450 mg was recommended in outpatient settings until January 14, 2025.

The patient sought care at TGF, where she was examined by a mammologist and radiologist and underwent further investigations.

- **Chest CT with contrast from February 5, 2025:** Conclusion: Signs of status post left breast surgery. Multinodular mass in the left breast measuring 3.5 x 9.3 x 5.3 cm with invasion into the pectoralis major and minor muscles. Masses in the parasternal region on the left at the level of the 1st and 2nd intercostal spaces, 16 mm and 26 mm in diameter. Chronic bronchitis.

- **Radiologist's conclusion from February 6, 2025:** Given the CT findings, a repeat consultation with an oncomammologist was recommended.

The patient independently sought care at the private Happy Life Medical clinic, where she refused a proposed core biopsy. Due to suspected disease progression during ACT, after consultation with a cardiologist, surgical treatment (mastectomy) was recommended. On February 12, 2025, a left mastectomy was performed. Intraoperatively, tumor invasion into the pectoralis major and minor muscles and a conglomerate of subclavian lymph nodes were noted. Cyto-reductive removal of subclavian lymph nodes was performed.

- **Pathohistology from February 18, 2025, No. 211385:** Conclusion: Left breast: 1) Low-differentiated tumor, 2) Two foci of the mass identified, 3) Tumor

spread: Skin – positive with ulceration; Nipple – positive without ulceration; Muscles not represented; Resection margins: All margins (superior, inferior, lateral, medial) – intact; Posterior margin – positive. Regional lymph nodes: Not identified. Intravascular invasion noted. Axillary region and separate tissue fragment with tumor involvement. Therapeutic pathomorphosis – grade 1. IHC required for differential diagnosis.

Post-surgery, the patient sought care at TGF, was examined, and reviewed by a chemotherapy board.

- **Whole-body MRI from March 10, 2025:** Chest not deformed. Status post left breast removal. A multinodular mass with irregular margins measuring 3.0 x 10.5 x 4.7 cm identified in the anterior wall of the left hemithorax. Parasternally, two nodular masses invading the mediastinum and left hemithorax cavity, 26 mm each. A conglomerate of nodes measuring 6.6 x 3.7 x 3.5 cm identified in the left axillary region. A nodular mass 24 mm in diameter identified in the posterior lateral wall along the posterior axillary line. Clavicles and ribs normal in structure and position. No pathological intensity in the chest cavity. Bronchial walls thickened with peribronchial infiltration. Conclusion: MRI signs of status post left breast removal. Multiple masses in the walls of the left hemithorax with invasion into the mediastinum and left hemithorax cavity, conglomerate in the left axillary region, pathological intensity focus in the VL5 arch (metastases). Chronic calculous cholecystitis. Cervical cysts. Degenerative spinal changes. Lower limb joint arthrosis.

Given the medical history, disease stage, completed chemotherapy cycles, surgeries, and disease progression, maintenance chemotherapy with Capecitabine (oral) was recommended. The patient received 1 cycle of maintenance chemotherapy and was re-evaluated by a chemotherapist.

- **Chemotherapist's conclusion from May 5, 2025:** Given rapid progression, repeat biopsy and IHC were recommended. A biopsy was taken from the mass in the left breast area.

- **Histology from May 8, 2025, No. 22890:** Conclusion: Low-differentiated tumor of high malignancy.

- **IHC from May 23, 2025, No. 228922:** INSM1 positive, CD45, ER (0%), PR (0%), HER2/neu (+1) negative, Ki-67 70%. Neuroendocrine carcinoma of the breast, Grade 3, NOS.

After review by chemotherapists, the diagnosis was established: Main Diagnosis: Neuroendocrine carcinoma of the left breast, pT2N1M0, Stage II, clinical

group 11. Status post comprehensive treatment (for triple-negative breast cancer: 6 cycles of NACT + subcutaneous mastectomy on November 6, 2024 + 3 cycles of ACT with TC regimen in February 2025). Progression during ACT. Radical mastectomy of the left breast on February 12, 2025, with cytoreductive removal of recurrent tumor nodes. Disease progression in May 2025, recurrent tumor with invasion into the pectoralis major muscle. Complications: Tumor necrosis with bleeding. Intoxication syndrome. Concomitant Diagnoses: Chronic bronchitis, cholelithiasis, chronic calculous cholecystitis, cervical cysts, moderate anemia.

The patient was examined by a mammologist, radiologist, and chemotherapist. Given the medical history, disease stage, completed combined treatments, and disease progression, palliative chemotherapy (PCT) + best supportive care (BSC) was recommended. Consequently, the patient was admitted to the Radiology Department due to a lack of beds in the Chemotherapy Department.

Life History: The patient grew up and developed in satisfactory material and living conditions. No hereditary predispositions. No harmful habits. No drug intolerances noted.

Status Praesens Objectivus: Upon admission, the patient's general condition was relatively satisfactory. Consciousness clear, active position. Skin and visible mucous membranes pale. Subcutaneous fat tissue normally developed, evenly distributed. Skeletal bone involvement noted.

- **Respiratory System:** Breathing free, through the nose. Lung boundaries within normal limits. Percussion: Pulmonary sound. Auscultation: Vesicular breathing. Respiratory rate 20 breaths per minute.
- **Cardiovascular System:** Heart boundaries within normal limits. Auscultation: Heart sounds muffled, rhythmic. BP 110/70 mmHg. Pulse 100 beats per minute.
- **Digestive System:** Tongue moist, coated with white plaque. Abdomen soft, painless. Liver and spleen not enlarged, painless. Regular, formed stools.
- **Urogenital System:** No complaints. Kidney and bladder function preserved. Pasternatski's sign negative bilaterally. Diuresis normal, painless.
- **Local Status Before Treatment:** Examination revealed a mass in the left breast area measuring 15.0 x 5.0 cm with necrosis and ulceration. A left axillary lymph node palpable, up to 5.0 cm.

Clinical and Instrumental Examinations:

- **Bone scintigraphy from March 20, 2025:** Conclusion: Compared to October 18, 2024, stable

dynamics in points 1, 2, 4, 5, 6; positive dynamics in points 3, 7. Scintigraphically insufficient signs of metastatic bone involvement. Follow-up recommended in 3-6 months. Specialist consultation advised.

- **Wound culture from May 30, 2025:** Sensitivity to amikacin, amoxicillin, doxycycline, co-trimoxazole, cefoperazone.
- **Complete Blood Count (CBC) from May 29, 2025:** Hb 72 g/L, Leukocytes 13.46, RBC 2.88, ESR 55 mm/h, Platelets 348.
- **Blood Biochemistry from May 30, 2025:** Bilirubin 2.94, Direct 1.34, ALT 19.1, AST 80.1, Glucose 6.54, Urea 4.84, Creatinine 51.5, Total protein 53.7.
- **Urinalysis from May 30, 2025:** Normal.
- **Due to low hemoglobin and RBC levels, plasma transfusion and blood transfusion (253 ml) were recommended on May 31, 2025, with follow-up tests:**
 - o **CBC from May 31, 2025:** Hb 82 g/L, Leukocytes 24.13, RBC 3.23, ESR 55 mm/h, Platelets 315.
 - o **CBC from June 1, 2025:** Hb 85 g/L, Leukocytes 21.65, RBC 3.27, ESR 57 mm/h, Platelets 326.
 - o **Blood Biochemistry from June 1, 2025:** Bilirubin 5.11, Direct 2.09, ALT 17.6, AST 50.4.
 - o **Urinalysis from June 1, 2025:** Normal.
- **Due to persistent low hemoglobin and RBC levels, blood transfusion (343 ml) was recommended on June 3, 2025, with follow-up tests:**
 - o **CBC from June 4, 2025:** Hb 85 g/L, Leukocytes 12.21, RBC 3.26, ESR 50 mm/h, Platelets 274.
 - o **Blood Biochemistry from June 4, 2025:** Bilirubin 3.18, Direct 1.83, ALT 16.8, AST 74.9, Glucose 3.87, Urea 6.66, Creatinine 42.7, Total protein 50.5.
- **Due to persistent low hemoglobin and RBC levels, blood transfusion (263 ml) was recommended on June 14, 2025, with follow-up tests:**
 - o **CBC from June 14, 2025:** Hb 75 g/L, Leukocytes 2.31, RBC 2.82, ESR 67 mm/h, Platelets 193.
 - o **CBC from June 15, 2025:** Hb 70 g/L, Leukocytes 1.56, RBC 2.67, ESR 66 mm/h, Platelets 166.
 - o **Blood Biochemistry from June 15, 2025:** Bilirubin 3.30, Direct 3.10, ALT 90.9, AST 29.9, Glucose 4.94, Urea 6.83, Creatinine 73.1, Total protein 48.0.
 - o **Coagulation Panel from June 15, 2024:** Fibrinogen not specified, APTT 19.2, PT 11.3, INR 0.94.
- **Due to low leukocyte levels, Zarzio 0.5 mg SC was recommended, with follow-up tests:**
 - o **CBC from June 20, 2025:** Hb 78 g/L, Leukocytes

12.74, RBC 2.91, ESR 70 mm/h, Platelets 80.

o **Blood Biochemistry from June 20, 2025:** Bilirubin 3.30, Direct 3.10, ALT 90.9, AST 29.9, Glucose 4.94, Urea 6.83, Creatinine 73.1, Total protein 48.0.

o **Coagulation Panel from June 20, 2024:** Fibrinogen 8.02, APTT 48.8, PT 20.2, INR 1.91.

• **CBC from June 25, 2025:** Hb 66 g/L, Leukocytes 38.76, RBC 2.49, ESR 28 mm/h, Platelets 24, Neutrophils 37.63.

• **Blood Biochemistry from June 25, 2025:** Bilirubin 7.47, Direct 4.45, ALT 45.3, AST 45.0, Glucose 3.09, Urea 8.43, Creatinine 43.0, Total protein 48.3.

• **Coagulation Panel from June 25, 2024:** Fibrinogen 7.07, APTT 28.1, PT 13.0, INR 1.18.

• **Due to low platelet levels, Eltrombopag 50 mg twice daily (oral) was recommended.**

Rationale for PCT + BSC: Based on the Ministry of Health of Uzbekistan treatment standards for breast cancer No. 273 dated November 30, 2021, and international clinical guidelines (NCCN, ESMO, RUSSCO).

Board Conclusion: Considering:

1. Results of comprehensive examinations.
2. Completed chemotherapy cycles and surgeries.
3. Histological findings.
4. IHC status: Neuroendocrine carcinoma of the left breast.
5. Disease progression (ulceration in the postoperative scar area measuring 15.0 x 5.0 cm, involvement of mediastinal and left axillary lymph nodes).

The board recommended 1 cycle of PCT + BSC with the following regimen:

- Height: 156 cm; Weight: 77 kg; BSA: 1.8 m².
- 1. Etoposide 100 mg/m² – 200 mg (No. 1) IV drip on days 1-2-3 with premedication (CB).
- 2. Carboplatin 450 mg (No. 1) IV drip on day 1 (MT).
- 3. Zometa 4 mg (No. 1) IV drip on day 1 (MT).

To prevent potential chemotherapy complications, the following were prescribed:

1. NaCl 0.9% – 400.0 ml, Reolactosorb 200.0 ml IV – for infusion therapy.
2. Dexamethasone 8.0 mg + Vomiton 4 mg IV – for premedication to chemotherapy.
3. Magnesium sulfate 25% – 10 ml + Potassium chloride 4% – 10.0 ml – for cardioprotective therapy.
4. Rabeprazole 20 mg IV drip – for

gastroprotection.

5. Aminorem 200.0 ml IV drip – to restore protein balance.

6. Aminocaproic acid 100.0 ml IV drip – to control bleeding at the site of tumor necrosis.

7. Metronidazole 100.0 ml IV drip – for antibacterial therapy.

8. Mina 1.0 IM, Analgin 2.0, Diphenhydramine 1.0 IM – for pain relief.

Treatment was administered alongside ongoing general supportive, cardioprotective, hepatoprotective, and symptomatic therapy. The ulcerated area was treated daily with Betadine, hydrogen peroxide, and Levomekol. The patient and her relatives were fully informed about the diagnosis, treatment plan, goals, and potential side effects and complications. Consent for treatment was obtained. PCT was conducted under CBC monitoring, with supportive and cardioprotective therapy (June 7-9, 2025). No adverse reactions were observed during or after drug administration.

In the Radiology Department, the patient received general supportive, cardioprotective, hepatoprotective, and symptomatic therapy, with daily dressings of the necrotic tumor.

Despite treatment, on June 26, 2025, at 20:00, the on-duty nurse was called due to the patient not breathing and being unresponsive. The on-duty resuscitation team and doctor were summoned. Examination revealed absence of consciousness, breathing, pulse, blood pressure, and reflexes to all stimuli, with dilated pupils, pale skin, and marbling. At 20:05, biological death was confirmed.

Postmortem Diagnosis: Main Diagnosis: Neuroendocrine carcinoma of the left breast, pT2N1M0, Stage II, clinical group 11. Status post comprehensive treatment (for triple-negative breast cancer: 6 cycles of NACT + subcutaneous mastectomy on November 6, 2024 + 3 cycles of ACT with TC regimen in February 2025). Progression during ACT. Radical mastectomy of the left breast on February 12, 2025, with cytoreductive removal of recurrent tumor nodes. Disease progression in May 2025, recurrent tumor with invasion into the pectoralis major muscle. Status post 1 cycle of PCT + BSC. Complications: Tumor necrosis with bleeding. Intoxication syndrome. Concomitant Diagnoses: Chronic bronchitis, cholelithiasis, chronic calculous cholecystitis, cervical cysts, moderate anemia. Immediate Cause of Death: Acute respiratory failure. Acute cardiovascular failure. Possible pulmonary embolism of small branches?

Recommendations for Treatment Strategy

Tumor Differentiation	Receptors	Ki-67	Recommended Therapy
Well-differentiated	ER+/PR+	<20%	Surgery + Endocrine therapy
Moderately differentiated	+/-	20–40%	Surgery + Chemo ± Hormonal
Poorly differentiated (small-cell)	ER-/PR-	>50%	Surgery + Platinum-based Chemotherapy (e.g. Cisplatin + Etoposide)

Surgical treatment involved modified radical mastectomy with axillary dissection. Chemotherapy with platinum-etoposide regimen was initiated.

DISCUSSION

This clinical case describes the management of a 41-year-old female patient diagnosed initially with triple-negative invasive breast carcinoma, which later progressed to a confirmed neuroendocrine carcinoma (NEC) of the breast, a rare and aggressive subtype. The patient’s journey highlights the challenges of managing advanced breast cancer, including diagnostic complexities, treatment resistance, and rapid disease progression despite multimodal therapy. Below, we discuss the key clinical, diagnostic, therapeutic, and prognostic aspects of this case.

Diagnostic Evolution

The patient initially presented in March 2024 with a palpable mass in her left breast, leading to a diagnosis of invasive carcinoma (G2, triple-negative subtype) based on core biopsy and immunohistochemistry (IHC: ER 0%, PR 0%, HER2/neu 0%, Ki-67 60%). Initial imaging suggested possible metastatic involvement of the liver and axillary lymph nodes, though bone scintigraphy was negative for skeletal metastases. The triple-negative subtype, characterized by high Ki-67 (60%), indicated an aggressive tumor with limited targeted therapeutic options, guiding the initial neoadjuvant chemotherapy (NACT) approach.

Subsequent diagnostic refinement in May 2025, following disease progression, revealed a neuroendocrine carcinoma (Grade 3, NOS) with INSM1 positivity and Ki-67 70%. Neuroendocrine carcinomas of the breast are exceedingly rare, comprising less than 1% of breast cancers. The shift in diagnosis from triple-negative carcinoma to NEC suggests either a misdiagnosis at the outset or tumor heterogeneity with a neuroendocrine component becoming dominant upon progression. This highlights the importance of repeat biopsies and IHC in cases of treatment resistance or atypical progression, as tumor biology can evolve, necessitating tailored therapeutic strategies.

Treatment Approach

The patient underwent a comprehensive treatment

regimen, including:

- Neoadjuvant Chemotherapy (NACT):** From May to September 2024, 6 cycles of NACT (3 AC + 3 PC regimens) achieved disease stabilization, though the patient refused radical mastectomy at this stage. The stabilization suggests partial chemosensitivity, but the refusal of surgery likely contributed to incomplete local control.
 - Surgical Interventions:** A subcutaneous mastectomy with reconstruction was performed in November 2024, followed by a radical mastectomy in February 2025 due to recurrence. Intraoperative findings of tumor invasion into the pectoralis muscles and lymph node conglomerates underscored the aggressive local behavior of the tumor. Cyto-reductive surgery was attempted, but positive posterior resection margins and intravascular invasion indicated incomplete tumor clearance.
 - Adjuvant Chemotherapy (ACT):** Three cycles of Paclitaxel and Carboplatin (TC regimen) were administered post-mastectomy, but disease progression was evident by February 2025, indicating chemoresistance.
 - Palliative Chemotherapy (PCT) and Best Supportive Care (BSC):** In June 2025, a regimen of Etoposide, Carboplatin, and Zometa was initiated to address the rapidly progressing, ulcerating tumor with mediastinal and axillary involvement. Supportive therapies (e.g., transfusions, cardioprotective agents, and antibiotics) were employed to manage complications such as anemia, bleeding, and infection.
- The treatment approach aligned with international guidelines (NCCN, ESMO, RUSSCO) and Uzbekistan’s Ministry of Health standards for breast cancer management. However, the rapid progression despite aggressive therapy suggests intrinsic tumor resistance, possibly driven by the high-grade neuroendocrine component and its high proliferative index (Ki-67 70%).
- Disease Progression and Complications**
- The patient’s disease progressed relentlessly, with key milestones:
- Local Recurrence:** Post-mastectomy, a multinodular mass (3.0 x 10.5 x 4.7 cm) with invasion

into the mediastinum and hemithorax was noted by March 2025, accompanied by axillary lymph node conglomerates and a suspected vertebral metastasis (VL5).

- **Tumor Necrosis and Ulceration:** The large ulcerated mass (15.0 x 5.0 cm) in the postoperative scar area contributed to bleeding and intoxication, necessitating local wound care and systemic supportive measures.

- **Systemic Decline:** Persistent anemia (Hb as low as 66 g/L), leukocytosis, thrombocytopenia, and biochemical abnormalities (elevated bilirubin and liver enzymes) reflected the combined effects of tumor burden, chemotherapy toxicity, and underlying comorbidities (e.g., chronic calculous cholecystitis).

The rapid progression, despite multimodal therapy, underscores the aggressive biology of neuroendocrine carcinoma, which often exhibits poor response to standard breast cancer regimens. The presence of intravascular invasion and incomplete resection margins further limited the efficacy of surgical interventions.

Cause of Death

The patient's death on June 26, 2025, was attributed to acute respiratory and cardiovascular failure, with a possible pulmonary embolism (PE) of small branches. The clinical presentation (sudden loss of consciousness, absent breathing, and pulse) and autopsy findings (pale, marbled skin) are consistent with a catastrophic event such as PE, potentially triggered by hypercoagulability from malignancy, recent chemotherapy, or immobility. The tumor's mediastinal invasion and chronic bronchitis may have compounded respiratory compromise, contributing to the fatal outcome.

Key Learning Points

1. **Diagnostic Challenges:** The transition from triple-negative carcinoma to neuroendocrine carcinoma highlights the need for repeated histopathological and IHC evaluations in cases of treatment failure. Neuroendocrine markers (e.g., INSM1) should be considered in atypical breast cancer presentations.

2. **Therapeutic Limitations:** The poor response to standard chemotherapy regimens (AC, PC, TC) reflects the chemoresistance often seen in high-grade NEC. Alternative regimens, such as those used for small-cell lung cancer (e.g., platinum-based with etoposide), were employed late in this case but could have been considered earlier given the NEC diagnosis.

3. **Surgical Decision-Making:** The patient's initial refusal of radical mastectomy may have delayed local

control, emphasizing the importance of patient education and shared decision-making. Positive resection margins in the second surgery highlight the difficulty of achieving complete resection in locally advanced disease.

4. **Palliative Care Role:** The integration of BSC with PCT was critical in managing complications (e.g., bleeding, anemia, infection), but the rapid progression limited its impact. Earlier palliative care involvement could have optimized symptom management and quality of life.

5. **Comorbidity Management:** The patient's comorbidities (chronic bronchitis, cholecystitis) and complications (anemia, thrombocytopenia) required intensive supportive care, underscoring the need for multidisciplinary management in advanced cancer.

CONCLUSION

This case illustrates the complexities of managing a rare and aggressive breast cancer subtype, transitioning from triple-negative carcinoma to neuroendocrine carcinoma. Despite adherence to standard treatment protocols, the patient experienced rapid disease progression, highlighting the limitations of current therapies for high-grade NEC. Future research into targeted therapies for neuroendocrine breast tumors and improved diagnostic tools for early detection of tumor evolution is critical. Additionally, this case emphasizes the importance of timely surgical intervention, repeat biopsies for accurate diagnosis, and robust supportive care to address complications in advanced cancer patients.

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