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Radiological and Histological Correlation in Small Cell Neuroendocrine Carcinoma of the Breast: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 39-year-old
Final Diagnosis: Primary neuroendocrine small cell carcinoma of the breast
Symptoms: Left breast mass • recurrent mastitis
Medication: —
Clinical Procedure: —
Specialty: Pathology • Radiology

Objective: Rare disease
Background: Primary breast small cell neuroendocrine carcinoma is a rare subtype of breast cancer with about 57 cases reported in the literature. This rare type of cancer represents about 0.1% of breast carcinomas. Recently, the World Health Organization defined this type of cancer as a separate entity from other breast cancer types. The diagnosis of this type of cancer in the breast is difficult because the histological pattern is similar to the small cell neuroendocrine carcinoma of other more common primary sites of origin, including the lung.
Case Report: A 39-year-old woman presented to our hospital with a left breast mass and recurrent mastitis. Physical examination revealed a painless lump in her left breast with a brown-colored discharge from the nipple, and her child refused breastfeeding from the left breast. A high-density well-defined rounded mass was observed upon mammography in the upper lateral aspect of the left breast. This mass lesion appeared hypoechoic with no posterior acoustic shadowing on ultrasound scan. A core-needle biopsy of the mass was performed and the diagnosis of small cell neuroendocrine carcinoma was rendered after histopathologic examination. Positron emission tomography scanning was helpful in the exclusion of primary origin from other organ sites; thus, the primary breast origin of the tumor was confirmed.
Conclusions: This case report provides a comprehensive approach to diagnose this type of small cell carcinoma originating primarily in the breast. The suspicion of this type of breast cancer should be raised if there is presence of characteristic histopathologic findings with the exclusion of any primary origin from other organ sites by the help of imaging studies.

Keywords: Breast Cancer 3 • Carcinoma, Neuroendocrine • Carcinoma, Small Cell • Mammography

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Background

Small cell neuroendocrine carcinoma arises predominantly in the lung and can be found in other extra-pulmonary sites like the gastrointestinal (GI) tract, larynx, breast, ovary, prostate, and cervix [1]. This type of cancer is rarely found in the breast and it represents about 0.1% of primary breast cancers [2].

The World Health Organization (WHO) classification of breast tumors typifies primary small cell carcinoma and primary large cell carcinoma as poorly differentiated neuroendocrine breast carcinomas (NEBC) [3]. The WHO defined 3 criteria to diagnose NEBC. The first one is when more than 50% of the tumor cells express 1 or more of the neuroendocrine markers. The second criterion is by excluding any primary cancer site in the body other than the breast by the use of imaging techniques other than mammography. The third method of diagnosis is by histopathologic testing of the breast when it shows carcinoma in situ [4].

The current case is interesting because the diagnosis of the primary origin of the tumor depended mainly on radiological features by excluding primary origin from other organ sites.

Case Report

Clinical Data

A 39-year-old female patient presented to the surgical clinic with a history of recurrent left breast mastitis and left breast brown discharge. She was doing well until 1 month prior to admission to our hospital, when she noticed a growing left breast mass in the upper outer quadrant. This mass was painless and associated with brown-colored nipple discharge, which was not affected by the menstrual cycle and the skin of the breast appeared normal. She had 5 children. She stated that she irregularly breastfed her child from the right breast and the child refused to feed from the left breast. There was no family history of breast cancer and no history of smoking or use of oral contraceptives. Her appetite was good, with no recent weight loss. She had no history of chronic diseases, trauma, or surgery.

Upon physical examination, a lump was found in the upper outer quadrant of the left breast and there was a brown-colored discharge from the nipple. There were no skin changes, retraction of the nipple, or prominent lymph nodes in the axillary region.

Radiological Findings

A digital mammogram showed a partially defined, spherical, high-density mass lesion in the left breast upper lateral

quadrant (**Figure 1A, 1B**). In correlation with an ultrasound scan, this mass appeared to be well-defined large, irregular, and heterogeneously hypoechoic, with no posterior acoustic shadowing or enhancement. The mass was located at the 2: 00 o'clock position of the left breast, measuring 1.52×0.89 cm (**Figure 1C**). An ultrasound-guided biopsy was done, which rendered a diagnosis of poorly differentiated neuroendocrine carcinoma (small cell carcinoma).

A metastatic workup, including computed tomography (CT) scans of chest, abdomen, pelvis, and brain, with intravenous contrast and positron emission tomography (PET) scan, showed only the left breast mass, with no evidence of metastasis or any other site of primary cancer (**Figure 2**).

Octreotide scanning is the most accurate imaging modality to exclude any other primary or metastatic site of neuroendocrine tumors. In our case, we did not perform an octreotide scan because, in the multidisciplinary team (MDT) meeting, it was decided that there is no need for further imaging and we depended mainly on PET scanning, as it is useful for identifying the aggressive and non-differentiated type of neuroendocrine tumors, as in our case [5].

The patient underwent wide local excision of the left breast mass with axillary clearance. The patient received adjuvant chemotherapy with Cisplatin 80 mg/m² on day 1 and Etoposide 100 mg/m² on days 1, 2, and 3, every 3 weeks, for a total of 4 cycles. The chemotherapy was well tolerated in general, with the exception of occasional mild bouts of nausea and vomiting. The patient also received adjuvant radiotherapy as 50 Gy/25 fractions to the left breast, supraclavicular, and internal mammary lymph nodes. The patient became pregnant and had a normal vaginal delivery on January 16, 2021. She was doing very well clinically at the time of writing this report.

Microscopic Description

Histologic examination showed a high-grade malignant tumor composed of small round-to-oval and short spindle-shaped cells arranged in solid sheets and nests, where the tumor cell nuclei had a size less than 3 lymphocytes. These cells had little cytoplasm, salt-and-pepper chromatin, and showed no distinct nucleoli. The tumor had an infiltrative border, with areas of necrosis and frequent mitoses (**Figure 3**).

With extensive sampling of the breast mass excision specimen, which showed the same tumor morphology as in the biopsy, a ductal carcinoma in situ (DCIS) was identified, with micropapillary and cribriform growth patterns, and a nuclear grade best assigned as low to intermediate (**Figure 4**). The tumor size was 2.5 cm in greatest dimension (pT2) with 15 lymph nodes harvested, and 1 of them was involved by the tumor (pN1).

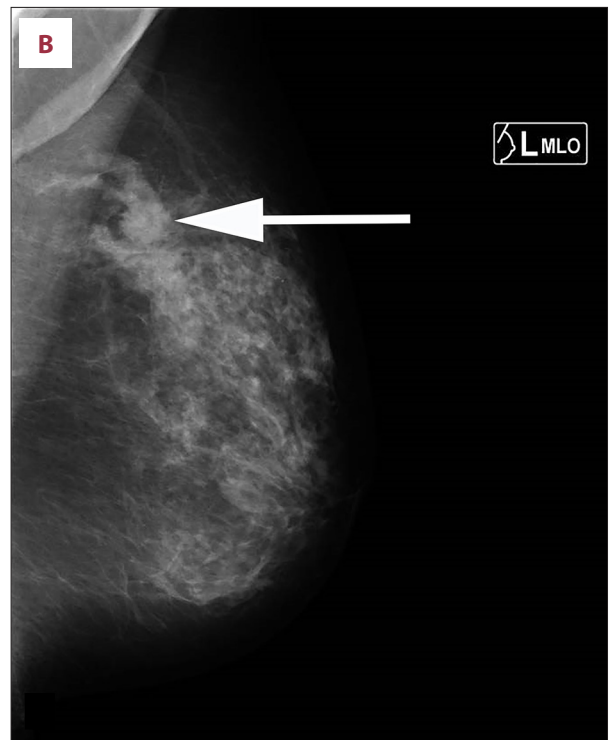
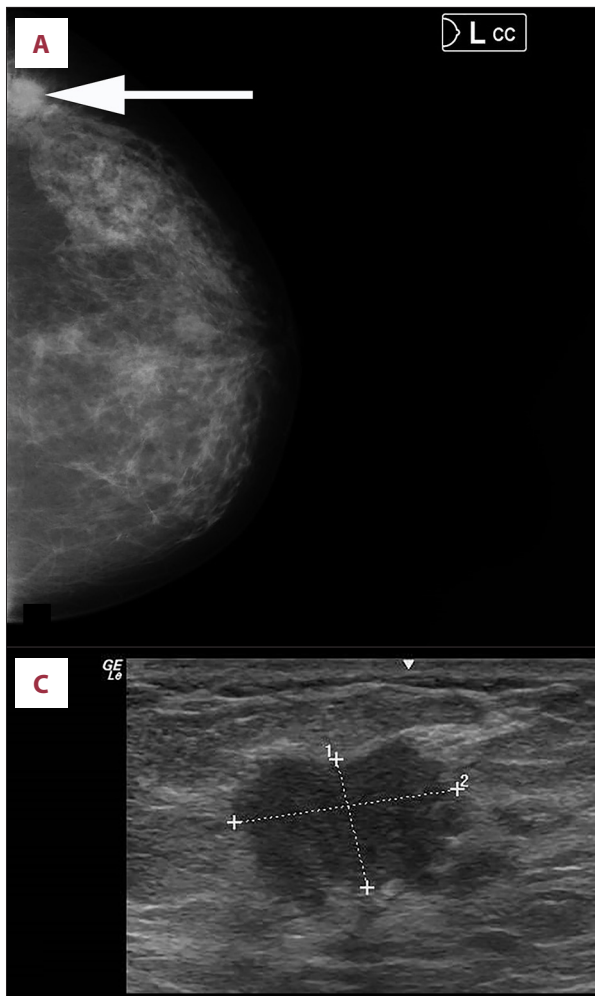


Figure 1. Left breast mass. Mammogram (A. Craniocaudal view [CC]. B. Mediolateral view [MLO]) shows a partially defined spherical hyperdense mass lesion seen in the left breast upper outer quadrant and a benign-appearing left axillary lymph node. Ultrasound scan (C) showed a well-defined solid hypoechoic mass lesion with irregular margin, measuring about 1.52×0.89 cm. There was no posterior acoustic shadowing or enhancement.

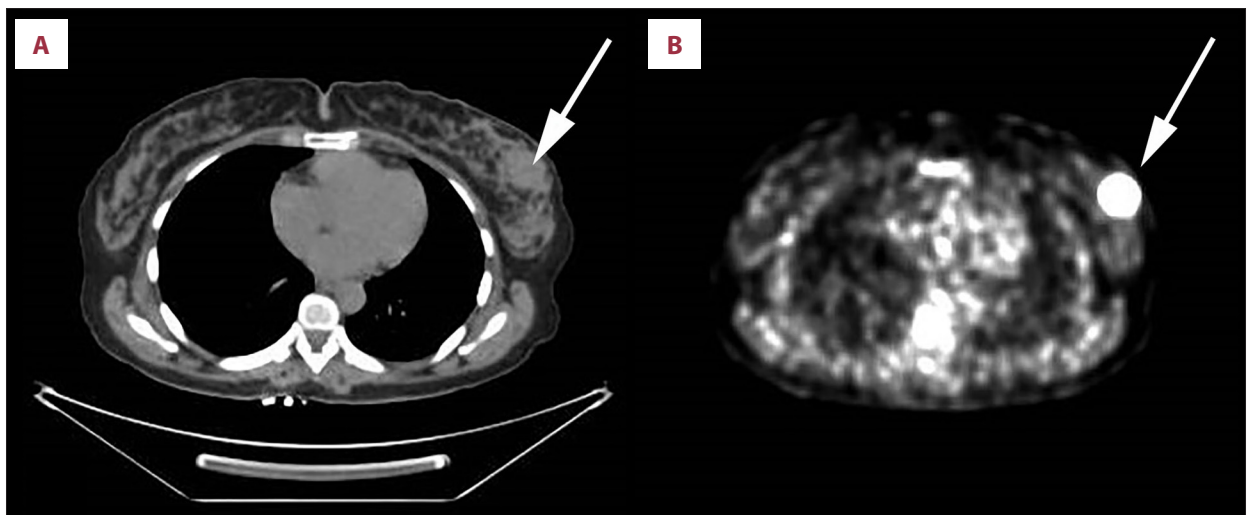


Figure 2. CT scan (A) and PET scan (B) showing the primary left breast mass lesion.

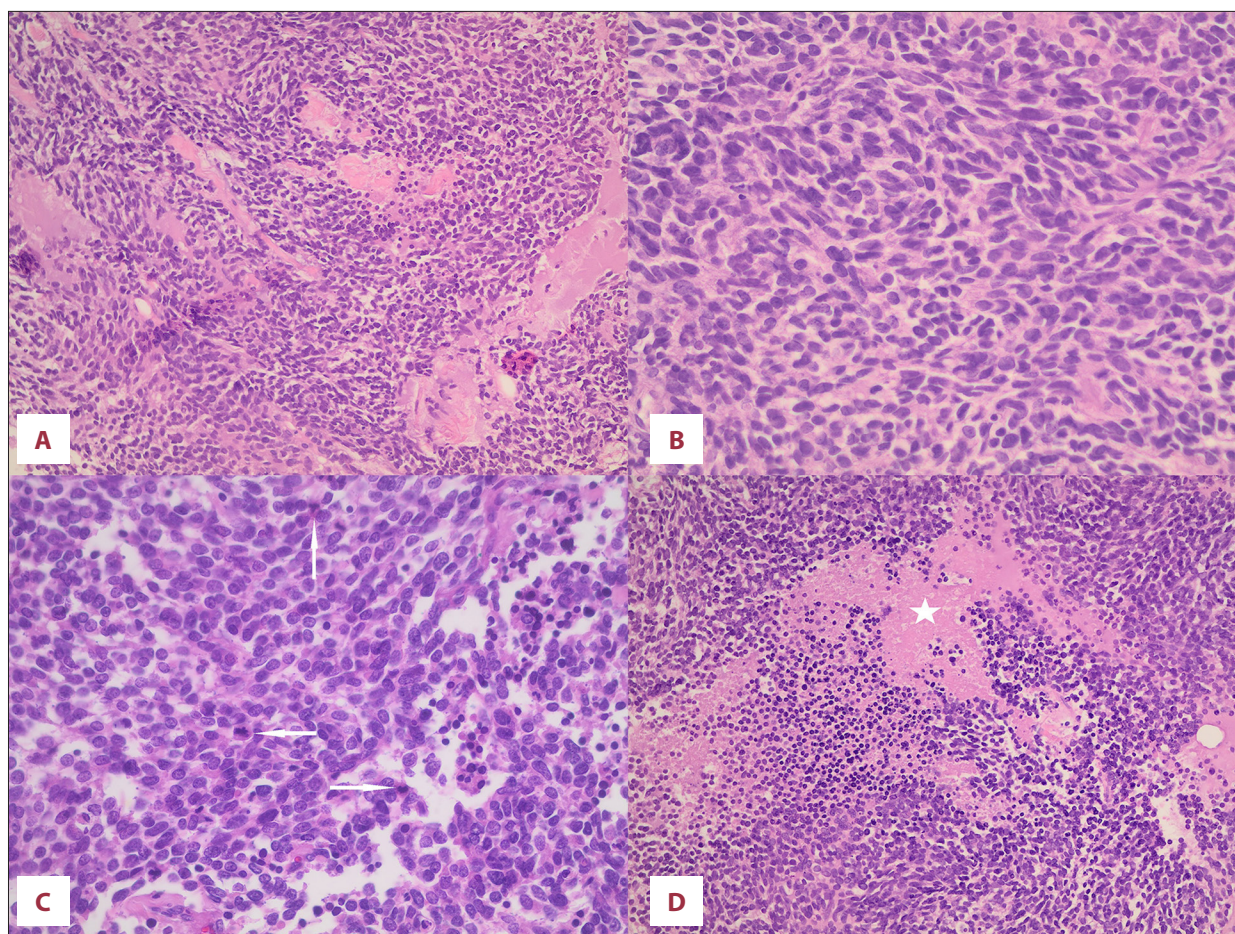


Figure 3. Core biopsy of breast lesion, showing small round-to-oval and short spindle-shaped cells arranged in sheets. These cells are characterized by high nuclear-to-cytoplasmic ratio, molded nuclei with salt-and-pepper chromatin, and no distinct nucleoli (**A, B**. Hematoxylin and eosin-stained sections, 200× and 400× total magnifications, respectively). High-grade malignancy is evidenced by frequent mitoses (**C** – highlighted by arrows) and areas of necrosis (**D** – highlighted by asterisk) – (**C, D**: Hematoxylin and eosin-stained sections, 400× total magnification).

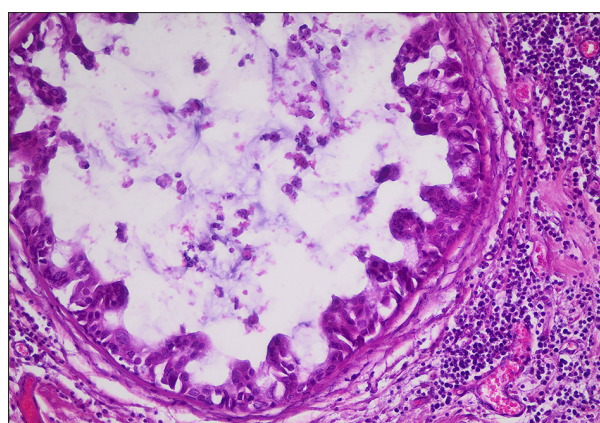


Figure 4. Ductal carcinoma in situ, micropapillary growth pattern, and a nuclear grade best assigned as low to intermediate (Hematoxylin & eosin-stained sections, 400× total magnification).

More than 50% of the tumor cells showed expression of neuroendocrine markers (synaptophysin, chromogranin, and CD56), consistent with primary neuroendocrine carcinoma of the breast rather than high-grade invasive mammary carcinoma with neuroendocrine differentiation. The tumor exhibited diffuse, uniform, and strong expression of CD56 marker, diffuse and moderately intense positivity for synaptophysin marker, and diffuse and weak positivity for chromogranin marker; findings that support neuroendocrine differentiation. Also, TTF1 marker exhibited the weak focal nuclear expression that is frequently seen in neuroendocrine carcinomas from any site, not just the lung. The Ki67 proliferation index was estimated to be positive in more than 60% of tumor cells (**Figure 5**). They were also positive for CK7, bcl2, and EMA markers, but were negative for pan-CK (AE1/AE3), p63, CK5/6, GATA3, vimentin, c-kit, CD34, desmin, CD99, LCA, CD30, and CD138 markers. Hormonal markers for estrogen receptor (ER) and progesterone receptor (PR), along with HER2-neu marker, were also

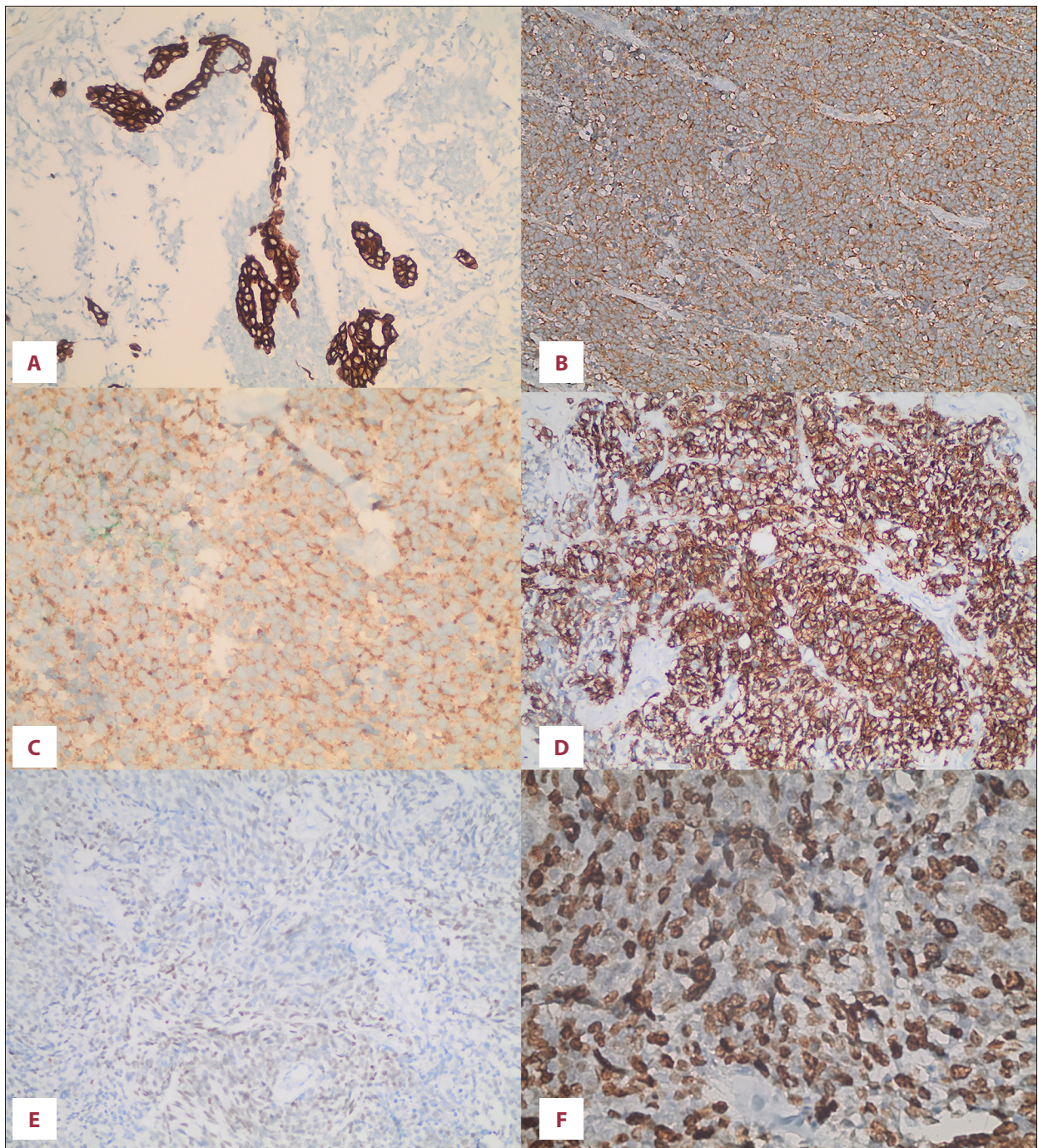


Figure 5. Immunohistochemical stains of the left breast tumor. **A.** The tumor shows patchy but strong immunoreactivity for CK7 (200× total magnifications). **B.** Synaptophysin marker with diffuse and moderate positivity (200× total magnifications). **C.** Chromogranin marker with diffuse and weak positivity (400× total magnification). **D.** CD56 marker with diffuse and strong positivity (400× total magnification). **E.** Focal and weak positivity for TTF1 marker (200× total magnification). **F.** Ki67 proliferation index estimated to be more than 60% in tumor cells (400× total magnification).

performed, and were negative. The reported DCIS component proved to be negative for the neuroendocrine markers synaptophysin and CD56.

Discussion

Small cell cancer primarily originates from the lung, but it can also originate from different extra-pulmonary regions, including the GI tract, urinary bladder, prostate, breast, cervix, and other sites [1]. This type of cancer is rarely diagnosed in the breast, accounting for only 0.1% of all breast cancers [2].

Boutrid et al [6] collected data from the literature for all patients diagnosed with primary breast small cell carcinoma until 2020, finding 6 cases; the age at diagnosis was 40-70 years and the stage of presentation was usually stage 3. Our case was at the younger end of this age range, at 39 years old.

Small cell carcinoma, whether the primary site is the breast or any other site of the body, the histopathologic features and immunohistochemical findings are the same. Therefore, to diagnose a primary breast small cell carcinoma we need to exclude if there is any other primary cancer outside the breast with the help of imaging studies, neuroendocrine differentiation not less than 50%, and/or presence of in situ carcinoma component histologically [4]. A case reported by Adegbola et al [1] exhibited foci of an in situ component of neuroendocrine pattern which confirms the primary breast origin. As mentioned above, our case contained ductal carcinoma in situ component which, although negative for neuroendocrine markers, acted along with the radiological exclusion of other sites of involvement to support primary breast origin of the tumor even with absence of positivity for breast differentiation markers like ER, PR and GATA3. Shin et al [7] explained that hormonal markers' positivity was variable in the 9 cases in their study; both were expressed together in 5 cases and both were negative in 3. Therefore, these markers are necessary to be performed and assessed, but their positivity is not mandatory to make the diagnosis. Also, 3 cases reported by Adegbola et al [1] were triple-negative.

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The imaging characteristics of this type of tumor are non-specific, and the most common mammographic imaging characteristic was smooth margins, oval or rounded dense lesion. On ultrasound scan, the mass appears hypoechoic and solid with an irregular margin with or without posterior acoustic enhancement [8]. Our case presented with this same most common characteristic.

Due to the paucity of breast small cell carcinoma cases and a small number of studies, the standard treatment is not well established; therefore, the treatment regimen varies between a combination of surgery with neoadjuvant/adjuvant chemotherapy or radiotherapy according to tumor size and lymph node status. Adding hormonal treatment depends on the expression of appropriate receptors. Hormonal markers (ER or PR) were positive in 35-54% of cases and HER2-neu was almost always negative [9]. The case reported by Abou Dalle et al [4] was receiving tamoxifen since progesterone receptor was positive in 20% of the tumor cells. Her2-neu, PR, and ER were negative in our case.

Conclusions

This case report provides a comprehensive approach to diagnosing this type of small cell carcinoma originating primarily in the breast. The suspicion of this type of breast cancer should be raised if there is presence of characteristic histopathologic findings with the exclusion of any primary origin from other organ sites by the help of imaging studies.

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