Journal of Medical Case Reports and Case Series ISSN:2692-9880

Case Report Volume 4 Issue 12

Primary Neuroendocrine Tumor of The Breast: A Rare Entity

Layla Abou Khana MD[1*], Raffi Boyrazian MD[1], Jinane Slaba MD[3], Georges Aftimos MD,PHD[2]

[1]Pathologist, lebanon

[2]Pathologist, USEK (Holy spirit university of Kaslik) and UOB (University of Balamand), Lebanon.

[3]Radiologist, Lebanon

[*]**Corresponding Author:** Layla Abou Khana MD, Pathology, USEK (Holy spirit university of Kaslik) Lebanon.

Received date: 15 May 2023; **Accepted date:** 17 July 2023; **Published date:** 27 July 2023

Citation Khana LA, Boyrazian R, Slaba J, Aftimos G (2023) Primary Neuroendocrine Tumor of The Breast: A Rare Entity. J Med Case Rep Case Series 4(12): https://doi.org/10.38207/JMCRCS/2023/JUL04120479

Introduction

Neuroendocrine neoplasms can be found in nearly all organ systems due to the distribution of neuroendocrine cells throughout the body. These cells are unique and have dual characteristics: an endocrine-like biological activity and a nerve cell-like structure. **[1]** They contain neurosecretory granules that are reactive to neuroendocrine markers, which can be helpful in the diagnosis of these tumors.

Neuroendocrine tumors of the breast account for less than 1 % of breast carcinomas. **[2]** These tumors were primarily described by Cubilla and Woodruffs, who published the first case series in 1977. **[3]**

In 2019, the WHO sub-classified neuroendocrine neoplasms into well-differentiated tumors (NET), highly aggressive carcinomas (NEC), and invasive carcinoma of no particular type with neuroendocrine differentiation. **[2]**

Case Presentation

An 85 years old woman (gravida 4) presented for a left breast mass. The patient had a history of a uterine neoplasm of an unknown type, for which she underwent a hysterectomy without chemotherapy several years ago, as by her son.

On physical examination, the left nipple was retracted with a palpable retro-areolar nodule. The rest of the physical examination was regular.

Mammography and breast ultrasound showed two masses in the left breast: the large, palpated retro-areolar mass, measuring 4.5 cm, and a minor lesion mid-laterally, measuring 15 mm and located at 2 cm from the leading group. A PET scan was performed, and no other lesions were detected elsewhere.

A biopsy was taken from the mid-lateral mass. Histological examination showed an infiltrating neoplastic proliferation comprised of polygonal cells with moderately irregular nuclei that were primarily arranged in trabeculae embedded within a fibrous stroma. Areas of necrosis and scattered mitotic figures were also noticed. A grade 2 neuroendocrine tumor diagnosis was made, confirmed by significant diffuse positivity for synaptophysin with negative expression of E-cadherin by tumor cells.

The patient was then lost to follow-up.

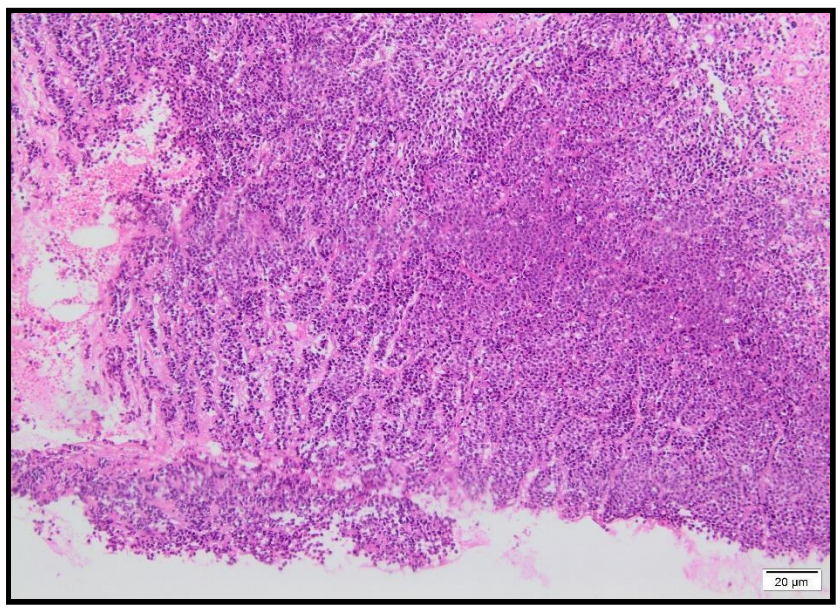

Figure 1: Tumor cells arranged in trabeculae

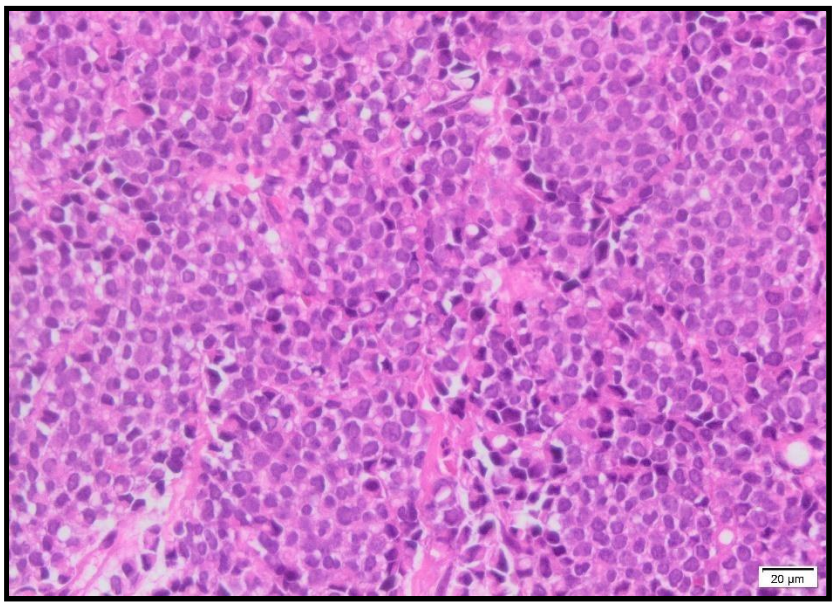

Figure 2: Polygonal cells with mildly irregular nuclei

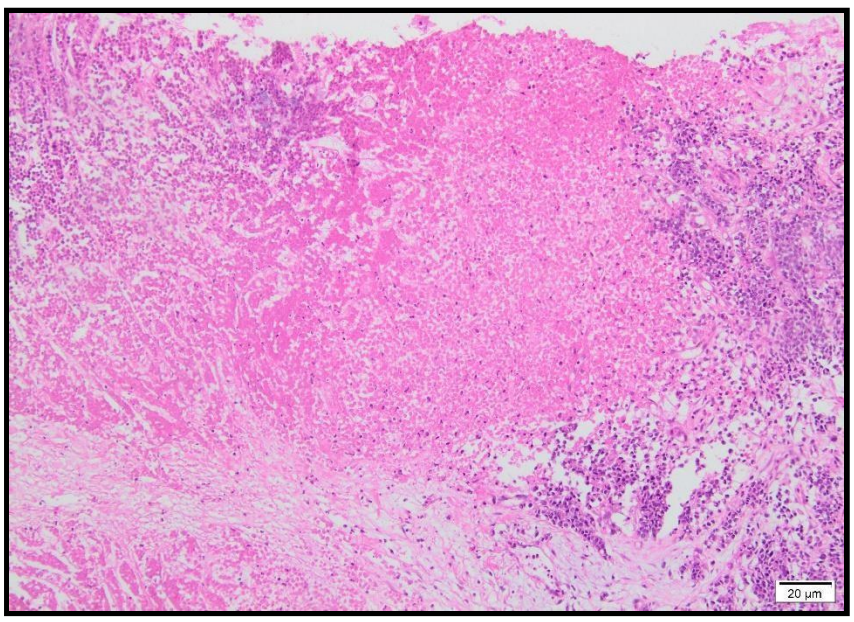

Figure 3: Areas of necrosis.

Discussion

Primary mammary neuroendocrine neoplasm is a rare and unique subtype that accounts for less than 1 % of breast cancers. **[2]** Patients are usually in the sixth and seventh decades. **[2]**

Clinically, there is no specific presentation. The most common features are palpable breast lump, bloody discharge, ulceration, and nipple retraction. Radiologic features are non-specific as well. **[1]**

Most commonly, patients present with stage 2 disease, and compared with invasive ductal carcinoma, they are at increased risk for lymph node metastasis. **[4]**

Unlike in other organs, neuroendocrine cells have not been found in normal breast parenchyma; thus, the pathogenesis of the primary NET of the breast remains not fully understood. They probably result from the early differentiation of stem cells into epithelial and neuroendocrine lineages. **[2]** As opposed to this, Tomonori et al. showed that benign neuroendocrine cells exist in the background breast parenchyma in cases with neuroendocrine neoplasms and are structured in a specific way. **[1]**

Macroscopically, primary neuroendocrine tumors of the breast are firm in consistency, appear yellowish, and can be round or multilobulated. They can have a gelatinous cut surface if associated with a mucinous component. **[5]**

Microscopically, they are characterized by the presence of solid nests and trabeculae of tumor cells with spindled, plasmacytoid, and polygonal morphologies, showing eosinophilic, granular or clear cytoplasm, separated by delicate fibro-vascular stroma. **[2]**

The World Health Organization (WHO), in its 2003 edition, defined neuroendocrine neoplasms of the breast as tumors expressing neuroendocrine markers in more than 50 % of neoplastic cells. **[1]**

In 2012, the WHO suggested that the diagnosis can be made regardless of the percentage of cells expressing the biomarkers and substituted the term neuroendocrine carcinoma of the breast with "carcinoma with neuroendocrine features". **[1]**

The latest WHO classification divides tumors with neuroendocrine features into 3 groups: well-differentiated neuroendocrine tumor (WD-NET), which resembles the carcinoid tumors of other sites; poorly differentiated neuroendocrine carcinoma (PD-NEC) or small cell carcinoma, which is similar to its pulmonary counterpart; and invasive breast carcinoma with neuroendocrine differentiation (IBC-NED). **[2]**

Small-cell and large-cell NECs are classified in the high Nottingham histologic grade group. About 0.1 % of all breast tumors and 3–10 % of extrapulmonary neuroendocrine carcinomas are small cell NECs. Instead of the malignant transformation of specific neuroendocrine cells in the normal breast tissue, small cell NEC may be caused by the particular differentiation line of mammary cancer stem cells toward the neuroendocrine/small cell type, which can occur at the in-situ

stage or later at the invasive stage. Small cell NEC exhibits an infiltrative growth pattern of relatively homogeneous cells, with a high N: C ratio, disclosing small and dark nuclei with molding, inconspicuous nucleoli, sparse cytoplasm, and weakly defined cytoplasmic borders. **[2]**

A very uncommon subtype of NECB is the large cell NEC. Its cells have a moderately abundant cytoplasm with extremely pleomorphic nuclei containing coarse chromatin.

It is important to note that metastatic well-differentiated NET and moderately differentiated NEC, especially those with pulmonary, gastrointestinal, and pancreatic origin, should be excluded first to be able to make the diagnosis of primary NET of the breast. **[2]**

By exhibiting immunoreactivity to chromogranin, A, synaptophysin, and neuron-specific antigens, the IHC approach has made it possible to identify the neuroendocrine phenotypes in breast cancer subpopulations. The most sensitive neuroendocrine markers are chromogranin and synaptophysin, while NSE and CD56 are less sensitive and specific. **[1]**

As previously mentioned, a metastatic NET from an extramammary location is the critical differential diagnosis for NECB. Differentiation is challenging because metastatic NEC and NECB have significant morphologic similarities. Site-specific lineage markers such as GATA3, mammaglobin, GCDFP15, TTF1, CDX2, and PAX8/PAX6 can aid in separating NECB from metastatic NET. **[6]** According to Mohanty et al., CDX2 is consistently negative in NECB, TTF1 is positive in about 70 % of lung metastases, and CDX2 is positive in 100 % of gastrointestinal metastases. **[6]** Positive results for PAX8/PAX6 may suggest that the origin is from pancreatic islets. Additionally, IHC staining for myoepithelial cells can help distinguish in-situ cancer from metastatic neuroendocrine neoplasms. **[6]**

Most NECB exhibits a luminal-like phenotype and is hormone receptor (ER) positive but HER-2 (human epidermal growth factor receptor 2) negative. **[7]** However, because ER-positive is neither generally expressed in common breast malignancies nor particular to breast tumors, it is insufficient to confirm the primary mammary origin of the tumor.

A metastatic tumor overlap can be seen in the morphology or IHC markers of NECB. As a result, a pertinent clinical history must be considered while making a final diagnosis.

There are no established standards for grading, staging, or managing primary NETs of the breast. According to the most recent WHO categorization, grading is not anticipated to have clinically relevant effects. **[2]** It is advised that breast NETs be staged and treated like that of conventional breast cancer. **[3]**

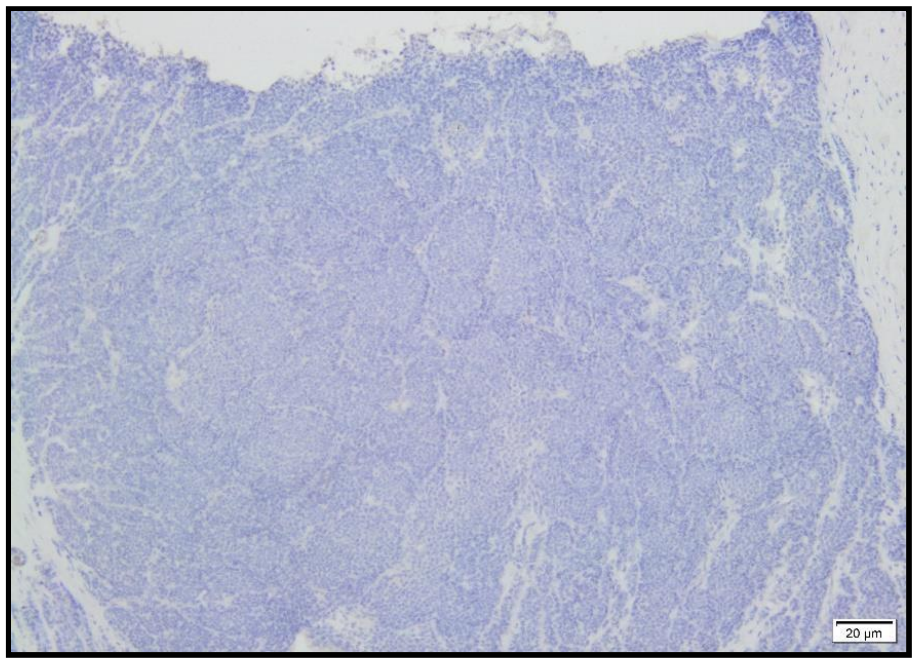

Figure 4: Negative E-cadherin

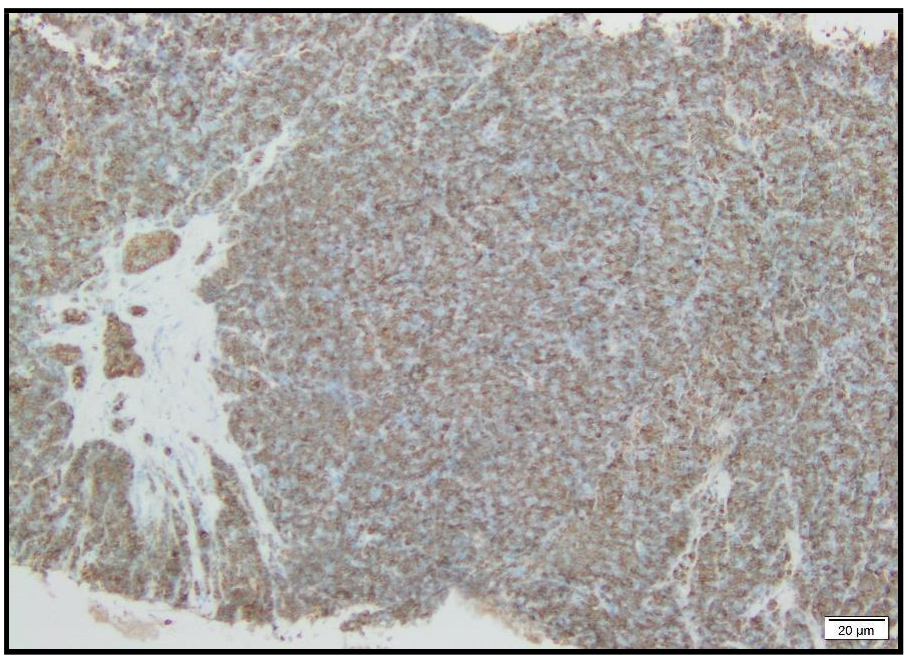

Figure 5: Positive synaptophysin

Conclusion

Neuroendocrine neoplasm of the breast is a diverse illness with numerous subgroups and a wide range of clinical traits. Due to the rarity of these tumors, extramammary metastasis must be ruled out at diagnosis. The ability to distinguish neuroendocrine tumors is determined mainly by their architecture and, to a lesser extent, by the nuclear characteristics of neuroendocrine differentiation. Their accurate diagnosis can only be made through the histopathological investigation with adequate immunohistochemical staining panels. Until now, these tumors' clinical and prognostic importance is subject to disagreement. Thus, studies on more extensive series are required better to understand the biological dynamics of mammary neuroendocrine tumors.

References

1. Sun H, Dai S, Xu J, Liu L, Yu J, et al. (2022) Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives. Front Oncol. 12: 848485.
2. Organisation mondiale de la santé, ed. Breast Tumours. 5th ed. OMS
3. Rosen LE, Gattuso P (2017) Neuroendocrine Tumors of the Breast. Arch Pathol Lab Med. 141(11): 1577-1581.
4. Wei B, Ding T, Xing Y, Wei W, Tian Z, et al. (2010) Invasive neuroendocrine carcinoma of the breast: A distinctive subtype of aggressive mammary carcinoma. Cancer. 116(19): 4463-4473.
5. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ (2012) WHO Classification of Tumours of the Breast. 4th ed. International agency for research on cancer. Organisation mondiale de la santé, Centre international de recherche sur le cancer, eds.
6. Mohanty SK, Kim SA, DeLair DF, Bose S, Laury AR, et al. (2016) Comparison of metastatic neuroendocrine neoplasms to the breast and primary invasive mammary carcinomas with neuroendocrine differentiation. Mod Pathol. 29(8): 788-798.
7. Ang D, Ballard M, Beadling C, Warrick A, Schilling A, et al. (2015) Novel Mutations in Neuroendocrine Carcinoma of the Breast: Possible Therapeutic Targets. Appl Immunohistochem Mol Morphol. 23(2): 97-103.