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Case Report

Neuroendocrine Tumor of Breast: A Rare Case Report

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Introduction

The reported incidence of the rare neuroendocrine breast tumors comprises 2–5% of all breast carcinomas. The diagnosis depends mainly on the radiologically and histopathologically detected criteria [1, 2]. The World Health Organization categorized these tumors as a subtype of invasive breast cancer based on endocrine features [3].

NENs of the breast (Br-NENs) are the rarest of all NENs (accounting for less than 1% of all NENs) [4–6], and comprise a heterogeneous group of tumors. All Br-NENs are invasive carcinomas, by definition.

Neuroendocrine differentiation is observed in up to 20% of mammary carcinomas, so the real incidence of NEBCs is difficult to evaluate because immunohistochemical neuroendocrine markers are not usually used in the diagnosis of breast cancer [5].

The clinical and radiological features may not differ from other invasive cancers; however, the diagnosis is solely made on the discovery features similar to neuroendocrine tumors arising from the gastrointestinal tract or lungs. These tend to express neuroendocrine markers in >50% of cases [7]

Case Report

A 58-year-old female, a mother of 1 noticed a mass in left breast since 6-month duration. There were no associated pain, discharge, skin changes, or systemic manifestations. Gynecological history was unremarkable with regular menstrual cycles and intermittent use of oral contraceptive pills. There was no family history of breast cancer or similar a presentation.

General Examination Was Unremarkable

Local examination revealed breast asymmetry, with a 3-fold increase in the left breast size. A 7 × 7-cm mass occupied both lower and lateral quadrants extending from 2 and 5 o'clock. The overlying skin was normal. Nipple and the areola complex were stretched but uncompromised. No lymph node was palpated in the ipsilateral axilla (Fig. 1).

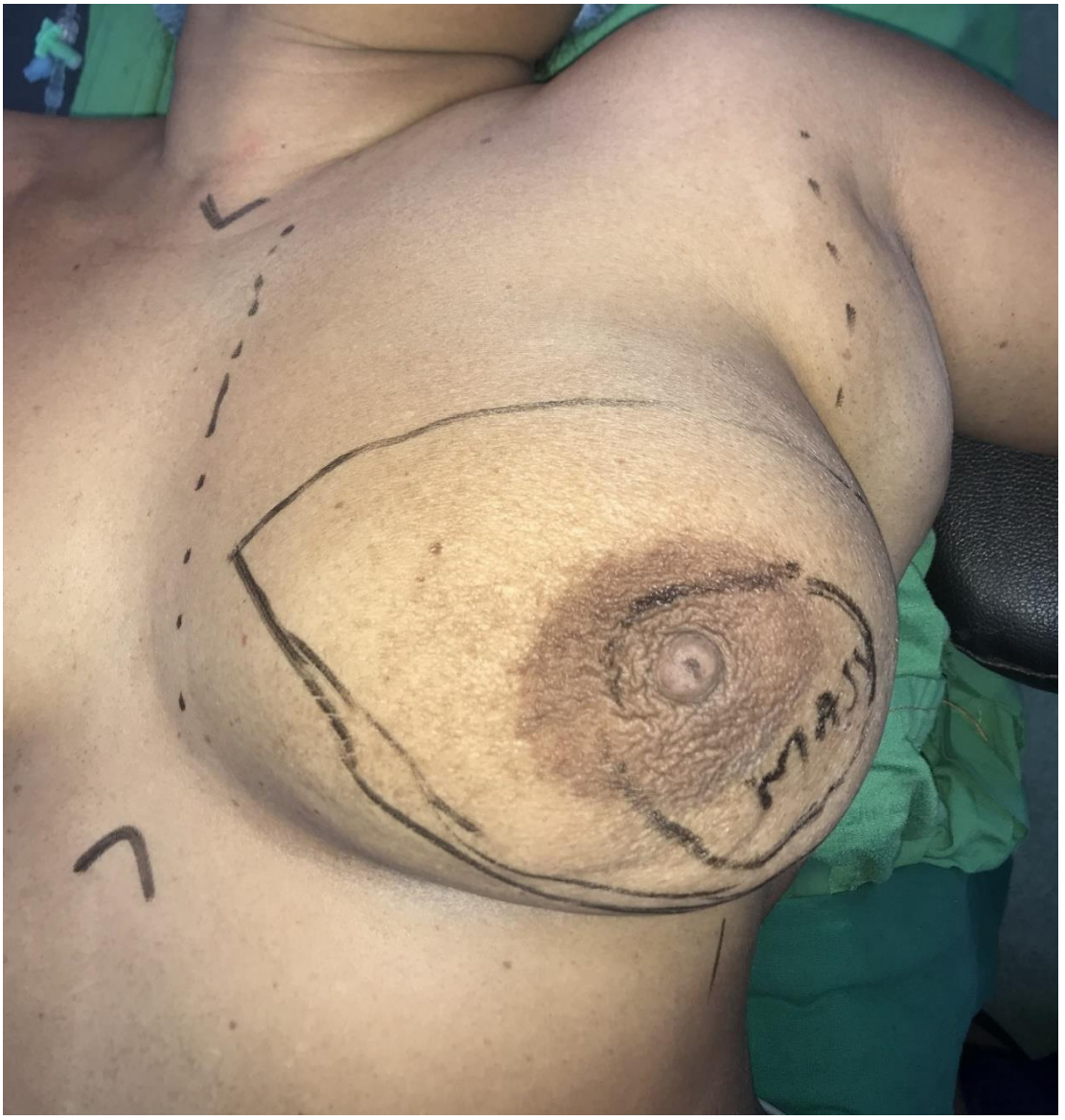

Figure 01

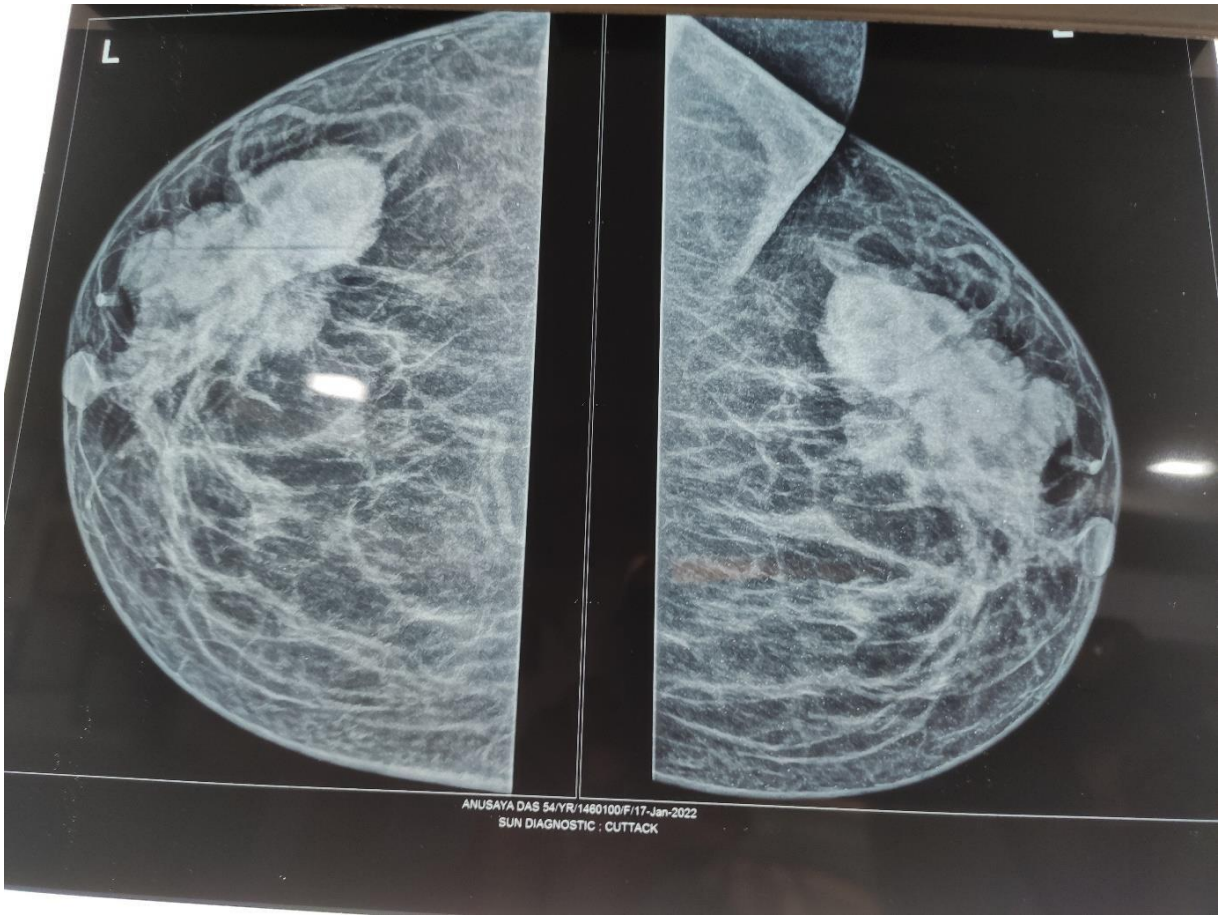

Fig 2. On Mammography- An Irregular Lobulated Large Density Noted in the Upper Outer Quadrant of Left Breast Extending Towards the Retro Areolar Region s/o Suspicious Left Breast Mass Lesion. Few Prominent Nodes with Maintained Fatty Hilum noted in Left Axilla. (BIRADS-IVA)

The primary clinical impression was locally advanced breast cancer. Initial standard investigations included mammogram (Fig. 2), followed by core needle biopsy. Core biopsy was Suggestive of Invasive Ductal carcinoma. (Grade -1)

Ultrasound of Abdomen and nuclear bone scans both demonstrated the breast lesion with no evidence of distal metastasis.

Patient underwent Modified Radical Mastectomy with Axillary Lymphnode dissection.

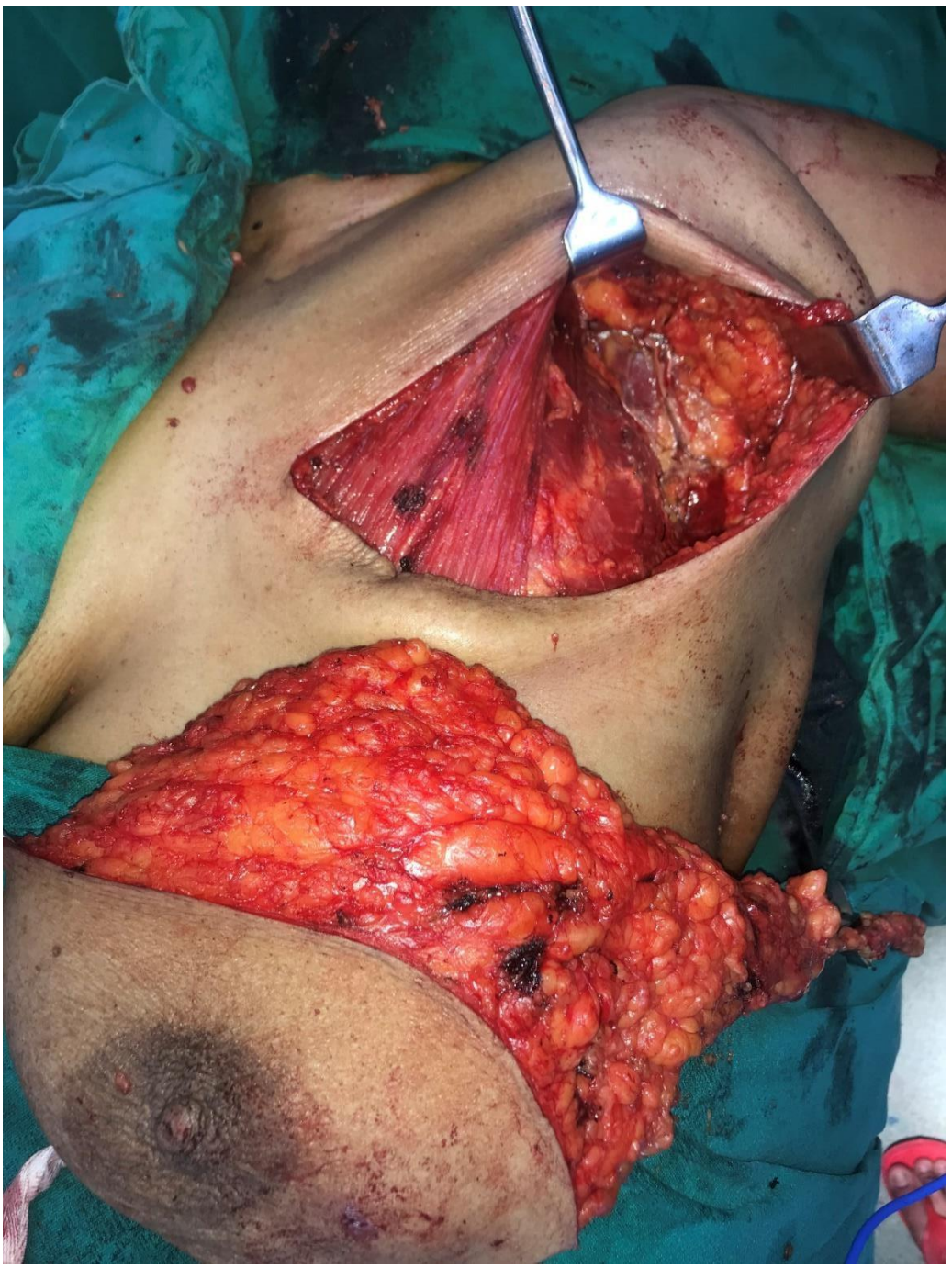

Fig 3: Modified Radical Mastectomy Specimen and Tumor Bed.

On Histopathological examination, the tumor histology came out to be Neuroendocrine Carcinoma, small cell type, grade 3, Poorly Differentiated. Tumor size was 9x6x4 cm. On, Immunohistochemistry, Synaptophysin was focally positive and Non Specific Enolase was strongly positive. Chromogranin was Negative. ER, PR and Her2Neu were Negative and KI 67 was 55%. Total of 32 Lymph nodes were retrieved out of which none were positive.

So, the Patient was diagnosed to have a Poorly differentiated Neuroendocrine Carcinoma of left breast. The patient had an uneventful postoperative course and was discharged in a good condition to be followed up in our hospital.

Discussion

NEBC was first described in 1963 by Feyrter and Hartmann as carcinoid growth pattern within two cases of breast cancer [8]. Later, in 1977, Cubilla and Woodruff classified eight cases of breast cancers as "carcinoid" [9]. Only several years later, in 2003, the World Health Organization (WHO) recognized

NEBC as a separate entity of breast cancer, showing morphological characteristics similar to gastrointestinal and pulmonary neuroendocrine tumors (NETs), with the expression of a neuroendocrine marker in at least 50% of tumor cells [10]. In the subsequent updates WHO further classified these tumors based on their expression of neuroendocrine markers.

2003 Third edition	2012 Fourth edition	2019 Fifth edition
Neuroendocrine (NE) tumor • Morphological features similar to those of NE tumors both GI tract and lung • Express NE markers more than 50% ● **Solid neuroendocrine carcinoma** ● **Small cell/oat cell carcinoma** ● **Large cell neuroendocrine carcinoma (LCNEC)**	Carcinoma with neuroendocrine tumor • Morphological features similar to those of NE tumors of the GI tract and lung • Express NE markers a greater or lesser degree ● **NET, well differentiated** ● **NEC, poorly differentiated /small cell carcinoma** ● **IBC with NE differentiation** ● **Solid papillary carcinoma** ● **Hypercellular mucinous carcinoma**	Neuroendocrine neoplasm (NEN) • Cancers with >90% NEN pattern ● **Neuroendocrine tumor (NET)** ● **Neuroendocrine carcinoma (NEC)** ● **Small cell carcinoma** ● **LCNEC** Invasive breast cancer NST (or other special type) with NE features • ≤90% NE histological features or NE expression ● 10-90%: **Mixed invasive NST (or other special type) and NET/NEC** ● <10%: **Invasive NST (or other special type) with a comment on the focal NE pattern** Other specific breast cancer subtypes ● **Solid papillary carcinoma** ● **Hypercellular mucinous carcinoma**

Table 1. WHO classifications from 2003 , 2012 and 2019

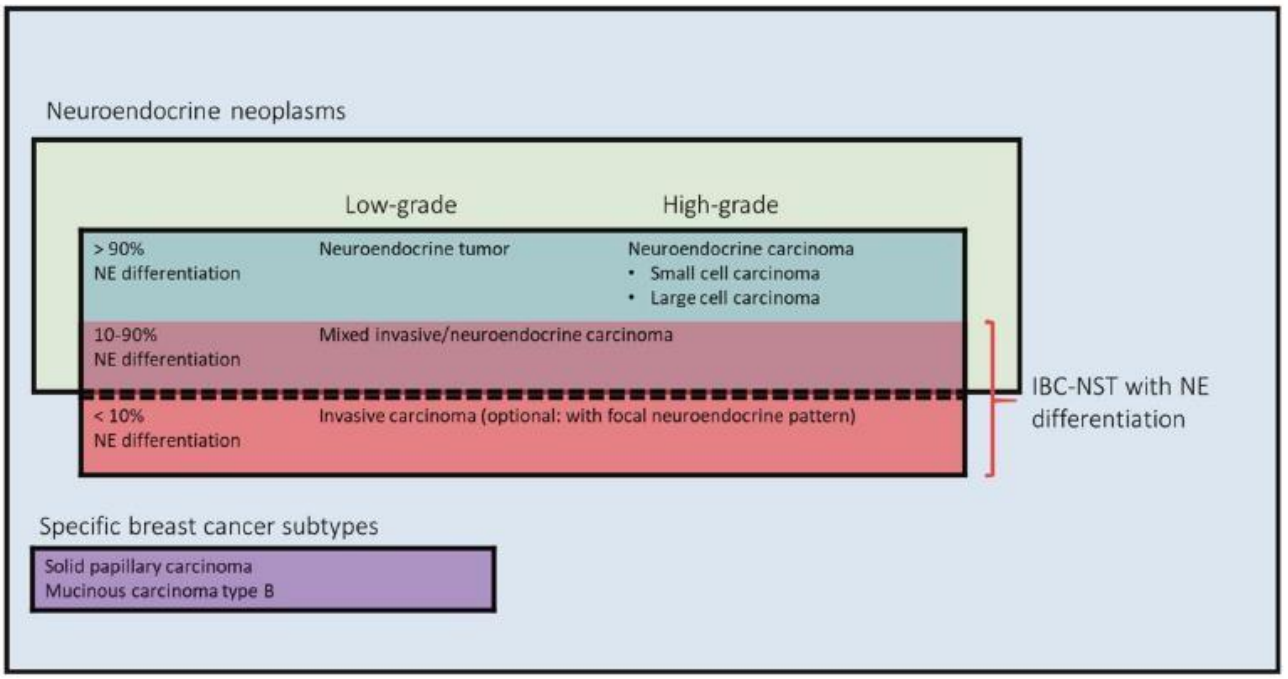

Fig 4. 2019 updated WHO classification for NET.

A NET of breast is a subtype of breast cancer with similar morphological characteristics to gastrointestinal/lung NETs while displaying some degree of heterogeneity, including certain features that are usually difficult to identify from IBCNST. Therefore, NECB may be misdiagnosed as metastatic breast cancer, carcinomas of IDC-NST, or breast carcinoma with neuroendocrine differentiation.

As the incidence of NECB is low, there is limited knowledge about the specific clinical characteristics of NECB. Most of the data comes from case reports and retrospective studies. The clinical feature of NECB is mainly characterized by a solitary breast lump, probably accompanied by skin ulceration, bloody nipple discharge, skin retraction, palpable axillary mass, and breast discomfort. Some people may have complications such as bone pain, respiratory symptoms, abnormal liver function, hematuria, and neuralgia caused by metastasis.While some people have no symptoms, they occasionally discover the disease due to routine mammographic screening. A few patients may suffer from carcinoid syndrome or hormonal hypersecretion. Patient age at diagnosis is mainly between the fifth and seventh decade of life (majority aged >60 years), ranging from 26to 99 years, and most patients are postmenopausal women with higher clinical stage and histologic grade.[11]

Compared to IDC-NST, NECB patients are more likely to present systematic metastasis at initial diagnosis, and the most common metastatic sites are bone, liver, lungs, brain, bone marrow, and pleura, and several cases involve skin (12-15). In addition, Kawasaki et al. reported peculiar endovascular spread (16).

There are no specific radiological features of primary Br-NENs [17], and the diagnosis is confirmed on the basis of the histopathological findings. Gallo et al. recently reviewed the mammographic findings in case reports and case series of Br-NENs and reported that the most common mammographic appearance was a hyperdense, irregularly shaped solitary mass without calcifications [18]. Computed tomography (CT) is performed to detect distant metastases and the possibility of the breast tumor being a metastasis from primitive NETs arising in other organs. It is reasonable to perform somatostatin receptor scintigraphy or positron emission tomography (PET)-CT with gallium-68-labeled somatostatin analogues to evaluate the disease location in cases of well-differentiated NETs and indication of peptide receptor radionuclide therapy (PRRT). PET-CT with 18-fluorodeoxyglucose can be performed in patients with poorly differentiated tumors or high-grade carcinomas.[19]

Currently, there is a lack of clinical trials specifically on NE breast cancers, and surgery remains the mainstay of treatment, with supplementary hormonal therapy. Chemotherapy is reserved for those with high risk of recurrence. The choice of treatment for NE breast cancers is based on the main prognostic factors (including TNM stage, Nottingham histologic grade, ER, PR and HER2 status) as for the other types of breast cancer. NE breast cancers appear to have a worse prognosis than other breast cancers. Data on treatment response of NE breast cancers are scarce. A trend of better outcome for NE breast cancers (basing on WHO 2003 classification) receiving hormonal therapy and radiotherapy has been demonstrated, but an opposite trend for chemotherapy has been shown in one report. However, the data did not reach statistical significance.

Endocrine therapies may have an advantage in susceptible tumors. Somatostatin analogues are suggested for tumors with somatostatin receptor expression [20,21]. The diagnosis of primary poorly differentiated invasive neuroendocrine carcinoma is an uncommon challenging entity that requires diligent multimodality management.

References

1. Miremadi A, Pinder SE, Lee AH, Bell JA, Paish EC, Wencyk P, et al. Neuroendocrine differentiation and prognosis in breast denocarcinoma. Histopathology. 2002; 40(3): 215–22.
2. Makretsov N, Gilks CB, Coldman AJ, Hayes M, Huntsman D. Tissue microarray analysis of neuroendocrine differentiation and its prognostic significance in breast cancer. Hum Pathol. 2003; 34(10): 1001–8.
3. Ellis IO, Schnitt SJ, Sastre-Garau X, Bussolati G. Invasive breast carcinoma. In: Tavassoli FA, Devilee P, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003. p. 32–4.
4. Marinova, L.; Malinova, D.; Vicheva, S. Primary Neuroendocrine Carcinoma of the Breast: Histopathological Criteria, Prognostic Factors, and Review of the Literature. Case Rep. Pathol. 2016, 2016, 1–4. [CrossRef]
5. Wang, J.; Wei, B.; Albarracin, C.T.; Hu, J.; Abraham, S.C.; Wu, Y. Invasive neuroendocrine carcinoma of the breast: A populationbased study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 2014, 14, 147. [CrossRef][PubMed]
6. Hauso, O.; Gustafsson, B.I.; Kidd, M.; Waldum, H.L.; Drozdov, I.; Chan, A.K. Neuroendocrine tumor epidemiology: Contrasting Norway and North America. Cancer 2008, 113, 2655–2664. [CrossRef] [PubMed]
7. Inno, A.; Bogina, G.; Turazza, M.; Bortesi, L.; Duranti, S.; Massocco, A.; Zamboni, G.; Carbognin, G.; Alongi, F.; Salgarello, M.; et al. Neuroendocrine Carcinoma of the Breast: Current Evidence and Future Perspectives. Oncologist 2016, 21, 28–32. [CrossRef] [PubMed]
8. Feyrter F, Hartmann G. On the carcinoid growth form of the carcinoma mammae, especially the carcinoma solidum (gelatinosum) mammae. Frankf Z Pathol. 1963;73:24–39.
9. Cubilla AL, Woodruff JM. Primary carcinoid tumor of the breast: a report of eight patients. Am Surg Pathol. 1997;1:283–92.
10. Tavassoli FA, Devilee P. World Health Organization Classification of tumours: pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003. p. 32–34.

11. Sun H, Dai S, Xu J, Liu L, Yu J and Sun T (2022) Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives. Front. Oncol. 12:848485. doi: 10.3389/fonc.2022.848485

12. Lavigne M, Menet E, Tille J, Lae M, Fuhrmann L, Bonneau C, et al. Comprehensive Clinical and Molecular Analyses of Neuroendocrine Carcinomas of the Breast. Modern Pathol (2018) 31:68–82. doi: 10.1038/modpathol.2017.107

13. Santos-Juanes J, Fernández-Vega I, Coto-Segura P, Vivanco-Allende B, García-Pravia C. Cutaneous Spread of Primary Neuroendocrine Breast Carcinoma With Apocrine Differentiation. J Eur Acad Dermatol Venereology JEADV (2015) 29:1440–1. doi: 10.1111/jdv.12486

14. Vidulich K, Donley S, Duvic M. Multinodular Cutaneous Spread in Neuroendocrine Tumor of the Breast : An Unusual Presentation. Am J Clin Dermatol (2007) 8:379–83. doi: 10.2165/00128071-200708060-00008

15. Yang L, Roy M, Lin H, Shen Y, Albarracin C, Huo L, et al. Validation of Prognostic Significance of the Proposed Uniform Classification Framework in Neuroendocrine Neoplasms of the Breast. Breast Cancer Res Treat (2021) 186:403–15. doi: 10.1007/s10549-021-06099-6

16. Kawasaki T, Bussolati G, Marchiò C, Castellano I, Daniele L, Molinaro L, et al. Well-Differentiated Neuroendocrine Tumour of the Breast Showing Peculiar Endovascular Spread. Histopathology (2014) 64:597–600. doi: 10.1111/his.12276

17. Ogawa, H.; Nishio, A.; Satake, H.; Naganawa, S.; Imai, T.; Sawaki, M.; Yamamoto, E.; Miyata, T. Neuroendocrine tumor in the breast. Radiat. Med. 2008, 26, 28–32.

18. Gallo, M.; Campione, S.; Di Vito, V.; Fortunati, N.; Calzo, F.L.; Messina, E.; Ruggeri, R.M.; Faggiano, A.; Colao, A.A.L. Primary Neuroendocrine Neoplasms of the Breast: Still Open Issues. Front. Endocrinol. 2020, 11.

19. Arslan, E.; Çermik, T.F.; Trabulus, F.D.C.; Talu, E.C.K.; Ba¸saran, ¸S. Diagnostic impact of 18F-FDG PET/CT on the management of rare breast carcinomas: Apocrine and neuroendocrine carcinomas. Rev. Esp. Med. Nucl. Imagen Mol. 2019, 38, 147–153.

20. Watrowski R, Jäger C, Mattern D, Horst C. Neuroendocrine carcinoma of the breast: diagnostic and clinical implications. Anticancer Res. 2012; 32(11): 5079–82.

21. Saeed A, Rehman A, Zaidi SA, Shaukat T, Jamil K, Abdullah K. Neuroendocrine carcinoma of breast. J Coll Physicians Surg Pak. 2011; 21(6): 371–3.

22. [4]Righi L, Sapino A, Marchiò C, Papotti M, Bussolati G. Neuroendocrine differentiation in breast cancer: established facts and unresolved problems. Semin Diagn Pathol. 2010; 27(1): 69–76.