Primary neuroendocrine tumor of the breast: A case report

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Received April 15, 2024; Accepted October 18, 2024

DOI: 10.3892/ol.2024.14825

Abstract. Primary neuroendocrine neoplasm of the breast (PNENB) is a rare subtype of breast cancer, accounting for <1% of all breast tumors. The morphological features of PNENB are similar to those of neuroendocrine tumors originating in the lungs or gastrointestinal system, with tumor cells exhibiting the strong expression of neuroendocrine markers, including chromogranin A and synaptophysin. Since this type of cancer was first reported, the definition, classification and diagnostic criteria of PNENB have evolved and changed. However, accurate diagnostic criteria and standard treatment guidelines are lacking. The present report describes a specific case of PNENB, which was consistent with the morphological and molecular features of other cases in most previous studies. In addition, the current body of literature on PNENB, including its development, diagnosis, molecular features, treatment and prognosis is reviewed.

Introduction

Neuroendocrine neoplasms (NENs) can originate from several regions of the body, but are most commonly observed in the gastrointestinal tract, and, to a lesser extent, in the lungs, breast, larynx, prostate, bladder, ovaries and cervix. Included among these, primary NEN of the breast (PNENB) is a rare subtype of breast cancer, accounting for <1% of all breast tumors (1). Current understanding of this disease is limited, as researchers have not detected neuroendocrine cells in normal breast tissue, and it has been suggested that PNENB may be derived from an early-stage differentiation of breast cancer tumor cells (2). The definition of PNENB as well as the diagnostic criteria have been under debate since this type of cancer was first reported (1,3,4). The different criteria used for the definition of cases, due to the overlap in diagnostic features between PNENB and invasive breast cancer (IBC) with neuroendocrine differentiation (5), have led to a lack of comparability between studies on the treatment and prognosis of the disease. In the present article, a case of a patient with PNENB is described and the current body of literature on PNENB is reviewed.

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Key words: breast tumor, neuroendocrine tumor of the breast, molecular characteristic, diagnosis

Case report

A 70-year-old woman was admitted to the Affiliated Hospital of Inner Mongolia Medical University (Hohhot, China) on May 22, 2014 with a left breast mass that had been detected >1 month earlier. On examination, a medium-sized (~15x20 mm) mass with unclear borders was palpable in the upper outer quadrant of the left breast. Enlarged lymph nodes were also palpable in the left axilla. An ultrasound on May 24, 2014 showed a 15x20-mm irregular hypoechoic solid mass, identified at 1 o'clock in the left breast, and two transverse fingers from the nipple, 7.6 mm below the surface of the skin, with no clear borders. Striated blood flow signals were observed at the margins of the lesion by color Doppler flow imaging, which was assessed as Breast Imaging Reporting and Data System (BI-RADS) category 4b (6) (Fig. 1). A mammography on May 25, 2014 showed a nodular hyperdense shadow in the upper quadrant of the left outer breast, ~15x20 mm in size, which was assessed as BI-RADS 4a (Fig. 2). Subsequently, left breast lumpectomy followed by intraoperative frozen section analysis was performed. The gross pathological examination revealed a piece of light-yellow soft tissue of 5x4x3 cm, with a bleeding gray-white mass inside. The maximum diameter of the mass was 2 cm. Hematoxylin and eosin staining and immunohistochemical (IHC) staining were performed to further define the tumor. For hematoxylin and eosin staining, tissues were fixed with 10% neutral formalin at 24˚C for 20 h. Tissue sections were 4 μm thick. Tissues were immersed in xylene for 5 min, and 75, 85 and 95% gradient ethanol for 1 min. Tissues were stained with hematoxylin for 6 min at 37˚C, differentiated with 0.5% hydrochloric acid ethanol for 10 sec, incubated with 0.2% ammonia water for 40 sec and stained with eosin staining solution for 3 min at 60˚C. Staining was observed under a light microscope. For IHC staining, tissues were fixed with 10% neutral formalin at 24˚C for 20 h and embedded in paraffin. The tissue sections were 4 μm thick. The tissue sections were blocked with 15% blocking serum (Fish Serum Blocking Buffer; Thermo Fisher Scientific, Inc.) for 20 min at 37˚C. Tissue sections were incubated with Cyclin

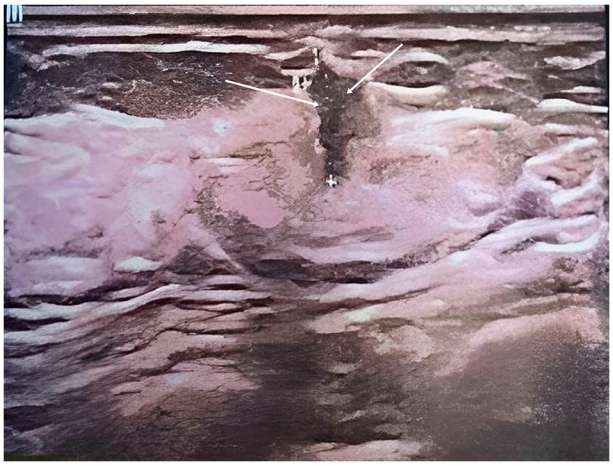

Figure 1. Ultrasound image of the tumor. A 15x20 mm irregular hypoechoic solid mass is visible (arrows), two transverse fingers from the nipple and 7.6 mm below the surface. This was assessed as Breast Imaging Reporting and Data System 4b at 1 o'clock in the left breast.

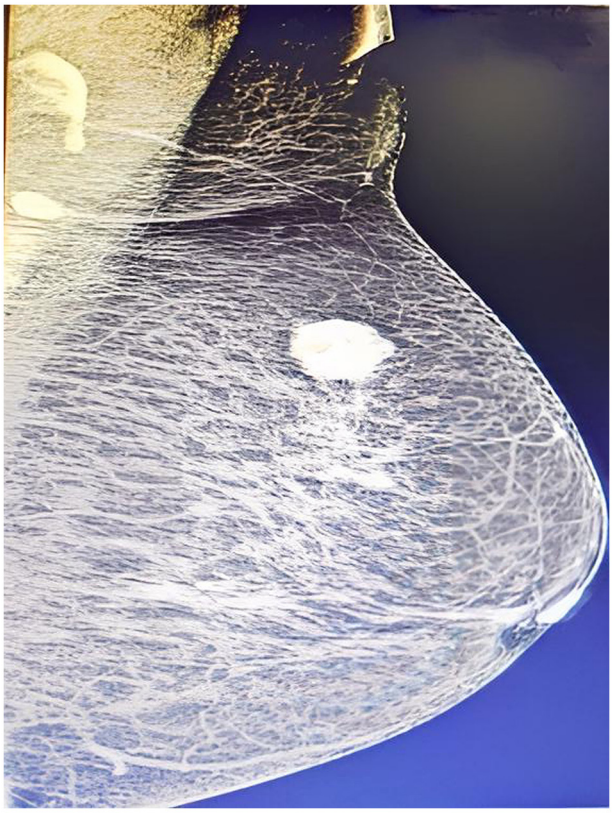

Figure 2. Mammogram of the tumor. A 15x20 mm nodular hyperdense shadow was observed, which was assessed as Breast Imaging Reporting and Data System 4a.

D1 Recombinant Rabbit Monoclonal Antibody (SP4; dilution, 1:100; cat. no. MA5-14512; Cusabio Technology, LLC) for 2 h at 37˚C, followed by incubation with Goat anti-Human IgG (H+L) Cross-Adsorbed Secondary Antibody (conjugate, Alexa Fluor™ 488; dilution, 1:100; cat. no. A-11013; Cusabio Technology, LLC) for 2 h at 37˚C and sealing with neutral resin. Tissue sections were observed under a light microscope. A simple left mastectomy and anterior lymph node biopsy were also performed. The postoperative pathological results suggested that the mass was a low-grade neuroendocrine tumor (NET) with negative margins.

Gross pathological examination confirmed that the mass had a maximum diameter of ~2 cm. Hematoxylin and eosin staining showed that it comprised tumor cells that were uniform in size and rounded, with well-defined nuclei (Fig. 3A) and CD56 negative (Fig. 3B). IHC staining for chromogranin A (CgA) (Fig. 3C) and synaptophysin (Syn) (Fig. 3D) was positive, and detected in >50% of the tissue. Postoperative pathological diagnosis suggested a low-grade NET of the left breast. IHC staining results also revealed the presence of estrogen receptors (ERs, >90%; Fig. 4A), progesterone receptors (>90%; Fig. 4B) and Ki67 (~10%; data not shown), while IHC staining for human epidermal growth factor receptor 2 (HER-2) was negative (Fig. 4C).

Because anterior lymph node metastasis was not found, the patient did not receive any chemotherapy or other treatment after surgery. The patient has been followed up for 12 months, with a monthly telephone follow-up, with no axillary lymph node metastases, and no tumors at other sites have been detected.

Discussion

PNENB can be distinguished from other types of breast tumors based on morphological features as well as neuroendocrine markers. The neuroendocrine differentiation of breast cancer was first observed in 1963 by Feyrter and Hartmann (7) in mucinous carcinoma of the breast. This was followed by the discovery of breast tumors that were morphologically similar to carcinoid tumors of other organs by Cubilla and Woodruff (8) in 1977, who named them primary carcinoid tumors of the breast. In 1985, Bussolati *et al* (9) detected CgA in breast tissue, which provided evidence that some cells in the breast can exhibit neuroendocrine features. In 2002, Sapino and Bussolati (10) proposed the first diagnostic criteria for PNENB. In 2003, the World Health Organization (WHO) officially recognized PNENB as a distinct type of breast cancer, and defined PNENB as a tumor of epithelial origin (11). Following the diagnostic criteria of Sapino and Bussolati, breast tumors with morphological features similar to those of NENs originating in the lungs and gastrointestinal system in which >50% of the tumor cells expressed neuroendocrine markers were referred to as PNENB, with CgA and Syn considered as the most sensitive and specific neuroendocrine markers (11). These cancers were subdivided into large-cell neuroendocrine carcinomas (LCNEC), small-cell neuroendocrine carcinomas (SCNEC), and solid carcinomas based on their morphological features. In 2012, the WHO Classification of Breast Tumors defined PNENB as a carcinoma with morphological features similar to those of NEN originating in the lungs and gastrointestinal system, irrespective of the percentage of tumor cells expressing neuroendocrine biomarkers. In addition, it suggested that based on morphology, PNENB can be classified into three subgroups: Well-differentiated NET of the breast (NETB), poorly differentiated neuroendocrine carcinomas of the breast (NECB)/SCNEC, and IBCs with neuroendocrine differentiation, including solid papillary and mucinous carcinomas (12).

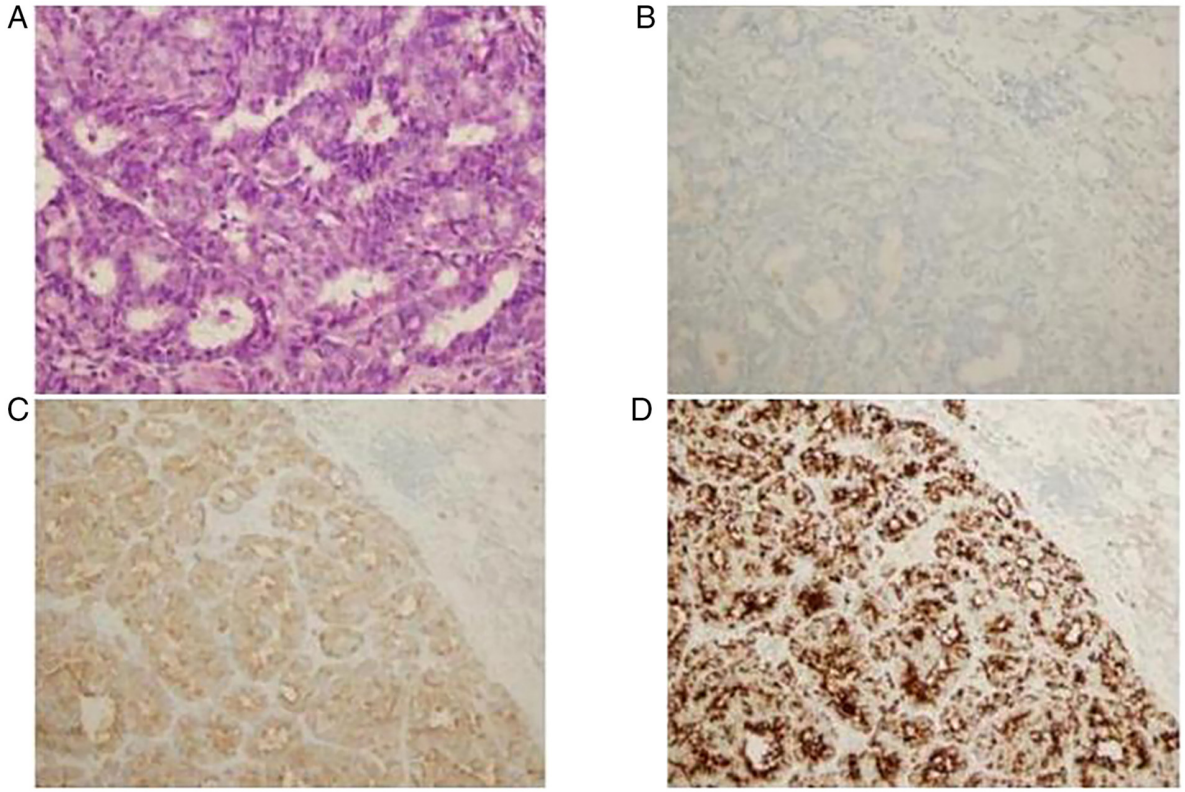

Figure 3. Pathology and immunohistochemistry of neuroendocrine markers. (A) Hematoxylin and eosin staining of the tumor tissue. The tumor cell sizes were consistent, and the cells were circular, with the nucleolus clearly visible (magnification, x400). Immunohistochemical staining of the tumor tisse showed that the tumor was (B) CD56 negative, (C) chromogranin A positive and (D) synaptophysin positive (magnification, x200).

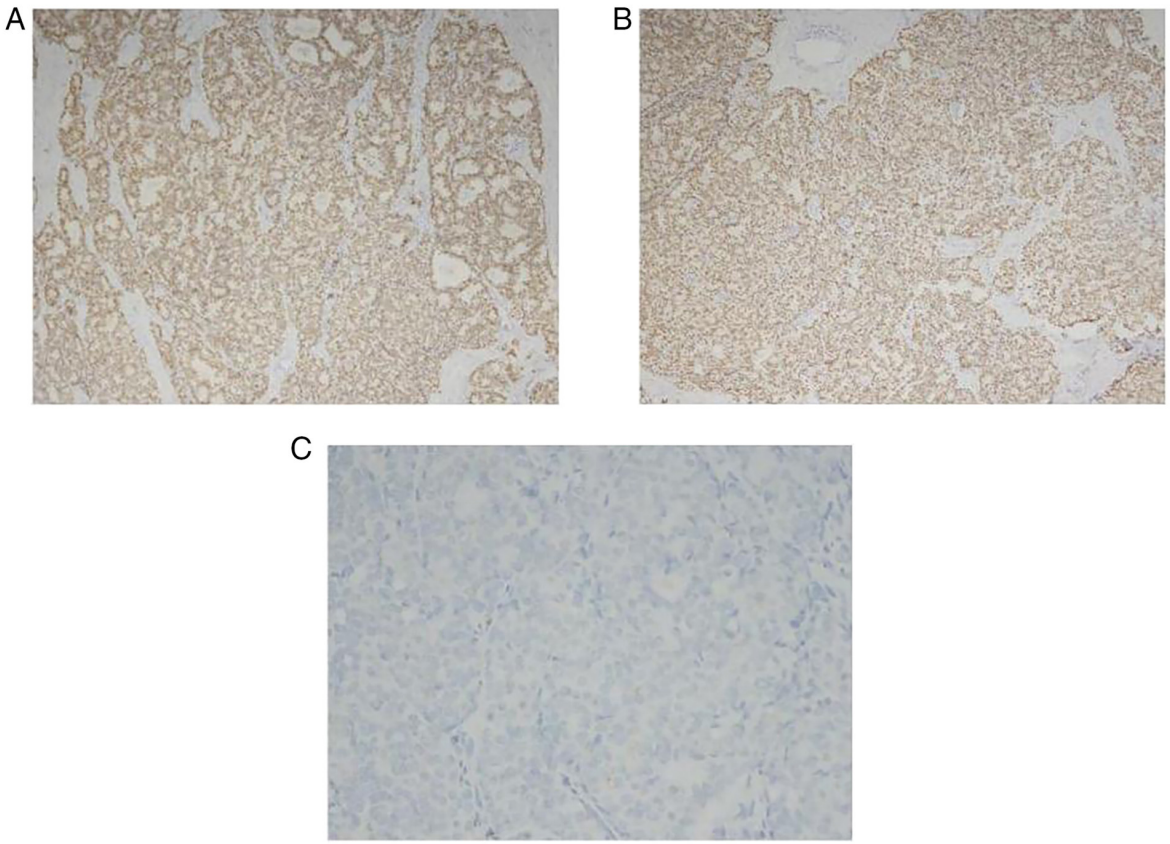

Figure 4. Immunohistochemistry of hormone receptors and HER-2 in the tumor. Immunohistochemical staining of (A) estrogen receptors (magnification, x100) and (B) progesterone receptors was positive (magnification, x100), while that of (C) HER-2 was negative (magnification, x400). HER-2, human epidermal growth factor receptor 2.

The 5th edition of the WHO Classification of Breast Tumors, published in 2019, uses the same classification criteria for PNENB, gastroenterology-pancreas NETs and lung NETs. It also divides breast tumors in which >90% of tumor cells have neuroendocrine features into two main categories based on the degree of differentiation: Well-differentiated NETB and poorly differentiated NECB, including SCNEC and LCNEC. LCNEC was added to the classification, and special tissue-type breast cancers, including solid breast cancer and mucinous carcinoma, were removed from the PNENB category (13). Breast tumors in which 10-90% of the cells exhibit neuroendocrine differentiation are referred to as mixed IBCs or NETs/neuroendocrine carcinomas (NECs), and tumors in which <10% of the cells exhibit neuroendocrine differentiation are classified as either IBC of no special type (IBC-NST) or IBCs of other special types. The Nottingham grading system can be used to grade PNENB tumors based on their specific characteristics, independent of the parameters used in neuroendocrine tumors originating from other parts of the body (13). It is noteworthy that although NETB has been classified in the framework of NETs, it has no defined morphological features, and its identification among other breast tumors relies on the staining of neuroendocrine markers, including Syn and CgA, which are also expressed in non-PNENB tumors. Based on a review of previous reports, the molecular and genetic characteristics of NETB are not similar to those of well-differentiated NENs from other sites, but resemble those of luminal A breast cancer (14). In contrast to NETB, NECB represent a well-defined entity, showing morphological and clinical analogies with pulmonary and extra-pulmonary NECs (15).

PNENB occurs predominantly in >60-year-old postmenopausal women, is very rare in men, and does not differ markedly from other types of breast cancer in terms of clinical presentation (16). The majority of patients present with isolated breast lumps as the primary symptom, and may also have carcinoid syndrome and clinical manifestations associated with ectopic hormone secretion, such as paraneoplastic thrombocytosis and hyperprolactinemia, as well as rare elevations of α-fetoprotein (17-19). NECB is a high-grade tumor, most often detected at an advanced stage, and metastasized at the time of initial diagnosis (20). The imaging features of PNENB are not specific. Previous studies have reported that mammography reveals round, ovoid, lobulated or irregularly shaped masses, most of which have poorly defined borders with surrounding tissues and burr-free margins, whereas IBC-NST tends to have an irregular shape with burr-like margins, and is associated with microcalcifications (21,22). The majority of cases present on breast ultrasound as an irregular mass that is hypoechoic or poorly defined, with absent or enhanced posterior acoustic features (23). Park *et al* (22) suggested that neuroendocrine differentiation in tumors may influence the imaging presentation, and that the absence of burr edges on mammograms and of posterior echo enhancement on ultrasound images may be indicative of a tumor with neuroendocrine features. When morphological features of PNENB are not evident, imaging is necessary to rule out metastatic malignancy in the breast since ≥97% of NECs originate from the gastrointestinal tract or lungs (24).

The absence of specific features in the routine examination of PNENB underscores the importance of accurately diagnosing this condition, as the diagnosis directly influences the subsequent treatment and prognosis. Diagnosis relies on morphological features, IHC staining and genetic analyses to determine the type of cancer and identify therapeutic targets. Morphologically, NETB consists of dense nests of cells and cellular trabeculae, and the cells may show spindle, plasma cell-like or polygonal features, with eosinophilic or thylakoid cytoplasm separated by a fibrovascular stroma, with little morphological resemblance to NETs at other sites (14,25). SCNEC tumors exhibit infiltrative growth, darkly stained nuclei, inconspicuous nucleoli, high nucleoplasmic ratios, sparse cytoplasm and ill-defined cytoplasmic boundaries, while LCNEC tumors have darkly stained nuclei, diverse nuclear morphology and more cytoplasm than SCNEC tumors (26). The IHC markers commonly used to identify the presence of neuroendocrine differentiation are Syn, CgA, neuron-specific enolase (NSE) and CD56. Syn and CgA are diffusely positive in NECB and are specific markers, whereas NSE and CD56 are less sensitive and specific. The transcription factor insulinoma-associated protein 1 (INSM1) is a relatively novel marker that is detected in the cytosol and differs from other neuroendocrine markers, which are detected in the cytoplasm; however, its sensitivity and specificity are not significantly different from those of Syn and CgA (27). Zhong *et al* (28) investigated the expressed pattern of 'second generation' neuroendocrine markers INSM1, achaete-scute homolog 1 (ASCL1) and POU class 2 homeobox 3 (POU2F3) in breast cancers with neuroendocrine morphology. The study found that INSM1 was more specific than Syn and more sensitive and specific than CgA, but the positivity rates of ASCL1 (4/35) and POU2F3 (1/35) were too low to support routine testing of their expression. Recent studies have demonstrated that syntaxin-1 (STX1) is a sensitive and specific marker of neuroendocrine cells (29-31). For example, in a study of NECB in which STX1 and INSM1 were compared with neuroendocrine markers such as Syn, CgA and CD56, a sensitivity of 84.7% (50/59) and specificity of 98.1% were recorded for STX1, suggesting that STX1 has potential as an NE marker (31). However, to the best of our knowledge, no studies have assessed the expression of these newer NE markers in the rare PNENB subtype. Juhlin *et al* (32) suggested that NE markers such as INSM1, secretagogin, and ISL LIM homeobox 1 are tissue-specific, which may aid in the detection of the primary tumor site. These new NE markers may provide novel avenues for research into the clinical implications of NE differentiation in PNENB. Another study found that the expression of transcription factors GATA-binding protein 3 (GATA3) and gross cystic disease fluid protein 15 was positive in tumors originating from the breast and negative in metastatic tumors, while the expression of caudal-type homeobox 2 and thyroid transcription factor-1 (TTF-1) was suggestive of metastatic tumors (33). Notably, TTF-1 also exhibited strong positivity in high-grade NECB. In addition, the expression of hormone receptors (HRs) has been shown to contribute to the diagnosis of PNENB. Specifically, strongly positive HR expression and negative HER-2 expression is observed in the majority of PNENBs, which, according to their molecular subtypes, exhibit tubulointerstitial characteristics (34,35). However, the proportion of cases of PNENB that are negative for HR and HER-2 expression is greater than that for invasive ductal carcinoma (IDC). Several studies have

reported ER positivity in NEN of the lung, pancreas, small intestine and ovary (36-38). Although ER positivity is not specific, it can be used as a target for therapeutic agents. For example, Zhang *et al* (39) found that the tumor in a patient with poorly differentiated NEC of the breast shrank by 78.87% after 3 months of neoadjuvant endocrine therapy.

PNENB is genetically heterogeneous. It has a different mutational spectrum from other ER-positive and HER 2-negative IBC-NSTs. In one study, lysine-specific methyltransferase 2C was found to be the most commonly mutated gene in PNENB (3/17, 17.6%) and predicted to serve as a driver gene that may play an important role in the neuroendocrine differentiation of breast cancer (40). PNENB was also indicated to have common copy number variants (CNVs) such as 8q, 11q and 17q amplification, with variants in 8q being high-frequency CNVs and potential targets for tumor therapy (40). Wei *et al* (40) found that the mutation rates of members of the PI3K and MAPK signaling pathway in NETB were higher than those in NECB, suggesting that breast NET and NEC may have different genetic phenotypes and prognoses, and thus require different therapeutic strategies. A study by Marchiò *et al* (41) showed that the most commonly mutated genes were GATA3, forkhead box protein A1 (FOXA1), T-box transcription factor 3 (TBX3) and AT-rich interactive domain-containing protein 1A in 3/18 cases (17%), and PI3K catalytic subunit α (PIK3CA), AKT1 and cadherin 1 in 2/18 cases (11%). In addition, the study indicated that NECB is characterized by a lower frequency of tumor protein P53 (TP53) and PIK3CA mutations, and enrichment of FOXA1 and TBX3 mutations compared with common forms of ductal breast cancer. In another study, co-mutations in TP53 and RB transcriptional corepressor 1 (RB1) were found in 6/7 cases of SCNEC (86%), 2/2 cases ambiguous for small cell vs. large cell morphology (100%) and 2/4 LCNEC cases (50%). In addition, one case of wild-type TP53/RB1 SCNEC had other p53 pathway aberrations, specifically amplification of mouse double minute 2 and 4 homologs, and was found to be RB-negative by IHC analysis (42). It was suggested that co-inactivation of TP53 and RB1 may be important for the pathogenesis of the NEC phenotype in the mammary gland. Vranic *et al* (43) detected the expression of folate receptor 1 (FOLR1), trimethylated Lys-36 of histone 3 (H3K36me3) and tumor-associated calcium signal transducer 2 (TROP-2) in a subset of NECBs; however, they did not detect any biomarkers indicating that immune checkpoint inhibitors could be used, including programmed death ligand 1 expression, tumor mutational burden and microsatellite instability. However, based on the detection of TROP-2, FOLR1 and H3K36Me3, they suggested that antibody-drug conjugates or inhibitors of these proteins may be potential therapeutic options for the treatment of NECB. Mutations in the epidermal growth factor receptor (EGFR) gene serve as a suitable target for most cancers. In one study a rare EGFR p.Thr790Met (T790M) mutation was found in a patient with poorly differentiated NEBC, which was suggested to be responsible for the resistance of the tumor to tyrosine kinase receptor inhibitors (44).

Due to the rarity of PNENB, no standard treatment guideline currently exists. Surgery is the first-line treatment option, as it is for other IBC-NSTs (16,45). Other treatment modalities include adjuvant radiotherapy, chemotherapy, endocrine therapy, targeted therapy and neoadjuvant chemotherapy (16,46). NECB has been typically treated with chemotherapy in previous cases in the relevant literature due to its high histological grade and metastasis at the time of detection. Adjuvant chemotherapy can be used in patients at a high risk of recurrence and neoadjuvant chemotherapy can be used in patients with preoperative downstaging or locally advanced disease before surgery (16,45,47). Platinum-based drugs and etoposide chemotherapeutic agents are the most widely used chemotherapeutic agents for small cell lung cancer and extrapulmonary poorly differentiated LCNEC or SCNEC, while combinations of anthracycline- and paclitaxel-containing chemotherapeutic agents are generally used for other types of PNENB (48). Somatostatin (SS) therapy is mediated through the SS receptor (SSTR) on the surface of tumor cells. SSTR2A, SSTR2B, SSTR3 and SSTR5 have been found to be expressed in breast NET and NEC (49,50), of which SSTR2A and SSTR5 exhibit a high affinity for growth inhibitor analogs. Positron emission tomography using gallium-68-labelled SS analogs has potential for use in the diagnosis of PNENB, while SS analogs combined with a β-emitting lutetium-177 radioisotope are now approved for use in the treatment of NET (50), and may also serve as a therapeutic option in the management of PNENB.

To date, the prognosis of PNENB is unclear, which may be attributed to the different diagnostic criteria used for the inclusion of cases in different studies and the small sample sizes. However, most studies have shown that PNENB has a poorer prognosis than NST-IDC (51,52). Tumor staging and histological grading remain the primary prognostic factors. An analysis of PNENB using data from the Surveillance, Epidemiology, and End Results database indicated that age, marital status, the place of registration, surgery, American Joint Committee on Cancer staging and breast subtype are independent prognostic factors (53). Although race was found to be significantly associated with PNENB in univariate Cox and Kaplan-Meier analyses, no significant association was observed in multivariate Cox analysis, which may be attributed to the elimination of spurious associations when confounding variables were accounted for in the multivariate analysis (53). The analysis also showed that, compared with non-surgical treatment, surgical intervention for excision of the primary tumor or for non-cancer-related purposes was effective in improving prognosis. It was suggested that in the latter scenario, the surgery may improve the prognosis by improving the quality of life of the patient (53).

In conclusion, PNENBs are a rare, heterogeneous subtype of breast tumors, which are yet to be fully understood. Although previous studies have identified several driver genes and mutated genes with high mutation rates, the exact diagnosis continues to rely on the examination of traditional neuroendocrine markers, namely Syn and CgA. Moreover, there are no standard treatment guidelines for this disease, with surgery being the first-line approach, as it is for other IBC-NSTs.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HJ collected the clinical, imaging and pathological data of the patient, and wrote the manuscript. ML conceived and designed the study, and revised the manuscript. HJ and ML confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent for publication was obtained from the patient. All identifying information has been removed or anonymized to ensure confidentiality.

Competing interests

The authors declare that they have no competing interests.

References

1. Rosen LE and Gattuso P: Neuroendocrine tumors of the breast. Arch Pathol Lab Med 141: 1577-1581, 2017.
2. Rakha E and Tan PH: Head to head: Do neuroendocrine tumours in the breast truly exist? Histopathology 81: 2-14, 2022.
3. Lebeau A and Denkert C: Updated WHO classification of tumors of the breast: The most important changes. Der Pathologe 42: 270-280, 2021 (In German).
4. Pareja F, Vahdatinia M, Marchio C, Lee SSK, Da Cruz Paula A, Derakhshan F, da Silva EM, Selenica P, Dopeso H, *et al*: Neuroendocrine tumours of the breast: A genomic comparison with mucinous breast cancers and neuroendocrine tumours of other anatomic sites. J Clin Pathol 75: 10-17, 2022.
5. Salemis NS: Primary neuroendocrine carcinoma of the breast: A rare presentation and review of the literature. Intractable Rare Dis Res 9: 233-246, 2020.
6. Spak DA, Plaxco JS, Santiago L, Dryden MJ and Dogan BE: BI-RADS® fifth edition: A summary of changes. Diagn Interv Imaging 98: 179-190, 2017.
7. Feyrter F and Hartmann G: On the carcinoid growth form of the carcinoma mammae, especially the carcinoma solidum (gelatinosum) mammae. Frankf Z Pathol 73: 24-39, 1963 (In German).
8. Cubilla AL and Woodruff JM: Primary carcinoid tumor of the breast: A report of eight patients. Am J Surg Pathol 1: 283-292, 1977.
9. Bussolati G, Gugliotta P, Sapino A, Eusebi V and Lloyd RV: Chromogranin-reactive endocrine cells in argyrophilic carcinomas ("carcinoids") and normal tissue of the breast. Am J Pathol 120: 186-192, 1985.
10. Sapino A and Bussolati G: Is detection of endocrine cells in breast adenocarcinoma of diagnostic and clinical significance? Histopathology 40: 211-214, 2002.
11. John E, Fattaneh N, Tavassoli A and Devilee A: Pathology and genetics of tumors of the breast and female genital organs. Iarc, 2003.
12. Eymard H Pittella J and Alfredo JA B: The new WHO classification of breast tumors. J Brasileiro de Patologia e Medicina Laboratorial 48: 406-407, 2012.
13. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, *et al*: The 2019 WHO classification of tumors of the breast. Histopathology 77: 181-185, 2020.
14. Uccella S, Finzi G, Sessa F and La Rosa S: On the endless dilemma of neuroendocrine neoplasms of the breast: A journey through concepts and entities. Endocr Pathol 31: 321-329, 2020.
15. La Rosa S and Uccella S: Classification of neuroendocrine neoplasms: Lights and shadows. Rev Endocr Metab Disord 22: 527-538, 2021.
16. Sun H, Dai S, Xu J, Liu L, Yu J and Sun T: Primary neuroendocrine tumor of the breast: Current understanding and future perspectives. Front Oncol 12: 848485, 2022.
17. Kherbek H, Skef J, Kherbek S, Abdulrahman SA, Alshehabi Z and Zahlouk N: Primary neuroendocrine carcinoma of the breast with paraneoplastic thrombocytosis; a rare case report. Ann Med Surg (Lond) 77, 103664, 2022.
18. Wang J, Wang X, Du W, Guo Y, Yang X, Pan J and Yin L: Primary neuroendocrine carcinoma of the breast with markedly elevated alpha-fetoprotein: A case report. Transl Cancer Res 10: 2503-2508, 2021.
19. Zhang Q, He L, Lv W and Wang N: Neuroendocrine carcinoma of the breast with hyperprolactinemia: Report of two cases and a minireview. Int J Clin Exp Pathol 13: 1457-1462, 2020.
20. Lavigne M, Menet E, Tille JC, Lae M, Fuhrmann L, Bonneau C, Deniziaut G, Melaabi S, Ng CCK, Marchiò C, *et al*: Comprehensive clinical and molecular analyses of neuroendocrine carcinomas of the breast. Modern Pathol 31: 68-82, 2018.
21. Kayadibi Y, Erginoz E, Cavus GH, Kurt SA, Ozturk T and Velidedeoglu M: Primary neuroendocrine carcinomas of the breast and neuroendocrine differentiated breast cancers: Relationship between histopathological and radiological features. Eur J Radiol 147: 110148, 2022.
22. Park YM, Wu Y, Wei W and Yang WT: Primary neuroendocrine carcinoma of the breast: Clinical, imaging, and histologic features. Am J Roentgenol 203: W221-W230, 2014.
23. Chang ED, Kim MK, Kim JS and Whang IY: Primary neuroendocrine tumor of the breast: Imaging features. Korean J Radiol 14: 395-399, 2013.
24. Hörsch D, Schmid KW, Anlauf M, Darwiche K, Denecke T, Baum RP, Spitzweg C, Grohé C, Presselt N, Stremmel C, *et al*: Neuroendocrine tumors of the bronchopulmonary system (typical and atypical carcinoid tumors): Current strategies in diagnosis and treatment. Conclusions of an expert meeting February 2011 in Weimar, Germany. Oncol Res Treat 37: 266-276, 2014.
25. Pareja F and D'Alfonso TM: Neuroendocrine neoplasms of the breast: A review focused on the updated World Health Organization (WHO) morphologic classification. Br J 26: 1160-1167, 2020.
26. Adegbola T, Connolly CE and Mortimer G: Small cell neuroendocrine carcinoma of the breast: A report of three cases and review of the literature. J Clin Pathol 58: 775-778, 2005.
27. Roy M, Buehler DG, Zhang R, Schwalbe ML, Baus RM, Salamat MS, Lloyd RV and Rosenbaum JN: Expression of insulinoma-associated protein 1 (INSM1) and orthopedia homeobox (OTP) in tumors with neuroendocrine differentiation at rare sites. Endocr Pathol 30: 35-42, 2019.
28. Zhong E, Pareja F, Hanna MG, Jungbluth AA, Rekhtman N and Brogi E: Expression of novel neuroendocrine markers in breast carcinomas: A study of INSM1, ASCL1, and POU2F3. Human Pathol 127: 102-111, 2022.
29. Zombori T, Turkevi-Nagy S, Sejben A, Juhász-Nagy G, Cserni G, Furák J, Tiszlavicz L, Krenács L and Kővári B: The panel of syntaxin 1 and insulinoma-associated protein 1 outperforms classic neuroendocrine markers in pulmonary neuroendocrine neoplasms. APMIS 129: 186-194, 2021.
30. Kővári B, Turkevi-Nagy S, Báthori Á, Fekete Z and Krenács L: Syntaxin 1: A novel robust immunophenotypic marker of neuroendocrine tumors. Int J Mol Sci 21: 1213, 2020.
31. Turkevi-Nagy S, Báthori Á, Böcz J, Krenács L, Cserni G and Kővári B: Syntaxin-1 and insulinoma-associated protein 1 expression in breast neoplasms with neuroendocrine features. Pathol Oncol Res 27: 1610039, 2021.
32. Juhlin CC, Zedenius J and Höög A: Clinical routine application of the second-generation neuroendocrine markers ISL1, INSM1, and secretagogin in neuroendocrine neoplasia: Staining outcomes and potential clues for determining tumor origin. Endocr Pathol 31: 401-410, 2020.
33. Mohanty SK, Kim SA, DeLair DF, Bose S, Laury AR, Chopra S, Mertens RB and Dhall D: Comparison of metastatic neuroendocrine neoplasms to the breast and primary invasive mammary carcinomas with neuroendocrine differentiation. Mod Pathol 29: 788-798, 2016.

34. Ang D, Ballard M, Beadling C, Warrick A, Schilling A, O'Gara R, Pukay M, Neff TL, West RB, Corless CL and Troxell ML: Novel mutations in neuroendocrine carcinoma of the breast: Possible therapeutic targets. Appl Immunohistochem Mol Morphol 23: 97-103, 2015.
35. Martinez EO, Jorns JM, Kong AL, Kijak J, Lee WY, Huang CC and Cortina CS: Primary breast neuroendocrine tumors: An analysis of the national cancer database. Ann Surg Oncol 29: 6339-6346, 2022.
36. Castellanos MR, Fanous E, Thaker R, Flory MJ, Seetharamu N, Dhar M, Starr A and Strange TJ: Expression patterns and clinical significance of estrogen receptor in non-small cell lung cancer. Pathol Res Pract 241: 154298, 2023.
37. Mohanty SK, Kim SA, DeLair DF, Bose S, Laury AR, Chopra S, Mertens RB and Dhall D: Comparison of metastatic neuroendocrine neoplasms to the breast and primary invasive mammary carcinomas with neuroendocrine differentiation. Mod Pathol 29: 788-798, 2016.
38. Perry KD, Reynolds C, Rosen DG, Edgerton ME, T Albarracin C, Gilcrease MZ, Sahin AA, Abraham SC and Wu Y: Metastatic neuroendocrine tumour in the breast: A potential mimic of in-situ and invasive mammary carcinoma. Histopathology 59: 619-630, 2011.
39. Zhang Y, Liu C, Zheng C, Ren Q, Wang Q, Gao X, He Y, Wu J, Chen G, Li X and Ma Z: Efficacy of neoadjuvant endocrine therapy in patients with poorly differentiated neuroendocrine carcinoma of the breast: A case report. Medicine (Baltimore) 99: e22652, 2020.
40. Wei Y, Ke X, Yu J, Jing Q, Bu H, Zeng X and Wei B: Clinical and genomic analyses of neuroendocrine neoplasms of the breast. Mod Pathol 35: 495-505, 2022.
41. Marchiò C, Geyer FC, Ng CK, Piscuoglio S, De Filippo MR, Cupo M, Schultheis AM, Lim RS, Burke KA, Guerini-Rocco E, *et al*: The genetic landscape of breast carcinomas with neuroendocrine differentiation. J Pathol 241: 405-419, 2017.
42. Bean GR, Najjar S, Shin SJ, Hosfield EM, Caswell-Jin JL, Urisman A, Jones KD, Chen YY and Krings G: Genetic and immunohistochemical profiling of small cell and large cell neuroendocrine carcinomas of the breast. Mod Pathol 35: 1349-1361, 2022.
43. Vranic S, Palazzo J, Sanati S, Florento E, Contreras E, Xiu J, Swensen J and Gatalica Z: Potential novel therapy targets in neuroendocrine carcinomas of the breast. Clin Breast Cancer 19: 131-136, 2019.
44. Sagan OA, Rothstein A, Jambunathan B, Hadziahmetovic M, Antoniolli A and Rashid MH: Case report: Neuroendocrine breast carcinoma with a germline EGFR T790M mutation. Front Oncol 13: 1176868, 2023.
45. Acar A, Tolan HK, Ozbagriacik M and Ezberci F: Primary neuroendocrine carcinoma of the breast: A 5-year experiences. Ann Ital Chir 91: 23-26, 2020.
46. Irelli A, Sirufo MM, Morelli L, D'Ugo C, Ginaldi L and De Martinis M: Neuroendocrine Cancer of the Breast: A Rare Entity. J Clin Med 9: 1452, 2020.
47. Gallo M, Campione S, Di Vito V, Fortunati N, Lo Calzo F, Messina E, Ruggeri RM, Faggiano A and Colao AAL: Primary neuroendocrine neoplasms of the breast: Still open issues. Front Endocrinol (Lausanne) 11: 610230, 2021.
48. Frame MT, Gohal J, Mader K and Goodman J: Primary small cell carcinoma of the breast: An approach to medical and surgical management. Cureus 15: e47981, 2023.
49. Kontogeorgos G, Thodou E and Choreftaki T: Investigation of somatostatin receptor profile of neuroendocrine carcinomas of the breast. Pathol Res Pract 216: 153066, 2020.
50. Harris PE and Zhernosekov K: The evolution of PRRT for the treatment of neuroendocrine tumors; what comes next? Front Endocrinol (Lausanne) 13: 941832, 2022.
51. Wang J, Wei B, Albarracin CT, Hu J, Abraham SC and Wu Y: Invasive neuroendocrine carcinoma of the breast: A population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 14: 147, 2014.
52. Yang L, Roy M, Lin H, Shen Y, Albarracin C, Huo L, Chen H, Wei B, Bedrosian I, Bu H and Wu Y: Validation of prognostic significance of the proposed uniform classification framework in neuroendocrine neoplasms of the breast. Breast Cancer Res Treat 186: 403-415, 2021.
53. Xia L, Lai J, Liu X, Kong F, Qiu S, Hu H, Zhu S and Cao J: Epidemiological and survival outcomes of neuroendocrine carcinoma of the breast: A SEER data analysis. Transl Cancer Res 12: 1951-1962, 2023.