

Neuroendocrine Tumor of Breast: A Rare Case Report

Sujata S Giriyan¹, Deepti Dixit², Kanchana R H³

¹Professor and Head, Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka

²Post Graduate Student, Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka

³Tutor, Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka

Abstract: Neuroendocrine tumors are rare, slow growing tumors derived from neuroendocrine cells, which are present throughout the body. Neuroendocrine tumors of the breast are rare, accounting for less than 1% of all breast cancers. Although some invasive ductal carcinomas of the breast show areas of neuroendocrine differentiation, the World Health Organization (WHO) recognized this category and defined mammary neuroendocrine carcinoma as expression of neuroendocrine markers in more than 50% of tumor cells. Reported here is a case of 52 years female presenting with lump in breast gradually increasing in size. Conventional Fine Needle Aspiration Cytology was done and features were suggestive of ductal adenocarcinoma with metastatic deposits to axillary lymph node and liver. Modified radical mastectomy was done and histopathologically, the tumor showed features suggestive of neuroendocrine tumor of breast. Immunohistochemistry was confirmatory showing positivity for synaptophysin. Being aware of the existence of this disease may allow for timely diagnosis and help the patient because misdiagnosing or underdiagnosing it may prevent optimal adjuvant treatment they need.

Keywords: neuroendocrine, breast, histopathologically, immunohistochemistry, synaptophysin

1. Introduction

Neuroendocrine tumors are rare, slow growing tumors derived from neuroendocrine cells, which are present throughout the body; most commonly involving bronchopulmonary system and gastrointestinal system. Neuroendocrine tumors of the breast are rare, accounting for less than 1% of all neuroendocrine tumors.^[1] In 2003, the World Health Organization (WHO) recognized this category and defined mammary neuroendocrine carcinoma as expression of neuroendocrine markers in more than 50% of tumor cells. Rest of the cases with neuroendocrine component were designated as carcinoma with neuroendocrine differentiation.^[2] The presence of intraductal components is strong evidence for certifying the origin of a carcinoma as the breast.^[3]

2. Case Report

A 52 years old female without any prior medical history, presented with a lump in right breast for 4 months gradually increasing in size. On examination, a breast lump measuring 8cmx6cm was present involving right upper outer and lower outer quadrant with engorged overlying veins. The lump was hard, non tender and was not adhered to underlying tissue or overlying skin. Solitary lymph node was palpated in right axillary region which measured 2cmx1cm and was firm, mobile and non-tender. However, the left breast appeared to be normal.

Fine needle aspiration cytology (FNAC) of the breast lump as well as right axillary lymph node was done by conventional method. Smears from FNAC of right breast lump showed hemorrhagic background with round to oval malignant ductal epithelial cells in irregular clusters and some of them having plasmacytoid appearance. Nuclei of

these cells were large, hyperchromatic with prominent nucleoli. Also seen were scattered malignant bare nuclei. The features of FNAC from breast lump were suggestive of ductal adenocarcinoma. Smears studied from right axillary lymph node showed metastatic deposits of above tumor. Thus a cytological diagnosis of ductal adenocarcinoma of right breast with metastasis to right axillary lymph node was made.

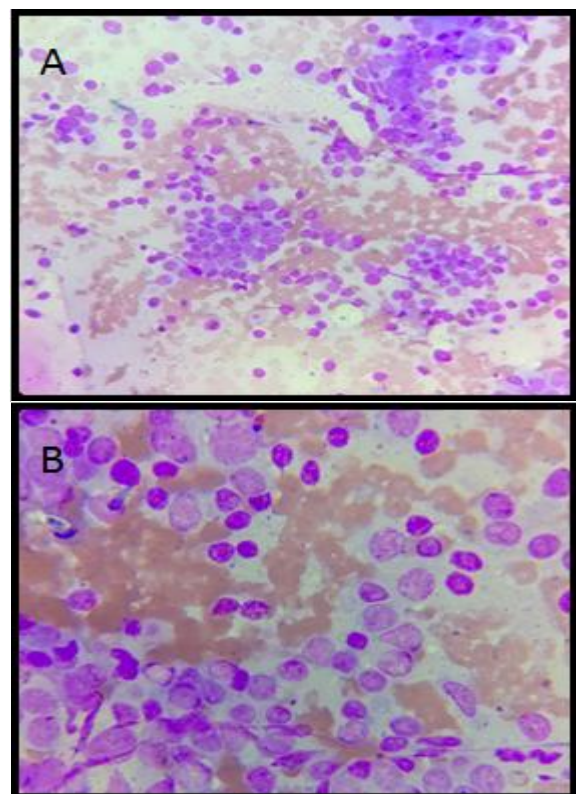


Figure 1: FNAC smear from breast lump [(A): 10x, (B): 40x]

In further work up of the patient, ultrasonography of abdomen revealed multiple heterogenous lesions in liver, largest measuring 13cmx 12.2cm noted in right lobe of liver. The lesion showed high vascularity. Ultrasonography guided FNAC of the liver lesion was done and the smears were cellular. The smears showed clusters of reactive hepatocytes along with neutrophils, lymphocytes and few stromal fragments. Amidst them were seen round to oval cells having plasmacytoid features in irregular clusters and acinar pattern. These cells showed large hyperchromatic nuclei with prominent nucleoli and moderate amount of cytoplasm. Thus, a cytological diagnosis of metastatic adenocarcinoma deposits was made.

The patient was given 2 cycles of neo-adjuvant chemotherapy consisting of cyclophosphamide, doxorubicin and 5-fluorouracil. The patient also received paclitaxel. It was followed by modified radical mastectomy.

Histopathological examination of the mastectomy specimen was done. Histologically, sections studied showed tumor cells arranged in nested, organoid and acinar patterns separated by thin fibro-vascular connective tissue. Tumor cells showed round to oval nucleus with stippled (salt-pepper) chromatin and one to two nucleoli with moderate amount of eosinophilic cytoplasm and focal areas of mucoid change. Tumor emboli were also seen at places. Thus, the features were suggestive of neuroendocrine tumor of breast.

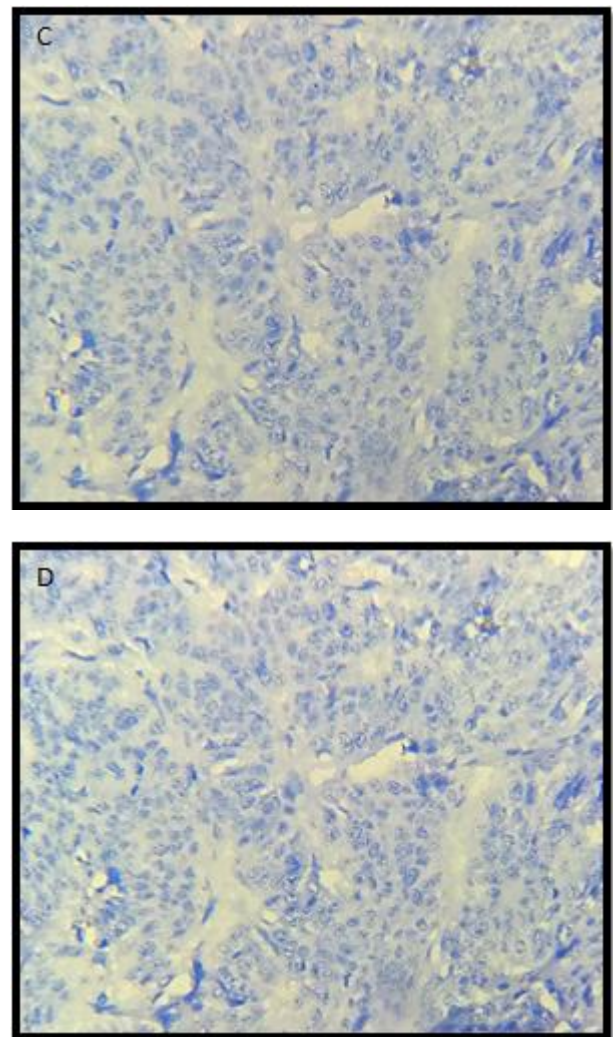
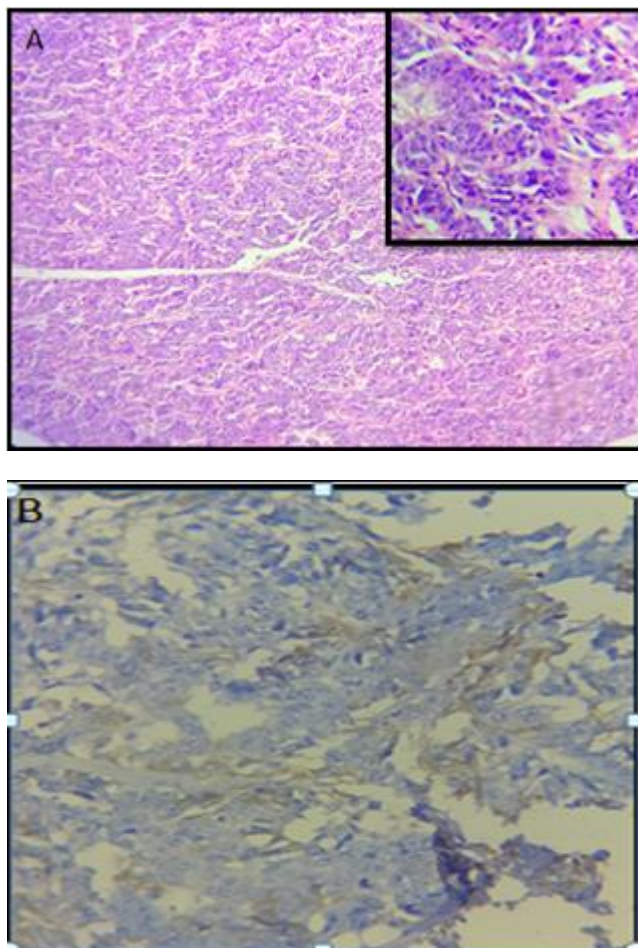


Figure 2: (A) Histopathological findings in neuroendocrine tumor of breast: Tumor cells showing moderate amount of eosinophilic cytoplasm, round to oval nucleus with stippled (salt-pepper) chromatin (H&E, 40x, 10x), (B) Immunohistochemistry showing Synaptophysin positivity, (C) Estrogen receptor negativity and (D) Progesterone receptor negativity.

Immunohistochemistry was done for confirmation which showed tumor cells positivity for neuroendocrine marker-Synaptophysin in more than 50% of tumor cells. However, the tumor cells were negative for Estrogen receptors and Progesterone receptors.

3. Discussion

The existence of mammary tissue neuroendocrine cells was shown by Volger in 1947.^[4] Later in 1977, Cubilla and Woodruff were the first to describe neuroendocrine tumors of breast.^[5] They initially named these tumors as argyrophilic breast carcinoma, breast carcinoid tumor or endocrine carcinoma, but after WHO laid the definitive criteria they labeled them as Primary Neuroendocrine tumor of breast. The histogenesis of the tumor is still unclear; Some have postulated it to arise from endocrine differentiation of breast carcinoma rather than preexisting neuroendocrine cells in the breast while some stated that they arise from multipotential stem cells which differentiate along neuroendocrine phenotype.^[6,7]

Unlike other special types of breast carcinoma such as tubular carcinoma (2% of invasive breast carcinomas), invasive cribriform carcinoma (0.5 to 3.5%), medullary carcinoma (1 to 7%) and mucinous carcinoma (2%) the biological behavior of neuroendocrine tumor of the breast and its treatment have not been well studied.^[8]

The clinical presentation of the tumor is similar to ordinary breast carcinoma and usually the patients do not present with carcinoid syndrome even in presence of widespread disease.^[9,10]

In cytological examination, smears are cellular with mainly dispersed uniform plasmacytoid cells with a coarse granular chromatin pattern resembling the cells of carcinoid or other neuroendocrine tumor. The cells may or may not stain positively for neuroendocrine markers like Synaptophysin and chromogranin. Distinction from ductal adenocarcinoma of no special type with dispersed and small, relatively uniform nuclei may not be possible without Immunohistochemistry but seems to be of no clinical significance as the behavior is same.^[10]

The neuroendocrine component resembles lung and gastrointestinal neuroendocrine tumors. It is characterized by cellular monotony, nuclear palisading, pseudorosette formation, loss of cell cohesion, and abundant eosinophilic cytoplasm and nuclei with stippled ('salt and pepper') chromatin.^[11]

Immunohistochemical positivity for neuroendocrine markers: Synaptophysin, chromogranin and Neuron Specific Enolase has been obtained.^[9,12]

The hormonal receptors (Estrogen and Progesterone receptors) are frequently positive, however they were negative in present case. In a study conducted on six patients of neuroendocrine tumor of breast, 6/7 cases (85%) were positive for Estrogen receptor and Progesterone receptor immunoreactivity. All the 7 selected cases (100%) were positive for synaptophysin or chromogranin in >50% tumor cells.^[13] Another study has shown an Estrogen receptor and progesterone receptor positivity of 68%.^[14] However, their expression in the breast does not suggest the evidence of mammary origin, the diagnosis is made if non mammary sites are confidently excluded or if an *in situ* component can be found.^[15] Studies have shown that positive Estrogen status does not appear to confer a prognostic benefit as it does in other invasive mammary carcinomas.^[14]

Studies have shown that Chromogranins are representative proteins contained in endocrine cells of various organs including some ductal cells of the breast. Homology between the BRCA1 protein and the chromogranins has been detected and suggests that chromogranin may play the role of tumor suppressor like BRCA1. Expression of BRCA1 significantly influenced the expression of chromogranin A while no factor significantly influenced to the expression of Chromogranin B. The survival curves of the patients with chromogranin A negative tumor indicated a tendency to a poorer prognosis than that seen with Chromogranin A positive tumor. The patients with Chromogranin B negative tumors demonstrated a

poorer prognosis than seen with patients with Chromogranin B positive tumors. Chromogranin A and Chromogranin B may mediate tumor progression through some unknown function besides the BRCA1 related function.^[16]

4. Conclusion

Primary neuroendocrine tumor of breast is a rare tumor which can be easily overlooked preoperatively because of similar presentation with other breast carcinomas. A knowledge of existence of this entity allows timely diagnosis of the disease and thus proper treatment. Also, the homology between chromogranin and BRCA1 protein may lead to targeted therapy against these proteins in future.

References

- [1] Ogawa H, Nishio A, Satake H, Naganawa S, Imai T, Sawaki M, et al. Neuroendocrine tumor in the breast. *Radiat Med.* 2008;26:28–32.
- [2] G. Bussolati and S. Badve, "Carcinomas with neuroendocrine features," in *WHO Classification of Tumours of the Breast*, S. R. Lakhani, I. O. Ellis, S. J. Schnitt, P. H. Tan, and M. J. van de Vijver, Eds., pp. 62–63, IARC Press, Lyon, France, 2012.
- [3] T Shogo and H Hajime. Neuroendocrine Tumor, Well Differentiated, of the Breast: A relatively High-Grade Case in the Histological Subtype. *Case Reports in Pathology Volume 2013*.
- [4] Akhtar K, Zaheer S, Ahmad SS, Hassan MJ. Primary neuroendocrine carcinoma of the breast. *Indian J Pathol Microbiol.* 2009;52:71–3.
- [5] Cubilla AL, Woodruff JM. Primary carcinoid tumor of the breast: A report of 8 patients. *Am J Surg Pathol.* 1977;1:283–92.
- [6] Bigotti G, Coli A, Butti A, del Vecchio M, Tartaglione R, Massi G. Primary small cell neuroendocrine carcinoma of the breast. *J Exp Clin Cancer Res.* 2004;23:691–6.
- [7] Stita W, Trabelsi A, Gharbi O, Mokni M, Korbi S. Primary solid neuroendocrine carcinoma of the breast. *Can J Surg.* 2009;52:E289–90.
- [8] Yoshida R, Ohuchi N, Kimura N. Clinicopathological study of chromogranin A, B and BRCA1 expression in node-negative breast carcinoma. *Oncol Rep.* 2002 Nov-Dec;9(6):13637.
- [9] Juan Rosai. *Breast. Rosai and Ackerman's Surgical pathology.* 10th Edition. Elsevier. 2011;1659-1770
- [10] Joan Cangiarella and Aylin Simsir. *Breast.* In: Svante R Orell and Gregory F Sterrett. *Orell and Sterrett's Aspiration Cytology.* 5th Edition. Elsevier. 2012;156-209.
- [11] Fernando A, Angarita Jorge, L Rodríguez, Eugenio Meek, Jesus O Sánchez, Mauricio Tawil and Lilian Torregrosa. Locally-advanced primary neuroendocrine carcinoma of the breast: case report and review of the literature. *World Journal of Surgical Oncology* 2013; 11:128.
- [12] VS Murthy, K Geethamala, BD Kumar, and M Sudharao. Primary Neuroendocrine Carcinoma of Breast: A Rare Case Report. *Ann Med Health Sci Res.* 2013 Nov; 3(1): 35–37.
- [13] S. Ghanem, H. Kabaj, S. Naciri, M. Glaoui, N. Ismaili, N. Benjaafar and H. Errihani. Primary neuroendocrine

carcinoma of the breast: A rare and distinct entity.
Journal of Cancer Research and Experimental
Oncology. 2011 August; 3(5): 50-54.

- [14] Jun Wang, Bing Wei, Constance T Albarracin, Jianhua Hu, Susan C Abraham and Yun Wu. Invasive neuroendocrine carcinoma of the breast: a population based study from the surveillance, epidemiology and end results (SEER) database.
- [15] Tsai WC, Yu JC, Lin CK, Hsieh CT. Primary alveolar-type large cell neuroendocrine carcinoma of the breast. Breast J. 2005; 11: 487.
- [16] Yoshida R, Ohuchi N, Kimura N. Clinicopathological study of chromogranin A, B and BRCA1 expression in node-negative breast carcinoma. Oncol Rep. 2002 Nov-Dec; 9(6): 13637.