

CASE REPORT

Fine needle aspiration cytology of neuroendocrine carcinoma of the breast - a case report and review of literature

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Abstract

Neuroendocrine carcinomas of the breast are uncommon tumors known to occur in the elderly. While focal neuroendocrine differentiation may be noted in many ductal and lobular carcinomas, the term neuroendocrine carcinoma is to be applied when more than 50% of the tumor shows such differentiation. This case report details the cytological features of a neuroendocrine carcinoma that was encountered in our hospital. The fine needle aspiration (FNA) smears showed discohesive polygonal cells with abundant cytoplasm, many of which contained eosinophilic granules located at one pole. Histology of the mastectomy and axillary lymph nodes specimen from this patient showed features of neuroendocrine carcinoma - solid type, with metastasis, confirmed with immunohistochemistry. The patient is disease free seven months after surgery. This case highlights the need to closely observe cytological details to identify this rare tumor that may otherwise appear to be invasive duct carcinoma – not otherwise specified on FNA. The implications of diagnosing neuroendocrine differentiation for prognosis and management are also discussed.

Keywords: Fine needle aspiration, breast, neuroendocrine carcinoma.

INTRODUCTION

Neuroendocrine (NE) carcinomas are uncommon tumors of the breast which have distinct morphological features, but poorly defined treatment strategies. The fine needle aspiration (FNA) cytological findings of breast carcinoma with NE differentiation have previously been described¹ in both primary and metastatic locations. However, because of their rarity, these lesions may be overlooked by cytopathologists. We present a case of primary breast carcinoma with NE differentiation in an 84-year-old female initially diagnosed as infiltrating ductal carcinoma on FNA and review the available literature on its cytomorphologic features.

CASE REPORT

Clinical presentation

An 84-year-old female patient presented with a firm, non-tender, 2cm mass in the lower outer quadrant of the right breast. General examination did not show any other abnormality.

The patient underwent FNA procedure followed by mammography and ultrasound examination. Mammogram showed predominantly fat replaced breasts. Vascular calcification was present bilaterally. A 2.5cm × 2cm lesion in left lower outer quadrant was seen. No suspicious calcifications were present. Ultrasound examination showed a well-defined but lobulated lesion in the lower outer quadrant of the left breast measuring 1.6cm x 2.2cm x 1.9cm. The right breast appeared unremarkable.

Cytological findings

FNA smears stained with May Grunwald Giemsa (MGG) stain showed moderate cellularity with clusters of mildly pleomorphic and plasmacytoid epithelial cells, arranged in acinar and cribriform pattern with many dissociated cells (Fig.1 a & b). Occasional cells with prominent nucleoli were also seen. On review, it was noticed that there were cells containing coarse azurophilic granules in the cytoplasm, particularly evident at cell borders and poles (Fig.1 c, d).

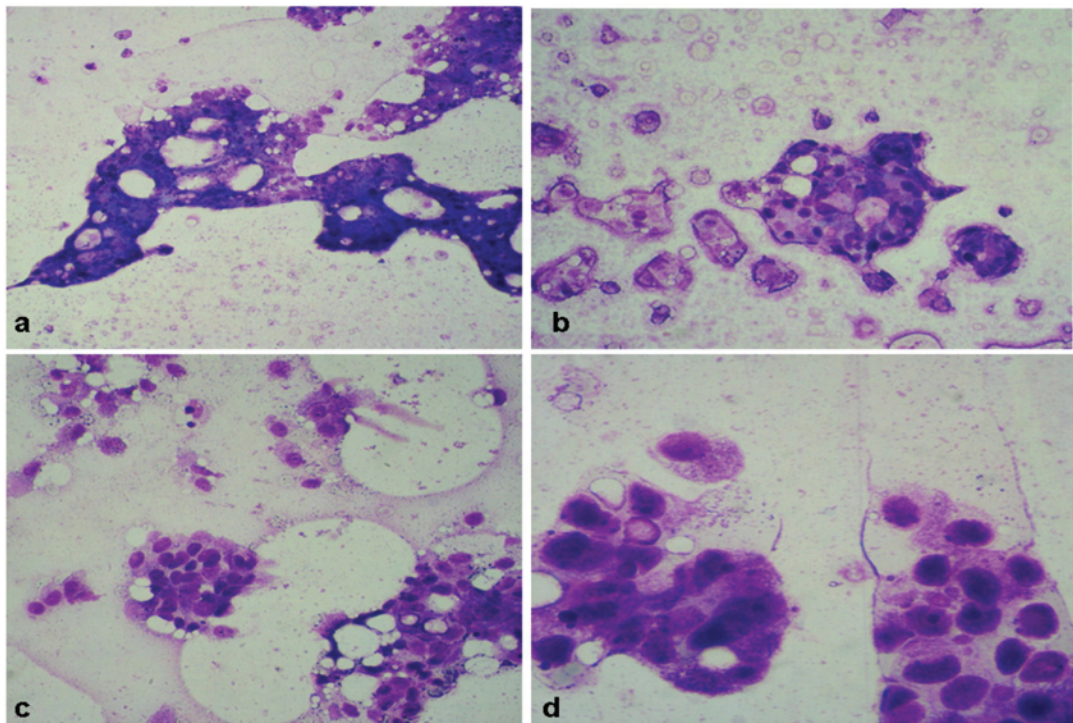


FIG. 1: a and b. Cribriform and acinar clusters in FNA cytology. MGG, X200; c. Azurophilic granules in the cytoplasm of tumour cells (MGG, X400); d. the granules showing a polar distribution (MGG, X1000, oil imm.).

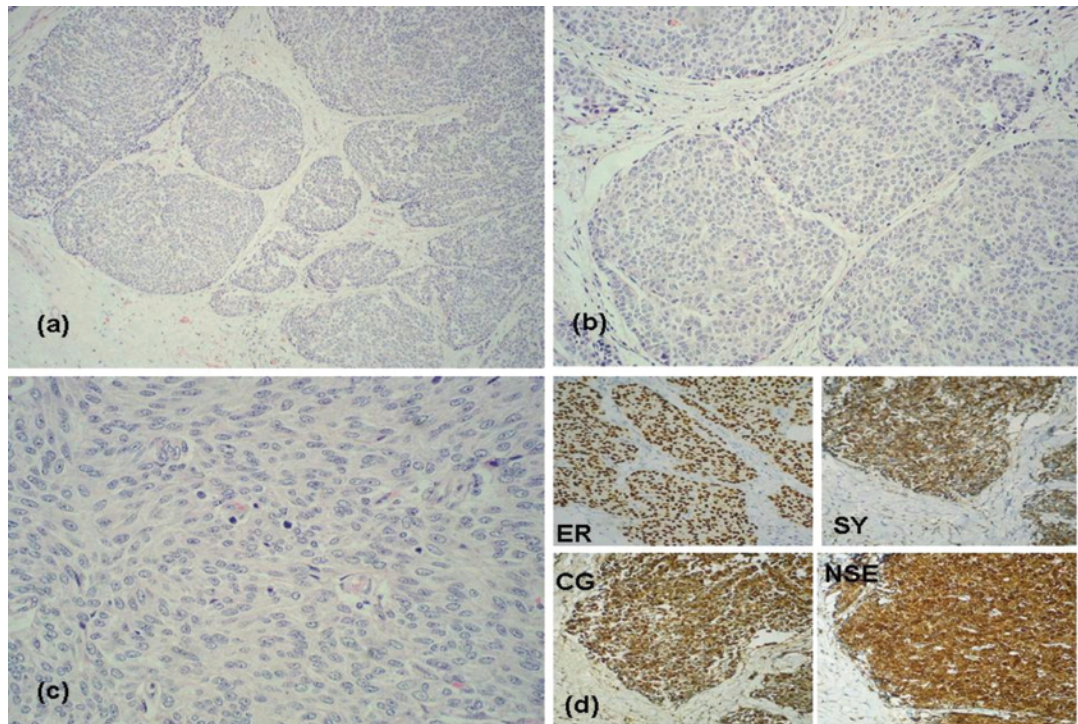


FIG. 2. Tumour cells (a) forming solid nests separated by thin fibrous stroma (H&E, x100); (b) vague rosetting (H&E, x200); (c) Spindle shaped cells displaying a few mitosis (H&E, x400); (d) positive for oestrogen receptor (ER), chromogranin (CG), synaptophysin (SY) and neuron specific enolase (NSE). (DAB chromogen, x100).

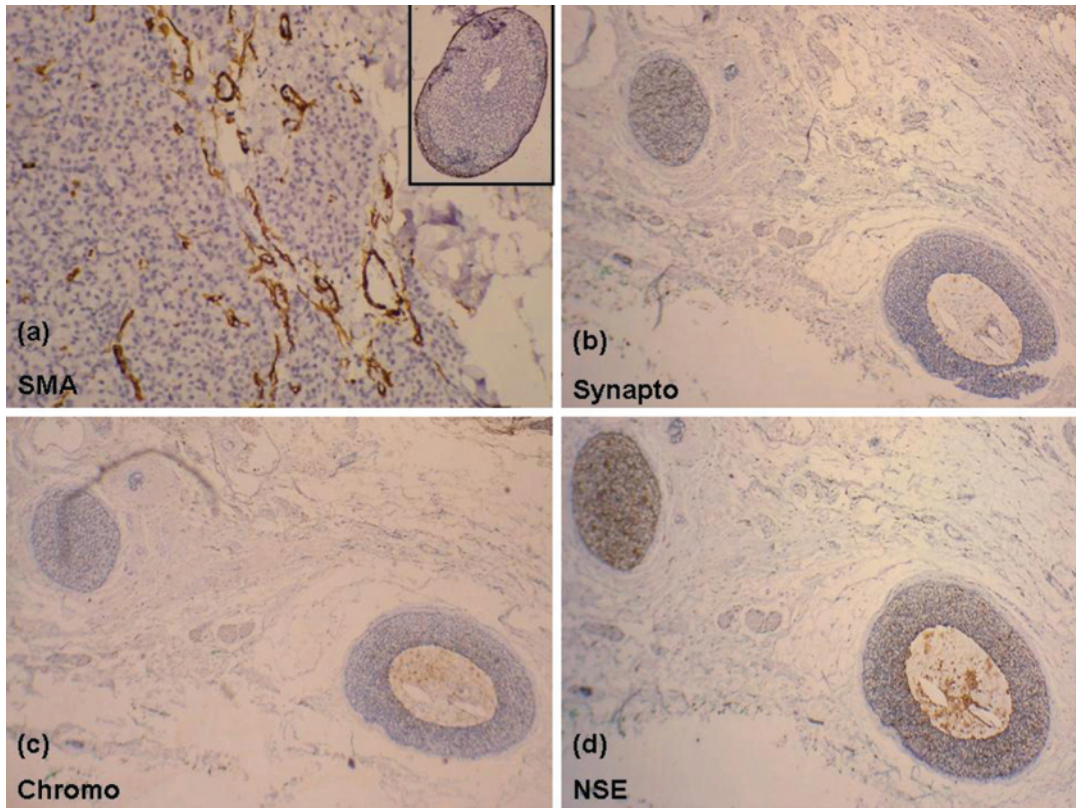


FIG 3. a. Absence of myoepithelial investment around the tumour islands in contrast to DCIS areas (inset). (Smooth Muscle Actin (SMA), DAB; X200); b, c, d. Synaptophysin, Chromogranin and Neuron Specific Enolase (NSE) respectively, were patchily positive in the DCIS areas. (DAB; X40).

Histopathological findings

The tumour was 1.5cm in diameter with a well-defined but lobulated margin and a whitish-gray homogenous cut surface. Light microscopy (Fig. 2 a,b,c) revealed a cellular tumour, composed of solid nests and trabeculae without tubule formation and forming palisades and rosette structures focally. The tumour cells ranged from oval to spindle and plasmacytoid, separated by delicate fibrous stroma. They had mildly pleomorphic elliptical nuclei with fine chromatin. The cytoplasm was eosinophilic and finely granular. There were 10 mitoses per 10 HPF and no lymphovascular permeation. The adjacent breast tissue showed cribriform type of ductal carcinoma-in-situ (DCIS) with similar cytomorphology. Islands of invasive duct carcinoma showed deficient myoepithelial layer (Fig. 3a) in contrast to the DCIS component as shown by immunohistochemical staining for smooth muscle actin (SMA) (Dako, Denmark). Three out of 17 axillary lymph nodes showed metastasis with perinodal tumour deposits.

Immunohistochemical examination was

performed on formalin-fixed paraffin-embedded (FFPE) tissue after antigen retrieval in Tris-EDTA buffer for 12 minutes in a standard pressure cooker. Immunohistochemistry showed positive expression of oestrogen receptor (ER) (NeoMarkers, Fremont, USA), progesterone receptor (PR) (Dako, Denmark), neuron specific enolase (NSE) (Dako, Denmark), synaptophysin (SY) (Dako, Denmark) and chromogranin (CG) (Dako, Denmark), by the tumour cells (Fig. 2 d). The DCIS areas showed patchy positivity with neuroendocrine markers (Fig. 3, b, c and d). There was no overexpression of c-erbB-2 oncoprotein. The case was signed out as “solid neuroendocrine carcinoma, with lymph node metastasis and axillary fat deposits”. Post operative recovery and subsequent follow up were uneventful.

DISCUSSION

Although NE tumours may arise anywhere in the body producing well-defined clinical entities, primary NE tumour of the breast is uncommon.² They occur in older women and are often

positive for oestrogen receptor. A relatively high proportion (20%) of carcinomas of the male breast show evidence of endocrine differentiation in contrast to 5% of breast tumours in women. Most of the tumours in men have the pattern of low-grade insular ductal carcinomas.² Strict histological criteria have been defined for the diagnosis of primary NE carcinoma of the breast that include demonstration of in-situ component histologically (as in the present case) and/or absence of a non-mammary site clinically.³

Three histological characteristics that suggest endocrine differentiation² in a breast carcinoma include low nuclear grade (with the exception of small cell undifferentiated type), palisading of nuclei at the periphery of the tumour islands and dense, sparsely cellular collagenous stroma surrounding it. Spindle cells, cytoplasmic granules and intra or extracellular mucin production are other features that may be present. Sapino *et al*, in one of the largest series of these tumours, have described five subtypes: solid cohesive; alveolar; small cell; solid papillary and cellular mucinous.⁴ Neuroendocrine papillary DCIS may present with bloodstained nipple discharge in an elderly woman.

In FNA smears, the most important feature to recognize in this tumour is the presence of cytoplasmic granules. These granules are particularly evident in Romanowsky-stained smears and are located at the apex of the plasmacytoid cells or diffusely in the cytoplasm of mucinous or spindle cells.¹ It is likely that the cytological features may vary depending on histological type, but are not well-characterized because of the rarity of the condition. A high index of suspicion may help one to consider this possibility and apply immunocytochemistry for identification. The tumour cells have been shown to be invariably positive for chromogranin. Although NSE, CG and SY are all common NE markers, CG is considered more appropriate because of its localization in the neurosecretory granules.⁵

Dense core granules have been shown to be present in the apical cytoplasm of normal breast epithelial cells. These, however are believed to indicate protein secretion and not endocrine nature.² It is believed that NE differentiation does not indicate an origin from preexisting endocrine cells, but one expression of differentiation potential that is inherent in several conventional type of breast carcinoma. Unlike NE carcinomas of the lung which have a definite association with tobacco smoking, primary sporadic NE tumours

in other organs have not been linked with any definite pathogenetical factors and they often demonstrate dissimilar cytogenetical changes as well.⁸

At present, a diagnosis of NE carcinoma does not lead to treatment different from that for other types of breast carcinoma of the same stage. The present case showed nodal metastasis; however, prognosis cannot be commented upon because of the short follow-up period. Recent evidence suggests that chromogranin production in NE breast carcinomas might have clinical and genetic implications, owing to the biochemical analogy between granins and BRCA protein.⁶ Hence, therapy directed against these genetic markers may be a future treatment strategy. Likewise, it has been shown that these tumours express somatostatin receptors which may be responsible for their slow progression through autocrine inhibition.⁷ It would be interesting to see if a relationship exists between the presence of chromogranin and tumour progression as well. It has also been shown that serial evaluation of circulating plasma chromogranin A(CgA), a specific marker of neurosecretory activity, is useful in the follow-up of patients, especially to detect occult metastasis.⁷

Conclusion: A diagnosis of NE carcinoma of the breast is possible in FNA cytology material and its identification could allow an accurate clinical study of patients and make it possible to plan staging and therapy.

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