



## Case Report

# Primary neuroendocrine tumor of the breast - report of 2 cases

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## Abstract

### Background:

Primary neuroendocrine tumor of the breast is rare, although 20-30% of primary breast carcinomas show neuroendocrine differentiation to some degree. According to the 2012 WHO Classification of Tumours of the Breast the current classification recognizes 3 subgroups of breast tumors with neuroendocrine features: Neuroendocrine tumor, well-differentiated; Neuroendocrine tumor, poorly-differentiated; Invasive breast carcinoma with neuroendocrine differentiation. Due to the low prevalence of this disease our understanding of its development, prognosis and effective therapy is limited. Up to date there are approximately 125 cases reported in the English and non-English literature. Here we report two further cases.

### Material and Methods:

Our first patient was 63 years old and presented with a 3 cm large mobile nodule in the upper outer quadrant of her right breast. After a complete clinicopathological work-up of imaging techniques and core needle biopsy with an initial diagnosis of invasive carcinoma of no special type (IBC NST), lumpectomy and sentinel node biopsy was recommended by the institutional tumor board. The second patient was 75 years old and presented with a 2 cm large mobile nodule in the upper outer quadrant of her left breast. Lumpectomy was performed based on



fine needle aspiration cytology results that revealed the malignant proliferation.

#### Results:

Histological examination of the surgical specimens revealed neuroendocrine differentiation in approximately 90% of the tumor cells in both cases. Immunohistochemical studies and additional imaging studies disclosed the possibility of metastasis to the breast.

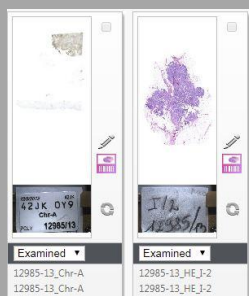
#### Discussion:

Neuroendocrine differentiation of breast tumors is a controversial issue and there are numerous questions in terms of histogenesis, diagnostics and clinical considerations. To establish the correct diagnosis, characteristic growth patterns and cytological and immunohistochemical features of neuroendocrine differentiation should be carefully evaluated.

Keywords: [neuroendocrine differentiation](#), [primary breast cancer](#), [neuroendocrine tumor](#), [differential diagnosis](#)

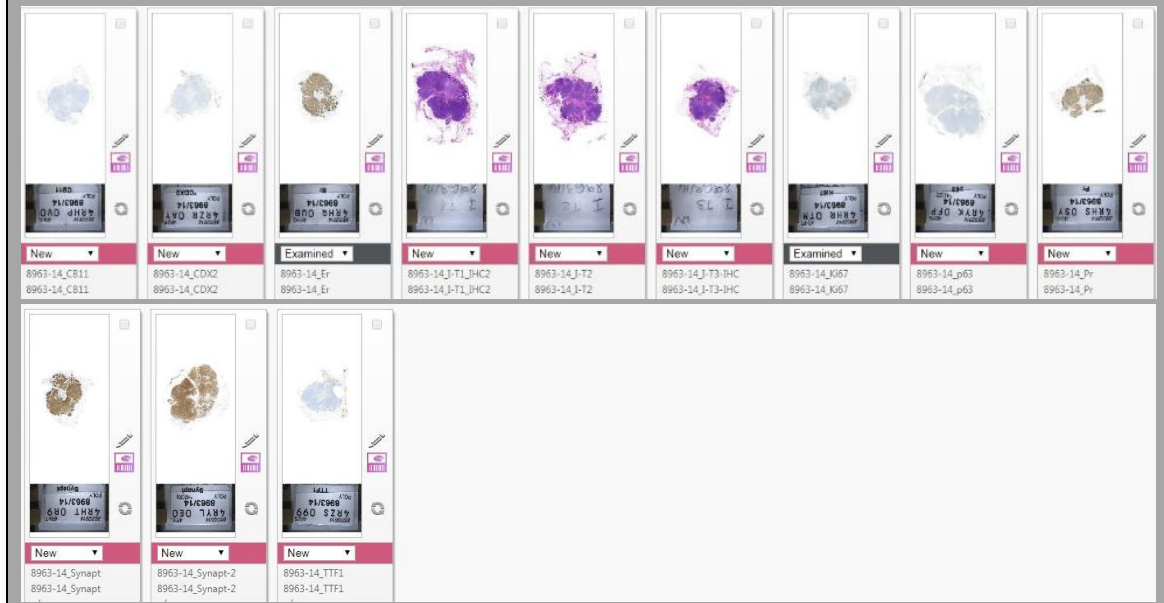
#### Virtual Slides:

##### Case 1:





### Case 2:



## Introduction

The first case of primary neuroendocrine carcinoma of the breast was described by Feyrter, in 1963.[1] Although 20-30% of primary breast carcinomas show neuroendocrine differentiation to some degree, true primary neuroendocrine tumor of the breast is rare.[2] The 2003 WHO Classification of tumors of the breast had strict criteria to establish a diagnosis of such tumor[3], after incorporating diagnostic criteria described by Sapino et al, as at least 50% of the tumor cells have to be positive with at least one neuroendocrine immunohistochemical marker, while excluding other primary sites and a metastatic nature of the lesion before making the diagnosis[4]. Unfortunately in the current 2012 WHO Classification of Tumours of the Breast this 50% threshold had been removed because it is believed that it was arbitrary now leaving practicing pathologists without reproducible criteria[5]. The 3 subgroups of breast tumors with neuroendocrine features are: well differentiated neuroendocrine tumor – which is morphologically similar to “carcinoid” tumors of other sites; poorly differentiated neuroendocrine tumor/carcinoma – which is morphologically identical to small cell carcinoma of the lung, and invasive breast carcinoma with neuroendocrine differentiation as it could be highlighted by immunohistochemistry.



Due to the low prevalence and the probable high number of unrecognized cases it is very hard to estimate the true incidence of this disease. In the literature it is referred between 1-5%[6], the WHO estimates approximately 2-5%.[5,6] Recognizing characteristic morphological patterns and the use of immunohistochemistry could facilitate the correct diagnosis, however some potential diagnostic pitfalls have also been described previously[7]. For example papillary or nested growth of the tumor cells should draw the pathologist's attention and prompt specific immunohistochemical stains, such as synaptophysin and/or chromogranin. Cytological features vary and sometimes could be misleading. Some tumors show typical neuroendocrine-like cells with finely granular ("salt and pepper") chromatin of the nuclei and granular cytoplasm, others have characteristic small cells with hyperchromatic nuclei and scant cytoplasm, while the poorly-differentiated ones could show less specific cellular morphology.[8] Recognizing an in situ component of the tumor with similar cytological features and immunophenotype enables confirming the primary nature of the tumor.[9]



## Clinical presentation, morphology, diagnosis

### CASE-1

A 63 years old female was presented with a 3 cm large, palpable, mobile nodule in the upper outer quadrant of her right breast. Mammography showed a ~15 mm large, spiculated, dense nodule, ultrasonography revealed malignant microcalcification and normal axilla. Ultrasound guided core needle biopsy was taken. Histology showed an infiltrative tumor with poor

gland formation. In other areas the tumor was growing in cord like structures of various size. The nuclear grade was between 1 and 2 varying between different areas, scattered mitotic figures was observed too. ER/PR were strongly positive, HER2 receptor was weakly positive (+). A diagnosis of *Invasive breast carcinoma of no special type* was made. Lumpectomy and sentinel node sampling was performed. Microscopic examination showed a lobulated tumor. On medium power cords and nests and larger sheets of tumor cells appeared, separated by delicate fibrous stroma and minimal gland formation or tubular structures, mostly at the edge of the lesion. The tumor cells had ill-defined borders, the cytoplasm was light eosinophilic with some granulation, the nuclei were vesicular, prominent nucleoli and abnormal mitotic figures were readily found (Figure 1.A). The H&E morphology raised the possibility of neuroendocrine differentiation and immunohistochemical stains for synaptophysin and Chromogranin-A were performed, both showing ~90 % strong positivity (Figure 1.B). Approximately 35% of the tumor cells were positive with Ki67 reaction. TTF-1 and CDX2 reactions were negative. In retrospective analysis, synaptophysin and Chromogranin-A immunoreactions were positive on the retrieved core biopsy sample as well. The sentinel lymph node was tumor-free. A final diagnosis of *Poorly-differentiated neuroendocrine tumor of the breast, pT2N0* was established. The comment for the pathology report highlighted the low incidence of the entity and a suggestion to clinically exclude other primary tumor. PET-CT and octreotide scans were performed with negative results, colorectal endoscopy found a sessile polyp which histologically was a tubular adenoma. The serum Chromogranin-A level was also tested. The first result, after surgery showed a fivefold increase of Chromogranin-A (584.2 ng/mL; normal range: 19.4-98.1 ng/mL) which had dropped to normal range after one month (69.3 ng/mL). The patient received aromatase inhibitor therapy and is free of progression after four years of initial diagnosis.



## CASE-2

A 2 cm large nodule was found during regular breast cancer screening of a 75 years old female. FNAB was performed. Cytology was positive for tumor cells, showing atypical cells with moderate nuclear polymorphism, eccentric nuclei and prominent nucleoli. Based on the cytology result lumpectomy was performed. Histology showed a lobulated tumor growth formed by nests of monomorphic cells with loose nuclear chromatin and finely granulated cytoplasm and occasional mitotic figures (Figure 2.A). Immunohistochemical stains for synaptophysin showed ~90 % strong positivity of tumor cells. Cells with similar morphology were also found in smaller ductal structures, surrounded by an intact layer of p63 positive myoepithelial cells (Figure 2.B-C). The tumor cells were strongly positive for ER/PR , HER2 score was 0, approximately 15% of the tumor cells were positive with Ki67 reaction. TTF-1 and CDX2 reactions were both negative. The sentinel lymph node was tumor-free. A final diagnosis of *Well-differentiated neuroendocrine tumor of the breast* was established. The patient is undergoing aromatase inhibitor therapy. The octreoscan examination and other imaging studies revealed no primary tumor or metastasis at other body sites and up to date there is no sign of progression after 3.5 years of initial diagnosis.



## Clinical significance

Neuroendocrine differentiation of breast tumors is a controversial issue and there are numerous questions in terms of

- histogenesis and molecular features
- diagnostics
- clinical considerations.

It is likely that there is no neuroendocrine progenitor cell within the breast giving rise to neuroendocrine tumors but these tumors derive from progressive neuroendocrine differentiation of a subset of neoplastic cells. This theory is also supported by the general observation that there is no benign neuroendocrine tumor or precursor in the breast as opposed to other body sites.[10] Most breast carcinomas with neuroendocrine features are luminal subtypes, A or B, depending on Ki-67 index on IHC, with only a smaller subset of HER2 receptor positive tumors.[6]

In terms of the diagnostic workup of this entity it is important to know that there are no distinct clinical differences from other types of breast cancers. However there are some radiological signs suggestive of a neuroendocrine lesion, such as oval and lobulated growth with indistinct margins[11]. The correct diagnosis is based on pathological evaluation of the tumor. The first question needs to be addressed if the lesion was a primary or of a metastatic origin. Metastases to the breast are unusual and accounts less than 1% of all malignant neoplasms of the breast. Metastatic neuroendocrine neoplasms to the breast are even less frequent and comprise only 1-2% of all metastasis.[9] If there is a pathological suspicion of neuroendocrine differentiation and it is supported by IHC a possible metastatic origin needs to be excluded both clinically, by imaging techniques, possibly in combination with somatostatin receptor scintigraphy and pathologically using further IHC tests. To exclude the two most common primary sites (lung, gastro-entero-pancreatic) TTF-1 and CDX2 antibodies could be used, mentioning the controversial finding that lower grade tumors could show less reactivity for these markers. GATA3 positivity on the other hand supports a primary breast tumor.[9,12] After excluding a



metastatic origin the lesion has to be subcategorized according to the WHO classification.[5] As mentioned earlier the previous diagnostic aid of a 50% threshold in immunoreactivity of the tumor cells had been abandoned leaving the pathologists without a reproducible guideline to follow when making the diagnosis of neuroendocrine breast tumor. Another controversial issue is the grading of these lesions. There is no generally accepted way of grading and according to the WHO categories a tumor with high mitotic index and high Ki-67 reactivity but without small cell features should be categorized as a low grade tumor not even mentioning the possibility of a high grade, large cell neuroendocrine carcinoma.

The prognostic relevance and treatment approaches of neuroendocrine differentiation in breast carcinomas are also unclear.[7,13-16] One of the largest population-based study revealed a shorter overall survival and suggested neuroendocrine differentiation as an independent adverse prognostic factor.[17] However the treatment approaches rarely follows this consideration and early stage tumors are usually treated with the same strategy used for other types of invasive breast cancer. Anthracycline-and taxane-based regimens represent the most frequently administered chemotherapy in neoadjuvant and adjuvant setting, as well as for metastatic disease, although combinations of platinum compounds and etoposide have been widely used, in particular for small-cell histology and tumors with a high proliferation index.[6]

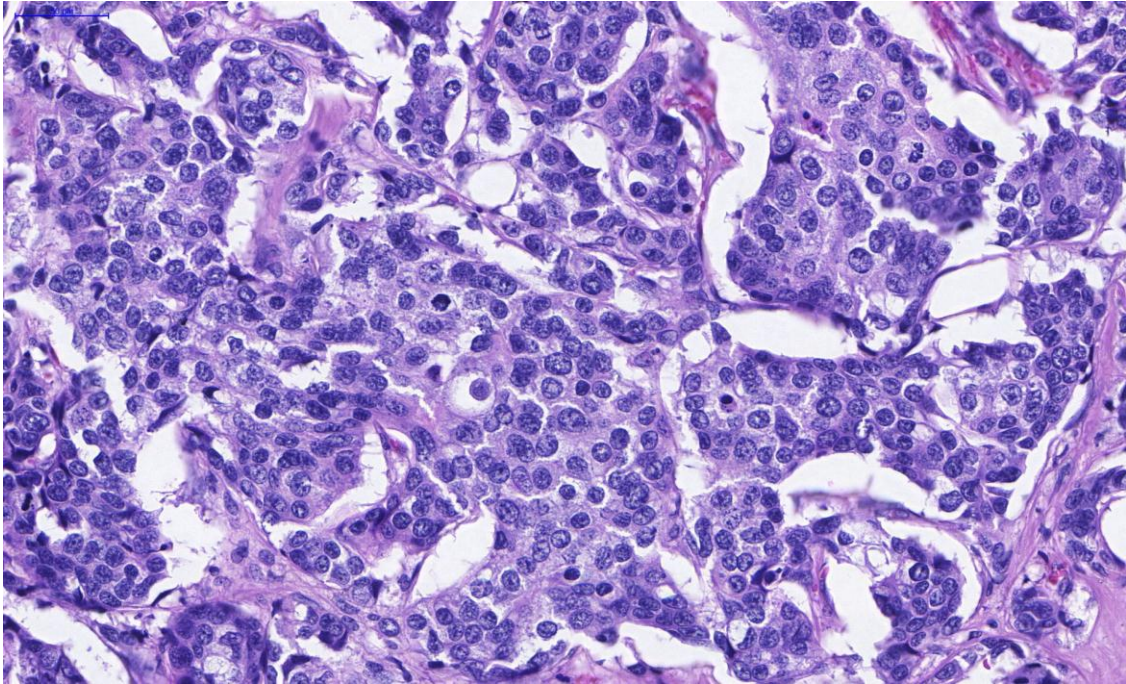
Primary neuroendocrine tumors of the breast are rare. To establish the correct diagnosis, characteristic growth patterns and cytological features of neuroendocrine differentiation should be carefully evaluated. In questionable cases the presence of a ductal in situ component with similar cytological appearance and immunophenotype could be helpful. Estrogen and/or progesterone receptor positivity are not useful to prove the primary nature of the tumor as these markers could be positive in other primaries as well. Other markers, such as CDX2 or TTF1 could be applied aiming to exclude metastasis. Communication to the clinician about any controversies is important to facilitate thorough imaging and patient follow up to choose the best treatment for the patient.



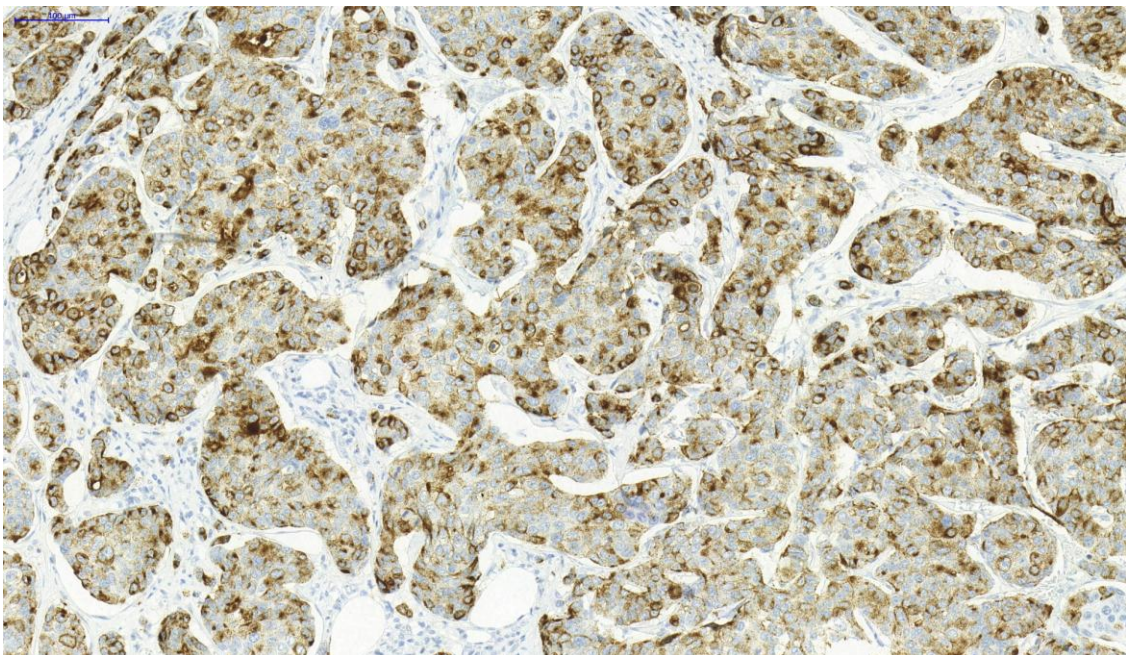


## Figures

**Fig.1.A.**



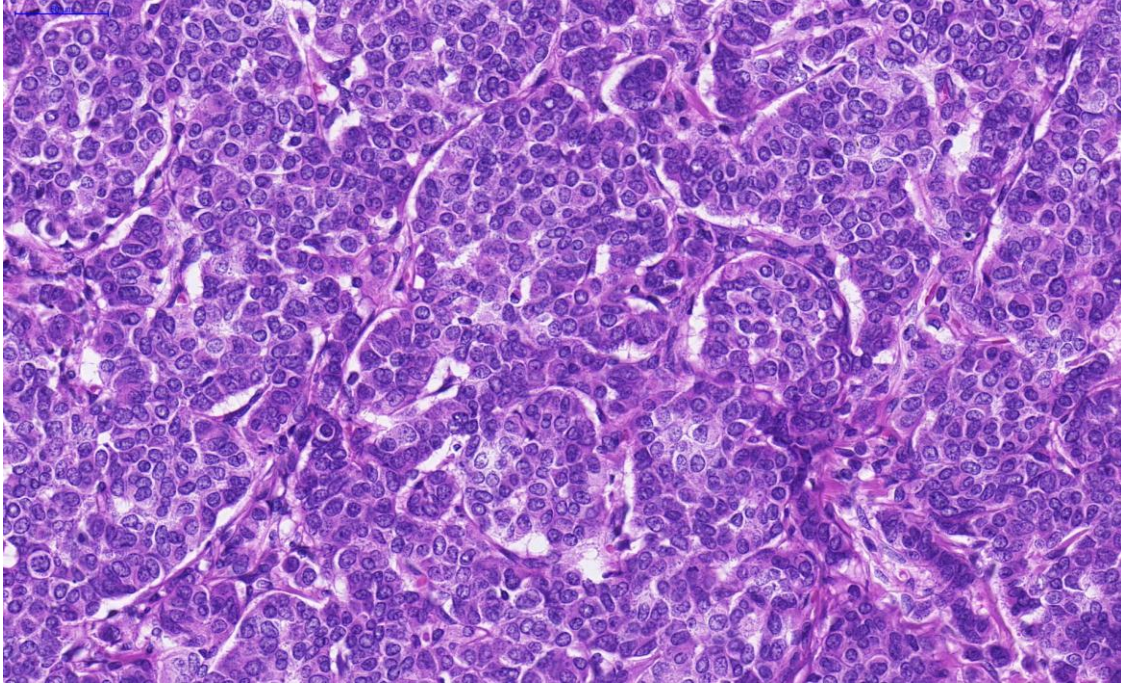
**Fig.1.B.**





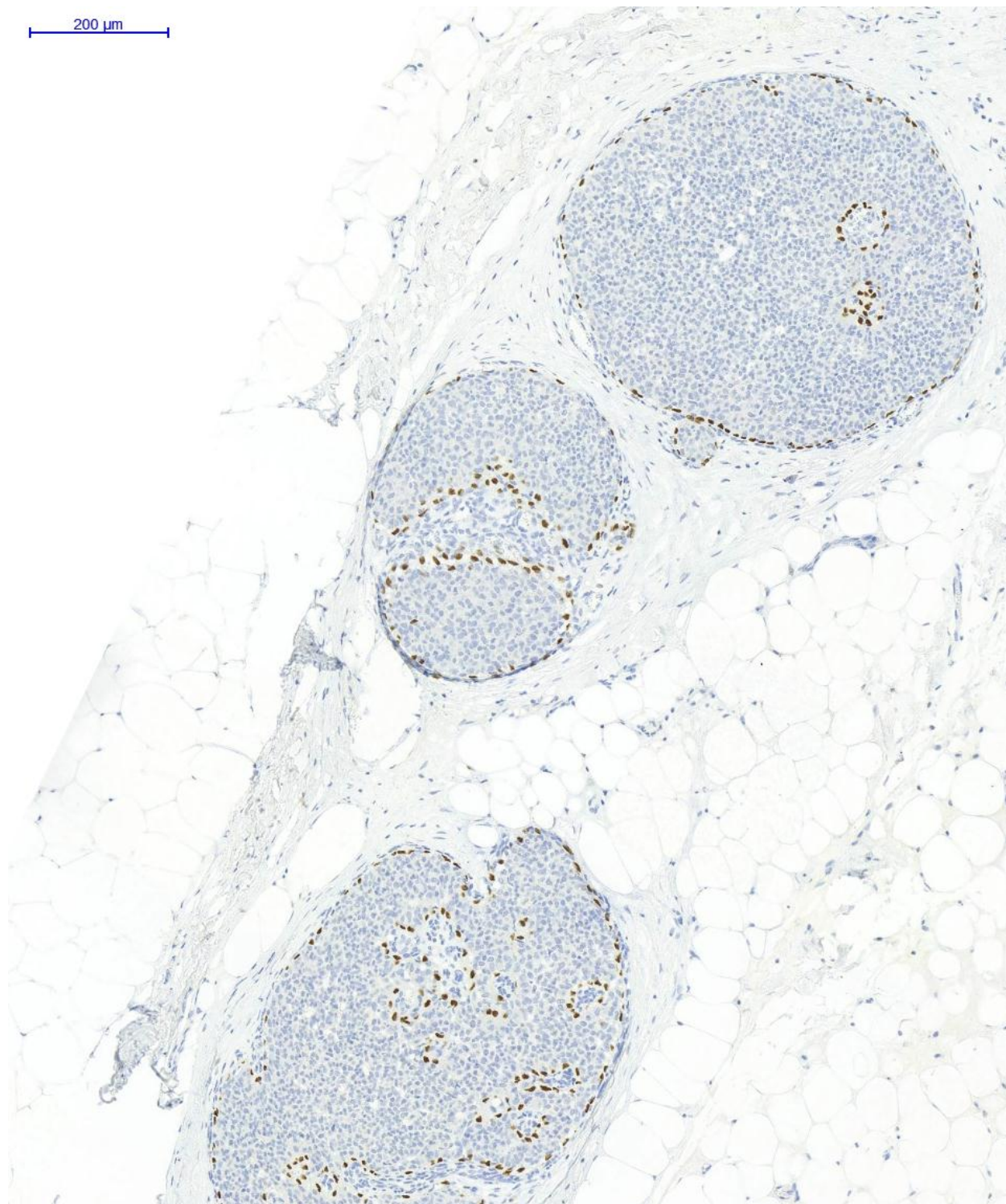


**Fig.2.A**





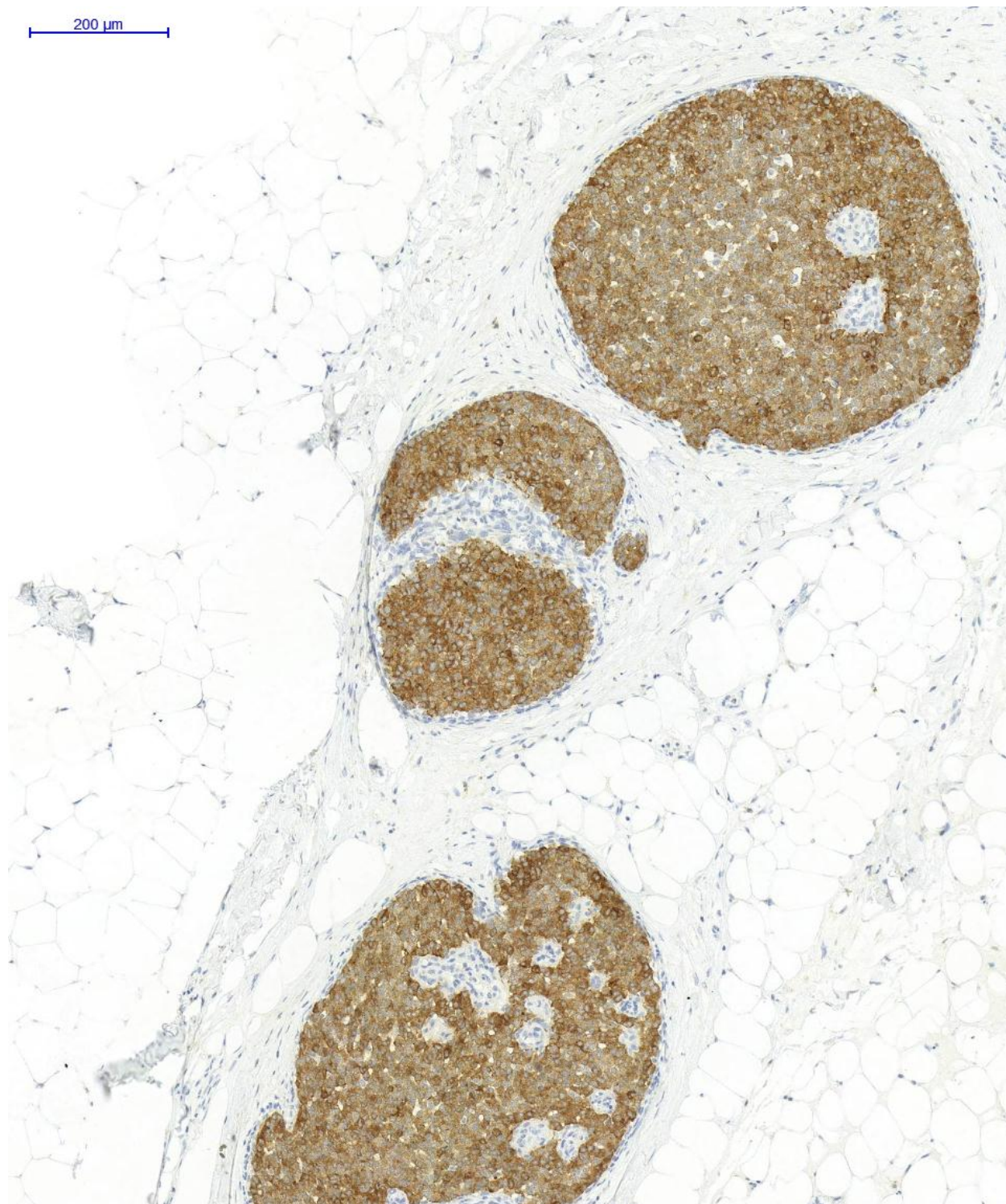
**Fig.2.B**







**Fig.2.C**





## Competing Interest

Authors declare that there is no conflict of interest.

## Authors' contribution

LP took part in the surgical procedure and drafted the manuscript; LF and GA carried out the histopathological examinations, JK gave expert consultation of the case. All authors read and approved the final manuscript.

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