



Primary neuroendocrine carcinoma of the breast — a report of four cases

Pierwotne guzy neuroendokrynne piersi — opis czterech przypadków

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Abstract

Breast neuroendocrine tumours are rare, accounting for up to 5% of all breast tumours and approximately 1% of all neuroendocrine tumours. In most cases, breast neuroendocrine tumours are histologically and moderately well differentiated. Neuroendocrine breast tumours lack characteristic imaging patterns. The histopathological assessment of these tumours is difficult, and in most cases the correct diagnosis is made after proper examination of the postsurgical specimen. (*Endokrynol Pol* 2017; 68 (5): 597–602)

Key words: neuroendocrine breast cancer

Streszczenie

Guzy neuroendokrynne piersi są rzadkimi nowotworami, stanowią do 5% guzów piersi i około 1% wszystkich guzów neuroendokrynnych. Większość zmian jest dobrze i umiarkowanie zróżnicowana, jednak w badaniach obrazowych trudno wskazać cechy morfologiczne, które byłyby charakterystyczne dla tej grupy nowotworów. Ocena histopatologiczna również jest trudna i najczęściej właściwe rozpoznanie stawiane jest dopiero na podstawie materiału pooperacyjnego. (*Endokrynol Pol* 2017; 68 (5): 597–602)

Słowa kluczowe: guz neuroendokrynny piersi

Introduction

Neuroendocrine tumours (NET) constitute a large and heterogeneous group of rare neoplasms with non-specific clinical symptoms, frequently originating from the GI tract (bowel and pancreas) and respiratory system [1, 2], and less frequent from endocrine glands (adrenals, thyroid, hypophysis, thalamus) [3]. The usual form is a singular lesion, and sporadically they contribute in MEN syndromes (multiple endocrine neoplasia).

The primary neuroendocrine tumours of the breast were not separately classified by the WHO until 2003 and account for 0.1% [4] to 5% [5, 6] of breast tumours and approximately 1% of all neuroendocrine tumours.

According to the WHO modification from 2012 [7, 8], neuroendocrine tumours are divided into the following groups: well differentiated, poorly differentiated (small cell), and cancers with neuroendocrine differentiation [4]. A local accumulation of neuroendocrine cells is present in many sub-types of breast cancers [9].

The definition of primary neuroendocrine breast tumour is reserved for cases with over 50% of neoplastic cells showing expression of the markers typical for these tumours: chromogranin and synaptophysin [9].

The majority of tumours are well or moderately differentiated. Over 50% of the poorly differentiated tumours are positive for oestrogen and progesterone receptors [7].

The differentiation between primary and secondary neuroendocrine carcinoma of the breast is possible only after the other primary site is excluded [4].

Description of the cases

Patient no. 1

A 65-year-old woman with palpable tumour of the left breast. In spectral mammography, there was an 8 × 4-cm mass with strong contrast enhancement in the in lower quadrants of the left breast (Figure 1A, 1B). A BLESS biopsy under mammographic guidance revealed invasive ductal carcinoma G3. The patient

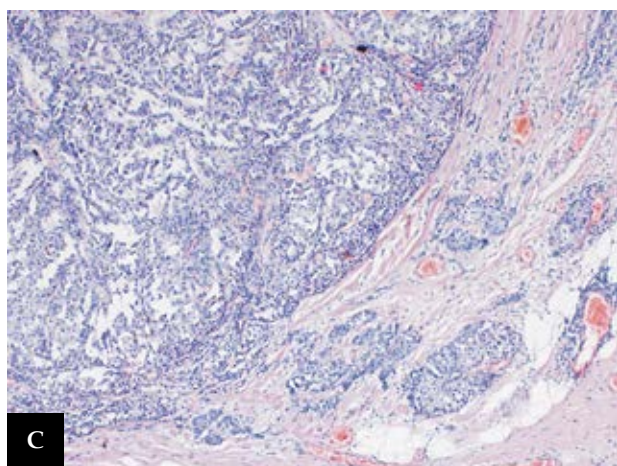
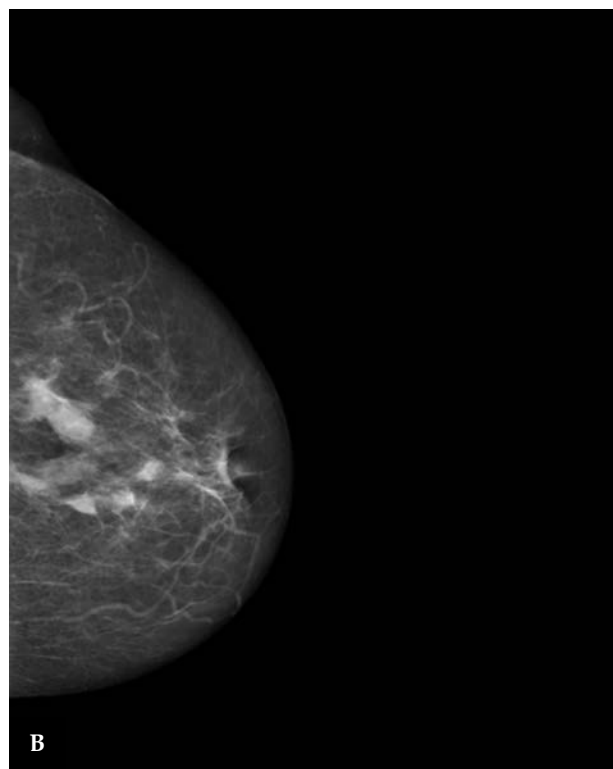
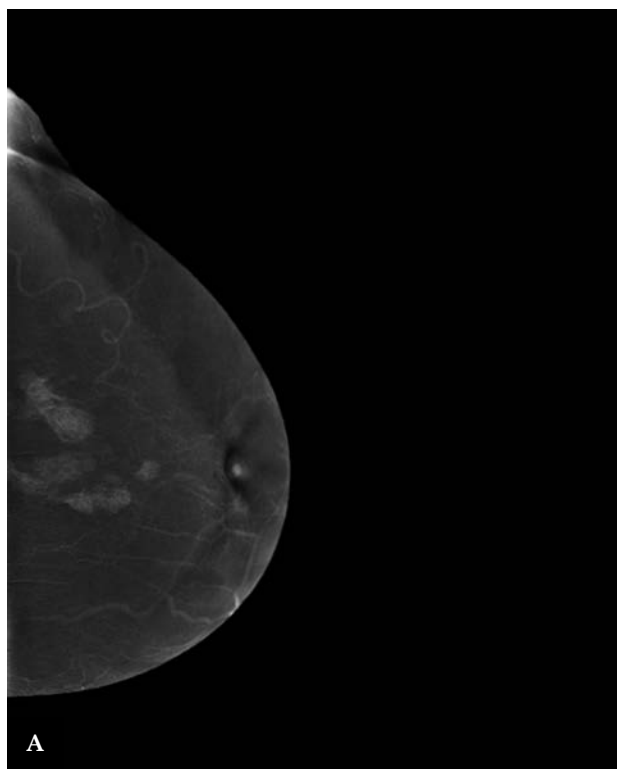


Figure 1A, B. Spectral mammography: Neuroendocrine tumour of the breast; **C.** Neuroendocrine tumour with small foci of connective tissue infiltration; H-E, 40x

Rycina 1A, B. Mammografia spektralna — guz neuroendokryny piersi; **C.** Guz neuroendokryny z drobnoogniskowym naciekiem tkanki łącznej 40x H-E

underwent mastectomy, and the final pathology report revealed the neuroendocrine tumour with small foci of connective tissue infiltration (Figure 1C). The size of the tumour was 5 × 1.7 × 1.5 cm, and the tumour was positive for oestrogen and progesterone receptors, Her-2 negative, Ki 67 1%, synaptophysin (+), and chromogran (-). The axillary lymph nodes were negative.

Patient no. 2

A 77-year-old woman after positive FNA of the left breast under US guidance, referred for a mammography, which revealed an oval, 31 × 22-mm lesion with microlobular and somewhat spiculated margins in the upper outer quadrant of the left breast (Figure 2A, 2B). The core biopsy under US guidance revealed invasive

ductal carcinoma. After the BCU meeting decision the patient was referred for a mastectomy. The pathologic examination revealed a grey, solid tumour 2.7 × 2 × 1.9 cm with final description as the neuroendocrine ductal carcinoma G2 (Figure 2C — multifocal neuroendocrine tumour with infiltration on fat tissue H-E stain, Figure 2D — synaptophysin stain) with positive progesterone and oestrogen receptors, Her-2 negative, and Ki 67 positive in 10%. The axillary lymph nodes were negative.

Patient no. 3.

A 52-year-old woman with positive US examination of the left breast. The spectral mammography showed 3.9 × 2.2 cm strongly enhancing mass in the upper outer quadrant of the left breast. Behind the dominant

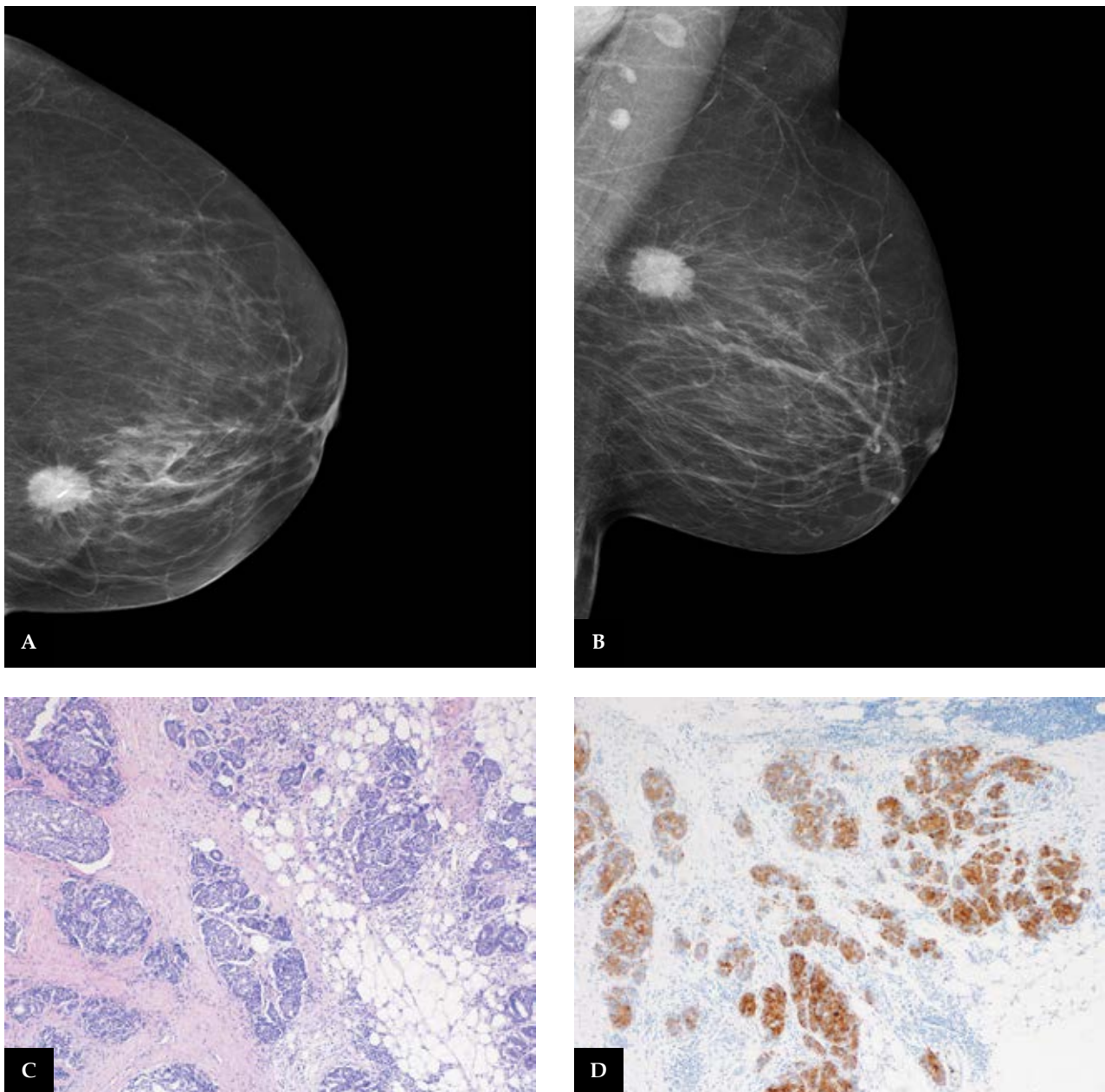


Figure 2A, B. Spectral mammography: Multifocal neuroendocrine tumour of the breast; **C.** Multifocal neuroendocrine tumour infiltrating fatty tissue; H-E, 40x; **D.** Multifocal neuroendocrine tumour infiltrating fatty tissue; synaptophysin, 40x

Rycina 2A, B. Mammografia spektralna — guz neuroendokrynnny piersi wieloogniskowy; **C.** Wieloogniskowy guz neuroendokrynnny z naciekiem tkanki tłuszczowej H-E 40x; **D.** Wieloogniskowy guz neuroendokrynnny z naciekiem tkanki tłuszczowej — synaptofizyna 40x

mass the mammography revealed a second, similar but smaller 2.5 x 1.3-cm lesion (Figure 3A, 3B). The core biopsy of the dominant mass revealed invasive ductal carcinoma G2. The patient underwent mastectomy, and the post-surgical diagnosis was invasive ductal carcinoma with focal neuroendocrine differentiation and focal mucinous differentiation (Figure 3C — H-E stain, Figure 3D — synaptophysin stain). The cancer was positive for progesterone and oestrogen receptors, Her-2 negative, Ki67 positive in 15%, and synaptophysin positive. The axillary lymph nodes were negative.

Patient no. 4.

A 65-year-old woman with positive US examination of the left breast. The spectral mammography showed enhancing, spiculated tumour in the upper outer quadrant, measuring 2.5 x 2.2 cm, with intense desmoplastic reaction on the area of 3–3.5 cm (Figure 4A, 4B). The core biopsy of the tumour, performed in a different hospital, showed invasive ductal carcinoma G2. The BCU meeting referred the patient for conserving breast treatment. The radiograph of the specimen (Figure 4C) shows the excised tumour. The final pathological diagnosis

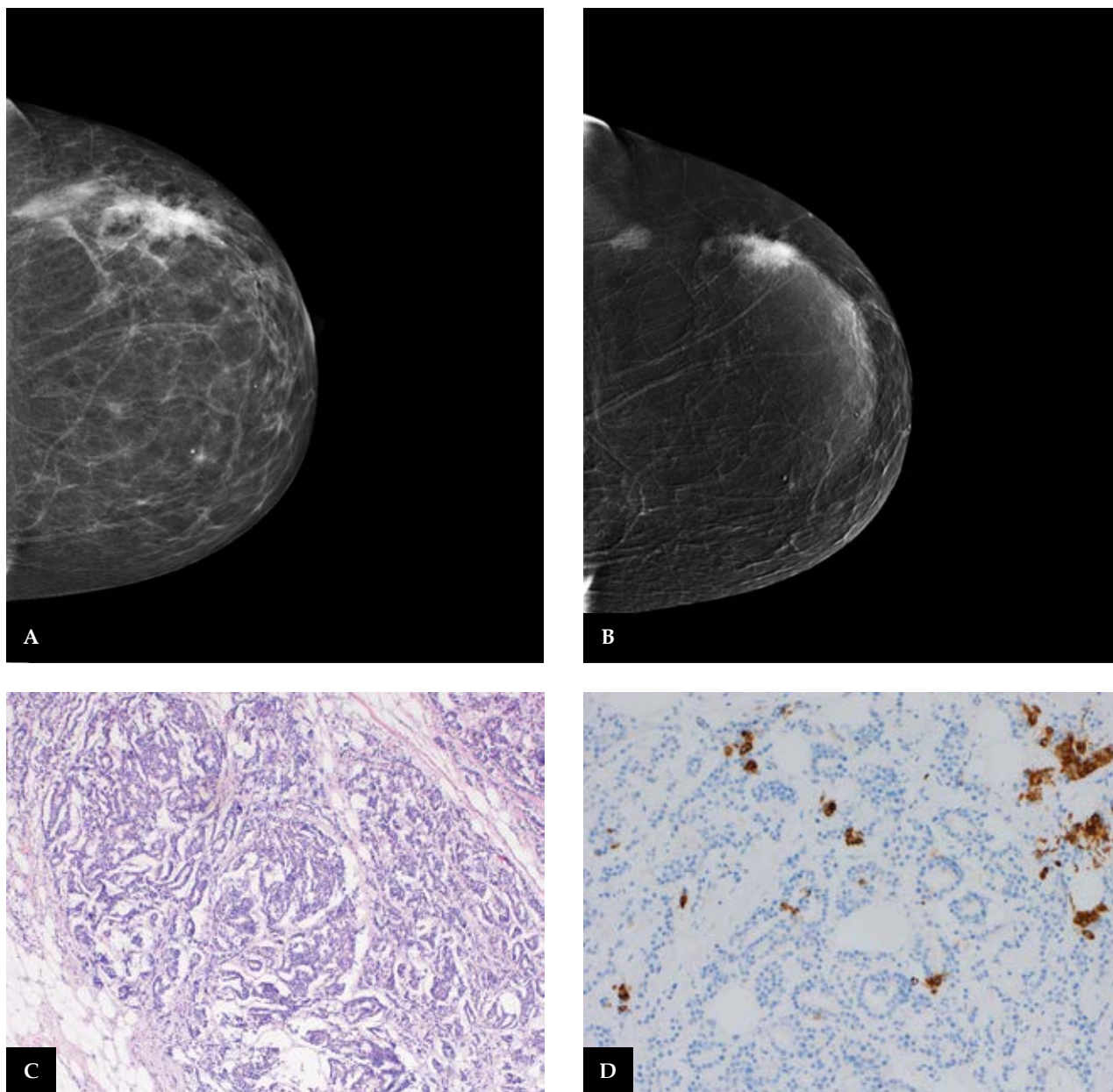


Figure 3A, B. Spectral mammography: Invasive carcinoma NST G2 with focal neuroendocrine differentiation; **C.** Invasive carcinoma NST G2 with focal neuroendocrine differentiation; H-E, 40x; **D.** Invasive carcinoma NST G2 with focal neuroendocrine differentiation; synaptophysin, 100x

Rycina 3A, B. Mammografia spektralna — rak inwazyjny NST GII z ogniskowym zróżnicowaniem neuroendokrynnym; **C.** Rak inwazyjny NST GII z ogniskowym zróżnicowaniem neuroendokrynnym H-E 40x; **D.** Rak inwazyjny NST GII z ogniskowym zróżnicowaniem neuroendokrynnym — synaptofizyna 100x

was neuroendocrine tumour NET G2 (Figure 4D) with positive progesterone and oestrogen receptors, Her-2 negative, Ki67 5%, synaptophysin (+), chromogranin (+), and serotonin (-). The axillary lymph nodes were negative.

Discussion

Primary neuroendocrine breast tumours are extremely rare, with no typical clinical symptoms, and the diagnosis

of the primary tumour is always done by exclusion [4]. Older women, in their 60s and 70s, are more affected, commonly one decade later than invasive breast cancer [10]. From 10 to 50% of the breast tumours can contain dispersed singular neuroendocrine cells; it is important is to distinguish cancer with focal neuroendocrine differentiation from “proper” neuroendocrine tumours [5]. In the literature, there are no cases of benign neuroendocrine tumours of the breast [6], thus one hypothesis suggests that they originate as a result of

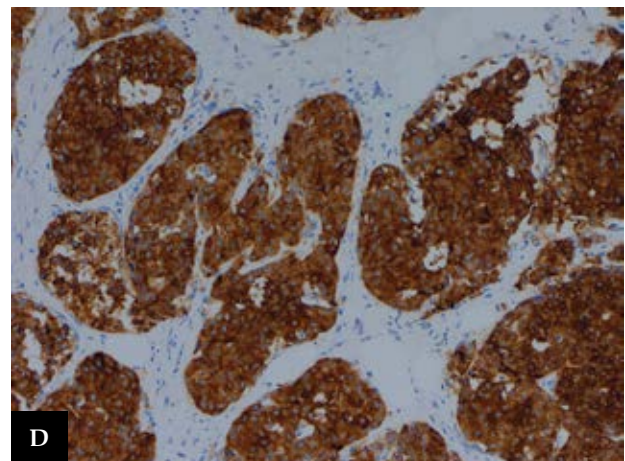
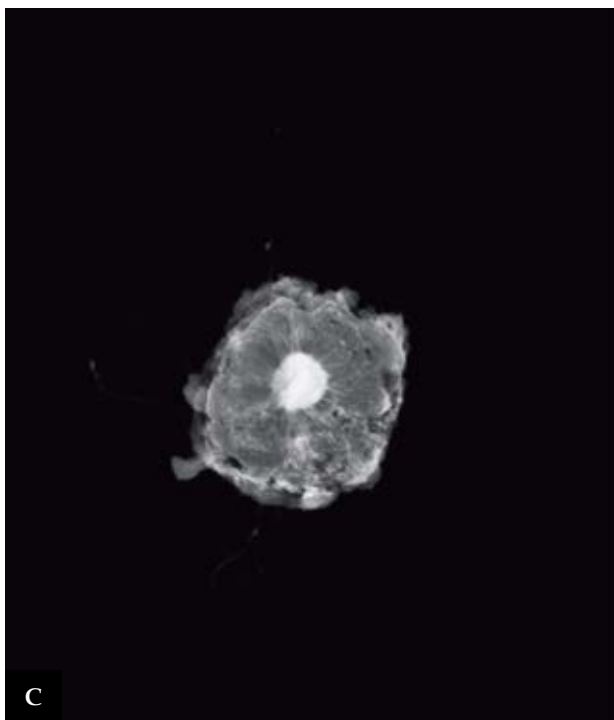
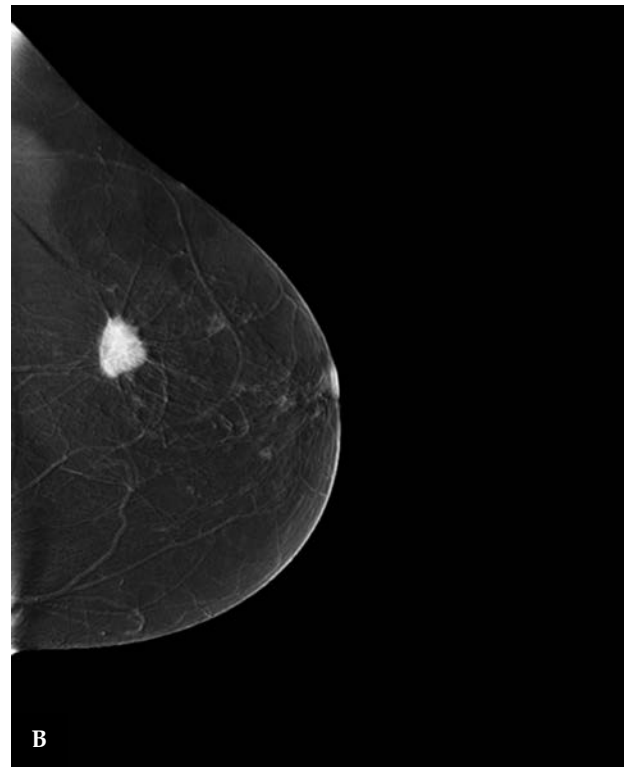
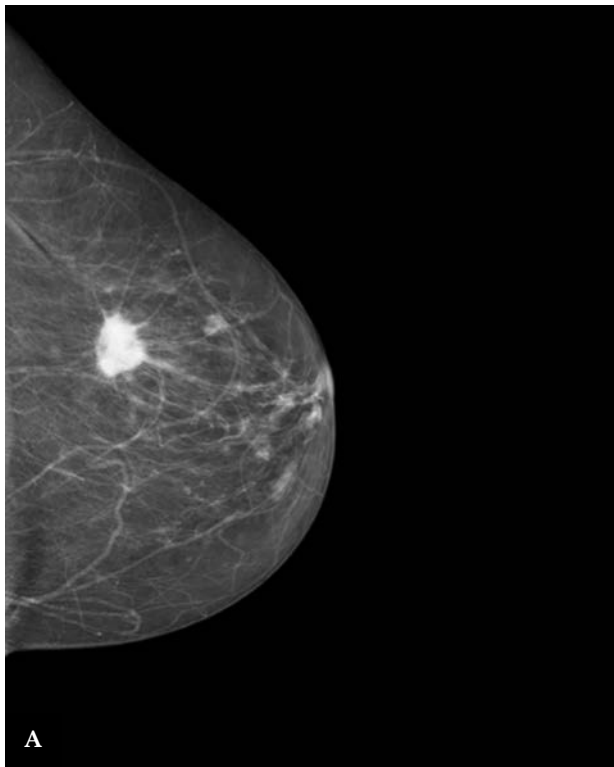


Figure 4A, B. Spectral mammography: Neuroendocrine tumour NET G2; **C.** Intraoperative mammography of the specimen; **D.** Neuroendocrine tumour NET G2; chromogranin (+), 100x

Rycina 4A, B. Mammografia spektralna — guz neuroendokryny NET G2; **C.** Mammografia śródoperacyjna preparatu; **D.** Guz neuroendokryny NET G2 — chromogranina (+) 100x

the differentiation of the breast cancer and not directly from preserved endocrine cells [9].

Most neuroendocrine cells coexist with invasive ductal cancer or cancer with mucinous component,

and typically tumours show expression of oestrogen and progesterone receptors (4.10)

The specific radiological symptoms are still questioned. According to Park [2], in mammographic evalu-

ation the neuroendocrine tumour was most frequently described as a mass (82%) with no calcifications in 75% of cases. Most tumours were oval, round, or lobular (70%). In our material, three of the four lesions were morphologically similar and the margins were poorly defined. According to Park [2], spiculated margins, considered as a radiological sign of malignancy, were present only in 22% of lesions; similarly, in our cases only one in four had spiculated margins. However, in accessible case descriptions there are no specific features of NEC in the radiological imaging (6.10).

The retrospective analysis of a large group of patients (142 persons) performed by Wang et al. [10] revealed that neuroendocrine tumours at the time of the diagnosis are larger than invasive cancers (over 20 mm) and more frequently have metastases to the lymph nodes. In our material, the lesions were bigger than 2 cm in all four patients, but no preoperative FNA showed dissemination to the lymph nodes, although all the patients were qualified for sentinel lymph node procedure. In histopathological material also no dissemination to lymph nodes was found. In every case, tests for hormonal receptors confirmed expression of PR and E receptors.

Neuroendocrine tumours and cancer with neuroendocrine differentiation according to WHO classification are included to the special sub-types of breast neoplasms. The pathologic assessment of neuroendocrine tumours can be challenging in cases where the material has been obtained by core biopsy. The morphological characteristics of the neuroendocrine cancer cell, especially of the pseudo adenomatous form, is very similar to invasive NST cancer. The assessment of hormone receptors and Her-2 protein carried out by core biopsy in invasive cancers adds no value to diagnosis because both NST G1/G2 and neuroendocrine tumours are hormonally positive and Her-2 negative. Positive Her-2 could indicate invasive NST cancer. The diagnosis of the neuroendocrine tumour is based on immunohistochemical positive reaction of chromogranin A and/or synaptophysin.

The finding in a postoperative specimen of solid or lobular foci arranged in nests entwined by a narrow layer of connective tissue with cells of bright cytoplasm and bright chromatin with nucleolus indicates suspicion of neuroendocrine tumour, requiring immunohistochemical confirmation.

The Ki 67 proliferative index allows differentiation of neuroendocrine tumours (Ki 67 up to 20%) from neuroendocrine cancers (Ki 67 over 20%).

Sometimes, poorly differentiated neuroendocrine breast cancer is morphologically very similar to small cell lung neuroendocrine cancer, and in those cases is called small cell neuroendocrine cancer.

It should not be forgotten that in some cases the breast is a metastatic destination for neuroendocrine cancer of the lung and GI tract. In such cases in the histopathological examination, apart from positive neuroendocrine markers, positive antibodies CD56 (lung) and serotonin (GI tract) could be helpful. In the case of the papillary cancer the neuroendocrine markers could be also positive. In such cases neoplastic cells are small with hyperchromatic fusiform or multiform nuclei and lay in foci with intense desmoplastic reaction. The foci can be surrounded by a layer of myoepithelial cells. Steroid receptors are usually positive and Her 2-protein negative. Positive cytokeratin 8 and 18 can be helpful, but the morphology of the routinely stained sample decides on the final diagnosis of cancer.

Neuroendocrine breast cancers are a small group of neoplasms with different degrees of malignancy, thus the prognosis differs. It should be noted that they can be primary or secondary. In order to establish proper diagnosis a multidisciplinary approach is mandatory, with a special role played by immunohistochemical tests.

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