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# Eccrine spiradenoma of the nipple: Case report, differential diagnosis and literature review

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**Running title:** Eccrine spiradenoma of the nipple.

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**Abstract:**

Eccrine spiradenoma is a rare lesion originating from eccrine sweat glands, with only few cases reported in breast tissue: we here describe for the first time, an eccrine spiradenoma arising in the nipple. An 84 year-old woman with a lesion enlarging her right nipple, showing ulcerations and eczema-like changes of the covering skin, was admitted to our hospital. Surgical excision of the central quadrant with nipple-areola complex was performed, followed by histopathological evaluation which revealed an adenoma with predominantly basaloid epithelial cells. The lesion was composed of tightly packed small and large groups of cells, arranged in diffuse alveolar/pseudorosette formations. The small cells expressed p63 and calponin, while a positive expression of CK7 and CD117 was detected in large cells. After careful and detailed examination, excluding various similar entities, a diagnosis of eccrine spiradenoma has been rendered.

Although extremely rare, eccrine spiradenoma should be taken into account in the differential diagnosis of subcutaneous primary breast tumors.

**Keywords:** Eccrine spiradenoma, breast, nipple-areola complex, pitfalls

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## Introduction

Eccrine spiradenoma is a rare, benign tumor, which originates from eccrine sweat glands and mainly occurs in young adults (Kaleeswaran et al., 2002; Sharma et al., 2014). Kersting and Helwig (1956) described this lesion for the first time in 1956 as a skin adnexal neoplasm with a slow growth pattern. Essentially, it is considered a benign lesion although occasionally undergoes malignant transformation (Ishikawa et al., 2001; Braun-Falco et al., 2003; Leonard et al., 2003). Eccrine spiradenoma commonly arises in the upper part of the body, as head, neck and trunk (Park et al., 1983) and rarely can be congenital (Noto et al., 1994). In general, it presents as a solitary lesion, even though cases of multiple variant have been reported (Yoshida et al., 2010). In the present work, we describe a case of eccrine spiradenoma arisen under the nipple in an 84 year-old woman, which represents a possible diagnostic pitfall and a challenge in the differential diagnosis workout.

## Material and methods

*Case report*

An 84 year-old female underwent medical evaluation at our hospital for an enlargement of her right nipple. The patient didn't have any medical history regarding breast lesions.

The skin covering her nipple was focally ulcerated, with micro-erosions and superficial eczematous changes. There was no nipple discharge.

Mammography examinations were performed on both breasts and confirmed a nodular mass confined in the right nipple, without any distortions, microcalcifications or involvement of the breast parenchyma (Fig. 1). Dermatoscopy examination revealed scaly skin of the nipple with

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crusty, eczema-like changes, therefore a possible lesion associated to Paget disease was suspected. After multidisciplinary discussion, the patient was operated under local anesthesia and a central quadrant excision, including the nipple areola complex, was carried out (Fig. 2A). Grossly, a nodular 2 cm white mass completely occupying the nipple and in close connection with the skin was observed (Fig. 2B).

*Methods*

The surgical specimen was fixed in 10% formalin. Macro-sections together with conventional paraffin blocks were performed (Fig. 3A). Tissue sections (2-µm thick) were obtained and stained with hematoxylin-eosin (H&E) according to routine protocol.

Immunohistochemistry (IHC) was performed using an automated slide processing platform (Ventana BenchMark AutoStainer, Ventana Medical Systems Inc., Tucson, AZ, USA) with the following primary antibodies: prediluted anti-ER rabbit monoclonal antibody (SP1, Ventana Medical Systems Inc), prediluted anti-PgR rabbit monoclonal antibody (1E2, Ventana Medical Systems Inc), anti-AR mouse monoclonal antibody (AR441, diluted 1:50, Dako, Glostrup, Denmark) and anti-HER2 polyclonal antibody (A0485, diluted 1:800, Dako). Evaluation of proliferation index (Ki-67) was performed by an anti-Ki67 mouse monoclonal antibody (MIB1, diluted 1:50, Dako). For PAS staining, the sample was incubated in 0.1% periodic acid for 10 min, washed in running water for 1 min and immersed in Schiff's reagent for 17 min. Subsequently it was washed in tap water for 3 min, counterstained with Mayer's hematoxylin for 2 min, again washed in tap water for 3 min, and dehydrated in two changes of 96% alcohol.

To further characterize the lesion we expanded our IHC panel to following antibodies: prediluted anti-P 63 mouse monoclonal antibody (4A4, Ventana Medical Systems Inc), prediluted anti-

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Calponin-1 rabbit monoclonal antibody (EP798Y, Ventana Medical Systems Inc), prediluted anti-Cytokeratin 7 rabbit monoclonal antibody (SP52, Ventana Medical Systems Inc), prediluted anti-CD117 c-kit rabbit monoclonal antibody (YR145, Cell Marque), prediluted anti-CEA mouse monoclonal antibody (TF 3H8-1, Ventana Medical Systems Inc), prediluted anti-EMA mouse monoclonal antibody (E29, Ventana Medical Systems Inc), prediluted anti-GCDFP-15 rabbit monoclonal antibody (EP1582Y, Ventana Medical Systems Inc), anti-GATA-3 mouse monoclonal antibody (HG3-31, Santa Cruz Biotechnology, Inc., 1:50). Positive and negative controls were included for each immunohistochemical run.

**Results**

Microscopically, the lesion was entirely located in the dermis and subcutis, with no sign of invasion of the epidermal layer of the nipple, with no involvement of ductal structures or parenchymatous tissue. It was composed of nests with tightly packed biphasic cell population, arranged in alveolar/pseudorosette formations (Fig. 3B). Peripherally, small cells with hyper-chromatic nuclei were present, which surrounded larger cells with pale nuclei. Neither nuclear atypia nor necrosis were observed, and mitotic index counted 3/10 HPF. No signs of vascular invasion were noted.

At IHC analysis, both cell groups were negative for estrogen receptor (ER), progesterone (PgR), androgen receptor (AR) and HER2, and lesion showed low proliferation index (<5%). Otherwise, small cells resulted positive for p63 and calponin (Fig. 4 A/B), whereas the large cells were immunoreactive for cytokeratin 7 (CK7) and CD117 (Fig. 4 C/D). A suspect of eccrine spiradenoma was taken into account, however, other lesions that are linked on hystogenetic level, such as cylindroma and hidradenoma were considered in differential



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diagnosis. A panel of additional markers is shown in Fig 5.

The breast tissue under the nipple areola complex had adipose involution and only residual atrophic ducts were found. Due to the morphological and IHC evaluation, the final diagnosis of eccrine spiradenoma was made. Patient was recommended to follow regular yearly controls with no additional therapy. Written informed consent was obtained at the time of surgery.

**Discussion**

We here describe the first case of eccrine spiradenoma arising under the nipple. Eccrine spiradenomas are benign tumors that originate from sweat glands, occurring typically as a solitary painful mass located within the deep dermis or subcutaneous tissue (Maize et al., 1998). This type of neoplasm is usually cured by surgery with wide margins, with a few recurring lesions reported as a consequence of incomplete excisions (Panico et al., 1996).

Differential diagnosis of eccrine spiradenoma, due to its rare occurrence and occasional coexistence with other lesions, is rather challenging. The entities that should be considered in differential diagnosis include cylindroma, hidradenoma and malignant lesions such as spiradenocarcinoma and adenoid cystic carcinoma (ACC) (Maize et al., 1998; Cacchi et al., 2011; Zheng et al., 2014).

Although numerous eccrine neoplasms with benign and malignant differentiation have been described in the literature (Panico et al., 1996; Gingrich et al., 2015) their histiogenesis and differentiation based on IHC assessment still remain debatable. However, lack of typical features in apocrine differentiation (glandular structures with brightly eosinophilic cytoplasm, secretory fringes bridging the glandular structures and nuclei located at the base bottom), as well as negative expression of AR, led us to the conclusion that this tumor has eccrine differentiation.

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Eccrine spiradenoma and cylindroma both belong to a group of adenomas with predominantly basaloid epithelial cells. Being linked on a histogenetic level, occasionally they coincide (Goette et al., 1982). Morphologically, what distinguishes cylindroma from eccrine spiradenoma is puzzle-like cell architecture within non-encapsulated dermal nodules, with PAS-positive, hyalinized basement membrane material. In our case, we did not observe any of the above mentioned features (Fig 5A); however, some eccrine spiradenoma may contain an amount of eosinophilic, PAS-positive material surrounding atrophic glandular lobules, that resembles hyaline in cylindroma (Maize et al., 1998), adding to the complexity of differential diagnosis between these two lesions.

Concerning the diagnosis of hidradenoma, it was excluded due to different morphology and immunophenotype. In fact, hidradenoma generally consists of uniform polygonal cells occasionally showing squamoid features (Maize et al., 1998) and expresses carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA) and GCDFP15 (Lee et al., 2011; Shukla et al., 2016), that resulted negative in our case.

Nevertheless, differential diagnosis with ductal adenoma and nipple adenoma should also be taken into account. Similarly, these lesions may be clinically presented as hard mass or rarely as bloody nipple discharge, with nipple erosion. Mammography exam in general reveals a round lesion with well-defined margins. However, histopathological characteristics of these lesions consisting of glandular structures, with a typical dual cell layer of epithelial and myoepithelial cells surrounded by a thick fibrous wall in ductal adenoma, and with sclerosing adenosis in nipple adenoma, evidently exclude these two entities from differential diagnosis (WHO, 2012).

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Although eccrine spiradenoma is by definition a benign lesion, malignant neoplasms, such as spiradenocarcinoma, cylindromatous carcinoma and ACC should be taken into account in differential diagnosis (Cooper et al., 1985; Kolda et al., 1997; Maize et al., 1998), considering that foci of malignant neoplastic transformation may be concomitantly present (Granter et al., 2000; Ishikawa et al., 2001) and in only two cases de novo occurrence has been observed (Yildirim et al., 1987; Hantash et al. 2006).

Typically, malignant transformation into spiradenocarcinoma or into cylindromatous carcinoma implies a loss of two-cell population or absence of puzzle-like growth pattern, described in their benign counterparts. Additionally, malignant lesions present prominent cytological pleomorphism, architectural heterogeneity, increased mitotic index, vascular invasion and focal necrosis (Cooper et al., 1985; Galadari et al., 1987; Maize et al., 1998).

With regard to ACC, the tumor population consists of uniform, basaloid cells forming cribriform, and tubular structures. Perineural invasion is a characteristic finding, together with the positive expression of CEA, EMA and GATA3 (Kolda et al., 1997; Petersson et al., 2009). On the contrary, architecture growth pattern of our case is quite different, represented by tightly packed cells arranged in diffuse alveolar or pseudorosette formations and no expression of CEA, EMA and GATA 3 was observed.

In this case report, we want to underline the importance of diagnostic pitfalls, as only a careful and detailed histopathological and IHC examination, supported by panel of various markers, led to the diagnosis of eccrine spiradenoma.

To date, only seven cases of eccrine benign spiradenoma arising in breast tissue have been reported (Zawirska et al., 1983; Bosch and Boon, 1992; Thomas et al., 1993; Panico et al., 1996; Lee* et al., 2011; Benedict and Ozerdem, 2015; Hemalatha et al., 2015), none of them in



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the nipple region. Table 1 summarizes the main features of currently reported cases, most of them arising in the upper outer quadrant as a palpable mass of about 2 cm in size. In the majority of cases, the diagnosis was made based on morphological appearance rather than IHC evaluation. Unusually, ER and PgR were positive in one case, only (Panico et al., 1996). Although these lesions are benign in nature, there are four malignant cases reported in the breast tissue (Tanaka et al., 2008; Jukic et al., 2009; de Andrés Gómez et al., 2015; Gingrich et al., 2015) presenting high mitotic index, high grade of atypia and metastases.

Even though eccrine spiradenomas rarely occur, this tumor entity should be taken into account in the differential diagnosis of subcutaneous neoplasms of the breast region, including the nipple-areola complex.

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Table 1: Description of literature data.

| | AGE | SITE | SIZE (cm) | PALPABLE | PAINFUL | P63 in basaloid cells | CALPONIN in basaloid cells | CK7 in inner cells | CD117 in inner cells |
|---|---|---|---|---|---|---|---|---|---|
| Panico et al., 1996 | 43 | Q5 | 3 | YES | NR° | NR | NR | + | NR |
| Lee* et al., 2011 | 47 | Q1 | 1 | YES | YES | NR | NR | NR | NR |
| Benedict and Ozerdem, 2015 | 39 | Q1 | 1,8 | YES | NO | + | + | + | + |
| Hemalatha et al., 2015 | 80 | Q1 | 2 | YES | NO | NR | NR | NR | NR |
| Present case | 84 | Q5 | 2 | YES | NO | + | + | + | + |

° NR – NOT REPORTED

## Figure legends

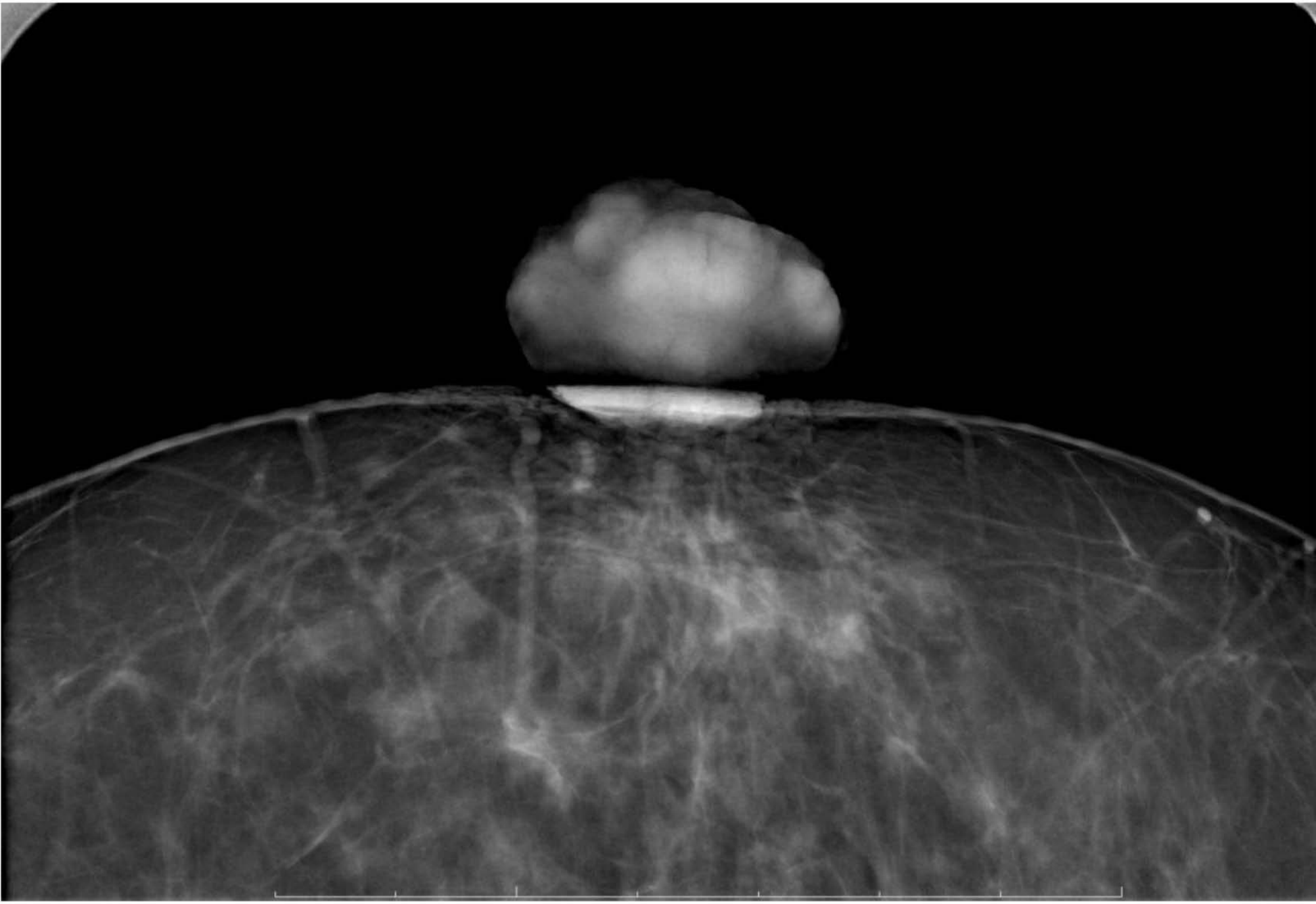
**Fig. 1:** Mammography appearance showing a nodular mass in the nipple, without any distortions, microcalcifications or involvement of the breast tissue.

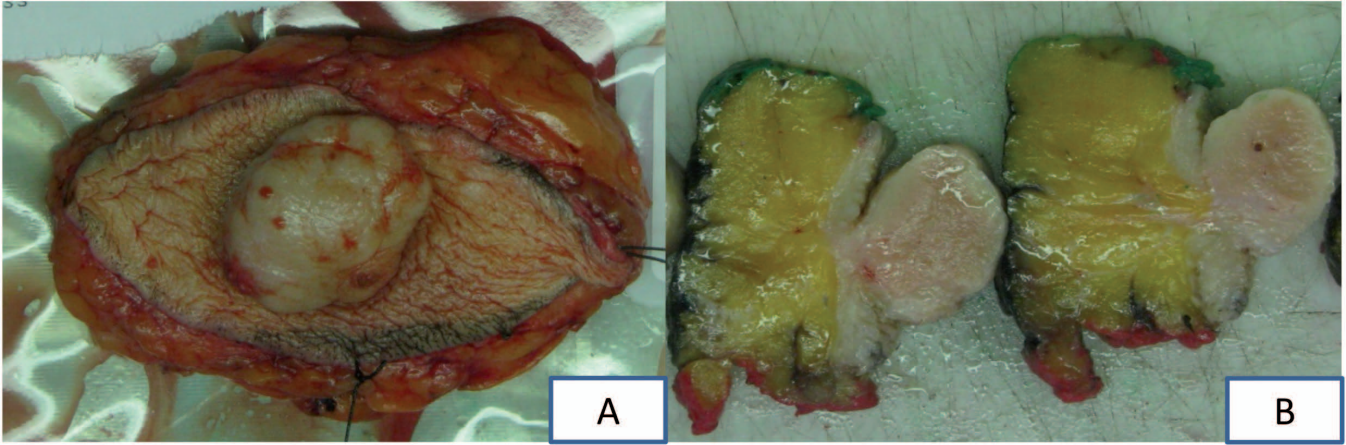
**Fig 2. A:** Central quadrant excision with resection of the nipple-areola complex. The nipple is enlarged and on the nipple surface were present focal superficial erosions. **B:** Perpendicular sections of the nipple, showing a white mass of about 2 cm with regular round shape.

**Fig. 3. A:** The nipple tissue showing nodular lesion. The rest of breast tissue appeared normal with lipoinvolution (H&E, 2x). **B:** The tumor is under the nipple skin without signs of invasion (H&E, 20x). **C/D:** Two types of cell were observed: peripheral, small cells with hyper-chromatic nuclei, and inner, larger cells with pale nuclei. Mitoses were not present (H&E, 40x).

**Fig 4:** Eccrine spiradenoma contains small cells positive for p-63 (**A**) and calponin (**B**), while large cells are immunoreactive for CK7 (**C**) and CD117 (**D**) (20x).

**Fig 5:** Additional panel of markers. **A-D:** PAS staining, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA) and GCDFP-15 resulted negative (20x).

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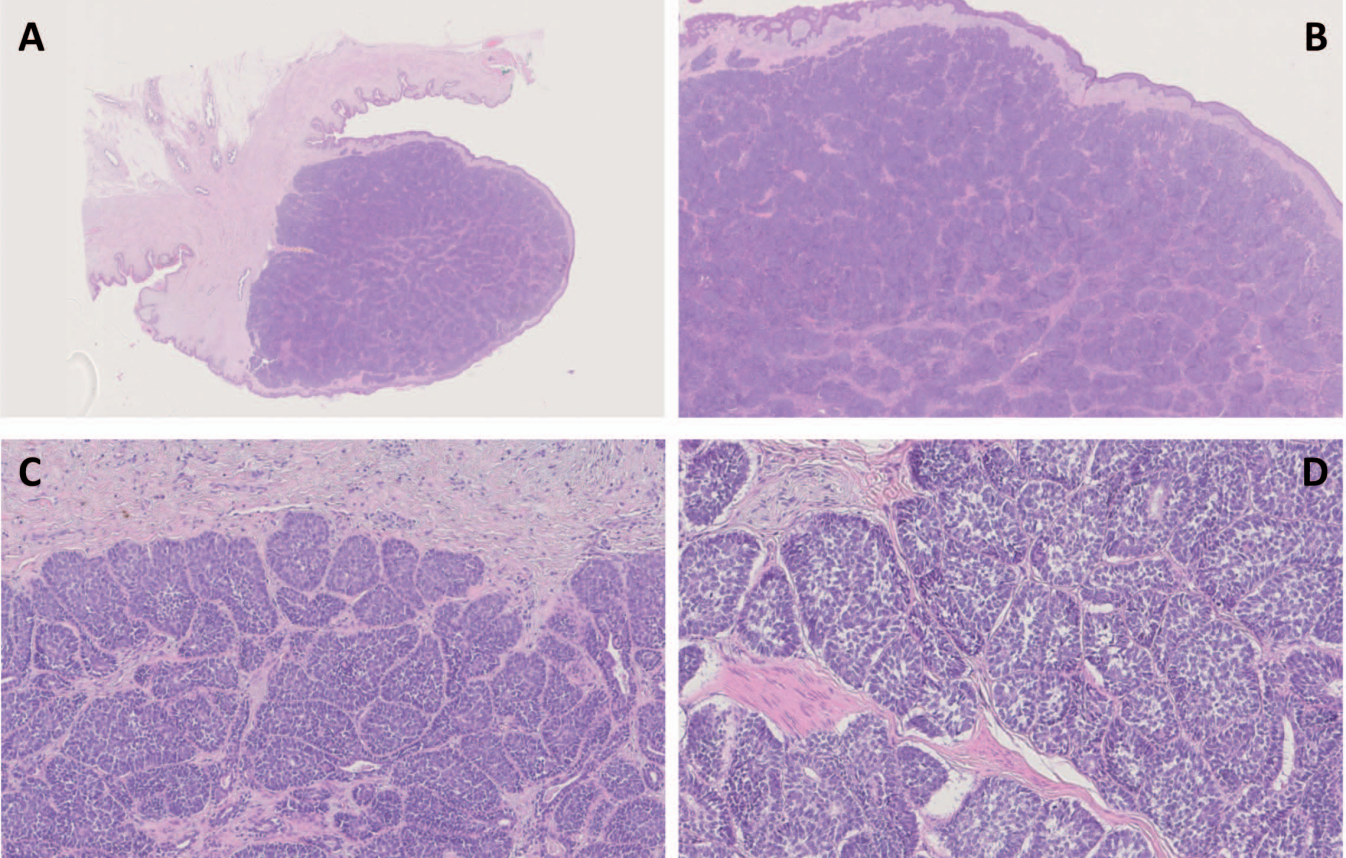
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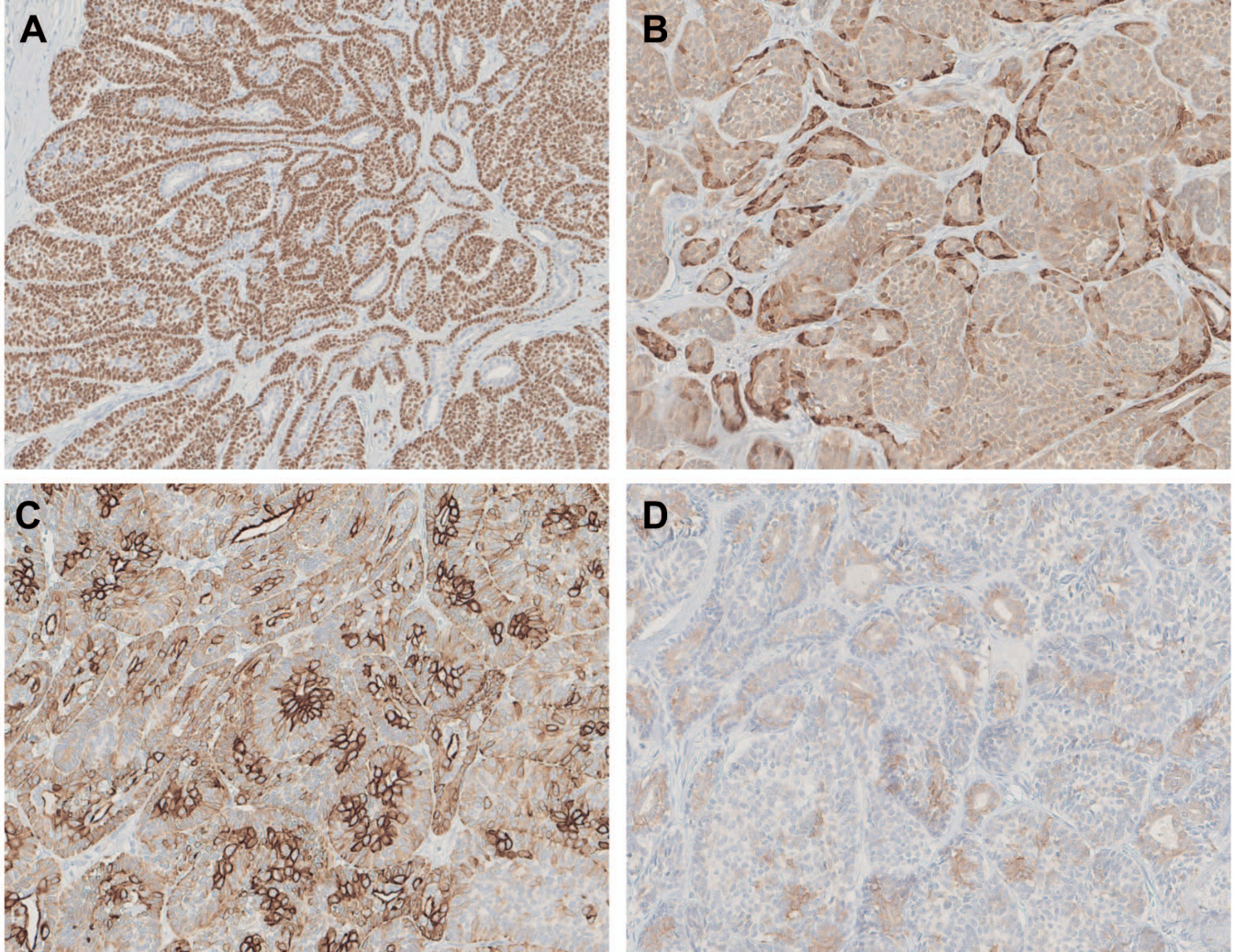
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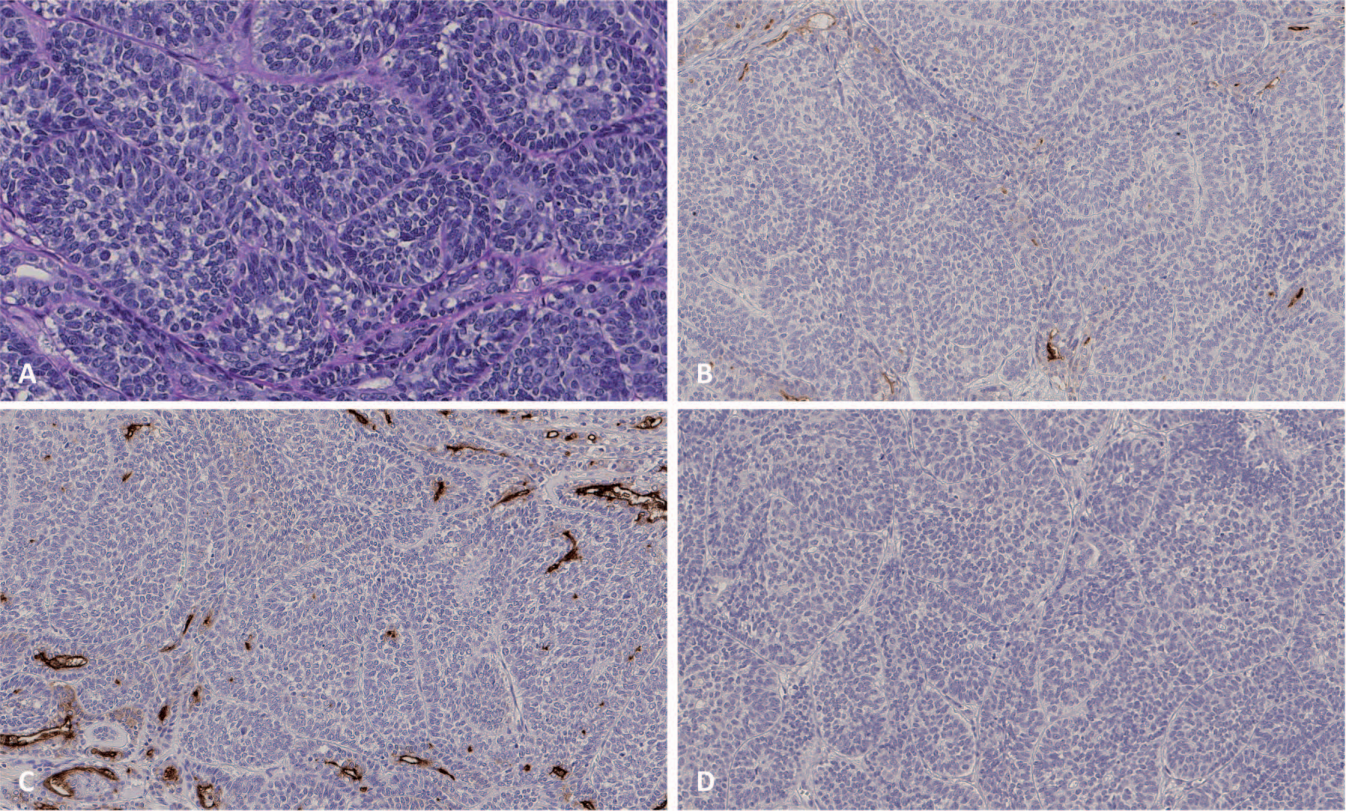
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