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TEACHING CASE

Solid variant of mammary "adenoid cystic carcinoma with basaloid features" merging with "small cell carcinoma"

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Abstract

We describe a rare case of a solid variant of a mammary adenoid cystic carcinoma with basaloid features (sbACC) and its coexistence with a "small cell" carcinoma (SCC), identified and confirmed by histological and immunohistochemical observations: the absence of glandular structures and PAS-positive globules, positivity for neuroendocrine markers (NSE, synaptophysin and chromogranin), and negativity for 34betaE12 and SMA actin were the aspects suggesting the presence of SCC.

Furthermore, positivity for CD10 was found both in sbACC and in SCC, supporting the hypothesis that the two components share the same histogenetic myoepithelial origin and represent an example of dedifferentiation along neuroendocrine phenotype lines occurring in a multipotential neoplastic stem line, already committed towards a myoepithelial phenotype.

To our knowledge, this is the first reported case of a solid basaloid adenoid cystic carcinoma merging with an SCC carcinoma. Furthermore, it is the first study in which CD10 was used to investigate the histogenesis of the two neoplastic components.

Keywords: Breast; Basaloid adenoid cystic carcinoma; Small cell carcinoma

Introduction

Adenoid cystic carcinoma (ACC) of the breast is a rare neoplasm (<1% of breast carcinomas) with an excellent prognosis. As in salivary glands, a variety of microscopic growth patterns (cribriform, glandular, trabecular, solid, and basaloid) have been described in the breast. It has been reported that solid and basaloid variants are associated with a more aggressive clinical course [2,8,9] and have been considered as" high grade" tumors. Recently, Shin and Rosen [11] have described a series of nine cases of a rare subtype of "solid adenoid cystic carcinoma with basaloid features"(sbACC) in the breast, reporting on a differential diagnosis from other neoplasias, including primary small cell carcinoma (SCC) of the breast. This study describes a very rare case of mammary neoplasia in which solid, basaloid adenoid cystic areas (sbACC) merge with more extensive areas of primary "SCC".

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Since these two neoplastic histotypes are very rare in the breast, their histological and immunohistochemical features have been studied to provide a pathogenetic explanation for their coexistence in the same neoplasia.

Case report

A 40-year-old woman, with type I diabetes mellitus, no risk factors for oncological disease, presented a nodule (about 2 cm) discovered in the central quadrant in the retro-areolar zone of the left breast 4 months previously.

Clinical examination showed that the nodule was circular, with indistinct limits, subcutaneously mobile, but partly attached to the underlying glandular layer. No alterations of the areola or nipple were observed. Palpation of the left armpit identified a mobile, non-painful lymph node not larger than 0.5 cm.

Ultrasound examination showed a hypoechogenic nodular area with irregular margins and absorption of the transonic layer. An X-ray of the left breast showed an area of nodular opacity in the central quadrant with indistinct limits and of a maximum diameter of about 2 cm.

A needle-core biopsy gave a diagnosis of "SCC with neuroendocrine aspects" (focal positivity for NSE, Leu7, and synaptophysin).

The following instrumental examinations were carried out for the clinical staging of the neoplasia: a total body skeletal scintigraph, abdominal ultrasound, CT with contrast medium of the chest and brain; no secondary tumors were found. The patient, therefore, underwent central quadrantectomy together with axillary lymphadenectomy by axillary "contra-incision". Post-operative adjuvant radiotherapy was performed on the left breast, and the patient was given the appropriate chemotherapy.

Macroscopic findings

The tumor measured 2.5 cm in its maximum diameter and was ill-circumscribed. The cut surface was of grayish-tan color; gross examination did not show any particular calcification, hemorrhage, or necrosis.

Microscopic findings

The tumor was microscopically unicentric and had invasive borders. Two histological patterns were present in the neoplasia, blending into each other without any distinct boundary between them.

The clearer pattern, representing more than 70% of the neoplasia, was an "undifferentiated small cell" pattern (SCC) reminiscent of an oat cell carcinoma and was the only one presenting at the edge of the tumor. It consisted of islands and nests with a monotonous small round cell population, with a high nuclear-cytoplasmic ratio, dispersed or dark nuclear chromatin, inconspicuous nucleoli, ill-defined, scant cytoplasm, and a tendency towards streaming artifacts (Figs. 1a–b) The neoplastic nests were embedded in myxoid or focally hyalinized stroma and irregularly infiltrated the surrounding breast tissue.

Within the "small cell" areas, there were no particular structures such as ductules, pseudoglandular structures, or PAS-positive homogeneous globules.

Extra-cellular Alcian Blue-positive mucin was present in some areas of the tumor (Fig. 1c).

The second histological pattern, less frequent and present mainly in the central zone of the neoplasia, was similar to the "ACC of salivary glands with basaloid aspects", as described by Fukuoka [2] and by Shin and Rosen [11]. It consisted of islands with basaloid, medium cells with oval hyperchromatic nuclei, small distinct nucleoli, and scanty mildly eosinophilic cytoplasm.

Atypia was mild to moderate. Within basaloid areas, ductules resembling intercalated ducts in salivary gland tumors were present, consisting of larger cells with eosinophilic cytoplasm bordering the empty lumina (Fig. 1d). Moreover, rare small cysts and pseudoglandular structures filled with Alcian blue-positive mucous or, more characteristically, with globular homogeneous, strongly PAS-positive material were occasionally seen (Figs. 1e–f).

These two histological patterns blended into each other, there being a transition zone.

At the tumor edge, there were scattered foci of intraductal carcinoma of "small cell" type.

Axillary lymph nodes were negative.

It is worth mentioning that, in the core biopsy obtained before surgical treatment, only the" small cell" pattern was evident. In fact, no particular structures reminiscent of sbACC (such as ductules, pseudoglandular structures, or PAS-positive homogeneous globules) were present.

The immunohistochemical findings of the core biopsy were analogous to those of the "small cell" pattern of the resected material (see below).

Immunohistochemical findings

Immunohistochemically, there was strong and diffuse positivity for cytokeratins AE1/AE3, Ck7, vimentin, S100, Bcl2, CD117, and progesteron receptors (50% of cells) in both the "sbACC" and "SCC" areas.

Synaptophysin, Leu7 (CD57), and NSE were negative in "sbACC" areas, whereas "SCC" areas were positive (Fig. 2).

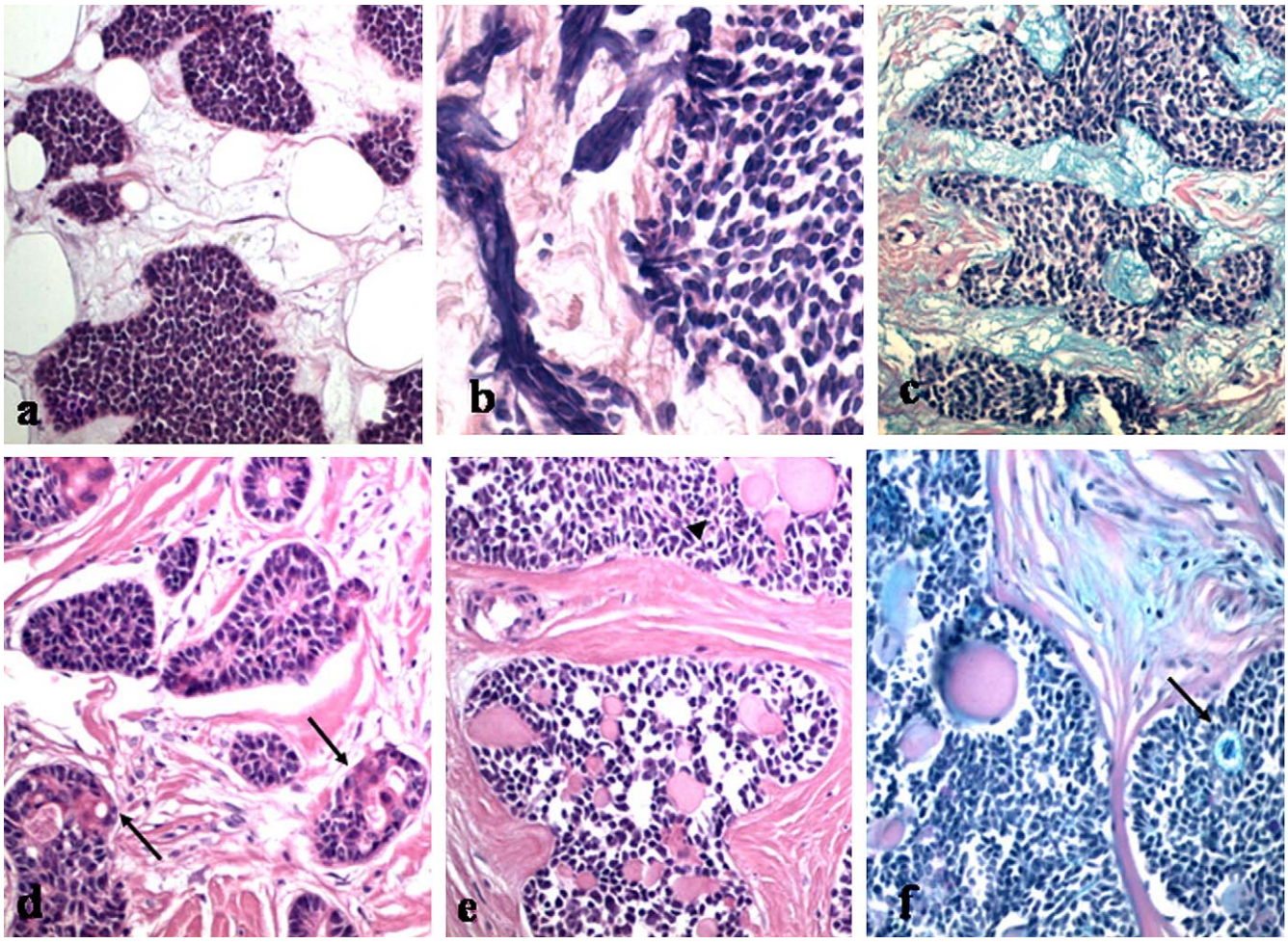

Fig. 1. Small cell carcinoma (SCC) areas: (a) and (b) Nests of small round cells showing a high nuclear–cytoplasmic ratio, dark nuclear chromatin, inconspicuous nucleoli, scant cytoplasm, and streaming artefacts. (c) Extra-cellular, alcian blue-positive mucin. Solid basaloid adenoid cystic carcinoma (sbACC) areas: (d) and (e) Islands of basaloid cells encompassing ductules made up of larger cells with eosinophilic cytoplasm (arrows) and globular homogeneous material (arrowheads). (f) Alcian blue positivity in pseudoglandular structures (arrow) and PAS positivity in globular, homogeneous material (arrowhead).

Only in sbACC areas focal positivity for actina SMA and 34betaE12 was noted (Fig. 3). EMA and CEA highlighted ductules, pseudoglandular structures, and globules of homogeneous material scattered throughout the sbACC areas (Fig. 4a) and the transition zone (Fig. 4b). These were absent in SCC areas (Fig. 4c).

CK20, actin HHF35, TTF-1, HER-2 Neu, and estrogen receptors (ERs) were negative in both SCC and sbACC areas.

P63 staining was positive only in the nuclei of residual myoepithelial cells bordering the *in situ* neoplastic proliferations, but was absent in the neoplastic cell population of both areas. Mib1 (Ki67) immunostaining was positive in less than 10% of cells in sbACC areas (Fig. 5a), and in more than 30% of cells in SCC areas (Fig. 5b).

Nuclear staining for p53 was present only in "SCC areas".

CD10 showed para-nuclear, dot-like positivity in both "SCC" and "sbACC" areas, highlighting pseudoglandular structures and homogeneous, globular material (Figs. 4d,e,f). ICH results are summarized in Table 1.

Discussion

Mammary ACC is a tumor with a good prognosis and is histologically indistinguishable from ACC arising from other sites. As in the salivary glands, a variety of microscopic growth patterns (cribriform, glandular, trabecular, solid, and basaloid) have been described in the breast.

The solid and basaloid variants have been reported to be associated with a more aggressive clinical course [2,8,9] and have been considered "high grade" tumors.

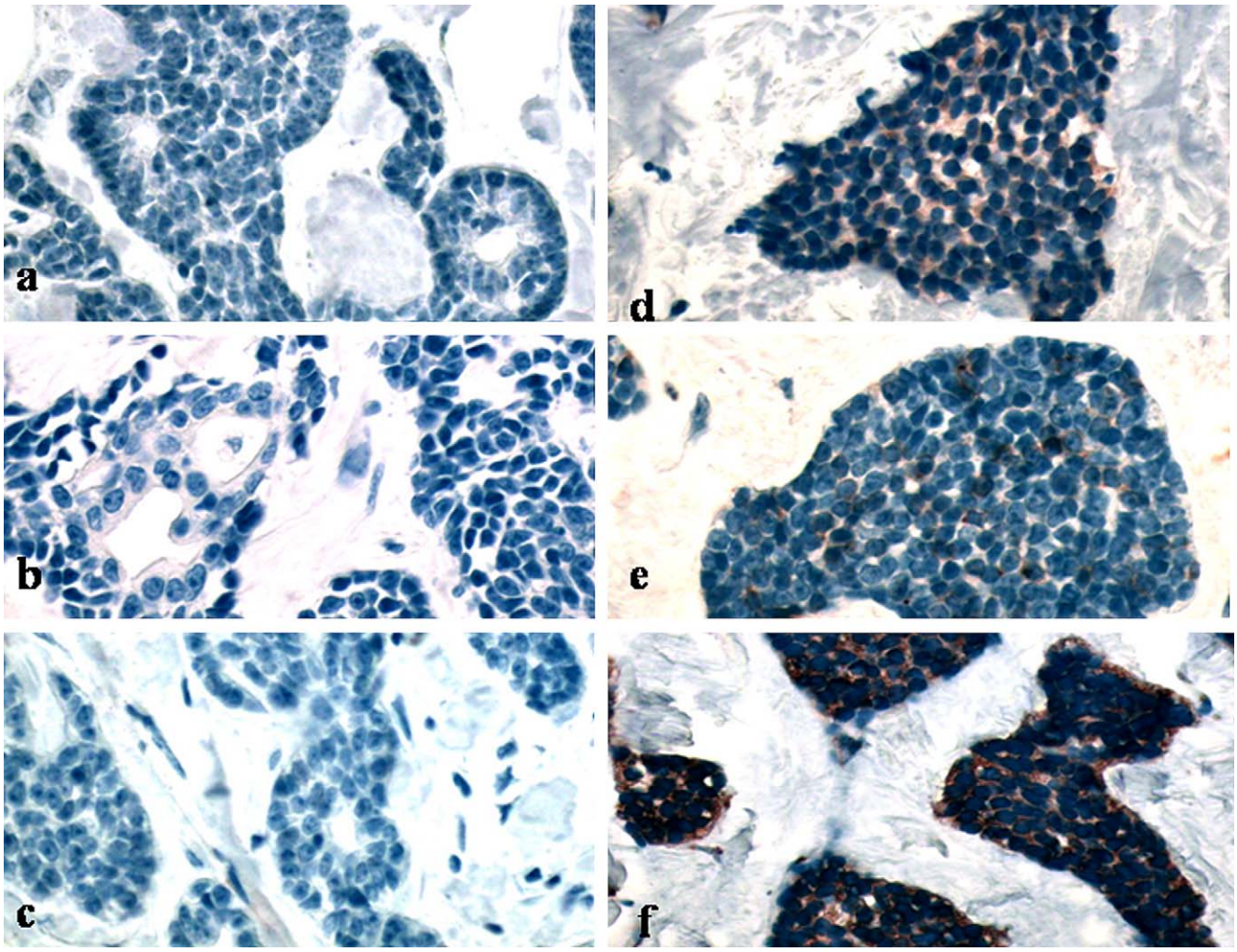

Fig. 2. Synaptophysin, Leu7 (CD57), and NSE are negative in solid basaloid adenoid cystic carcinoma (sbACC) areas (a,b,c) and are positive in small cell carcinoma (SCC) areas (d,e,f).

The "sbACC" is a rare subtype of ACC, described by Fukuoka et al. in 1999 [2]. Recently, a series of nine cases affecting the breast was reported by Shin and Rosen [11]. The authors confirmed a more aggressive clinical course, with a greater propensity for axillary lymph node spread than conventional ACC, but not for local or systemic recurrence. Therefore, they conclude that, although being more aggressive than traditional mammary ACC, this type of tumor probably leads to a better outcome than an invasive, poorly differentiated duct carcinoma of similar size.

Distinction should be made between sbACC and primary SCC of the breast, which has a worse prognosis and requires a different therapeutic approach.

SCC of the breast is an uncommon neoplasm representing both the most distinctive and the least common type of breast carcinoma. It has rarely been reported in the literature, and, in fact, the largest published series is that of the nine cases reported by Shin et al. [10]. It is considered the "undifferentiated" variant of NE breast cancer and usually shows the most aggressive behavior.

The differential diagnosis between SCC and sbACC is often difficult: histologically, the absence of glandular structures and of PAS-positive globules are the more striking differences, suggesting a diagnosis of SCC over sbACC [11]. Immunohistochemically, the two neoplasias share a lot of immunohistological markers such as AE1/AE3, CK7, vimentin, and S100. Furthermore, Bcl2 and CD117 have recently been observed in both types [1,10–12].

According to Shin and Rosen [11], the immunohistochemical differential diagnosis between sbACC and SCC is based only on neuroendocrine markers (NSE, synaptophysin and chromogranin), and their positivity suggests a diagnosis of SCC over sbACC.

Other studies [5] have reported that 34betaE12 and SMA actin are also useful, because they are positive in sbACC and are completely lacking in SCC.

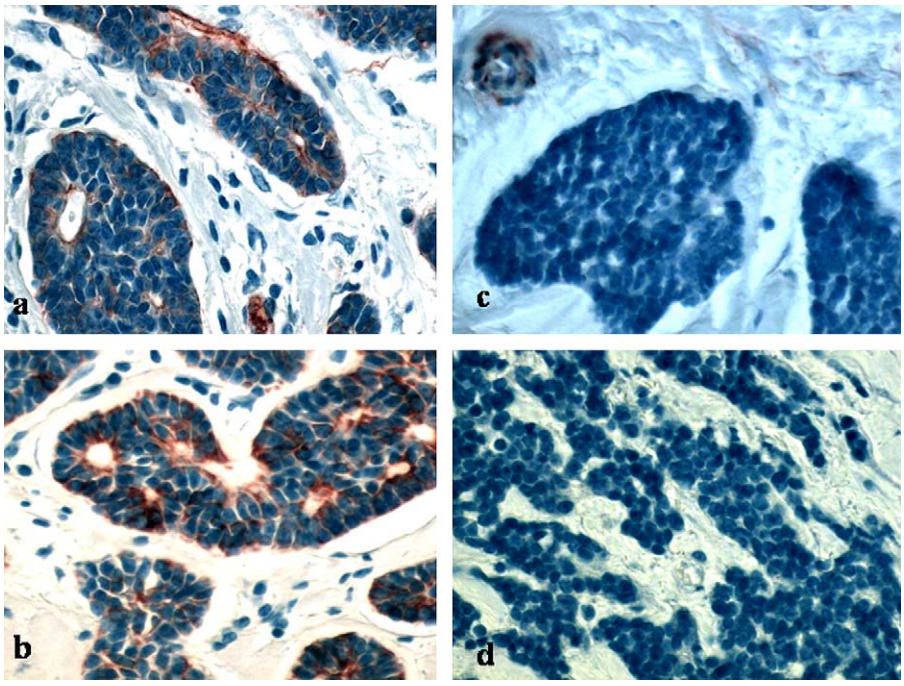

Fig. 3. Focal positivity for actin SMA (a) and 34betaE12 (b) in solid basaloid adenoid cystic carcinoma (sbACC) areas, whereas small cell carcinoma (SCC) areas are negative (c,d).

In our case, there were large areas with a "small cell" carcinoma-like aspect, completely devoid of PAS-positive spherules and ductular or pseudo-glandular structures. On the contrary, these features were focally observed in the central areas of the tumor, conferring to the neoplasia a morphological aspect compatible with "sbACC".

Both areas with histological aspects of sbACC and areas with histological aspects of SCC were indifferently positive for AE1/AE3, CK7, vimentin, S100, Bcl2, and CD117 (Table 1).

By contrast, areas with histological aspects of SCC were positive for some neuroendocrine markers, (NSE, CD57, synaptophysin) and were negative for 34beta E12 and SMA actin, whereas areas with a histological aspect of sbACC were negative for NSE, CD57, synaptophysin and P53, and positive for 34beta E12 and actin SMA.

Our immunohistochemical findings were thus in keeping with most of the above mentioned criteria for a differential diagnosis between SCC and sbACC, supporting the morphological observation of two different patterns coexistent in the same neoplasia.

Moreover, Mib1 (Ki67) immunostaining was positive in less than 10% of cells in sbACC areas and in more than 30% of cells in SCC areas; P53 nuclear staining was restricted to SCC areas. This might be related to the higher aggressiveness of SCC areas.

To investigate the histogenesis of these two different neoplastic patterns coalescing in the same neoplasia, we assessed p63 and CD10, two recently recognized markers of myoepithelial cells in the breast.

In our case, p63 was completely absent not only in "small cell" areas (as expected), but also in sbACC areas despite the commonly accepted myoepithelial origin of sbACC.

This is, perhaps, in analogy with the absence of a smooth muscle myosin heavy chain (another marker specific for myoepithelial cells) as observed by Shin and Rosen [11]. As their nine cases failed to demonstrate an evident myoepithelial origin of basaloid cells with a smooth muscle myosin heavy chain, they concluded that "basaloid cells are primitive cells capable of multi-directional differentiation, and the absence of myoepithelial markers does not exclude the diagnosis of solid variant mammary ACC".

On the other hand, we found diffuse CD10 positivity (with a para-nuclear, dot-like pattern) in both basaloid and "small cell" areas.

CD10 is a recently recognized marker of myoepithelial cells in the breast [6].

We therefore conclude that CD10 might prove to be more sensitive than P63 and smooth muscle myosin heavy chain as regards the assessment of a myoepithelial origin of both sbACC and SCC areas.

Furthermore, CD10 and S100 positivity, together with ER negativity, have been identified in normal basal, including myoepithelial, cells of the breast [4]. Our findings of positivity for CD10 and S100 and negativity for ER are therefore in keeping with a myoepithelial origin of both neoplastic areas.

In our case, the coexistence of two different histological and immunohistochemical patterns might

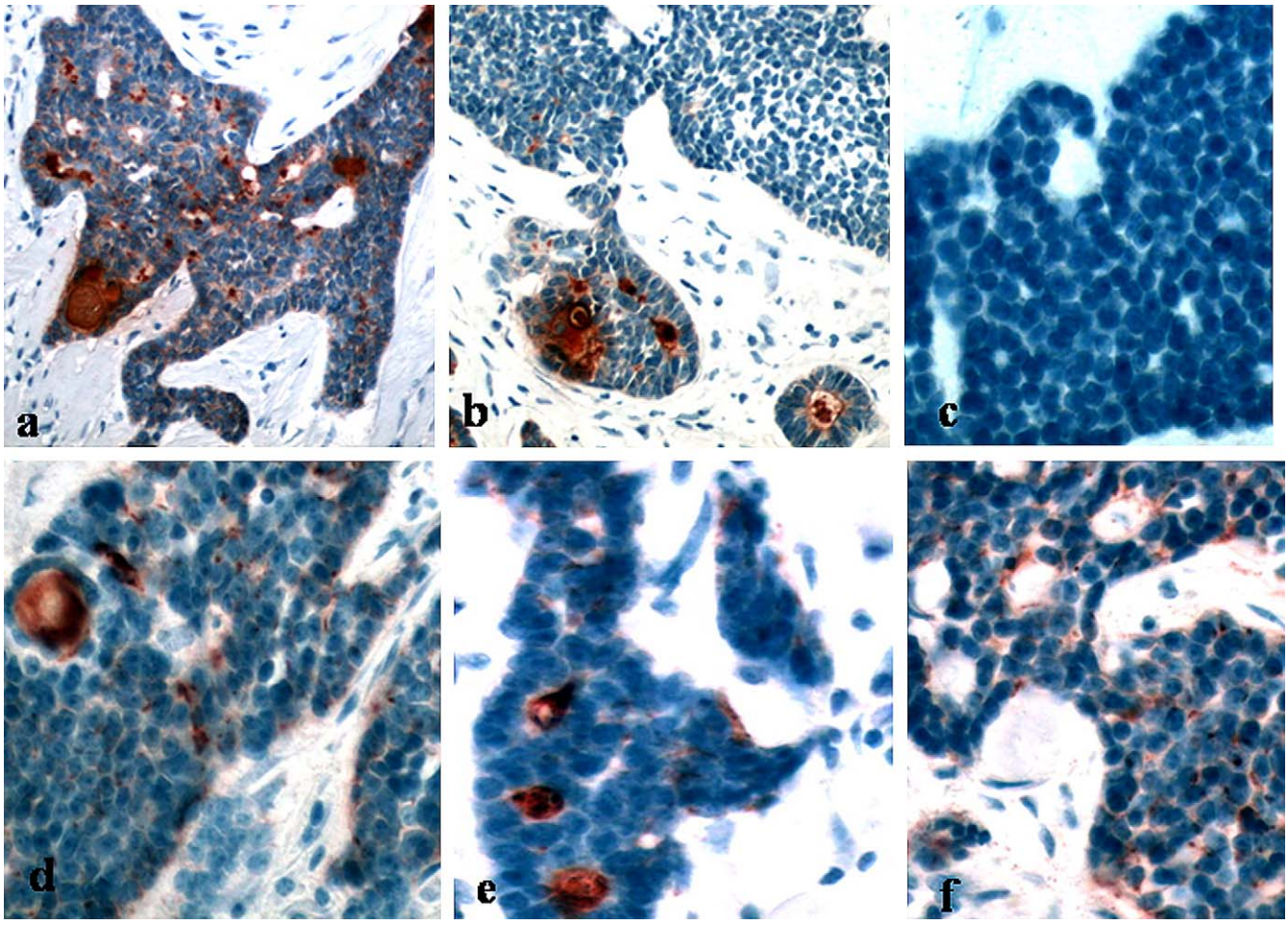

Fig. 4. (a,b,c) CEA highlights ductules and pseudoglandular structures in solid basaloid adenoid cystic carcinoma (sbACC) areas (a) and in transition zone (b), whereas small cell carcinoma (SCC) areas are negative (c), (d,e, f): CD10 shows para-nuclear, dot-like positivity in "sbACC" areas (d,e) and in "SCC" areas (f). In "sbACC" areas, moreover, CD10 highlights globular homogeneous material and pseudoglandular structures.

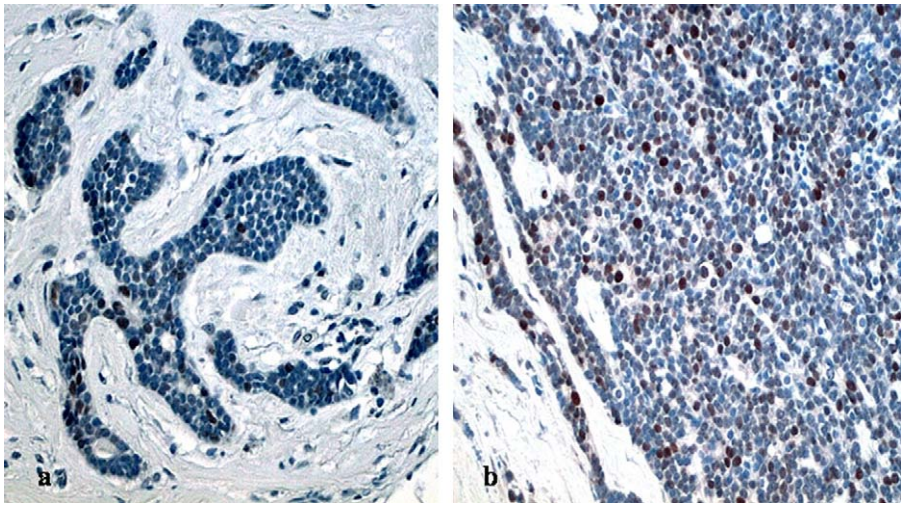

Fig. 5. Mib1 (Ki67) immunostaining is positive in less than 10% of cells in solid basaloid adenoid cystic carcinoma (sbACC) areas (a) and in more than 30% of cells in small cell carcinoma (SCC) areas (b).

Table 1. Immunohistochemical pattern of "small cell carcinoma" (SCC) areas and "solid basaloid adenoid cystic carcinoma" (sbACC) areas

	"SCC" areas	"sbACC" areas
AE1/AE3	+++	+++
CK7	+	++
Vimentina	+++	++++
S100	++	++
NSE	++	++
Bcl2	+++	+++
CD117	+++	+++
CD10	+++[a]	+++[a,b]
Synaptophysine	++	—
CD57	++	—
P53	+	—
Actin SMA	—	++
34beta E12[b]	—	++[b]
EMA[b]	—	+[b]
CEA[b]	—	+[b]
CK20	—	—
P63[a]	—	—
HER-2	—	—
ER	—	—
Progesterone receptors	+	+
Mib1 (Ki67)	<10%	>30%

[a]Diffuse positivity with para-nuclear dot-like pattern.
[b]Focal positivity in sbACC areas, highlighting ductules and pseudoglandular structures.

represent an example of dedifferentiation along neuroendocrine phenotype lines occurring in a multipotential neoplastic stem line, already committed towards a myoepithelial phenotype.

CD10 positivity might therefore be an immunohistochemical marker of histogenesis not only of sbACC, in which p63 and a smooth muscle myosin heavy chain fail to demonstrate an evident myoepithelial origin of basaloid cells [11], but also of some cases of SCC in which the histogenesis often remains unexplained.

We conclude that, in our case, the presence of a transition zone and CD10 positivity of the two components (suggesting an identical myoepithelial origin for both) distinguish our tumors from true collision tumors and support the hypothesis that these two components represent different steps in the process of dedifferentiation (in which p53 overexpression, restricted to the SCC component, may have a role, which is in keeping with the more aggressive potential of SCC).

Previous studies have reported foci of dedifferentiation in ACC [3,7] consisting of either poorly differentiated adenocarcinoma or undifferentiated, large cell carcinoma, with negativity for myoepithelial markers and occasional positivity for p53.

To our knowledge, dedifferentiation in breast ACC consisting of SCC has never been described. In SCC of the breast, the presence of a dimorphic population (i.e., the association of SCC and invasive ductal or lobular carcinoma) may prove to be a more favorable prognostic finding than pure SCC [10]. In our opinion, a longer follow-up and a larger number of cases are necessary to assess the real prognostic significance of this rare association of SCC with sbACC.

As far as we know, this is the first case of breast "sbACC" merging with "SCC" and the first study in which CD10 was used to investigate the histogenesis of two neoplastic components.

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