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Case Report

Dedifferentiation-like progression of breast carcinoma: report of a case showing transition from luminal-type carcinoma to triple-negative carcinoma with myoepithelial features

Shogo Tajima[1], Kenji Koda[2]

[1]Department of Pathology, Shizuoka Saiseikai General Hospital, Shizuoka, Japan; [2]Department of Pathology, Fujieda Municipal General Hospital, Shizuoka, Japan

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Abstract: Certain genetic events that occur at various stages of carcinogenesis can result in phenotypic changes. In breast carcinoma, these changes may occur either in situ, at the primary invasive site, or at a distant metastatic site. This report presents a case of dedifferentiation-like progression of breast carcinoma showing transition from luminal-type carcinoma to triple-negative carcinoma (i.e. negative for estrogen receptor, progesterone receptor, and HER2) with myoepithelial features. An 87-year-old woman was referred to us from another hospital for surgery. Preoperative ultrasonography revealed a mass measuring 16 × 12 × 8 mm. Following partial mastectomy, gross examination revealed a whitish tumor on the cut surface measuring 15 × 10 × 8 mm. Histopathological investigation revealed a predominant high-grade carcinoma containing some short spindle-shaped cells and expressing p63, muscle-specific actin, and alpha smooth muscle actin. The tumor also showed decreased expression of pan-cytokeratin and increased expression of vimentin on immunohistochemistry. Estrogen receptor was not detected by immunostaining. A high Ki-67 labeling index and diffuse nuclear accumulation of p53 were observed in the high-grade carcinoma. In the peripheral area, low-grade carcinoma with estrogen receptor expression was observed, but appeared displaced by the high-grade carcinoma. The high-grade carcinoma exhibiting myoepithelial carcinoma-like morphology and molecular phenotype was deemed to be carcinoma showing dedifferentiation-like changes arising from the peripherally situated pre-existing low-grade carcinoma. Thus, follow-up ought to be mandatory, considering the presumably aggressive nature of the predominant carcinoma showing dedifferentiation-like changes in this case.

Keywords: Breast, carcinoma, dedifferentiation, luminal-type, myoepithelial features

Introduction

Breast carcinoma can be classified into four distinct molecular subtypes based on gene expression profiling using DNA microarray: luminal, HER2-enriched, basal-like, and normal breast-like carcinoma [1]. Luminal breast carcinomas can further be divided into luminal A and luminal B, and this distinction was shown to be of prognostic significance [2, 3]. Immunohistochemical markers such as estrogen receptor (ER), progesterone receptor (PR), HER2, cytokeratin (CK) 5/6, and EGFR are used as surrogates for microarray-based expression profiling [4].

Myoepithelial carcinoma belongs to the category of metaplastic carcinoma [5]. According to the microarray-based gene-expression profile, metaplastic carcinoma is preferentially classified as a basal-like subtype [5]. The basal-like subtype expresses genes characteristic of basal/myoepithelial cells, whereas the luminal subtype expresses genes characteristic of luminal mammary epithelial cells [1, 2]. The basal-like subtype is thought to possibly originate from the luminal subtype; this illustrates the concept of phenotypic change of a carcinoma at a later stage [6]. This process is known as dedifferentiation or transdifferentiation [6].

In this report, we present a case of dedifferentiation-like progression of breast carcinoma showing transition from luminal-type carcinoma to triple-negative (ER-, PR-, HER2-) carcinoma with myoepithelial features. To describe the

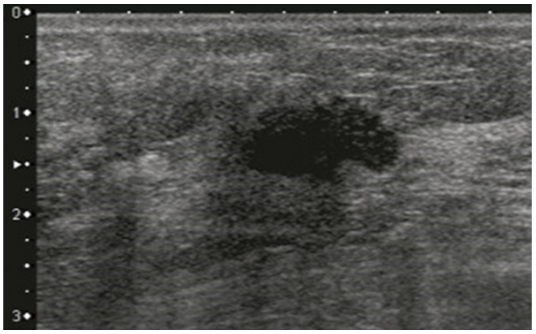

Figure 1. Ultrasonographic image. Ultrasonography revealed an irregular hypoechoic mass measuring 16 × 12 × 8 mm.

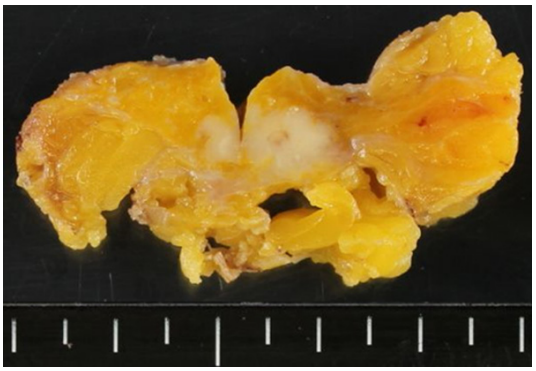

Figure 2. Gross examination. Examination displayed an irregular whitish tumor on the cut surface which measured 15 × 10 × 8 mm. The appearance was homogenous.

progression to carcinoma with myoepithelial features, the term, transdifferentiation, also seemed to be appropriate since some degree of myoepithelial differentiation might be present. However, we used the term, dedifferentiation, rather than transdifferentiation because the appearance of high-grade carcinoma with myoepithelial features was described as dedifferentiation in a previous report [7]. This transformed lesion with myoepithelial features is expected to belong to the basal-like subtype, since it is regarded as a kind of metaplastic carcinoma. At an area on the periphery, however, carcinoma that is probably of the luminal subtype remained. The two carcinoma subtypes were located in close proximity and appeared to show gradual transition. This is a unique case of breast carcinoma showing dedifferentiation-like progression at the primary site.

Clinical summary

An 87-year-old woman was referred from another hospital for treatment of a carcinoma in the right breast. The diagnosis had already been made through biopsy. Preoperative ultrasonography revealed an irregular hypoechoic mass 16 × 12 × 8 mm in size (**Figure 1**). Subsequently, partial mastectomy and sentinel lymph node dissection were performed. Intraoperative examination of the lymph node revealed no malignancy. The postoperative course was uneventful, and the patient was discharged without any complaints.

Pathological findings

The surgically resected specimen displayed an irregular whitish tumor on the cut surface measuring 15 × 10 × 8 mm (**Figure 2**). The appearance was homogenous, and the entire tumor seemed to be composed of a single component.

Histopathologically, the tumor was predominantly composed of high-grade carcinoma with a solid, trabecular growth pattern and variably-sized nests with no gland formation (**Figure 3A**, lower right). The constituent cells were short spindle-shaped to oval. The nuclear-to-cytoplasmic ratio was high; nuclei showed prominent hyperchromasia with a coarse granular chromatin pattern. Mitotic figures were easily observed (16/10 high-power fields), and necrosis was not apparent (**Figure 3B**). At the periphery, a narrow rim of low-grade carcinoma with nested growth patterns was observed (**Figure 3A**, upper left). The nuclei of the low-grade carcinoma were smaller, and hyperchromasia was less prominent. Mitotic figures were rarely seen (1/10 high-power fields) (**Figure 3C**). The high-grade and low-grade carcinomas seemed to be superimposed in a manner that indicated gradual transition (**Figure 3D**). The high-grade carcinoma was suspected to be a carcinoma showing dedifferentiation-like changes arising from the peripherally situated pre-existing low-grade carcinoma. Intraductal spread was mild and only identified in the low-grade carcinoma. The surgical margin was free of malignancy.

On immunohistochemistry (IHC), the low-grade carcinoma expressed ER (**Figure 4A**) but did not express PR, HER2, CK5/6, CK14, EGFR, or c-kit. The high-grade carcinoma did not express ER (**Figure 4B**) or any of the aforementioned markers. The Ki-67 (MIB-1) labeling index, based on counting 1000 cells, was 36% in the high-grade carcinoma and 8% in the low-grade carcinoma (**Figure 4C**). Nearly all cells of the

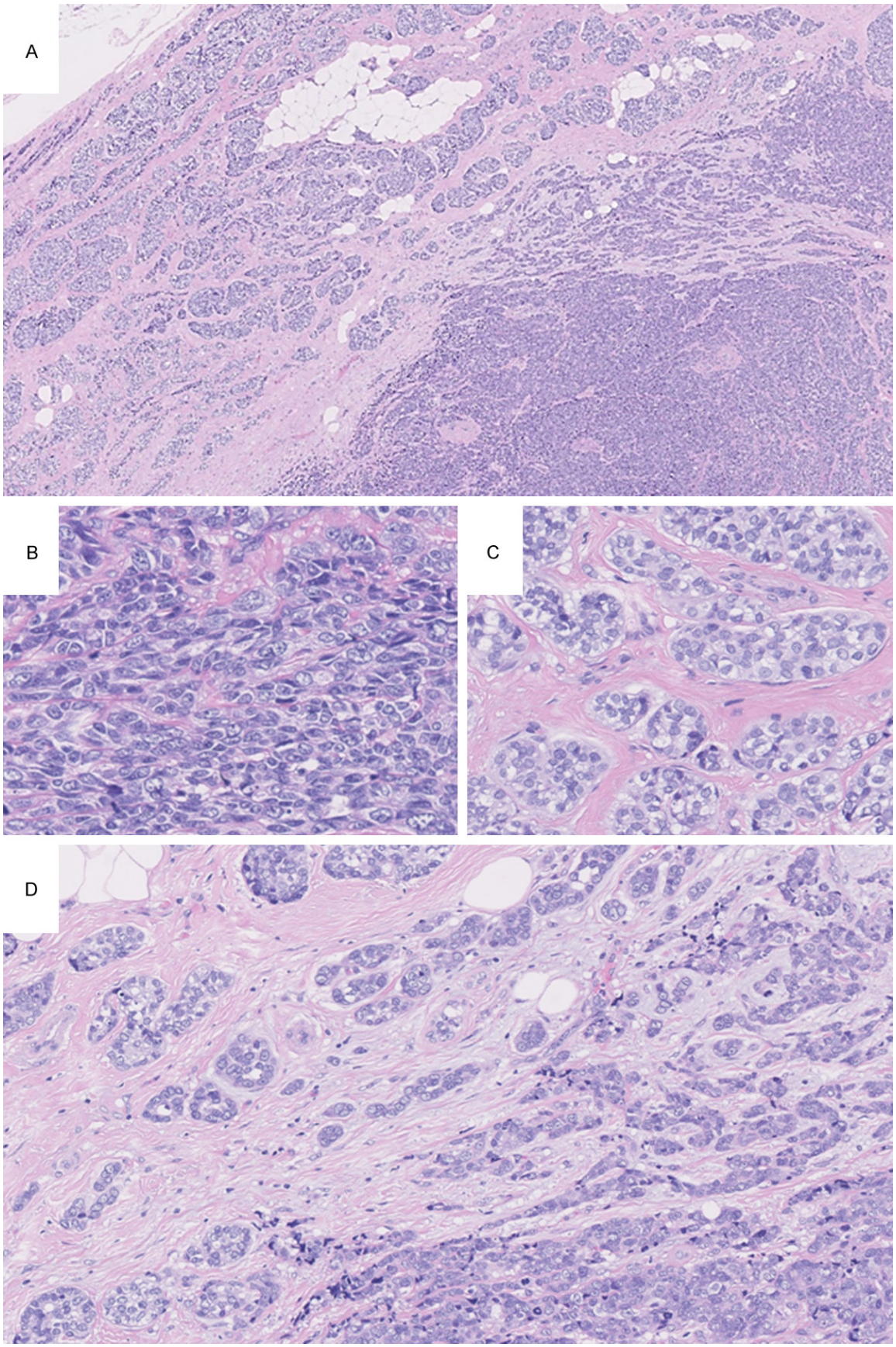
A
B
C
D

Figure 3. Histopathological findings. A. High-grade carcinoma showing a solid and trabecular growth pattern with variably-sized nests was observed, with no gland formation (lower right). Low-grade carcinoma with nested growth patterns was also present at the periphery of the tumor (upper left) (×20). B. High-power view of high-grade carcinoma showed short spindle to oval cells. The nuclear-to-cytoplasmic ratio was high; nuclei showed prominent hyperchromasia with a coarse granular chromatin pattern (×400). C. High-power view of low-grade carcinoma showed that the nuclei were smaller than those of the high-grade carcinoma, and hyperchromasia was less prominent (×400). D. The high-grade carcinoma and low-grade carcinoma seemed to show gradual transition at an area (×200).

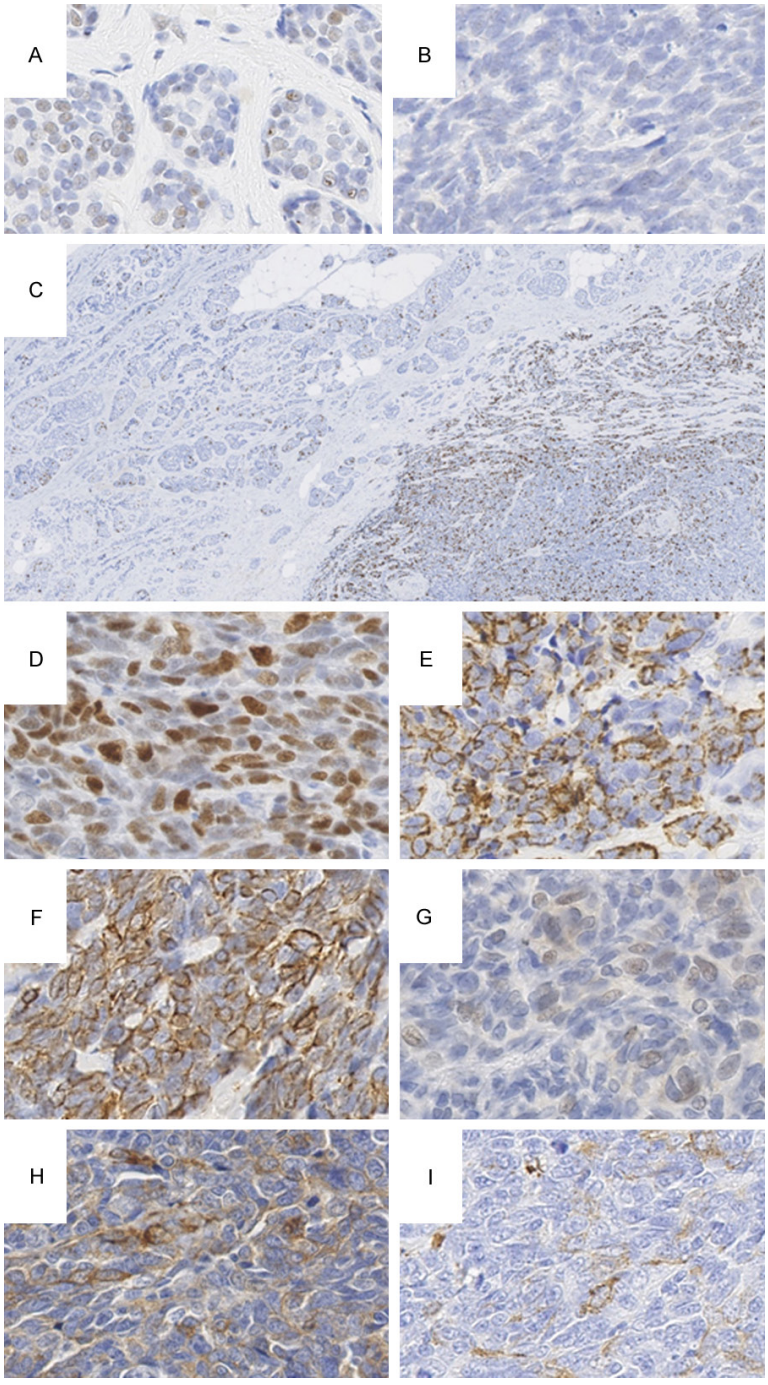

Figure 4. Immunohistochemical findings. A. Estrogen receptor was expressed in the low-grade carcinoma (×400). B. Estrogen receptor was not expressed in the high-grade carcinoma (×400). C. The Ki-67 (MIB-1) labeling index was much higher in the high-grade carcinoma (lower right) than in the low-grade carcinoma (upper left) (×20). D. Diffuse nuclear accumulation of p53 with variable intensity in the high-grade carcinoma was depicted (×400). E. Decreased expression of pan-cytokeratin (AE1/AE3) was observed in the high-grade carcinoma (×400). F. Increased expression of vimentin was identified in the high-grade carcinoma (×400). G. Some high-grade carcinoma cells expressed p63 (×400). H. Immunoreactivity for muscle-specific actin was widespread in the high-grade carcinoma (×400). I. Immunoreactivity for alpha smooth muscle actin was observed in some cells in the high-grade carcinoma (×400).

high-grade carcinoma showed variable degrees of p53 accumulation in the nuclei (**Figure 4D**), in contrast to the low-grade carcinoma, where the accumulation of p53 was scattered. In the high-grade carcinoma, each of the constituent cells showed decreased expression of pan-CK (AE1/AE3) (**Figure 4E**) and increased expression of vimentin (**Figure 4F**). The high-grade carcinoma showed immunostaining with p63 in some cells (**Figure 4G**), whereas the low-grade carcinoma did not. High-grade carcinoma cells were also immunoreactive for muscle-specific actin (MSA) (**Figure 4H**) and some cells also showed positive immunostaining for alpha smooth muscle actin (αSMA) (**Figure 4I**).

The high-grade lesion was considered to be a carcinoma with myoepithelial features showing dedifferentiation-like changes because it contained short spindle-shaped tumor cells and displayed immunoreactivity for p63, MSA, and αSMA. The tumor also showed decreased expression of pan-CK and increased expression of vimentin on IHC. The peripheral low-grade carcinoma was a luminal-type carcinoma based on the expression of ER.

Discussion

Gene expression profiling of breast carcinoma revealed that the basal-like subtype expresses genes characteristic of basal/myoepithelial cells, while the luminal subtype expresses genes characteristic of luminal mammary epithelial cells [1, 2]. These observations suggest that the phenotype of breast cancer inherits that of the cell of origin: the basal-like subtype is derived from basal/myoepithelial stem/progenitor cells, while the luminal subtype is derived from luminal (glandular) stem/progenitor cells. A more recent study, however, indicated that the majority of carcinomas of the basal-like subtype arise from luminal stem/progenitor cells rather than from basal/myoepithelial stem/progenitor cells [8]. Certain genetic events occurring at various stages of carcinogenesis can elicit the phenotypic change; this process is called dedifferentiation or transdifferentiation [6]. A phenotypic change of breast carcinoma may occur either in situ, at the primary invasive site, or at a distant metastatic site [6]. In the case presented here, it is likely that the triple-negative carcinoma with myoepithelial features, which probably belonged to the basal-like subtype, derived from a carcinoma of the luminal subtype through dedifferentiation-like progression at the primary invasive site. The former may have then superseded the latter, due to higher proliferative activity.

The carcinoma with dedifferentiation-like changes in the present case resembled a morphologically- and immunohistochemically-defined basal-like carcinoma at first glance. Morphologically basal-like carcinoma is a poorly differentiated invasive carcinoma with a high nuclear grade and brisk mitoses without tubule formation [9]. On IHC, one of the marker panels used to define basal-like carcinomas includes the following characteristics: lack of expression of ER, PR, and HER2 along with expression of CK5/6 and/or EGFR [10]. The carcinoma showing dedifferentiation-like changes in our case did not meet these criteria, as it did not express CK5/6 and EGFR. Other markers used for the detection of basal-like carcinomas are CK14 and c-kit, which are sometimes expressed [9]. Immunostaining for these markers was also negative in our case. However, expression of p63, MSA, and αSMA, in conjunction with decreased expression of pan-CK and increased expression of vimentin, suggested a myoepithelial feature; morphologically, the presence of short spindle cells also indicated this feature. On the other hand, luminal-type breast carcinomas are defined by positivity for ER and/or PR and negativity for HER2 based on IHC [11]. The expression of ER and lack of HER2 expression were observed in the peripherally situated low-grade carcinoma in our case, which was consistent with luminal-type carcinoma.

A high Ki-67 labeling index and diffuse nuclear accumulation of p53 in the carcinoma showing dedifferentiation-like changes indicated its aggressive potential. Indeed, it had probably superseded the pre-existing low-grade carcinoma located at the periphery, from which it was postulated to have originated. Rigorous follow-up should be mandatory, considering the aggressive nature of the predominant carcinoma showing dedifferentiation-like changes in this case.

In conclusion, we report an unusual case of dedifferentiation-like progression of breast carcinoma showing transition from luminal-type carcinoma to triple-negative carcinoma with myoepithelial features. At the periphery, luminal-type carcinoma was present, but this was largely displaced by highly proliferative carcinoma with myoepithelial features. The latter was probably derived from luminal-type carcinoma via phenotypic change at the primary invasive site due to genetic events.

Disclosure of conflict of interest

None.

Address correspondence to: Shogo Tajima, Department of Pathology, Shizuoka Saiseikai General Hospital, 1-1-1 Oshika, Suruga-ku, Shizuoka 422-8021, Japan. Tel: +81-54-285-6171; Fax: +81-54-285-5179; E-mail: stajima-tky@umin.ac.jp

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