

# Metaplastic Carcinoma with Extensive Chondroid Differentiation in the Breast (Chondroid Carcinoma)

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Metaplastic breast carcinoma is very rare, and metaplastic carcinoma with chondroid differentiation is even rarer. Here, we report a case of metaplastic carcinoma with extensive chondroid differentiation mimicking chondrosarcoma that was challenging to diagnose. The tumor was characterized by an abundant chondromyxoid matrix. The definitive area of classic invasive ductal carcinoma was minimal. The peripheral portion of the tumor showed increased cellularity with pleomorphism and definitive invasive growth. Tumor cells in the chondrosarcomatous areas were diffusely immunoreactive for S-100 protein, patchy positive for cytokeratin, but negative for epithelial membrane antigen (EMA). Tumor cells in carcinomatous areas were diffusely positive for cytokeratin, S-100 protein, and patchy positive for EMA. In both areas, tumor cells were negative for smooth muscle actin (SMA) and CD34, while oncoprotein p53 was overexpressed. When pathologists encounter breast tumors with chondroid differentiation, careful sampling and immunohistochemistry for cytokeratin and SMA are most helpful to differentiate metaplastic carcinoma from malignant phyllodes tumor and malignant adenomyoepithelioma.

**Key Words:** Breast, carcinoma, metaplasia, cartilage, immunohistochemistry

## INTRODUCTION

In the human breast, the incidence of cartilaginous lesion is very rare. In less than 5% of breast carcinomas, part or all of the carcinomatous epithelium is transformed into a mesenchymal histo-

logical pattern by metaplastic processes.<sup>1</sup>

Metaplastic carcinomas (MCs) are highly heterogeneous groups of tumors that are characterized by an admixture of adenocarcinoma with dominant areas of spindle cell, squamous, and/or mesenchymal differentiation.<sup>1,2</sup> Heterologous mesenchymal elements range from areas of bland to frank sarcoma such as chondrosarcoma (CS), osteosarcoma, rhabdomyosarcoma, liposarcoma or fibrosarcoma, among which cartilaginous and osseous metaplasia are the most commonly encountered.<sup>3</sup>

We report a case of MC with extensive chondroid differentiation (so-called chondroid carcinoma), mimicking CS. Differentiating diagnoses was difficult, and possible diagnoses included malignant phyllodes tumor (PT), malignant adenomyoepithelial tumor with chondroid matrix, and MC with CS.

MCs require treatment as invasive ductal carcinomas, thus axillary lymph node dissection must be considered. As a result, differential diagnosis for MC is essential and can be achieved by careful sampling and immunohistochemistry for panels of epithelial markers such as cytokeratin and EMA, and myoepithelial markers such as S-100 protein and SMA.<sup>3-5</sup>

## CASE REPORT

A 59-year-old woman developed a breast lump in the right upper central area. She had received hormone replacement therapy for 1 year. Ultrasonogram revealed a 2.3 × 0.9 cm irregularly marginated mass with posterior enhancement. How-

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ever, Doppler ultrasonography demonstrated no increase in blood flow. Mammography showed an asymmetric parenchymal lesion, which appeared to be a malignant tumor. A partial mastectomy was performed, based on the diagnosis of malignant PT, using ultrasonography-guided core needle biopsy. The specimen obtained by partial mastectomy measured 17 × 13 × 2 cm. The cut surface showed a 3.3 × 1.3 cm mass with a lobulated margin. The cut surface of the tumor was whitish-gray, solid, and devoid of necrosis.

On histological examination, the tumor had a strikingly abundant chondromyxoid matrix with variable cellularity. The tumor cells were relatively small, monomorphous and round. However, a mild degree of anisocytosis was identified and mitotic figures were frequent, with an average of 5 mitotic figures per 10 high power fields. The tumor had an invasive lobulated margin. Tumor cells were more cellular in the peripheral margin of the nodules and had perinuclear clear spaces, suggesting a malignant tumor with chondrosarcomatous features.

Although definitive carcinomatous areas were minimal, tumor cells in those areas were diffusely positive for cytokeratin and S-100 protein, and were patchy positive for EMA (Fig. 1). In chondrosarcomatous areas, tumor cells were diffusely immunoreactive for S-100 protein and patchy positive for cytokeratin (Fig. 2), but were negative for EMA. In both chondrosarcomatous and carcinomatous areas, tumor cells stained negatively for both smooth muscle actin (SMA) and CD34 (Fig. 3). Estrogen and progesterone receptors were

absent. Tumor cells were found to overexpress the p53 oncoprotein, but not the HER-2/neu oncoprotein. The tumor was diagnosed as MC with chondroid differentiation, a so-called chondroid carcinoma.

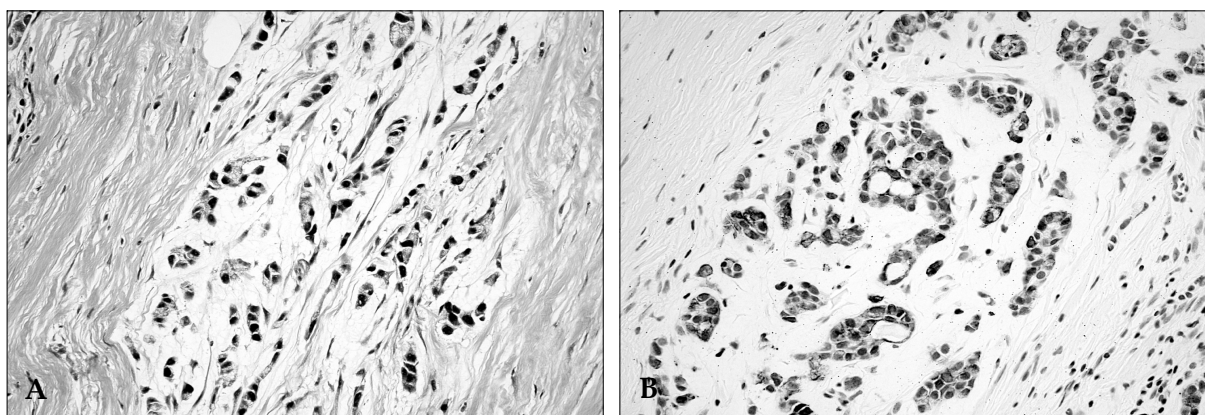
Postoperatively, the patient received 6 cycles of chemotherapy with actinomycin-D and cyclophosphamide. In addition, external radiation therapy (5940 cGy) was performed. The patient was doing well at the 5-month postoperative follow-up, without evidence of tumor recurrence or metastasis.

## DISCUSSION

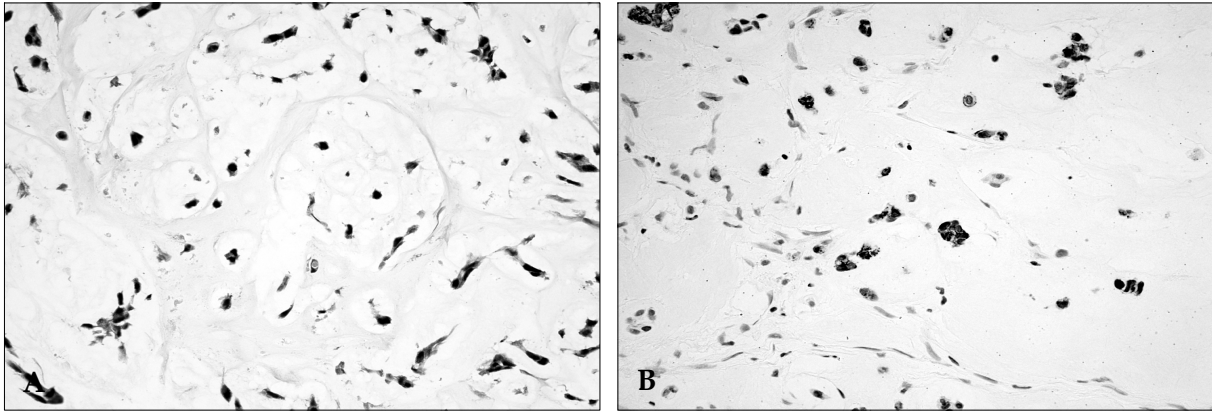
Cartilaginous lesions are very rare in the breast. Benign tumors, specifically chondrolipoma and pleomorphic adenoma, may contain benign chondroid tissue, but the presence of malignant chondroid tissue is indeed rare.

In the primary breast tumor, chondrosarcomatous lesions may occur in three different forms: a pure CS, as a heterologous component of a malignant PT or as a chondrosarcomatous differentiation in a MC.<sup>4</sup> In less than 5% of breast carcinomas, part or all of the carcinomatous epithelium is transformed into a nonglandular mesenchymal tissue by metaplastic processes.<sup>1</sup>

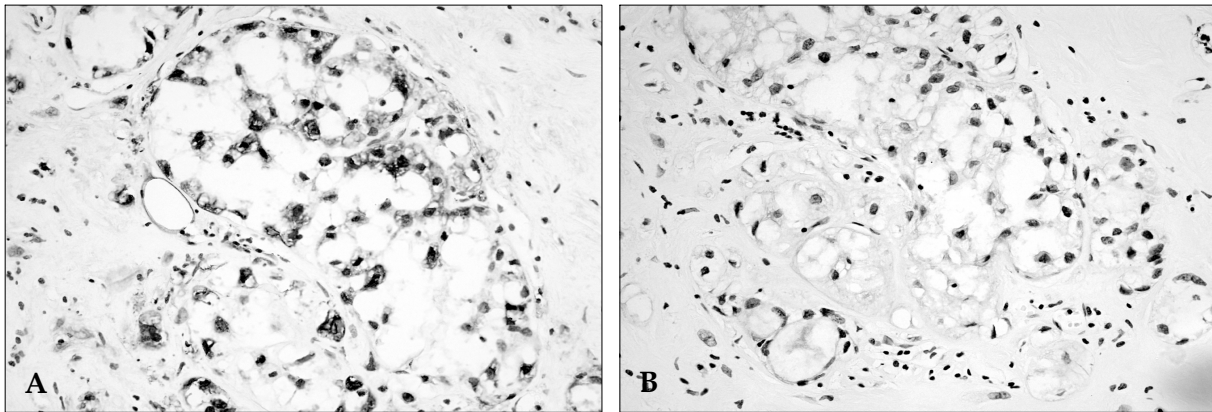
A case of malignant PT with chondrosarcomatous overgrowth was reported in which the chondrosarcomatous component constituted over 80% of the tumor volume.<sup>4</sup> If not well sampled for the areas of characteristic leaf-like pattern or benign



**Fig. 1.** The tumor cells grow in highly infiltrative pattern. In that carcinomatous area (A), the tumor cells are diffusely positive for cytokeratin (B).



**Fig. 2.** The tumor shows extensive chondroid matrix with perinuclear halo (A). In that chondrosarcomatous area, the tumor cells are patchy-positive for cyokeratin (B).



**Fig. 3.** Immunostaining shows diffuse positive reactivity with S-100 protein (A), but negativity with smooth muscle actin (B).

ductal epithelium, the malignant PT may be misdiagnosed as pure CS, especially in the case of a tumor with extensive chondrosarcomatous overgrowth. Therefore, complete and meticulous tumor sampling is very important as demonstrated by the present case. Even though PTs are biphasic tumors, cyokeratin is not expressed in the stromal element. Moreover, CD34 and bcl-2 are more frequently expressed in PTs than in MCs.<sup>3</sup> The tumor in our present case was negative for CD34 and had no characteristic features suggesting PT, such as cleft-like spaces or benign ductal elements. Immunohistochemistry for panels of epithelial markers, such as cyokeratin and EMA, can help differentiate malignant PT from MC with heterologous chondrosarcomatous elements.<sup>3,4</sup>

MCs are highly heterogeneous groups of tumors and can be classified into broad subtypes

according to the phenotypic appearance of the tumor: purely epithelial or mixed epithelial and mesenchymal. MCs are characterized by an admixture of adenocarcinoma with dominant areas of spindle cell, squamous, and/or mesenchymal differentiation.<sup>1,2</sup> Heterologous mesenchymal elements range from areas of bland chondroid and osseous differentiation to frank sarcoma such as chondrosarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma or fibrosarcoma, among which cartilaginous and osseous metaplasia are the most commonly encountered.<sup>3</sup> MC with sarcomatoid areas are much rarer than those with benign metaplasia. MCs predominantly composed of metaplastic elements with a minor component of invasive adenocarcinoma have been designated by varied terminology, including carcinosarcoma, sarcomatoid carcinoma, spindle cell carcinoma,

carcinoma with pseudosarcomatous metaplasia, and a spindle cell variant of MC. These diverse appellations can lead to confusion when diagnosed. Currently the favored explanation for the origin of the mesenchymal component of these tumors is a metaplastic change originating from epithelial or myoepithelial elements.<sup>2</sup> Even though the frequency of metaplasia, including both homologous and heterologous tissues in the breast, tends to be underreported, heterologous metaplasia is reported to occur in 0.2% of breast carcinomas.<sup>6</sup>

Myoepithelial neoplasms of the breast are extremely rare and have been thought to behave as low-grade malignant tumors with the potential to recur locally and, very rarely, to metastasize. The characteristics of malignant myoepithelioma (myoepithelial carcinoma) overlap with those of MCs in that both tumors express S-100 protein and cytokeratins.<sup>3</sup> SMA may be positive in epithelial areas in 25% of MCs, which indicates that MCs show strong immunohistochemical evidence of myoepithelial differentiation, in addition to expressing basal-specific cytokeratins.<sup>3,7</sup>

In summary, immunohistochemistry for epithelial markers, such as cytokeratin and EMA, is important to rule out pure sarcoma or PTs. Immunohistochemistry for SMA is useful to distinguish MC with chondroid differentiation from myoepithelial carcinoma with a chondroid matrix. Popnikolov et al. reported that increased EMA expression in carcinomas with chondroid matrix contrasts with decreased EMA expression in MCs with spindle cells, which tend instead to show higher expression of SMA.<sup>5</sup> Because MCs often appear to originate from poorly differentiated ductal carcinoma, they are usually negative for estrogen and progesterone receptors.<sup>1,8</sup> Even though overexpression of p53 supports a diagnosis of MC, it is only observed in fewer than 50% of the cases. In spindle cell type and matrix-producing type MCs, the frequency of HER-2/neu overexpression is variable, ranging from negative to 33%.<sup>5,9,10</sup> This suggests that HER-2/neu may not be helpful in differentiating those entities. The tumor in our present case was negative for hormonal receptors and HER-2/neu, but overexpressed p53 and had a high proliferation index.

Because MCs are so rare, and long-term follow-

up data in large series of cases are scarce, it has been difficult to predict the clinical behavior of these tumors. MCs with osteocartilaginous heterologous elements were reported to have a better prognosis, because axillary lymph node metastases are less frequent than in nonmetaplastic invasive ductal carcinoma.<sup>10</sup> Large collective case studies are needed to explore the clinical and physiological behavior of these tumors and to clarify the therapeutic options. MCs require treatment, as would the usual mammary carcinoma. According to the tumor stage, axillary lymph node dissection should be considered. Unfortunately, lymph node dissection was not undertaken in this case because it was originally misdiagnosed as malignant PT with chondrosarcomatous elements. However, the patient has been doing well after post-operative chemotherapy and radiation therapy.

In conclusion, when a pathologist encounters a malignant breast tumor with chondroid elements, MC with chondroid differentiation should be considered, even though an epithelial component may be minimal or absent. Thorough sampling and immunohistochemistry for cytokeratin and SMA are essential to confirm the diagnosis.

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