# Not all that glitters is gold – HER2 in a case of metaplastic breast carcinoma with heterologous mesenchymal differentiation

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## ABSTRACT

Human epidermal growth factor receptor 2 (HER2) is an important prognostic and predictive tool in the treatment of breast carcinoma, as the positive (HER2 3+) or the equivocal stain (HER2 2+) associated to amplification of the *HER2* gene using in situ hybridisation techniques (ISH), on one side is related to more aggressive neoplasms, while on the other one is a predictor of anti-HER2 therapies response, with good results.

Metaplastic breast carcinomas (MTBC) comprehend a wide spectrum of rare neoplasms, with different histological subtypes and variable prognosis and clinical course. Most of them are very aggressive diseases, usually with a triple negative molecular phenotype (TBNC) and high proliferation index. For these reasons, although surgery is widely used as first line treatment, some patients undergo neoadjuvant chemotherapy (NACT), with general poor response.

We present an exceeding rare case of metaplastic breast carcinoma with heterologous mesenchymal differentiation (chondromyxoid), diagnosed as no special type (NST) breast carcinoma on core needle biopsy. Ki-67 index was high (60% of neoplastic cells) and HER2 was assessed as equivocal (2+) on immunohistochemical (IHC) stain, with *HER2* being amplified on FISH, so the patient underwent NACT associated to anti-HER2 drugs, with almost no response.

This challenging case suggests that, despite HER2 status is a strong and well know predictive biomarker in breast carcinomas, recognising the correct histotype is mandatory, especially in preoperatory setting, as despite of the routinary predictive factors, it can drastically change the management of the patient.

**INTRODUCTION**

The human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor which belong to the Human Epidermal Receptor family. It is a well study prognostic and predictive factor, with a dual role, as it is usually expressed in clinically aggressive tumours and it is related to poor prognosis, but, on the other hand, it is targetable by anti HER2 therapies (trastuzumab, pertuzumab, lapatinib, tucatinib, and neratinib) in adjuvant, neoadjuvant and metastatic settings [1].

The overall proportion of breast carcinomas with *HER2* amplification is supposed to be around 15%[2], most of them being no special type breast carcinomas (NST). Regarding special types of carcinomas, HER2 can be found amplified in a small proportion of pleomorphic lobular carcinoma, mucinous carcinoma and carcinoma with apocrine differentiation.

In some recent studies, the theory that non only molecular expression, but also levels of HER2 protein can influence the amount of response to target therapy is proposed [3-4]. Indeed, some authors detect a higher amount of pathological complete response in HER2 3+ cases (55-70%) compared to HER2 2+, amplified tumors (17-20%). The latter results are quite comparable to those found in breast cancers that do not express HER2 (15-25%), so in the last few years an increasing use of anti-HER2 antibody-drug conjugates in these neoplasms is seen [3-4]. Consequently, anti-HER2 therapies are often proposed in combination with chemotherapy in cases of high-grade neoplasms, even if HER2 status is not 3+.

Metaplastic breast carcinomas were first described by Huvos and colleagues in 1973[5] and account for less than 5% of all breast tumors[6]. They comprehend a wide spectrum of lesions, characterized by the total or partial replacement of the typical glandular component of breast carcinomas with other cellular types, as squamous and sarcomatoid, including heterologous elements. The 5$^{th}$ edition of World Health Organisation (WHO) classification of breast tumors divided metaplastic breast carcinomas in low-grade adenosquamous carcinoma, fibromatosis-like, pure squamous cell carcinoma, pure spindle cell carcinoma, metaplastic carcinoma with heterologous mesenchymal differentiation and mixed metaplastic carcinoma[7]. Most of them are triple negative neoplasms, with variable

proliferation index depending on the subtypes. Usually, the first line treatment is surgical excision, followed by radiotherapy and/or systemic therapy based on the final pathological report and the type of surgery.

We present an exceeding rare case of metaplastic carcinoma with heterologous mesenchymal differentiation (chondromyxoid), misdiagnosed in the preoperative core needle biopsy and reported as NST breast carcinoma. For the high proliferation index and HER2 equivocal score on IHC, with FISH being positive for *HER2* amplification, patient underwent chemotherapy associated to anti-HER2 drugs. The tumor demonstrated poor clinical, radiological and pathological response, at it was recognised as metaplastic carcinoma only after the systemic treatments.

We conclude that even though HER2 is a good predictive marker of response to target therapy, it is mandatory to correlate the prognostic and predictive markers to the tumor histotype to optimise the patient management.

**CASE REPORT**

In August 2021, a 43 years-old woman, without previous clinical history, came to our attention after eight months of NACT associated to trastuzumab for a 25 mm lesion in the upper-inner quadrant of the breast, with clinical and radiological positive axillary lymph nodes. The diagnosis was made in another hospital and the pathological report described a high grade, NST invasive carcinoma. The immunohistochemistry showed negative stains for estrogenic and progesterone receptors (ER and PR), the Ki-67 index was highly (60% of neoplastic cells) and HER2 showed weak to moderate, complete membranous stain, in 70% of neoplastic cells (2+). FISH test demonstrated *HER2* amplification.
After chemotherapy, imaging analyses revelated the persistence of the disease both in the breast and in the lymph nodes and the patient underwent surgery, consisting in quadrantectomy (for the favourable ratio between tumor size and residual breast tissue) followed by axillary dissection.

Adjuvant treatment consisted in adjuvant radiotherapy both on breast and on axillary region and anti-HER2 drugs. The patient is free of disease at the time of writing.

**PATHOLOGIAL AND IMMUNOISTOCHEMICAL FEATURES**

Macroscopically the lesion had enhanced consistency, was firm and with a myxoid appearance, 22x20 mm wide. Fifteen lymph nodes were isolated from the axillary adipose tissue.

Microscopically the tumour consisted in a mixture of mesenchymal and epithelioid elements, strictly intermixed, with moderate to high grade pleomorphism, arranged in sheets, lobules and nodules, extensively infiltrating in breast parenchyma. The mesenchymal component was composed by ovoidal to spindle cells, with eosinophilic cytoplasm and moderate to high grade atypia, arranged in small nests, chords, with sparse single elements, in a myxoid and chondroid background. The epithelioid cells had large size, abundant cytoplasm, prominent nucleoli and high-grade atypia. Mitotic count in the epithelioid component was high, with mitosis up to 27 in 0,65 mm field diameter. The lesion was extensively sampled, for a correct evaluation of the amount of residual tumor and only scattered areas of oedema, fibrosis and fibrosclerosis were found (*Figure1*).

Immunohistochemistry was performed, confirming the dual cell population, with metaplastic component showing positivity to S100 and Cytokeratin K903 (34BE12), while epithelioid elements staining focally positive to CK AE1/AE3, and CAM 5.2 (*see Figure1*).

Regarding the breast prognostic and predictive factors, estrogen (ER) and progesteron (PR) receptors were not expressed in the nuclei of neoplastic cells. Ki-67 was present in about 60% of cancerous elements. HER2 presented a complete, weak to moderate membranous stain, so score 2+ was assess according to the current ASCO/CAP guidelines, and FISH was performed, showing *HER2* amplification. The same molecular phenotype was found on the initial core biopsy.

According to the 5$^{th}$ edition of WHO classification of breast tumors, the diagnosis of metaplastic breast carcinoma with heterologous mesenchymal differentiation (chondroid and myxoid) was made. Nottingham Bloom Richardson grading system was used in the assessment of histological grade, and tumor had score 9 (tumor tubule formation 3; tumor pleomorphism 3; mitotic count 3). Lymphatic and vascular invasion were present, while infiltration of perineural spaces was not found. Excisional margins were microscopically negative. Out of 15 lymph nodes isolated from the adipose tissue of the axillary region, 2

were positive for macro metastasis and 1 for micro metastasis. The case was studied by two breast pathologists.

Tumoral response to therapy was evaluated using two methods. Pinder score, which evaluates the ratio between the primary tumour bed and the residual one in breast tissue, and the presence of residual metastasis associate to the possible presence of chemotherapy effects, demonstrated the absence of significative tumoral regression in breast tissue and the presence of residual disease, in the absence of neoadjuvant therapy effects in lymph nodes. MD Anderson Residual Cancer Burden (RBC) assess different variables of both the primary tumours and lymph nodes (extension of the primary bed area, cancer cellularity, percentage of *in situ* disease in the breast tissue, numbers of positive lymph nodes and maximum diameter of lymph node metastasis). Our case presented a score III, which means the presence of extensive residual tumoral component.

**DISCUSSION**

The case herein described presents different challenging aspects. Indeed, in clinical practice HER2 positivity is one of the best predictive factors for target therapy, as high Ki-67 index predict response to NACT. Here, despite the tumour presents both *HER2* amplification and a high Ki-67 index, the histological subtype, correctly diagnosed in the post-NACT pathological report, demonstrates that other factors have an important role in predict the amount of pathological response as well.

For the high Ki-67 index, associated to the absence of ER and PR expression, patients underwent NACT. This decision is commonly made for TNBC, as in most cases patients experience significant amount of pathological response. Regarding metaplastic breast carcinomas, however, results are poor as, although occasionally complete pathological response (pCR) is described in literature[8-10], most of the studies reveals low rates of pCR, ranging from 10% to 17% compared to about 75% in TNBC.[8] Moreover, some cases of disease progression during NACT are reported, ranging from 27% to 62,5% of cases[8, 12, 14], leading to a delay of the surgical excision of the neoplasm and worse survival rates.

Our case was treated with anti-HER2 drugs, for the equivocal IHC score and *HER* amplified FISH results. HER2 is not usually used as a strong predictive factor in the neoadjuvant

treatment of MTBC, with only occasion cases described[8-13]. Results are limited, as Wong [8] and colleagues describe only 2 cases of *HER2* amplified MTBC which did not respond to target treatment and Han[13] reports that in his cohort out of 5 patients experiencing pCR, only one of them has *HER2* amplified.

Moreover, there is some evidence that the tumor subtype of MTBC can represent a predictive factor of good pathological response to therapy more than the immunophenotype. Indeed, some cases of matrix-producing MTBC show good pathological response, as one case reported by Wong[8] and 3 out of 5 cases in Han study[13], while other authors describe good results with target therapies in sarcomatous (ifosfamide and anthracycline), epidermoid (platinum based) and squamous cell (EGFR target-based therapy) MTBC[14].

Our case demonstrates that, even though HER2 is one of the most useful, reproducible and simple predictive markers of response to neoadjuvant systemic treatment in breast carcinomas, it has always to be related to the histological type of carcinoma, which can also widely influence the response to treatments.

**Figure 1**

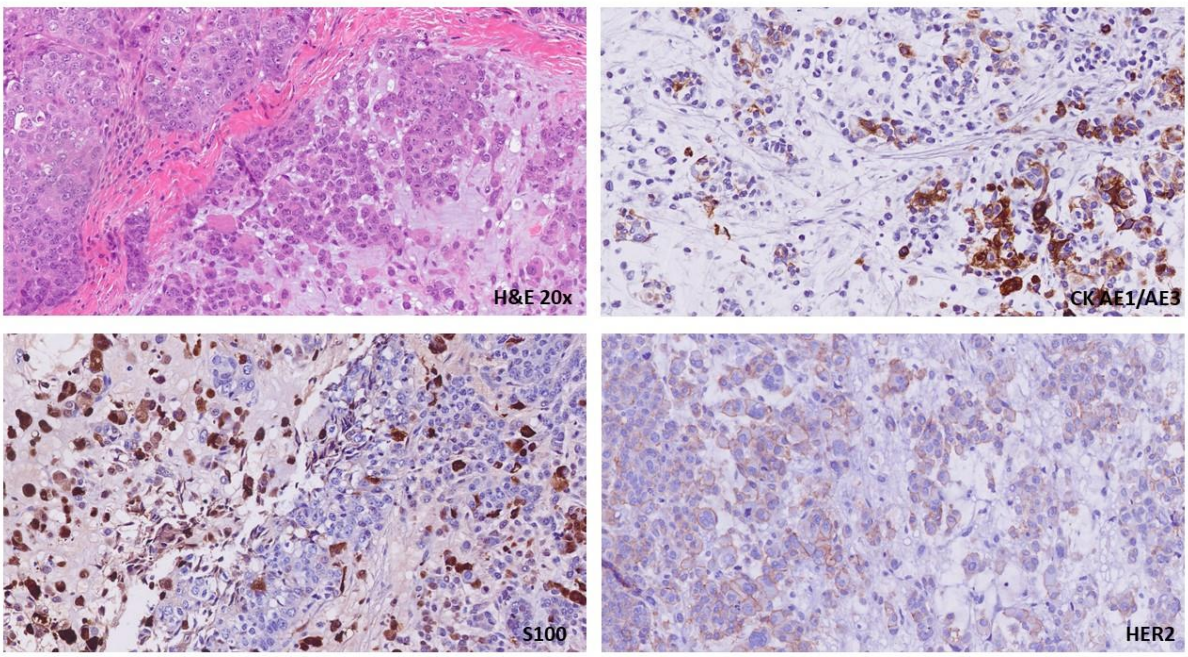


Figure 1: the tumor shows two cells types, with a mesenchymal, ovoidal to spindle cell component, dispersed in a chondroid and myxoid background, mixed to epithelioid, basaloid elements. Cells are arranged in nests, chords and dischoesive single elements with moderate to high grade cytological atypia. Epithelioid population demonstrates scattered positive stain to CK AE1/AE3, while metaplastic cells strong react to S100. HER2 shows a complete, weak to moderate, membranous expression, with equivocal result (2+).

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