

ORIGINAL ARTICLE

Metaplastic breast carcinomas are negative for Her-2 but frequently express EGFR (Her-1): potential relevance to adjuvant treatment with EGFR tyrosine kinase inhibitors?

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Background: Metaplastic carcinomas (MCs) of the breast rarely express steroid receptors and Her-2, which minimises the options for adjuvant treatment in patients with advanced disease.

Aims: To investigate the possible eligibility of patients with MCs for epidermal growth factor receptor (EGFR) targeted treatment.

Methods: Immunohistochemical assessment of the expression of steroid receptors and four members of the EGFR/Her family (EGFR/Her-1–4) in 20 MCs (eight with heterologous elements, seven spindle cell MCs, four carcinosarcomas, and one matrix producing carcinoma). Fourteen of the 20 MCs were positive for EGFR (Her-1). Among these cases, 1+, 2+, and 3+ reactivity were seen in two, four, and eight cases, respectively. Her-2 was only present in one MC with 1+ reactivity. Her-3 (1+ reactivity), Her-4 (2+ reactivity), and the androgen receptor (2+ reactivity) were also expressed by one tumour. Oestrogen and progesterone receptors (3+ reactivity each) were detected in the epithelial component only of two carcinosarcoma-type MCs.

Conclusions: MCs express EGFR considerably more frequently than the types of breast carcinomas that have been investigated previously. Although molecular analyses for possible genetic alterations in the EGFR might be required, these results suggest that women suffering from this aggressive form of breast carcinoma might benefit from treatment with protein kinase inhibitors, such as gefitinib.

Because metaplastic carcinomas (MCs) of the breast rarely express steroid receptors,^{1–3} adjuvant endocrine treatment is usually not an option for these patients. Whereas adjuvant chemotherapy with Her-2 monoclonal antibodies (trastuzumab) is currently being tested in randomised clinical trials of patients suffering from metastatic breast carcinoma,^{4,5} treatment with monoclonal antibodies (Cetuximab, ABX-EGF, RH3, and MDX-447) against EGFR (Her-1) and small molecule inhibitors of EGFR—such as gefitinib (Iressa, ZD1839), Erlotinib, and EKB-569—is currently being tested in clinical trials of patients suffering from lung and colorectal cancer.⁶ The aim of our study was to evaluate the expression of steroid receptors and four members of the EGFR/Her family (EGFR/Her-1–4) in a collection of 20 MCs with no areas of squamous differentiation.

MATERIALS AND METHODS

Twenty MCs without areas of squamous differentiation (eight MCs with heterologous elements, seven spindle cell MCs, four carcinosarcomas, and one matrix producing carcinoma) were retrieved from the files of the department of pathology, Medical University of Graz, Austria. In each case, the haematoxylin and eosin diagnosis was verified by several basal cell-type cytokeratin and myoepithelial markers (such as CD10, smooth muscle actin, p63, maspin, and S100) in MCs with weak cytokeratin expression to rule out primary sarcoma of the breast.⁷ Formalin fixed, paraffin wax embedded tissue blocks were cut into 4 µm thick serial sections that were mounted on precoated slides. The sections were dewaxed, rehydrated, and rinsed in distilled water. Immunohistochemical assays for EGFR (Her-1), Her-2, Her-3, Her-4, and the androgen receptor were performed on consecutive paraffin wax sections using standardised automated procedures on a Dako Autostainer (DakoCytomation,

Glostrup, Denmark). For EGFR, the EGFR pharmDX kit (Dako), and for Her-2, the HercepTest (Dako), was used according to the manufacturer's instructions. In brief, sections were rinsed in phosphate buffered saline. Antigen retrieval for Her-2, Her-3, Her-4, and the androgen receptor was achieved by heating in a 1/10 dilution of epitope retrieval solution (Dako) at 98°C for 40 minutes, and for EGFR in a proteinase K solution (Dako) for five minutes. After cooling for 20 minutes, sections were rinsed in tap water and then loaded into the Dako autostainer (Dako), according to the computer generated reagent map. The Dako ChemMate detection kit was also used for antigen receptor visualisation.

Antigen retrieval for oestrogen and progesterone receptors was achieved by microwave heating in citrate buffer (pH 6.0) for 30 minutes at 160 W. For the following standardised procedures a Ventana (Illkirch, France) autostainer and a Ventana "iview" detection system were used.

Thereafter, all slides were gently rinsed with warm tap water, counterstained with haematoxylin, dehydrated, and mounted after xylol treatment with Entellan (Merck, Darmstadt, Germany). Table 1 summarises the antibodies and methods used.

Negative controls included substitution of the primary antibody with normal serum or phosphate buffered saline, omission of the secondary antibody, and incubation of the primary antibody solution with lymphoid tissue, respectively. For EGFR and Her-2 the control cell lines provided by the manufacturer (Dako) were also used in each run as negative and positive controls. Normal pancreatic or liver tissues were used as positive external controls for Her-3 and Her-4. In each case, the intensity of the immunostaining (negative, 1+, 2+, or 3+) and the percentage of tumour cells with positive

Abbreviations: EGFR, epidermal growth factor receptor; MC, metaplastic breast carcinoma; NSCLC, non-small cell lung cancer

Antigen	Test kit or antibody clone (manufacturer)	Dilution	Incubation time	Antigen retrieval
EGFR (Her-1)	EGFRpharmDX™ (Dako*)	Prediluted	30 minutes	Proteinase K solution for 5 minutes
Her-2	HercepTest™ (Dako*)	Prediluted	30 minutes	1/10 epitope retrieval solution (Dako) at 98°C for 40 minutes, then cooling in epitope retrieval solution for 20 minutes
Her-3, Ab-8	Clone SGP1 (Lab Vision†)	1/50	60 minutes	
Her-4, Ab-4	Clone HFR-1 (Lab Vision†)	1/50	30 minutes	
AR	Clone AR441 (Dako*)	1/50	30 minutes	
ER	Clone 6F11 (Ventana‡)	Prediluted	30 minutes	Citrate buffer (pH 6.0) in microwave (160 W) for 30 minutes
PR	Clone 1A6 (Ventana‡)	Prediluted	30 minutes	

*Glostrup, Denmark; †Fremont, California, USA; ‡Illkirch, France.
AR, androgen receptor; EGFR, epithelial growth factor receptor; ER, oestrogen receptor; PR, progesterone receptor.

staining were assessed according to the manufacturer’s guidelines (Dako): 3+ membranous staining of more than 10% of tumour cells was required for Her-2 overexpression, and cytoplasmic only staining of EGFR was considered negative. All slides were evaluated independently by both authors. Those rare cases in which disagreement occurred were re-evaluated using a multihedded microscope; a final agreement was reached in all cases.

RESULTS

Table 2 summarises the clinicopathological features of the 20 MCs. Histologically, three subtypes were evident, namely: (1) solid spindle cell proliferations with large areas of heterologous elements—that is, chondroid or osseus differentiation (nine cases including one matrix producing carcinoma; fig 1C and E); (2) pure spindle cell proliferations, which mostly exhibited interlacing spindle cell fascicles or trabeculae

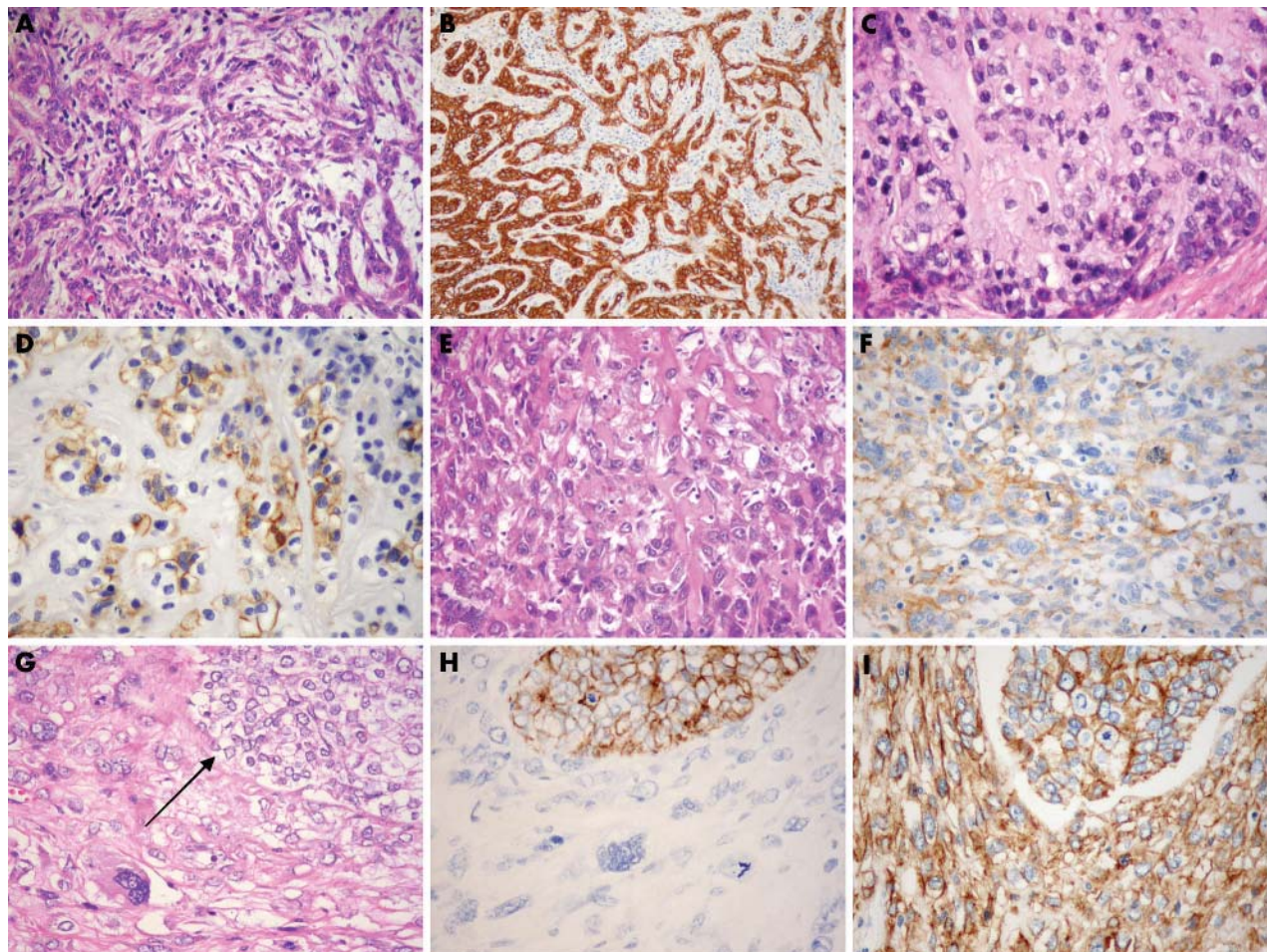


Figure 1 (A) A metaplastic breast carcinoma (MC) with spindle cells arranged in an anastomosing trabecular pattern (haematoxylin and eosin staining; original magnification, ×400), showing (B) 3+ epidermal growth factor receptor (EGFR) staining (original magnification, ×200). (C) An MC with chondroid differentiation (haematoxylin and eosin staining; original magnification, ×400) showing (D) 2+ EGFR staining (original magnification, ×400). (E) An MC with osseus differentiation (haematoxylin and eosin staining; original magnification, ×400) showing (F) 1+ EGFR staining; original magnification, ×400. (G) An MC of the carcinosarcoma subtype showing a high grade invasive ductal carcinoma (arrow) set in a highly polymorphic sarcomatoid spindle cell background (haematoxylin and eosin staining; original magnification, ×400). (H) Pan-cytokeratin staining highlighting the epithelial component of the carcinosarcoma shown in (G) (original magnification, ×400). (I) Coexpression of EGFR in the sarcomatoid and in the epithelial component of the same case (original magnification, ×400).

Table 2 Clinicopathological features of metaplastic breast carcinomas

Case/Histology	Age	T stage	N stage (n+/n)*
1 Spindle/het	64	pT3	pN1a /1/14)
2 Spindle/ep/het	91	pT1c	pN0
3 Spindle/ep/het/GC	37	pT2	pN1a (3/14)
4 Spindle/het/GC	62	pT2	pNx (0/1)
5 Spindle/het/GC	53	pT3	pN0 (0/12)†
6 Spindle/het/GC	41	pT2	pNx
7 Spindle/mat	60	pT1c	pN0 (0/9)
8 Spindle/het/GC	45	pT3	pN0 (0/37)‡
9 Spindle/het/apo	77	pT2	pN1a (3/12)
10 Spindle/fasc	75	pTx	pNx
11 Spindle/ep/GC	39	pT2	pN1a (1/18)
12 Spindle/fasc	73	pT2	pN0 (0/9)
13 Spindle/fasc	77	pT2	pN0 (0/10)
14 Spindle/fasc	74	pT4	pN0 (0/19)
15 Spindle/fasc	51	pT4a	pN0 (0/7)‡
16 Spindle/fasc	81	pT4c	pNx
17 Casa/spindle/GC	43	pT3	pN2a (5/12)
18 Casa/spindle	52	pT4c	pNx
19 Casa/spindle/fasc	44	pT1c	pN0 (0/9)
20 Casa/spindle/fasc	81	pT2	pNx

*n+/n, positive lymph nodes/total number of lymph nodes; †lung metastases 2 years after diagnosis of the primary tumour; ‡local recurrence 2 years after diagnosis of the primary tumour. apo, apocrine features; casa, carcinosarcoma; ep, epithelioid; fasc, fascicular; GC, giant cells; het, heterologous elements; mat, matrix producing.

arranged in a whorled pattern, often concentrated around pre-existing ducts (seven cases; fig 1A); and (3) carcinosarcomas with a high grade invasive ductal carcinoma set in a sarcomatoid spindle cell or highly polymorphic background (four cases; fig 1G). Using the World Health Organisation criteria,² all cases (including the invasive ductal component of the carcinosarcomas) qualified as high grade tumours.

Immunohistochemically, 14 of the 20 MCs were positive for EGFR (table 3). Among these cases, 1+, 2+, and 3+

reactivity was seen in two, four, and eight cases, respectively. The percentage of tumour cells with 1+ EGFR immunoreactivity was 20%, and the percentage with 2+ and 3+ EGFR reactivity was 20–40% (mean, 25%) and 50–100% (mean, 76%), respectively.

Her-2 was only present in the spindle cells of one MC (1+ reactivity, not overexpressed) and in the epithelial component of two carcinosarcoma-type MCs (1+ and 2+ reactivity). Her-3 (1+ reactivity), Her-4 (2+ reactivity), and the androgen receptor (2+ reactivity) were positive in the spindle cells of one tumour and in the epithelial component of one carcinosarcoma-type MC (1+ and 2+ reactivity). Oestrogen and progesterone receptors (3+ reactivity each) were detected in the epithelial component only of two carcinosarcoma-type MCs. One carcinosarcoma-type MC (fig 1) showed coexpression of EGFR in the sarcomatoid and carcinomatous areas.

DISCUSSION

MCs comprise a very heterogeneous group of neoplasms, which show immunohistochemical evidence of myoepithelial differentiation ranging from “carcinomatous types”, with strong expression of basal cell type cytokeratins, to “sarcomatoid types”, with weak or absent cytokeratin expression.^{3–7,13} The five year survival rates of MCs vary considerably within the range of 28% to 68%,^{11–15} and some subtypes (especially carcinosarcomas) are very aggressive tumours that can present clinically as massive lesions.² Eight of our 20 MCs were large stage pT3 or pT4 tumours (table 2). Two patients suffered a local recurrence two years after surgery of the primary tumour, and one patient presented with lung metastases after the same disease free interval. In addition, nine of the 20 MCs occurred in younger women aged between 37 and 53. Because oestrogen and progesterone receptors and Her-2 overexpression are negative in most MCs,^{1–3,14} adjuvant endocrine treatment or Her-2 targeted treatment with a monoclonal antibody (trastuzumab) is usually not a therapeutic option in patients with advanced disease, positive resection margins, or positive lymph nodes.

Table 3 Expression of EGFR (Her-1), Her-2, Her-3, Her-4, and steroid receptors in metaplastic carcinomas

Case/Histology	Antigens (% of positive tumour cells/staining intensity)						
	EGFR	Her-2	Her-3	Her-4	AR	ER	PR
1 Spindle/het	20	2+	50/1+	–	–	–	–
2 Spindle/ep/het	70	3+	–	–	–	–	–
3 Spindle/ep/het/GC	40	2+	–	–	–	–	–
4 Spindle/het/GC	–	–	–	–	90/2+	–	–
5 Spindle/het/GC	20	1+	–	–	–	–	–
6 Spindle/het/GC	30	2+	–	–	–	–	–
7 Spindle/mat	10	2+	–	–	–	–	–
8 Spindle/het/GC	–	–	–	40/1+	40/2+	–	–
9 Spindle/het/apo	70	3+	–	–	–	–	–
10 Spindle/fasc	–	–	–	–	–	–	–
11 Spindle/ep/GC	–	–	–	–	–	–	–
12 Spindle/fasc	90	3+	–	–	–	–	–
13 Spindle/fasc	90	3+	–	–	–	–	–
14 Spindle/fasc	100	3+	–	–	–	–	–
15 Spindle/fasc	80	3+	–	–	–	–	–
16 Spindle/fasc	20	1+	–	–	–	–	–
17 Casa/IDC	–	–	30/2+	–	–	70/2+	70/3+
17 Casa/spindle/GC	–	–	–	–	–	–	–
18 Casa/IDC	20	2+	–	–	–	–	–
18 Casa/spindle	50	3+	–	–	–	–	–
19 Casa/IDC	–	–	–	–	–	–	–
19 Casa/spindle/fasc	–	–	–	–	–	–	–
20 Casa/IDC	–	–	20/1+	20/1+	20/1+	–	30/3+
20 Casa/spindle/fasc	60	3+	–	–	–	–	–

apo, apocrine features; AR, androgen receptor; casa, carcinosarcoma—epithelial staining; casa, carcinosarcoma—stromal staining; EGFR, epithelial growth factor receptor; ep, epithelioid; ER, oestrogen receptor; fasc, fascicular; GC, giant cells; het, heterologous elements; IDC, invasive ductal carcinoma; mat, matrix producing; PR, progesterone receptor.

EGFR (Her-1) is homologous to other members of the EGFR/erbB family, including Her-2 (erbB2), Her-3 (erbB3), and Her-4 (erbB4). Because aberrant signalling through the EGFR is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, and angiogenesis,⁶ it has emerged as an attractive target for anticancer treatments. Among the agents targeting EGFR (monoclonal antibodies such as cetuximab and small molecule inhibitors), the inhibitor furthest in development is gefitinib (ZD1839, Iressa). It was approved by the US Food and Drug Administration in 2003¹⁷ on the basis of two randomised phase 2 trials, which reported tumour responses in patients with non-small cell lung cancer (NSCLC) who had previously been treated with at least one platinum based regimen or who had received both platinum based and docetaxel chemotherapies.¹⁸ Because two phase 3 trials showed no benefit for patients treated with gefitinib in combination with standard chemotherapy compared with standard chemotherapy alone,²⁰ gefitinib was only recommended for use as monotherapy. The EGFR protein is expressed by a variety of normal cells, including many epithelial cell types (such as squamous epithelium) and tumours derived from these cell types.²² In breast carcinomas, EGFR expression is associated with a poor prognosis,^{23–25} although its prognostic value seems to be dependent on the oestrogen receptor status of the patient also.²³ More recent studies that used immunohistochemical staining for EGFR instead of ligand binding assays reported positivity for EGFR in 16.4%,²⁶ 20.1%,²⁷ and 26.9%²⁵ of breast carcinomas, which were mainly of the invasive ductal not otherwise specified type. In our study, EGFR was identified in 70% of MCs, whereas only one weakly expressed Her-2. Her-3, Her-4, and the androgen receptor were only detected in the spindle cells of one tumour, and progesterone/oestrogen receptors were negative in the spindle cells of all MCs. These results clearly show the difficult therapeutic situation in MCs compared with other high grade carcinomas of the breast, some of which at least have been shown to exhibit androgen receptors²⁸ and overexpress Her-2 as potential targets for adjuvant treatment. However, the frequent expression of EGFR in the absence of steroid receptors or other receptors of the EGFR family might render MCs even more sensitive to EGFR tyrosine kinase inhibitors, because it may reflect the crucial role of this receptor for tumour progression in most MCs, whereas endocrine and Her-2 dependent stimuli do not seem to contribute to tumour cell proliferation in these high grade tumours.

“The frequent expression of epidermal growth factor receptors (EGFRs) in the absence of steroid receptors or other receptors of the EGFR family might render metastatic breast carcinomas even more sensitive to EGFR tyrosine kinase inhibitors”

Admittedly, the assessment of gefitinib sensitive NSCLC by immunohistochemistry has been seriously questioned by

Take home messages

- Metaplastic breast carcinomas express the epidermal growth factor receptor more frequently than the types of breast carcinomas investigated previously
- Women suffering from this aggressive form of breast carcinoma might benefit from treatment with protein kinase inhibitors, such as gefitinib

recent studies reporting that specific mutations in certain EGFR exons, not simply kinase expression, render NSCLC sensitive to selective inhibitors.^{29–31} These results are consistent with positive responses to a protein kinase inhibitor (Imatinib) in patients suffering from gastrointestinal stromal tumours with kinase mutations.³² However, one has to remember that kinases in other tumour types might not necessarily have to be genetically altered to play a significant role in tumour cell proliferation and survival. An experimental study using breast cancer cell lines showed that EGFR overexpressing MDA-MB-231 cell lines and Her-2 overexpressing KPL-4 cell lines were more sensitive to gefitinib than other cell lines.³³ Because MCs express EGFR considerably more frequently than the types of breast carcinoma investigated immunohistochemically in previous studies,^{25–27} they represent a promising target for future studies (especially molecular analyses) on EGFR expression in breast carcinomas. Based on our results, patients suffering from this aggressive variant of breast carcinoma might benefit from treatment with protein kinase inhibitors such as gefitinib.

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