Different expression patterns of KIT, EGFR, and HER-2 (c-erbB-2) oncoproteins between epithelial and mesenchymal components in uterine carcinosarcoma

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Uterine carcinosarcoma histologically comprises the components of epithelial and mesenchymal malignancies, and is known to be clinically highly aggressive. To reveal the significance of the expression of tyrosine-kinase-receptor-type oncoproteins in this tumor type, the incidence and distribution of the KIT, EGFR, and HER-2 (c-erbB-2) oncoproteins were immunohistochemically examined in 16 surgically resected cases. For 6 cases, the EGFR and HER-2 amplifications were also examined by fluorescence *in situ* hybridization (FISH). In the epithelial component, overexpressions of KIT, EGFR, and HER-2 were detected in 4 (25%), 5 (31%), and 9 (56%) cases, respectively, whereas these overexpressions in the mesenchymal component were detected in 6 (38%), 8 (50%), and 1 (6%) cases, respectively. KIT and EGFR were co-overexpressed in the mesenchymal component of 4 cases and in the epithelial component of 2 cases. However, HER-2 overexpression was mostly detected in the epithelial component only, and tended to occur independently of KIT and/or EGFR overexpression. By FISH, one of the 4 cases with HER-2 overexpression showed low-level gene amplification. In two cases with EGFR overexpression, the gain of EGFR alleles and/or polyploidization of chromosome 7 had occurred. The expression patterns of KIT, EGFR, and HER-2 differed between the epithelial and mesenchymal components, and the regulation of their expression appeared important in the acquisition of mesenchymal metaplasia in uterine carcinosarcoma. Structural and/or numerical alterations of chromosomes might be in part involved in EGFR and/or HER-2 overexpression in this tumor type. (Cancer Sci 2003; 94: 986–991)

Cancer of the uterine corpus is one of the most common gynecological malignancies in North America and North Europe, and its incidence is increasing in Asia and Africa. Most cases are detected at the early clinical stages and classified as histologically low-grade endometrioid carcinoma, and have an excellent clinical outcome after surgical treatment. On the other hand, a minor fraction of the cancer of the uterine corpus, comprising histologically high-grade endometrioid carcinoma, serous adenocarcinoma, clear cell adenocarcinoma, and carcinosarcoma, frequently shows metastasis and relapse after surgery.

Carcinosarcoma, formerly called malignant mixed mesodermal tumor, or malignant mixed müllerian tumor, accounts for approximately 2% to 5% of all malignancies of the uterine corpus.[1)] It had been believed that the uterine carcinosarcoma originates from immature müllerian duct cells that have a potential to differentiate into both epithelial and mesenchymal cells. However, it is a widely accepted idea today that uterine carcinosarcoma is derived from a single cell clone of epithelial cells of endometrial glands[2–7)] and that the sarcomatous cells emerge as a subclone from the carcinoma cells through mesenchymal metaplasia.[7)]

Uterine carcinosarcoma tends to be clinically diagnosed at the advanced stages. The 5-year survival of patients with carcinosarcoma is reported to be 18% to 39%.[8–10)] Hysterectomy with pelvic lymph node dissection is the standard treatment of choice, and systemic adjuvant therapies should often be considered in cases with extra-uterine tumor spread.[11)] However, chemotherapies are usually insufficient to control the growth of the metastatic foci.

The overexpression of proto-oncogenes has been identified in various human cancers in recent years. The *EGFR* (*HER-1*, *c-erbB-1*) proto-oncogene, located on chromosome arm 7p21, and the *HER-2* (*c-erbB-2*) proto-oncogene, located on chromosome arm 17q11.2-q21, encode growth factor receptors with tyrosine kinase activity. The EGFR oncoprotein is frequently overexpressed in various spectra of carcinomas,[12,13)] whereas overexpression of the HER-2 oncoprotein is detected in 10% to 30% of adenocarcinoma of breast, stomach, and ovaries.[14–19)]

The *KIT* proto-oncogene also encodes a growth factor receptor with tyrosine kinase activity, and the stem cell factor is identified as a ligand for the KIT receptor.[20–23)] The activation of the KIT receptor plays important roles in the differentiation and proliferation of melanocytes, neural crest cells, hematopoietic stem cells, mast cells, germ cells, and interstitial cells of Cajal.[24–27)] Mutational activation of the *KIT* gene and its protein overexpression commonly occur in gastrointestinal stromal tumors (GISTs).[28,29)] In addition, the KIT oncoprotein is expressed in various human tumors including chronic myelogenous leukemia,[30)] neuroblastoma,[31)] and cancers of the breast,[32,33)] colon,[34)] uterine cervix,[32,35)] and lung.[32,36)]

Recently, we found that the KIT and EGFR oncoproteins were frequently co-expressed in poorly differentiated breast carcinomas that were accompanied with mesenchymal metaplasia, e.g., spindle cells, and osseous and cartilaginous tissues.[37)] In contrast, HER-2 overexpression was preferentially detected in poorly differentiated breast carcinoma without mesenchymal differentiation.[37)] Based on these observations, we hypothesized that KIT and EGFR expressions could be common findings in carcinosarcomas, or poorly differentiated carcinomas with mesenchymal metaplasia, arising in various organs. In the present study, we immunohistochemically examined the expression pattern of these three oncoproteins in the epithelial and mesenchymal components of 16 carcinosarcomas of the uterine corpus.

Materials and Methods

Cases. The present study was approved by the internal review board for ethical issues. We collected formalin-fixed paraffin-

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embedded tissue blocks of carcinosarcoma of the uterine corpus resected from 16 patients who had undergone total abdominal hysterectomies with lymph node dissection at the Department of Obstetrics and Gynecology, National Defense Medical College Hospital, between 1994 and 2002. Fresh frozen tissue specimens of carcinosarcoma were also obtained from 6 patients and were stored at −80°C. The clinical stage of disease was I, II, III, and IV in 5, 1, 6, and 3 patients, respectively, but it was unclear in one case.

Immunohistochemistry (IHC). The expressions of KIT, EGFR, HER-2, vimentin, S-100, α-smooth muscle actin (SMA), and CD34 were examined by IHC in both epithelial and mesenchymal components of the 16 carcinosarcomas. Routinely processed formalin-fixed paraffin-embedded tissue specimens were cut into 4 μm-thick sections. In all cases, these tissue specimens contained both carcinosarcoma and adjacent normal myometrium. The antibodies used were polyclonal rabbit anti-human-c-KIT (1:50, Dako, Grostrup, Denmark), mouse monoclonal anti-EGFR (clone 31G7) (1:50, Zymed, South San Francisco, CA), and rabbit polyclonal anti-human HER-2 (1:200, Nichirei). We also used mouse monoclonal anti-CD34 (clone QBent 10) (1:50, Dako), mouse monoclonal anti-vimentin (clone V9) (1:200, Dako), rabbit polyclonal anti-cow S-100 (1:2000, Dako), and mouse monoclonal anti-α-SMA (clone 1A4) (1:15, Shandon-Lipshaw, Pittsburgh, PA) for the detection of mesenchymal differentiation.

Antigen retrieval of the tissue sections was performed as follows: incubation in 10 m*M* sodium citrate (pH 6.0) with 0.1% Tween 20 at 95°C for 20 min for KIT; pretreatment with 0.1% type XXIV protease (Sigma, St. Louis, MO) for 20 min at room temperature for anti-EGFR; and microwave treatment at 95°C for 15 min in 10 m*M* sodium citrate (pH 6.0) for anti-HER-2 and anti-CD34.

After the antigen retrieval, or without the antigen retrieval procedure for vimentin, S-100, and α-SMA, tissue sections were incubated in 0.3% hydrogen peroxide in methanol for 30 min, reacted with the primary antibody for 1–3 h, incubated with a dextran polymer reagent conjugated with peroxidase and secondary antibody (Envision+, Dako) for 1 h, and subsequently reacted with 3,3′-diaminobenzidine tetrahydrochloride-hydrogen peroxide as a chromogen.

Judgment of IHC. As the positive control of the expressions of KIT and vimentin, a case of GIST was used. A stomach cancer with EGFR amplification and another case of stomach cancer with HER-2 amplification, detected by fluorescence *in situ* hybridization (FISH), were used as the positive controls of EGFR and HER-2 overexpression, respectively. For the internal control of S-100, α-SMA, and CD34, peripheral nerve, smooth muscle, and endothelial cells in the adjacent normal tissues were used, respectively. As negative controls, tissue sections without loading of the primary antibody were included in each assay. In addition, the expression levels of the receptors were compared between the tumor tissues and the normal tissues adjacent to the tumor.

The KIT expression level was scored as 1+ if the cytoplasm was discretely and weakly to moderately stained and as 2+ if the cytoplasm was strongly stained with or without the staining of the cell membrane in 10% or more of the constituent cancer cells. If no staining was observed, or if staining was observed in fewer than 10% of the constituent cancer cells, a score of 0 was given. Cases with a score of 2+ were judged as overexpression.

In the epithelial components, the EGFR and HER-2 expressions were scored as 2+ and 3+ if the entire circumference of the cell membrane was weakly or moderately stained and strongly stained, respectively, in 10% or more of the constituent cells. A score of 1+ was given if incomplete membrane staining was observed in 10% or more of the cells, and a score of 0 was given if there was membrane staining in fewer than 10% of constituent cells or no membrane staining. In the mesenchymal components, EGFR and HER-2 were positive in the cytoplasm, and discrete and weak staining, moderate staining, and strong staining of the cytoplasm in 10% or more of the carcinoma cells were scored as 1+, 2+, and 3+, respectively. Cases with a score of 2+ or 3+ were judged as overexpression. When two of KIT, EGFR, and HER-2 were overexpressed in a component in a case, they were defined as co-overexpressed.

Vimentin, S-100, α-SMA, and CD34 were judged as expressed if the cytoplasm was moderately to strongly stained in 10% or more tumor cells.

FISH. FISH was performed using a PathVysion HER-2/neu DNA probe kit (Vysis, Downers Grove, IL) and an LSI EGFR/CEP7 kit (Vysis) according to the manufacturer's protocols. DNA probes used were the HER-2/neu DNA located on 17q11.2-12, CEP17 DNA located on 17p11.1-q11.1 (the locus of *D17Z1*), EGFR DNA located on 7p12, and CEP7 DNA located on 7p11.1-q11.1 (*D7Z1* locus). Fresh-frozen tissue of 6 tumors was embedded in the OCT compound (Sakura Finetechnical, Tokyo), cut into 5 μm-thick sections, and mounted on silane-coated slides (Muto, Tokyo). One of these sections was stained with hematoxylin and eosin and confirmed to contain epithelial or mesenchymal tumor tissue components. Serial sections were fixed with 10% formalin for 10 min, denatured at 72°C for 5 min in 70% formamide/2× standard saline citrate (SSC), and dehydrated in ethanol. These sections were hybridized at 37°C for 14–18 h with denatured probes (a mixture of SpectrumOrange-labeled HER-2/neu DNA and SpectrumGreen-labeled CEP17 DNA, or a mixture of SpectrumOrange-labeled EGFR DNA and SpectrumGreen-labeled CEP7 DNA). The sections were washed for 2 min with 2× SSC/0.3% NP-40 solution at 72°C for 2 min, at room temperature for 2 min, and at 72°C again for 2 min, and were counterstained with 4,6-diamidino-2-phenylindole (DAPI).

The evaluation of DNA amplification was performed using a Leica DMR fluorescence microscope (Leica Microsystems, Cambridge, UK). The acquisition of images was performed using a COHU CCD camera and a Leica Q550CW computer with QFISH software (Leica Microsystems). The total number of fluorescence signals of HER-2 and that of CEP17 were counted in 60 interphase tumor cell nuclei, and the HER-2/CEP17 ratio was calculated by dividing the former by the latter. The total number of the fluorescence signals of EGFR and that of CEP7 were also counted in 60 interphase tumor cell nuclei, and the EGFR/CEP7 ratio was calculated by dividing the former by the latter. A ratio of ≥2.0 was defined as specific HER-2 and EGFR amplification. The mean copy number of the HER-2 DNA and that of the EGFR DNA per tumor cell nucleus for each tumor were also calculated by dividing the total counts of HER-2 signals and that of EGFR signals, respectively, by the number of counted nuclei (usually 60).

Statistical analysis. The statistical significance of differences was analyzed by applying the χ^2 test or Fisher's exact test.

Results

KIT, EGFR, and HER-2 overexpression. In the negative control sections without loading the primary antibody, immunostaining was always negative. In the normal myometrium adjacent to the tumor tissue, KIT, EGFR, and HER-2 were always negative and scored as 0. Among 16 cases of carcinosarcoma, the overexpression of KIT was detected in 8 (50%). KIT overexpression was positive in the mesenchymal component of 6 cases and in the epithelial component of 4 cases (Table 1). In 2 cases, KIT was overexpressed in both the mesenchymal and epithelial components (Figs. 1A and 2A).

The overexpression of EGFR was detected in 10 (63%): in the mesenchymal component of 8 cases and in the epithelial

component of 5 cases (Table 1). In 3 cases, EGFR was overexpressed in both the mesenchymal and the epithelial components (Figs. 1B and 2B). The incidence of KIT and EGFR overexpression did not differ significantly between the epithelial component and the mesenchymal component in the 16 cases.

HER-2 overexpression was detected in 9 cases (56%), and eight of the overexpressions were observed in the epithelial component (Table 1). In one case, HER-2 was overexpressed in the mesenchymal component. Therefore, HER-2 overexpression was detected more frequently in the epithelial component than in the mesenchymal component ($P<0.05$) (Figs. 1C and 2C, Table 2). In the mesenchymal component of the 16 cases, HER-2 overexpression was less frequent than KIT and/or EGFR overexpression ($P<0.05$, Table 2).

Table 1. Overexpression of KIT, EGFR, HER-2, vimentin, and other mesenchymal markers in the epithelial and mesenchymal components of carcinosarcoma

Case No.	Expression of proteins by IHC (%)				
	KIT	EGFR	HER-2	Vimentin	Other mesenchymal markers
1	M	M	E	M	α-SMA (M)
2	M		E	E, M	
3			E	E, M	S100 (M)
4	E, M	M		M	
5				E, M	CD34 (M)
6		E		E, M	
7		M	E	E, M	CD34 (M)
8	M	M	E	M	α-SMA (M)
9		M	E	E, M	α-SMA (M)
10	E		E	E, M	S100 (E, M), CD34 (M)
11	M			E, M	S100 (M)
12		E, M		M	S100 (E), α-SMA (M)
13		E, M		E, M	
14				E, M	S100 (E), α-SMA (M)
15	E	E	M	E, M	α-SMA (M), CD34 (M)
16	E, M	E, M	E	E, M	S100 (E, M)
Total	8 (50)	10 (63)	9 (56)	16 (100)	10 (63)

E, epithelial component; M, mesenchymal component.

Among the 16 cases, KIT and EGFR were co-overexpressed in 5 cases (31%): this co-overexpression was detected only in the epithelial component of one, only in the mesenchymal component of three, and in both the mesenchymal and the epithelial components of one (Figs. 1A, 1B and 2A, 2B).

KIT and HER-2 were co-overexpressed in 2 cases (13%), and both occurred in the epithelial component. HER-2 and EGFR were co-overexpressed in only 1 case (6%), and that occurred in the epithelial component.

KIT and/or EGFR were overexpressed in 17 (53%) of 32 components (i.e., epithelial and mesenchymal components) of the 16 carcinosarcomas. Of these 17, 6 components (35%) showed co-overexpression of KIT and EGFR. In contrast, KIT and/or HER-2 were overexpressed in 17 components (53%), and only 2 (12%) showed co-overexpression of KIT and HER-2. EGFR and/or HER-2 were overexpressed in 21 components (66%), and only 1 component (5%) showed co-overexpression of EGFR and HER-2.

From these results, the occurrence of co-overexpression of KIT and EGFR was significantly higher than that of co-overexpression of EGFR and HER-2 ($P<0.05$), and also had a tendency to be higher than that of KIT and HER-2 overexpression.

Expression of mesenchymal markers. In the normal myometrium adjacent to the tumor tissue, vimentin and α-SMA were positive, but S-100 and CD34 were negative. In the mesenchymal component of the 16 carcinosarcomas, the expressions of vimentin, α-SMA, S-100, and CD34 were positive in 16 (100%), 4 (25%), 6 (38%), and 2 (13%), respectively (Figs. 1D and 2D). In the epithelial component of the 16 carcinosar-

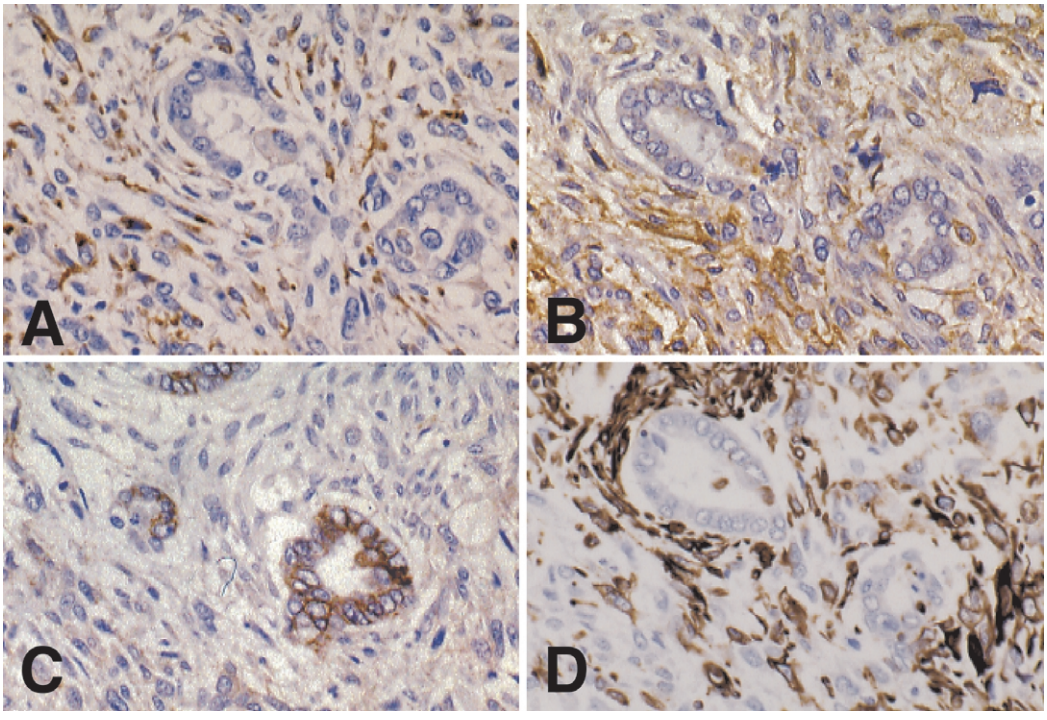

Fig. 1. Overexpression of (A) KIT, (B) EGFR, (C) HER-2, and (D) vimentin in a case of carcinosarcoma of the uterine corpus (case 1). The epithelial component demonstrates carcinomatous cells with tubule formation, whereas the mesenchymal component shows the diffuse proliferation of sarcomatous cells in spindle and/or pleomorphic shapes. KIT, EGFR, and vimentin are overexpressed in the mesenchymal component, whereas the HER-2 is overexpressed in the epithelial component. Immunoperoxidase stain (original magnification: ×200).

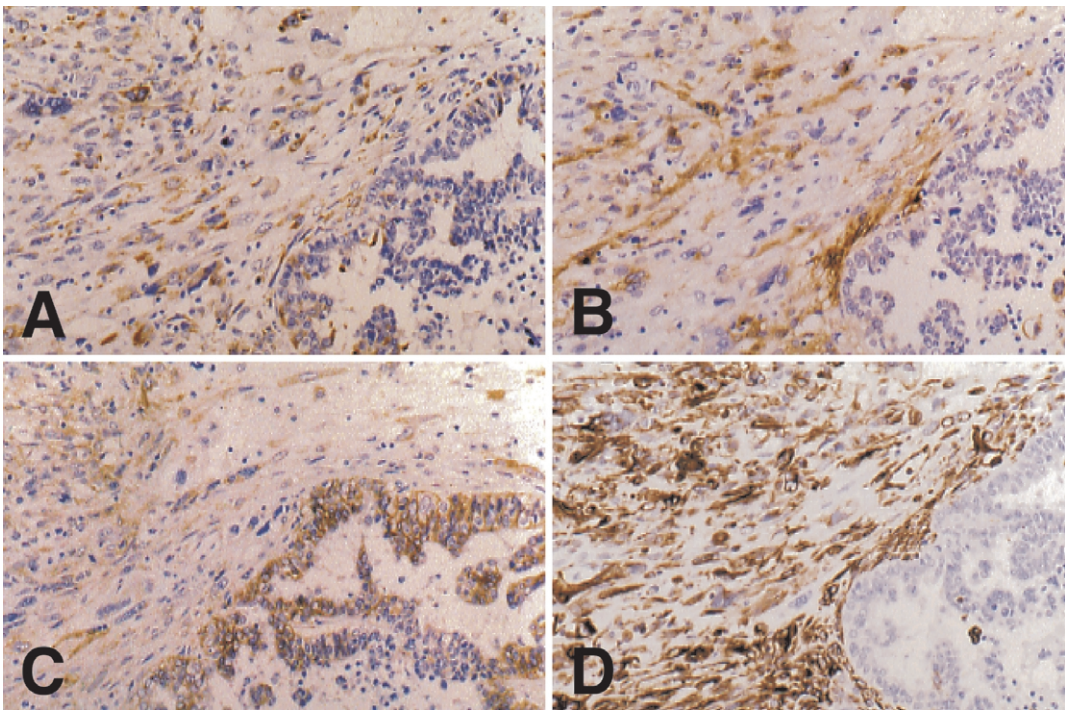

Fig. 2. Overexpression of (A) KIT, (B) EGFR, (C) HER-2, and (D) vimentin in a case of carcinosarcoma of the uterine corpus (case 8). The tumor is composed of epithelial (in the left of A–D) and mesenchymal (in the right of A–D) components. A. KIT is overexpressed in the mesenchymal component. B. EGFR is overexpressed in the mesenchymal component. C. HER-2 is overexpressed in the epithelial component and is weakly positive in the mesenchymal component. D. Vimentin is positive only in the mesenchymal component. Immunoperoxidase stain (original magnification: ×100).

Table 2. Correlation of KIT/EGFR overexpression and HER-2 (c-erbB-2) overexpression in epithelial and mesenchymal components of carcinosarcoma

	No. of cases (%)	
	Epithelial components (n=16)	Mesenchymal component (n=16)
KIT and/or EGFR overexpression	7 (44)[a]	10 (63)[b]
HER-2 overexpression	8 (50)[c]	1 (6)[d]

P<0.05 between b and d. P<0.05 between c and d.

comas, the expressions of vimentin, S-100, α-SMA, and CD34 were detected in 13 (81%), 4 (25%), 0, and 0, respectively (Table 1).

***EGFR* and *HER-2* gene amplification.** Of the 6 cases of carcinosarcoma for which FISH was performed, the epithelial component was examined in 4, and the mesenchymal component was examined in 1. In another case (case 7), it was undetermined whether the component was epithelial or mesenchymal (Table 3).

Among these 6 cases, EGFR overexpression and HER-2 overexpression were detected in 2 and 4, respectively. In 2 cases with EGFR overexpression, the mean copy numbers of EGFR DNA per tumor cell nucleus were 3.9 (ranging from 1 to 12) and 4.8 (ranging from 1 to 16). In the former, the EGFR/CEP7 ratio was 1.6, and the gain of one 7p arm or two, including the EGFR locus, with or without the polysomy of chromosome 7, was considered to have occurred. In the latter, the EGFR/CEP7 ratio was 1.1, and the increased copy number was considered to have resulted from the chromosome 7 polysomy. A significant portion of the constituent cells showed a large number of signals of both EGFR and CEP7 (Fig. 3A). In the other 4 cases that did not show EGFR overexpression, the mean copy numbers of EGFR DNA per tumor cell nucleus were 3.4, 3.3, 2.8, and 1.9, and the EGFR/CEP7 ratio was 1.0 or 1.1.

In 4 cases with HER-2 overexpression, the mean copy numbers of HER-2 DNA per tumor cell nucleus were 7.1, 2.9, 2.5, and 2.2. Of these 4, the HER-2/CEP17 ratio was 2.0 in the first case, and the case was judged to have low-level HER-2 DNA amplification (Fig. 3B). In 3 others with HER-2 overexpression and 2 others without overexpression, the HER-2/CEP17 ratio varied between 0.87 and 1.1.

Discussion

In the present study, we demonstrated that the KIT oncoprotein was frequently expressed in the mesenchymal component and/or the epithelial component in carcinosarcoma of the uterine corpus. There were two studies of KIT expression in cancers of the uterine corpus. Scobie *et al*. showed that the KIT oncoprotein was expressed in 58% of cases of endometrioid carcinoma. The positivity of KIT expression was especially high in grade 3 endometrioid adenocarcinoma, serous adenocarcinoma, and clear cell adenocarcinoma.[38] Klein and Kurman reported that KIT expression was rare in uterine carcinosarcoma (0 of 6), endometrial stromal sarcoma (1 of 12), and leiomyosarcoma (0 of 4).[39] The discrepancy between our data and Klein and Kurman's data might be derived from the difference in the lot of antibody used, although a commercially available antibody was used in both studies. The scale of dilution of the antibody also differed, being 1:50 in the present study and 1:2000 in Klein and Kurman's study. These authors did not describe how they evaluated positive controls.

The overexpression of EGFR protein was also detected in 10 cases of carcinosarcoma, in the mesenchymal component of 8 cases, and in the epithelial component of 5 cases. In endome-

Table 3. Statuses of the *EGFR* and *HER-2* genes, detected by FISH, in 6 cases of carcinosarcoma

Case	Component	EGFR			HER-2		
			FISH			FISH	
		IHC score	Mean EGFR No. per nucleus (range)	EGFR/CEP7 ratio	IHC score	Mean HER-2 No. per nucleus (range)	HER2/CEP17 ratio
2	E	1+	3.4 (2–10)	1.1	2+	2.5 (1–10)	1.1
3	E	0	2.8 (1– 9)	1.1	2+	7.1 (4–13)	2.0
4	M	2+	3.9 (1–16)	1.6	1+	2.8 (1–6)	1.0
7	E/M	2+	4.8 (1–12)	1.1	2+	2.2 (1–4)	1.0
10	E	1+	3.3 (1–7)	1.0	2+	2.9 (1–8)	0.87
11	E	0	1.9 (1– 4)	1.1	0	2.5 (1–6)	1.0

E, epithelial component; M, mesenchymal component; E/M, undetermined whether epithelial or mesenchymal component.

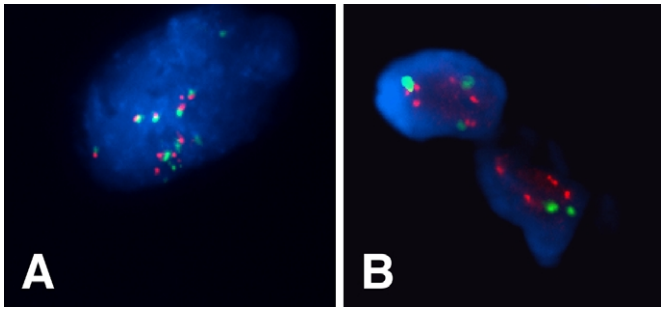

Fig. 3. Numerical changes in the EGFR and HER-2 DNA, detected by FISH, in a carcinosarcoma of the uterine corpus. A. A case (case 7) with a chromosome 7 polysomy. A tumor cell nucleus (blue) with 11 signals of EGFR (red) and 13 signals of chromosome 7 centromere (CEP7) (green). The EGFR/CEP7 ratio is 1.1 on average (original magnification: ×1000). B. A case (case 3) with *HER-2* gene amplification. Each tumor cell nucleus (blue) shows 5 signals of HER-2 (red) and 2 to 3 signals of chromosome 17 centromere (CEP17) (green). The HER-2/CEP17 ratio is 2.0 on average (original magnification: ×1000).

trial cancer, EGFR expression was reported to occur in 30% to 40% of cases and not to be correlated with the patients' prognosis.[40–42] Swisher *et al*. reported that EGFR expression was detected in 9 of 20 cases of uterine carcinosarcoma and tended to appear more frequently and/or strongly in the mesenchymal component than in the epithelial component,[43] which is compatible with our findings. In addition, we demonstrated that overexpressions of KIT and EGFR frequently concurred. The co-overexpression tended to be more frequent in the mesenchymal component. The co-overexpression of KIT and EGFR might be involved in mesenchymal metaplasia by carcinoma cells of the uterine corpus.

Differently from KIT and EGFR, overexpression of the HER-2 oncoprotein was mostly detected in the epithelial component. Its co-overexpression with KIT or EGFR was infrequent. Therefore, the expression patterns of KIT, EGFR, and HER-2 were different between the epithelial and mesenchymal components of uterine carcinosarcoma.

It might be possible to explain the typical developmental pathway of carcinosarcoma of the uterine corpus from the viewpoint of heterogeneous overexpression of these oncoproteins: in the early developmental stage, an adenocarcinoma with HER-2 overexpression arises, and, during the growth of the tumor, carcinoma cells come to overexpress the KIT and EGFR oncoproteins, but down-regulate HER-2 expression. As a result, morphological changes occur from carcinoma cells to sarcomatous cells that constitutively express the markers of mesenchymal differentiation.

In breast cancers, HER-2 overexpression is usually correlated with high-level (3-fold or higher) amplification of the *HER-2* gene. However, by FISH, only one (25%) of the cases of carcinosarcoma with HER-2 overexpression showed a low-level (2.0-fold) amplification. Therefore, in the other 3 cases, HER-2 overexpression appeared to arise through alterations at the transcriptional and/or translational levels.

Two cases with EGFR overexpression showed unique findings of EGFR DNA status by FISH. These cases appeared to be characterized by the gain of 7p arm(s) containing EGFR, chromosome 7 polysomy, or both of them. These kinds of increase in EGFR alleles might be directly involved in the up-regulation of EGFR through a dosage effect in combination with the regulation at the transcriptional and/or translational levels.

Our findings may be summarized as follows. KIT overexpression was frequent in uterine carcinosarcoma. KIT and EGFR were frequently co-overexpressed in the mesenchymal component, and their co-overexpression might play an important role in the acquisition of a carcinosarcoma phenotype by carcinoma cells. The overexpression of HER-2 was detected almost selectively in the epithelial component, although *HER-2* gene amplification was detected in only 25% of HER-2-overexpressing cases. The overexpression of HER-2 was considered to be involved in the growth of adenocarcinoma cells at the initial stage, and appeared to be down-regulated in accordance with mesenchymal metaplasia of the carcinoma cells.

These findings might suggest that molecular targeting therapy directed to KIT, EGFR, and HER-2 could be effective to inhibit the growth or progression of the epithelial and/or mesenchymal components of uterine carcinosarcoma. Further investigations are needed to establish the rationale for such molecular targeting therapies to treat this highly malignant cancer type.

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