E-Cadherin Expression in Primary and Metastatic Gastric Cancer: Down-Regulation Correlates with Cellular Dedifferentiation and Glandular Disintegration

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ABSTRACT

Expression of the epithelial cell adhesion molecule E-cadherin in primary and metastatic gastric carcinoma was examined using immunohistochemical analyses. Compared to normal mucosa, 92% of the primary tumors (n = 60) showed reduced E-cadherin expression, suggesting that down-regulation of this cell adhesion molecule is a common early event in gastric tumorigenesis. No significant correlation was found between E-cadherin expression and tumor diameter, lymphatic vessel invasion, Borrmann classification, lymph node status, or manifest metastases. Although advanced tumors (tumor stage 3/4) showed a loss of E-cadherin-positive cells (≤50% cells/lesion, P = 0.0168), the most significant correlation was observed between low E-cadherin expression and cellular dedifferentiation (grading 3/4, P = 0.0001) and disintegration of tissue architecture (Lauren and WHO classifications, P = 0.0001). Low E-cadherin expression (≤50% cells/lesion) was associated with tumor recurrence (P = 0.0013) and mortality (P = 0.0246). E-cadherin expression in metastatic lesions (n = 58) also correlated with the degree of glandular differentiation (P = 0.0001). Significant correlation (r = 0.666) was observed between E-cadherin expression in primary and metastatic lesions from individual patients (n = 39). However, while metastases derived from E-cadherin-negative tumors remained negative, those originating from E-cadherin-positive tumors frequently demonstrated increased levels of expression. Evaluation of multiple metastases in 11 patients revealed uniformly strong E-cadherin expression in liver metastases, suggesting a possible regulatory role of the microenvironment.

INTRODUCTION

The malignant potential of cancer is manifest in the ability of tumor cells to spread from the primary tumor and form metastases in distant organs. A number of different steps in the complex metastatic process are associated with alterations in the adhesive properties of the tumor cells (1–3). One of the major molecules mediating adhesion between epithelial cells is the calcium-dependent cell adhesion molecule E-cadherin (4) also known as uvomorulin, L-CAM, cell-CAM 120/80, and Arc-1. This 120-kilodalton transmembrane glycoprotein, predominantly localized to the lateral cell border and associated with the contractile cytoskeleton, mediates homotypic adhesion and plays a key role in the organization and maintenance of tissue structure (4–6).

In vitro, the selective loss of E-cadherin expression or function is associated with changes in cellular phenotype and with the development of invasive behavior of tumor cells, effects which can be reversed by transfection of E-cadherin-encoding cDNA (7–9). Evidence that down-regulation of E-cadherin can occur during tumorigenesis has been obtained in carcinogen-induced skin tumors in mice (10), and results of immunohistochemical investigations indicate that E-cadherin expression also is decreased in various human carcinomas in vivo (11–14). Although down-regulation of E-cadherin is predicted to lead to separation of cells from the primary tumor mass thereby facilitating their invasion, no consistent picture of E-cadherin expression in primary tumors and its relation to prognostic parameters has yet emerged from these studies.

Given the existence of a variety of distinct histomorphological tumor types which differ in prognosis and in the organotropism of distant metastasis (15, 16), gastric carcinoma appears to be an appropriate tumor in which to investigate the correlation between E-cadherin expression and clinical behavior. Two studies have been reported in which E-cadherin expression was examined in primary gastric tumors, but conflicting results were found. While Shiozaki et al. (17) reported a reduced E-cadherin expression in undifferentiated tumors, Shimoyama and Hirohashi (18) could find no correlation between E-cadherin expression and the differentiation of the tumor and, in fact, observed that nearly two-thirds of the undifferentiated gastric carcinomas investigated were E-cadherin positive. In the study reported here, we examined the expression of E-cadherin on a panel of primary gastric carcinomas encompassing a wide range of tumor stages and on autologous normal mucosa. We also compared the pattern of E-cadherin expression on these tumors with that in solid hematogenous and lymphogenous metastases in the same patients.

MATERIALS AND METHODS

Tissue Specimens. Tissue specimens from untreated patients with primary gastric cancer (n = 60) obtained up to 30 min after surgical removal were immediately snap frozen in liquid nitrogen and stored at −80°C until sectioning. In tumors of advanced stages, tissue samples of regional lymph node metastases (n = 31) and of distant metastases at different sites (liver, n = 10; omentum, n = 17) were available. From all tissue specimens, serial cryostat sections (5 μm) were prepared and air dried overnight for subsequent immunohistochemical staining.

Evaluation of Clinopathological Parameters. Immunohistochemical results were correlated with a variety of generally accepted prognostic parameters. Clinical staging for each gastric carcinoma was evaluated according to the TNM staging system indicating the extent of tumor spread (19). Gross appearance of the tumors was described according to the Borrmann classification (20). Histomorphological tissue architecture of the tumor samples, expressed according to the Lauren (21) and the WHO classifications (22), was evaluated on both paraffin sections and hematoxylin-eosin-stained frozen sections. Since histology often varied within the same tumor, the diagnosis was based on the dominant pattern. Alterations of tumor cell shape were described by grading (23). Furthermore, tumor diameter and lymphatic vessel invasion [discussed as a prognostic parameter in gastric cancer (24)] were determined. In addition, tumor recurrence and overall survival of the patients whose tumors were curatively resected were evaluated (follow-up period of 6 months to 3 years).

Monoclonal Antibodies. Indirect immunoperoxidase staining was performed with the mouse mab 6F9 (IgGl) directed against E-cadherin (8) used as an undiluted culture supernatant (commercially available from EMD, Germany). Isotype-matched mouse IgGl myeloma protein were used as isotype-matched controls. In addition, tumor recurrence and overall survival of the patients whose tumors were curatively resected were evaluated (follow-up period of 6 months to 3 years).

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3 The abbreviations used are: E-cadherin, epithelial cadherin; WHO, World Health Organization; mab, monoclonal antibody; TNM: T, tumor; N, nodes; M, metastases; G, grading; r, Spearman rank correlation coefficient.

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MOPC 21 (10 µg/ml; Sigma, St. Louis, MO) was used as a negative control. Epithelial regions, i.e., epithelium of normal mucosa and tumor areas in primary and metastatic cancer tissue sections, were identified with the mab HEA 125 (IgG1; Dako, Hamburg, Germany). The mab M701 clone 2B4 directed against the leukocyte common antigen T200 (IgG1; Dako) and mab M718 clone EBM11 (IgG1; Dako) were used to identify tumor-infiltrating leukocytes and macrophages, respectively.

**Indirect Immunoperoxidase Staining.** Tissue sections were stained with a standard indirect immunoperoxidase technique (25). Briefly, acetone-fixed serial cryostat sections were incubated with the primary mab for 1 h. After the sections were washed in phosphate-buffered saline (pH 7.4), peroxidase-conjugated rabbit anti-mouse immunoglobulin (Dianova, Hamburg, Germany), 0.1 M sodium acetate buffer, pH 4.9) containing 0.003% H2O2 for 10 min. After diluted 1:2(X) with 10% human serum, was applied for 30 min. The peroxidase reaction was developed in a 3-amino-9-ethyl-carbazole solution (0.25 mg/ml in 0.1 M sodium acetate buffer, pH 4.9) containing 0.003% H2O2 for 10 min. After the slides were counterstained with hematoxylin, they were mounted with Kaisers glycerol gelatin. All staining reagents were obtained from commercial sources (Sigma; Merck, Darmstadt, Germany).

**Evaluation of E-Cadherin Staining.** E-cadherin staining was evaluated semiquantitatively using an inverse light microscope. Cryostat sections of all tissue specimens available from one patient were placed on the same slide in order to directly compare primary and metastatic tumors with their normal counterparts. Tumor cells exhibiting a staining intensity similar to normal mucosa cells were considered to be positive, and a recognizable, but in comparison with normal cells reduced, staining intensity was judged to be weakly positive. If E-cadherin expression was completely lost, tumor cells were classified as negative. In each tissue section, the fraction (%) of E-cadherin-positive tumor cells was estimated in comparison with the HEA 125 expression pattern of the consecutive section.

**Statistical Analysis.** The correlation of E-cadherin expression (<50% versus >50% positive) with the various clinicopathological parameters was analyzed for statistical significance by the Fisher exact probability test. Correlation between E-cadherin expression in primary and metastatic lesions was assessed using the Spearman rank correlation coefficient. Overall survival rates were calculated by the Kaplan-Meier method. For differences between Kaplan-Meier curves the P value was calculated by log rank test. The Cox proportional hazard model was used in multivariate regression analyses of survival data.

**RESULTS**

**E-Cadherin Expression in Primary Gastric Cancer.** All benign gastric mucosa specimens including gastritis and intestinal metaplasia, which are considered to be precancerous lesions, demonstrated a strong and homogenous E-cadherin expression (Figs. 1 and 2a). In contrast, most of the investigated primary gastric carcinomas (92%) exhibited a reduced E-cadherin expression (Fig. 1), and this was heterogeneous both in terms of the fraction of positive cells and the staining intensity. Comparison with various clinicopathological features revealed no significant relationship between E-cadherin-staining pattern and tumor diameter (≤5 cm versus >5 cm, P = 0.6169) or lymphatic vessel invasion (+ versus −, P = 0.3922), whereas the Bormann classification, reflecting the gross appearance of the carcinomas, showed a slight, but nonsignificant, correlation between the presence of E-cadherin and Bormann types I and II (type II versus type III/IV, P = 0.0738). However, comparison of E-cadherin staining with the TNM staging system showed a significant correlation with the T stage, which refers to the infiltration depth of the primary tumor. Carcinomas extending through the serosa (stage T3) and involving contiguous structures (stage T4) exhibited <50% E-cadherin-positive cells more frequently than did stage T1/T2 tumors (P = 0.0168). A trend was also observed between the presence of lymph node metastases and the loss of E-cadherin expression (NO versus N1/2, P = 0.0579), while no correlation could be demonstrated with the M stage (M0 versus M1, P = 0.4673), which was evaluated at the time of diagnosis when metastatic disease was obviously evident.

The most significant correlation was found with differentiation parameters (Fig. 1). According to the Lauren classification, gastric carcinomas were classified as intestinal, intermediate, and diffuse tumor types. Intestinal tumors (n = 30), which are characterized by a distinct glandular formation, generally demonstrated positive or weakly positive E-cadherin staining, although the fraction of E-cadherin-positive cells varied (Fig. 1). Intestinal carcinomas could be further subdivided into well-differentiated (n = 5), moderately differ-

<table>
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<th>intermediate (n=9)</th>
<th>diffuse (n=21)</th>
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Fig. 1. E-cadherin expression in primary gastric cancer correlated with various histopathological classifications. The fraction of E-cadherin-positive cells (in percentage) was estimated in each tissue section as described in “Materials and Methods” and classified into the following groups: 0%, ≤30%, >30-50%, >50-70%, >70%. Each dot represents a single tumor. Staining intensity was evaluated in comparison to the normal counterpart: +, comparable to normal mucosa; ‡, less intensive than normal mucosa; , without any reaction. n, number of tumors of each type investigated. According to the WHO system, papillary, tubular, and mucinous types were combined under the term “adenocarcinoma” (adeno-ca.). Benign mucosa specimens include gastritis and intestinal metaplasia. Histomorphological parameters reflecting the degree of glandular and cellular differentiation showed a significant correlation with the E-cadherin expression. High E-cadherin expression (>50% positive cells) was associated with intestinal tumor type (intestinal versus diffuse, P = 0.0001), adenocarcinoma tumor type (adenocarcinoma versus signet ring cell carcinoma, P = 0.0001), and a high degree of cellular differentiation (G1/G2 versus G3/G4/GX, P = 0.0001).
E-CADHERIN EXPRESSION IN GASTRIC CANCER

Fig. 2. E-cadherin expression in primary and metastatic gastric cancer. a. intestinal metaplasia showing strong and homogeneous E-cadherin expression (× 100); b. a well-differentiated primary stomach carcinoma (G2) exhibiting intense E-cadherin staining comparable to normal mucosa (× 200); c. a primary tumor consisting of strongly E-cadherin-positive, well-differentiated, and weakly E-cadherin-positive, poorly differentiated areas (× 200); d. an E-cadherin-negative signet ring cell carcinoma (× 200); e. an E-cadherin-positive lymph node metastasis with well-differentiated tumor glands (× 100); f. an E-cadherin-negative lymph node metastasis showing no glandular formation (× 100); g. the same tumor as in f was stained with the epithelial mab HEA 125 to show the undifferentiated tumor cells (× 100).

In contrast to the glandular formations of intestinal type tumors, the polymorphic cells of diffuse carcinomas form spots and clumps in the surrounding tissue. None of these tumors (n = 21) showed any E-cadherin staining (Fig. 1). Intermediate type tumors contain both intestinal and diffuse areas. In these tumors, glandular structures were always E-cadherin positive, while specimens showing the typical diffuse morphology were E-cadherin negative (Fig. 2e). Intensely stained, well-differentiated and weakly stained, poorly differentiated
tumor areas could be seen adjacent to each other on the same tissue section. The correlation between E-cadherin expression and glandular differentiation in gastric cancer was also apparent when the tumors were classified according to the WHO system (Fig. 1). This histological classification distinguishes various types of adenocarcinomas such as papillary, tubular, and mucinous, as well as signet ring, cell types. All but one of the signet ring cell carcinomas (n = 25) were E-cadherin negative (Fig. 2d), while most of the other adenocarcinoma types (32 of 35) were E-cadherin positive. As in the intestinal type, the staining reaction depended on the degree of differentiation of tumor glands, and thus, the three E-cadherin-negative adenocarcinomas lacked any glandular formations. Another differentiation parameter which correlated with E-cadherin expression was the grading, which describes the morphological deviations of tumor cells from the typical epithelial phenotype of normal mucosa cells. Stomach carcinomas mainly composed of cells characterized by a columnar and polarized cell shape (G1, G2) showed intensive E-cadherin staining enriched at the lateral cell borders. G3 carcinomas, consisting of cells with abnormal mitoses and nuclear pleomorphism or large prominent signet ring cells, generally exhibited a reduced circumferential staining or a complete loss of the cell adhesion molecule. Small atypical malignant cells (G4, GX) were uniformly E-cadherin negative (Fig. 1). E-cadherin expression was also correlated with tumor recurrence and mortality. During the follow-up period of 6 months up to 3 years, 14 of 31 (42%) patients whose tumors were curatively resected developed local recurrence or distant metastases. This was significantly more frequent in patients whose primary tumors demonstrated low E-cadherin expression (≤50% cells/lesion, P = 0.0013). These patients also had a shorter survival time than those with strongly (>50% cells) E-cadherin-positive tumors (P = 0.0246, Fig. 4). However, when E-cadherin status and other clinicopathological parameters were analyzed by the Cox regression model, E-cadherin expression was not found to be an independent prognostic factor (P > 0.05).

E-Cadherin Expression in Metastatic Gastric Cancer. E-cadherin expression in metastatic lesions was also found to be correlated with glandular differentiation (Fig. 5). Well-differentiated metastases containing many glandular structures were strongly E-cadherin positive (Fig. 2e), while diffuse type metastases lacking glandular formations showed no E-cadherin reaction (Fig. 2f and g).

In the case of 39 patients, the E-cadherin-staining pattern in metastatic tumors was compared with that in the primary lesions (Fig. 6). We found a significant correlation between E-cadherin expression in primary and metastatic lesions (r = 0.686). With one exception, metastases derived from E-cadherin-negative primary tumors were also E-cadherin negative. The exception involved an E-cadherin-positive liver metastasis in a patient with negative primary tumor of intermediate type. Since intermediate type tumors contain both differentiated and undifferentiated regions, and since the sample examined for E-cadherin expression did not contain areas of glandular differentiation, the selected specimen might not be representative. However, the possibility that E-cadherin expression is modulated by particular organ environments can also not be ruled out (see below).

Metastases originating from E-cadherin-positive primary tumors were heterogeneous for E-cadherin expression. Less than 20% of the metastases derived from E-cadherin-positive gastric tumors were E-cadherin negative, and in fact, there was a clear tendency for the metastatic lesions to exhibit a higher frequency of E-cadherin-positive cells than was found in the primary tumors (Fig. 6), a situation which was always associated with increased glandular differentiation.

In the case of 11 patients, metastases at different sites were examined (Fig. 7). Large differences were observed in the degree of E-cadherin expression between different metastatic lesions, particularly in patients 5, 8, and 10. Only metastases to the liver showed a consistent pattern. These metastases all exhibited a high frequency of strongly E-cadherin-positive cells regardless of the pattern observed on the primary tumor. In fact, the liver metastasis of patient 5 was the only one of the four available tumor lesions from this patient which expressed E-cadherin.

### Table: Glandular Differentiation in Primary Gastric Cancer

<table>
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<tr>
<th>% positive cells</th>
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<th>Moderately differentiated (n=19)</th>
<th>Poorly differentiated (n=6)</th>
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Fig. 3. E-cadherin expression in primary gastric cancer correlated with the glandular differentiation. Intestinal type tumors were histopathologically classified according to the dominant morphology of the glands and the cells in the tumor. High E-cadherin expression associated with well-differentiated glandular structures (well versus moderately/poorly differentiated, P = 0.009); see Fig. 1 for symbols.

Fig. 4. Kaplan-Meier survival curves for patients with curatively resected gastric cancers, subdivided according to E-cadherin expression. Patients with low E-cadherin-expressing tumors (≤50% ≤50% cells/lesion, n = 20) had poorer prognoses than did the patients with strongly E-cadherin-positive carcinomas (>50% = >50% cells/lesion, n = 13, P = 0.0246).

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The cell adhesion molecule E-cadherin plays a key role in the establishment and maintenance of epithelial tissue structure and its down-regulation is potentially important in the formation of metastases. The degree of the glandular differentiation was determined from an estimate of glandular structures in the tissue sections: well differentiated, ≥50% of the section consisted of glandular structures; poorly differentiated, <50%; undifferentiated, without any glandular formation. High E-cadherin expression (≥50% positive cells) was associated with well-differentiated glandular structures (well versus poorly/undifferentiated, P = 0.0001); see Fig. 1 for symbols.

Fig. 5. E-cadherin expression in metastatic gastric cancer correlated with the glandular differentiation in metastatic gastric cancer

<table>
<thead>
<tr>
<th>% positive cells</th>
<th>well differentiated (n=23)</th>
<th>poorly differentiated (n=8)</th>
<th>undifferentiated (n=27)</th>
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<td>&gt; 70</td>
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Fig. 6. Comparison of E-cadherin expression in primary and metastatic lesions of individual patients. Each symbol represents a single patient. Abscissa, fraction of E-cadherin-positive cells (%) of the metastases; ordinate, fraction of E-cadherin-positive cells (%) of the primary tumor; circles, regional lymph node metastases; triangles, liver metastases; squares, omental metastases; closed symbols, metastases derived from the intestinal tumor type; half symbols, metastases originating from the intermediate type; open symbols, metastases from the diffuse type. The correlation between E-cadherin expression of primary and metastatic lesions was assessed (r = 0.686). Diagonal represents r = 1.00.

Fig. 7. Comparison of E-cadherin expression in multiple metastases from individual patients. □, primary tumor (pt); □, regional lymph node metastases (rln); ■, liver metastases (lm); □, omental metastases (om). Patients 1–4 (three diffuse and one intermediate type tumor) showed identical pattern of E-cadherin expression. The primary tumors of patients 5 and 10 were intermediate type, while those from patients 6–9 and 11 were intestinal. Surs. lesions not available.

DISCUSSION

The cell adhesion molecule E-cadherin plays a key role in the establishment and maintenance of epithelial tissue structure and its down-regulation is potentially important in the formation of metastases from carcinomas. To examine how the expression of E-cadherin changes during the development and progression of gastric carcinomas, 60 primary tumors were immunohistochemically analyzed. The E-cadherin expression patterns were correlated with a number of histopathological parameters and compared with that observed in autologous mucosae and solid metastases of different localizations. Comparison with autologous benign mucosae revealed a reduction of E-cadherin expression in 92% of the primary gastric carcinomas. In both primary and metastatic tumors, low expression of E-cadherin (<50% positive cells) and dispersion of the molecule over the entire cell surface significantly correlated with cellular dedifferentiation and glandular disintegration, culminating in the complete loss of E-cadherin in undifferentiated carcinomas. These findings are consistent with the observations of Shiozaki et al. (17) who used the independently isolated monoclonal antibody HEC1D1. Although Shimoyama and Hirohashi (18) could not find any correlation between E-cadherin expression and differentiation of primary gastric carcinomas also using HEC1D1, such a correlation has now been reported for a wide variety of human carcinomas (11–14, 26). Recent studies have shown that transfection of E-cadherin-encoding cDNA into fibroblasts and dedifferentiated carcinoma cell lines leads to the development of cellular polarity and the redistribution of cytoskeletal proteins (8, 9, 27). Since these events are fundamental to the establishment of epithelial structures it would appear that E-cadherin itself induces cellular differentiation, and therefore, its down-regulation leads to the disintegration of glandular structures. The reduced expression of E-cadherin and its dispersion over the entire cell surface (31), possibly associated with the disarrangement of the cytoskeletal network, are postulated to free the cells from a variety of contact-mediated controls and to encourage the successful escape of tumor cells from the primary tumor. This speculation is supported by in vitro experiments showing that the loss of E-cadherin is correlated with dedifferentiation and invasive behavior of epithelial cell lines (7–9), as well as by the correlation between reduced E-cadherin expression and tumor recurrence and mortality demonstrated in the present study.

In contrast to the observations in squamous cell carcinoma (14), most of the gastric carcinoma metastatic lesions were found to express E-cadherin. This is not necessarily in opposition to a role for down-regulation of this molecule in metastasis formation since minor changes in E-cadherin expression and/or distribution have been shown to be sufficient to cause a loss of cell adhesion (27). Observations on cell lines transplanted into nude mice indicate that E-cadherin expression can be readily modulated in vivo (10, 28), suggesting that the expression of this molecule in the metastatic lesions may in part reflect a reexpression of E-cadherin occurring after the tumor cells have left the primary tumor mass. The direct comparison of E-cadherin-staining patterns in metastatic lesions with that in the autologous primary tumors also suggests that modulation of E-cadherin expression may be occurring in these patients. While metastases derived from E-cadherin-negative tumors were also E-cadherin negative, metastases originating from E-cadherin-positive primary tumors were heterogeneous. In a number of cell
cases, E-cadherin expression in the metastatic lesions was in fact stronger than in the primary tumor. The observation that the liver metastases examined were always uniformly and strongly E-cadherin positive, regardless of the E-cadherin expression pattern in the other autologous lesions, suggests a modulating or selecting role of the liver in the development of the diffuse type are an apparent exception in that they were uniformly E-cadherin negative and were never observed to give rise to E-cadherin-positive metastatic lesions. This might indicate that in these tumors, which epidemiologically seem to have a unique origin (29), the loss of E-cadherin expression is irreversible, perhaps reflecting genetic alterations (30). An understanding of how E-cadherin expression is regulated in normal and malignant cells (30) is, therefore, a critical point in understanding tumor progression of gastric carcinoma. In view of these findings, E-cadherin represents a differentiation marker whose down-regulation might play an important role in early gastric cancer metastasis.

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REFERENCES

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