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症 例 報 告

Expression of CD44 and laminin in hepatoid gastric cancer with liver metastasis

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Abstract

Hepatoid carcinoma of stomach is a feasible clinical model of liver metastasis of gastric cancer, because it has a high incidence of liver metastasis, but reports on its biological features related to its clinicopathological characteristics are rare. We report such a case with synchronous liver metastasis. Immunohistochemical study showed that cell adhesion molecule CD44 was strongly expressed both in primary tumor and metastatic liver lesions, but cell basement membrane laminin was negative both in the primary and metastatic tumor tissue. This suggested that these molecules might play some role in liver metastasis of this special type of disease.

Introduction

Hepatoid adenocarcinoma of stomach resembles hepatoma histologically and produces excessive amounts of alpha-fetoprotein (AFP) [5]. The main clinicopathological characteristics of gastric hepatoid carcinoma are high incidence of liver metastasis, frequent venous and lymphatic invasion, rapid progression and poor prognosis [1-4]. The biological factors related to the clinicopathological characteristics remain unclear. CD44 is a multistructral and multifunctional cell surface adhesion molecule involved in cell to cell and cell to matrix interaction as well as cell migration, and is the principle receptor of extracellular matrix (ECM) component hyaluronate [11, 17]. Laminin is the major glycoprotein confined to basement membrane, which is one of the major barriers to tumor invasion. It promotes cellular adhesion, growth, migration, cell differentiation as well as neurite outgrowth and collagenase Ⅳ production [6, 7]. The contradictory findings do not allow the establishment of a conclusive concept regarding the role of CD44 and laminin in the development of gastrointestinal cancer or the prognostic value of these molecules [8-15].

We attended to demonstrate the expression condition of CD44 and laminin in this case of gastric hepatoid carcinoma by immunohistochemical staining.

Case report

A 64-year-old Japanese man suffered from epigastralgia for half a year. The laboratory analysis showed that serum AFP level increased from 4678.5 ng/ml to 7305.7 ng/ml (normal:

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10 ng/ml) within two weeks, TPA: 239 U/L (normal: 70 U/L), CEA: 15 ng/ml (normal: 5.0 ng/ml), PIVKA-Ⅱ: 6060 mAU/ML (normal: 40 mAU/ml). HBSAg: (−), HCVAb: (−). The findings of gastric endoscopy showed a submucosal tumor-like lesion at the greater curvature of the antrum with ulceration that rapidly enlarged within two weeks (Fig. 1a). Abdominal CT angiography demonstrated both an extragastric growth pattern tumor in the stomach and a huge mass in the left lateral segment of the liver. No localized lesion was observed in the colon. We performed D2 distal gastrectomy, and left lateral segmentectomy of the liver, a 7-mm lesion in S7—8 was treated by microwave coagulation under ultrasonographic guidance. We did adjuvant chemotherapy by 5-FU orally and intrahepatic arterial chemotherapy. The serum level of AFP decreased to 50 ng/ml one month after the operation. The patient died of multiple metastases of the liver one year after the operation.

Macroscopically, the resected gastric tumor was 7.2 × 5.0 × 4.8 cm in size, developing from the greater curvature of the antrum with an extragastric growth pattern. The liver tumor was 10.0 × 6.5 × 5.0 cm in size in the entire left lateral segment and a tumor embolism in left hepatic vein was observed (Fig. 1b, c).

Formalin-fixed, paraffin-embedded resected materials were used for hematoxylin and eosin staining, and immunohistochemical staining with LSAB method was performed to identify the expression of AFP (anti-AFP mAb, Dako, Glostrup, Denmark), CD44 (anti-CD44 mAb, Dako, Glostrup, Denmark), and laminin (anti-laminin mAb, TRI, Framingham, USA). Histologically, the gastric tumor showed mainly solid proliferation with little stroma, coexisting with tubular adenocarcinoma. The tumor cells were principally large and polygonal with abundant eosinophilic and granular cytoplasm, and formed trabecular, medullary arrangements and sinusoid structures, which strongly resembled hepatoma (Fig. 2a). Venous and lymphatic invasion were also recognized. The findings of metastastic liver lesion were similar. This case was diagnosed as stageⅣ (T4N2H2P0M0)[5]. In both gastric cancer and liver metastatic tissue, the cytoplasm of many tumor cells were AFP-positive (Fig. 2b). CD44 was strongly expressed on the tumor cell membrane of both stomach and liver lesions

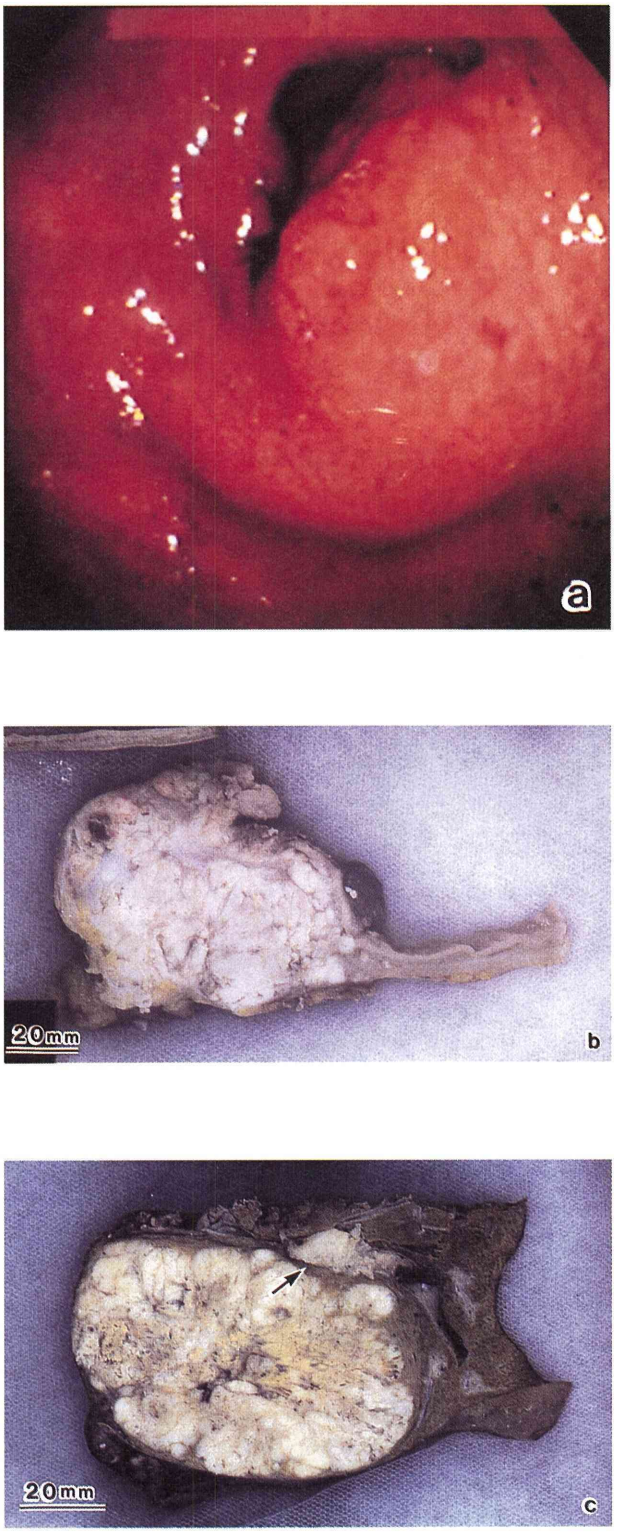

Fig. 1a, b, c (a) Endoscopy revealed a submucosal tumor-like lesion with shallow ulceration at the greater curvature of the antrum, (b) cut section of the gastric tumor shows an extragastric growth pattern with a large area of necrosis, (c) cut section of metastatic liver lesion shows a well-defined tumor with a large tumor embolus in the left hepatic vein (arrow).

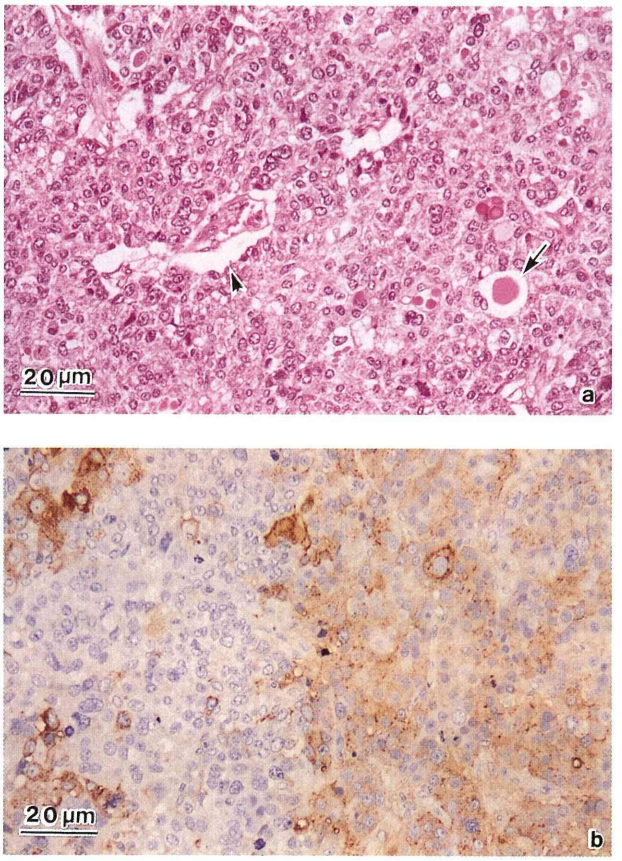

Fig. 2a, b (a) Tumor cells formed a trabecular arrangement with sinusoid structures (arrowhead), so called hepatoid carcinoma, hyaline globules (arrow) were scattered among the tumor cells (H&E, × 200), (b) expression of AFP in primary tumor cells cytoplasm (× 200).

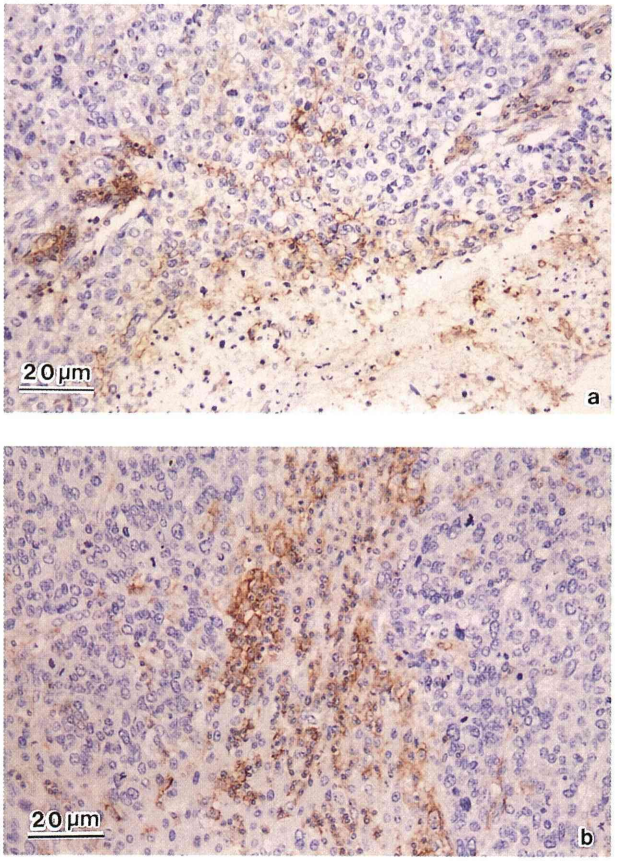

Fig. 3a, b (a) Expression of CD44 in the primary tumor (× 200) and (b) in the metastatic liver lesion (× 200).

(Fig. 3a, b). Laminin expression was negative both in primary tumor and liver metastatic tumor cell basement membrane.

Discussion

AFP-producing gastric carcinoma was first reported by Bourreille et al. in 1970[1]. The concept of hepatoid adenocarcinoma was proposed by Ishikura et al. in 1986[2]. The incidence of hepatoid adenocarcinoma was reported to be 0.39% (28/7200) in gastric cancer patients [4]. It is usually reported within AFP-producing gastric cancer cases. Chang et al. described 24 cases of AFP-producing gastric cancer (4.3%, 24/556), showing a significant correlation with Borrmann type 2 and 3 (83.3%), liver metastasis, lymphatic and venous invasion. The incidences of synchronous and metachronous liver metastasis were 31.8% and 40.9%, respectively. The prognosis was dismal, the 1-, 3-, 6-year survival rates being 37.5%, 8.3%, 8.3%, respectively [3]. Nagai et al., comparing 28 cases of hepatoid gastric cancer and 22 cases of non-hepatoid type of AFP-producing gastric cancer, concluded that hepatoid gastric cancer had a poor prognosis and should be distinguished from AFP-producing gastric cancer without hepatoid features [4]. Its frequent liver metastases make hepatoid carcinoma of the stomach a good entity to study liver metastases of gastrointestinal cancer. The biological factors contributing to rapid progression and high incidence of liver metastases are still not clear.

CD44 is a family of molecules consisting of many isoforms. Some tumors, such as gliomas, exclusively express standard CD44 (CD44s), other neoplasms including gastrointestinal cancer also express CD44 variants (CD44v) [17]. Gastric cancer of the intestinal type is strongly positive for CD44v5 and CD44v6, whereas diffuse type tumor predominantly expresses CD44v5 [15, 16]. The lymph node

metastases of both intestinal and diffuse gastric cancer express CD44v6, suggesting that CD44v6 is important for lymphogenic dissemination [16]. Mayer et al. reported that expression of CD44 was significantly related to poor prognosis in gastric cancer [14]. Conversely, Hong et al. showed that patients with pan-CD44 or CD44v6 expressing gastric cancer survived as long as patients without CD44 expression [15]. Similar discrepancies were observed for colorectal cancer [12, 13]. In the present case, CD44 was strongly expressed both in primary tumor tissue and in metastatic liver lesion suggesting that CD44 expression might be related to tumor development and liver metastasis in hepatoid gastric cancer.

Laminin expression in tumor tissue was proved to have a close relationship with tumor metastasis. Forster et al. showed that laminin-negative tumors developed distant metastasis more frequently than laminin-positive tumors [9]. Liotta suggested that laminin might become degraded in the course of the destruction of basement membrane [8]. Conversely, Orita et al. suggested that the presence of laminin containing basement membrane in the deep periphery of gastric tumor was significantly associated with liver metastasis [10]. In the present case, neither the primary tumor tissue nor the secondary liver lesion expressed laminin, supporting Liotta's hypothesis.

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肝転移を伴った肝細胞癌様胃癌組織のCD44，Laminin発現の意義

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【要旨】 肝細胞癌様胃癌は悪性度高く，高率に肝転移を来すため，良い胃癌肝転移のモデルになっている．本症の生物学的な特徴と臨床病理学的な特徴との関連についての報告は稀である．我々は肝転移を伴う肝細胞癌様胃癌（hepatoid carcinoma）の一例を経験した．癌転移の関連因子として，細胞間接着因子の一つであるCD44及び細胞基底膜の主な成分の一つであるlaminの発現状態を調べ，合わせ報告する．免疫染色にて，原発巣と肝転移巣の癌細胞内にCD44の発現が強陽性であったが，laminの発現は陰性を示した．これらは肝細胞癌様胃癌の高率な肝転移との関連を示唆した．

キーワード：肝細胞癌様胃癌，肝転移，CD44，laminin