CD54 Expression Is Predictive for Lymphatic Spread in Human Gastric Carcinoma

MASAKAZU YASHIRO, MD, TAKESHI SUNAMI, MD, and KOSEI HIRAKAWA, MD

Even among gastric carcinoma cases with a similar extent of lymphatic invasion, the number of diseased lymph nodes may vary. Other factors might also contribute to the process of lymphangitic metastasis. Primary gastric tumors with the same extent of pathologic lymphatic invasion were studied in 78 patients. We investigated the correlation between CD54 expression on cancer cells and clinicopathologic features. Decreased CD54 expression on cancer cells was significantly correlated with the number of involved lymph nodes and the extent of lymph node spread. The number of diseased lymph nodes was associated with the prognosis of patients with gastric carcinoma. The CD54-negative group had a significantly worse prognosis than the CD54-positive group. These findings suggested that CD54 expression is predictive for lymphatic spread and prognosis in human gastric carcinoma.

KEY WORDS: CD54; gastric cancer; lymph node metastasis; predictive factor.

Survival of patients with gastric cancer has improved with the development of diagnostic and operative techniques (1, 2). However, gastric cancer still remains a major cause of death worldwide. Lymph node (LN) spread is one of the most important prognostic factors in patients with gastric cancer; however, the mechanisms responsible for LN spread are still unclear (3, 4). Lymphangitic invasion consists of cancer cell infiltration into lymph vessels at the primary tumor, migration to LNs, and proliferation in LN. It is widely accepted that LN disease is closely related to lymphatic invasion (5, 6). However, patients with lymphatic infiltration by cancer cells do not always develop LN disease. Even among cases with the same extent of lymphatic invasion, the number of involved LNs or the extent of LN spread differs. These findings suggest that not only lymphatic invasion but other factors might contribute to the process of lymphatic carcinoma.

Recent advances in immuno-oncology have clarified the mechanisms of immunologic tolerance. Escape of cancer cells from immunosurveillance may be responsible for progression of various types of carcinomas (7, 8). Immunologic tolerance has been associated with major histocompatibility complex class I antigen and decreased expression of costimulatory molecules including CD54 (ICAM-1; intercellular adhesion molcule-1) on cancer cells (9–11), Fas ligand on cancer cells (12, 13), and immunosuppressive factors such as transforming growth factor-β1 (14). CD54, a member of the immunoglobulin superfamily, is a Mr 70–110 kDa type I transmembrane glycoprotein with five immunoglobulin-like extracellular domains (15). CD54 is found on the surface of numerous cells including vascular endothelial cells, fibroblasts, dendritic cells of the nervous system, leukocytes, monocytes, and hematopoietic cells. After binding to the ligands CD11a/CD18 (LFA-1; lymphocyte function antigen-1) and Mac-1 (CD11b/CD18) on the surface of T lymphocytes, it plays a role in their activation, by enhancing the TCR/CD3 receptor signal. It has been reported that high expression of CD54 on a tumor cell’s surface increases the susceptibility of such tumor cells to lymphocyte-mediated tumor cytotoxicity through the
CD54/LFA-1 system (16, 17). We previously reported that decreased CD54 expression on cancer cells is closely associated with LN disease using gastric cancer cell lines (18). CD54 on cancer cells plays an important role in adhering to natural killer cells or lymphocyte-activated killer cells via LFA-1 (19). Moreover, CD54 contributes to optimal cytotoxic lymphocyte activation as a costimulatory molecule transmitting a second signal (20, 21). The decrease in CD54 on cancer cells might be associated with a decrease in cytotoxicity of immune effector cells, which may result in cancer progression. However, some researchers have reported a positive relationship between CD54 expression on cancer cells and tumor progression or metastasis (22, 23), but others have reported negative relationships (24, 25). In this study, we investigated the relationship between CD54 expression on cancer cells and clinicopathologic factors in gastric cancer patients with the same extent of pathologic lymphatic invasion.

MATERIALS AND METHODS

Clinical Materials. Resected primary tumors from 78 patients with gastric cancer, all with lymphatic invasions judged moderate by pathologic assessment, were studied. We analyzed patients with moderate lymphatic invasion by pathologic assessment because we focused on the effect of CD54 expression on LN spread by excluding the effect of overwhelming lymphatic invasion by cancer cells. Lymphatic invasion was identified on the basis of conventional hematoxylin and eosin (H&E) staining as the presence of cancer emboli within channels lined by a single layer of endothelial cells without smooth muscle. The “grading” of lymphatic invasion was determined as moderate when the lymphatic invasions were found at more than two spots and fewer than five spots in a field of carcinoma under 40× magnification. All patients were treated surgically between 1985 and 1995 at our department. No patients had received preoperative therapy. The age of the patients ranged from 41 to 86 years (mean, 60.5 ± 11.2 years); 46 were men and 32 were women. The primary tumors and LNs were fixed in 10% buffered formaldehyde and embedded in paraffin. Sections (4 µm thick) cut from the formalin-fixed and paraffin-embedded tissue from 23 cases of gastric cancer was prepared in 4-µm-thick sections and stained with Toluidine blue.

Statistical Analysis. The χ² test or Mann–Whitney U test was used to determine the significance of the difference between the covariates. Survival durations were calculated using the Kaplan–Meier method. The log-rank test (Stat View; Abacus Concepts, Inc., Berkeley, CA) was used to compare the cumulative survival durations in the patient groups. Also, the Cox proportional hazards model was used to compute univariate and multivariate hazards ratios for the study parameters. In all of the tests, a P value <0.05 was defined as statistically significant. The SPSS software program (SPSS Japan, Tokyo) was used for the analyses.

RESULTS

CD54 Expression in Primary Gastric Cancer. Normal gastric mucosa was not stained with anti-CD54 antibody. However, vascular endothelium and monocytes were well stained. A variable percentage of gastric cancer cells showed strong staining. Figure 1 shows a tumor positive for CD54. Expression of CD54 was recognized in the membrane and cytoplasm of the cancer cells. CD54-positive specimens were found in 24 of 78 (31%) primary gastric tumors.

CD54 Expression and Clinopathologic Factors. Table 1 shows the correlation between CD54 expression and various clinicopathologic factors. CD54 expression was not significantly correlated with T stage by the

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