Hiroshima J. Med. Sci.
Vol.39, No.2, 29~37, June, 1990
HIJM 39-7

Gastric Carcinoma with Lymphoid Stroma: Pathological and Immunohistochemical Analysis

Hisao ITO[1], Hirohisa MASUDA[1], Fumio SHIMAMOTO[2], Chiaki INOKUCHI[3] and Eiichi TAHARA[1]

1) *Department of Pathology, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan*
2) *Section of Clinical Pathology, Kure Mutual Aid Hospital, 3-28, Nishichuo 2-chome, Kure, Hiroshima 737, Japan*
3) *Inokuchi Geka-Hospital, 951-1 Toyomaru Saijyocho, Higashi-Hiroshima 724, Japan*

ABSTRACT

Nineteen gastric carcinomas with lymphoid stroma were selected from 554 surgical cases and examined pathologically and immunohistochemically using formalhyde-fixed, paraffin embedded materials. Most showed ulcerative lesion and 15 cases located in fundic and cardiac gland regions. They were subdivided histologically into three groups, early (group I), localized (group II) and infiltrative tumors (group III), the number of cases being 2, 10 and 7, respectively. Lymph node metastases occurred in 3 cases in group II and 6 in group III, the latter showing a significantly higher incidence. The number of carcinoembryonic antigen and CA19-9 immunoreactive tumor cells was apparently smaller in gastric carcinomas with lymphoid stroma than in ordinary gastric carcinomas. Frequent presence of alpha$_1$-antichymotrypsin immunoreactivity characterized the tumor cells of gastric carcinoma with lymphoid cells. Stroma cells consisted of lymphocytes, plasma cells, granulocytes and histiocytes. Of these, the greatest number examined immunohistochemically was B cells and IgG cells, followed in descending order by T cells, IgA cells and IgM cells in the order given. A variable number of lysozyme immunoreactive histiocytes were also detected in all the cases. Gastric carcinoma with lymphoid stroma might be subclassified as a separate entity, although short term follow-up study did not demonstrate a favorable prognosis for this type of gastric cancer.

Key words: *Gastric carcinoma, Lymphoid stroma, Immunohistochemistry*

Massive lymphoid infiltration is not infrequently observed in the stroma of some solid tumors[2,4,5,16,23,29]. Such a carcinoma of the stomach was first reported by MacCarty et al[12] in 1922 and has sebsequently been described under a variety of separate diagnosis including blue cell carcinoma[23], medullary carcinoma with lymphoid infiltration[4] and gastric carcinoma with lymphoid stroma[29]. Its frequency within gastric carcinomas varies considerably ranging from 1.3 to 20%[4,23,29], probably due to the different histological criteria employed by the investigators. Watanabe et al[29] has reported a favorable postoperative prognosis of the patients with gastric carcinoma with lymphoid stroma, but other researchers have failed to demonstrate this[24]. Moreover, gastric carcinoma with lymphoid stroma has not been listed as a separate pathological entity in the major classification systems of the gastric carcinoma until now[9,13-15,30].

Against this background, we attempt to analyse the phenotypic expressions of the tumor cells and the cellular constitutions of the stromal cells of gastric carcinoma with lymphoid stroma. The relationship between the histologic picture and prognosis of the patient is also re-evaluated in order to clarify the biological behavior and progression of such carcinomas in the stomach.

MATERIALS AND METHODS

A total of 475 cases with gastric carcinoma were resected from 1975 to 1985 in Kure Mutual Aid Hospital and 79 cases from 1978 to 1985 in Inokuchi-Surgical Hospital. For each case, 8 to 50 tissue blocks including the main lesions were excised longitudinally after fixing in 4% formaldehyde and then embedded in paraffin wax. We reviewed all the cases histologically and then selected 19 cases (3.4%) of gastric carcinoma with lymphoid stroma according th Watanabe's[29] criteria (Table 1). Briefly, the tumor cells are poorly differentiat-

Supported in part by Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture and Tsuchiya Medical Foundation, Hiroshima, Japan.
Address for reprint: H. Ito (address see above)

Table 1. Clinical and Pathological Findings from 19 Cases of Gastric Carcinoma with Lymphoid Stroma

Patient No.	Age	Sex	Site of Tumor	Gross Findings	Depth of Invasion	Group	Lymph node Metastases	Postoprative Survival/ Cause of Death
1.	40	M[a)]	M[b)]	depressed	m[d)]	Ia[e)]	—	alive, 3yr
2.	70	F	MC	depressed	sm	Ib	—	alive, 6yr 8mo
3.	68	F	M	depressed	sm	II	—	alive, 5yr 5mo
4.	45	M	C	depressed	sm	II	—	alive, 2yr10mo
5.	53	M	C	depressed	sm	II	—	alive, 2yr 4mo
6.	80	M	A	B-3[c)]	ss	II	+	alive, 3yr10mo
7.	48	M	MAC	B-2	ss	II	—	unknown
8.	75	F	CM	B-2	se	II	+	died, 3yr not available
9.	62	M	AM	B-2	pm	II	—	alive, 9yr 8mo
10.	81	F	C	B-1	ss	II	—	alive, 3yr 3mo
11.	44	M	MC	B-3	ss	II	—	alive, 2yr 7mo
12.	51	M	CM	B-2	se	II	+	alive, 2yr 1mo
13.	58	M	M	B-3	ss	III	+	alive, 2yr 5mo
14.	43	M	M	B-3	ss	III	+	alive, 2yr 4mo
15.	58	M	A	B-3	pm	III	—	alive, 2yr10mo
16.	58	M	MC	B-3	ss	III	+	alive, 3yr 4mo
17.	67	M	M	B-3	ss	III	+	died, 6yr with multiple metastases
18.	82	F	M	B-3	pm	III	+	died, 1yr with renal insufficiency
19.	46	M	A	B-3	pm	III	+	died, 1yr with multiple metastases

a: M; male, F; female
b: A; Antrum, M; Middle third of stomach includes bulk of the corpus, C; Upper third of stomach includes the cardiac and fundus
c: Macroscopic classfication of advanced gastric carcinoma is based on Borrmann's classification
d: m; mucosa, sm; submucosa, pm; muscle layer, ss; subserosa, se; serosa exposed
e: Definition of the group used in the present study is described in Table 2

ed showing a less pleomorphic appearance without apparent glandular formations, distributed sparsely in the nondesmoplastic, lymphoid tumor stroma which often form lymphoid follicles.

Two or three representative paraffin blocks were selected from each case for light microscopy and immunohistochemistry. Serial sections 4 μm in thickness from the tissue blocks were stained with hematoxylin and eosin, periodic acid Schiff (PAS) reagents, Alcian blue (AB; pH 2.5), and Grimelius silver nitrate technique for argyrophil reaction. 28 control cases of the ordinary gastric carcinoma without any notable lymphoid infiltration were selected at random and immunostained. They consisted of 11 early and 2 advanced carcinomas in stage I, 9 carcinomas in stage II and 6 in stage III according to the criteria of the Japanese Research Society for Gastric Cancer[9].

Immunohistochemistry

Avidin-biotin peroxidase complex (ABC) method after Hsu et al[6] was used to demonstrate several antigens. Incubation with antibodies or rinsing in phosphate-buffered saline (PBS) in each step was performed at least for 30 minutes at room temperature. Endogenous peroxidase activity was inactivated by immersing the specimens in 0.03% hydrogen peroxide in absolute methanol for 20 minutes. In some instances (e.g. immunoglobulin, alpha$_1$-antitrypsin), the dewaxed sections were pretreated with 0.1% trypsin for 20 minutes at 37 °C to enhance immunostaining sensitivity.

Antibodies

The following were used as primary antibodies in this study. Rabbit conventional antibodies to alpha$_1$-antitrypsin (AAT; working dilution 1:300), alpha$_1$-antichymotrypsin (ACT; 1:300), lysozyme (1:800), carcinoembryonic antigen (CEA; 1:400), IgG (1:600), IgA (1:600), IgM (1:600) and mouse monoclonal antibodies to pan T (DAKO-UCHL1) were purchased from DAKO Immunoglobulins (Copenhagen, Denmark). Mouse monoclonal antibody to pan B (MX-Pan B) was obtained from Kyouwa (Tokyo, Japan) and employed at a 1:100 dilution. CEA antiserum was not preabsorbed with nonspecific cross-reacting antigen (NCA). Preparation and characterization of pan B and pan T antibodies have been described previously[7,18,22,29]. Briefly, pan B antibody is known to react with a part of pre-pre B cells and B immunoblasts, but not with immunoglobulin producing plasma cells. Pan T antibody reacts with about one half of helper T cells and one third of suppressor T cells. Mouse monoclonal antibody CA19-9 was a gift from Toray-Fuji Bionics Inc. (Tokyo, Japan) and employed at a 1:600 dilution. Biotinylated anti-rabbit and anti-mouse IgG, and avidin-biotinylated horse radish peroxidase complex (ABC) were purchased from Vector Laboratories, Inc, CA, U.S.A.

Table 2. Group of Gastric Carcinoma with Lymphoid Stroma and Metastasis

Group	Number of Cases	Cases with Metastasis
I: Early gastric cancer		
a, Mucosal carcinoma	1	0
b, Early invasion into submucosa	1	0
II: Tumor cells are localized within the lymphoid stroma	10	3
III: Tumor cells in variable number infiltrate out of the lymphoid stroma	7	6

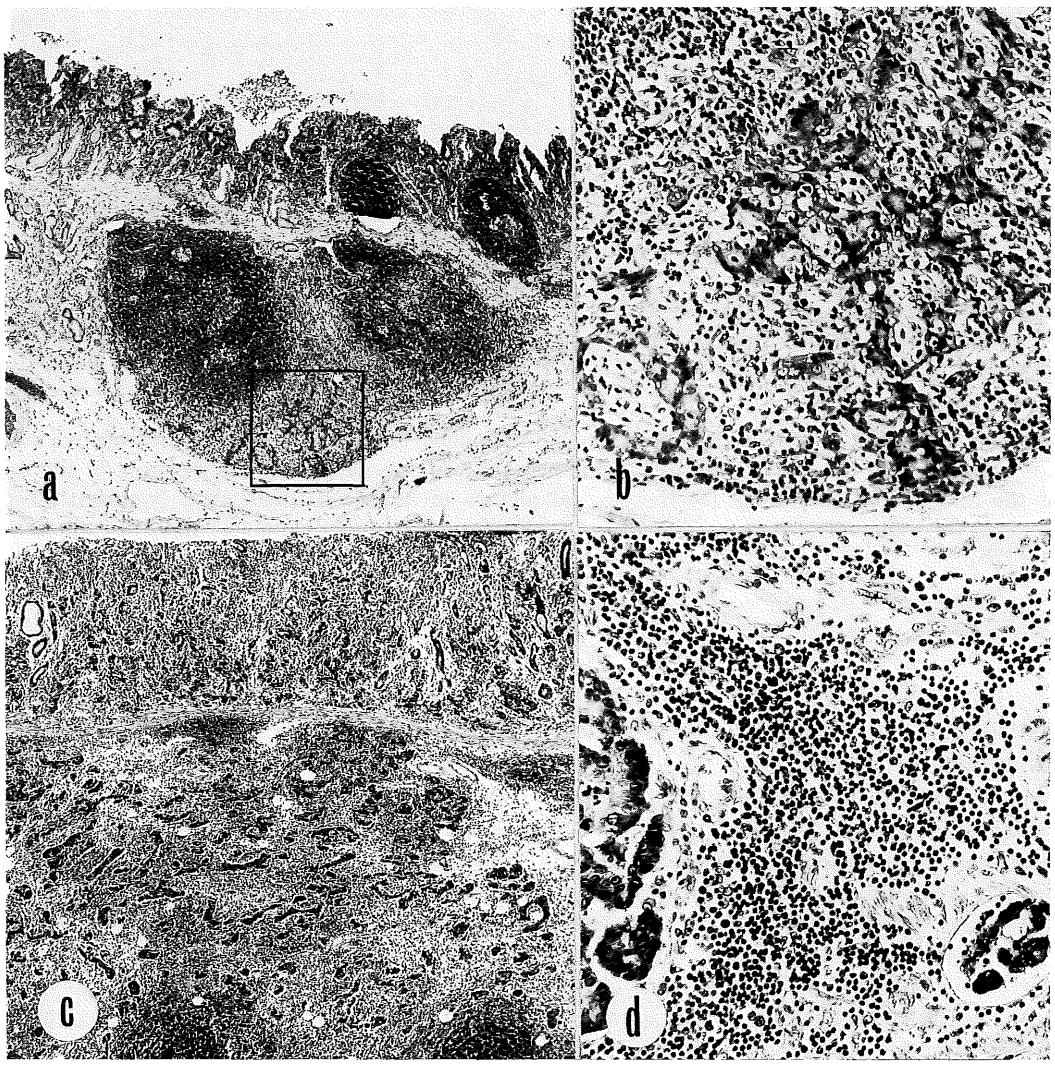

Fig. 1. Histological pictures of gastric carcinoma with lymphoid stroma. (a) Gastric carcinoma with lymphoid stroma of group Ib. Lymph nodules are noted in submucosa subjacent to the mucosal carcinoma. H & E. (×35) (b) A higher magnification in square area of photograph a. A few tumor cells in trabecular pattern infiltrate in submucosa. H & E. (×175) (c) Gastric carcinoma with lymphoid stroma of group III. Tumor cells distribute sparsely throughout the lymphoid stroma. H & E. (×35) (d) Tumor cells infiltrate out of lymphoid stroma and invade lymph vessel. Same case as c. H & E. (×175)

Subclassification of the Gastric Carcinoma with Lymphoid Stroma

Gastric carcinomas with lymphoid stroma were divided into three groups in the present study (Table 2). Group 1 was subdivided into two: Ia and Ib. Tumor in group Ia corresponds to mucosal carcinoma and tumor cells are restricted in the mucosa. In group Ib, a few tumor cells invade submucosa (Figs. 1a and b). In group II, tumor cells extend into or beyond the submucosa but are localized within the lymphoid stroma. In group III, tumor cells in variable number infiltrate beyond the lymphoid stroma, irrespective of the tumor size and depth of invasion (Figs. 1c and d).

A follow-up study could be made on all the cases except for one, which was lost to follow-up shortly

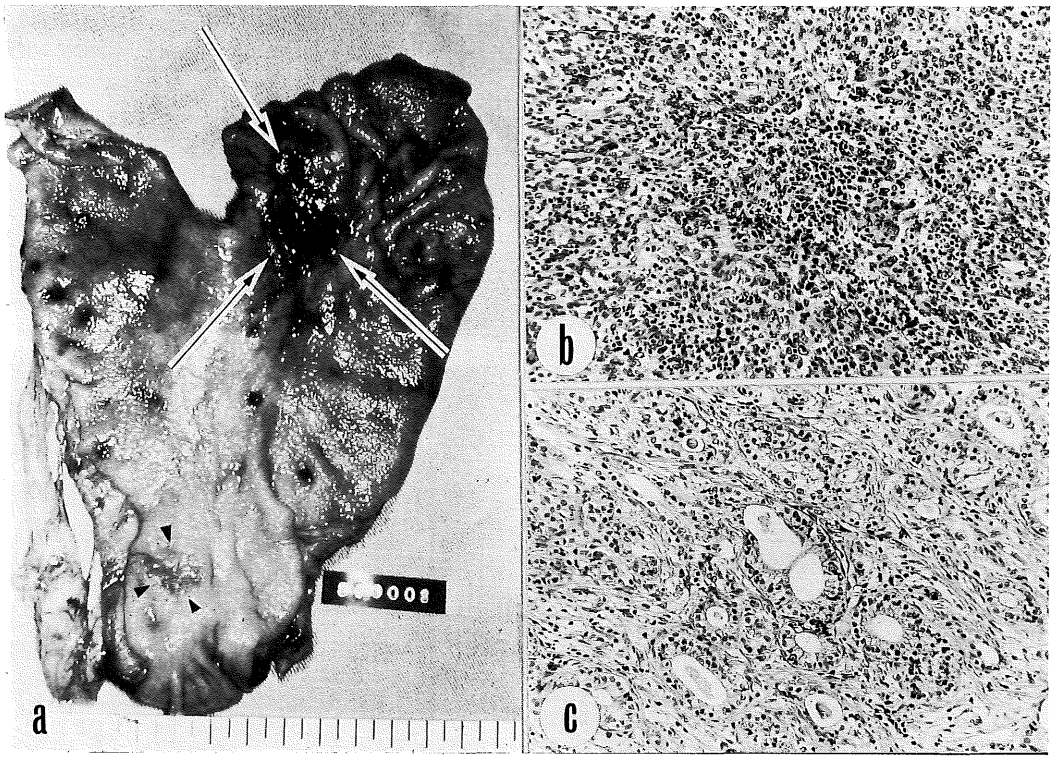

Fig. 2. (a) Gross appearance of gastric carcinoma with lymphoid stroma (Case No. 18). Ulcerative advanced tumor is present in the posterior wall of the fundus (arrows) and depressed early cancer in the anterior wall of the antrum (arrow heads). (b) Histological picture of advanced tumor with lymphoid stroma. H & E. (×125) (c) Histological picture of depressed early cancer without notable lymphoid infiltrations. H & E. (×125)

after surgical procedure.

RESULTS

1. Clinical and Pathological Findings of Gastric Carcinoma with Lymphoid Stroma

Table 1 shows age, sex and pathological findings such as localization, depth of the tumor invasion or presence of lymph nodes metastasis of 19 gastric carcinomas with lymphoid stroma. The mean age of 19 patients was 59.4 and male to female ratio was 2.8:1. Five cases were early gastric carcinoma, being free from metastases. All but one revealed macroscopically slightly depressed lesion (IIc) in cardia or fundic region. Among the 14 advanced carcinomas, 9 had already revealed metastases in the perigastric lymph nodes at operation. Thirteen of the 14 advanced carcinomas were ulcerative tumor, Borrmann's type 2 or 3, and localized in the intermediate zone or fundic region. Thus, 15 cases (78.9%) were developed in fundic and cardiac gland regions.

Histologically, the tumor cells were polygonal and medium in size without marked cellular atypia (Fig. 1). The nuclei with finely granular chromatin and less prominent nucleoli were round or oval. Mitotic figures were generally rare. The cytoplasm was mostly clear or slightly eosinophilic. The tumor cells showed thin trabecular, microalveolar or cord-like arrangement, but conspicuous glands were rare. They were distributed uniformly throughout the tumor tissue and separated by an intervention of broad lymphoid stroma (Fig. 1c) except for two cases in group I. In group Ia (Case No. 1) corresponding to mucosal carcinoma, tumor cells proliferated more or less compactly in the mucosa and lymph nodules with germinal center were present in the submucosa subjacent to the tumor. Case No. 2 was classified in group Ib and a few tumor cells invaded into lymphoid tissues located in submucosa (Figs. 1a and b). Neither necroses nor hemorrhage was noted. Tumors classified into group III frequently showed invasion into lymph and blood vessels,

PAS and/or AB staining revealed mucin-production by tumor cells in 15 (78.9%) of 19 cases, but the number of the tumor cells was obviously smaller than that of ordinary gastric carcinomas. A few tumor cells with argyrophilia by Grimelius staining were noted in one (5.3%) of 19 gastric carcinomas with lymphoid stroma.

The tumor stroma consisted of lymphocytes, plasma cells and histiocytes, but granulocytes were few. Lymph nodules with or without germinal center formation were found in a variable number in each case.

Case No.18 (IGH 83088): A 82-year-old woman was subjected to subtotal gastrectomy because of the endoscopic and histopathological diagnosis of

Table 3. Immunohistochemical Findings on the Tumor Cells of 19 Gastric Carcinomas with Lymphoid Stroma and 28 Ordinary Gastric Carcinomas

Antigens	Number of Cases of Gastric Carcinoma with Lymphoid Stroma (19 Cases)					Number of Cases of Ordinary Gastric Carcinoma (28 Control Cases)				
	0[a)]	1+	2+	3+	4+	0	1+	2	+3	4+
AAT	6	8	3	1	1	12	7	4	4	1
ACT	0	0	6	7	6	3	4	8	9	4
Lysozyme	5	3	7	3	1	15	5	4	3	1
CEA	3	3	8	1	4	1	1	8	11	7
CA19-9	12	4	3	0	0	8	5	8	5	2

a: These reactions are graded on the basis of the number of positive staining tumor cells; 1+, scattered; 2+, under 25% of tumor cells; 3+ between 25% and 50% of tumor cells; 4+; over 51% of tumor cells
AAT; alpha$_1$-antitrypsin; ACT; alpha$_1$-antichymotrypsin;
CEA; Carcinoembryonic Antigen

Table 4. Comparison between the Numbers of AAT and ACT Immunoreactive Tumor Cells in 19 Gastric Carcinomas with Lymphoid Stroma and 28 Ordinary Gastric Carcinomas

AAT and ACT Immunoreactivity	No. of Cases of Gastric Carcinoma with Lymphoid Stroma	No. of Cases of Ordinary Gastric Carcinoma
AAT > ACT	0	4
AAT = ACT	0	7
AAT < ACT	19	17

AAT: alpha$_1$-antitrypsin; ACT: alpha$_1$-antichymotrypsin
AAT<ACT: Tumor cells with ACT immunoreactivity are more dominant than those with AAT immunoreactivity.

gastric adenocarcinoma. Macroscopically, there were two types of gastric tumor: depressed type advanced lesion in the posterior wall of the corpus and depressed early cancer in the anterior wall of the antrum (Fig. 2a). Histologically, the former showed gastric carcinoma with lymphoid stroma (Fig. 2b), whereas the latter was tubular adenocarcinoma without notable lymphoid infiltration (Fig. 2c).

2. Immunohistochemical Findings

Table 3 shows immunohistochemical findings of the 19 gastric carcinomas with lymphoid stroma and 28 ordinary gastric carcinomas. Alpha$_1$-antichymotrypsin (ACT) immunoreactivity was detected in all the cases of gastric carcinoma with lymphoid stroma and 25 (89.3%) of ordinary gastric carcinoma. Although there was no significant difference in the frequency of ACT immunoreactivity between two groups, the number of ACT immunoreactive tumor cells was apparently greater in the gastric carcinomas with lymphoid stroma. Alpha$_1$-antitrypsin (AAT) immunoreactivity was found in 13 (68.4%) gastric carcinomas with lymphoid stroma and in 16 (57.1%) ordinary gastric carcinomas. There was no significant difference in the frequency. Table 4 shows the relationship between the tumor cells with AAT and ACT.

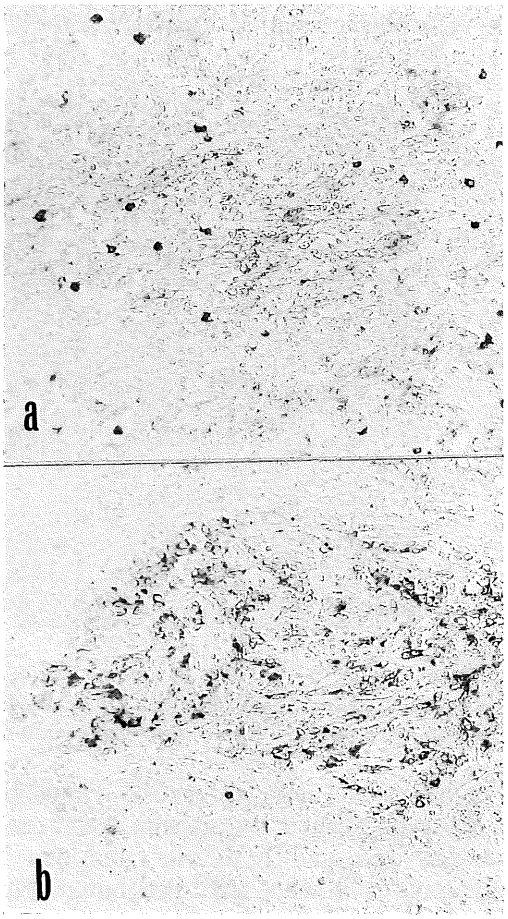

Fig. 3. Lysozyme immunostaining of case No. 18. (a) A good number of lysozyme-containing histiocytes are found in the tumor stroma. ABC methods. (×160) (b) Most of the tumor cells show lysozyme-immunoreactivity, whereas lysozyme-containing histiocytes are few. ABC method. (×160)

Predominance of ACT immunoreactive tumor cells is shown in all the cases of gastric carcinoma with lymphoid stroma in contrast to 17 (60.7%) out of 28 cases of ordinary gastric carcinoma. Difference in immunoreactivity for lysozyme was insignificant between two groups. They were found in 13 (68.4%) cases with lymphoid stroma (Fig. 3) and 13

(46.4%) of ordinary type. CA 19-9 containing tumor cells were detected in 7 (36.8%) cases with lymphoid stroma and 20 (71.4%) of the ordinary type, both the frequency and number being significantly higher in the latter ($p < 0.05$). CEA immunoreactivity was found in high frequency in both gastric carcinomas with lymphoid stroma and ordinary gastric carcinomas. Although there was no significant difference in its frequency, the number of CEA immunoreactive tumor cells was apparently greater in the ordinary gastric carcinomas. In three cases of gastric carcinoma with lymphoid stroma of group III, CEA-immunoreactivity was detected mainly in the tumor cells which infiltrated beyond the lymphoid stroma (Fig. 4).

Lymphoid stroma consisted of various lymphoid cells and histiocytes. The majority of germinal center cells showed pan B immunoreactivity (Fig. 5a). Abundant IgG immunoreactive lymphoid cells were observed around the germinal centers (Fig. 5b). A few IgA and IgM cells, and pan T immunoreactive cells were also distributed (Figs. 5c and d). In general, the greatest number was occupied by IgG cells and pan B cells, followed in descending order by pan T cells, IgA cells and IgM cells in the order given. Lysozyme immunoreactive histiocytes were detected in a variable number in all the cases. An inverse correlation was apparent between the number of lysozyme immunoreactive tumor cells and histiocytes (Figs. 3a and b).

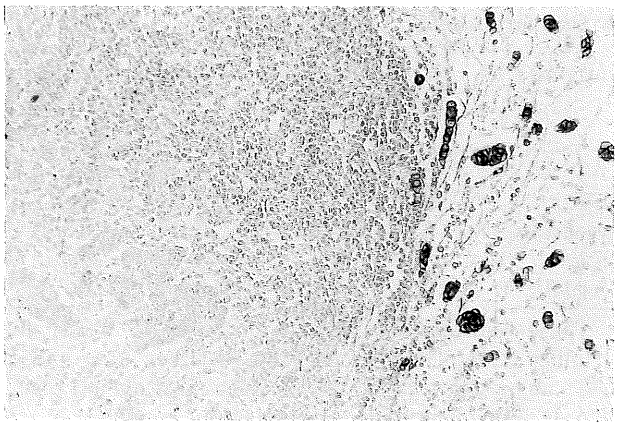

Fig. 4. CEA immunoreactivity is noted in most of the tumor cells infiltrating out of lymphoid stroma. ABC method. (×130)

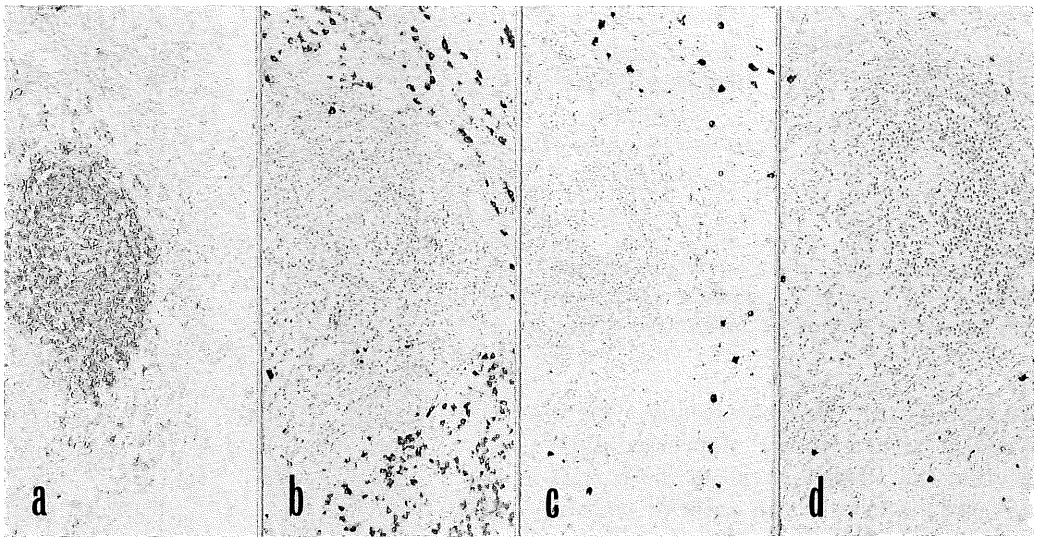

Fig. 5. Semiserial sections of gastric carcinoma with lymphoid stroma. (a) Germinal center cells show pan B immunoreactivity. (b) Abundant IgG cells distributed around the lymph nodules. (c) and (d). A good number of IgA (c) and IgM (d) cells are also noted intermingled with IgG cells. ABC methods. (×95)

3. Classification of the Gastric Carcinoma with Lymphoid Stroma and Prognosis

Tumor metastases to the perigastric regional lymph nodes occurred in three (30%) of the 10 cases in group II and in six (85.7%) of the 7 cases in group III. The frequency of metastases was significantly higher ($p < 0.05$) in the latter than in the former.

Review of follow-up records disclosed that 14 of the 18 patients were alive without apparent evidence of the disease and four had died. Autopsy was not done in the latter cases, but multiple metastases to the lung and liver were clinically recorded in two cases in group III (No. 17 and 19). The remaining two patients had died of renal insufficiency (No. 18) and unknown cause (No. 8).

DISCUSSION

Watanabe et al[29] analysed 42 (4%) gastric carcinomas with lymphoid stroma out of a total of 1041 surgical cases. On the whole, the clinical and pathological findings in the present study coincided well with their results, with respect to the frequency, mean age, sex ratio, and macro-and microscopic features. A minor difference from their

report was seen in the localization of the tumor. Most of the gastric carcinomas with lymphoid stroma in the present study were located in the fundic and cardiac gland regions in contrast to only 10 out of 42 cases in Watanabe's series. Although 14 patients are alive without apparent recurrence, the follow-up period in the present study seems to be too short to evaluate a favorable postoperative prognosis of the patients.

Histologically, tumor cells of gastric carcinoma with lymphoid stroma revealed a thin trabecular, microalveolar or cord-like arrangement but obvious gland formations were less frequent. The tumor might correspond to poorly differentiated adenocarcinoma, medullary type after the classification by Japanese Research Society for Gastric Cancer[9], and to poorly differentiated tubular adenocarcinoma or undifferentiated carcinoma by WHO classification[30]. Mild cellular atypia of the tumor cells, however, was not necessarily suitable for the classifications.

Immunohistochemically, the tumor cells with lymphoid stroma revealed quantitative difference in the phenotypic expressions from those of ordinary gastric cancers, the latter being in good agreement with our previous reports[8,25-27]. The tumor cells with lymphoid stroma were characterized by less frequent production of CA 19-9 and CEA. CEA immunoreactivity was, however, frequently found in those tumor cells infiltrating out of lymphoid stroma. These findings indicate the heterogeneity of tumor cells of the gastric carcinoma with lymphoid stroma, and some tumor clones might be capable to infiltrate over the lymphoid stroma, resulting in a high frequency of metastases. The frequency and number of the tumor cells with alpha$_1$-antichymotrysin (ACT) was significantly higher in gastric carcinoma with lymphoid stroma than in ordinary gastric carcinomas, whereas alpha$_1$-antitrysin (AAT) showed no significant difference between the two groups. The predominance of ACT immunoreactive tumor cells might be related to the biological role of ACT, which is known to enhance the antibody formation[27]. Contrarily, AAT has been recently demonstrated to inhibit, nonspecifically, the blastogenic response of normal lymphocytes to phytohemagglutinin (PHA)[1,17,19].

Attempting to analyse the progression of gastric carcinoma with lymphoid stroma, we divided the gastric carcinoma with lymphoid stroma into three groups in this study; early (I), localized within lymphoid stroma (II) and infiltrative tumor out of lymphoid stroma (III). In group I, lymphoid tissues were present mainly in submucosa subjacent to mucosal carcinoma, indicating a close relation between tumor cells and lymphoid cells even in this early stage. In group II, tumor cells were restricted within lymphoid stroma, and metastases to perigastric regional lymph nodes were relatively rare. On the other hand, a variable of tumor cells frequently metastasized to the regional lymph nodes in group III. Moreover, two patients in group III died with metastases to several organs, one and six years after surgical procedure, respectively. Thus, the subclassification used in this study appears to have been valuable in predicting the prognosis for the patients of gastric carcinoma with lymphoid stroma. Attention should be, therefore, paid to the presence of the tumor cells infiltrating out of lymphoid stroma in the histological sections.

Much interest has been focused upon the correlation between lymphocytes infiltrating into the stroma and biological behavior of the gastric cancer[3,12]. In 1922, Mac-Carty and Mahle[12] had already stressed the prognostic significance of lymphocytic infiltration in gastric cancer. More recently, interest has focused mainly upon the analysis of the lymphocyte-subpopulations in the tumor stroma, especially of T cell subsets. Kikuchi et al[10,11] have reported that the majority of lymphocytes were T cells in the stroma of gastric cancer, whereas B cells, especially IgA cells, were found in gastric mucosa with gastritis or near ulcer lesion. They also found that Leu-2 positive (cytotoxic/suppressor) T cells were more dominant than Leu-3 positive (inducer/helper) T cells in most of the advanced gastric cancer. Predominance of T cells in the tumor stroma was also confirmed in breast cancer[20,21]. On the contrary, lymphocytes consisted mainly of B cells and immunoglobulin-producing plasma cells in gastric carcinoma with lymphoid stroma. In view of the lymphocyte subpopulations in the tumor stroma and the absence of tumor cell necrosis in gastric carcinoma with lymphoid stroma, the interaction between tumor cells and lymphocytes might be different from those of ordinary gastric carcinoma without notable lymphoid stroma. Lymphocytes forming lymphoid stroma seem to prevent the progression and metastasis of the tumor, but they might have no cytotoxic activity on the tumor cells.

We have assumed that tumor cells play an important role in the histogenesis of lymphoid stroma. This speculation might be supported by case No. 18 which contained both gastric carcinoma with lymphoid stroma and ordinary tubular adenocarcinoma in the removed stomach. New parameters or markers of the tumor cells should be sought to demonstrate the phenotypic differences of tumor cells between gastric carcinoma with lymphoid stroma and ordinary ones.

In addition to the characteristic histological appearance reported by Watanabe et al[29] we have demonstrated some additional properties of gastric carcinoma with lymphoid stroma: (1) less frequent production of CEA, CA19-9 and mucin than that of ordinary gastric carcinoma, (2) predominance of B cells in the tumor stroma and (3) high incidence of metastases to the perigastric regional lymph nodes in group III. These findings might support

our contention that gastric carcinoma with lymphoid stroma should be classified as a separate pathological entity, although a favorable prognosis of the patients was not confirmed in this study because of the short follow-up period. The histogenesis of the lymphoid stroma remains to be elucidated in the future.

(Received December 15, 1989)
(Accepted May 14, 1990)

REFERENCES

1. **Arora, P.K. and Miller, H.C.** 1978. Alpha$_1$-antitrypsin is an effector of immunological stasis. Nature **274**: 589–590.
2. **Bassler, R., Dittman, A.M. and Dittrich, M.** 1981. Mononuclear stromal reactions in mammary carcinoma with special reference to medullary carcinomas with lymphoid infiltrate. Analysis of 108 cases. Virchows Arch [Pathol Anat] **393**: 75–91.
3. **Black, M.M., Freeman, C., Mork, T., Harvei, S. and Cutler, S.J.** 1971. Prognostic significance of microscopic structure of gastric carcinomas and their regional lymph nodes. Cancer **27**: 703–711.
4. **Hamazaki, M., Sawayama, K. and Kuriya, T.** 1968. Stomach cancer with lymphoid stroma. J. Karyopathol. **12**: 115–120 (in Japanease).
5. **Hasumi, K., Sakamoto, G., Sugano, H., Masubuchi, K. and Kubo, H.** 1974. Medullary carcinoma with marked lymphoid infiltration of the uterine cervix. Jap. J. Cancer. Clin. **20**: 207–210 (in Japanese with English Abstract).
6. **Hsu, S.M., Raine, L. and Fanger, H.** 1981. Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: A comparison between ABC and unlabeled antibody (PAP) procedures. J. Histochem. Cytochem. **29**: 577–580.
7. **Ishii, Y., Takami, T., Yuasa, H. and Kikuchi, K.** 1984. Two distinct antigen systems in human B lymphocytes: identification of cell surface and intracellular antigens using monoclonal antibodies. Clin. Exp. Immunol. **58**: 183–192.
8. **Ito, H., Masuda, Y., Nakai, H., Hata, J., Yokozaki, H. and Tahara, E.** 1986. Carbohydrate antigen (CA 19-9) in human gastric mucosa, adenoma and carcinoma: Immunohistochemical study and comparison with preoperative serum level. Pathology and Clinical medicine (Tokyo) **4**: 1081–1088 (in Japanese with English Abstract).
9. **Japanese Research Society for Gastric Cancer.** 1985. The general rules for gastric cancer study. 11th ed. Kanahara Shuppan, Tokyo.
10. **Kikuchi, K., Ishii, Y. and Koshiba, H.** 1977. Identification of T and B cells in human cancer tissue, p. 236–246. *In* Y. Terry and Y. Yamada (eds.), Immunobiology and Immunotherapy of Cancer. Elsevier North Holland, Amsterdam.
11. **Kikuchi, K.** 1983. Analysis of lymphocytic surface antigens and its application. Tr. Soc. Pathol. Jpn **72**: 3–28 (in Japanese).
12. **MacCarty, W.C. and Mahle, A.E.** 1922. Relation of differentiation and lymphocytic infiltration to postoperative longevity in gastric carcinoma. J. Lab. Clin. Med. **6**: 473–480.
13. **Ming, S-C.** 1973. Tumors of the esophagus and stomach. In: Atlas of Tumor Pathology. Second Series. Fascicle 7. Armed Forces Institute of Pathology, Washington, D.C.
14. **Ming, S-C.** 1977. Gastric carcinoma. A pathobiological classification. Cancer **39**: 2475–2485.
15. **Ming, S-C.** 1985. Tumors of the esophagus and stomach. Supplement. In: Atlas of Tumor Pathology. Armed Forces Institute of Pathology, Washington, D.C.
16. **Moore, O.S., Jr. and Foote, F.W.J.** 1949. The relatively favorable prognosis of medullary carcinoma of the breast. Cancer **2**: 635–642.
17. **Nakanishi, K.** 1983. Experimental and clinical studies of serum immunosuppressive factors in tumor bearing host. Med. J. Hiroshima. Univ. **31**: 855–867 (in Japanese with English Abstract).
18. **Nicholson, J.K.A., McDougal, J.S., Spira, T.J., Cross, G.D., Jones, B.M. and Reinherz, E.L.** 1984. Immunoregulatory subsets of the T helper and T suppressor cell populations in homosexual men with chronic unexplained lymphadenopathy. J. Clin. Invest. **73**: 191–201.
19. **Samsk, R., Edelstein, R. and Israel, L.** 1982. Immunosuppressive effect of acute phase reactant proteins in vitro and its relevance to cancer. Cancer Immunol. Immunother. **13**: 38–43.
20. **Schoorl, R., Brutel, de la R.A., von dem Borne, A.E.G., Jr. and Feltkamp-Vroom, Th.M.** 1976. Identification of T and B lymphocytes in human brease cancer with immunohistochemic techniques. Am. J. Pathol. **84**: 529–544.
21. **Shimokawara, I., Imamura, M., Yamanaka, N., Ishi, Y. and Kikuchi, K.** 1982. Identification of lymphocyte subpopulations in human breast cancer tissue and its significance. An immunoperoxidase with antihuman T-and B-cell sera. Cancer **49**: 1456–1464.
22. **Smith, S.H., Brown, M.H., Rowe, D., Callard, R.E. and Beverley, P.C.L.** 1986. Functional subsets of human helper-inducer cells defined by a new monoclonal antibody, UCHL1. Immunology **58**: 63–70.
23. **Steiner, P.D., Maimon, S.N., Palmer, W.L. and Kirsner, J.B.** 1948. Gastric cancer- Morphologic factors in five-year survival after gastrectomy. Am. J. Pathol. **24**: 947–961.
24. **Syrjanen, K.J. and Hjelt, H.** 1978. Prognostic factors in gastric carcinoma. Neoplasma **25**: 365–374.
25. **Tahara, E., Ito, H., Shimamoto, F., Iwamoto, T., Nakagami, K. and Niimoto, H.** 1982. Lysozyme in human gastric carcinoma: A retrospective immunohistochemical study. Histopathology **6**: 409–421.
26. **Tahara, E., Ito, H., Nakagami, K., Shimamoto, F., Yamamoto, M. and Sumii, K.** 1982. Scirrhous argyrophil cell carcinoma of the stomach with multiple production of polypeptide hormones, amine, CEA, lysozyme, and hCG. Cancer **49**: 1904–1915.
27. **Tahara, E., Ito, H., Taniyama, K., Yokozaki, H., and Hata, J.** 1984. Alpha$_1$-antitrypsin, alpha$_1$-antichymotrypsin, and alpha$_2$-macroglobulin in human gastric carcinomas: A retrospective immunohistochemical study. Hum. Pathol. **15**: 957–964.
28. **Takami, T., Ishii, Y., Yuasa, H. and Kikuchi, K.** 1985. Three distinct systems on human B cell subpopulations as defined by monoclonal antibodies. J.

Immunol. **134**: 828–834.

29. **Watanabe, H., Enjoji, M. and Imai, T.** 1976. Gastric carcinoma with lymphoid stroma. Its morphologic characteristics and prognostic correlations. Cancer **38**: 232–243.

30. **World Health Organization** 1977. Histological typing of gastric and oesophagus tumours. In: International Histological Classification of Tumours, 18. Geneva.