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Primary gastric non–Hodgkin's lymphomas in Japan*

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Summary. A pathological study was carried out on 124 cases of primary gastric non-Hodgkin's lymphoma (NHL) in Japan. Macroscopically the cases were divided into three groups; flat, polypoid, and ulcerative types. Early lymphomas were distinguished from advanced by the depth of infiltration. Histologically the commonest type was ML, immunoblastic (ML, ibl.). Most were high grade malignancy, in terms of morphology. Lymph node involvement was found in 44 cases. Correlation between macroscopical appearance, histological diagnosis, stage and accompanying reactive lymphoid hyperplasia (RLH) was studied. Three main prototypes of gastric NHL were noted: The first was macroscopically ulcerative type, histologically high grade malignancy and lacked RLH; the second was mostly flat, ML, lymphoplasmacytic/lymphoplasmacytoid (ML, l-p.) or ML, ibl., associated with RLH, and arose from neoplastic proliferation of the interfollicular lymphoid cell in RLH (termed gastric NHL of interfollicular type); the third was mostly flat, ML, centroblastic (ML, cbl.) or lymphoblastic (ML, lbl.), associated with RLH, and originated from neoplastic proliferation of the follicular center cell in RLH (gastric NHL of follicular type).

Key words: Non-Hodgkin's lymphoma – Reactive lymphoid hyperplasia – Stomach – Immunohistochemical study – Japan

Introduction

Gastric cancer is still the commonest cause of death from malignant disease in Japan. Primary gastric non–Hodgkin's lymphoma (NHL) is much less common than cancer and the number of NHL is only about 1% of all gastric malignancy in the resected stomachs in the Tokyo University Hospital (Mohri and Shimamine 1983). With the progression of diagnostic skills in gastroenterology, the number of gastric NHL resected in their early stage is now increasing, like gastric cancer. Accordingly, the associated changes in the gastric wall around early NHL of the stomach have been carefully studied.

This paper presents clinicopathological findings including associated changes such as reactive lymphoid hyperplasia (RLH) or pseudolymphoma of the stomach, together with data on immunohistochemical study of gastric NHL in Japan.

Materials and methods

One hundred and twenty-four operatively resected primary gastric NHL were studied, consisting of 63 cases resected in the Tokyo University Hospital from 1955 to 1985 and 61 cases from consultations. Thirty-two cases of RLH were also examined. The criteria applied in the diagnosis of RLH were fundamentally those described by Faris and Saltzstein (1964) but there were several cases, in which a definite histological diagnosis of NHL or RLH could not be made. Among them the cases which were later found by immunohistochemistry to be a monoclonal proliferation of lymphoid cells, were reclassified as NHL.

The main localization of NHL was divided into lesser or greater curvature, anterior or posterior wall, and cardiac, fundic, pyloric gland area or intermediate zone. Macroscopically, NHL and RLH were classified as flat or superficial spreading, polypoid, simulating Borrmann I type of gastric cancer, and ulcerative types, simulating Borrmann II–III types (Figs. 1 and 2). In the flat type, the lesion was macroscopically flat and ill-definedly thickened, and was usually associated with multiple shallow ulcers or erosions. Infiltration of NHL in this type was mostly limited to submucosa. However, infiltration into the subserosa or serosa was revealed in several cases. The term "flat" type was thus preferred when compared with "superficial spreading" type. Flat type is different from Borrmann

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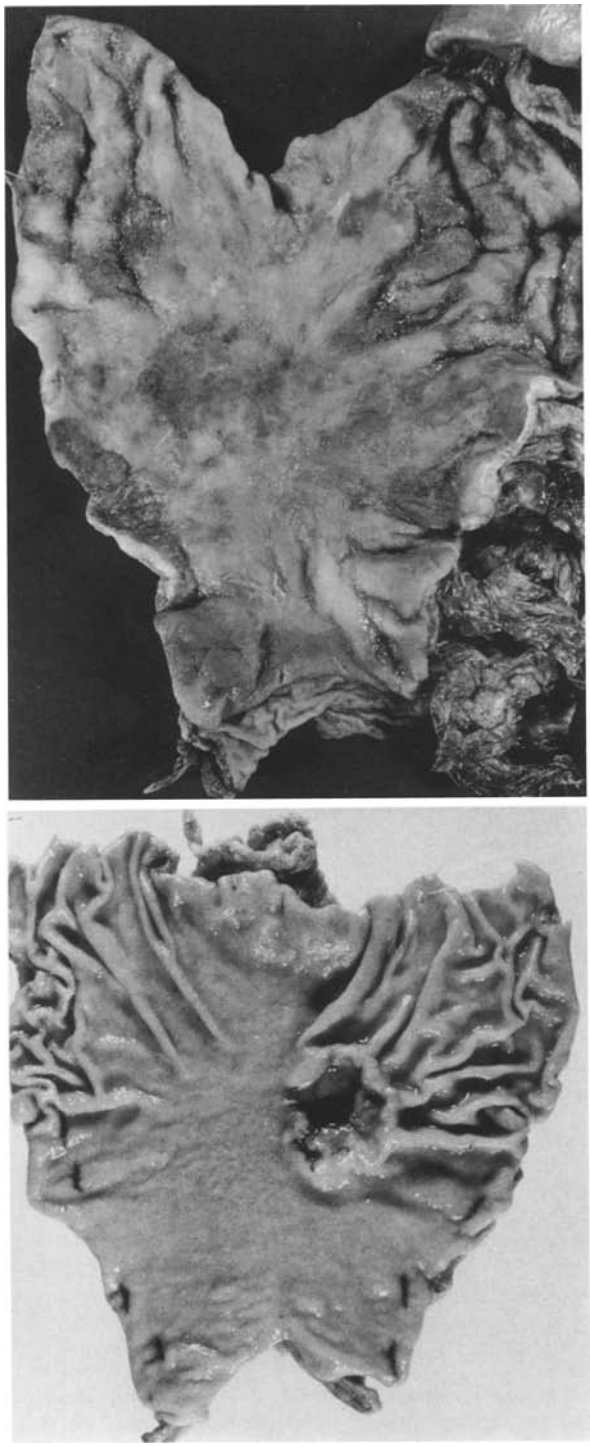

Fig. 1. Primary gastric NHL, flat type, of lesser curvature of the intermediate zone. Diffuse flat infiltration with multiple shallow ulcers, except the prepyloric region and a part of fundic gland area are noted. Spleen in the right upper

Fig. 2. Primary gastric NHL, ulcerative type, of posterior wall of the intermediate zone. A part in lesser curvature was excised for study by frozen sections

IV type; in the former more obvious superficial spreading of tumour is evident and there is less desmoplastic contraction of lesions than in the latter. Several sections were taken for microscopical study of NHL and changes in the surrounding area. All dissected lymph nodes were also studied microscopically.

H & E, Giemsa and PAS stains and silver impregnation were prepared. For detection of cytoplasmic immunoglobulins (C-Igs), the immunoperoxidase technique including the peroxidase-antiperoxidase complex (PAP) or avidin biotin peroxidase complex (ABC) methods was introduced when paraffin blocks were available. For immunohistochemical study, rabbit antisera specific for gamma, alpha, mu, kappa and lambda chains of immunoglobulins were purchased from Hoechst Japan LTD, Japan and rabbit PAP were obtained from Dakopatts, Denmark and ABC staining kits were from Vector Laboratories, Inc., USA. Immunostaining was performed following the method of Hsu et al. (1981). Antibodies (1:200, diluted in phosphate buffered saline) listed above were used as the first reagent, and the PAP or ABC staining kits for rabbit immunoglobulins were introduced as the second and third reagents. Briefly, four micron thick sections were cut from the paraffin blocks. After deparaffinizing with xylene and blocking tissue peroxidase with 3% H_2O_2 in ethanol, slides were incubated with first, second and third reagents succeedingly with wash by phosphate buffered saline after each step. Diaminobenzidine was used as chromogen. And for counterstaining, haematoxylin was used. In a few cases, immunohistochemical study on frozen sections was done using monoclonal antibodies of the Leu series (Becton Dickinson) or the rosette technique was done. For histological diagnosis of NHL, the Kiel classification (Lennert and Mohri 1978) was applied. The cases of RLH were classified histologically as follicular, interfollicular and combined types. In the follicular type, the lesion consisted predominantly of follicular hyperplasia of lymphoid cells. In the interfollicular type, the lesion consisted mainly of hyperplasia of interfollicular cells. In the combined type, the lesion was composed of both follicular and interfollicular hyperplasia of lymphoid cells. Coexistence of NHL and RLH in the stomach and the relationship between them was also studied. Finally, the overlap of other NHL of the stomach or other organs at the same or at different times, and other malignancy of the stomach was also sought.

Results

The age distribution and sex ratio of NHL and RLH is shown in Fig. 3. The peak of NHL and RLH was in the sixth decade respectively. Both the average and median ages of NHL were about 5 years older than those of RLH.

The main localization of NHL and RLH is shown in Fig. 4. The commonest site of NHL and RLH was the lesser curvature of the intermediate zone; the second was the lesser curvature in the pyloric gland area.

The relation between macroscopical appearance and depth of infiltration of NHL in 122 cases is shown in Table 1. Based on the depth of infiltration, the cases were divided into two groups, namely "early lymphoma", infiltrating up to the submucosa and "advanced lymphoma", infiltrating the muscularis propria or deeper. Of 69 cases of

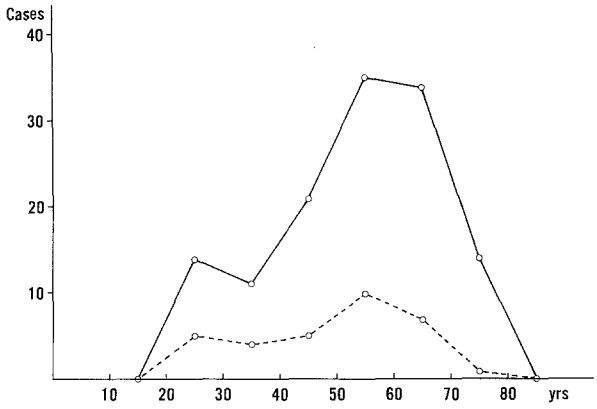

Fig. 3. Age distribution and sex ratio of NHL (124 cases) and RLH (32 cases) of the stomach. o—o NHL: range: 20–77 years; average: 53.0 years; median: 56 years; male: female = 1.0:0.75. o----o RLH: range: 21–71 years; average: 48.1 years: median: 51 years; male: female = 1.0:0.88

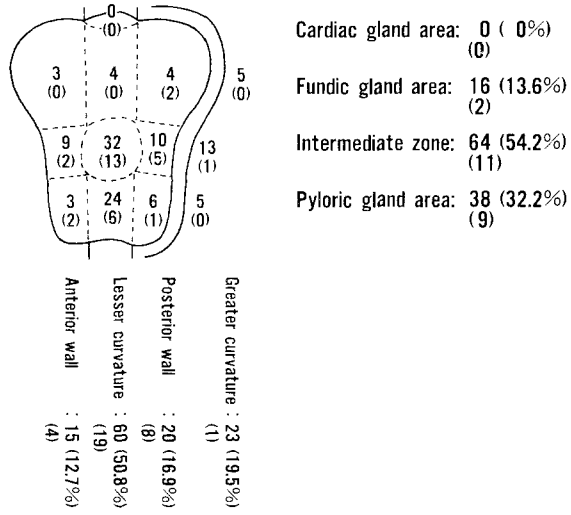

Fig. 4. Localization of NHL (118 cases) and RLH (32 cases) (in parentheses) of the stomach

Table 1. Macroscopical appearance and depth of infiltration of NHL of the stomach (122 cases)

Type	Early lymphoma		Advanced lymphoma			Total
Depth	m	sm	pm	ss	s	
Flat	6	47	5	4	7	69
Polypoid	0	1	0	0	0	1
Ulcerative	0	2	9	18	23	52
Total	6	50	14	22	30	122

Depth m: Infiltration only in mucosa; sm: Infiltration up to to submucosa; pm: Infiltration up to muscularis propria; ss: Infiltration up to subserosa; s: Infiltration up to serosa

Table 2. Histological classification of NHL of the stomach (124 cases)

	Cases	%
Low grade malignancy	20	16.1
ML, lymphocytic (ML, lc.)	0	0
ML, lymphoplasmacytic/ lymphoplasmacytoid (ML, l-p.)	17	13.7
ML, centrocytic (ML, cc.)	1	0.8
ML, centroblastic/centrocytic (ML, cbl/cc.)	2	1.6
High grade malignancy	104	83.9
ML, centroblastic (ML, cbl.)	23	18.6
ML, lymphoblastic (ML, lbl.)	36	29.0
Burkitt type	0	0
Convoluted-cell type	0	0
Unclassified	36	29.0
ML, immunoblastic (ML, ibl.)	45	36.3
Total	124	100.0

the flat type, 53 (75.4%) were early lymphoma. The majority of the ulcerative type was advanced lymphoma. Macroscopically, most of RLH (26/32 cases) were flat, 3 were polypoid and 3 were ulcerative type. Histological classification of NHL is shown in Table 2. The commonest type was ML, ibl., and ML, lbl, Ml, cbl. and ML, l-p. followed in the order of frequency. No case of ML, Burkitt type or ML, convoluted-cell type was found in the present study. Most of the low grade malignancy cases (16/20 cases, 80.0%) belonged to early lymphoma and the majority of high grade malignancy (63/104 cases, 60.62%) came under the category advanced lymphoma. Fifteen cases (21.7%) of the 69 flat type and only 3 (5.8%) of 52 ulcerative type, were of low grade malignancy, the remainder were high grade. Only 1 of the polypoid type was ML, cbl/cc., which was included in the low grade malignancy group. Ten of 32 cases of RLH were included in the follicular, 10 in the interfollicular and 12 in the combined type. Most (28/32 cases) of RLH were associated with shallow ulcers or erosions.

In Table 3, data of immunohistochemical study by PAP or ABC method on paraffin sections in each histological type of 98 cases are given. Collectively, C-Ig was monoclonally positive in about one-fourth cases. All of ML, l-p. and one-third of ML, ibl. were positive. In 9 cases, monoclonal C-Ig was proved to be IgM, kappa type, and in 10 IgM, lambda type, in 1 IgA, lambda type and in another 1 IgG, lambda type. One of ML, ibl.

Table 3. Immunohistochemical study by PAP or ABC method using paraffin sections of the stomach (98 cases)

	Monoclonally positive cases	Studied cases	%
ML, lymphocytic (ML, lc.)	0/0		–
ML, lymphoplasmacytic/lymphoplasmacytoid (ML, l-p.)	13/13		100.0
ML, centrocytic (ML, cc.)	0/1		0
ML, centroblastic/centrocytic (ML, cbl/cc.)	0/2		0
ML, centroblastic (ML, cbl.)	2/22		0
ML, lymphoblastic (ML, lbl.)	0/26		0
ML, immunoblastic (ML, ibl.)	12/34		35.3
Total	25/98		25.5

was proved to have only kappa type light chain and 3 only lambda chain. In total, 19 cases were shown to have mu type heavy chain, 1 alpha type and another 1 gamma type, and 10 cases kappa type light chain and 15 lambda type. Besides, each 1 case of ML, cbl. and ML, lbl. were found to be B cell lymphoma following immunostaining of frozen sections. Another case of ML, cbl. was demonstrated to be IgM, lambda type B cell lymphoma. Furthermore, a case of ML, ibl. was also shown to be a B cell lymphoma by the rosette technique. Immunohistochemical data of RLH by the PAP method on paraffin sections were previously reported in collaboration with Mori et al. (1980) and showed that many lymphoid cells bearing different classes of immunoglobulin were present in RLH in an intermingled way (polyclonal). Therefore it was strongly suggested that RLH was a lesion based on severe reactive, not neoplastic, lymphoid cell infiltration induced by something in association with erosions or ulcerations. In many cases of ML, l-p., transition from polyclonal to monoclonal proliferation of lymphoplasmacytoid cells between remaining germinal centers was shown by immunohistochemical study of paraffin sections. In some cases of ML, ibl., focal monoclonal proliferation of immunoblasts within the area of polyclonal proliferation of lymphoplasmacytoid cells between germinal centers was found. In a few cases of ML, cbl. or lbl., monoclonal proliferation of B cell in part of the hyperplastic germinal centers was shown and gradual replacement of hyperplastic germinal centers by monoclonal proliferation of blastic cells was demonstrated by immunohistochemical study of frozen sections.

Lymph node involvement was found in 44 of 124 cases (36.1%). In the flat type 25 (36.2%) showed lymph node involvement and in ulcerative type 19 (36.5%) were affected, none in the polypoid type were involved. Lymph node involvement was found less frequently in early than in advanced lymphoma (15/56 cases, 26.8% vs. 29/66 cases, 43.9%, $p<0.05$). It was noteworthy that in 6 cases of early lymphoma where infiltration was confined to the mucosa, no lymph node involvement was found, while 15 of 50 cases (30.0%) of early lymphoma infiltrating to the submucosa showed lymph node involvement. Lymph node involvement was most frequently seen in ML, cbl. (13/23 cases, 56.5%). In low grade malignancy, lymph node involvement was seen in 4 of 20 cases (20.0%) and in high grade malignancy in 40 of 104 cases (36.7%). The difference between them was not statistically significant.

Table 4. Coexistence of NHL and RLH of the stomach (123 cases)

	RLH		
	Negative	Positive	Total
Early lymphoma	19 (33.3%)	38 (66.7%)	57 (100.0%)
Advanced lymphoma	55 (83.3%)	11 (16.7%)	66 (100.0%)
Total	74 (60.2%)	49 (39.8%)	123 (100.0%)

	RLH		
	Negative	Positive	Total
Low grade malignancy	3 (15.0%)	17 (85.0%)	20 (100.0%)
High grade malignancy	71 (68.9%)	32 (31.1%)	103 (100.0%)
Total	74 (60.2%)	49 (39.8%)	123 (100.0%)

Coexistence of NHL and RLH is presented in Table 4. Forty-nine cases (39.8%) showed coexistence of NHL and RLH. It was demonstrated more frequently in early lymphoma than in advanced lymphoma ($p<0.001$) and more frequently in low grade malignancy than in the high grade malignancy group ($p<0.001$). Among 38 cases of early lymphoma associated with RLH, 13 were with the follicular type of RLH, 19 with the combined type and 6 with only several scattered lymphoid cell aggregations in the tumour tissue. Three of 11 cases of advanced lymphoma associated with RLH were with the follicular type, 5 with the combined and 3 with only scattered lymphoid cell aggregations in the tumour tissue. All 17 cases of low grade malignancy associated with RLH were histo-

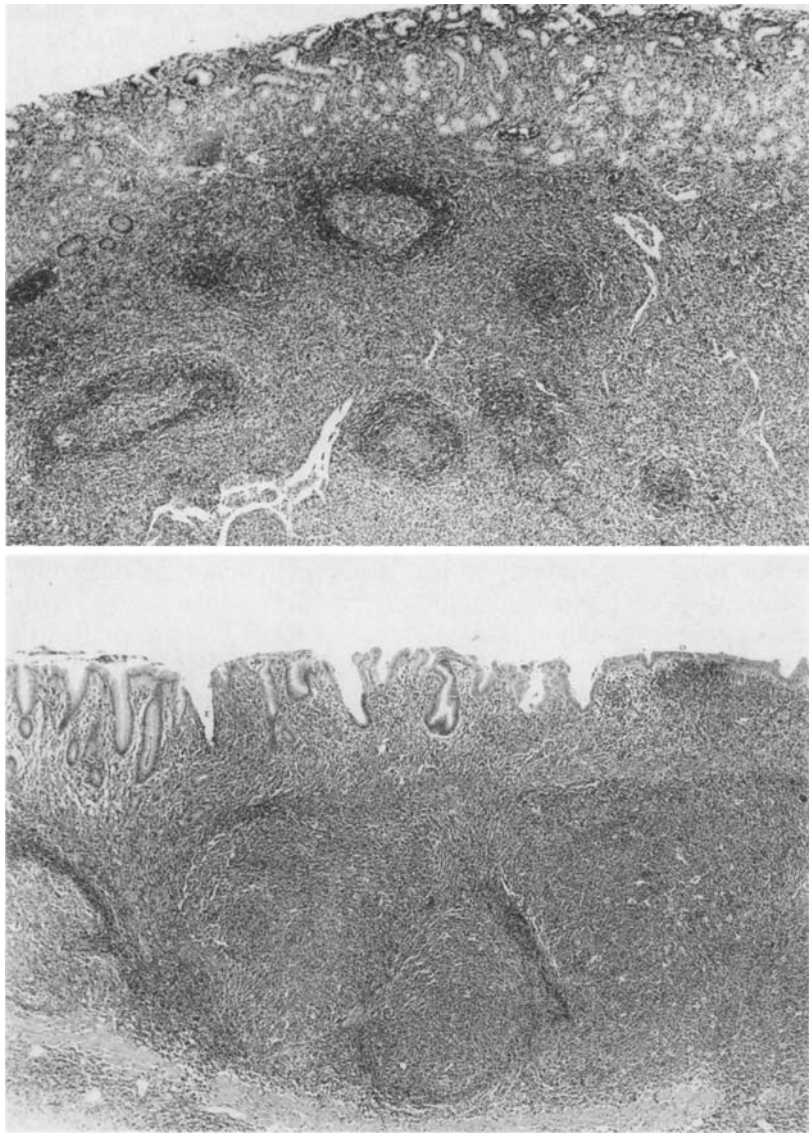

Fig. 5. Primary gastric NHL associated with RLH – "interfollicular type". In the center and left a few non-neoplastic, slightly hyperplastic germinal centers and in the right, diffuse neoplastic, proliferation of interfollicular lymphoid cells between regressive non-neoplastic lymph follicles are seen. HE 31.5×

Fig. 6. Primary gastric NHL associated with RLH – "follicular type". In the left, hyperplastic non-neoplastic germinal center with focal infiltration of neoplastic cells in the lower right, and in the center as well as right, follicular or diffuse monotonous proliferation of neoplastic follicular center cells are seen. HE 31.5×

logically ML, l-p.. Among these 17 cases, 6 were associated with follicular type of RLH, 7 with combined type and 4 with scattered lymphoid cell aggregations in the tumour tissue. Among 32 cases of high grade malignancy associated with RLH, 10 were with follicular type of RLH, 17 with combined type and 5 with only scattered lymphoid cell aggregations in the tumour tissue.

Macroscopically, 43 (87.8%) out of 49 cases with RLH were the flat type and the remaining 6 were ulcerative. However, of 73 cases without RLH, 26 were flat type, 1 was polypoid and 46 were ulcerative. Consequently, it was evident that cases with RLH belonged mostly to the flat type ($p<0.001$) and to the low grade malignancy ($p<0.001$), and that cases without RLH were in both flat and ulcerative, and histologically mostly in high grade malignancy.

Forty-nine cases with RLH were grouped histologically into the following three types: In the first type, diffuse proliferation of lymphoid cells were noted in the center of NHL lesion, with residual non-neoplastic regressive lymphoid tissue within them, and gradual transition from monoclonal to polyclonal proliferation of lymphoid cells was seen at the periphery (Fig. 5), shown by the immunohistochemical method for detection of C-Ig. These findings suggested that this type of NHL develops from neoplastic proliferation of interfollicular lymphoid cells in RLH. Twenty-nine cases (59.2%), consisting of all 17 cases of ML, l-p., 11 of ML, ibl. and 1 of ML, lbl. were included in

this type. In 17 cases of this type, associated RLH was recognized as combined type of RLH, in 6 cases as follicular type and in other 6 cases only as scattered lymphoid cell aggregations with or without regressive germinal centers, in the tumour tissue.

In the second type, diffuse or follicular neoplastic proliferation of atypical lymphoid cells was noted in the center of the lesion, and gradual transition from neoplastic proliferation of atypical lymphoid cells to reactive hyperplasia of germinal centers was demonstrated at the periphery. Occasionally partial infiltration of atypical lymphoid cell nests within reactive hyperplastic germinal centers was revealed (Fig. 6). These findings suggest that this type of NHL arose from neoplastic proliferation of germinal center cells in RLH. Fourteen cases (28.6%), consisting of 9 of ML, cbl. and 5 of ML, lbl. were included in this tpye. In 8 cases of this type, associated RLH was recognized as follicular type of RLH, in 4 cases, as combined type and in 2 cases, only as several lymphoid cell aggregation only.

In the third type, there was no special histological correlation between NHL and RLH. Six cases (12.2%), consisting of 3 ML, lbl., 2 ML, cbl. and 1 ML, ibl. were classified in this way. In 2 cases, associated RLH was found as follicular, in 3 cases as the combined type and in 1 case only as scattered several lymphoid cell aggregations in the tumour tissue.

There were 7 cases (5.1%), in which gastric NHL and NHL of other organs coexisted. Of 7 cases, 3 had NHL of the faucial tonsils and 4 NHL of the small intestines. All 7 cases represented same histology in both sites. All 3 NHLs of the stomach were found, 7mos, 1yr and 7yrs, after presentation of the tosillar NHL, respectively. NHLs of the stomach and small intestine were found roughly at the same time. In another case, coexistence of two histologically different gastric NHLs were revealed simultaneously and in different regions. In 2 cases of ML, l-p., marked amyloid deposition was found.

Furthermore, in 3 cases overlapping gastric cancer was found.

Discussion

Gastric malignant lymphoma (ML) holds an important position among extranodal lymphomas (Freeman et al. 1972; Mohri and Shimamine 1983). There are many clinicopathological studies on gastric ML or NHL, however, there are only a few which are oriented towards the development of gastric NHL or to its associated lesions. Isaacson (1981) discussed a relationship between coeliac disease and ML of the gastrointestinal tract, and Vanden Heule et al. (1979), Mohri et al. (1981), Wolf and Spjut (1981), Brooks and Enterline (1983a, 1983b), Murayama et al. (1984), Moriwaki et al. (1985), and Scoazec et al. (1986) stressed a close relationship between gastric NHL and RLH or pseudolymphoma. Some of these authors have demonstrated that several cases of gastric NHL were preceded by RLH or pseudolymphoma.

From the present study, the following conclusions can be reached: Gastric NHL develops about 5 years later than RLH, the localization of gastric NHL and RLH was almost identical, coexistence of gastric NHL and RLH is more frequently found in early than in advanced lymphoma and more frequently in low grade malignancy than in high grade malignancy type. From this we may conclude that coexistence of RLH is more frequently found in the earlier stage of NHL and in more slowly progressive cases. Three main histological correlations were found between gastric NHL and RLH; there was a type without coexistence of NHL and RLH, mainly showing a macroscopically ulcerative type, a histologically high grade malignancy, and advanced lymphoma. It is suggested that in most of ulcerative type, gastric NHL developed de novo or evidence of coexistence of NHL and RLH had been lost in the early stage of NHL. Another type existed, probably arising from gradual transition from reactive to neoplastic lesions in the interfollicular areas of RLH. For this type, the designation "interfollicular" was proposed. Most of ML, l-p., and a part of ML, ibl. belonged to this category. The third type probably arises from gradual transformation of reactive follicular center cells to neoplastic cells and finally to diffuse proliferation. For this type, the designation "follicular" was warranted. About a half of ML, cbl. and one-seventh of ML, lbl. were included in this type. A possible relationship of NHL and RLH of the stomach is represented in Fig. 7.

When the incidence of lymph node involvement in gastric NHL was compared with gastric cancer, the rate of involvement of early lymphoma was shown to be almost equal to early cancer (Iwanaga et al. 1979; Yoshino et al. 1979), but the rate of involvement in advanced lymphoma was far lower than in advanced cancer (Yoshino et al. 1979) ($p < 0.001$).

It is not easy to compare the incidence of each histological type of NHL in the present study with that of other series, because of different histologi-

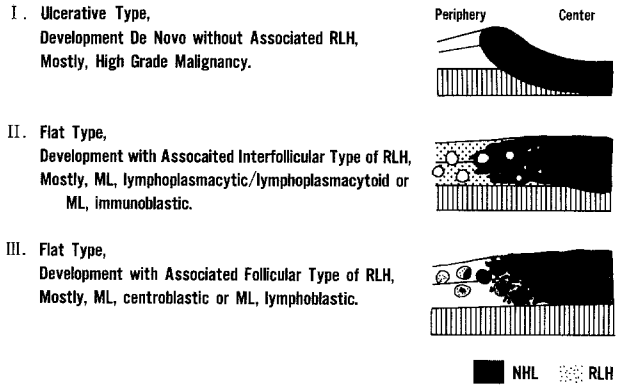

Fig. 7. Schematic representation of three main prototypes of NHL of the stomach

cal classifications. Radaszkiewicz and Dragosics (1980) reported that in their series the commonest type of NHL was ML, cbl/cc. and NHL of follicular center cell origin were the majority of cases (30/46 cases, 65.2%). They also reported that the number of cases of low grade malignancy and of high grade malignancy were almost equal. Hirota et al. (1980) reported on gastric NHL in Japan that 23 out of 41 cases of gastric NHL were "histiocytic", and 11 were "poorly differentiated lymphocytic". If we suppose that "histiocytic" and "poorly differentiated lymphocytic" were equivalent to high grade malignancy in the Kiel classification, NHL of high grade malignancy are the majority (34/41 cases, 82.8%). In the present study, similar results to Hirota's study in Japan were obtained, namely high grade malignant NHL were the majority of the cases (109/124 cases, 83.9%). It was found that cases of follicular center cell origin in the present study were fewer than those of Radaskiewicz and Dragosics (1980).

In a surface marker study of the tumour cells of gastric NHL, most have reported that almost all cases were of B cell origin (Yamanaka et al. 1980; Minato et al. 1980; Grody et al. 1985; Isaacson et al. 1986). In the present study it was impossible to make a conclusive comment, because only a few cases were studied in detail on frozen sections. However, there was no case which appeared to be of T cell origin histologically or was shown to have T cell markers by using the Leu series or the rosette technique. In an immunohistochemical study on paraffin sections, cases of B cell origin, which were shown to bear monoclonal C-Ig, were limited to the cases of ML, l-p. and ML, ibl. Heavy chain in these cases was mostly mu chain and the ratio of kappa to lambda light chains was 2:3. It was interesting that all of the ML, l-p. had a complete C-Ig with both heavy and light chains, but one-third of the cases of ML, ibl. had an incomplete C-Ig, consisting only of light chain.

The following comments may be useful in differential diagnosis:

1. In the cases consisting of a monotonous diffuse proliferation of large lymphid cells, microscopical study of H&E, Giemsa, PAS stain and silver impregnation preparations are enough for a definitive diagnosis.

2. In cases consisting of diffuse monoclonal proliferation of lymphoplasmacytic or lymphoplasmacytoid cells, associated with RLH, immunohistochemical study for C-Ig by PAP or ABC method on paraffin sections is valuable.

3. In cases consisting of partly follicular and mostly diffuse monoclonal proliferation of atypical follicular center cells, immunohistochemical study by frozen sections for demonstration of monoclonality of proliferating cells is occasionally indispensable.

In the literature, coexistence of gastric NHL and NHL of other organs has been well documented (Banfi et al. 1972; Rudders et al. 1978; Ree et al. 1980), and a theory of "homing" has seemed to gain an advantage. No support for this was found in the present study.

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