We recently showed that *Helicobacter pylori* (HP)-positive gastric ‘pure’ diffuse large B-cell lymphoma (DLBCL) may respond to HP eradication therapy. However, whether these HP-related ‘pure’ DLBCL of the stomach may differ fundamentally from those unrelated to HP remains unclear. In this study, we compared the clinicopathologic features of these two groups of patients who had been uniformly treated by conventional chemotherapy. Forty-six patients were designated HP-positive and 49 were HP-negative by conventional criteria. HP-positive patients had a lower International Prognostic Index score (0–1, 65% vs 43%, \(P = 0.029\)), a lower clinical stage (I-IIIE1, 70% vs 39%, \(P = 0.003\)), a better tumor response to chemotherapy (complete pathologic response, 76% vs 47%, \(P = 0.004\) and significantly superior 5-year event-free survival (EFS) (71.7% vs 31.8%, \(P < 0.001\)) and overall survival (OS) (76.1% vs 39.8%, \(P < 0.001\)). To draw a closer biologic link with HP, HP-positive tumors were further examined for CagA expression in lymphoma cells. Compared with CagA-negative cases (\(n = 16\), CagA-positive cases (\(n = 27\)) were associated with high phosphorylated SHP-2 expression (\(P = 0.016\)), and even better 5-year EFS (85.2% vs 46.3%, \(P = 0.002\)) and OS (88.9% vs 52.9%, \(P = 0.003\)). HP-related gastric ‘pure’ DLBCL may be a distinct tumor entity, which is less aggressive, and responds better to conventional chemotherapy.

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INTRODUCTION

Previous studies have shown that gastric ‘pure’ diffuse large B-cell lymphomas (DLBCLs), that is, tumors without any histologic evidence of mucosa-associated lymphoid tissue (MALT) origin, may be epidemiologically associated with *Helicobacter pylori* (HP) infection.1,2 We recently reported that a substantial portion of patients with gastric ‘pure’ DLBCLs can be cured by HP eradication therapy.3 These findings suggest that gastric ‘pure’ DLBCLs can be further divided into HP-related and -unrelated subtypes. These two groups of gastric tumors may differ from each other in cell origins, carcinogenesis mechanisms and clinicopathologic features.

To explore the differences of these two groups of tumors, we reviewed all patients with primary gastric ‘pure’ DLBCL who were treated with conventional chemotherapy as front-line therapy, and further divided them into HP-positive and -negative groups based on the presence or absence of HP infection. We analyzed the histomorphologic findings, molecular subclassification, clinical stage, International Prognostic Index (IPI) score, tumor response to chemotherapy, event-free survival and overall survival (OS) in these two patient groups. Because HP can be an innocent bystander infection in certain HP-positive cases, we further examined the HP-positive group for CagA tumor expression, a marker that we recently found useful in detecting a direct HP relevance of gastric low-grade MALT lymphoma.4 Our results indicated that HP-related gastric ‘pure’ DLBCL, particularly that with CagA expression, is a distinct entity associated with less aggressive tumor behavior and a better patient prognosis.

PATIENTS AND METHODS

Patients, treatment and evaluation of tumors

The medical records and pathologic specimens of consecutive patients with histologically confirmed primary gastric DLBCL that had no histologic evidence of MALT origin were reviewed. These patients were all diagnosed at our institutions from 1 January 1999 to 30 December 2009. Patients with histologic features of MALT lymphoma, including dense infiltration of centrocyte-like cells in the lamina propria and typical lymphoepithelial lesions, in initial and in follow-up samples were excluded.5–7 Specimens were immunohistochemically stained with CD20, CD5, CD3 and CD43 for routine diagnostic purposes. In this study, the median number of gastric biopsies for each patient was 6 (range, 2–23). The presence of HP infection was confirmed in each case, using histologic examination, urease test or bacterial culture.3,8

Staging workups included a physical examination with an inspection of Waldeyer’s ring, a detailed history, a hemogram with leukocyte differential count, serum lactate dehydrogenase (LDH) evaluation, computed tomographic scan of the chest, abdomen and pelvis, bone marrow aspiration and biopsy, an upper gastrointestinal examination, using endoscopy and gallium scintigraphy or fluorine-18 fluorodeoxyglucose positron emission tomography. The staging and classification of lesions were based on the Musshoff modification of the Ann Arbor staging system. The diagnosis of
primary gastric ‘pure’ DLBCL must fulfill the modified criteria of Lewin et al.10 and Herrmann et al.10 (1) the presence of a predominant gastric lesion, with or without expansion to regional lymph nodes, and no involvement of distal lymph nodes; (2) peripheral blood smears revealing no leukemic or lymphomatous abnormalities.11 This definition also excluded patients with gastric involvement who were detected following previously diagnosed extra-abdominal lymphoma.11 Patients were stratified according to the IPI for intermediate- and high-grade non-Hodgkin’s lymphoma.12

Systemic chemotherapy consisting of either anthracycline- or anthracycline- nedione-containing regimens or rituximab-containing regimens was administered as the initial therapy for all patients with primary gastric ‘pure’ DLBCL. To exclude confounding factors (e.g., a synchronous therapy using HP eradication therapy and chemotherapy may potentially increase treatment efficacy in gastric DLBCL13), patients who received either surgical resection, HP eradication therapy or combined with HP eradication therapy and chemotherapy as their primary treatment were excluded in this study. Surgery and local radiotherapy were reserved for patients whose localized disease did not respond to chemotherapy or who developed treatment-related complications that warranted further treatment. Every patient underwent a follow-up endoscopic examination with a biopsy for suspicious lesions and an imaging examination to document their response to chemotherapy. Tumors were considered to have a biopsy for suspicious lesions and an imaging examination to document their response to chemotherapy. Tumors were considered to have a biopsy for suspicious lesions and an imaging examination to document their response to chemotherapy. Tumors were considered to have a biopsy for suspicious lesions and an imaging examination to document their response to chemotherapy.
Table 1. Clinicopathologic features of gastric ‘pure’ DLBCL with and without HP infection

| Variable                        | Total (%) | HP positive (%) | HP negative (%) | P-value |
|---------------------------------|-----------|-----------------|-----------------|---------|
| Total no.                       | 95 (100)  | 46 (48)         | 49 (52)         |         |
| Sex                             |           |                 |                 |         |
| Female                          | 52 (55)   | 23 (50)         | 29 (59)         | 0.369   |
| Male                            | 43 (45)   | 23 (50)         | 20 (41)         |         |
| Age (years old)                 |           |                 |                 |         |
| <60                             | 43 (45)   | 20 (44)         | 23 (47)         | 0.735   |
| ≥60                             | 52 (55)   | 26 (56)         | 26 (53)         |         |
| Endoscopic features             |           |                 |                 |         |
| Ulceration or ulcerated mass    | 54 (57)   | 31 (57)         | 23 (47)         | 0.044   |
| Non-ulcerative lesions          | 41 (43)   | 15 (33)         | 26 (53)         |         |
| Location of tumor (s)           |           |                 |                 |         |
| Proximal or ≥2 components       | 49 (52)   | 19 (41)         | 30 (61)         | 0.052   |
| Distal                          | 46 (48)   | 27 (59)         | 19 (39)         |         |
| Presence of B symptoms          |           |                 |                 |         |
| Yes                             | 16 (17)   | 3 (6)           | 13 (27)         | 0.009   |
| No                              | 79 (83)   | 43 (44)         | 36 (73)         |         |
| Stage                           |           |                 |                 |         |
| I-IIE2/III/IV                   | 51 (62)   | 32 (70)         | 19 (39)         | 0.003   |
| IIE2/III/IV                     | 44 (38)   | 14 (30)         | 30 (61)         |         |
| ECOG                            |           |                 |                 |         |
| 0–1                             | 80 (84)   | 42 (91)         | 38 (78)         | 0.066   |
| ≥2                              | 15 (16)   | 4 (9)           | 11 (22)         |         |
| LDH                             |           |                 |                 |         |
| Normal                          | 53 (56)   | 31 (67)         | 22 (45)         | 0.027   |
| High                            | 42 (44)   | 15 (33)         | 27 (55)         |         |
| IPI risk group                  |           |                 |                 |         |
| 0–1                             | 51 (54)   | 30 (55)         | 21 (43)         | 0.029   |
| ≥2                              | 44 (46)   | 16 (33)         | 29 (57)         |         |
| Chemotherapy response           |           |                 |                 |         |
| pCR                             | 58 (61)   | 35 (76)         | 23 (47)         | 0.004   |
| PR + SD + PD                    | 37 (39)   | 11 (24)         | 26 (53)         |         |
| Histologic subclassification     |           |                 |                 |         |
| (n = 78)                        |           |                 |                 |         |
| GCB                             | 44 (56)   | 25 (64)         | 19 (49)         | 0.171   |
| Non-GCB                         | 34 (44)   | 14 (36)         | 20 (51)         |         |
| Chemotherapy regimen            |           |                 |                 |         |
| Anthracycline-based             | 61 (64)   | 26 (57)         | 35 (71)         | 0.511   |
| Rituximab/anthracycline-based   | 22 (23)   | 12 (45% )       | 9 (18)          |         |
| Rituximab/nonanthracycline-based| 5 (5)     | 3 (6)           | 2 (4)           |         |
| Others                          | 7 (8)     | 4 (9)           | 3 (6)           |         |

Abbreviation: ACE, doxorubicin, cyclophosphamide and etoposide; CHOP, cyclophosphamide, epirubicin (≥70 mg/m²), vincristine and prednisolone; COP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CNOP, cyclophosphamide, mitoxantrone, vincristine and prednisolone; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HP, H. pylori; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PACE, prednisolone-AE; pCR, complete pathologic remission; PR, partial remission; SD, stable disease; PD, progression; GCB, germinal center B-cell. Proximal: Middle body, upper body, fundus or cardia; distal: antrum, angle or lower body. Non-ulcerative lesions: gastritis-like or multiple erosion on infiltrative mucosa, erosions on giant nodular folds or mixed lesions. Total, stage I-IIE2/III/IV, 14/23/7; HP-positive, stage I-IIE2/III/IV, 6/7/1; HP-negative, stage I-IIE2/III/IV, 8/16/6; stage IV (n = 7), four bone marrow involvement, two bone involvement and one malignant pleural effusion. PR, n = 3; HP-positive, n = 1; HP-negative, n = 2. Anthracycline-based: CHOP, CEP, ACE and PACE. Rituximab/anthracycline-based: rituximab-CHOP or rituximab-CEP. Rituximab/nonanthracycline-based: rituximab-COP. Others: CNOP and COP.
group had better 5-year EFS and OS than HP-negative group (5-year EFS, 80.6% vs 46.8%, \( P = 0.003 \); 5-year OS, 90.6% vs 68.0%, \( P = 0.023 \)). Among those who received rituximab/anthracycline-based regimens, we observed that HP-positive group had a better trend for 5-year EFS and OS than HP-negative group (5-year EFS, 84.8% vs 64.8%, \( P = 0.176 \); 5-year OS, 93.3% vs 66.7%, \( P = 0.091 \)). Similarly, in patients treated with anthracycline-based chemotherapy (\( n = 61 \); Table 1), HP-positive group had better 5-year EFS and OS than HP-negative group (5-year EFS, 71.8% vs 32.4%, \( P = 0.006 \); 5-year OS, 76.0% vs 34.0%, \( P = 0.001 \)). Even in localized stage I-IIIE1 patients, we found that HP infection was associated with a better 5-year EFS (87.7% vs 50%, \( P = 0.078 \) and OS (88.9% vs 56.3%, \( P = 0.017 \)) for those treated with anthracycline-based chemotherapy. A similar trend of better 5-year EFS (87.5% vs 83.3%, \( P = 0.274 \)) and OS (100% vs 83.3%, \( P = 0.221 \)) was observed in those treated with rituximab/anthracycline-based regimens.

### Table 2. Univariate analysis of stage, LDH, IPI score, HP status and histologic subclassification in EFS and OS of gastric ‘pure’ DLBCL patients

| Variable              | 5-Year EFS (%) | S.e. (%) | P-value | 5-Year OS (%) | S.e. (%) | P-value |
|-----------------------|----------------|----------|---------|---------------|----------|---------|
| Age (years old)       |                |          |         |               |          |         |
| <60                   | 61.8           | 7.5      | 0.048   | 68.9          | 7.2      | 0.032   |
| ≥60                   | 42.3           | 7        |         | 48.5          | 6.9      |         |
| Sex                   |                |          |         |               |          |         |
| Male                  | 48.8           | 7.6      | 0.452   | 60.5          | 7.5      | 0.767   |
| Female                | 53             | 7.1      |         | 55            | 7        |         |
| Stage                 |                |          |         |               |          |         |
| I-IIIE1               | 73.8           | 6.3      | <0.001  | 82.2          | 5.4      | <0.001  |
| IIIE2/III/IV          | 24.8           | 6.5      |         | 28.7          | 7        |         |
| LDH                   |                |          |         |               |          |         |
| Normal                | 71.5           | 6.3      | <0.001  | 81.3          | 5.3      | <0.001  |
| High                  | 24.4           | 6.7      |         | 26.2          | 7        |         |
| IPI risk group        |                |          |         |               |          |         |
| 0–1                   | 58             | 5.5      | <0.001  | 65.5          | 5.3      | <0.001  |
| ≥2                    | 7.7            | 7.4      |         | 7.7           | 7.4      |         |
| HP status             |                |          |         |               |          |         |
| Positive              | 71.7           | 6.7      | <0.001  | 76.1          | 6.3      | <0.001  |
| Negative              | 31.8           | 6.8      |         | 39.8          | 7.1      |         |

Abbreviation: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EFS, event-free survival; LDH, lactate dehydrogenase; HP, H. pylori; IPI, International Prognostic Index; OS, overall survival; s.e., standard error.

### Table 3. Multivariate analysis of prognostic factors and EFS and OS for gastric ‘pure’ DLBCL patients

| Characteristics | EFS | OS |
|-----------------|-----|----|
|                 | HR  | 95% CI | P-value | HR  | 95% CI | P-value |
| HP status       |     |       |         |     |       |         |
| Negative vs positive | 2.509 | 1.279–4.924 | 0.007 | 2.666 | 1.279–5.553 | 0.009 |
| Age (years old) |     |       |         |     |       |         |
| ≥60 vs <60      | 1.559 | 0.785–3.096 | 0.204 | 1.639 | 0.779–3.450 | 0.193 |
| Stage           |     |       |         |     |       |         |
| I-IIIE2/III/IV vs I-IIIE1 | 2.174 | 0.854–5.533 | 0.103 | 3.9 | 1.451–10.479 | 0.007 |
| ECOG            |     |       |         |     |       |         |
| ≥2 vs 0–1       | 2.867 | 1.350–6.088 | 0.006 | 4.308 | 1.872–9.917 | 0.001 |
| LDH             |     |       |         |     |       |         |
| High vs normal  | 1.754 | 0.538–5.714 | 0.351 | 1.755 | 0.366–8.406 | 0.482 |
| IPI risk group  |     |       |         |     |       |         |
| ≥2 vs 0–1       | 1.139 | 0.296–4.379 | 0.849 | 1.306 | 0.244–6.998 | 0.755 |

Abbreviation: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HP, H. pylori; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival.

Prognostic significance of CagA expression in gastric ‘pure’ DLBCL
Using a technique that we described recently,\(^4\) 43 HP-positive patients with available tumor specimens for CagA expression were analyzed. The CagA protein was expressed in gastric mucosa or submucosa tumor cells and showed scattered expression in the adjacent tumor-free gastric mucosa (Figure 2). Hematoxylin–eosin staining and immunohistochemical staining showed that most CagA-positive cells were morphologically abnormal and expressed CD20 (Figure 2). Positive CagA expression was observed in 27 (62.8%) of the 43 HP-positive cases and was closely associated with p-SHP-2 expression (17 (63.0%) of 27 CagA-positive cases vs 4 (25.0%) of 16 CagA-negative cases, \( P = 0.016 \)). Compared with the 16 HP-positive but CagA-negative cases, the 27 patients who were HP- and CagA-positive had a lower clinical stage (I-IIIE1, 82% vs 47%, \( P = 0.017 \)), a better tumor response to chemotherapy (complete response, 89% vs 59% \( P = 0.030 \)) and significantly better 5-year EFS (85.2% vs 46.3%, \( P = 0.002 \)) and OS (88.9% vs 52.9%, \( P = 0.003 \)) (Figure 3).

Among HP-positive patients who received rituximab/anthracycline-based regimens (\( n = 13 \)), we observed that patients with CagA expression had a trend for better 5-year EFS and OS than those without CagA expression (5-year EFS, 83.3% vs 67.7%, \( P = 0.052 \); 5-year OS, 100.0% vs 66.7%, \( P = 0.058 \)). Similarly, in patients treated with anthracycline-based chemotherapy (\( n = 25 \)), those with CagA expression had better 5-year EFS and OS than those without (5-year EFS, 91.7% vs 40.0%, \( P = 0.002 \); 5-year OS, 91.7% vs 50%, \( P = 0.005 \)).

### DISCUSSION
We have shown that HP-positive gastric ‘pure’ DLBCL has a lower clinical stage, a lower IPI score, a better tumor response to...
chemotherapy and superior 5-year EFS and OS. These findings indicate that HP-related gastric ‘pure’ DLBCL shares clinicopathologic features of conventional gastric MALT lymphoma, suggesting an overlapping etiology between the two gastric lymphoma groups.

We fully understand that HP is a common infection in the general population, a coincidental infection of this microorganism in some cases of gastric ‘pure’ DLBCL is highly possible. To improve the reliability of a true relationship, we provided evidence that CagA expression in the tumor cells may be a useful marker to distinguish a true from a spurious causative relationship between HP infection and lymphomagenesis of gastric ‘pure’ DLBCL. For example, in HP-positive cases, we showed that CagA-positive cases had an even better response to chemotherapy and a favorable outcome and that CagA expression was closely associated with p-SHP-2 expression. These findings concur with our previous observation that translocation of CagA into human B lymphocytes biologically activates the relevant cellular pathways and promotes B lymphoid cell proliferation, and CagA expression in tumor cells is closely associated with HP dependence in gastric MALT lymphoma. In a CagA-transgenic mouse model, Ohnishi et al. demonstrated that CagA has an important role in the development of HP-associated B lymphoma cells through SHP-2-tyrosine phosphorylation-dependent pathway. Other investigators have also demonstrated that translocated CagA can promote B-cell proliferation and inhibit apoptosis through ERK activation, BAD phosphorylation and p53 accumulation. Based on these findings, we hypothesized that HP-positive gastric ‘pure’ DLBCLs, particularly those with CagA expression in tumor cells, are HP related, and are clinicopathologically distinct from HP-unrelated gastric ‘pure’ DLBCLs. Further, the dependence on CagA-regulated signaling pathway for the growth of malignant B-cell clones may explain the tendency of CagA-positive gastric ‘pure’ DLBCLs to remain localized and thus enjoy a lower clinical stage of disease.

However, in light of the complex interaction between micromes and the genome/epigenome, conclusion of our study should be validated in another cohort of a diverse population. For example, epidemiologic studies have reported that the occurrence of gastric MALT lymphoma in East Asia is higher than in Western countries, and most of HP strains from East Asian are CagA-positive. East Asian CagA carries the lutamic acid-proline-isoleucinetyrosine-alanine (EPIYA)-D segment, which differs from the EPIYA-C motif of Western CagA. As EPIYA-D exhibits greater SHP-2-binding affinity and tyrosine phosphorylation activity than EPIYA-C, HP-positive lymphomas in this study may be more closely linked to HP-related signaling pathway.

The cell origin of HP-related ‘pure’ DLBCL of stomach is obscure. Previous clonal, cytogenetic and transcriptional profiling studies suggest that a proportion of gastric ‘pure’ DLBCLs may be transformed from the HP-related MALT lymphoma components. However, in contrast to the canonical concept that HP-related lymphomas are of marginal zone B-cell origin, a recent multicenter phase II study (HG-L1 trial) showed that...

Figure 2. Examples of immunohistochemical analysis of CagA protein on tumor cells of gastric ‘pure’ DLBCL. (a) Diffuse large cells infiltrating the mucosa are observable on histopathologic examination (hematoxylin–eosin (H&E), × 400) (arrow, HP). (b) Diffuse large cells infiltrating the submucosa are observable on histopathologic examination of an HP-positive case (H&E, × 400). (c) The same HP-positive case (b) shows CagA expression in the tumor cells (right bottom inset, × 1000). (d) HP-positive case shows CagA expression in the tumor cells of gastric mucosa. (e) HP-positive case shows CagA expression in the tumor cells of gastric submucosa (right bottom inset, × 1000). (f) Double stains: tumor cells with CagA nuclear staining (brown color) are also CD20-positive (red color) (right bottom inset, × 1000).
a proportion of HP-dependent gastric ‘pure’ DLBCLs are of GCB origin.\textsuperscript{35} In this study, we demonstrated that 25 (64\%) of 39 HP-positive gastric ‘pure’ DLBCL patients had the GCB immunophenotype. These crucial findings have raised a hypothesis that HP may transform GCB cells into lymphoma cells in certain HP-related gastric ‘pure’ DLBCL, especially in HP-dependent ‘pure’ DLBCL.\textsuperscript{35–38}

To exclude the possibilities that localized diseases may be associated with less aggressive behavior and nodal DLBCL may benefit more from rituximab/anthracycline-based regimens,\textsuperscript{39} we demonstrated that HP infection remains a superior prognostic factor for EFS and OS in patients with localized disease (stage I-IIIE1), and in patients who received conventional anthracycline-based chemotherapy alone. Even with the same extent of rituximab/anthracycline-based regimens treatment, HP-positive patients still had a better outcome than HP-negative patients. A similar trend of better 5-year EFS and OS was both observed in localized stage I-IIIE1 HP-positive patients treated with anthracycline-based and with rituximab/anthracycline-based regimens.

Our results indicate that HP-related gastric ‘pure’ DLBCL, and particularly those with CagA expression in tumor cells, is associated with less aggressive tumor behavior, enhanced response to chemotherapy and a better prognosis. The cell origin of these lymphomas needs to be pursued.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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