

Analysis of clinical characteristics, diagnosis, treatment and prognosis of 46 patients with primary gastrointestinal non-Hodgkin lymphoma

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Received August 23, 2013; Accepted December 5, 2013

DOI: 10.3892/mco.2013.224

Abstract. Primary gastrointestinal non-Hodgkin lymphoma (PGI NHL) is one of the most common types of extranodal lymphoma, accounting for ~30-50% of all extranodal lymphomas. The aim of the present study was to investigate the clinical characteristics, diagnosis, treatment and prognosis of patients with PGI NHL. A total of 46 patients with PGI NHL (mean age, 50 years) were enrolled in this study, with a male:female ratio of 1.3:1. The most common site of PGI NHL was the stomach (52.2%), followed by the colon (34.8%) and small intestine (8.7%). The most common symptoms of PGI NHL included abdominal pain or discomfort (91.3%), loss of appetite (65.2%) and weight loss (56.5%) and the most common pathological subtype of PGI NHL was diffuse large B-cell lymphoma (DLBCL) (78.3%). Lesions were identified in 95.7% of PGI NHL patients under preoperative endoscopic examination, whereas the diagnosis rate was only 21.7% during preoperative endoscopic biopsy. All 46 patients underwent surgical treatment and 36 also received postoperative chemotherapy or radiotherapy. The follow-up time was 6-70 months in 37 PGI NHL patients, with 1-, 3- and 5-year survival rates of 81.1, 62.16 and 50.0%, respectively. The 5-year survival rate differed significantly according to clinical stage ($P=0.002$) and tumor size ($P=0.0017$) among patients with PGI NHL. However, there was no statistically significant difference

in the 5-year survival rate between patients who received surgery alone and those who received surgery plus postoperative chemotherapy or radiotherapy ($P=0.1371$). Furthermore, there were no statistically significant differences in gender ($P=0.127$), clinical stage ($P=0.828$), histological subtype ($P=1.000$) and surgical modality ($P=0.509$) between patients with primary gastric non-Hodgkin lymphoma (PG NHL) and those with primary intestinal non-Hodgkin lymphoma (PI NHL). In conclusion, PGI NHLs are a heterogeneous group of diseases, whereas clinical stage and tumor size were identified as adverse prognostic factors of PGI NHL. Further studies, including a larger number of patients treated with surgery alone, are required in order to elucidate the precise role of surgery combined with postoperative chemotherapy or radiotherapy in the prognosis of PGI NHL.

Introduction

Primary gastrointestinal non-Hodgkin lymphoma (PGI NHL) is one of the most common types of extranodal lymphoma, accounting for ~30-50% of all extranodal lymphomas (1). The stomach is the predominant site of PGI NHL, followed by the colon and small intestine (2) and the most common pathological subtype of PGI NHL is diffuse large B-cell lymphoma (DLBCL). The clinical manifestations of PGI NHL are not specific and may be indistinguishable from those of other gastrointestinal benign and malignant tumors, which may result in missed diagnosis or misdiagnosis. Currently, novel adjuvant diagnostic methods, including balloon-assisted endoscopy, capsule endoscopy and endoscopic ultrasonography are used for detecting diminutive lesions and improving the diagnostic rate of PGI NHL (3-5). Although there are currently established treatment strategies for NHL, the optimal therapeutic methods for PGI NHL remain a matter of controversy. Surgery, chemotherapy and radiotherapy are currently used, alone or in combinations, for the treatment of PGI NHL (6-8). The prognostic factors of PGI NHL include gender, pathological subtype, tumor stage and the use of radical surgery (9-11). Notably, the clinicopathological characteristics and treatment strategies for PGI NHL differ from those for other types of extranodal lymphomas. Therefore, it is vital to determine the clinical characteristics of PGI NHL. The aim of

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Key words: non-Hodgkin lymphoma, gastrointestinal lymphoma, diagnosis, therapy, prognosis

the present study was to determine the clinical characteristics, diagnosis, treatment and prognosis of PGI NHL patients.

Materials and methods

Patients. The medical records of 46 patients with PGI NHL, who underwent surgical treatment at the First and Second Affiliated Hospitals of Dalian Medical University (Dalian, China) between January, 1998 and December, 2012, were retrospectively reviewed. In this study, PGI NHL was defined as predominant lesions in the gastrointestinal tract or gastrointestinal symptoms according to the definition provided by Lewin *et al* (12). The pathological specimens were obtained from endoscopic biopsies and surgical resections and all the cases were classified based on morphological and immunophenotypic criteria according to the 2008 World Health Organization (WHO) classification (13). The clinical staging of PGI NHL patients was performed according to the Ann Arbor classification modified by Musshoff (14) for gastrointestinal tract lymphoma. All patients underwent preoperative endoscopic biopsy, whereas a proportion of the patients underwent simultaneous gastrointestinal barium meal radiography, ultrasonography or computed tomography. Furthermore, all PGI NHL patients underwent surgical resection, with or without chemotherapy or radiotherapy. The patients who received adjuvant chemotherapy were administered either cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP regimen), or cyclophosphamide, vincristine, procarbazine and prednisolone (COPP regimen). The survival rate was measured from the first day of treatment, with no reported mortality during the perioperative period. Furthermore, the follow-up data of the 46 PGI NHL patients were obtained through letters, telephonic communication or in person at the clinic. A total of 37 out of the 46 cases completed the follow-up.

Statistical analysis. The statistical significance of the comparison between patients with primary gastric non-Hodgkin lymphoma (PG NHL) and those with primary intestinal non-Hodgkin lymphoma (PI NHL) according to gender and clinical stage were determined with the χ^2 test. The difference between patients with PG NHL and those with PI NHL by histological subtype and surgical modality was assessed using the χ^2 test with continuity correction. Correlations of prognosis with clinical stage, tumor size and surgical modality in patients with PGI NHL were performed using the Fisher's exact test. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics. The present study included 26 men and 20 women, with a mean age of 50 years (range, 21-81 years). The male:female ratio was 1.3:1, with 24 cases of PG NHL and 22 cases of PI NHL. The PG NHL group comprised 16 cases of NHL located in the gastric antrum, 6 in the gastric body and 2 in the gastric fundus. The PI NHL group comprised 2 cases located in the jejunum, 2 in the ileocecum, 16 in

the ascending colon and 2 in the rectum. According to the WHO classification, 36 cases were classified as DLCBL, 4 as mucosa-associated lymphoid tissue lymphoma, 3 as follicular lymphoma and 3 as T-cell derived NHL. According to the Ann Arbor classification, 11 cases were classified as stage I, 6 as stage IE, 8 as stage II, 5 as stage IIE, 14 as stage III and 2 as stage IV. Furthermore, the gross type of PGI NHL was ulcerative in 29 patients, protruding in 10 patients and diffuse infiltrative in 7 patients. Notably, PGI NHL was frequently encountered as single lesions, with a mean size of 8.1 cm (range, 0.7-22 cm), with only 19.6% of the cases displaying multiple ulcers or nodules. The time period from the appearance of clinical symptoms or signs to treatment ranged from 2 days to 3 years, with a mean time of 8.5 months, with 72.1% of the cases receiving treatment in < 6 months. The common clinical manifestations in PGI NHL patients were abdominal pain or discomfort (91.3%), non-specific gastrointestinal symptoms (including loss of appetite, nausea, vomiting, abdominal mass, bleeding, obstruction and melena), fever and weight loss. The clinical characteristics of the PGI NHL patients are listed in Table I and the clinical manifestations are summarized in Table II.

Auxiliary examinations. A total of 24 PG NHL patients underwent gastroscopic examination and lesions were identified in 91.7% (22/24) of the cases. Under gastroscopic examination, the majority of the cases exhibited irregular ulcers with a large amount of necrotic tissue, surrounded by a nodular bump. Notably, only 25.0% (6/24) of the cases were diagnosed as PG NHL, whereas 12 cases were misdiagnosed as moderately or poorly differentiated gastric cancer, 2 were misdiagnosed as benign giant gastric ulcers and 2 were misdiagnosed as gastric stromal tumors. A total of 22 patients subsequently underwent ultrasonographic examination or computed tomography and lesions were identified in 45.5% (10/22) of the cases. Furthermore, 6 patients underwent gastrointestinal barium meal radiography and lesions were identified in 66.7% (4/6) of the cases. Notably, under gastrointestinal barium meal radiographic examination, the majority of the cases exhibited a filling defect, stiffness of the gastric wall, mucosal disruption and destruction. Similarly, 22 PI NHL patients underwent enteroscopic examination and lesions were identified in each case. Under enteroscopic examination, the majority of the cases exhibited an intestinal annular stricture. Of note, only 18.2% (4/22) of the cases were diagnosed as PI NHL, whereas 16 cases were misdiagnosed as intestinal cancer and 2 were misdiagnosed as intestinal stromal tumors. Subsequently, all the PI NHL patients underwent ultrasonography or computed tomography and lesions were identified in 45.5% (10/22) of the cases. Furthermore, 8 patients underwent gastrointestinal barium meal radiography and lesions were identified in 75% (6/8) of the cases. Under gastrointestinal barium meal radiography, the majority of the cases exhibited a localized or multiple nodular filling defect. The results of the preoperative endoscopic biopsy are shown in Table III.

Treatment strategies. A total of 46 patients with PGI NHL underwent surgical treatment at the First and Second Affiliated Hospitals of Dalian Medical University. Among the 24 PG NHL patients, 14 received a radical gastrectomy,

Table I. Clinical characteristics of 46 cases of PGI NHL.

Variables	Stomach (n=24)	Small intestine (n=4)	Colon (n=16)	Rectum (n=2)	Total (n=46)
Gender					
Male	11	3	10	2	26
Female	13	1	6	0	20
Age (years)					
Mean	52	45	48	47	50
Range	21-81	27-69	42-72	39-75	21-81
Size (cm)					
Mean	8.3	6.7	7.5	3.9	8.1
Range	0.7-22	4-22	4-10	1.5-9	0.7-22
Gross morphology					
Ulcerative	17	0	10	2	29
Protruding	3	3	4	0	10
Diffuse infiltrative	4	1	2	0	7
Clinical stage					
I	8	1	7	1	17
II	8	1	4	0	13
III	7	2	4	1	14
IV	1	0	1	0	2

PGI NHL, primary gastrointestinal non-Hodgkin lymphoma.

Table II. Clinical symptoms or signs in 46 cases of PGI NHL.

Clinical symptoms or signs	No. of cases (%)
Abdominal pain or discomfort	42 (91.3)
Loss of appetite	30 (65.2)
Weight loss	26 (56.5)
Nausea and/or vomiting	22 (47.8)
Melena	16 (34.8)
Anemia	14 (30.4)
Fever	14 (30.4)
Gastrointestinal bleeding	6 (13.0)
Obstruction	4 (8.7)
Abdominal mass	4 (8.7)
Ascites	2 (4.3)
Pelvic nodules	2 (4.3)
Generalized abdominal pain	2 (4.3)
Dysphagia	0

PGI NHL, primary gastrointestinal non-Hodgkin lymphoma.

6 underwent complete gastrectomy and esophageal anastomosis, 2 received palliative distal gastrectomy and 2 patients underwent gastrectomy combined with splenectomy and pancreatic body and tail resection. Among the 22 patients with PI NHL, 2 underwent segmental small bowel resection, 2 received an ileocecal resection, 16 underwent right colon resection and 2 underwent Miles' operation for radical rectal resection. All surgeries were successful and there

were no reported mortalities during the postoperative period. Furthermore, 78.3% (36/46) of the patients received postoperative chemotherapy or radiotherapy.

Prognostic factors. In the present study, 80.4% (37/46) of the PGI NHL patients completed the follow-up. The follow-up time was 6-70 months, with 1-, 3- and 5-year survival rates of 81.1 (30/37), 62.16 (23/37) and 50.0% (17/37), respectively. During the 5-year follow-up period, 10 patients succumbed to extensive abdominal metastases, 4 to pulmonary metastases, 3 to osseous metastases, 3 to brain metastases, 3 to cerebral hemorrhage and 1 to other causes. Furthermore, patients with early-stage lymphoma (I/II) had a significantly higher 5-year survival rate (68.2%) compared with those with late-stage lymphoma (III-IV) (13.3%; $P=0.002$). Similarly, patients with a tumor size of <10 cm had a significantly higher 5-year survival rate (64%) compared to those with a tumor size of >10 cm (8.3%; $P=0.0017$). However, there were no significant differences in the 5-year survival rate between patients who received surgery alone and those who received surgery combined with postoperative radiotherapy or chemotherapy (22.2 and 53.6%, respectively; $P=0.1371$). Our results demonstrated that clinical stage and tumor size were adverse prognostic factors for PGI NHL. The 5-year survival rate and prognostic factors of PGI NHL are shown in Table IV.

Comparison of PG NHL and PI NHL. There were no statistically significant differences between PG NHL and PI NHL patients according to gender ($P=0.127$), clinical stage ($P=0.828$), histological subtype ($P=1.000$) and surgical modality ($P=0.509$) (Table V).

Table III. Results of preoperative endoscopic biopsy for 46 cases of PGI NHL.

Variables	Classification	No. of cases (%)
Gastroscopic biopsy (n=24)		
Diagnosis	Primary gastric non-Hodgkin lymphoma	6 (25)
Misdiagnosis	Moderately or poorly differentiated gastric carcinoma	12 (50)
	Gastric stromal tumor	2 (8.3)
	Gastric ulcer	2 (8.3)
Lesions undetected		2 (8.3)
Enteroscopic biopsy (n=22)		
Diagnosis	Primary intestinal non-Hodgkin lymphoma	4 (18.2)
Misdiagnosis	Intestinal carcinoma	16 (72.7)
	Intestinal stromal tumor	2 (9.1)

PGI NHL, primary gastrointestinal non-Hodgkin lymphoma.

Table IV. Comparison of the 5-year survival rate according to clinical stage, tumor size and therapeutic method in PGI NHL patients.

Variables	No. of cases	Five-year follow-up			P-value ^a
		Survival	Mortality	Survival rate	
Clinical stage					
I-II	22	15	7	68.2	0.0020
III-IV	15	2	13	13.3	
Tumor size (cm)					
≤10	25	16	9	64	0.0017
>10	12	1	11	8.3	
Therapeutic methods					
Surgery alone	9	2	7	22.2	0.1371
Surgery+radiotherapy/chemotherapy	28	15	13	53.6	

^aFisher's exact test. PGI NHL, primary gastrointestinal non-Hodgkin lymphoma.

Table V. Comparison between PG NHL and PI NHL patients.

Variables	PG NHL (n=24)	PI NHL (n=22)	P-value
Gender			
Male	11	15	0.127 ^a
Female	13	7	
Clinical stage			
I-II	16	14	0.828 ^a
III-IV	8	8	
Histological subtype			
B-cell	22	21	1.000 ^b
T-cell	2	1	
Surgical modality			
Radical resection	22	22	0.509 ^b
Palliative resection	2	0	

^a χ^2 test. ^b χ^2 test with continuity correction. PG NHL, primary gastric non-Hodgkin lymphoma; PI NHL, primary intestinal NHL.

Discussion

Primary gastrointestinal lymphomas (PGILs) are considered to be uncommon tumors, although the gastrointestinal tract is one of the major sites of extranodal lymphomas and previous time-trend analyses indicated an increase in the incidence of 2.7% per annum (15,16). PGI NHL represents ~5-10% of all gastrointestinal malignancies (1,17,18), with a mean age at onset of 45-70 years for PI NHL (11). In the present study, the mean age of the patients with PGI NHL was 48 years. With regard to gender distribution, our results demonstrated that the incidence of PGI NHL in men is higher compared with that in women, with a male:female ratio of 1.3:1, which was in accordance with previous studies (1,19,20). The stomach was identified as the main site of PGI NHL, with a frequency of 37.8-86% (1). In our study, the most common site of PGI NHL was the stomach (52.2%), followed by the colon (34.8%), small intestine (8.7%) and rectum (4.3%), which was in agreement with the results of Koch *et al* (1). Furthermore, the main clinical presentations of PGI NHL were non-specific gastrointestinal symptoms, including abdominal pain, nausea, vomiting, loss of appetite and

weight loss. Liang *et al* (18) reported that the 3 most common symptoms at onset in 425 PGI cases were abdominal pain, gastrointestinal bleeding and nausea or vomiting. Furthermore, Radic-Kristo *et al* (20) reported that the majority of cases of PGI NHL presented with epigastric pain (85%) and dyspepsia (30%). However, the 3 most common symptoms of PGI NHL in the present study were abdominal pain or discomfort (91.3%), loss of appetite (65.2%) and weight loss (56.5%), which was consistent with the findings of previous studies (1,21). With regard to pathological subtype, our results confirmed DLBCL as the most common type of gastrointestinal NHL (1,20).

In general, the clinical manifestations of PGI NHL are non-specific, resulting in difficulties in clinical diagnosis. Consequently, auxiliary examination is crucial in improving the early diagnostic rate of PGI NHL. Currently, the diagnosis of PGI NHL is mainly based on thorough endoscopic biopsies obtained from suspicious gastrointestinal lesions. However, the endoscopic appearance of PGI NHL also lack specificity and may vary from minimal mucosal irregularities to sizeable ulcers. Additionally, non-specific tissues adjacent to PGI NHL may be collected under endoscopic biopsy and contribute to missed diagnosis or misdiagnosis. In the present study, lesions were identified in 95.7% (44/46) of the cases with PGI NHL, whereas the diagnostic rate was only 21.7% (10/46) with preoperative endoscopic biopsy. Therefore, multiple endoscopic examinations and biopsies may be required to improve the diagnostic rate of PGI NHL. Kav *et al* (22) reported that confocal laser endomicroscopy decreased the non-diagnostic rate of endoscopic biopsy and may be performed successfully in cases of gastric lymphoma. Notably, tissue histology may be examined *in vivo* and a range of diseases may be identified using this technique. Therefore, confocal laser endomicroscopy may be a promising technique for the diagnosis and differential diagnosis of PGI NHL. Furthermore, endoscopic ultrasonography-guided fine-needle aspiration biopsy may be used to determine nodal involvement and depth of invasion in PG NHL (5,23). Moreover, Akamatsu *et al* (24) reported that double-balloon enteroscopy and video capsule endoscopy may be useful for the diagnosis and management of primary follicular lymphoma in the gastrointestinal tract. Furthermore, repetitive endoscopic biopsies may also improve the accuracy of diagnosis. Ouakaa-Kchaou *et al* (25) reported that under endoscopic examination the lesions were mainly identified as ulcers and ulcerations (93.75%) and the endoscopic biopsy confirmation rate reached 87.5% when biopsies were repeated. In conclusion, multiple endoscopic examinations with repetitive biopsies may improve the diagnostic rate of PGI NHL.

Currently, the therapeutic modalities for PGI NHL include surgery, chemotherapy and radiotherapy, alone or in various combinations. Although the treatment modalities for PGI NHL remain a subject of controversy, surgical resection is generally accepted as the primary treatment strategy (8,26). Furthermore, several previous studies reported that surgery is associated with a favorable outcome (17,27-29). However, the results of a controlled clinical trial demonstrated that the outcome following chemotherapy (10-year survival rate of 92%) was superior to that of surgery alone or surgery in combination with chemotherapy (10-year survival rate of 28 and 82%, respectively) and chemotherapy was thus considered to be the optimum treatment for PG NHL (30). In addition,

other studies reported no difference in survival following chemotherapy vs. surgery combined with chemotherapy in patients with PGI NHL (1,7,8,21). In our study, the outcome of surgery combined with chemotherapy or radiotherapy (5-year survival rate of 53.6%) was superior to that of surgery alone (5-year survival rate of 22.2%), although the difference was not statistically significant. Therefore, further studies are required to confirm our results by expanding the sample size of surgery alone and determine the optimal therapeutic strategy for PGI NHL.

Based on the analysis of the follow-up data of 37 patients, it was observed that the main prognostic factors for patients with PGI NHL were clinical stage and tumor size. However, there was no difference in the 5-year survival rate between the surgery alone and the surgery combined with postoperative radiotherapy or chemotherapy groups. Lee *et al* (9) reported that advanced stage, poor performance and T-cell phenotype were adverse prognostic factors for intestinal lymphoma. Furthermore, Gou *et al* (11) reported that male gender, a performance status (PS) score of ≥ 2 , hypoproteinemia, intestinal perforation, T-cell type, advanced stage (III/IV), no radical surgery and no chemotherapy, were associated with a relatively poor prognosis. In particular, pathological subtype and radical surgery were identified as independent prognostic risk factors for PI NHL. Furthermore, stage-modified international prognostic index and PS were also found to be independent predictors of PG NHL patient survival (31).

In conclusion, PGI NHLs are a group of heterogeneous diseases and the optimal therapeutic strategy has not yet been fully established. In this study, clinical stage and tumor size were identified as adverse prognostic factors for PGI NHL. However, further studies, including a larger number of patients undergoing surgery alone, are required in order to elucidate the precise role of surgery combined with postoperative chemotherapy or radiotherapy in the prognosis of PGI NHL.

Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China (no. 31270867), the Chinese State Key Program in Basic Research (no. 2012CB822103) and the project of the Ministry of Health: The colorectal laparoscopic minimally invasive surgery standardization research (no. W2012RQ23).

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