Original Article

A retrospective analysis of clinical pathological characteristics and prognosis of 82 patients of primary intestinal lymphoma

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Background: To evaluate the histological type, clinical presentation, treatment and prognosis of primary intestinal lymphoma (PIL).

Methods: From 2003 to 2015, in a single institution in China, 82 patients with a diagnosis of PIL were enrolled in our study. According to World Health Organization (WHO) classification and Lugano staging system for gastrointestinal lymphoma, we divided patients into different subtypes and stages.

Results: Male to female ratio was 1.8:1 and the median age was 59.5 years. Of the 82 patients, 68 patients (82.9%) suffered from intestinal B-cell lymphoma (IBCL) and 14 patients (17.1%) suffered from intestinal T-cell lymphoma (ITCL). Diffuse large B cell lymphoma (DLBCL) was the predominant histological subtype (59.8%) in all of the PIL cases. Mucosa-associated lymphoid tissue-type lymphoma (MALT) was the second most common subtype (15.9%). From the study we also concluded that PIL mostly occurred in the small intestine (45.1%), followed by colon and rectum (26.8%). The univariate prognosis analysis revealed that Lugano stage I/II, B-cell phenotype and treatment based on surgery plus chemotherapy were independent prognostic factors (P=0.003, 0.000 and 0.000, respectively). According to multivariate analysis, age of onset, Lugano stage, immunophenotype and the method of treatment were significant predictive factors for better survival (P=0.005, 0.005, 0.000 and 0.000, respectively).

Conclusions: The patients with younger age of onset, B cell lymphoma, earlier stages, and treatment based on surgery plus chemotherapy have a better prognosis. To ensure the diagnosis of PIL to be made as soon as possible, we should make efforts to select the proper laboratory parameters and imaging findings of PIL.

Keywords: Intestinal lymphoma; T cell lymphoma; B cell lymphoma; histological type; prognosis

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Introduction

The gastrointestinal tract is the most common extranodal site of involvement in Non-Hodgkin lymphoma (NHL), representing 30–45% of all extranodal lymphoma (ENL) cases. The gastric lymphoma is the predominant location for ENL (55–70%) whereas intestinal lymphoma is less frequently observed in small intestines (20–35%) and large intestines (5–10%) (1).

Nowadays, due to the lack of characteristic clinical symptom, specific serum and imaging test results, it is still

difficult for physicians to make early diagnosis of primary intestinal lymphoma (PIL) which might cause the delay of treatment and affect the prognosis of patients.

In order to better master and treat this neoplasm, we make a retrospective study involving 82 patients with PIL who were diagnosed in Ruijin Hospital from 2003 to 2015. This study occurred in a single institution in China, which analyzed the clinical features, histological subtype, method of treatment and prognosis of PIL.

Methods

Eighty-two adult patients with PIL were enrolled in our retrospective study from December 2003 to June 2015. During this period, 99 patients were diagnosed with PIL in our hospital, but we excluded juvenile patients and those out of follow-up visit. Our study finally collected complete clinical, pathological and follow-up data of 82 patients with PIL. All cases were confirmed according to the pathological samples from endoscopic biopsy or surgical resection. Patients were included in current analysis if they met the following Dawson's criteria: (I) absence of palpable superficial lymphadenopathy; (II) normal leukocyte and differential counts; (III) non-enlargement of mediastinal lymph nodes on chest X-ray; (IV) no grossly demonstrable involvement beyond the affected segment of the intestine and its regional mesenteric lymph nodes at the time of diagnosis; and (V) absence of tumor involvement of the liver and spleen (2). All patients were performed with immunohistochemical detection. And if tumor shows one or more B cell, markers were identified as IBC; and if the tumor shows one or more T cell, markers were identified as ITCL. Furthermore, the accurate immunophenotypic subtype was identified by the World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues in 2008 (3). And the staging of those patients was confirmed by Lugano staging system for gastrointestinal lymphoma (4). The Lugano staging system was concluded by physical examination, radiological imaging, positron emission tomography/computed tomography (PET/CT) and the pathological result by endoscopic biopsy and the surgical sample. In our study, we divided patients into two groups (stage I/II and stage III/IV) for a comparative analysis.

The follow-up data of the 99 PIL patients were obtained through medical records of hospitalization, telephonic communication or in person at the clinic. A total of 82 out of the 99 cases completed the follow-up and the follow-up rate was 82.8%. The follow-up data began with the first day of diagnosis and ended up with the last connection with patients or relatives of patients. And the deadline of follow-up was September 30, 2015.

Statistical analysis

The comparative analysis between intestinal B-cell lymphoma (IBCL) and ITCL were tested by χ^2 test. We used overall survival (OS) to evaluate the prognosis of patients with PIL. OS was defined as the interval from the date of diagnosis to the date of death from any cause or the last follow-up date. All deaths from other causes were recorded as censored. OS was estimated using the Kaplan-Meier product-limit method and was compared by means of the log-rank test. Cox's proportional hazard regression analysis was used to evaluate prognostic factors. The following clinical and pathological factors were chosen for survival analysis: gender, age of onset (<60 or ≥60 years), B symptom (presence or absence), complication (obstruction and perforation included), phenotype (IBCL or ITCL), location (small intestines, ileocecal region, large intestines, colon and rectum, or multiple sites), Lugano stage (Stage I/II or Stage III/IV) and treatment (surgery alone, chemotherapy alone, surgery and chemotherapy combined or neither surgery nor chemotherapy). $P<0.05$ was considered to indicate a statistical difference. The statistical data were obtained using an SPSS software package (SPSS 21.0, IBM, Chicago, Illinois, USA).

Results

Patient characteristics

From December 2003 to June 2015, a total of 82 patients with PIL were enrolled in our study. The characteristics of patients are summarized in *Table 1* and *Table 2*. The study cohort consisted of 53 men and 29 women (the ratio was 1.8:1) with a median age of 59.5 years (range, 18–81 years). Regarding histological subtype classification, IBCL accounted for 82.9% and ITCL accounted for 17.1%. PIL mostly occurred in small intestines (45.1, duodenum, jejunum and ileum included), followed by colon and rectum (26.8%), ileocecal region (20.7%) and multiple sites (7.3%). Most patients had localized disease with earlier Lugano stage I/II (92.7%) while a small part of patients (7.3%) had further involvement with Lugano stage III/IV. Between the group of IBCL and ITCL, there is no statistic difference for the proportion of gender and Lugano stage.

The clinical symptoms of PIL were unspecific which contain abdominal pain, diarrhea, vomiting, melena, abdominal mass, obstruction, perforation, B symptom etc. B symptom is defined as: fever 38 ℃ above, for three consecutive days or more without infection reason; weight loss more than 10% in 6 months and night sweat. A conclusion can be drawn from *Table 2* that in the group of ITCL, the proportion of diarrhea, perforation and B symptom is higher than the group of IBCL, which has a statistic difference (P<0.05).

Table 1 Clinicopathological features of 82 cases of PIL

Parameters	Number of patients (%)	P value (IBCL/ITCL)
Gender		
Male	53 (64.6)	0.132
Female	29 (35.4)	
Cell type		—
B	68 (82.9)	
T	14 (17.1)	
Localization		—
Small intestine	37 (45.1)	
Ileocecal region	17 (20.7)	
Colon and rectum	22 (26.8)	
Multiple sites	6 (7.3)	
Lugano stage		
I/II	76 (92.7)	0.592
III/IV	6 (7.3)	

PIL, primary intestinal lymphoma; IBCL, intestinal B-cell lymphoma; ITCL, intestinal T-cell lymphoma.

Histological subtype and locations

The various histological subtype along the anatomic sites are shown in *Table 3*. According to the WHO classification, in the group of IBCL, 49 cases were classified as DLBCL which was the predominant histological subtype, followed by 13 as MALT, 3 as follicular lymphoma (FL). Mantle cell lymphoma (MCL), lymphoblastic lymphoma (LBL) and B-cell lymphoma difficult to identify between burkitt lymphoma and diffuse large B cell lymphoma (DLBCL + BL) all have only one case. The other group of ITCL includes 8 of peripheral T-cell lymphoma (PTCL), 4 of enteropathogenic

Table 2 Clinical symptoms of 82 cases of PIL (%)

Parameters	B cell lymphoma	T cell lymphoma	P value
Abdominal pain	41 (60.3)	10 (71.4)	0.631
Diarrhea	12 (17.6)	6 (42.9)	0.038
Vomiting	8 (11.8)	1 (7.1)	0.973
Melena	12 (17.6)	2 (14.3)	1.000
Abdominal mass	12 (17.6)	2 (14.3)	1.000
Obstruction	12 (17.6)	1 (7.1)	0.563
Perforation	1 (1.5)	4 (28.6)	0.001
B symptom	19 (27.9)	9 (64.3)	0.021

Table 3 Histological subtypes and locations of 82 cases of PIL

Histological subtype	Duodenum	Jejunum	Ileum	Ileocecal region	Colon	Rectum	Multiple sites	Total	%
DLBCL	1	4	11	14	14	0	5	49	59.8
MALT	1	5	5	0	0	2	0	13	15.9
FL	1	0	1	0	0	0	1	3	3.6
MCL	0	0	0	0	0	1	0	1	1.2
LBL	0	0	0	0	0	1	0	1	1.2
DLBCL+BL	0	0	0	1	0	0	0	1	1.2
PTCL	1	3	1	1	1	0	1	8	9.8
EACL	1	0	1	0	2	0	0	4	4.9
NK/T	0	0	0	1	1	0	0	2	2.4
Total	5	12	19	17	18	4	7	82	100
Percent	6.1	14.6	23.2	20.7	22.0	4.9	8.5	100	

PIL, primary intestinal lymphoma; DLBCL, diffuse large B cell lymphoma; MALT, mucosa-associated lymphoid tissu-type lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; LBL, lymphoblastic lymphoma; DLBCL+BL, B-cell lymphoma difficult to identify between burkitt lymphoma and diffuse large B cell lymphoma; PTCL, peripheral T-cell lymphoma; EACL, enteropathogenic T-cell lymphoma; NK/T, natural killer-cell and T-cell lymphoma.

Table 4 Clinical pathologic factors associated with OS

Characteristics	No. of patients (%)	P log-rank test
Gender		0.579
Male	53 (64.6)	
Female	29 (35.4)	
Age (y)		0.088
<60	40 (50.0)	
≥60	40 (50.0)	
B symptom		0.355
Yes	28 (34.1)	
No	54 (65.9)	
Complications (obstruction and perforation		0.252
Yes	18 (22.0)	
No	64 (78.0)	
Phenotype		0.000
B	68 (82.9)	
T	14 (17.1)	
Location		0.286
Small intestine	37 (45.1)	
Ileocecal region	17 (20.7)	
Colon and rectum	22 (26.8)	
Multiple sites	6 (7.3)	
Lugano stage		0.000
I/II	76 (92.7)	
III/IV	6 (7.3)	
Treatment		0.000
Surgery alone	10 (12.2)	
Chemotherapy alone	14 (17.1)	
Surgery and chemotherapy combined	53 (64.6)	
Neither surgery nor chemotherapy	5 (6.1)	

T-cell lymphoma (EACL), 2 of natural killer-cell and T-cell lymphoma (NK/T). From the study we also concluded that PIL mostly occurred in ileum (23.2%), followed by colon (22.0%), ileocecal region (20.7%), jejunum (14.6%), multiple sites (8.5%), duodenum (6.1%) and rectum (4.9%).

Prognostic factors

Univariate analysis using Kaplan-Meier product-limit method was compared by means of the log-rank test. The results indicated that Lugano stage, immunophenotype and the method of treatment were significant predictive factors for better patient survival (P=0.003, 0.000 and 0.000, respectively, *Table 4*).

Furthermore, we select the factors whose P value is under 0.1 according to the univariate analysis to make a multivariate analysis. The factors included age of onset, Lugano stage, phenotype and treatment and all had statistical differences in multivariate analysis. A conclusion could be drawn that younger age of onset (<60 years), Lugano stage I/II, IBCL and treatment based on surgery and chemotherapy were significant predictive factors (P=0.005, 0.005, 0.000 and 0.000, respectively, *Figures 1-4*).

Discussion

In recent decades, the incidence of PIL augments gradually. The etiology of PIL is not clear, on the one hand it perhaps results from the virus infection, genetic variation, other chronic intestinal infection, etc. On the other hand, the treatment of immunosuppressive drugs, infection of HIV, organ transplantation, autoimmune diseases, immunodeficiency diseases, and inflammatory bowel diseases may increase the incidence of PIL obviously (5).

This retrospective study analyzed the clinical features, histological subtype, treatment and prognosis of PIL in China. In our research, the median age of patients at diagnosis was 59.5 years (range, 18–81 years). The patients with PIL tend to be middle-to-old age population. The male to female ratio was 1.8:1. According to the histological subtype classification, IBCL accounted for 82.9% and ITCL accounted for 17.1%. The incidence of IBCL was much higher than T-cell lymphoma. And DLBCL was the predominant histological subtype followed by MALT and PTCL. Furthermore, in our study the proportion of DLBCL (n=49, 59.8%) was significantly higher than MALT (n=13, 15.9%) and PTCL (n=8, 9.8%). One study of PIL in Korea had a similar result with our study. In their research, the median age was 56 years (range, 15–92 years) and the male to female ratio was 1.8:1. The main subtype was DLBCL followed by MALT and PTCL (6).

In our study, most patients had earlier Lugano stage I/II (n=76, 92.7%) which revealed that PIL predominantly presents as a localized disease. This result was strongly supported by the previous studies (1,7-10).

In terms of location, in our study the small intestine was the most common site (n=37, 45.1%), followed by colon and rectum (n=22, 26.8%), ileocecal region (n=17, 20.7%) and multiple sites (n=6, 7.3%). Another study of anatomic sites with PIL in China turned out similarly as above (11).

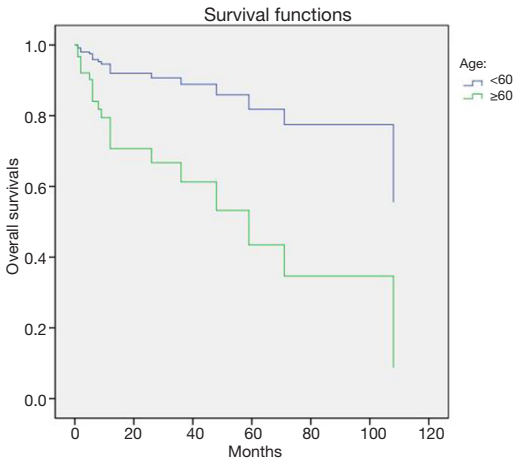

Figure 1 Overall survival according to age of onset (P=0.005).

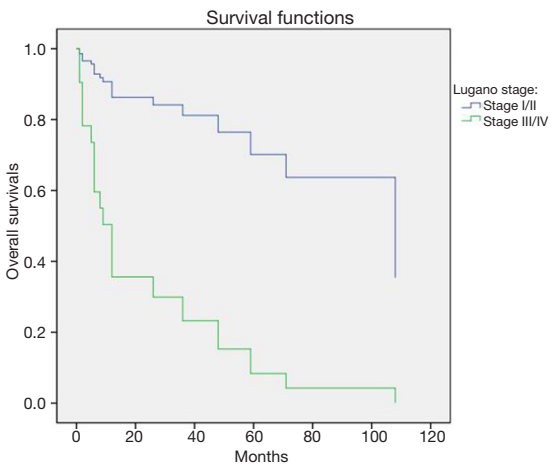

Figure 2 Overall survival according to Lugano stage (P=0.005).

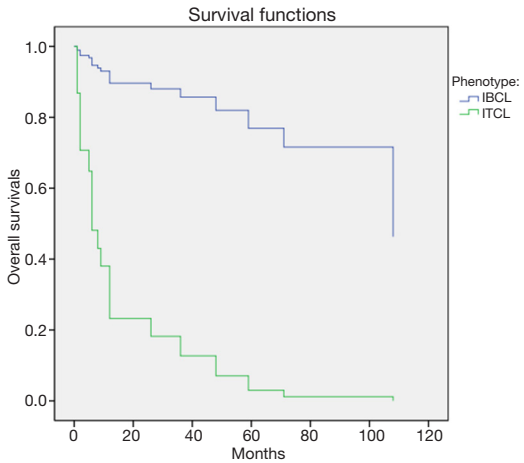

Figure 3 Overall survival according to phenotype (P=0.000). IBCL, intestinal B-cell lymphoma; ITCL, intestinal T-cell lymphoma.

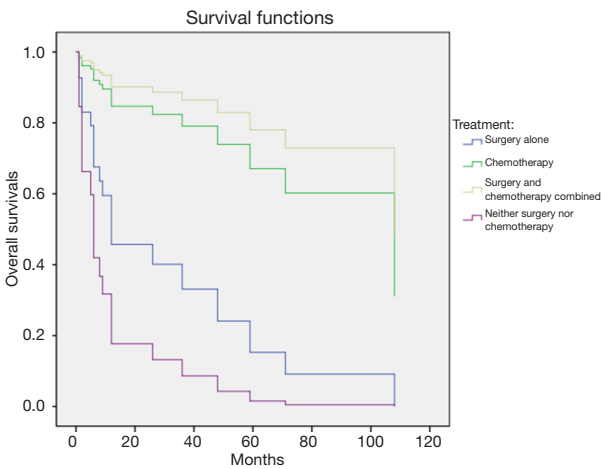

Figure 4 Overall survival according to treatment (P=0.000).

However, the result is in disagreement with other previous studies (10,12,13) which revealed that the colon was the most common site. And there are also another conclusion that the ileocecal region is the predominate site (6,7).

Regarding the clinical symptoms of PIL, including abdominal pain, diarrhea, vomiting, melena, abdominal mass, obstruction, perforation, B symptom etc., we can draw a conclusion that in the group of ITCL, the proportion of diarrhea, perforation and B symptom is higher than the group of B cell lineage lymphoma (P<0.05). The prevalence of perforation and diarrhea in ITCL may be due to the invasion of ITCL to the vascular wall, causing vascular occlusion and ischemic necrosis, and finally resulted in perforation and diarrhea (14).

In this study, we used univariate and multivariate analyses to analyze OS for patients with PIL with regard to numerous clinicopathologic factors. In univariate analysis, Lugano stage, immunophenotype and treatment significantly influenced OS in patients with PIL. Application of the multivariate Cox proportion hazard model revealed that besides factors above, the OS was also dependent on the age of onset. The younger age of onset (<60 years) had a better prognosis in the multivariate Cox proportion hazard model. The advanced international research also indicated the age was the independent factor of prognosis (10).

Considering about the survival benefit, IBCL had a better prognosis than ITCL which was the same to the previous studies (6,15-17). The better prognosis of IBCL may be due to the following reasons: in IBCL the indolent Lymphoma has a higher proportion such as MALT and FL etc. These tumors have a lower growth rate and take a longer time to form the neoplasm. Furthermore the majority of ITCL has a higher malignant degree and rapid progress of growth which might cause the poorer prognosis than IBCL.

According to the Lugano staging system, the advanced stage III/IV had been associated with a relatively poor prognosis compared to those with early stage I/II, which was the same to the previous studies (15,17).

However, OS in different anatomic sites of PIL in our study had no statistic difference. In another study (17), OS in the small intestine and ileocecal region were significantly longer compared with rectum and multiple sites. The various results perhaps result from the different precise definition of anatomic sites and racial difference: (I) in our study, we divided cases into four groups (small intestines, ileocecal region, colon and rectum, and multiple sites); (II) the different definition of ileocecal region: in our study, ileocecal region included the terminal ileum, cecum and vermiform appendix; (III) the sample size is not large enough.

Nowadays, there is still no accurate strategy of treatment for PIL. The optimal treatment for PIL is still a work challenging and controversial. We should make the treatment plan according to the immunophenotype and clinical stage. The previous reports on the treatment results for patients with PIL indicated a superior survival in patients treated with multiple treatment including surgery, chemotherapy, and radiotherapy in comparison with patients treated with a single modality (8,18). The intestine is less suitable for radiotherapy than the stomach, so in our hospital patients with PIL were rarely treated with radiotherapy. In our study, according to the method of treatment, we divided the patients with PIL into four groups (surgery alone, chemotherapy alone, surgery plus chemotherapy and neither surgery nor chemotherapy). The result turned out that the group of patients received treatment with surgery plus chemotherapy was significantly longer than patients without surgery or chemotherapy (*Figure 4*). The another research of Khosla suggested that the 5-year OS rate in group of patients with surgery plus chemotherapy was higher than patients with chemotherapy alone (79.5% *vs*. 13.9%) (19). These findings suggest that the better outcome in the surgery plus chemotherapy group might be related to the complete resection of the bowel segment. However, the effect of surgical treatment still remains controversial. Previous studies reported that primary surgical treatment had a favorable influence on the prognosis of PIL (17,20). Primary surgical resection has been proposed as a rational treatment choice, as it simultaneously establishes the diagnosis and reduces the tumor burden (17). But there is no demonstration of the theoretical basis regarding the reason why reducing tumor burden is important in improving survival in PIL. More studies will be needed in the future to understand the reason. And due to the difficulties in preoperative pathologic diagnosis and the risk of complications requiring surgery, the use of surgical resection for PIL was widely applied. PIL are heterogeneous diseases. In our opinion, the controversial treatment may be caused by the different constitution of these subtypes, ignoring racial and environment factors.

Conclusions

The optimal management of primary lymphoma of PIL is not established. The prognosis of PIL was influenced by the disease staging, the histological type and treatment, etc. (5,21,22). In our study, younger age, earlier-stage and IBCL cases may achieve better survival benefit from the treatment of surgery plus chemotherapy. In consequence, the pathologists and clinicians should synthesize the clinical pathological information to make the early diagnosis and the proper treatment of PIL which could prolong the survival time of patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.07.10). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Ruijin Hospital (2016-022), Shanghai Jiao Tong University School of Medicine, and written informed consent was obtained from all patients.

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