Clinical and Pathological Features of Primary Gastrointestinal Non-Hodgkin’s Lymphoma

OBJECTIVE The study was initiated to obtain histologic distribution, clinical features, and treatment results in patients with primary gastrointestinal non-Hodgkin’s lymphomas.

METHODS Between January 1990 and January 2000, 89 PGI NHL patients were eligible to evaluate clinical features. Histological and immunohistological studies were routinely used and all the specimens were reclassified according to the recently published WHO classification system.

RESULTS (1) Clinically, among the 89 patients, there were 24 patients in stage IE, 33 in stage IIIE, 19 in stage IIIE, and 13 in stage IVE. (2) Immunohistological studies revealed 72 patients were with B-cell type and only 17 with T-cell type. (3) Altogether, 15 MALT lymphoma were diagnosed among 89 PGI NHL patients, and 14/15 were found primary in the stomach. (4) The 3-year and 5-year overall survival were 77.0% (57/74) and 53.6% (30/56) for the total group.

CONCLUSION No clinical symptoms and signs were found to be specific for the diagnosis of PGI NHL. Most patients were in stage IE and IIIE when diagnosed and the intermediate grade and B-cell type were more common than the others. Surgical resection of the tumor and standard combined chemotherapy post surgery were suggested to be the most effective measures for the long term survival of the PGI NHL patients.


Malignant lymphoma is a tumor originating from lymphatic hemopoietic tissue, the gastrointestinal tract being the most common site of the lymphoma other than lymph nodes. Primary gastrointestinal non-Hodgkin’s lymphoma (PGI NHL) is seldom seen clinically, short of specific clinical manifestations, so is frequently misdiagnosed. Routine pathology and immunohistochemical staining (including CD3, CD5, CD7, CD10, CD20, CD23, CD45RO, Kappa, Lambda, CyclinD1 and Ki-67) were conducted for 89 PGI NHL cases diagnosed from January 1990 to January 2000 for recategorization on the basis of WHO Classification Criteria so as to evaluate the relationship between the pathologic classification of PGI NHL and clinical effects and/or prognosis.

MATERIALS AND METHODS

General data
The 89 cases of PGI NHL made up 15.1% (89/590) of the total
non-Hodgkin's lymphomas (NHL) of the same period, 50 male patients and 39 female; ages were 14-86 years. Among them 56 cases were in the stomach (62.9%), 10 cases in the small intestine (11.2%), 9 in the colon (10.1%) and 14 in the ileocecum (15.7%); 72 were of the B-cell type (80.9%) and 17 cases of the T-cell type (19.1%). This group of cases conformed to the standard of Dawson diagnosis,\cite{4} i.e.: (1) no systemic lymphadenopathy (2) no mediastinal lymphadenopathy found in chest X-ray films (3) normal total leucocyte count and differential count (4) the lesion was limited to the gastrointestinal tract and the lymph drainage area as proved by operation observation (5) with normal liver and spleen.

**Clinical symptoms**

The main symptoms in the 56 patients with NHL of the stomach included epigastric illness (52 cases), epigastric dull pain (48 cases), anorexia (54 cases), cachexia (14 cases), nausea and vomiting (25 cases), hemorrhage of the upper gastrointestinal tract (10 cases). In those with colon tumors and those with small intestine lesions the principal symptoms included abdominal pain (18 cases), diarrhea or melena (6 cases), abdominal mass (8 cases), intestinal obstruction and perfection (2 cases). All 14 patients with ileocecal tumors had symptoms of intermittent or continuous pain in the right lower abdomen, one with melanin and another with intestinal obstruction, 7 cases were misdiagnosed for acute appendicitis. Among the 89 cases 56 had fever, cachexia and night sweating, and 33 had no such symptoms.

**Auxiliary preoperative examinations**

Gastroscopy was performed for 54 patients, 4 of them were misdiagnosed as gastric carcinoma, 8 cases as gastric ulcer, 2 as hypertrophic gastritis, 2 as atrophic gastritis; in 10 cases the initial diagnosis was NHL and in 32 cases the diagnosis of NHL was confirmed by gastroscopic biopsy and pathology. Colonoscopy was performed for 12 patients among the 89 cases, 3 of them were misdiagnosed as ulcerative colitis, 4 as colon carcinoma. By means of B-ultrasonic and CT examinations in 19 cases the diagnosis of a tumor in the upper abdomen was suggested, and in 10 cases a tumor in the lower abdomen, in 2 cases pancreatic cancer was suggested, in 5 cases involvement of the liver, in 3 cases involvement of the spleen, in 5 cases involvement of the bone marrow, and in 6 cases retroperitoneal lymphadenopathy was found. Pathologic study showed dissemination of tumor cell in the lymph nodes of the gastric omentum in 18 cases and in the mesenteric lymph nodes in 15 cases.

**Therapeutic methods**

In the series two patients died 2-3 months after their operation, another one failed to tolerate postoperative chemotherapy.

All the other patients received chemotherapy 3-4 weeks after surgery, mainly with the CHOP regime (Cyclophosphamide, Vincristine/Vindesine, and prednisone). For those patients when there was progress after the CHOP regimen or recurrence following a short remission, the CHOPE regimen (Etoposide [VP-16] or Teniposide [VM-26] added to CHOP) or the third generation chemotherapeutic regimen ProMACE-CytaBOM (Mitoxantrone, Cytosine Arabinoside, Adriamycin, VP-16/VM-26, Bleonycin, Amethopterine, Vincristine and prednisone) was used.

For the 5 patients with bone marrow involvement, the VDCP regime (Vincristine/Vindesine, Adriamycin, Cyclophosphamide and prednisone) was used. The average number of therapeutic courses for each patient was $8 + 2.4$ (0-15). For the 10 patients with huge focal lesions (max. diameter $> 10$ cm) and those with residual foci after chemotherapy, radiotherapy was given (3000-5000 cGy).

**RESULTS**

**Clinical staging**

Clinical staging was carried out according to the revised standard determined in Ann Arbor.\cite{5} In the series 24 cases were classified into stage IE. Among the 24 cases, the lesion was in the stomach in 21 cases, in the small intestine in 1 case, in the ileocecum in one case and in the colon in one case; 33 cases were classified into stage IIE, among them the lesion was in the stomach in 21 cases, in the small intestine in 2 cases, in the ileocecum in 7 cases and in the colon in 3 cases; 19 cases were classified into stage IIE, among them the lesion was in the stomach in 10 cases, in the small intestine in 4 cases; in the ileocecum in 7 cases and in the colon in 3 cases; 19 cases were classified into stage IIE, among them the lesion was in the stomach in 10 cases, in the small intestine in 4 cases; in the ileocecum in 2 cases and in the colon in 3 cases, 13 cases were classified into stage IVE, among them the lesion was in the stomach in 4 cases, in the small intestine in 3 cases, in the ileocecum in 4 cases and in the colon in 2 cases.

**Pathologic classification**

According to updated WHO Classification Criteria 17 cases were classified into T-cell lymphomas (in 8
Table 1. Comparison of clinical characteristics between T- & B- PGI NHL

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Staging</th>
<th>Sex</th>
<th>Mean age</th>
<th>IE</th>
<th>IIE</th>
<th>Fever%</th>
<th>Large tumor%</th>
<th>LDH%</th>
<th>IPI%</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>T-cell</td>
<td>17</td>
<td>12</td>
<td>5</td>
<td>39</td>
<td>41.2</td>
<td>58.8</td>
<td>47.1</td>
<td>11.8</td>
<td>23.5</td>
<td>47.1</td>
</tr>
<tr>
<td>B-cell</td>
<td>72</td>
<td>38</td>
<td>34</td>
<td>50</td>
<td>69.4</td>
<td>30.6</td>
<td>16.7</td>
<td>23.6</td>
<td>4.2</td>
<td>75</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<td>&lt;0.05</td>
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Follow-up study and prognosis

In the series of 89 cases the follow-up period for 22 cases was ≤ 3 yrs; for 18 cases ≥3 yrs and for 46 cases ≥5 yrs. The follow-up rate was 95.5% (88/90), the survival time was counted from the date of initial diagnosis to the date of the last follow-up visit or of death. Failure of follow-up was considered as death (except for three patients over 75 yrs). The results of a direct calculation method of overall 3-and 5-year survival rates were 77.0% (57/74) and 53.6%(30/56) respectively. In those in stage IE, the overall 3-and 5-year survival rates were 100% (19/19) and 85.7% (21/14) respectively; 33 cases belonged to stage IIE, the overall 3-and 5-year survival rates were 85.2% (23/27) and 65.0% (13/20) respectively; 19 cases belonged to stage IIE, the overall 3-and 5-year survival rates were 58.5% (10/17) and 30.8% (4/13) respectively; 13 cases belonged to stage IV, the overall 3-and 5-year survival rates were 45.5% (5/11) and 11.1%(1/9) respectively. As to the comparison of effectiveness and prognosis of lymphoma between different stages and different cellular types refer to Table 2.

Table 2. All the MALT lymphoma patients survived five years or longer.

Table 2. Comparison of effect and prognosis of PGI NHL

<table>
<thead>
<tr>
<th>Stages</th>
<th>T-cell</th>
<th>B-cell</th>
</tr>
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<tbody>
<tr>
<td>%</td>
<td>IE</td>
<td>IIE</td>
</tr>
<tr>
<td>CR+PR</td>
<td>96.5</td>
<td>53.1**</td>
</tr>
<tr>
<td>3-yr survival rate</td>
<td>91.3</td>
<td>53.6**</td>
</tr>
<tr>
<td>5-yr survival rate</td>
<td>73.5</td>
<td>22.7**</td>
</tr>
</tbody>
</table>

CR: Complete Relief, PR: Partial Relief; *P<0.05, **P<0.01.

DISCUSSION

Primary gastrointestinal non-Hodgkin's lymphoma is a group of diseases with a great heterogeneity of clinical manifestations, staging tissue pathologic typing and sensitivity to therapeutic treatment. According to the pathogenesis difference it can be divided into the gastric NHL and intestinal NHL, the latter may further be classified into the small intestinal NHL and colon NHL. The stomach is the most frequently involved organ in the body. In this series, 62.9% of the 89 cases had gastric lesions, basically in conformity with the statistical figures of 51.0%-62.8% published in the literature. [41] The percentage of PGI NHL was the largest, 40%-50% of lymphomas other than in the lymph nodes, and 8%-14% of the total NHL during the same period. [4] Similar percentages were shown in this series, 48.5% of lymphomas other than in the lymph nodes and 15.1% of the total NHL during the same period. Clinical staging IE and IIE were the main stages, mostly moderately malignant and of B-cell type, conforming to a previous report. [10]

The incidence of PGI NHL is low, [2] the clinical manifestations are complicated, though not specific, and with many similarities with those in gastric ulcer, gastric carcinoma, chronic gastritis and chronic ulcerative colitis. The symptoms and sings of the ileocecal lesions are similar to those of acute and chronic appendicitis because of the pain in the right lower abdomen. Clinicians lacking knowledge of this
disease frequently made a misdiagnoses. Analysis of this group of patients revealed the main clinical manifestations of PGI NHL in the stomach might show symptoms such as epigastric pain, anorexia, nausea and vomiting, and upper gastrointestinal tract bleeding; and for those with enteral PGI NHL, abdominal mass, diarrhea and melena were commonly found. No specific features were found by CT and B-ultrasonographic examinations. Endoscopic sono-graphy is helpful in judging the depth and staging of the lesions. For the difficult and complicated cases the operation should be performed as early as possible. Endoscopic biopsy with tissue pathologic examination is the most reliable method to confirm the diagnosis and most effective measure to increase the accurate diagnosis rate as well.

On the basis of analysis of clinical and pathologic data most of the 89 patients had a lymphomas that were moderately malignant. The proportion of lowly malignant MALT lymphoma was lower than that published abroad. Clarlson and Wootherspoon suggested that most gastric MALT lymphomas were chronically infected by Helicobacter pylori (Hp), inducing continuous proliferation of part of the lymph in lymphatic tissue related to gastric mucosa resulting in evolution into malignant lymphoma. This discovery has provided a theoretical basis for application of antibiotics to clear up Hp so as to treat malignant lymphoma. The result of the study has greatly enriched people's knowledge on the pathogenesis of lymphoma and provided up-to-date effective means for the clinical therapy of malignant lymphoma. But therapy for lymphoma by clearing away Hp is solely limited for treatment of patients with an early-stage tumor that only involves mucosa. The 15 MALT lymphoma patients in this group belonged to stage IIE or later, so they all lost the opportunity of treatment by internal medicine alone. However, they obtained excellent results through surgical resection of the foci and postoperative chemotherapy, with an overall 5-year survival rate of 100% . The two cases of intestinal T-cell lymphoma suffered the worst prognosis, with one having died at 2 months and at the other 3 months after the operation.

In this series most of them belonged to B-cell type PGI NHL and with clinical staging IE and IIE. People can be affected at any age. The frequency is higher in males, the ratio of male to female being1:3:1. As compared with B-cell PGI NHL patients, clinical staging IIE and IVE, with fever and an increased serum lactate dehydrogenase (LDH) level and IPI integral ≥ 3 were frequently seen in T-cell PEI NHL patients. The therapeutic effective rate and the overall 3-and 5-year survival rates of T-cell PGI NHL patients were obviously worse than those of B-cell PGI NHL patients, indicating the greater invasive property of T-cell PGI NHL.

So far there is still some dispute regarding the optimal therapeutic regimen for PGI NHL. In China at present, the therapeutic principles are mainly surgical resection of the lesion with postoperative combined chemotherapy. The effect and prognosis of PGI NHL were closely related to the clinical staging at the time of diagnosis, tissue pathological typing, size of the tumor as well as the therapeutic measures. In this group of cases, since comprehensive treatment such as radical surgery in combination with chemotherapy was used, a satisfactory result was earned with a 5-year survival rate over 53.6%.

It is suggested that combined chemotherapy after pathological diagnosis should be instituted to all patients with PGI NHL, whether or not the focus is removed surgically. The common treatment is with the CHOP and CHOPE chemotherapy plan. Remission should best be achieved after 1-2 therapeutic courses; the complete treatment should include 6-8 courses; continuous chemotherapy should be given if there is a residual focus; and when the disease is completely in remission another 2 therapeutic courses should be added. Regional radiotherapy may be adopted for patients with any of the following conditions: (1) as supplementary treatment for a huge tumor mass after surgical resection, (2) residual tumor found at the incisional edge through postoperative pathological examination,(3) after palliative resection or extenuated operation of partial removal of the focus, (4) recurrent tumor after operation.

In recent years combined large-dosage radiotherapy and chemotherapy with hematopoietic stem-cell transplantation have been used in the treatment of PGI NHL with good effects. Monoclonal antibody CD20 or combination of monoclonal antibody CD20 with chemotherapy has also been used to treat partial CD20 + lymphoma; and the application of biologic agents such as interferon and tumor vaccines for the treatment of lymphoma have been employed. We have also tried these measures in a few cases, however, it is still difficult to compare the different effects between these measures and the conventional therapeutic methods.

In conclusion, early diagnosis, comprehensive evaluation of the condition, and prompt selection of an appropriate therapeutic regimen are the key points of
improving the survival rate and of prolonging the survival time of PGI NHL patients.

REFERENCES