Med. J. Kagoshima Univ., Vol. 51. Suppl. 17-21, July, 1999

Diagnosis and Treatment of Primary Malignant Gastric Lymphoma

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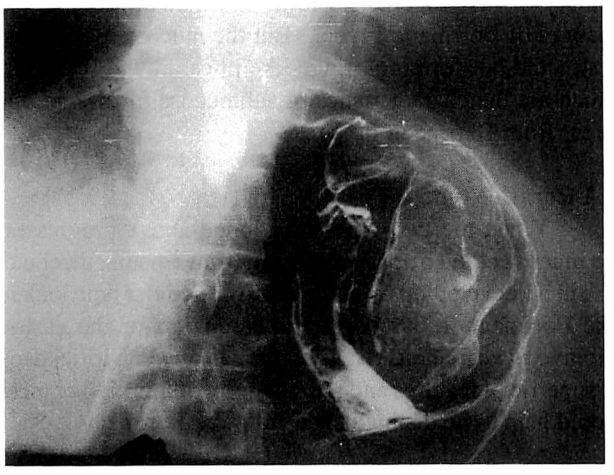
Primary gastric lymphoma (PGL) occupied 1- 4% of malignant tumors[1], and it was the most common non-epithelial originated gastric malignant tumors. The incidence of PGL tended to increase in the last 20 years. Because of its low incidence and deficiency of specific clinical manifestation, PGL could not be distinguished from gastric cancer easily, which caused relatively high misdiagnosis rate. However, it is very important to identify PGL from gastric cancer due to the different biological behavior and treatment method between them and relatively better prognostics of PGL[2]. Clinical diagnosis and treatment data of 307 cases, reported in our nation between 1976 and 1995, was collected and analyzed on the diagnosis, staging and of treatment of PGL.

Clinical Data

The 307 cases consist of 167 male and 140 female, male/female was about 1.2/1, ranging in age from 13 to 82 years old (46 years old in average). Among the main clinical manifestations, the incidence of upper abdominal pain was 75.6%, while abdominal mass was 36% and hematemesis and hemafecia 32%. And nausea, vomit, anorexia and loss of weight are the minor clinical manifestations. The symptoms appear in about l0.2 to 13 months before treatment, and most cases are misdiagnosed as gastric ulcer or cancer. Pre-operation diagnosis accordance is 15% by X-ray, 17% by endoscopy, and 38% by mucous biopsy. Site of lesion: 38% in lower part of stomach, 26% in gastric body, 13% in entire stomach, 13% in greater curvature. Gross type of tumor: 36% were massive type, 40% were ulcerative type, 24% were diffuse infiltration, and others were mixed type. Pathologic type of 7 cases is Hodgkin's lymphoma and others are non-Hodgkin's lymphomas.

Figure 1-4 A: Massive type



Discussion

1. Diagnosis and differential diagnosis

1.1: Clinical features

Although there are many similar aspects between PGL and gastric cancer in clinical manifestations, the following features are quite different.

1) Average onset age of gastric cancer is 55 years old, and PGL patients were 10 years younger than gastric cancer patients were.

2) Taking domestic and foreign data in consideration, female has a higher incidence: male /female was 3-4/1 in gastric cancer while it was I.2/1 for PGL in this study and I.5/1 as for foreign data.

3) The incidence of abdominal mass and hemorrhage of digestive tract was higher than gastric cancer.

4) Physical signs were obvious, Such as mass and anemia etc. But its subjective symptoms were very slight.

5) With the same tumor size, infiltrating depth and lymph node metastasis, PGL has better biological behavior and higher excision rate than gastric cancer. Five-year survival rate was 40-47% for stage II or worse in PGL and was 30-35% for advanced gastric cancer, which implied the better prognosis of PGL.

1.2 X-ray characters

The misdiagnosis rate of PGL by X-ray was very high. The traditional diagnosis accordance of X-ray was

Figure 1-4 B: Ulcerative type

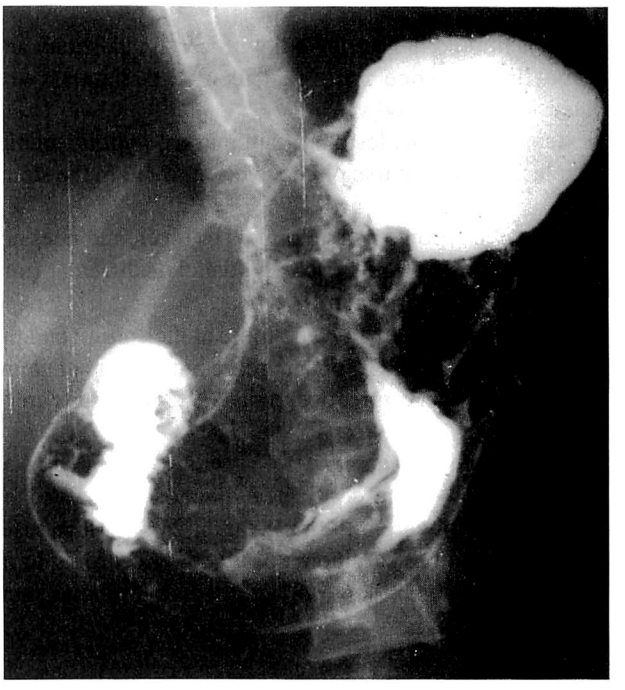


Figure 1-4 C: Coarse plica type

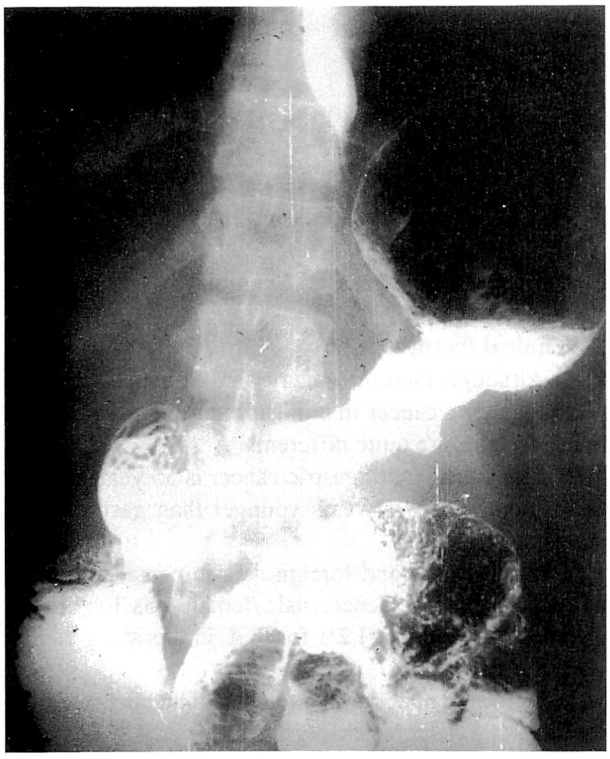
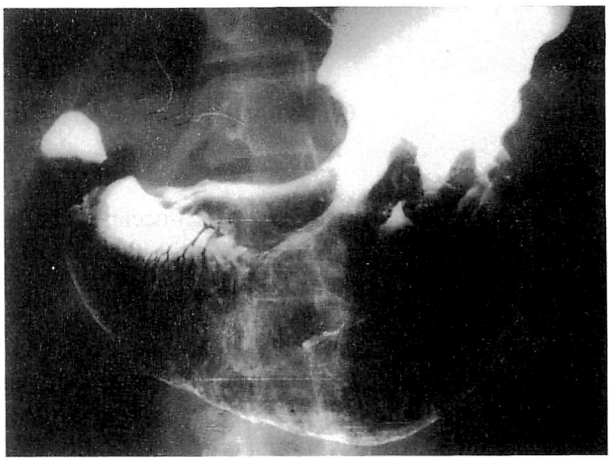


Figure 1-4 D: Mixed type



less than 20%[3]. Most cases were diagnosed as gastric cancer or gastric ulcer because of the insufficient recognition to PGL. PGL was classified into 5 types according to X-ray: Superficial type, massive type, ulcerative type, coarse-plica type and mixed type. Massive type may be misdiagnosed as gastric cancer of Borrmann 1 type or leiomyoma. Ulcerative type as gastric cancer of Borrmann 2, 3 types or gastric ulcer. Bold-Plica type as gastric cancer of Borrmann IV type. With the popularity of stomach double contrast radiography recently, the diagnosis accordance had been improved. The differences of X-ray between PGL and gastric cancer are as follows:

1) PGL is limited in gastric wall with certain elasticity and without interference with gastric wall peristalsis and stenosis of gastric cavity.
2) Extensive multiple lesions, giant mass, polypoid nodule, multiple ulcer and coarse plica are often found in the stomach.
3) Coarse plica grows around polyps or ulcer, and does not cause the stenosis of gastric cavity, which is different from gastric cancer of Borrmann IV type.
4) The gastric carcinoma occurs more at the antrum and the less curvature while PGL occurs more at the body of stomach and greater curvature, occupying 39% in this group[3,4].

1.3 Endoscopic characters

The rate of the confirmed diagnosis achieved by endoscopic examination in this group is 17%. More cases are misdiagnosed as carcinoma or ulcer. According to its gross appearance, the domestic and overseas scholar sums up 5 types.

1) Superficial type

The early stage of this disease can show the mucosa changes like the early gastric cancer. The early gastric cancer infiltrates submucosa, while this disease often occurs at the submucosal lymphatic tissue and spreads between the mucosa and the muscle layer. If the mucosa is infiltrated and destructed, it will show the appearances of the early gastric cancer such as IIa, IIc+IIa, cluster IIa type superficial spreading type etc. But the malignant lymphoma is soft for the lack of fiber contents, and haven't the tenacity of cancer under the endoscopic biopsy, which is different from early gastric cancer.

2) Coarse plica type

The mucosa and muscular layer could be separated when the tumor cells proliferate and infiltrate extensively into the submucosa. Because of the crush or infiltration of the tumor cells, the mucosa would be edematous and form coarse ruga showing the changes of the gyrus, just like the mucosal image of the Borrmann 4 type. But the mass is soft with some elasticity and without the stenosis of gastric cavity, which is different from the type 4.

3) Massive nodular type (massive type)

Besides the diffusive infiltration in submucosa, the tumor cells can also proliferate locally, bulging into the gastric cavity to form massive nodules, the nodules can be solitary or fuse together to form enormous mass like the changes of Borrmann I type. But the mucosa may not be destructed but forming bridge-like plica around the mass, which are the characteristics of submucosal mass and different from Borrmann I type.

4) Ulcerative type

When the two types mentioned above progresses, the mucosa could be destructed and form erosion, ulcer etc. The ulcer developing from the massive nodular type looked like Borrmann 2, 3 type gastric carcinoma or the gastric leiomyoma, carcinoid etc. But the radiate, dendritic, deep or superficial features and the soft body of this kind of ulcer would help to be distinguished from the Borrmann 2, 3.

Figure 5-8 A: Superficial type

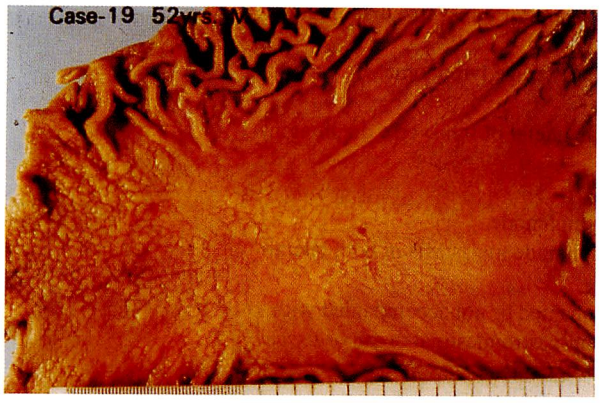


Figure 5-8 B: Coarse plica type

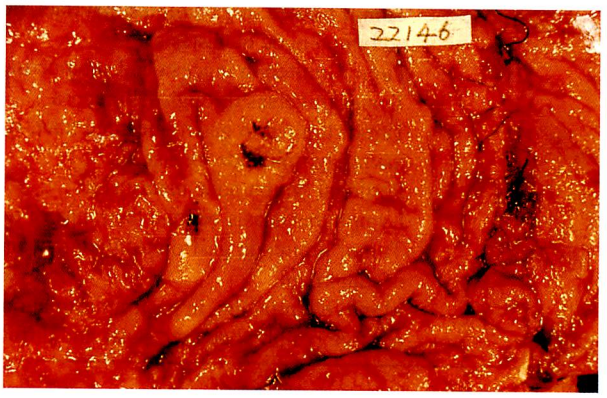


Figure 5-8 C: Massive type

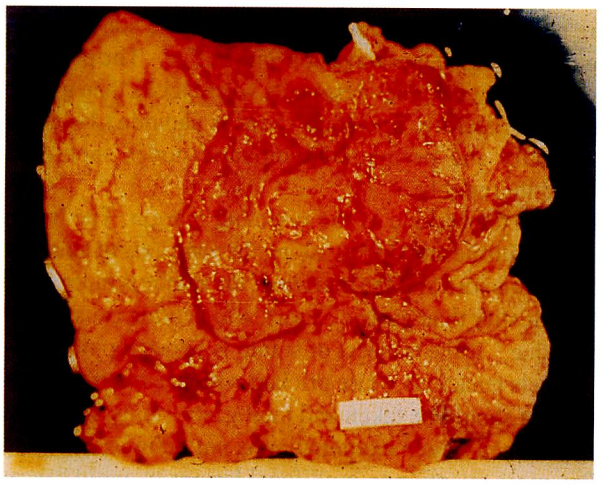
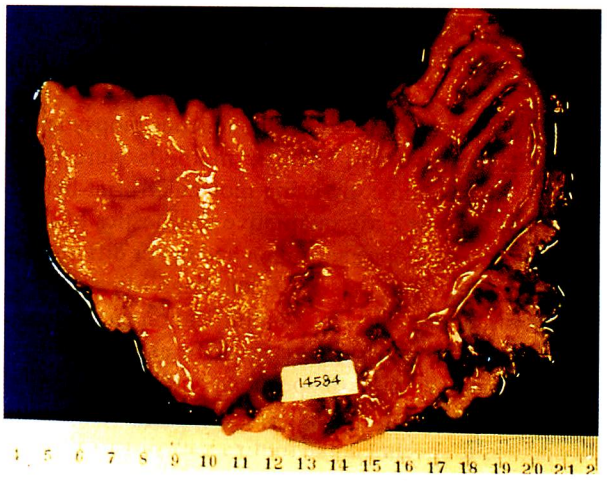


Figure 5-8 D: Ulcerative type



5) Mixed type

At the late stage of malignant lymphoma, the above types can appear simultaneously with multifocal, polymorphic, diffusive appearance or superficial erosion, large nodules, coarse plica, multiple ulcer, polyps, etc. But the ulcerative type is more common in gastric carcinoma with deep and definite margin, and the lesion is relatively single and limited despite of its prominence and infiltration [3 4].

1.4 Biopsy diagnosis

The biopsy is a reliable method for almost all malignant gastric tumors except for malignant lymphoma. One reason is the lack of experience of pathology doctors who only pay attention to the differentiation between the malignant and benign but not keeps this disease in alert. Another reason is the difficult distinction from the undifferentiated cancer without glandular structures in the small sampling tissue. Positive biopsy results is very difficult to achieve because of its origination from submucosa, so when it is considered under the endoscope, more and deeper sampling should be executed and the immunohistochemical examination and electron examination are also needed besides the optical microscope, in order to excluding the undifferentiated cancer, lymphorecticulosis (pseudolymphoma), ulcer, inflammation, etc[5,6].

1.5 Intraoperative diagnosis

To those misdiagnose cases by preoperative X-ray, endoscopy, mucosa biopsy examination, operative exploration is the last chance. An experienced surgeon could often confirm the diagnosis according to intra-operational exploration. The large and softness of mass are the main difference between this disease and gastric carcinoma. It spreads diffusely in gastric wall but not severely infiltrate adjacent organs, which contributes to more opportunity to be resected. Therefore, the frozen pathologic examination should be demanded with suspicious. When the difference from undifferentiated cancer is not definite, the gross appearance and clinic experience should be combined and further examinations would be needed until right diagnosis and reasonable therapy are set down.

1.6 Other diagnostic techniques

Recently, endoscopic ultrasonography (EUS) had been used in the examination of gastric malignancy. It can display the infiltrating depth, periphery lymph node metastasis and the relation with adjacent organs besides the gross appearance of tumor, which is important to diagnostics, staging and the treatment. Its diagnostic accuracy was obviously higher than routine endoscopy in examining malignant lymphoma. At the same time the accuracy might reach 92 percent in determining the infiltrating-depth and

Table I. Clinical stage of NHL (mended Ann Arbor method)

I	Tumor limited in gastrointestinal tract, lies in one lateral of transverse diaphragm, no lymph node metastasis.
I_1	Tumor limited in mucosa and submucosa, called early stage lymphoma.
I_2	Tumor traverses through submucosa.
II	Tumor limited in gastrointestinal tract, Iying in one lateral of transverse diaphragm, having lymph node metastasis.
II_1	Regional lymph node metastasis.
II_2	Lymph metastasis beyond the range of regional lymph node.
III	Tumor limited in gastrointestinal tract and/or lymph node metastasis in both lateral of diaphragn.
IV	Massive lymphoma in gastrointestinal tract accompanied or not accompanied with relative lymph node metastasis and diffusion to non-gastrointestinal organ or tissue.

44 percent in lymph node metastasis. It was believed that EUS could replace laparotomy and pathologic examination in the diagnostics and clinic staging of malignant lymphoma, but was not accurate enough in the early diagnostics[7,8].

In addition, by the use of the mucous biopsy specimen, more sensitive and specific methods were being searched. For example, by using molecular-print-hybridizing techniques, the early qualitative diagnostics of DNA extracted from the biopsy specimen had better differentiating value, especially to those difficult diagnostic specimen under microscope. The DNA-amplification technique of polymerase chain reaction (PCR) could be used in the diagnostics of minute amount of specimen and had high sensitivity, but it also had some false positive. So, to those difficult diagnostic specimen, the routine pathologic examination, electron-microscopy-imnumo-histo-chemical and molecular biologic techniques should be combined and analyzed comprehensively in order to diagnose more accurately[9,10].

2. Clinic staging and the essential point of treatment

The clinic staging is important to the treatment and the prognostic estimation, but many staging methods existing had not been unified. At present, the clinic staging as follows is mainly claimed for non-Hodgkin lymphoma (NHL) [11], providing references for clinic doctors. (Table I)

The 244 pieces of clinic materials of gastric NHL reported by Radaszkiewicz[11] displayed the close relationship between clinic stage and prognostics. The survival rate (69%) of stage I was higher than stage II (41%), and the 5-year-survival rate could reach 90% in stage 11 but 30% in stage 11 2. So, if clinic doctors can grasp rightly the clinic stage standard and arrange treatment based on the prognostic effect by different stage, the survival period would be prolonged.

3.Treatment

3.1 Essential point of operation

Operation treatment is the first selection when this disease is diagnosed, and the operation should obeyed requirement of curative gastrectomy but the following questions should be paid more attention to:

1) Resect completely primary focus together with peripheral lymph nodes: Although the tumor is larger and has more periphery lymph nodes metastasis. The adherence to neighboring tissue is always non-infiltrative. The possibility of resection is higher despite its worse looks than gastric cancer. Therefore, operation chances shouldn't be given up casually and peripheral lymphatic nodes should be resected thoroughly.

2) Prevent the residue of the resecting margin: The lesion usually infiltrate and diffuse along the long axis of stomach under submucosa and the margin of the tumor is more difficult to identify than gastric cancer, which often causes cancer residue. If the transect of stump is hypertrophic, grayish or feels tenacious while pricked with needle, frozen examination should be taken and total gastrectomy should be adopted when frozen examination is not definite.

3) Pay more attention to multifocal lesions to avoid cancer residue. This disease always lies in the greater curvature of stomach and has multicentric onset; the preserved gastric cavity should be dissected to find cancer residue or other lesions when subtotal gastrectomy is performed.

4) The question of palliative or extenuation operation. Trying to perform palliative resection when curative resection was not suitable during operation, adjuvant radiotherapy could be adopted for residual lesion. Short circuit operation is appropriate to those obstructive cases: lay aside vacantly, and label the tumor with silver clip for radiotherapy after operation. In conclusion, more active surgical treatment should be taken for such cases than for gastric cancer patients to acquire satisfied effects. Bartlett reported that the 10-year survival rate of the malignant lymphoma of stomach could reach 88%, the 5-10-year survival rates for stage I and 11 after curative resection are 66% and 51% respectively. The 2-year survival rate after palliative operation is 26% and is 0 for those without operation, so operation should be the preferred treatment[3,12,13].

3.2 Radiotherapy

At present, some controversies still exist regarding the question of radiotherapy after operation, and most scholars stand for radiotherapy. But the conventional radiotherapy could not increase the 5-year survival rate and often companies with severe complications without consideration about the staging and extent of cure. The indication for postoperational radiotherapy are as follows:

1) Tumor has broken out serosa or lymph nodes metastasis exits.
2) The cases who has multicentric foci or infiltrated adjacent organs directly.
3) The cases after palliative operation.
4) The cases with recurrence[3]

3.3 Chemotherapy

Because of the different objective between radiotherapy and chemotherapy, the malignant lymphoma is more sensitive to chemotherapy than gastric cancer, and have higher incidence of distant recurrence after operation. Pasini reported that the 10-year survival rate is 91% for 38 cases who underwent operation and accompanied with radiotherapy. In contrast, the 10-year survival rate after only operation is 60%. So the supplementary therapy is necessary whether the recurrence is early or late. The effect of conventional chemotherapy scheme such as COP, CHOP, COAP is perfect. Some advocated recently that non-operative treatments including radiotherapy, chemotherapy et al, are efficient for stage I and ll cases. But most scholars held that comprehensive treatment scheme in which operation is leading are better[2,3,14].

Because primary malignant lymphoma of stomach is seldom seen and liable to cause confusion with gastric cancer, it is necessary to grasp the clinical features and enhance the understanding of this disease during X-ray and endoscopic examination. EUS and other biological technique could increase the diagnosis rate of the tumor. Correct clinical staging is useful for arranging treatment and estimating prognosis. This disease is sensitive to radiotherapy and chemotherapy. Therefore, if comprehensive treatments in which operation is leading are performed, the prognosis is superior to that of gastric cancer.

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