

## —Reports on Experiments and Clinical Cases—

Spontaneous gastrointestinal perforation in patients with  
lymphoma receiving chemotherapy and steroids

Report of three cases

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Norio Matsukura<sup>2)</sup>, Kiyonori Furukawa<sup>2)</sup>, Kaku Egami<sup>1)</sup> and Kiyohiko Yamashita<sup>2)</sup><sup>1)</sup>Department of Surgery, Tama-Nagayama Hospital, Nippon Medical School<sup>2)</sup>First Department of Surgery, Nippon Medical School**Abstract**

Spontaneous gastrointestinal perforations in three patients with lymphoma were considered to be treatment-related conditions. All three were diagnosed as having malignant lymphoma by histological examination, and treated with chemotherapy and steroids. Four to 14 days after the start of chemotherapy, they complained of abdominal pain and plain rentogenograms revealed pneumoperitoneum. The interval between the onset of peritonitis and operation was almost 24 h. Emergency operations were carried out ; one patient with a jejunal perforation underwent resection of the jejunum, another with a gastric perforation received a simple closure with omental patch, and the third with a gastric perforation underwent gastrectomy. Two patients recovered from the surgery, while the gastrectomy patient died due to sepsis. The favorable outcome of the surgical intervention is attributed to early diagnosis, prompt exploration, and selective operative procedures. We recommended a simple closure with omental patch for gastroduodenal perforation. Resection and primary anastomosis are possible only in the small bowel. (J Nippon Med Sch 1999 ; 66 : 37—40)

**Key words** : malignant lymphoma, spontaneous perforation of gastrointestinal tract, chemotherapy, steroids

**Introduction**

Spontaneous perforation of the gastrointestinal tract is an uncommon but life-threatening complication of systemic chemotherapy for non-Hodgkin lymphoma. The perforation can occur at any point in the GI tract including the stomach and intestine<sup>1-5</sup>. Information about spontaneous gastrointestinal perforation during cytotoxic therapy in the absence of tumor cell involvement is limited. Early diagnosis with aggressive surgical intervention is essential to improve the chances of survival.

Factors thought to be responsible for the morbidity of this complication include myeloid toxicity, immuno-

suppression, and protein malnutrition<sup>6,8</sup>. Traditional signs and symptoms of a localized inflammatory process or peritonitis are often muted by the anti-inflammatory effects of steroids. Diagnosis is often delayed and gastrointestinal perforation may go unrecognized until shock following unexplained sepsis and multiple organ failure. Here, we report three cases of spontaneous gastrointestinal perforation associated with cytotoxic therapy and steroids for non-Hodgkin lymphoma (**Table 1**).

**Case reports**

**Case 1** : A 43-year-old man was admitted to an

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Table 1-1 Clinical findings of spontaneous gastrointestinal perforation in patients with lymphoma

Case	Sex	Age	Primary site	Chemotherapy regimen	Time between start of therapy and onset (days)
1	M	43	skeletal muscle	CHOP	4
2	M	60	hypopharynx *	ProMACE-MOPP	14
3	F	67	retroperitoneum	CHOP	7

\* Seven months before spontaneous perforation, jejunal resection was carried out due to perforation by tumor cells.

Table 1-2 Clinical findings of spontaneous gastrointestinal perforation in patients with lymphoma (continued)

Case	Time between onset and operation (h)	Disease site	Surgical procedure	Outcome
1	20	Jejunum	Jejunal resection	Survived
2	25	Stomach (cardia)	Simple closure +omental patch	Survived but died due to relapse of lymphoma 1 year after surgery
3	22	Stomach (middle body)	Gastrectomy	Died due to sepsis 31 days after surgery

other hospital in July 1998 due to fever of unknown origin and melena. Neck and inguinal lymph nodes were palpable and mesenteric lymph node swelling was revealed on computed tomography. He was transferred to our hospital in August 1998 and complained of multiple intramuscular tumors. A biopsy revealed a malignant, anaplastic large cell type lymphoma. Systemic chemotherapy with cyclophosphamide, vincristine, procarbazine hydrochloride and predonin (CHOP) was started in September 1998. Four days later he complained of low abdominal pain and a plain roentgenogram revealed pneumoperitoneum. At laparotomy, perforation of the jejunum without macroscopic tumor cell involvement was found and resection of the jejunum carried out. Pathological examination confirmed spontaneous perforation of the jejunum. He recovered from the surgical insults. Two weeks after surgery, he complained of tarry stools due to a peptic gastric ulcer. Blood vessels clipping was carried out endoscopically. His condition was still improving as of January 1999.

**Case 2 :** A 60-year-old man had been treated with radiation in 1983 and systemic chemotherapy (VEMP) in 1984 for a lymphoma of the hypopharynx. After 2 cycles of combined chemotherapy with CHOP, he experienced abdominal pain and showed evidence of peritonitis with shock in June 1987. A plain roentgenogram revealed pneumoperitoneum. At emergency laparotomy, a small perforation of the jejunum with multiple areas of macroscopic lymphomatous involvement was found. Resection of the small intestine,

including the perforation, was carried out. The histological finding was a lymphoma similar to that in his hypopharynx. He recovered from his illness 1 month after surgery.

He complained of general fatigue and was admitted to our hospital in January 1988. Another regimen of systemic chemotherapy with etoposide, cyclophosphamide, procarbazine hydrochloride, methotrexate, predonin, nitrogen mustard, vincristin, procarbazine, and prednison (ProMACE-MOPP) was started. Two weeks later he complained of abdominal pain and was diagnosed as having gastric or intestinal perforation because of pneumoperitoneum observed on a plain roentgenogram. At laparotomy, perforation of the gastric cardia was found and subsequent simple closure of the perforation with an omental patch performed. He recovered again but died of a relapsed lymphoma in the hypopharynx in January 1989.

**Case 3 :** A 67-year-old woman was admitted to our hospital in March 1986 with a 29-day history of jaundice without fever or pain. She had inguinal and axillary tumors and was diagnosed with a non-Hodgkin lymphoma by excisional biopsy. Computed tomography revealed a mass measuring 7.0 × 8.5 cm in the right retroperitoneal space and enlarged para-aortic lymph nodes, a dilated intrahepatic bile duct, and stricture of the common bile duct at the site of hepatic hilum, consistent with extrinsic compression by enlarged lymph nodes. Staging evaluation of the disease revealed a stage II lymphocytic lymphoma. Fifty Gy of limited field radiation focused on the mass in the

retroperitoneal space and the para-aorta lymph nodes produced regression of the jaundice and normalization of liver function values. Systemic chemotherapy with CHOP was started 2 months after radiation therapy. A week later, she had abdominal pain and evidence of peritonitis. A plain roentgenogram of the abdomen showed pneumoperitoneum. Gastrectomy was carried out due to a perforation in the anterior wall of the stomach body observed at laparotomy. The histological findings indicated a peptic ulcer. Her condition deteriorated in spite of postoperative intensive care, and she died of sepsis 31 days after surgery.

### Discussion

Spontaneous gastrointestinal perforation is a potentially lethal complication of anti-lymphoma therapy. Reports of gastrointestinal perforation secondary to systemic chemotherapy are sparse in the literature<sup>2-5</sup>. The use of systemic chemotherapy and steroids in patients with lymphoma is the most common cause. When lymphoma invades the gastrointestinal tract and is treated with effective chemotherapy, tumor necrosis with perforation is the potential complication<sup>9-11</sup>. One of our patients was operated on for perforation due to tumor lysis of the jejunum 7 months before simple closure of a peptic ulcer. Spontaneous gastrointestinal perforation can occur in the stomach and bowel wall, however, in patients receiving systemic chemotherapy and/or steroids even if there is no tumor<sup>12</sup>. The etiology is not known, but may be a complex mechanism. Both the systemic chemotherapy and steroids can induce the perforation. In our patients, severe epigastralgia occurred 2 to 5 days after the start of chemotherapy. The combination of the drugs most likely leads to the development of ulcer perforation.

The morbidity and mortality of gastrointestinal perforation is high if a major medical illness exists concomitantly with the perforation<sup>13-15</sup>. In patients with lymphoma, the complications are increased by the toxicity of chemotherapy. Diagnosis is often delayed because symptoms are often muted by steroids. Gastrointestinal perforation may go unrecognized until shock following panperitonitis. The time interval from the onset of symptoms caused by the perforation to the time of operation can affect the outcome. Preoperative shock is also a significantly poor prognostic

factor for such patients. In our 3 cases, the time interval from the onset of symptoms to the time of operation was almost 24 h. Early diagnosis of ulcer perforation in patients with lymphoma during systemic chemotherapy is therefore mandatory. We recommend that patients who complain of epigastralgia be checked for gastrointestinal ulcers or even perforation if they are receiving chemotherapy or steroids for lymphoma. A strikingly low incidence of mortality after spontaneous perforation was reported in patients with Crohn's Disease<sup>16</sup>. Resection and primary anastomosis was restricted to selected patients with small bowel perforation. Among our 3 cases, one underwent simple closure of a perforation and another jejunal resection. These two patients recovered from the surgical insults. The other one who underwent gastrectomy died due to sepsis. Simple closure is preferable, and a more radical procedure, such as gastrectomy, would likely add to the operative morbidity and mortality associated with surgery. The excellent outcome of surgical intervention is attributed to an early diagnosis, prompt exploration, and selective operative procedures. We recommend a simple closure with omental patch for gastroduodenal perforation. Resection and primary anastomosis are possible only in the small bowel.

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