

Spontaneous Intestinal Perforation Due to Non-Hodgkin's Lymphoma: Evaluation of Eight Cases

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Abstract Primary intestinal lymphoma with spontaneous perforation and after systemic chemotherapy is rare. The present study summarizes retrospectively the outcome of eight free intestinal perforated patients diagnosed with intestinal non-Hodgkin's lymphoma. Two patients had a history of systemic chemotherapy before perforation. The most common symptoms of the patients were abdominal pain, nausea, vomiting, weight loss, and fever. Sites of perforation were ileum in four, jejunum in two, cecum in one, and sigmoid colon in one patient. Synchronous lymphoma was present in three patients. The perforation was closed by primary closure in three patients. Resection/anastomosis was performed in four patients and sigmoid colostomy was performed in one patient. Three patients were lost due to leakage or septicemia. Intestinal lymphoma might be kept in mind as a cause in free intestinal perforations. Because of the high mortality rate early diagnosis and treatment are important to improve the prognosis of bowel perforation in patients with non-Hodgkin's lymphoma.

Keywords Intestinal lymphoma · Perforation · Chemotherapy · Treatment

Introduction

Lymphoma is the third most common malignant tumor of small intestine after adenocarcinoma and carcinoid tumor

[1, 2]. The small intestine is the second most common site of malignant lymphoma of the alimentary tract perforation [3]. Primary colorectal lymphoma accounts for less than 0.5% of colorectal malignancies [4]. Perforation of intestine is an uncommon complication of non-Hodgkin's lymphoma (NHL). Very few cases of small bowel and large bowel perforation occurring in association with primary intestinal malignant lymphoma were reported in previous studies [5–7].

The present study summarizes retrospectively the outcome of eight free intestinal perforated patients diagnosed with intestinal NHL.

Case 4

A 65-year-old woman hospitalized with the diagnosis of a 6 × 8-cm-diameter abdominal mass. The biopsy revealed malignant large cell-type lymphoma. She had manifested abdominal pain after receiving systemic chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP). On physical examination her abdomen was tender and rigid. Serum lactate dehydrogenase (750 IU/L; normal range, 234–484 IU/L) and white blood cell count (16,000 cells/mm³) were elevated. Abdominal ultrasonography showed free fluid in the Douglas pouch and between intestinal segments. She had undergone surgery because of acute abdomen. A perforated tumor mass, approximately 13 × 13 cm, in the jejunum was revealed and primary closure was performed. The patient was lost because of leakage at postoperative day 4.

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Patients and methods

We reviewed 50 patients operated on for free intestinal perforations due to various causes at Turgut Ozal Medical Center between February 1995 and June 2005. Eight (16%) of them were diagnosed with intestinal lymphoma (other diagnoses were intestinal tuberculosis in 12, Crohn's disease in 4, typhoid perforation in 2, foreign body in 4, Behçet disease in 3, intestinal tumor in 2, femoral hernia in 2, strangulated hernia in 4, ileus related to intestinal adhesion in 5, and delayed mesentery artery ischemia in 4 patients). Their clinical history, symptoms, and preoperative investigations and details of their management were analyzed. A complete blood count, liver and renal function tests, plain x-ray of the abdomen, chest x-ray, and abdominal ultrasonography were performed. There was no history of lymphoma in six patients. Patient 7 had a history of primary gastric lymphoma. He had been treated with systemic chemotherapy (CHOP) before perforation.

Results

The median age of eight patients with intestinal malign lymphoma (three females, five males) was 59.5 years (range, 18–70 years). The laboratory and operative findings for and outcome of patients are summarized in Table 1. The most common symptoms were acute abdominal pain, nausea, vomiting, weight loss, and fever. Physical examinations showed abdominal tenderness and muscular rigidity. There were no palpable lymph nodes in the cervical, axillary, or inguinal regions. In all patients, abdominal ultrasonography showed free fluid in the rectovesical or Douglas pouch

and between intestinal segments. Evidence of pneumoperitoneum was present in five patients. On plain x-ray of the abdomen, air-fluid levels were presented in three patients. Lactate dehydrogenase was increased significantly at the time of admission in all patients. Comparisons of our cases with similar reports in the literature are summarized in Table 2.

All patients underwent laparotomy after nasogastric suction and appropriate fluid replacement. At laparotomy synchronous lymphomas were present in patients 4, 6, and 7. The site of perforation was the terminal ileum in four, jejunum in two, cecum in one, and sigmoid colon in one patient. There were multiple hard lymph nodes in the adjacent mesentery in all patients. The liver and spleen were normal. In patient 1 laparotomy revealed a perforated tumor mass, approximately 4 × 5 cm, in the jejunum, and resection and end-to-end anastomosis were performed. At postoperative day 7, a leakage was noticed and the patient underwent a reoperation in which jejunum resection and end jejunostomy were performed. The patient was lost due to sepsis on postoperative day 32. In patient 8 a perforated tumor mass, approximately 5 × 6 cm, in the cecum was realized after right hemicolectomy and end ileostomy were performed, and the patient was lost due to sepsis. In these three patients a common factor was the long interval from the onset of symptoms to the operation.

Histopathologic examinations and types of lymphoma for all patients are reported in Table 1 according to WHO classification and International Prognostic Index (IPI score) [8, 9]. Living patients were transmitted to the oncology department for chemotherapy. Six, three, one, and two cycles of CHOP chemotherapy were administered to patients 3, 5, 6, and 7, respectively. Six months after chemotherapy brain metastases were revealed in patient 3, and a 3000-cGy (Gray) dose of radiation therapy was administered. These patients have

Table 1 Laboratory and operative findings and outcome of patients

Patient no	Age/ sex	Perforation site	Operation	WHO classification	IPI score	Outcome
1	65/M	Ileum	R&A ^a	Diffuse large B cell lymphoma	High risk	Leak; died
2	18/F	Ileum	R&A	Anaplastic large cell lymphoma	Low-grade intermediate	2 mo
3	66/F	Jejunum	Primary closure	Precursor T cell lymphoblastic lymphoma	High-grade intermediate	24 mo
4	65/F	Jejunum	Primary closure	Diffuse large B cell lymphoma	High risk	Leak; died
5	70/M	Ileum	Primary closure	Precursor T cell lymphoblastic lymphoma	High risk	4 mo
6	60/M	Ileum	R&A	Anaplastic large cell lymphoma	High-grade intermediate	2 mo
7	65/M	Sigmoid colon	Sigmoid loop colostomy	Precursor T cell lymphoblastic lymphoma	High risk	3 mo
8	57/E	Cecum	Right hemicolectomy and end ileostomy	Anaplastic large cell lymphoma	High-grade intermediate	Died

^aResection and anastomosis.

Table 2 Comparison of gastrointestinal perforation cases in the literature with our patients

First author [ref. no.]	Age	Gender	Radiology	Perforation site	Preop chemotherapy	Operation	Reoperation	Pathology	Outcome
Kataoka [26]	66	M	Free air	ileum	No	Resection	Anastomosis	T cell enteropathy type	Died
Webber [11]	8	M	Normal	Colon	Yes	Resection	Stoma	Invasive large cell	Discharged well
Hata [19]	17	M	Not known	Duodenum	Yes	Primary suture	No	Not known	
Ara	65	M	Free air	ileum	No	Resection	Anastomosis	Diffuse large B cell	Died
Ara	18	F	Free air	ileum	No	Resection	Anastomosis	Anaplastic large cell	Discharged well
Ara	66	F	Free air	Jejunum	No	Primary suture	No	T cell lymphoblastic lymphoma	Discharged well
Ara	65	F	Free air	Jejunum	Yes	Primary suture	No	Diffuse large B cell	Died
Ara	70	M	Free air	ileum	No	Primary suture	No	T cell lymphoblastic lymphoma	Discharged well
Ara	60	M	Normal	ileum	No	Resection	Anastomosis	Anaplastic large cell	Discharged well
Ara	65	M	Normal	Colon	Yes	Resection	Stoma	T cell lymphoblastic lymphoma	Discharged well
Ara	57	F	Normal	Colon	No	Resection	Anastomosis	Anaplastic large cell	Died
Wada [10]	43	M	Free air	Jejunum	Yes	Resection	Not known	Anaplastic large cell	Discharged well
Wada [10]	60	M	Free air	Stomach	Yes	Primary suture	No	as hypopharynx ca	Died 12 mo later
Wada [10]	67	F	Free air	Stomach	Yes	Resection	Anastomosis	Lymphocytic lymphoma	Died
Freeman [5]	74	F	Free air	Jejunum	Not known	Not known	Not known	Not known	
Freeman [5]	70	M	Free air	Duodenum- jejunum- ileum	Not known	Not known	Not known	Not known	
Freeman [5]	47	F	Free air	Jejunum	Not known	Not known	Not known	Not known	
Freeman [5]	25	F	Free air	Colon	Not known	Not known	Not known	T cell	
Freeman [5]	65	F	Free air	Jejunum	Not known	Not known	Not known	T cell	
Freeman [5]	72	F	Free air	Jejunum	Not known	Not known	Not known	B cell	
Aydin [16]	17	M	Free air	Jejunum && ileum	No	Resection && primary suture	Anastomosis	diffuse large cell	discharged well
Sakakura [17]	78	M	Free air	Jejunum	Yes	Resection	Not known	diffuse large cell	discharged well
Yabuki [27]	53	M	Free air	Stomach	No	Resection	Anastomosis	diffuse B cell	discharged well
Yokota(18)	31	f	normal	ileum	received	resection	anastomosis	diffuse large cell	discharged well
Aydin(16)	17	m	free air	jej and ileum	not received	resection and primary suture	anastomosis	diffuse large cell	discharged well

Table 2 Continued

First author [ref. no.]	Age	Gender	Radiology	Perforation site	Preop chemotherapy	Operation	Reoperation	Pathology	Outcome
Sakakura(17)	78	m	free air	jejunum	received	resection	not known	diffuse large cell	discharged well
Yabuki(27)	53	m	free air	stomach	not received	resection	anastomosis	diffuse B cell	discharged well
Yokota [18]	31	F	Normal	ileum	Yes	Resection	Anastomosis	Diffuse large cell	Discharged well
Aydin [16]	17	M	Free air	Jejunum & ileum	No	Resection & primary suture	Anastomosis	Diffuse large cell	Discharged well
Sakakura [17]	78	M	Free air	Jejunum	Yes	Resection	Not known	Diffuse large cell	Discharged well
Yabuki [27]	53	M	Free air	Stomach	No	Resection	Anastomosis	Diffuse B cell	Discharged well

been followed up for 2 years and 2 months after operation and the mean survival rate is 7 months.

Discussion

Gastrointestinal involvement is one of the important determinants of the subsequent clinical course of lymphoma. Free gastrointestinal perforation is a potentially lethal complication of NHL. The perforation can occur at any point in the gastrointestinal tract including the stomach, jejunum, ileum, and colon [5, 6, 10–11]. In the present study, the site of perforation was localized in the ileum in four, in the jejunum in two, and in the colon in two patients. Lymphoma presents with nonspecific abdominal pain in 70% to 80% of cases and weight loss in 30% [12]. Changes in bowel habits and such nonspecific signs as weakness, nausea, vomiting, and fever also occur. Abdominal pain, nausea, vomiting, weight loss, and fever were the main symptoms in our patients. Most of the radiological images were not diagnostic.

Although most patients with intestinal lymphoma respond favorably to medical therapy, lymphoma surgery should be reserved for complications such as obstruction, free perforation, fistula, and bleeding [4, 5, 13, 14]. Small bowel perforation due to intestinal lymphoma has been reported by many observers. Amromin and Solomon [15] reported 69 patients with necrotizing enteropathy; only 4 of these patients had NHL. A recent study reported free intestinal perforations due to NHL in six patients [5]. As reported in previous studies free intestinal perforations due to NHL may occur both spontaneously and after chemotherapy [11, 16–19]. In the present study, free intestinal perforation was demonstrated in patients 4 and 7 after chemotherapy. When lymphoma invades the gastrointestinal tract and is treated with effective chemotherapy, tumor necrosis with perforation is the

potential complication [20, 21]. In patients with NHL, the complications are increased by the toxicity of chemotherapy. Diagnosis is often delayed because steroids often mute symptoms. Small bowel and colon perforations may go unrecognized until the development of acute abdomen.

Colorectal lymphomas may be even more obscure than small intestinal lymphomas and may exist without diagnosis for even longer periods. Indeed up to 10% of colonic lymphomas are incidental findings. This reflects the larger lumen of the colon, which delays obstruction, and the comparatively lower tendency (4%) of large intestinal lymphomas to produce abdominal emergencies due to perforation and bleeding [5]. In our study, in two patients (nos. 7 and 8) perforations were present due to colon obstruction. Synchronous primary lymphoma involving both the small and the large intestines is not uncommon [22], but in our study, synchronous lymphoma was present in three patients (nos. 4, 6, and 7). Surgical treatment for small intestinal and colon lymphoma for localized lesions is resection of the affected segment and mesentery and primary anastomosis [6, 10, 23, 24]. For synchronous lymphoma, curative resection may not be performed effectively. In the treatment of a high-grade intestinal NHL, a multimodality approach is superior to surgery or chemotherapy alone. Perforated intestinal lymphomas usually are of a higher stage and have a bad prognosis [25]. High levels of serum lactate dehydrogenase, older age (>60 years), extranodal involvement, high stage, and bad performance were the bad prognostic factors that effected the survival of our patients.

In conclusion, in the case of free perforation of the intestine, we keep lymphoma in mind as a cause. Systemic administration of chemotherapy may increase the possibility of perforation if gastrointestinal involvement is present. In these cases the presence of free fluid on ultrasonography may be due to intestinal perforation despite normal plain

abdominal X-ray findings. Therefore early diagnosis and treatment are important to improve the prognosis of bowel perforation in patients with NHL.

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