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Original Research Article

Clinical trends and management outcome of primary intestinal lymphoma

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ABSTRACT

Background: Primary gastrointestinal lymphomas are the most common type of primary extra nodal lymphomas. In particular, primary intestinal lymphomas constitute about 25-40% of all gastrointestinal lymphomas. Our aim in this study is to find out the clinical patterns and surgical outcome in management of patients with primary intestinal lymphoma.
Methods: A retrospective study at Sohag University Hospital from January 2013-to February 2017, included 17 cases, diagnosed histopathologically as primary intestinal lymphoma and subjected to surgical treatment. Demographic data, clinical presentations and management outcome were analyzed.
Results: Seventeen consecutive patients with primary intestinal lymphoma, presented mainly by abdominal pain and abdominal mass. The definite preoperative diagnosis was detected only in 7 patients (41%) via preoperative histopathologic biopsy (3 by CT guided biopsy, 2 via diagnostic laparoscopy and remaining 2 by lower endoscopic biopsy). The other 10 patients (59%) were discovered incidentally during laparotomy. Radical resection was performed to 11 cases (65%), while palliative resection was employed to the remaining 6 cases. All patients received postoperative adjuvant chemotherapy. Two patients were lost to follow up, while the remaining investigated 15 cases, 3 of them were died (20%), 2 of the 3 total deaths presented with preoperative acute symptoms necessitating urgent laparotomy.
Conclusions: Primary intestinal lymphomas are commonly diagnosed incidentally during abdominal exploration and most of them presented with abdominal pain. Complete surgical resection followed by adjuvant chemotherapy seems to be effective treatment in most cases. Surgical outcome of urgent cases of primary intestinal lymphoma carries poor prognosis.

Keywords: Diagnosis, Primary intestinal lymphoma, Treatment

INTRODUCTION

Gastrointestinal tract is the most common extra nodal site involved by lymphoma, accounting 5%-20% of all cases.[1] Primary small intestinal lymphomas account for 20% - 30% of all primary gastrointestinal lymphomas. While, colorectal lymphomas constitute 6%-12% of all gastrointestinal lymphomas and most of them are secondary involvement of the wide spread diseases. Ileum is the most common site (60%-65%) involving small intestinal lymphoma followed by jejunum (20%-25%), duodenum (6%-8%) and other sites (8%-9%). Caecum, ascending colon and rectum are the more often affected sites in colorectal lymphomas.[2,3]

The most common initial clinical presentation of these tumors is abdominal pain, palpable mass, nausea, vomiting, weight loss, bowel obstruction, hematochezia,

jaundice, fever and coexistence of bowel perforation and peritonitis.[4]

Primary intestinal lymphoma grossly appeared as a mass, polyp or ulcer.[5] Radiologic findings of small intestinal lymphomas are non-specific, thus posing a difficulty in distinguishing it from other benign and malignant lesions. The common features of small intestinal lymphoma were seen in barium studies and computed tomogram (CT) include polypoid form, multiple nodules, infiltrative form, endoexoenteric form with excavation and fistulation, and mesenteric invasive form with an extraluminal mass. The radiologic findings usually do not correlate to its pathologic subtypes.[6]

Treatment strategies for primary intestinal lymphomas are well established, but there still remains much debate and controversy regarding the optimal approach for proper management.[7-10]

The role of surgery in intestinal lymphoma remains equivocal. The decision to resect the tumor before chemotherapy depends on several factors including the location and extent of the disease and whether resection would result in long term complications such as short gut syndrome.[11]

The overall survival analysis in many current studies showed that patients with chemotherapy after surgery have a better prognosis than patients with surgery alone.[4,11,12]

The primary aim of this study is to find out the clinical patterns and surgical outcome in management of patients with primary intestinal lymphoma.

METHODS

This retrospective study was carried out in Surgery Department at Sohag University Hospital from January 2013 to February 2017. Patients files were reviewed for demographic data, clinical presentations, laboratory and imaging studies, treatment modalities and management outcome.

Patients in this study included 17 cases, diagnosed histopathologically as primary intestinal lymphoma and subjected to surgical treatment whether resectable or irresectable tumors. The included cases were those who met the criteria developed by Dawson et al., 13 no peripheral or mediastinal lymph nodes at diagnosis, normal total and differential white blood cell count, involvement of only the regional lymph nodes with no involvement of the liver or spleen.

All cases were subjected to surgical treatment. Our goal in surgical management was complete resection of primary resectable tumors with safety margins. The extent of resection in this study varied from complete radical excision to debulking, incisional biopsy or just bypasses procedure in advanced and irresectable tumors. Radical excision was defined as completely removed tumor with free gross and microscopic margins, and as palliative if the patients had an inadequate gross or microscopic safety margins.

The diagnosis was established by preoperative histopathologic biopsy (Imaging guided or endoscopic biopsy) and other cases diagnosed via postoperative biopsy in incidentally discovered tumors during surgical exploration.

Staging work-up after establishing the diagnosis of primary intestinal lymphoma was done for all cases and included:

- Detailed history and physical examination
- Laboratory studies including complete blood picture, liver and kidney function, lactic dehydrogenase and serum uric acid.
- Bone marrow aspirate and /or biopsy
- CT scan studies for staging
- Histopathologic examination of either the resected tumor bearing intestinal segment or the biopsy specimen.
- Immunophenotyping to clarify the exact cell lineage of the tumor which affects both the prognosis and the line of treatment to be received
- Clinical staging of the disease was based on the principles of Ann Arbor conference criteria that was modified according to the staging classification published by the international workshop group in Lugano.[8]

Postoperatively, all patients were referred to Oncology Unit for secondary adjuvant therapy. Clinical evaluation and follow up was done to all cases every 3 months during the first year and each 6-months later on in a regular outpatient visits. The patients were evaluated by clinical examination and imaging study via abdominal ultrasound and CT in certain cases.

RESULTS

This retrospective study included 17 patients, diagnosed as primary intestinal non-Hodgkin's lymphoma and subjected to surgical treatment, 12 males (71%) and 5 females (29%); their ages ranged from 8-62 years with a mean of 46±32 years.

Clinical presentation

The symptoms were variable according to the site and extent of the lesion. The most common predominant presenting symptom was abdominal pain in 8 patients.

Other symptoms included palpable abdominal mass in 4 patients, intestinal obstruction in 2, rectal bleeding in 2 and the remaining case presented with peritonitis (Table 1).

Table 1: Demographic data and clinical presentation.

Patient's character	No. of patients (n=17) (%)
Gender	
Male	12(71%)
Female	5(29%)
Main symptom	
Abdominal pain	8(47%)
Abdominal mass	4(24%)
Intestinal obstruction	2(12%)
Rectal bleeding	2(12%)
Peritonitis	1(6%)

Diagnosis and staging

Routinely, all patients were subjected to a through medical history and physical examination, chest radiography, serum chemistry, and complete blood cell count. The initial investigations for diagnosis included abdominal ultrasound and CT of the abdomen and pelvis that were done to all patients (Figure 1a, 1b and 1c). Colonoscopy was performed in 2 patients who presented with rectal bleeding where endoscopic biopsy was taken (one patient from sigmoidal mass and the other from rectal mass). Diagnostic laparoscopy was done to 2 cases where diagnostic biopsies were taken. The definite preoperative diagnosis was detected only in 7 patients (41%) via preoperative histopathologic biopsy (3 of them by CT guided biopsy, 2 via diagnostic laparoscopy and the remaining 2 by lower endoscopic biopsy). The other 10 patients (59%) were discovered incidentally during laparotomy due to abdominal pain (5 cases), abdominal mass (2 cases), intestinal obstruction (2 cases) and perforated viscus in the last one.

Table 2: Tumor's localization and pathologic patterns.

Clinical pattern	Number (%)
Tumors localization	
Ileocecum	9(53%)
Small intestine	6(35%)
Sigmoid colon	1(6%)
Rectum	1(6%)
Number of involvement sites	
Single site	15(88%)
Multiple site	2(12%)
Staging	
I	6(35%)
II	9 (53%)
IV	2(12%)
Histopathologic subtype	
DLBCL	11(65%)
Burkitt's lymphoma	3(18%)
MALT (mucosa associated lymphoid tissue) lymphoma	2(12%)
Small lymphocytic NHL	1(6%)

After establishing the diagnosis of primary intestinal lymphoma by preoperative or postoperative histopathologic study, staging work-up was done according to modified Ann Arbor criteria (Table 2).

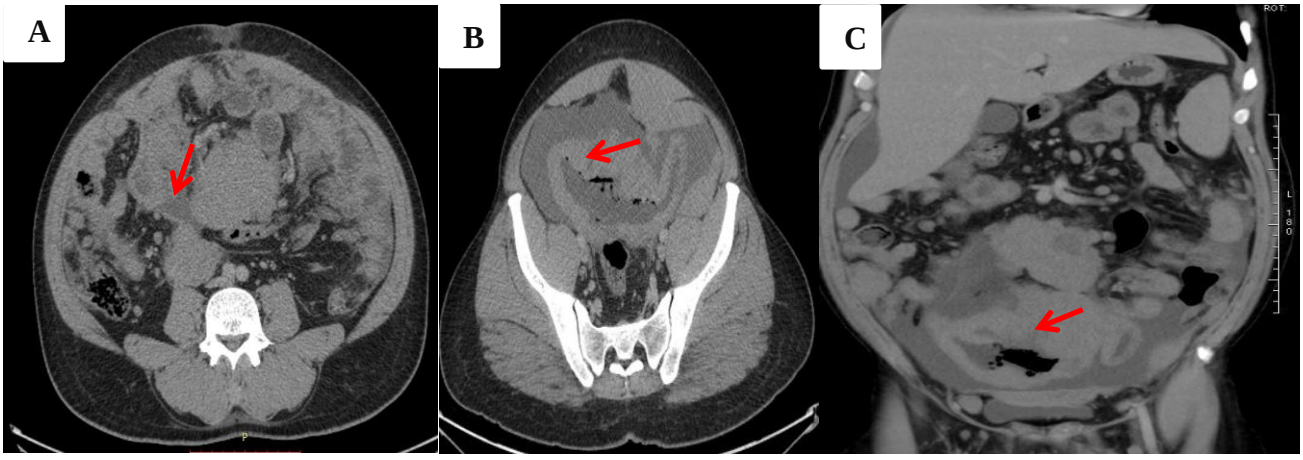

Figure 1: Contrast-enhanced MDCT axial images (A and B) and coronal reformate (C) shows a markedly thickened small bowel loops (black arrows) that show aneurysmal dilatation. There is no evidence of obstruction. Enlarged mesenteric lymph nodes, stranding of the adjacent mesentery and evidence of mild amount of ascites. There is no involvement of the liver and spleen; the findings are suggestive of primary intestinal lymphoma.

Tumor's localization and histopathologic subtype

Nine patients had lesions in the ileocecum, 6 in the small bowel, 1 in the rectum and the remaining one in the sigmoid colon.

The tumor involved one site of the intestine in all cases except in 2patients where the lesion was multi-centric in the small intestine. Diffuse large B-cell lymphoma (DLBCL) was the common histopathologic subtype of our series (Table 2).

Treatment modalities

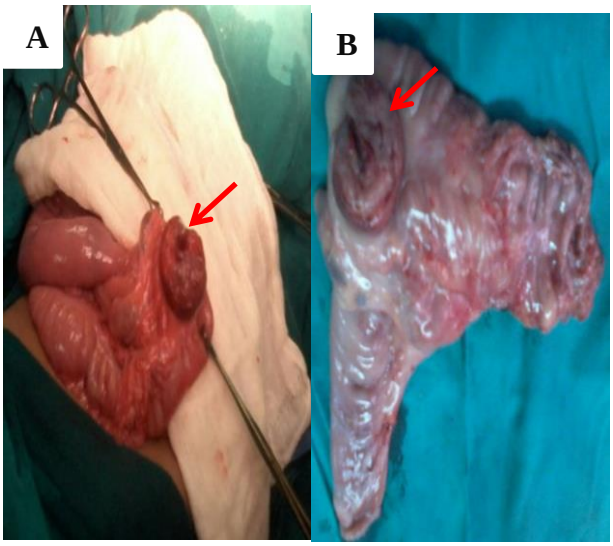

Figure 2: (A) Intraoperative photo of perforated intestinal lymphoma;(B) Postoperative specimen of the resected perforated loop of the same patient.

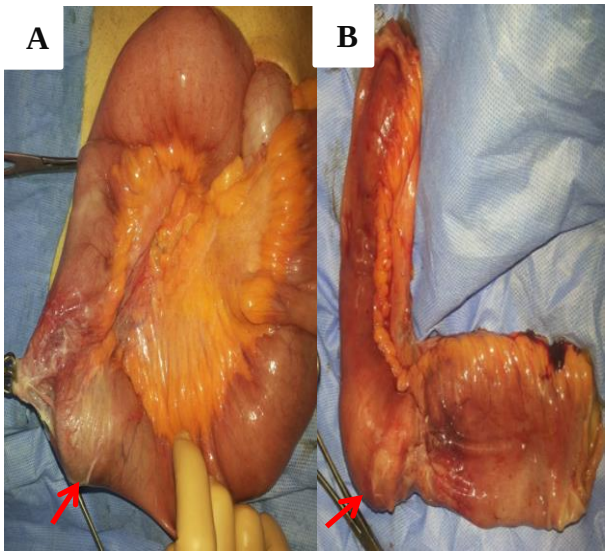

Figure 3: (A) Intraoperative photo of primary intestinal lymphoma presented by acute intestinal obstruction; (B) Postoperative specimen of the resected intestinal loop of the same patient.

All patients in this study were submitted to surgical interference that was varied from radical resection to just biopsy.

Radical resection was performed to 11 cases (65%) without evidence of macroscopic or microscopic residue after resection at the time of surgery. Palliative resection was employed to 4 cases (2 of them underwent resection with incomplete safety margin and the other 2 cases had multi-centric lesions that were submitted to just debulking). While, the remaining 2 cases had irresectable tumors and fixed to important structures in the posterior abdominal wall; one of them just biopsy was taken and the last one subjected to biopsy and enteric bypass (to bypass fixed obstructing mass in the ileocecal region). Elective surgical interference was done to all cases except in 5 patients; 2 due to acute abdomen that mimics acute appendicitis, 2 due to intestinal obstruction and the remaining due to perforated viscus, (Table 3).

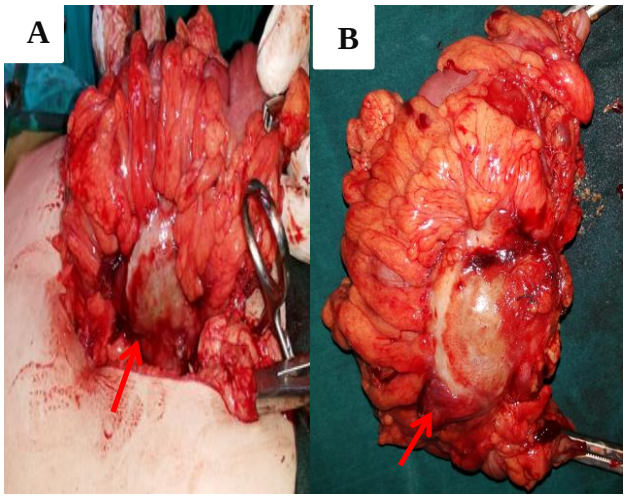

Figure 4: (A) Dissection of primary lymphoma of the sigmoid colon; (B) Primary intestinal lymphoma of the sigmoid colon with extra luminal infiltration of the same patient.

Table 3: Surgical treatment.

Procedure	Number (%)
Extent of surgical resection	
Radical resection	11(65%)
Palliative resection	6(35%)
Operative interference	
Elective procedure	12(71%)
Urgent procedure	5(29%)
Cause of emergent procedure	
Acute abdomen	2(12%)
Intestinal obstruction	2(12%)
Perforated viscus	1(6%)

All the patients received postoperative combination chemotherapy CHOP regimen (Cyclophodamide, Doxorubicin, Oncovin and Prednisone) in the Oncology Unit Department during their follow up period. Chemotherapy was given as every 3-week cycles for 4 cycles for localized tumors (15 cases) and 6-8 cycles for multi-centric cases (2 patients).

Rituximab (monoclonal antibody- anti CD20 positive cells) was added to CHOP regimen in cases with positive CD20 antigen (5 cases).

Postoperative morbidity and mortality

Early postoperative complication (during the first postoperative month) occurred in 6 patients and all of

them improved by conservative treatment expect 2 cases that were in need for surgical exploration (one of them for drainage of sub-phrenic abscess and the other case was submitted to intestinal re-anastomosis due to anastomotic leakage) (Table 4).

Table 4: Postoperative outcomes.

Character	Number (%)
Early postoperative complication	
Wound infection	3(18%)
Prolonged gastric emptying	1(6%)
Sub phrenic abscess	1(6%)
Anastomotic leakage	1(6%)
Mortality rate (2 cases missed to follow up)	3/15(20%)

In this study, 2 patients were lost to follow up, while the remaining 15 cases were followed up with a mean 28 months (range 8-42 months). The remaining investigated 15 cases, 3 of them died on, 7, 10 and 12 months postoperatively (20%) the cause of death in all cases due to disease progression in addition to the side effects of the chemotherapeutic agent. It was noticed that 2 of the 3 total deaths presented with acute symptoms, necessitating urgent exploration (one had intestinal obstruction and the other had perforated viscus).

DISCUSSION

Primary gastrointestinal lymphoma is the predominant site of extra nodal lymphoma, accounting for 5-20% of all extra nodal Non-Hodgkin lymphoma. Primary intestinal lymphoma is the third common intestinal neoplasm after adenocarcinoma and carcinoid tumor. However, the incidence of the disease has been increasing by 5% per year in Westernized countries, peaking at 1.73 per 100.000 in North America.[14-16]

In this study the mean age at time of presentation is 46±32 year this is near to what reported by different groups.[10,12] Primary intestinal lymphoma usually affects males than females. In the present study the males to female ratio was 2.4:1 which is close to what detected by other studies.[16,17]

Also, in the current study, the initial clinical presentation of our patients was non-specific, including abdominal pain, abdominal mass, intestinal obstruction, rectal bleeding and perforated viscus. This is consistent with other many studies which reported that primary intestinal lymphoma patients are usually presented by vague symptoms and easily misdiagnosed or discovered incidentally during laparotomy due to associated serious acute complications.[4,16,17]

Additionally, the definite preoperative histopathological diagnosis was detected in 7 patients only (41%) (3 of them by CT guided biopsy, 2 via diagnostic laparoscopic biopsy and the remaining 2 by lower endoscopic biopsy), while the other 10 patients (59%) were discovered incidentally during abdominal exploration due to variable aetiological indications, necessitating laparotomy (5 of them had acute symptoms and underwent urgent abdominal exploration) This is consistent with other many studies which stated that primary intestinal lymphoma usually discovered at the time of operation during surgical exploration.[1,10,12]

In this literature the ileocecum was the predominant site of involvement and the common histopathological subtype was DLBCL. This is parallel to many other similar studies.[1,3,12]

The included patients in this study were verified according to the standard diagnostic criteria for primary intestinal lymphoma, as established by Dowson et al in 1961.[13] However, the recommendations of Rohatiner et al., in the fifth international Conference on malignant lymphoma, also included patients with involvement of inguinal lymph nodes, but no patients in this study had inguinal lymphadenopathy at time of presentation.[8]

To stage primary gastrointestinal Non-Hodgkin lymphoma, the majority of studies used either the Ann Arber staging with modification or Lugano staging system.

Collection of series of 23 studies was found that the majority of patients were concerned to stage I and II at diagnosis (77%).[16] In our study, most of our series were found at stage I and II at time of diagnosis.

Appropriate management of primary gastrointestinal lymphoma is still controversial. The most controversial issue on the treatment of gastrointestinal lymphoma is whether surgical role is necessary or not.[10] Although, there are a lot of studies on the advantage of surgical treatment especially in early stages.[9,18-22] Another issue is to what extent of surgery is necessary.[23] On the other hand, some studies reported that surgery may delay the use of chemotherapy which may cause some morbidity and also has a postoperative mortality rate of up to 10 %.[10, 24]

In this literature, all patients subjected to surgical treatment and postoperative adjuvant chemotherapy. Surgical management was varied from complete radical excision with safety margin in 11 patients (65%), to palliative procedures in the remaining 6 cases.

On my opinion, I think that surgical treatment is beneficial for radical excision in most of the tumors (65%). Even the other cases with palliative excision or just biopsy, an established and accurate histopathologic diagnosis were achieved for proper selection of the postoperative adjuvant therapy. Also, the majority of authors concluded that the initial management with surgery followed by adjuvant chemotherapy resulted in the best overall survival.[4,11,25-27] Meanwhile, surgical

resection is beneficial to prevent spontaneous perforation and/or hemorrhage during chemotherapy or radiotherapy, also to relieve symptoms and for accurate diagnosis and staging of the disease.[11]

In the present study, 2 patients were missed to follow up, while the remaining 15 cases were followed up for a mean 28months (range 8-42 months). Three cases were died from the remaining 15 studied patients with a mortality rate 20%. It is fairly considered to be acceptable as compared with other many recent studies that reported the 5 years survival rate is (52-86%), considering our results performed in a small number of cases and during less follow up period.[16] Additionally, we observed that 2/3 of total deaths had acute complications, necessitating urgent laparotomy and this is consistent with Lightner et al., who noticed that urgently operated patients with primary intestinal lymphoma carried poor prognosis.[16] These variations in the results of surgical outcome of our series in comparison with other studies may be due to difference in patient's clinical criteria, tumor size and location, histopathologic subtype, in addition to the available facilities of early diagnosis.

CONCLUSION

Primary intestinal lymphomas are commonly diagnosed incidentally during abdominal exploration and most of them presented with abdominal pain. Complete surgical resection followed by adjuvant chemotherapy seems to be effective treatment in the majority of cases. Surgical outcome of urgent cases of primary intestinal lymphoma carries poor prognosis, but further clinical trials are needed to establish this risk factor.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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