

The diagnostic and surgical challenges of small bowel disease not involving the duodenum.



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BACKGROUND: Because of the lack of specific signs and symptoms, benign and malignant small bowel disease (SB) diagnoses and their treatments are very difficult. The aim of this study was to determine the challenges of diagnostic and surgical treatment of SB diseases.

MATERIAL AND METHODS: Of 51 patients, 29 (56.9%) had undergone surgery for non-malignant small bowel (NMSB) diseases, whereas 22 (43.1%) had malignant small bowel (MSB) diseases. All data were collected and compared between the two groups.

RESULTS: Patients with MSB had statistically higher levels of disease in the jejunum (50% versus 10.3%; $p=0.004$), while patients with NMSB had statistically higher disease levels in the ileum (89.7% versus 50%; $p=0.002$). Twelve (54.5 %) patients in MSB and 18 (62%) patients in NMSB had emergent laparotomy ($P=0.76$). There were not significant differences in postoperative complications (8 [36.4%] in MSB versus 4 [13.8%] in NMSB; $p=0.10$ and 5 [22.7%] versus 3 [10.3%]; $p=0.374$). Patients in the MSB group had a statistically significant lower 5-year survival rate ($p=0.038$).

CONCLUSION: Overall this study showed that preoperative evaluation may not always be capable of differentiating MSB from NMSB disease. Therefore, most patients present with advanced disease stages.

KEY WORDS: Adenocarcinoma, Ileum, Small bowel, Jejunum

Introductions

Although the small bowel (SB) comprises the longest part of gastrointestinal system (GIS), the rate of malignant disease is the lowest in GIS cancers ¹. The true prevalence might be higher, but it may be concealed by a missed diagnosis in some patients ². Malignant and non-malignant SB (MSB and NMSB, respectively) diseases generally present with similar non-specific symp-

toms and signs such as occult blood loss, lower GIS bleeding, bowel obstruction, abdominal pain, diarrhea, constipation, and weight loss, especially in malignant diseases ^{3,4}.

SB cancers are classified histologically as adenocarcinomas, lymphomas, sarcomas, gastrointestinal stromal tumors, and neuroendocrine tumors ⁵. Surgery is still the mainstay of treatment for SB cancers ⁶. It is well known that Crohn's disease (CD) eventually requires surgical treatment in about 70%-90% patients due to its complications ⁷. Confusion may exist if patients did not have previous CD and present with its complications. Although the rate of complicated Meckel's diverticulum (MD) is low in adults, adult patients still can have complications such as diverticulitis, GI bleeding, and obstruction that generally require surgical treatment ⁸. Benign SB disease polyps can cause intussusceptions that may require surgical treatment, but this occurrence is very rare ⁹.

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Overall, neither MSB nor NMSB have specific symptoms and signs; thus, it can cause a delay in diagnosis and treatment that results in poor prognosis. The aim of this study was to analyze clinical presentation, challenges of diagnosis, and surgical treatment of MSB and NMSB.

Material and Methods

Between January 2013 and January 2018, 51 patients underwent surgery for non-duodenal primary SB diseases. Fifty-one patients were divided into two groups: (1) MSB disease or (2) non-malignant (NMSB). Preoperative clinical signs and symptoms, radiological images, enteroscopy, and laboratory findings, including white blood count (WBC), hemoglobin, hematocrit, and carcinoembryonic antigen (CEA) were used for diagnosis. Preoperative, operative, and postoperative data including age, gender, indications for surgery, operation time, postoperative hospital stay, postoperative recurrence and complications, and postoperative mortality rates were retrospectively investigated. Patients with previous diagnosed SB disease were excluded. Polyps, lipoma, leiomyoma, CD, non-specific inflammation and stricture, and complicated MD were considered primary NMSB. Primary small bowel cancers included adenocarcinomas, lymphomas, sarcomas, gastrointestinal stromal tumors (GIST), and neuroendocrine tumors.

Statistical analyses

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. In order to analyze the data, a Student's t-test was used to compare definitive statistical methods (mean, standard

deviation, median, frequency, rate, minimum and maximum) in addition to evaluating the normally distributed quantitative data. However, non-distributed quantitative data were compared between two groups using the Mann Whitney U test. To compare qualitative data between two groups Pearson chi-squared, Fisher-Freeman-Halton, and Fisher's Exact tests were used. The effects of risk factors in the 10-year survival analysis was done using a Cox Regression analysis. Survival in two groups was analyzed using a Kaplan-Meier analysis. $P < 0.05$ was considered significant.

Results

This study was performed with a total of 51 patients. Of these, 24 (47.1%) were female, and 27 (52.9%) were male. The mean age was 52.6 ± 18.1 (range: 18–90) years old. Of these patients, 22 (43.1%) had MSB disease, whereas 29 (56.9%) had NMSB disease. Although the mean age was higher in MSB than in NMSB patients, the differences were not significant (57.5 ± 17 versus 48.8 ± 16 years; $p = 0.08$). The differences in gender rate was not statistically significant (45.5% female in MSB versus 41.4% in NMSB; $p = 0.771$). The preoperative symptoms and diagnostic values between the two groups were analyzed (Table I).

There were no significant differences in preoperative abdominal pain, GIS bleeding, diarrhea, and weight loss between the two groups (Table I). However, patients in the MSB group presented with statistically higher GIS obstruction signs and symptoms such as abdominal distention, nausea, and vomiting (63.6% versus 31%; $p = 0.02$). Although the rate of palpable mass is numerically higher in MSB patients, the differences were not significant (13.6 % versus 0; $p = 0.074$). There were no

TABLE I - The preoperative symptoms and diagnostic values.

		MSB (n=22)	NMSB (n=29)	p
Abdominal pain		15(68.2%)	21 (72.4%)	b0.743
GIS bleeding		1 (4.5%)	1 (3.4%)	c1.000
GIS Obstruction		14 (63.6%)	9 (31%)	b0.020*
Abdominal mass		3 (13.6%)	0	c0.074
Weight loss		1 (4.5%)	1 (3.4%)	c1.000
Diarrhea		0	4 (13.8%)	c0.124
The lenght of complaining (day)	Min-Max (Median)	1-90 (3)	1-90 (7)	d0.418
	Mean±SD	9.86±19.57	14.41±21.62	
Hemoglobin level	Min-Max (Median)	5.1-16.8 (10.8)	8.5-16.9 (11.9)	a0.133
	Mean±SD	10.97±2.37	11.84±1.7	
Hematocrit level	Min-Max (Median)	3.6-50.1 (31.9)	26.5-49.3 (36.3)	a0.049*
	Mean±SD	32.07±9.38	36.12±4.68	
WBC	Min-Max (Median)	0.7-20.3 (8.7)	3.6-25.5 (10)	a0.045*
	Mean±SD	8.93±4.48	12.04±6.32	
Tumor marker (higher CEA)		11(50%)	0	b0.001**

aStudent t Test; bPearson Chi-Square Test; cFisher's Exact TestdMann Whitney U Test; * $p < 0.05$; ** $p < 0.01$

significant differences in preoperative hemoglobin between two groups whereas the hematocrit level was statistically lower in the MSB group (32.07 ± 9.38 versus 36.12 ± 4.68 ; $p=0.049$). The white blood count (WBC) was statistically higher in NMSB patients (12.04 ± 6.3 versus 28.93 ± 4.48 ; $p=0.045$). As expected, the tumor marker CEA was statistically higher in MSB patients (50% versus 0; $p=0.001$).

In preoperative evaluation, seven (31.8%) patients in MSB and 10 (34.5%) patients in NMSB had preoperative device-assisted enteroscopy (DAE) ($p=0.940$). Of these patients, three (42.9%) patients in MSB and four (40%) patients in NMSB had a diagnosis via enteroscopy ($p=0.95$). The consistency between a preoperative radiological diagnosis and postoperative pathological diagnosis was higher in NMSB, but the differences were not significant (71.4% versus 42.1%; $p=0.071$). Overall, there were no significant differences in the rate of consistency between pre and intraoperative diagnoses in the groups (69% in NMSB versus 59.1% in MSB; $p=0.656$). Although almost all patients had surgery during the first admission to the hospital, 54.5% of the MSB and 62% of the NMSB patients had emergent laparotomy due to SB obstruction, acute peritonitis, or GIS bleeding ($P=0.76$). Five (22.7%) patients had tumor perforation

in MSB while 6 (20.7%) had SB perforation in NMSB ($p=0.860$).

MSB patients had statistically higher number of diseases in the jejunum (50% versus 10.3%; $p=0.004$) while patients in NMSB had statistically higher disease in ileum (89.7% versus 50%; $p=0.002$ [Table II]). No statistical differences were found between the two groups in terms of the length of the resected SB (38.77 ± 48.31 versus 19.37 ± 10.46 cm in NMSB; $p=0.205$), the length of the operation (2.23 ± 0.75 versus 2.69 ± 0.93 h; $p=0.08$), and blood transfusions in operating room (1.50 ± 1.90 versus 0.83 ± 1.47 ; $p=0.146$).

As pathological diagnosis of MSB, nine (40.9%) patients had SB adenocarcinomas, six (27.3%) had lymphomas, four (18.2%) had GIST tumor, two (9%) had mesenchymal tumors, and one (4.6%) had malign melanoma of the SB. Of these, four GIST tumors (3 [75%]) were staged as high grade one (25%), which is an intermediate grade. Nine (50%) patients had stage-3, six (33.3%) had stage-4, and three (16.7%) had stage-2. Surgical margin were clear in all patients. In NMSB patients, 10 (34.5%) had complicated CD, 10 (34.5%) had non-specific chronic inflammation, four (13.8%) had complicated meckel diverticulitis, three (10.3%) had polyps, and two (6.9%) had lipomas of the SB.

TABLE II - The analysis of intraoperative values

		MSB(n=22)	NMSB(n=29)	p
The location of disease in SB	Ileum	11 (50 %)	26 (89.7%)	a0.002a0.004
	Jejunum	11 (50%)	3 (10.3)	
The length of resected SB (cm)	Min-Max(Median)	6-220 (20.5)	3-50 (17)	b0.205
	Mean±SD	38.77±48.31	19.37±10.46	
The length of operation (h)	Min-Max(Median)	1-4 (2)	1-5 (3)	b0.080
	Mean±SD	2.23±0.75	2.69±0.93	
Erythrocyte suspension transfusion (U)	Min-Max (Median)	0-7 (0.5)	0-5 (0)	b0.146
	Mean±SD	1.50±1.90	0.83±1.47	

aPearson Chi-Square Test; bMann Whitney U Test, SB: Small bowel SD: Standard deviation

TABLE III - Postoperative outcomes in both groups

		MSB (n=22)	NMSB(n=29)	p
Total complication rate		8 (36.4%)	4 (13.8%)	b0.10
Surgical wound infection		5 (22.7%)	3 (10.3%)	c0.374
Anastomosis leak		1 (4.5%)	1 (3.4%)	c1.000
The length of ICU stay (day)	Min-Max (Median)	0-11 (1)	0-5 (0)	d0.006**
	Mean±SD	2.18±3.13	0.59±1.27	
The length of hospital stay (day)	Min-Max (Median)	5-20 (7.5)	0-28 (9)	d0.250
	Mean±SD	9.05±3.93	10.34±5.53	
Metastasis		10 (45.5%)	0	c0,001**
Chemotherapy		14 (63.6%)	0	b0,001**

bPearson Chi-Square Test; cFisher's Exact Test; dMann Whitney U Test ** $p<0,01$; ICU: Intensive care unit

TABLE IV - The analysis of univariate and multivariate Cox Regression analysis of the risk factors

	Univariate			Multivariate		
	p	HR	%95 CI	p	HR	%95 CI
The lenght of complaining (d)	0,643	0,994	0,967-1,021			
Tumor marker (CEA)	0,183	2,554	0,643-10,152			
The lenght of removed SB (cm)	0,013*	1,012	1,002-1,021	0,013*	1,012	1,002-1,021
Total postoperative complication	0,224	1,882	0,680-5,212			
Surgical wound infection	0,036*	2,971	1,072-8,233			
Metastasis	0,587	1,328	0,477-3,695			

*p<0,05

Although postoperative total complications and surgical wound infection rates were numerically higher in MSB patients, there were no statistically significant differences (eight [36.4%] versus four [13.8%]; $p=0.10$ and five [22.7%] vs three [10.3%]; $p=0.374$ as shown in Table III). Although the length of the intensive care unit (ICU) stay was statistically higher in MSB patients (2.18 ± 3.13 versus 0.59 ± 1.27 days; $p=0.006$), no significant differences were found in the length of hospital stay (9.05 ± 3.93 versus 10.34 ± 5.53 ; $p=0.250$). The univariate analysis showed that the lenght of the removed SB and wound infection had significant effects on survival rate ($p=0.013$ and $p=0.036$, respectively; Table IV). The multivariate Cox regression analysis was done for those factors that were significant in univariate analysis, and it showed that only the length of the removed SB had significant effects on the 10-year survival ($p=0.013$; Table IV).

During the follow-up period, only 14 (63.6%) patients received chemotherapy in the MSB group, and 10 (45.5%) had metastasis or recurrences. Overall, 35 (68.6%) patients were surviving at the time that this study was concluded (Fig. 1). Ten (45.5%) patients in the MSB group had survived for 31.50 ± 5.68 months while 25 (86.2%) patients in the NMSB group had survived for 49.12 ± 5.06 months during the follow-up period. The 5-year survival rates in the two groups were analyzed using the log rank test, and it was noted that patients in the MSB group had significantly lower survival rates ($p=0.038$; Fig. 2)

Discussion

Although the SB consists of the duodenum, jejunum, and ileum, we excluded duodenal diseases due to the relative ease of reaching these diseases using endoscopy, which was done routinely making it easier to diagnose duodenal diseases than jejunal and ileal diseases. As expected in this study in addition to information reported in literature, most patients with jejunum and ileum malignancies presented with complication at the time of diagnosis¹⁰. As reported in literature, small bowel dis-

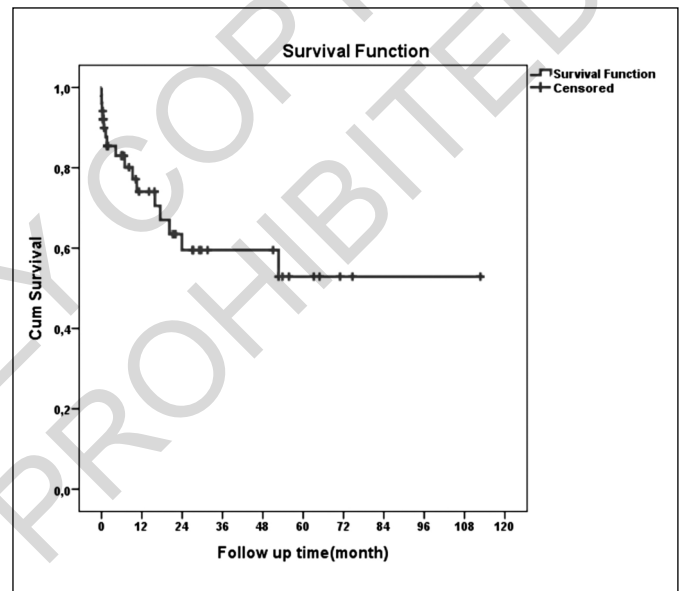


Fig. 1: The survival analysis in all patients.

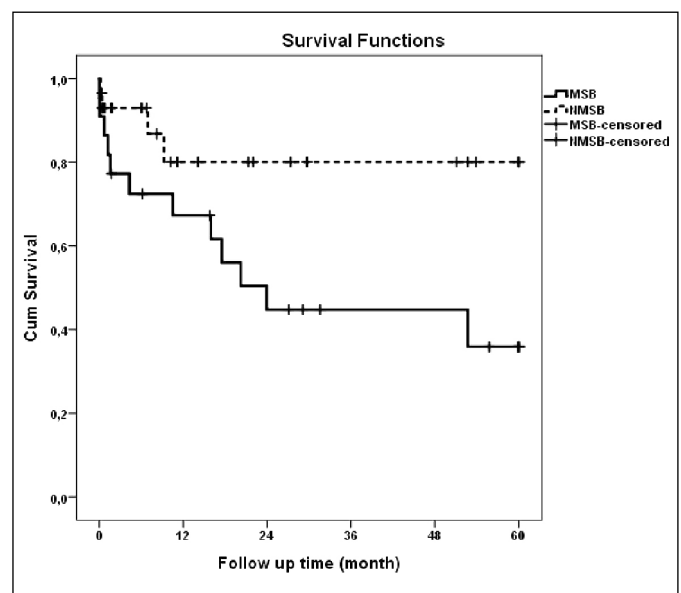


Fig. 2: The survival rate in the two groups.

eases are difficult to diagnose because they require complex diagnostic instruments such as device-assisted enteroscopy (DAE) or capsule enteroscopy (CE) ^{11,12}. However, all of the needed instruments and experienced physicians may not be available everywhere. In this study, only about 30% of patients had enteroscopy that was consistent with some other centers ¹³, but no patients had CE. Although DAE and CE are valuable special instruments, their diagnostic accuracy is limited as reported in literature ^{14,15}. Our study was consistent with those in the literature with respect to the limited diagnostic accuracy of DAE in SB disease that was around 40%, which was even lower than the values reported in literature studies ^{14,15}. There are contradicting reports in the literature in terms of the sensitivity of radiology in malignant SB diseases ^{16,17}. The radiological diagnostic accuracy in this study was 42% that was consistent with some studies but contradicted others ^{16,17} that may be due to the percentage of variety in tumors because the sensitivity of radiology can be different in certain kind of SB cancers. It has been reported that the sensitivity of radiology is higher in GIST compared with adenocarcinoma because the rate of adenocarcinoma was higher in this study; this finding may have caused the lower sensitivity of radiology in this study ¹⁷. There are not consistency in literature in terms of the sensitivity of radiology in non-malignant SB diseases due to most likely the variety of diseases and their sensitivity to radiology. The sensitivity for non-malignant SB, which was 71% in this study, was consistent with some studies but contradictory to other studies ¹⁸⁻²⁰. Overall, the concordance between pre and postoperative diagnoses of SB disease by using DAE and abdominal computerized tomography (CT), tumor markers, physical examination, and symptoms was 59.1% in MSB and 69% in NMSB diseases in this study.

The main obstacles for early diagnosis of SB diseases are not only the difficulties of making an earlier diagnosis, limited diagnostic tools, and lack of experienced physicians but also the symptoms that patients presented, including non-specific symptoms that may not alert physician for possible SB diseases; thus, it can result in a delay in diagnosis at the time of presentation at the hospital ^{21,22}. The delay in diagnosis of SB malignancy resulted in a delay in treatment, and subsequently poor prognosis resulting from this delayed diagnosis was shown in this study and also reported in literature ²³. Most patients presented with abdominal pain in both groups that was consistent with reports in the literature (8). However, in this study, the cases of SB obstruction due to intestinal intussusception presenting with abdominal distention, nausea, vomiting, and palpable abdominal mass were higher in MSB compared to NMSB in this study, consistent with reports in the literature ²⁴. Weight loss and GI bleeding were identified at similar percentages in both groups. In terms of expected laboratory parameters, WBCs were higher in NMSB diseases

resulting from complicated MD and CD that presented with abscesses or fistulas that may result in elevated inflammatory markers ²⁵. Most MSB patients had lower hematocrits, which was most likely due to occult bleeding from malignant lesions that generally present with either overt or obscure GI bleeding ²⁶.

In this study, adenocarcinomas were about 40% of SB cancers, which was consistent with reports in the literature ²⁷. Also consistent with reports in the literature, most malignant tumors were located in the jejunum (3), while most non-malignant diseases such as complicated adult MD and CD were located in ileum in this study, a finding that was consistent with reports in the literature ^{8,28}. In this study, in patients presenting with advanced stage cancers, about 50% patients had stage-3 and 33% were at stage-4 when they had surgery, consistent with reports in the literature ^{3,21}. Moreover, in this study 21% of NMSB patients had SB perforation when surgery was done, and 23% patients presented with perforated tumors. This finding was consistent with a study in the literature, which included only lymphomas in their study ²⁹. In this study, the rate of perforation was similar in both groups. The length of operating times, intraoperative blood transfusions, and postoperative complications were similar in two groups.

Similar to malignant SB diseases, non-malignant SB diseases also lacked specific symptoms and signs that could cause delays in diagnosis and treatment. Similar to NMSB diseases, patients with MD can present with spontaneous perforations and intraabdominal abscesses. This occurrence is very rare as reported in literature and also confirmed by our study ³⁰. Resection and anastomosis is a safe treatment for patients with complicated CD and MD that require surgical treatment ^{8,31}. Moreover, treating CD complication such as fistulas and strictures improve postoperative patients' situations ³¹. In this study, no anastomosis-related complications occurred in patients with complicated CD who underwent SB resection and anastomosis. Postoperative surgical wound infections were reported to be higher in benign SB diseases such as complicated CD than cancers ³², but in this study even surgical site infection rates were higher in NMSB although it was not significant.

Overall, in this study, the 5-year postoperative survival rate for small bowel malignancy was 45%, which was consistent with reports in the literature ^{33,34}. As expected in this study, the 5-year survival was lower in MSB compared with non-malignant diseases. The risk analysis done by Cox regression analysis showed that the length of the removed SB had effects on the 10-year survival in this study, which was consistent with the literature ³⁵.

This study had some limitations. First, in general, any retrospective study has limitations. Second, the number of patients could have been higher, but it is accepted that isolated jejunal and primary ileal diseases for a single center may not be as many as desired. Third, even though we divided patients into two groups, each group

still had different disease natures that may have different presentations and treatment responses. Since there are only a few studies in the literature for non-duodenal SB disease, we thought that this study would contribute more information to the literature.

Conclusion

Primary SB diseases present challenges for diagnosis and intraoperative decision making. As reported in the literature, patients present with a combination of non-specific symptoms and signs, which may not alert physician for a possible SB diseases, thus so it can causing a delay in diagnosis. A delayed in diagnosis can result in a poor prognosis. Overall, this study showed that preoperative evaluation may not be able differentiate malignant SB disease from non-malignant SB diseases in some patients. The definitive diagnosis can only be made intraoperatively and confirmed pathologically. In order to avoid the risk of delayed diagnosis, non-specific abdominal symptoms and signs with uncertain diagnosis should alert physician for possible non-duodenal SB diseases, and patients should be referred to an advanced center in which there is an experienced physician with available advanced diagnostic instruments for SB. The main points in SB diseases are early diagnosis and immediate and effective treatments.

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