

Comparative study of intestinal tuberculosis and primary small intestinal lymphoma

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Abstract

AIM: To characterize the clinical, radiological, endoscopic and pathological features of intestinal tuberculosis (ITB) and primary small intestinal lymphoma (PSIL).

METHODS: This was a retrospective study from February 2005 to October 2012 of patients with a diagnosis of ITB ($n = 41$) or PSIL ($n = 37$). All patients with ITB or PSIL underwent computed tomography (CT) and pathological examination. Thirty-five patients with ITB and 32 patients with PSIL underwent endoscopy. These patients were followed for a further 18 mo to ascertain that the diagnosis had not changed. Clinical, endoscopic, CT and pathological features were compared between ITB and PSIL patients.

RESULTS: Night sweating, fever, pulmonary TB and ascites were discovered significantly more often in ITB than in PSIL patients ($P < 0.05$), however, abdominal mass, hematochezia and intestinal perforation were

found significantly more frequently in PSIL than in ITB patients ($P < 0.05$). Ring-like and rodent-like ulcers occurred significantly more often in ITB than in PSIL patients ($P < 0.05$), however, enterorrhagia and raised lesions were significantly more frequent in PSIL than in ITB patients ($P < 0.05$). The rate of granuloma was significantly higher in ITB than in PSIL patients (87.8% vs 13.5%, $\chi^2 = 43.050$, $P < 0.05$), and the incidence of confluent granulomas with caseous necrosis was significantly higher in ITB than in PSIL patients (47.2% vs 0.0%, $\chi^2 = 4.034$, $P < 0.05$). Multi-segmental lesions, mural stratification, mural gas sign, and intestinal stricture were more frequent in ITB than in PSIL patients ($P < 0.05$), however, a single-layer thickening of bowel wall, single segmental lesions, and intussusception were more common in PSIL than in ITB patients ($P < 0.05$). Necrotic lymph nodes, comb sign and inflammatory mass were more frequent in ITB than in PSIL patients ($P < 0.05$). The bowel wall enhancement in ITB patients was greater than that in PSIL patients ($P < 0.05$), while the thickening and lymph node enlargement in PSIL patients were higher than those in ITB patients ($P < 0.05$).

CONCLUSION: Combined evaluation of clinical, radiological, endoscopic and pathological features is the key to differentiation between ITB and PSIL.

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Key words: Intestinal tuberculosis; Primary small intestinal lymphoma; Clinical features; Endoscopic features; Computed tomography

Core tip: Treatment for intestinal tuberculosis (ITB) differs completely from that for primary small intestinal lymphoma (PSIL). Differentiating ITB from PSIL continues to be a challenge. Combined evaluation of clinical, radiological, endoscopic and pathological features is the key to differentiation between ITB and PSIL. For

example, night sweating, ascites, ring-like and rodent-like ulcers, granuloma, multi-segmental lesions, mural stratification, necrotic lymph nodes, comb sign, and inflammatory mass are more suggestive of ITB. However, abdominal mass, hematochezia, enterorrhagia, raised lesions, single-layer thickening of bowel wall, single segmental lesions, and intussusception are more suggestive of PSIL.

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INTRODUCTION

Intestinal tuberculosis (ITB) is a specific chronic intestinal disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) infection^[1]. In recent decades, with improvement of economics, quality of life, and sanitary conditions, the incidence of TB has declined and the prevalence of ITB has gradually decreased^[2]. However, there is still no sensitive, accurate, convenient and specific marker to diagnose ITB. Therefore, clinicians still need to pay much attention to ITB.

The clinical manifestations of primary small intestinal lymphoma (PSIL) are nonspecific, such as abdominal pain, vomiting, weight loss and intestinal perforation^[3]. Although the incidence is not high, it is similar to ITB in clinical manifestations and still needs to be distinguished^[4].

Many studies have reported that ITB is similar to PSIL with regard to clinical, endoscopic, pathological and computed tomography (CT) features^[5,6]. Treatment for ITB is completely different from that for PSIL. The first-line therapy for ITB is the combined anti-TB medication, while the major therapies for PSIL patients include surgery and radiotherapy^[7]. It is clear that misdiagnosis between ITB and PSIL leads to severe clinical events, such as *M. tuberculosis* diffusion and delaying the medical management of PSIL^[8]. An accurate diagnosis is important for appropriate treatment. Therefore, the aim of this study was to investigate the clinical, CT, endoscopic and pathological features in 41 cases of ITB and 37 of PSIL.

MATERIALS AND METHODS

Patients

Upon searching our hospital pathology and image archiving and communications system, we found 41 patients with ITB and 37 with PSIL who were admitted to our hospital from February 2005 to October 2012. All patients with ITB or PSIL underwent CT and pathological examination. Thirty-five patients with ITB and 32

with PSIL underwent upper GI endoscopy.

Methods

The diagnosis of ITB complied with the established clinical, CT, histological and microbiological criteria. The diagnosis of PSIL conformed with the 1961 Dawson standards. All patients with ITB or PSIL were followed for a further 18 mo to ascertain that the diagnosis had not changed.

Statistical analysis

Two gastrointestinal radiologists analyzed the images together, which resulted in a consensus interpretation. Statistical analysis was undertaken using SPSS version 17.0 (SPSS, Chicago, IL, United States). Numerical data are expressed as mean and standard deviation, and categorical data are expressed as percentages. Evaluated characteristics were compared using the χ^2 test or independent-samples *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

Comparative study of clinical features in ITB and PSIL

Night sweating, fever, pulmonary TB, and ascites were discovered significantly more often in ITB than in PSIL patients ($P < 0.05$). However, abdominal mass, hematochezia and intestinal perforation were significantly more frequent in PSIL than in ITB patients ($P < 0.05$) (Table 1).

Comparative study of endoscopic and pathological features in ITB and PSIL

Rodent-like (Figure 1) and ring-like (Figure 2) ulcers were found significantly more often in ITB than in PSIL patients ($P < 0.05$). However, enterorrhagia (Figure 3) and raised lesions (Figure 4) were found significantly more frequently in PSIL than in ITB patients ($P < 0.05$). The rate of granuloma was significantly higher in ITB than in PSIL patients (87.8% *vs* 13.5%, $\chi^2 = 43.050$, $P < 0.05$), and the incidence of confluent granulomas with caseous necrosis was significantly more frequent in ITB than in PSIL patients (47.2% *vs* 0.0%, $\chi^2 = 4.034$, $P < 0.05$) (Table 2).

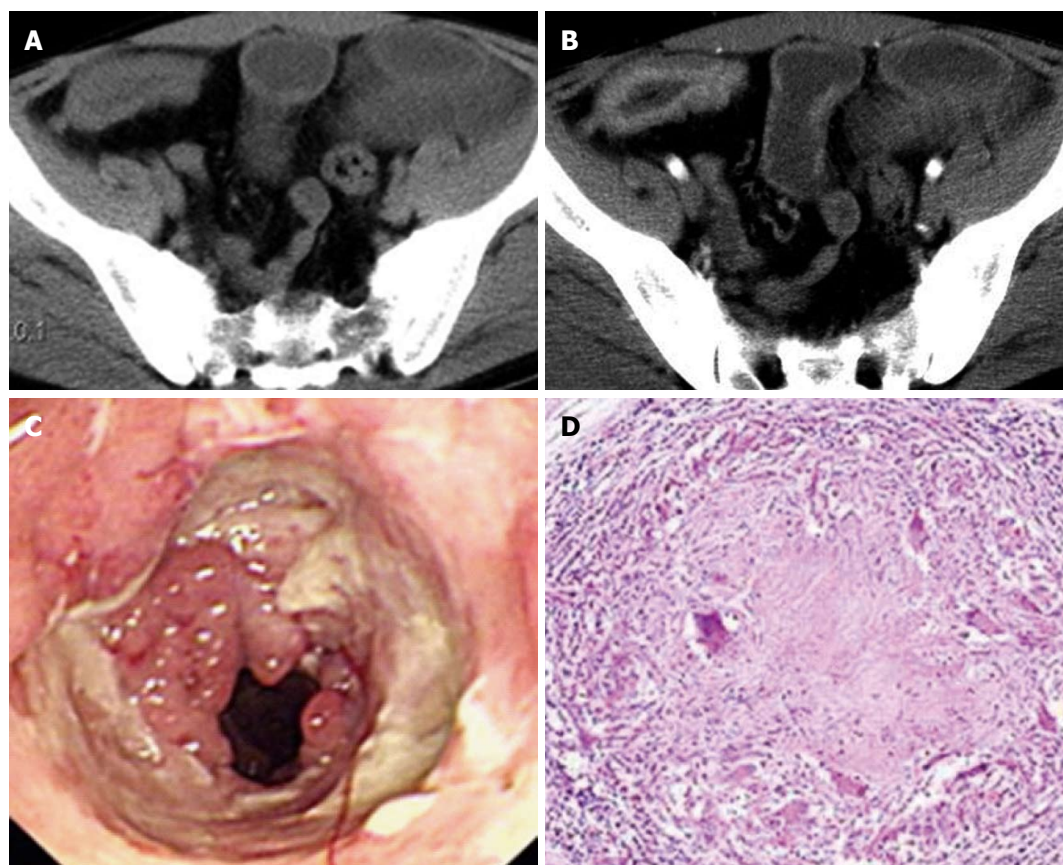
Comparative study of CT features in ITB and PSIL

Multisegmental lesions, mural stratification (Figure 1), mural gas sign, and intestinal stricture (Figure 1) were seen significantly more often in ITB than in PSIL patients ($P < 0.05$). Single-layer thickening of the bowel wall, single segmental lesions, and intussusception were significantly more frequent in PSIL than in ITB patients ($P < 0.05$). Necrotic lymph nodes (Figure 2) and comb sign were discovered significantly more often in ITB than in PSIL patients ($P < 0.05$). Bowel wall enhancement in ITB patients was significantly greater than that in PSIL patients (83.3 ± 7.6 HU *vs* 55.9 ± 4.2 HU, $P < 0.05$), while lymph node enlargement (Figure 3) (19.6 ± 3.2 mm *vs* 9.8 ± 2.7 mm) and bowel thickening (Figure 4) (18.6 ± 3.3 mm *vs* 11.1 ± 3.7 mm) were more common

Table 1 Comparative study of clinical features of intestinal tuberculosis and primary small intestinal lymphoma, *n* (%)

	Diarrhea	Ascites	Febrility	Night sweating	Hematochezia	Pulmonary TB
ITB	12 (29.2)	22 (53.6)	23 (56.1)	25 (60.9)	3 (7.3)	26 (63.4)
PSIL	10 (27.0)	8 (21.6)	2 (5.4)	5 (13.5)	19 (51.3)	2 (5.4)
χ^2 value	0.048	8.434	22.948	18.510	18.623	28.441
<i>P</i> value	0.826	0.004	0.000	0.000	0.000	0.000

ITB: Intestinal tuberculosis; PSIL: Primary small intestinal lymphoma.

**Figure 1** Computed tomography, endoscopic and pathological changes of intestinal tuberculosis in a 38-year-old man. A: Plain computed tomography (CT) scan showed bowel-wall thickening (7.2 mm) and intestinal stricture in the ileocecum; B: During the arterial phase, contrast-enhanced CT demonstrated moderately stratified enhancement; C: Endoscopic examination showed rodent-like ulcer, ring-like ulcer and intestinal stricture in the ileocecum; D: Microscopic findings showed granulomas with caseous necrosis (hematoxylin and eosin staining; original magnification, 400 \times).**Table 2** Comparative study of endoscopic features of intestinal tuberculosis and primary small intestinal lymphoma, *n* (%)

	Ring-like ulcer	Rodent-like ulcer	Enterorrhagia	Raised lesions	Stricture
ITB	13 (37.1)	12 (34.3)	3 (8.6)	0 (0)	22 (62.8)
PSIL	0 (0)	0 (0)	17 (53.1)	21 (65.6)	6 (18.7)
χ^2 value	14.747	13.365	15.846	33.454	13.369
<i>P</i> value	0.000	0.000	0.002	0.000	0.000

ITB: Intestinal tuberculosis; PSIL: Primary small intestinal lymphoma.

in PSIL than in ITB patients ($P < 0.05$) (Tables 3 and 4).

DISCUSSION

The differential diagnosis between ITB and PSIL is still a challenge because of the lack of an economic, simple

and reliable diagnostic method. Current clinical research demonstrates that ITB and PSIL have marked overlap in clinical, CT and endoscopic features, thus, differentiating between ITB and PSIL can be a major diagnostic challenge, particularly in developing countries where ITB remains common^[9]. The misdiagnosis of ITB and PSIL

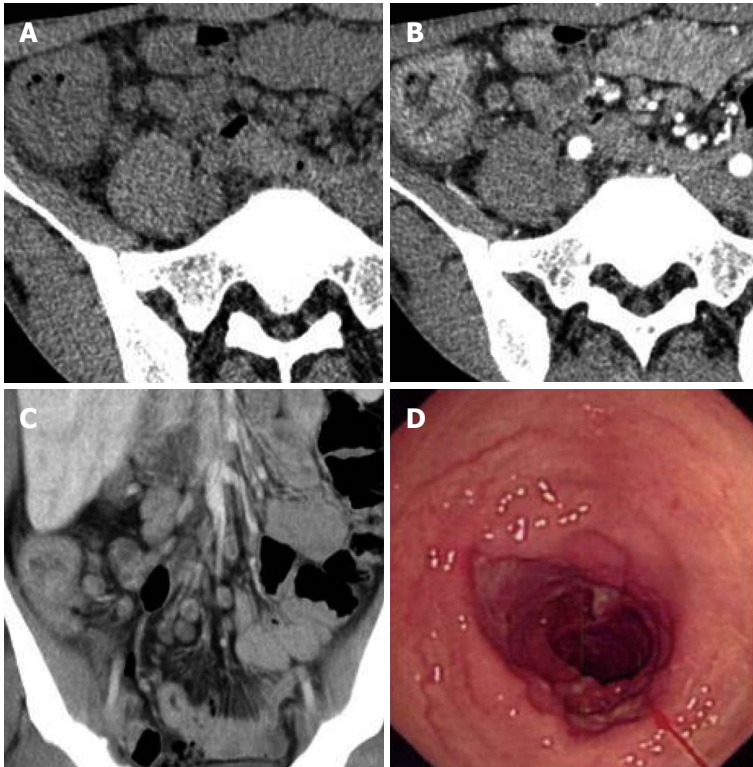


Figure 2 Computed tomography and endoscopic changes of intestinal tuberculosis in a 43-year-old man. A: Plain computed tomography (CT) scan showed bowel-wall thickening in the ileocecum; B: During the arterial phase, contrast-enhanced CT scan demonstrated moderate homogeneous enhancement; C: Mesenteric necrotic lymph nodes and comb sign were noted on coronal CT imaging; D: Endoscopic examination showed a ring-like ulcer in the ileocecum.

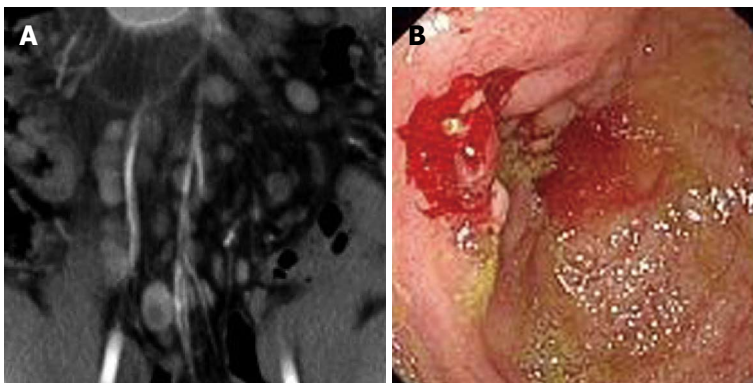


Figure 3 Computed tomography and endoscopic changes of primary small intestinal lymphoma in a 37-year-old man. A: Plain computed tomography scan showed mesenteric lymphadenectasis (19 mm); B: Endoscopic examination showed intestinal hemorrhage in the ileocecum.

Table 3 Comparative study of computed tomography imaging features of intestinal tuberculosis and primary small intestinal lymphoma, *n* (%)

	Mural stratification	Mural single layer	Bowel gas sign	Multi segmental lesions
ITB	24 (58.5)	6 (14.6)	13 (31.7)	35 (85.4)
PSIL	4 (10.8)	27 (73.0)	0 (0)	8 (21.6)
χ^2 value	19.251	27.119	14.078	31.947
<i>P</i> value	0.000	0.000	0.000	0.000

ITB: Intestinal tuberculosis; PSIL: Primary small intestinal lymphoma.

can lead to serious problems in the subsequent treatment of these two conditions^[10]. Therefore, it is particularly important to distinguish ITB from PSIL.

In our study, we found that the first symptom of ITB was abdominal discomfort or pain, while that of PSIL tended to be hematochezia or intestinal perforation. This

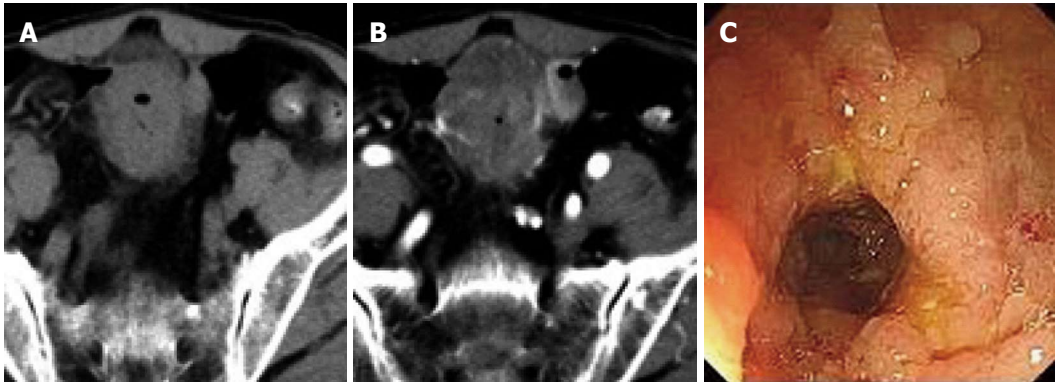


Figure 4 Computed tomography and endoscopic changes of primary small intestinal lymphoma in a 39-year-old man. A: Plain computed tomography (CT) scan showed bowel thickening in the distal ileum; B: During the arterial phase, contrast-enhanced CT scan demonstrated mild enhancement; C: Endoscopic examination showed a raised lesion in the ileum.

Table 4 Comparative study of mesenteric findings and complications of intestinal tuberculosis and primary small intestinal lymphoma, *n* (%)

	Inflammatory mass	Comb sign	Peritoneal abscess	Necrotic lymph nodes	Intussusception
ITB	5 (12.2)	26 (63.4)	3 (7.3)	19 (46.3)	0 (0)
PSIL	0 (0)	4 (10.8)	1 (2.7)	2 (5.4)	21 (56.7)
χ^2 value	4.821	22.738	0.851	16.565	31.844
<i>P</i> value	0.0285	0.000	0.356	0.000	0.000

ITB: Intestinal tuberculosis; PSIL: Primary small intestinal lymphoma.

differed from diarrhea as the first symptom of Crohn's disease (CD). We speculated that ITB lesions were not only inflammatory ulcers^[11], but also proliferative lesions, whereas in PSIL, inflammation and ulcers were both involved in intestinal wall thickening and damage^[12]. Therefore, when symptoms in patients are complex and lack specificity, the first symptom plays a role in differentiating ITB and PSIL.

Both ITB and PSIL are chronic granulomatous conditions and show an overlap in their histological features. PSIL lesions are located in the ileocecum and more limited than those of ITB^[13]. PSIL endoscopic mucosal biopsies are mainly taken from a single lesion, whereas for ITB, there are multiple biopsy sites due to the wide range of lesions. This may have an impact on the efficiency of endoscopic biopsy^[14].

Mucosal hallmarks of CD, such as ulcer shape, also contribute to the differential diagnosis between CD and ITB^[15]. For example, ring-like and rodent-like ulcers suggest a diagnosis of ITB, while enterorrhagia and raised lesions suggest PSIL. However, longitudinal and grid-like ulcers and cobblestone pattern suggest a diagnosis of CD.

In our study, granuloma detection rate in the ITB and PSIL groups was 87.8% (*n* = 36) and 13.5% (*n* = 5), respectively. Among these lesions, the incidence of confluent granulomas with caseous necrosis in the ITB group was 47.2% (*n* = 17), while that in the CD group was zero. Caseous granuloma remains a specific diagnostic marker for ITB. Therefore, if pathological examination only finds noncaseating granuloma, it is not imme-

diate evidence of PSIL, which requires a combination of other pathological changes^[16]. If pathological examination finds both noncaseating granuloma and submucosal lymphocyte aggregation, the patient is more likely to have a diagnosis of PSIL^[17].

Abdominal CT has a certain value for the differential diagnosis between ITB and PSIL^[18]. These two diseases have their own characteristic distribution of lesions, so it is important to master lesions by perfecting checks for the differential diagnosis of the diseases.

Bowel wall thickness normally measures 1-3 mm in distended small bowel, and generally ranges from 5 to 10 mm in bowel affected by ITB. Wall thickening is the most consistent imaging finding of ITB and has been shown to correlate with the presence and severity of disease^[19]. However, wall thickness generally ranges from 15 to 20 mm in bowel affected by PSIL. We noted significant differences in bowel wall thickness in patients with ITB and PSIL (*P* < 0.05).

Bowel wall enhancement plays an important role in determining disease severity and may be one of the earliest signs of disease^[20]. Enhancement can be assessed during several phases based on the timing of the scan relative to contrast injection. The optimal scan time has still not been determined. Peak wall enhancement in normal volunteers was 60-70 s (portal venous phase). However, Zappa *et al.*^[21] have found that differentiation is best achieved by the level of enhancement in delayed phase images. In our study, the enhancement was lower in PSIL than in ITB patients in the portal venous phase (*P* < 0.05).

Increased mesenteric blood flow resulting in vascular engorgement, known as the comb sign, has mostly been reported in active ITB disease^[22,23]. There was a significant difference in the comb sign in patients with ITB and PSIL. Mesenteric necrotic lymph nodes on CT scanning are suggestive of ITB, while lymph node enlargement in PSIL was more frequent than in ITB. Lymph node enlargement and the percentage of necrotic mesenteric lymph nodes were greater in ITB than in CD.

In our study, PSIL patients with hematochezia and intestinal perforation were common, however, these manifestations are rare in ITB patients^[24,25]. These differences may be due to mild progression of ITB in China, but the exact cause needs to be further studied. Besides, emergency surgery is more common in PSIL patients because of the serious complications^[26], whereas medicinal treatment is more common in ITB because complications of ITB are less severe and the disease course is chronic^[27]. This phenomenon indicates that complications are more frequent in PSIL than in ITB patients and their progression is faster. This indicates that patients with serious complications and surgical procedures are more likely to have a diagnosis of PSIL^[28].

In conclusion, differentiating ITB from PSIL continues to be a challenge. At present, combination of clinical, endoscopic, radiological and pathological features continues to be the key to differentiation between the two conditions. We need to continue to develop new differential diagnostic tests. Our study was limited by the relatively small number of patients with these two diseases. Further research is needed to verify these findings in larger patient populations.

COMMENTS

Background

Many studies have reported that intestinal tuberculosis (ITB) is similar to primary small intestinal lymphoma (PSIL) with regard to clinical, endoscopic, pathological and computed tomography (CT) features. Treatment for ITB is completely different from that for PSIL. Misdiagnosis between ITB and PSIL leads to severe clinical events, such as *Mycobacterium tuberculosis* diffusion and delaying the medical management of PSIL. Accurate diagnosis is important for appropriate treatment. Previously published reports on ITB and PSIL have documented the pathological and clinical features. However, there are only relatively small-sample reports focusing on a comparative study of CT imaging findings.

Research frontiers

Combined evaluation of clinical, radiological, endoscopic and pathological features is the key to differentiation between ITB and PSIL.

Innovations and breakthroughs

The authors used a multimodal method to characterize the differences between ITB and PSIL. The results showed that combined evaluation of clinical, radiological, endoscopic and pathological features was the key to differentiation between ITB and PSIL.

Applications

The results showed that radiological and endoscopic features were the key to differentiation between ITB and PSIL.

Terminology

Intestinal tuberculosis (ITB) is a specific chronic intestinal disease caused by *Mycobacterium tuberculosis* infection. The clinical manifestations of primary small intestinal lymphoma (PSIL) are nonspecific, such as abdominal pain, vomiting, weight loss and intestinal perforation.

Peer review

The paper has novel information on comparison between ITB and PSIL. This article presents useful information about differential diagnosis of intestinal diseases. The study was well designed and the experimental and statistical methods used are described in detail.

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