

World Journal of *Gastroenterology*

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OPINION REVIEW

- 5297** Management of Flood syndrome: What can we do better?
Strainiene S, Peculyte M, Strainys T, Stundiene I, Savlan I, Liakina V, Valantinas J

REVIEW

- 5306** Radiomics and machine learning applications in rectal cancer: Current update and future perspectives
Stanzione A, Verde F, Romeo V, Boccadifuoco F, Mainenti PP, Maurea S
- 5322** Could the burden of pancreatic cancer originate in childhood?
Diaconescu S, Gilcă-Blanariu GE, Poamaneagra S, Marginean O, Paduraru G, Stefanescu G

MINIREVIEWS

- 5341** Application of artificial intelligence in preoperative imaging of hepatocellular carcinoma: Current status and future perspectives
Feng B, Ma XH, Wang S, Cai W, Liu XB, Zhao XM
- 5351** Artificial intelligence application in diagnostic gastrointestinal endoscopy - Deus ex machina?
Correia FP, Lourenço LC
- 5362** Faecal microbiota transplantation enhances efficacy of immune checkpoint inhibitors therapy against cancer
Kang YB, Cai Y
- 5376** Immune checkpoint inhibitor-related hepatotoxicity: A review
Remash D, Prince DS, McKenzie C, Strasser SI, Kao S, Liu K

ORIGINAL ARTICLE

Basic Study

- 5392** Therapeutic effect of *Cistanche deserticola* on defecation in senile constipation rat model through stem cell factor/C-kit signaling pathway
Zhang X, Zheng FJ, Zhang Z
- 5404** Recombinant angiopoietin-like protein 4 attenuates intestinal barrier structure and function injury after ischemia/reperfusion
Wang ZY, Lin JY, Feng YR, Liu DS, Zhao XZ, Li T, Li SY, Sun JC, Li SF, Jia WY, Jing HR

Retrospective Study

- 5424** Prolonged survival in patients with hand-foot skin reaction secondary to cooperative sorafenib treatment
Ochi M, Kamoshida T, Araki M, Ikegami T

- 5438** Contrast-enhanced ultrasound imaging for intestinal lymphoma

Cui NY, Gong XT, Tian YT, Wang Y, Zhang R, Liu MJ, Han J, Wang B, Yang D

Observational Study

- 5448** Intestinal ischemic manifestations of SARS-CoV-2: Results from the ABDOCOVID multicentre study

Norsa L, Bonaffini PA, Caldato M, Bonifacio C, Sonzogni A, Indriolo A, Valle C, Furfaro F, Bonanomi A, Franco PN, Gori M, Smania V, Scaramella L, Forzenigo L, Vecchi M, Solbiati M, Costantino G, Danese S, D'Antiga L, Sironi S, Elli L

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Retrospective Study

Contrast-enhanced ultrasound imaging for intestinal lymphoma

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Abstract

BACKGROUND

Intestinal lymphoma is a rare tumor. Contrast-enhanced ultrasound (CEUS) findings of intestinal lymphoma have not been reported previously, and the relationship between CEUS and clinicopathological features and prognostic factors is still unknown.

AIM

To describe the B-mode US and CEUS features of intestinal lymphoma and investigate the correlation of CEUS and histopathological features.

METHODS

This was a single-center retrospective study. Eighteen patients with histologically confirmed intestinal lymphoma underwent B-mode US and CEUS examinations between October 2016 and November 2019. We summarized the features of B-mode US and CEUS imaging of intestinal lymphoma and compared the frequency of tumor necrosis in intestinal lymphomas with reference to different pathological subtypes (aggressive or indolent) and clinical stage (early or advanced). The time-intensity curve parameters of CEUS were also compared between patients with normal and elevated serum lactate dehydrogenase.

RESULTS

Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College under Application, No. NCC2016YZ-15.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to do the examination by written consent.

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There are no conflicts of interest to declare.

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No additional data are available.

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In B-mode imaging, four patterns were observed in intestinal lymphoma: Mass type (12/18, 66.7%), infiltration type (1/18, 5.6%), mesentery type (4/18, 22.2%) and mixed type (1/18, 5.6%). All cases were hypoechoic and no cystic areas were detected. On CEUS, most cases (17/18, 94.4%) showed arterial hyperechoic enhancement. All cases showed arterial enhancement followed by venous wash out. A relatively high rate of tumor necrosis (11/18, 61.1%) was observed in this study. Tumor necrosis on CEUS was more frequent in aggressive subtypes (10/13, 76.9%) than in indolent subtypes (1/5, 20.0%) ($P = 0.047$). There were no correlations between tumor necrosis and lesion size and Ann Arbor stage. There was no significant difference in time-intensity curve parameters between normal and elevated lactate dehydrogenase groups.

CONCLUSION

B-mode US and CEUS findings of intestinal lymphoma are characteristic. We observed a high rate of tumor necrosis, which appeared more frequently in aggressive pathological subtypes of intestinal lymphoma.

Key Words: Intestinal lymphoma; Contrast enhanced ultrasound; B-mode ultrasound; Histopathological features; Lactate dehydrogenase; Quantitative diagnosis

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Core Tip: This is a small pilot study that described the appearance and pattern of intestinal lymphoma on B-mode ultrasound (US) and contrast-enhanced US. We revealed an unexpected contrast-enhanced US enhancement pattern with a high rate of tumor necrosis, which was found more frequently in aggressive than in indolent subtypes. This might provide additional information for clinical diagnosis and treatment of intestinal lymphoma.

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INTRODUCTION

Gastrointestinal tract is the most common site for extranodal lymphomas[1,2]. Approximately 20%–25% of primary extranodal lymphomas occur in the gastrointestinal tract [3,4]. Around 50%–70% of the gastrointestinal lymphomas arise in the stomach, 20%–30% in the small bowel and 5%–20% in the large bowel[5]. Primary intestinal lymphomas are less common than gastric lymphomas and differ in clinical features, pathology, treatment and prognosis[6–10]. There are few studies on the ultrasound (US) diagnosis of intestinal lymphoma, most of which are case reports. Intestinal tumors are usually studied through endoscopic or radiological imaging techniques, which may explain the lack of studies on US in intestinal lymphomas[11]. However, previous studies have already shown that US is an effective method for detecting gastrointestinal lesions, especially in experienced hands[12]. US-guided biopsy can also establish a definite pathological diagnosis, avoiding unnecessary surgery.

Contrast-enhanced US (CEUS) has emerged as a new imaging technique that can evaluate tumor vascularity[13]. CEUS is now widely accepted and recommended in inflammatory bowel disease in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines. CEUS is suggested for assessment of the vascularity of the gastrointestinal wall and gastrointestinal tumors[14]. To the best of our knowledge, CEUS features of intestinal lymphoma have not previously been described. The aim of this study was to illustrate CEUS patterns of intestinal lymphoma for the first time and to investigate the relationship between CEUS and clinicopathological features and prognostic factors.

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MATERIALS AND METHODS

Patients

This is a single-center retrospective study based on a search of our imaging system from October 2016 to November 2019. Patients were excluded if they had a history of any other cancer or if they had previously received treatment. Written informed consent was obtained from each patient before the CEUS examinations.

Eighteen patients with histologically confirmed intestinal lymphoma were included, 10 men and 8 women, with age range 34–85 years. Definitive diagnosis for all the lesions was obtained by US-guided biopsy in 15 (83.3%) cases or by surgical resection in 3 (16.7%) cases. The diagnosis of intestinal lymphoma was based on the World Health Organization classification[15]. According to the Ann Arbor staging system, patients were classified into early stage (I/II) and advanced stage (III/IV). Pathological types were classified into aggressive and indolent lymphoma based on the World Health Organization classification. Primary intestinal lymphoma was defined as predominant intestinal lesion without previous peripheral lymphadenopathy or any lymphoma whose clinical presentation was related to intestinal involvement[16].

US examinations

All patients underwent B-mode US and CEUS with a 3.0–5.0 -MHz C5-1 probe for the iU22 sonography system (Philips Healthcare Ultrasound, Bothell, WA, United States) prior to surgery or biopsy. All patients were fasted for 8–12 h. CEUS was performed on all tumors under same protocols with the following parameters: Mechanical index 0.08–0.11, contrast gain 50%–60% and dynamic range 40 dB and focal zone was set at maximal depth. SonoVue (4.8 mL; Bracco, Milan, Italy) was administrated through a forearm vein in bolus within 1–2 s, followed by flush of 5 mL 0.9% saline. Images were acquired immediately after contrast agent was injected and lasted for 3 min and were recorded and stored as raw data on personal hard disks.

Image analysis

US and CEUS images were reviewed by two experienced radiologists, who were blinded to all clinical and pathological information. If there was disagreement between them, the final determination was made after discussion. The tumor size, internal echogenicity and presence of bowel wall thickening were recorded. Bowel wall thickening was defined as > 3 mm for small bowel and > 5 mm for large bowel. The enhancement pattern, enhancement distribution, tumor necrosis and presence of irregular and enlarged vessels (diameter > 5 mm) were recorded. The enhancement pattern was classified as homogeneous or heterogeneous. The enhancement distribution was clarified as diffuse, centripetal or centrifugal. Tumor necrosis was considered present if a nonenhanced area could be seen within the tumor during the arterial and venous phases.

According to the EFSUMB guidelines[14], the arterial phase is defined as the first 30 s after the contrast agent is injected, and the venous phase as the period between 30 and 120 s. By using Q lab software version 5 (Philips Medical Systems) on the workstation, we selected a region of interest (ROI) in the most enhanced area of the lesion, and the ROI area was set to 25 mm². The time-intensity curve (TIC) was automatically created for each ROI and then TIC parameters including rise time, time to peak, mean transit time, time from peak to one half, peak intensity, wash in slope and area under the curve were automatically obtained.

Statistical analysis

The Fisher's exact test was used to compare rate of tumor necrosis on CEUS between patients with Ann Arbor stage I/II and III/IV intestinal lymphomas and between patients with indolent and aggressive subtypes of intestinal lymphoma. Student's *t* test was used to compare the TIC parameters between normal and elevated serum lactate dehydrogenase (LDH) groups. Statistical significance was determined at *P* < 0.05 (two sided). Statistical analyses were performed using SPSS version 13.0 (SPSS Chicago, IL, United States).

RESULTS

Clinical and histological findings

This patient group comprised 18 patients with non-Hodgkin's lymphoma (NHL) of

various subtypes. Seventeen intestinal lymphomas were of B-cell origin; among which 11 were diffuse large B-cell lymphoma (DLBCL), 3 were follicular lymphoma, 2 were mucosa-associated lymphoid tissue lymphoma and 1 was mantle cell lymphoma. Only one case was of T-cell origin (enteropathy-associated T-cell lymphoma). No instances of intestinal Hodgkin's lymphoma were encountered. Primary intestinal lymphoma was diagnosed in 16 cases, whereas secondary lymphoma infiltration of the bowel was observed in 2 cases. Eight cases were classified as stage II, 4 as stage III and 6 as stage IV. The clinical presentations included abdominal pain ($n = 7$), palpable abdominal mass ($n = 5$), gastrointestinal bleeding ($n = 2$), constipation ($n = 2$), weight loss ($n = 1$) and fever ($n = 1$).

B-mode US

Four sonographic patterns of intestinal lymphoma were observed on B-mode imaging. The mass type ($n = 12$) presented as circumferential, marked bowel wall thickening forming masses, with loss of stratification, and hyperechoic lumen inside the mass (Figure 1A and B)[17,18]. The size of the masses ranged from 7.1 cm to 11.9 cm (mean 9.9 cm). The infiltration type presented as segmental bowel wall thickening without apparent mass formation ($n = 1$), with intestinal wall thickness of 2.6 cm (Figure 2A and B). The mesenteric type ($n = 4$) was characterized by multiple exophytic mesenteric masses with or without involvement of adjacent intestinal wall (Figure 3A and B) [19]. The lesion sometimes encapsulated mesenteric vessels without narrowing of the vascular lumen. The mixed type ($n = 1$) showed a combination of two patterns. Nine (50%) patients presented with bulky lesions (> 10 cm). Dilatation of the bowel was observed in 3 cases. Intestinal lymphomas were located in the small intestine in 5 cases, mesentery in 5, rectum in 1, ascending colon in 1, and 6 cases could not be clearly localized by US. Regional lymphadenopathy was found in 12 patients (66.7%), which manifested as aggregated nodules or masses in the mesentery or retroperitoneum.

CEUS

Rapid arterial enhancement followed by gradual washout in the venous phase was observed in all 18 patients (Figures 1C, 2C, and 3C). The peak enhancement was reached in the arterial phase or early venous phase. Seventeen cases presented with hyperechoic arterial enhancement, and only 1 case revealed hypoechoic arterial enhancement. Enhancement during the arterial phase was homogeneous ($n = 7$) or inhomogeneous ($n = 11$). Fifteen cases presented with diffuse enhancement, whereas three presented with centripetal enhancement. The visualization of irregular vessels was observed in 8 cases (44.4%). Tumor necrosis on CEUS was identified in 11 (61.1%) patients (Figure 1C), in which 1 case revealed extensive necrosis. Detailed information about B-mode US and CEUS findings of the 18 cases are shown in Table 1.

The mean diameter of the lesions with and without necrosis was 8.36 cm and 9.58 cm, respectively ($P = 0.6$). We compared the frequency of tumor necrosis in intestinal lymphomas with reference to different pathological subtypes or clinical stages. Tumor necrosis on CEUS was detected in 20.0% (1/5) of indolent intestinal lymphomas and in 76.9% (10/13) of aggressive subtypes ($P = 0.047$). Tumor necrosis was detected in 80% (8/10) of patients in III/IV stage and in 37.5% (3/8) patients in I/II stage ($P = 0.145$) (Table 2). Quantitative results of TIC parameters are shown in Table 3. The serum LDH value ranged from 130 to 968 U/L, with 10 patients' values exceeding the upper limit of normal (248 U/L). There was no significant difference in TIC parameters between normal and elevated LDH groups (Table 4).

DISCUSSION

In this study, we reported 18 cases of intestinal lymphoma. The mean age of our patients was 58.94 ± 15.89 years with most cases between 50 and 70 years. There was a male predominance with a male to female ratio of 1.25: 1. Lymphomas were predominantly located in the small bowel, and the most common symptoms included palpable abdominal mass and abdominal pain, which is in agreement with the literature[20]. All the intestinal lymphomas were NHL. B-cell lymphomas were more frequent than T-cell lymphomas (17: 1), and the most common pathological subtype was DLBCL (11/18, 61.1%). These results correlated well with previous studies[3,21].

We confirmed some of the sonographic features reported earlier and provided new information regarding the CEUS findings in intestinal NHL. Our data showed that mass type was the most frequent form of intestinal NHL on B-mode imaging (12/18,

Table 1 B-mode ultrasound and contrast-enhanced ultrasound patterns and clinicopathological characteristics of intestinal lymphoma in 18 patients

No.	Age (yr)	Sex	Location	Pathological subtype	B-mode US pattern	CEUS enhancement pattern	Necrosis
1	78	M	Ileocecal region	DLBCL	Mass type	Diffuse, inhomogeneous, arterial hyperechoic uptake. gradually venous wash-out	Yes
2	34	M	Rectum	MATL	Mass type	Diffuse, inhomogeneous, arterial hyperechoic uptake. gradually venous wash-out	Yes
3	43	M	Mesentery	DLBCL	Mesenteric type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
4	46	M	Small intestine	FL	Mass type	Diffuse, homogeneous, hypoechoic, arterial uptake. gradually venous wash-out	No
5	75	F	Ascending colon	DLBCL	Infiltration type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
6	78	F	Jejunum, ileum	EATL	Mass type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
7	52	F	Jejunum	DLBCL	Mass type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
8	74	M	Small intestine	DLBCL	Mass type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
9	52	M	Jejunum, ileum	MATL	Mass type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
10	61	M	Mesentery	DLBCL	Mesenteric type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
11	41	F	Mesentery	DLBCL	Mesenteric type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
12	46	F	Small intestine	DLBCL	Mass type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
13	64	M	Ileocecum, ascending colon	DLBCL	Mass type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
14	68	F	Small intestine	DLBCL	Mixed type	Diffuse, inhomogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes
15	61	F	Small intestine	FL	Mass type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
16	85	M	Small intestine	MCL	Mass type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
17	35	M	Mesentery	FL	Mesenteric type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	No
18	68	F	Small intestine	DLBCL	Mass type	Diffuse, homogeneous, hyperechoic arterial uptake. gradually venous wash-out	Yes

CEUS: Contrast-enhanced ultrasound; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; MCL: Medial collateral ligament; MATL: Melanoma-associated T-lymphocytes; EATL: Enteropathy associated T-cell lymphoma.

66.7%), which was in agreement with previous studies[22]. However, this finding was not specific because various intestinal abnormalities also can lead to bowel wall thickening. Nevertheless, bowel wall thickening in lymphoma is often significant (> 2 cm) compared to other malignancies and often located in the ileocecal region, with coexistence of perivisceral multiple lymph nodes. Diffuse or segmental bowel wall thickening is characteristic of intestinal lymphoma, especially when associated with bowel lumen dilation, but this US pattern only comprised 5.6% in our study.

In our study, rapid arterial enhancement followed by elimination of the contrast media in the venous phase was observed in all cases, which is similar with other malignancies. This finding is believed to be correlated with the presence of arteriovenous shunts and a well-represented circulatory bed. Thirteen cases exhibited diffuse enhancement, in accordance with previous studies[23]. Most (17/18, 94.4%) intestinal lymphomas displayed hyperechoic arterial enhancement, which is different from isoechoic or hypoechoic arterial enhancement observed in lymphoma infiltration

Table 2 Tumor necrosis and tumor size, clinical stage and pathological subtypes

Characteristic	With necrosis	Without necrosis
Tumor size (cm)	8.36	9.58
Stage		
Early stage	3	5
Advanced stage	8	2
Subtype ^a		
Indolent subtype	1	4
Aggressive subtype	10	3

^a*P* = 0.047.**Table 3 Time–intensity curve parameters of contrast-enhanced ultrasound**

TIC parameters	Range	mean ± SD
Rise time (s)	2.90-27.62	13.74 ± 6.11
Time to peak (s)	7.64-36.00	24.41 ± 6.61
Mean transit time (s)	29.94-77.75	49.94 ± 13.98
Time from peak to one half (s)	36.38-127.85	77.88 ± 24.12
Peak intensity (dB)	7.8-29.28	17.57 ± 5.98
WIS (dB/s)	0.53-29.28	1.35 ± 1.09
AUC	590.99-3616.03	1772.05 ± 824.89

AUC: Area under curve; WIS: Wash in slope; TIC: Time–intensity curve.

Table 4 Time–intensity curve parameters and serum lactate dehydrogenase level

TIC parameters	Normal LDH	Elevated LDH	<i>P</i> value
Rise time (s)	14.34	12.78	0.693
Time to peak (s)	27.17	27.07	0.982
Mean transit time (s)	53.39	46.21	0.382
Time from peak to one half (s)	82.70	72.49	0.442
Peak intensity (dB)	16.50	16.68	0.955
Wash in slope (dB/s)	1.38	1.26	0.824
Area under the curve (dBs)	1699.47	1712.42	0.979

TIC: Time–intensity curve; LDH: Lactate dehydrogenase.

of the spleen, lungs and kidneys[24-26]. The reason for this discrepancy is unclear and needs to be confirmed in larger populations.

It is notable that there was a high rate of necrosis (11/18, 61.1%) on CEUS, which is inconsistent with previous studies. Despite necrosis being prone to occur in large tumors, we found no correlation between the presence of tumor necrosis on CEUS and tumor size. Necrosis was not detected in 4 of the 9 cases with bulky lesions. Necrosis may indicate aggressive tumor growth, and thus be associated with poor prognosis. Some researchers have explored the prognostic implications of tumor necrosis at computed tomography (CT) or positron emission tomography in lymphoma. Saito *et al* [27] did not find an association between disease-free survival and presence of necrosis in lymph nodes in 60 patients with different NHL subtypes[27]. However, Adams *et al*

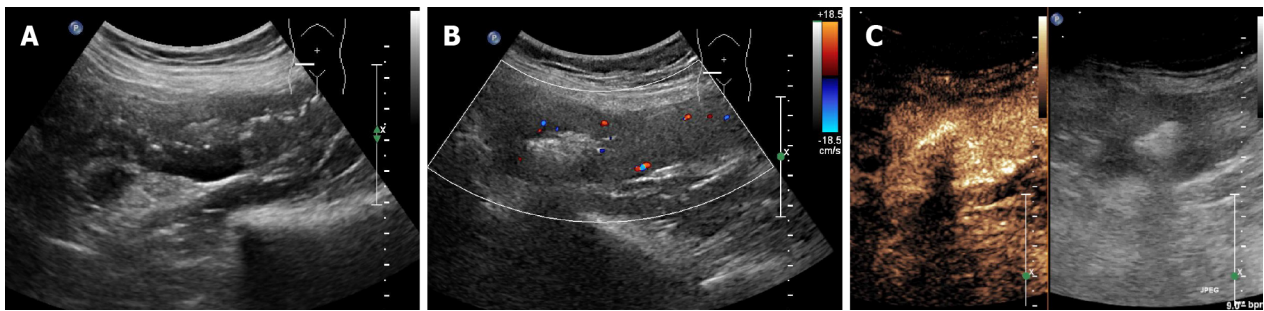


Figure 1 A 78-year-old female patient (case No. 6) with primary enteropathy-associated T-cell lymphoma in small intestine. A: B-mode imaging shows polypoidal lesions presenting “pseudo renal sign”; B: Color Doppler flow imaging shows abundant blood flow in bowel wall; C: Contrast-enhanced ultrasound showing inhomogeneous intense arterial enhancement with small non enhanced area.

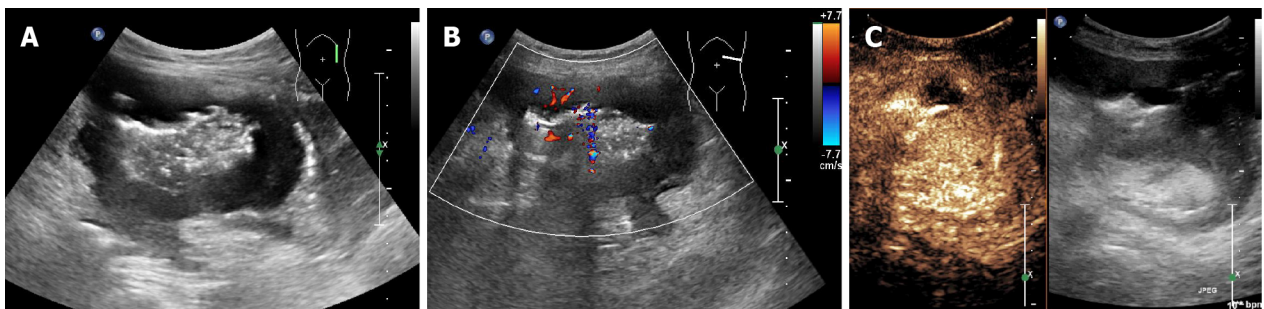


Figure 2 A 75-year-old female patient (case No. 5) with primary diffuse large B-cell lymphoma in the terminal ileum and ascending colon. A: B-mode imaging show circumferential bowel wall thickening with dilation of the bowel; B: Color Doppler flow imaging shows abundant blood flow in bowel wall; C: Contrast-enhanced ultrasound showing homogeneous intense arterial enhancement.

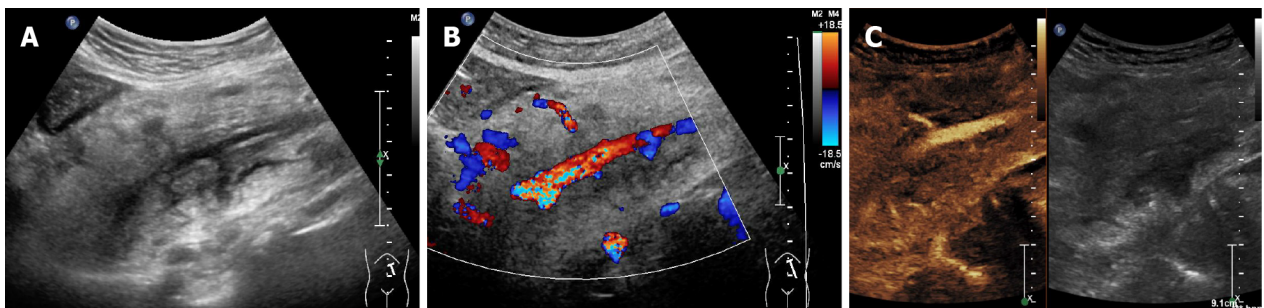


Figure 3 A 68-year-old female patient (case No. 14) with secondary diffuse large B-cell lymphoma intestinal lymphoma in mesentery. A: B-mode imaging shows large mesenteric mass encapsulating mesenteric vessels with ill-defined echoic region; B: Color Doppler flow imaging shows the abdominal aorta and its branches; C: Contrast-enhanced ultrasound showing inhomogeneous moderate arterial enhancement.

[28] showed that patients with newly diagnosed DLBCL with tumor necrosis at CT had significantly worse progression-free survival and overall survival than patients without tumor necrosis at CT. The National Comprehensive Cancer Network International Prognostic Index score did not differ significantly between the two groups. Our study showed that the frequency of necrosis on CEUS was different between indolent and aggressive lymphoma subtypes, but it was not related to clinical stage. Since it as a retrospective study, patients were not followed up to assess prognosis.

Evaluation of prognosis by imaging is desirable but often not possible. It is known that tumor growth is accompanied by neoangiogenesis. The assessment of the bowel vasculature can provide functional information about tumor perfusion, particularly with the advent of the second generation of contrast agents for CEUS. The generation of TICs allows for objective measurement of blood flow parameters[29]. In our previous study, we demonstrated that enhanced intensity is associated with microvascular density in rectal cancer[30]. In the present study, we investigated the relationship between TIC parameters and serum LDH level. LDH can reflect tumor load and is an independent prognostic factor of lymphoma[31]. However, we found no significant

difference in TIC parameters between normal and elevated serum LDH groups.

US is not the method of choice for the diagnosis of intestinal lymphoma, because it may not detect small or deep lesions that can be obscured by bowel gas; it is often used as targeted US for evaluation of suspected region but has difficulty in thorough assessment and staging for advanced lymphoma. Intestinal lymphoma is conventionally diagnosed by CT, magnetic resonance imaging and positron emission tomography/CT. However, CEUS used with second-generation contrast agent, offered a reasonable alternative imaging solution for those who are not suitable for nephrotoxic iodine-based contrast medium injection. Moreover, in our experience, CEUS guided biopsy allows targeting viable regions of the tumor; it has significantly improved our ability to obtain sufficient tissue for immunohistochemistry and molecular testing, which is particularly important in diagnosis and evaluation of lymphoma.

This study had some limitations. Intestinal lymphoma is a rare entity and the sample size was small. Furthermore, the patients included in this study who underwent CEUS examinations were usually referred for US-guided biopsy, which may have led to selection bias. As it was a retrospective study, some clinical data were missing and prognostic information was not included.

CONCLUSION

In this study, our findings on intestinal lymphoma contribute to knowledge of CEUS imaging. In this small group, intestinal lymphomas showed a characteristic enhancement pattern with rapid wash followed by early wash out of the contrast media. A high rate of tumor necrosis was detected, with a tendency to be more likely in aggressive subtypes, which needs to be confirmed in a larger population. Although US is not the primary imaging modality in diagnosis of intestinal lymphoma, it can play an important role in guidance of biopsy and provide more information.

ARTICLE HIGHLIGHTS

Research background

Contrast-enhanced ultrasound (CEUS) is a new imaging technique that can evaluate tumor vascularity, and it has been proved to have value in the diagnosis and assessment of inflammatory bowel disease. However, the CEUS features of intestinal lymphoma remain unclear.

Research motivation

There have been few studies on CEUS findings of intestinal lymphoma and their potential correlation with histopathological features.

Research objectives

Our present study aimed to describe the B-mode US and CEUS features of intestinal lymphoma and investigate the correlation of CEUS and histopathological features.

Research methods

We summarized the features of B-mode US and CEUS imaging of intestinal lymphoma of 18 patients and compared the frequency of tumor necrosis in intestinal lymphomas with reference to different pathological subtypes (aggressive or indolent) and clinical stage (early or advanced). Besides, the time-intensity curve parameters of CEUS were also compared between patients with normal and elevated serum lactate dehydrogenase (LDH).

Research results

In B-mode imaging, four patterns were observed in intestinal lymphoma: Mass type (12/18, 66.7%), infiltration type (1/18, 5.6%), mesentery type (4/18, 22.2%) and mixed type (1/18, 5.6%). All cases were hypoechoic and no cystic areas were detected. On CEUS, most cases (17/18, 94.4%) showed arterial hyperechoic enhancement. All cases showed arterial enhancement followed by venous wash out. A relatively high rate of tumor necrosis (11/18, 61.1%) was observed in this study. Tumor necrosis on CEUS was more frequent in aggressive subtypes (10/13, 76.9%) than in indolent subtypes (1/5, 20.0%) ($P = 0.047$). There were no correlations between tumor necrosis and lesion

size and Ann Arbor stage. There was no significant difference in time-intensity curve parameters between normal and elevated LDH groups.

Research conclusions

B-mode US and CEUS findings of intestinal lymphoma are characteristic. We observed a high rate of tumor necrosis, which appeared more frequently in aggressive pathological subtypes of intestinal lymphoma.

Research perspectives

Based on the present results, we will expand the number of enrolled patients and explore the advantages of US compared with other imaging techniques in diagnosing intestinal lymphoma.

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