Int J Clin Exp Pathol 2020;13(2):254-260
www.ijcep.com /ISSN:1936-2625/IJCEP0104861

Case Report

Primary colorectal diffuse large B-cell lymphoma initially presenting with pleural effusion: report of one case and review of literature

Tingzhen Xu, Lu Wang, Linshui Zhou, Zhen Wang, Yuanhong Zhu, Fanghe Ju

Department of Respiratory Medicine, The First Affiliated Hospital of Zhejiang Chinese Medicine University, Hangzhou, Zhejiang, P. R. China

Received November 13, 2019; Accepted January 23, 2020; Epub February 1, 2020; Published February 15, 2020

Abstract: Gastrointestinal (GI) diffuse large B-cell lymphoma (DLBCL) is one of the frequently reported histologic subtypes of non-Hodgkin lymphoma (NHL) that occur in the GI tract. However, the presentation of quite different clinical manifestations, morphologic characteristics, immunophenotypes, and molecular biologic features is challenging for its diagnosis. Herein, we describe a rare case of primary colorectal DLBCL that occurred in a 59-year-old immunocompetent Chinese female who attended our respiratory clinic for the third time with an asymptomatic pleural effusion and pleural thickening. In her clinical setting, there was no history of trauma or travel, and no evidence of infections, connective tissue diseases, or malignancies such as pleural mesothelioma. Lymphoma was highly suspected for the enlargement of systemic lymph nodes and the multiple polypoid appearance in the rectum found by endoscopy examination. In a repeated colonoscopy, immunohistochemical and molecular features of the multiple "polyps" allowed diagnosis of colorectal diffuse large B-cell NHL. To our knowledge, this is the first case of a verified diagnosis of pleural effusion associated with a primary colorectal DLBCL. The purpose of this report is to alert clinicians that when we evaluate the causes of unexplained pleural effusion, lymphoma should be considered, particularly when the available examination data cannot be corroborated by clinical manifestations.

Keywords: Gastrointestinal lymphoma, primary colorectal lymphoma, diffuse large B-cell lymphoma, pleural effusion

Introduction

Diffuse large B-cell lymphoma (DLBCL), first reported by Harris, is one of the most prominent histologic subtypes of malignant lymphoma and represents up to 30% of non-Hodgkin lymphoma (NHL) cases [1]. Studies show that gastrointestinal (GI) lymphoma accounts for 40% of extranodal DLBCL, and the lymphoma involvement in the GI tract leads to a variety of lesions and nonspecific symptoms that render the diagnosis particularly challenging [2]. Herein, we describe a rare case of rectal DLBCL that occurred in a 59-year-old immunocompetent Chinese female who had a 2-year history of unexplained pleural effusion and pleural thickening. To our knowledge, this is an unusual report of uniateral pleural effusion associated with primary rectal DLBCL.

A case report

A 59-year-old immunocompetent woman had a medical history of 20 years of large artery stenosis, seven years of controlled hypertension, and no history of smoking or alcohol consumption. She attended our respiratory clinic on July 25, 2018, for the third time in two years, with the primary clinical manifestation of unilateral pleural effusion. She denied having had fever, cough, rash, joint pain, or chronic diarrhea, and there was no history of trauma, travel, or surgery, and no family history of malignancy or connective tissue disease (CTD). Blood, urine, stool tests, as well as biochemical, coagulation, and thyroid function tests were within normal limits. The tumor biomarkers were almost normal, except for a slight increase of CA125 to 245.2 U/mL (Normal range: 0.0-22.0 U/mL). Infections

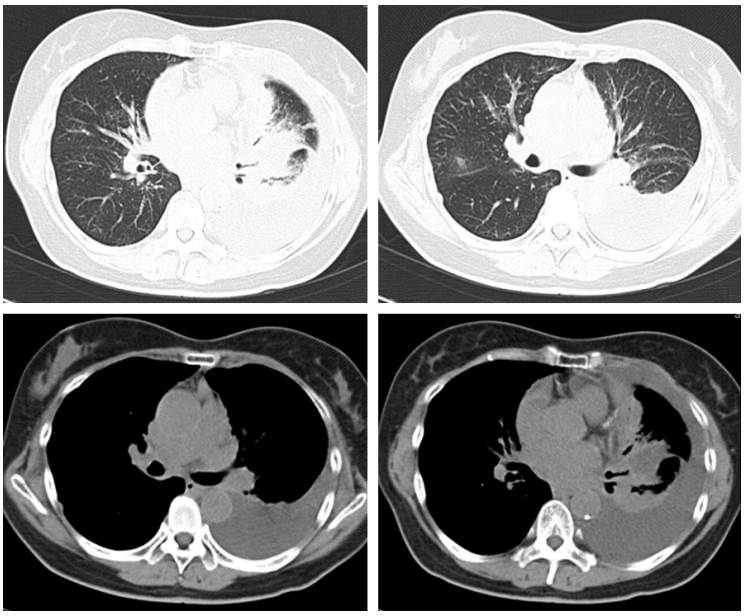

Figure 1. Chest CT revealed multiple high-density shadows, mediastinal lymph node metastatic nodules, and a left pleural effusion.

were also ruled out, including tuberculosis and human immunodeficiency virus (HIV), and CTD was also not considered. A computed tomography (CT) scan of the chest revealed multiple high-density shadows, enlarged lymph nodes in the mediastinum, and both a massive pleural effusion in the left thoracic cavity and small pleural nodular lesions thickening the pleura (**Figure 1**). Considering that the patient had never had thoracic surgery or experienced trauma, malignancy was suspected. However, subsequent bronchoscopy and thoracoscopy examinations demonstrated only mild chronic inflammation without any evidence of infection or malignancy (**Figures 2** and **3**). GI endoscopy was then carried out, and finally her second colonoscopy verified the diagnosis of left-sided pleural effusion associated with a rectal DLBCL (**Figure 4**). The symptoms and the pleural effusion disappeared after a traditional Chinese medicine treatment was administered.

Discussion

The GI tract is a common site for the presentation of extranodal lymphomas, with increasing incidence worldwide [1-3]. However, the primary colorectal lymphoma is quite rare, constituting only 0.2% of all colorectal malignancies. GI lymphomas can be difficult to diagnose, particularly in small samples, when early in development, or when unusual types are involved [1, 4, 5].

According to the existing literature, the clinical characteristics of GI DLBCL are always variable. In addition to the most commonly encountered GI symptoms of nausea, vomiting, dyspepsia, abdominal pain, mass or anemia, hypoproteinemia, and weight loss, GI DLBCL involves posterior peritoneum lymph nodes, the uterus, and pancreas; and it may present as a skin lesion, upper GI bleeding, ulcerative colitis, acute pancreatitis, ascites, or intestinal obstruction due to invasion into different organs [6, 7]. It occurs in a location-based manner. In a setting of colorectal DLBCL, abdominal pain, bowel obstruction, a palpable mass, and rectal bleeding occur most frequently [6-8]. However, isolated colorectal involvement and intestinal perforations are very rare, and only a few cases have been reported. **Table 1** summarizes some of the unusual manifestations of colorectal DLBCL: an 82-year-old female with acute chest pain, and others having acute pancreatitis or night sweats, fever, and cough. Certainly, it should be noted that some of the clinical features or those revealed by endoscopic investigation may be caused by metastatic GI lymphoma infiltration. As stated earlier, one-sided pleural effusion or pleural thickening is not commonly seen in either GI DLBCL or in patients with primary or metastatic rectal DLBCL. Only a few cases of peritoneal and omental infiltration have been reported in patients with GI DLBCL associated with ascites and pleural effusion [9]. Lymphomas can occur at any site of the body, but the diffuse and extensive involvement of the peritoneal cavity is unusual and rare. In fact, pleural thickening and enlarged lymph nodes may be more detected in the clinical practice of malignant mesothelioma, chronic pleural inflammation, or sarcoidosis. In the present case, the patient initially had unilateral pleural effusion, and this symptom had recurred three times. In particular, the pleural effusion could be

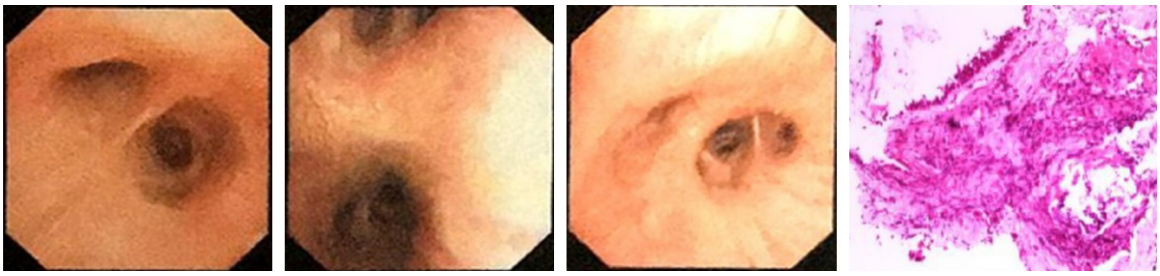

Figure 2. Autofluorescence bronchoscopy and histopathologic findings. The autofluorescence bronchoscopy revealed smooth bronchial mucosa and an unobstructed bronchial lumen. Histopathologic characteristics included chronic inflammation of the mucosa.

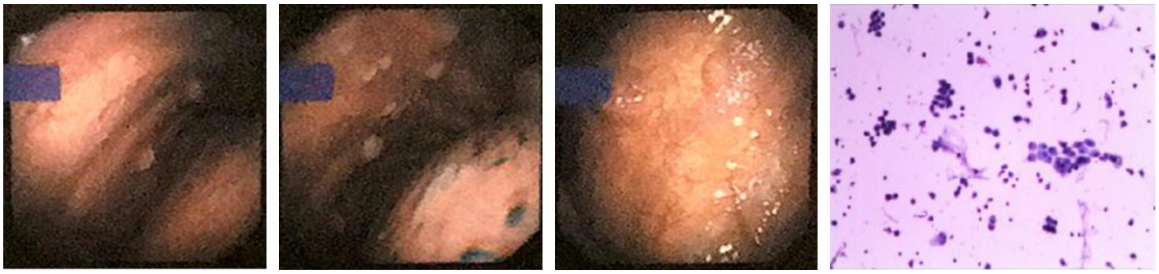

Figure 3. Thoracoscopic and histopathologic findings. The fibrous tissue of "parietal pleura" hyperplasia was accompanied by lymphoid tissue hyperplasia and mesodermal tissue hyperplasia.

absorbed without any treatment. It was a quite inert manifestation that rarely happens in malignant mesothelioma, chronic pleural inflammation, or sarcoidosis, reducing the suspicion of malignancy or malignant metastasis for clinicians. This study surmised that the reason for the pleural effusion in the patient was a tumor metastasis causing lymphatic obstruction.

Although a clear diagnosis was finally made, it took a long time. If an FDG-Positron Emission Tomography/Computed Tomography (PET/CT) scan had been performed, an early diagnosis could have been made. At diagnosis, the total-body FDG-PET/CT scan can identify areas of lymphoma missed by CT alone and avoid the undertreatment of patients with advanced disease stage who have been misclassified based on CT as suffering from limited-stage disease [22]. Particularly in Hodgkin lymphoma, the FDG-PET/CT scan offers a significant incremental benefit in the diagnosis and staging assessment, and a potential improvement in treatment strategies [23]. However, a whole-body scanning with PET/CT cannot be successfully carried out in resource-limited settings or rural areas of the country due to the cost and technical requirements. Notably, the patient in this study refused to undergo FDG-PET/CT scanning because of the huge cost.

Histopathology is the gold standard for the diagnosis. However, GI lymphomas usually pose difficulties in diagnosis, particularly in small samples, when early in development, or when of an unusual type. The reasons are essentially twofold: (1) the small size of biopsies, limiting the extensive evaluation usually performed on comparable lymph node samples, and (2) confusion of lymphoma with benign and reactive lymphoid proliferations in the GI tract [24, 25]. In the present study, the patient accepted colonoscopy twice, plus thoracoscopy and bronchoscopy. It may not be an individual phenomenon. Fortunately, the multiple polypoid appearance in the rectum raised the suspicion of GI lymphoid infiltration. *O'Malley* et al. [26] have already pointed out the need for additional evaluation for prominent GI intraepithelial infiltrates of small lymphocytes or lymphoepithelial lesions, dense infiltrates of large lymphoid cells, and multiple "polyps" containing dense lymphoid infiltrates. These data

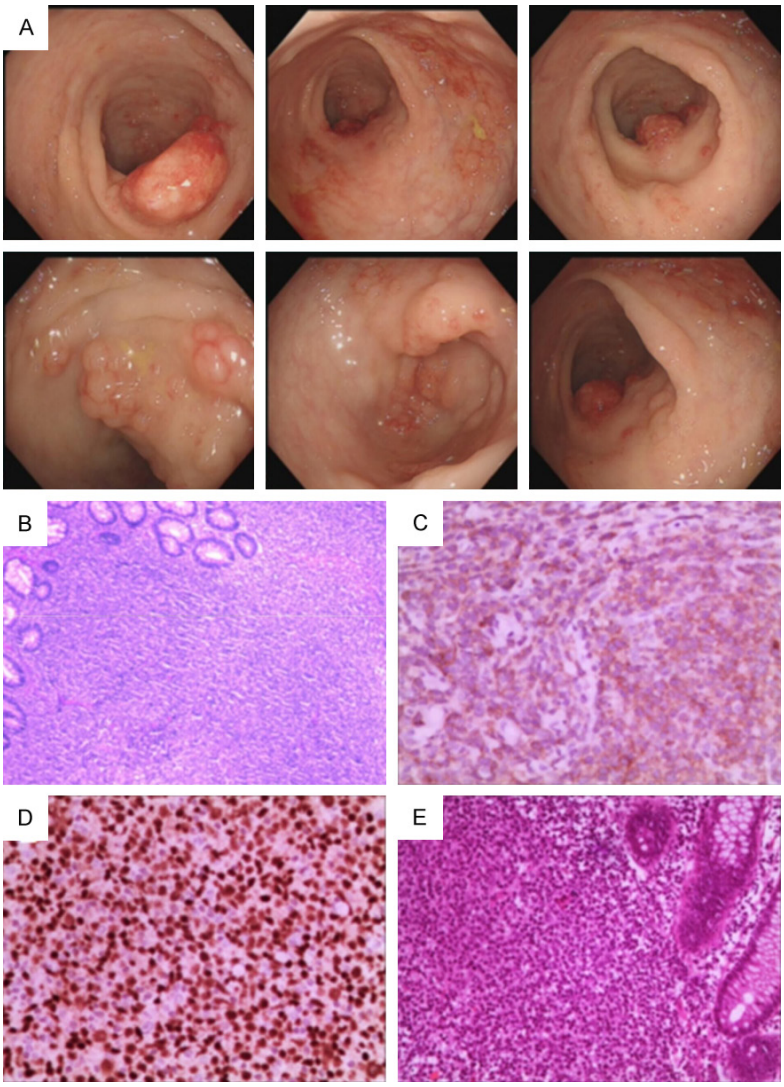

Figure 4. (A, B) Colonoscopic and histopathologic manifestations. Histopathologic and immunohistochemical studies of the rectal excision specimens demonstrated CD19 (+), CD20 (+), CD79a (+), CD30 (+), Bcl-2 (partial +), Bcl-6 (+), κ (partial +), CD10 (+), PAX-5 (+), CD38 (partial +), and Ki-67 (50%+). This was consistent with diffuse large B-cell lymphoma (DLBCL) cells. Original images are ×50 magnification. (C) Representative micrographs of immunohistochemical staining for Ki-67, (D) CD3, and (E) CD20. Original images of (C, D) are ×200 magnification, and (E) are ×100 magnification.

supported the initial hypothesis that a lymphoproliferative disease was involved in this case. The current report will improve the accuracy of diagnoses that take into consideration clinically or pathologically defined background settings defined in the literature.

Conclusion

A rare case of primary colorectal lymphoma initially presented with pleural effusion. Lymphoma involvement in the GI tract presents with a variety of lesions, and the nonspecific symptoms make the diagnosis challenging. A repeated pleural effusion is not just for a sign of infection, CTD or pleural mesothelioma. In certain clinical settings, malignancies, particularly nonsolid malignancies, should be considered. Despite its low probability, GI DLBCL with mediastinal lymph node metastasis may result in unexplained, repeated pleural effusion. Accordingly, the noninvasive imaging technique of PET/CT or at least a comprehensive CT scan or endoscopic examination is recommended in such conditions.

Acknowledgements

The Project Supported by Zhejiang Provincial Natural Science Foundation of China (LQ20H270014), Zhejiang provincial Traditional Chinese Medicine Research Foundation (2016ZA067) and Zhejiang Chinese Medical University Research Foundation (KC201931, 2019ZG-02).

Disclosure of conflict of interest

None.

Abbreviations

DLBCL, Diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; GI, gastrointestinal; CTD, connective tissue disease; HIV, human immunodeficiency virus; CT, computed tomography; PET/CT, Positron Emission Tomography/Computed Tomography.

Address correspondence to: Lu Wang, Department of Respiratory Medicine, The First Affiliated Hospital

Table 1. Review of cases of rare manifestations of GI diffuse large B-cell lymphoma (DLBCL)

Authors	Patient information	Clinical features or endoscopic investigation	Diagnosis
Papakonstantinou IP et al. [9]	A 66-year-old woman with low complement levels, resembling systemic lupus erythematosus	Persistent afebrile abdominal pain and bloody diarrhea	Primary colon DLBCL
Telci CO et al. [10]	A 77-year-old male with no risk factors	Hemorrhagic shock due to the massive hematemesis and hematochezia; GI endoscopy revealing a mosaic pattern and multiple ulcers	Primary gastric DLBCL
Tahir M et al. [11]	A 47-year-old male with no risk factors	Worsening RLQ abdominal pain, decreased appetite, and weight loss; imaging revealed cecal mass with distended bowel, and colonoscopy revealed a large mass obstructing the whole lumen of the cecum	Primary colon DLBCL
Jo HH et al. [12]	An 82-year-old female with no risk factors	Acute onset chest pain and vomiting; abdominal CT revealed a gastrogastric intussusception	Primary gastric DLBCL
Quera R et al. [13]	A 47-year-old male	Ulcerative colitis	Primary rectal DLBCL
Ohkura Y et al. [14]	A 53-year-old man	Spontaneous gastric perforation; a giant ulcer with the necrotic matter on the ulcer floor was seen on upper GI endoscopy	Primary gastric DLBCL
Genovese F et al. [15]	An 83-year-old Caucasian man	Intermittent anal bleeding and irregular bowel	Primary DLBCL developing within a rectal tubular adenoma with low-grade dysplasia
Santharam V et al. [16]		Sudden-onset abdominal pain with features of shock and peritonitis; jejunal perforation with abnormal lymph nodes	Primary jejunal DLBCL
Xu XQ et al. [17]	An 82-year-old man	Intermittent abdominal pain, nausea, and fatigue; CT scan of the abdomen revealed a mass in the terminal ileum with a sign of "bowel within bowel", which was suspicious for ileo-ileum intussusception	Primary ileum DLBCL
Tanaka S et al. [18]	A 38-year-old homosexual man diagnosed with human immunodeficiency virus infection	Anemia; GI endoscopy revealed multiple dish-like lesions, ulcerations, bloody spots, nodular masses with active bleeding in the stomach, erythematous flat lesions in the duodenum, and multiple nodular masses in the colon and rectum	AIDS-related GI DLBCL
Barbaryan A et al. [19]	An 84-year-old Caucasian female	Altered mental status, acute kidney injury, and hypercalcemia; colonoscopy showed a large ulcerated mass	Primary colorectal lymphoma
Yamada R et al. [20]	A 49-year-old man	Acute pancreatitis; upper GI endoscopy showed an all-round ulcerative lesion from the superior duodenal angle to the descending portion	Primary GI duodenal malignant lymphoma
Barut F et al. [21]	A 25-year-old male patient	Multifocal and skip involvement imitating Crohn's disease and attracting attention with a cobblestone-like appearance	Primary intestinal DLBCL forming multiple lymphomatous polyposis

of Zhejiang Chinese Medicine University, Hangzhou 310006, Zhejiang, P. R. China. E-mail: lulumm-8809@163.com

References

[1] Peng JC, Zhong L and Ran ZH. Primary lymphomas in the gastrointestinal tract. J Digest Dis 2015; 16: 169-176.

[2] Wu XC, Andrews P, Chen VW and Groves FD. Incidence of extranodal non-Hodgkin lymphomas among whites, blacks, and Asians/Pacific islanders in the United States: anatomic site and histology differences. Cancer Epidemiol 2009; 33: 337-346.

[3] Fujishima F, Katsushima H, Fukuhara N, Konosu-Fukaya S, Nakamura Y, Sasano H and Ichinohasama R. Incidence rate, subtype frequency, and occurrence site of malignant lymphoma in the gastrointestinal tract: population-based analysis in Miyagi. Tohoku J Exp Med 2018; 245: 159-165.

[4] Tevlin R, Larkin JO, Hyland JM, O'Connell PR and Winter DC. Primary colorectal lymphoma - A single centre experience. Surgeon 2015; 13: 151-155.

[5] Gay ND, Chen A and Okada CY. Colorectal lymphoma: a review. Clin Colon Rectal Surg 2018; 31: 309-316.

[6] Shen H, Wei Z, Zhou D, Zhang Y, Han X, Wang W, Zhang L, Yang C and Feng J. Primary extranodal diffuse large B-cell lymphoma: a prognostic analysis of 141 patients. Oncol Lett 2018; 16: 1602-1614.

[7] Peña C, Russo M, Martinez V and Cabrera ME. Extranodal lymphomas in the public health system in Chile: analysis of 1251 patients from the National Adult Cancer Program. Hematol Oncol 2019; 37: 47-53.

[8] Curakova E, Genadieva-Dimitrova M, Misevski J, Caloska-Ivanova V, Andreevski V, Todorovska B, Isahi U, Trajkovska M, Misevska P, Joksimovic N, Genadieva-Stavric S, Antovic S, Jankulovski N. Non-Hodgkin's lymphoma with peritoneal localization. Case Rep Gastrointest Med 2014; 2014: 723473.

[9] Papakonstantinou IP and Andreadis EA. Persistent afebrile abdominal pain: an unusual case of segmental colitis in an immunocompromised host. Cureus 2017; 9: e1033.

[10] Telci Caklili O, Mutlu HH, Colak Y, Ozturk E, Kosemetin Dover D and Tuncer I. Massive upper gastrointestinal bleeding caused by diffuse large B-cell lymphoma. Case Rep Gastrointest Med 2016; 2016: 5079709.

[11] Tahir M, Samad K, Koenig T and Viswanathan P. A rare case of primary diffuse large B-cell lymphoma of the colon. AME Case Rep 2018; 2: 28.

[12] Jo HH, Kang SM, Kim SH, Ra M, Park BK, Kwon JG, Kim EY, Jung JT, Kim HG, Ryoo HM and Kang UR. A case of gastro-gastric intussusception secondary to primary gastric lymphoma. Korean J Gastroenterol 2016; 68: 40-44.

[13] Quera R, Flores L, Simian D, Kronberg U, Vial MT, de Guevara DL and García-Rodríguez MJ. Rectal diffuse large B cell lymphoma appearing after immunosuppression for ulcerative colitis. Report of one case. Rev Med Chil 2017; 145: 1342-1348.

[14] Ohkura Y, Lee S, Kaji D, Ota Y, Haruta S, Takeji Y, Shinohara H, Ueno M and Udagawa H. Spontaneous perforation of primary gastric malignant lymphoma: a case report and review of the literature. World J Surg Oncol 2015; 13: 35.

[15] Genovese F, Becchina G, Nagar C, Ottoveggio G, Giacalone B, Scaglione G, Varriale E and Tralongo V. Primary diffuse large B-cell lymphoma developing within a rectal tubular adenoma with low-grade dysplasia: a case report. J Med Case Rep 2014; 8: 103.

[16] Santharam V, Kumar P and Lee LY. Case Report: Jejunal perforation: a rare presentation of B-cell lymphoma. BMJ Case Rep 2014; 2014.

[17] Xu XQ, Hong T, Li BL and Liu W. Ileo-ileal intussusception caused by diffuse large B-cell lymphoma of the ileum. World J Gastroenterol 2013; 19: 8449-8452.

[18] Tanaka S, Nagata N, Mine S, Igari T, Kobayashi T, Sugihara J, Honda H, Teruya K, Kikuchi Y, Oka S and Uemura N. Endoscopic appearance of AIDS-related gastrointestinal lymphoma with c-MYC rearrangements: case report and literature review. World J Gastroenterol 2013; 19: 4827-4831.

[19] Barbaryan A, Ali AM, Kwatra SG, Saba R, Prueksaritanond S, Hussain N, Mirrakhimov AE, Vladimirskiy N, Zdunek T and Gilman AD. Primary diffuse large B-cell lymphoma of the ascending colon. Rare Tumors 2013; 5: 85-88.

[20] Yamada R, Sakuno T, Inoue H, Miura H, Takeuchi T, Shiono Y, Okuse H, Nakamura M, Katsurahara M, Hamada Y, Tanaka K, Horiki N and Takei Y. A case of duodenal malignant lymphoma presenting as acute pancreatitis: systemic lupus erythematosus and immunosuppressive therapy as risk factors. Clin J Gastroenterol 2018; 11: 1-5.

[21] Barut F, Kandemır NO, Karakaya K, Kökten N and Ozdamar SO. Primary intestinal diffuse large B-cell lymphoma forming multiple lymphomatous polyposis. Turk J Gastroenterol 2011; 22: 324-328.

[22] El-Galaly TC, Villa D, Gormsen LC, Baech J, Lo A and Cheah CY. FDG-PET/CT in the management of lymphomas: current status and future directions. J Intern Med 2018; 284: 358-376.

[23] Paes FM, Kalkanis DG, Sideras PA and Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. Radiographics 2010; 30: 269-291.
[24] Banks PM. Gastrointestinal lymphoproliferative disorders. Histopathology 2007; 50: 42-54.
[25] Burke JS. Lymphoproliferative disorders of the gastrointestinal tract: a review and pragmatic guide to diagnosis. Arch Pathol Lab Med 2011; 135: 1283-1297.
[26] O'Malley DP, Goldstein NS and Banks PM. The recognition and classification of lymphoproliferative disorders of the gut. Hum Pathol 2014; 45: 899-916.