ORIGINAL ARTICLE

Primary Intestinal Lymphoma: Clinicopathological Characteristics of 55 Patients

Renuka Malipatel[1], Mallikarjun Patil[2], Pritilata Rout[3], Marjorie Correa[4], Harshad Devarbhavi[5]

Abstract

Introduction: Gastrointestinal (GI) tract is the most common site of extranodal lymphoma accounting for 30–40% of the cases. In Western countries, stomach is the most common site of GI lymphoma, whereas in the Middle East and Mediterranean countries, small intestine is commonly involved. Studies about primary intestinal lymphoma (PIL) are heterogeneous in anatomical distribution, presentation, and histological subtypes. The present study was aimed at studying the anatomical distribution, histological subtypes, and clinical characteristics at tertiary care centers.

Materials and methods: The present study was retrospective, conducted between 2006 and 2020. Patient's data were collected from institutional medical records. PIL was diagnosed by Lewin's criteria. After histological diagnosis, PIL was classified as per the World Health Organization (WHO) criteria and staging was done according to the Ann Arbor classification as modified by Musshoff.

Results: A total of 941 lymphoma cases were diagnosed during the study period between 2006 and 2020 consisting of 238 Hodgkin's lymphoma and 703 non-Hodgkin's lymphoma (NHL) cases. PIL constituted 5.8% of all lymphoma cases (55 out of 941) and 50.9% (55 of 108) of all primary GI lymphoma. Median age at diagnosis was 44 years and comprised predominantly males (85.45%). Diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma were the most common histological subtype (78%) seen. Two patients with primary Hodgkin's lymphoma involving the intestine were seen. T-cell lymphoma was seen in three (5.4%) patients. Ileocecal region was the most common site involved (27%). The common presenting complaints were intestinal obstruction (40%) requiring surgical resection and abdominal pain (32%). Majority of the patients presented in the early stages (I and II).

Conclusion: Our study demonstrates the pattern of distribution and various histological subtypes of PIL including the rare variants like primary intestinal Hodgkin's lymphoma. Relatively more number of patients presented with intestinal obstruction requiring surgery in comparison with other studies.

Keywords: Diffuse large B-cell lymphoma (DLBCL), Intestine, Lymphoma, Non-Hodgkin's lymphoma (NHL), Primary.

Euroasian Journal of Hepato-Gastroenterology (2021): 10.5005/jp-journals-10018-1345

Introduction

Overall, the incidence of lymphoma and extranodal lymphoma is increasing worldwide.[1,2] Gastrointestinal (GI) tract being one of the largest extranodal lymphatic organs is the most common site of extranodal lymphomas, accounting for 30–40% of all extranodal lymphomas.[3,4] GI lymphoma accounts for 1–4% of overall GI malignancies.[5] The anatomical distribution and histological subtype of GI lymphoma vary geographically possibly due to the difference in the prevalence of risk factors.[6,7] Stomach is the most common site of GI lymphoma followed by small and large intestine in Western countries, and majority of these lymphomas are diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type.[8,9] In contrast, primary small intestinal lymphoma accounts for 75% of the primary GI lymphomas in the Middle East and Mediterranean areas and vast majority of them are immunoproliferative small intestinal disease (IPSID).[10,11] The studies about the primary intestinal lymphoma (PIL) are scarce and are heterogeneous due to classification as small intestinal, ileocecal region and large intestinal lymphoma as separate entities.[6,7] The present study was done to ascertain the anatomical distribution, histological subtypes, and clinical characteristics of PIL at tertiary care centers.

Materials and Methods

It is a retrospective study conducted in the Departments of Gastroenterology and Pathology at St John's Medical College, Bengaluru, India, between 2006 and 2020. Patient's data were collected from institutional medical records. All patients who presented with intestinal symptoms like abdominal pain, diarrhea, GI bleeding, weight loss, intestinal obstruction/perforation, and detected to have tumor predominantly in the small or large intestine and histopathology showing lymphoma were included in the study, based on Lewin et al.'s definition.[12] Patients with systemic lymphomas involving the intestine were excluded. In all patients in whom surgery was not performed, enteroscopy-/colonoscopy-guided biopsy was done.

Based on the morphology, relevant Immunohistochemistry (IHC) markers were done. IHC panel consisted of pan-cytokeratin (CK), EMA, CD45 (LCA), CD3, CD20, CD79a, Bcl-2, CD10, CD5, CD23, cyclin-D1, Bcl-6, MUM-1, CD4, CD8, CD7, CD30, CD15, PAX5, CD138, CD56, Ki-67, kappa, lambda, ALK, CD34, Tdt, and granzyme B. Staging was done according to the Ann Arbor classification as

[1,3,4]Department of Pathology, St John's Medical College, Bengaluru, Karnataka, India

[2,5]Department of Gastroenterology, St John's Medical College, Bengaluru, Karnataka, India

Corresponding Author: Mallikarjun Patil, Department of Gastroenterology, St John's Medical College, Bengaluru, Karnataka, India, Phone: +91 08022065134, e-mail: drmalli_arjun@yahoo.co.in

How to cite this article: Malipatel R, Patil M, Rout P, *et al*. Primary Intestinal Lymphoma: Clinicopathological Characteristics of 55 Patients. Euroasian J Hepato-Gastroenterol 2021;11(2):71–75.

Source of support: Nil

Conflict of interest: None

modified by Musshoff.[13] Staging workup consisted of detailed history and complete physical examination, indirect laryngoscopy, and bone marrow examination; computed tomography scan of the chest, abdomen, and pelvis; positron-emission tomography (PET) scanning; and laparotomy in selected patients. PIL was classified according to the World Health Organization 2017 criteria.[14]

Results

A total of 941 lymphoma cases were diagnosed during the study period between 2006 and 2020 consisting of 238 Hodgkin's lymphoma and 703 NHL cases. PIL constituted 5.8% of all lymphoma cases (55 out of 941) and 50.9% (55 of 108) of all primary GI lymphoma. The median age at diagnosis was 44 years and comprised of 47 males (85.45%) with a male-to-female ratio of 5.8:1. The patient characteristics, clinical features, and the anatomical distribution of PIL are shown in Table 1. The various histological subtypes and staging at the time of diagnosis are shown in Table 2. There were eight patients with human immunodeficiency virus (HIV) infection. Overall, 26 (47%) patients underwent surgical resection. Diagnosis was established by enteroscopy-/colonoscopy-guided biopsy in 29 patients and in rest (26) after surgical resection. The enteroscopy/colonoscopy appearance included exophytic growth in 14, ulcerative lesion in 7, polyposis in 3, infiltrative lesion in 3, and stricture in 2 patients (Fig. 1).

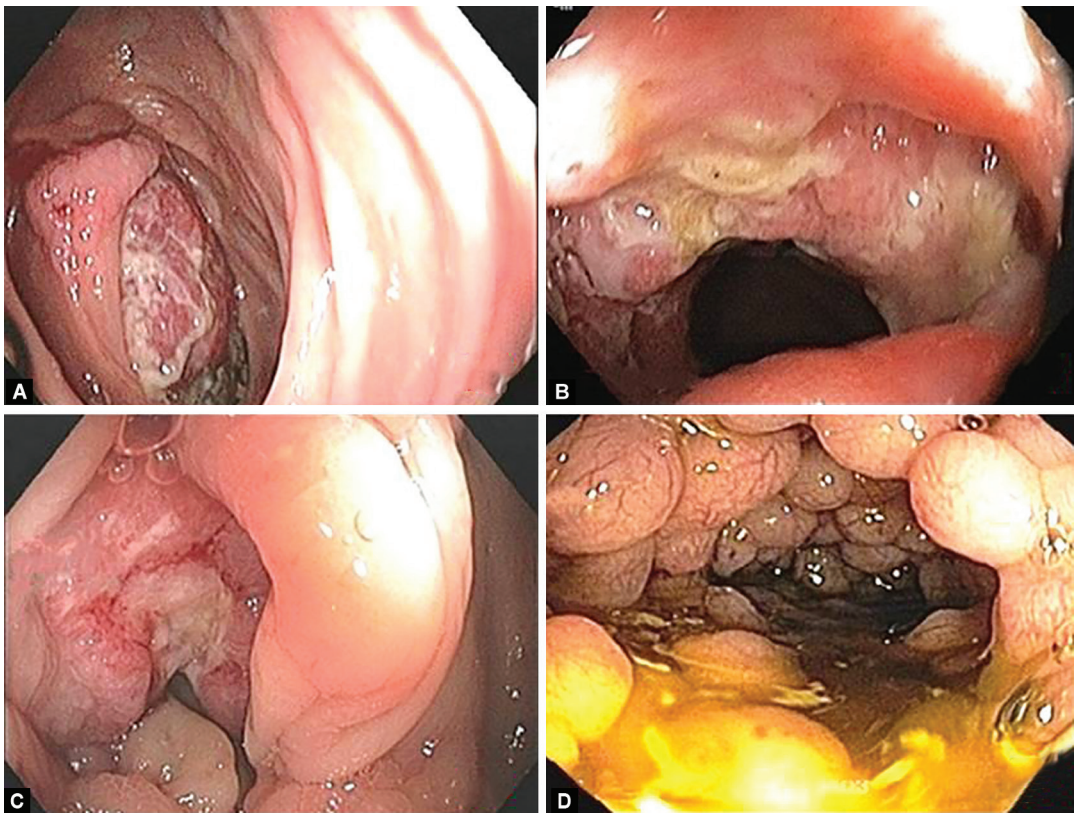
Table 1: Patient characteristics, clinical features, and the anatomical distribution of primary intestinal lymphoma (55 patients)

Median age (years, range)	*44 (7–85)*
Clinical features:	
• Subacute/acute intestinal obstruction	22 (40%)
• Abdominal pain	18 (32.7%)
• Gastrointestinal bleeding	4 (7.2%)
• Abdominal mass	4 (7.2%)
• Intestinal perforation	4 (7.2%)
• Obstructive jaundice	3 (5.4%)
B symptoms	20 (36%)
Duration of symptoms (mean, months)	5.5
Anatomical distribution:	
• Ileocecal junction	15 (27.2)
• Duodenum	14 (25.45%)
• Colon	14 (25.45%)
• Ileum	6 (10.9%)
• Jejunum	3 (5.45%)
• Multiple sites	3 (5.45%)

Table 2: Primary intestinal lymphoma: histological subtypes and staging

Histologic subtypes:	
• DLBCL	39 (70.9%)
• MALT lymphoma	4 (7.2%)
• Mantle cell lymphoma	4 (7.2%)
• T-cell lymphoma	3 (5.4%)
• Burkitt lymphoma	3 (5.4%)
• Hodgkin's lymphoma	2 (3.6%)
Staging:	
• I	10
• II-1	22
• II-2	6
• III	4
• IV	13

DLBCL, diffuse large B-cell lymphoma; MALT lymphoma, mucosa-associated lymphoid tissue lymphoma



Figs 1A to D: (A) Colonoscopy images showing exophytic growth involving the ileocecal valve; (B) Ulcerated lesion in ascending colon; (C) Stricturous lesion in descending colon; (D) Lymphomatous polyposis involving entire colon

Discussion

Our study findings demonstrate that PIL constitutes 5.8% of all lymphomas diagnosed over 15 years at our institute. Furthermore, PIL occurred predominantly in males with median age at diagnosis was 44 years which is in concordance with other studies. B-cell NHL is the most common histological subtype seen (90.9%). As observed in other studies, ileocecal junction is the most common site involved. However, higher proportion of patients (40%) are presented with subacute/acute intestinal obstruction requiring surgical resection.

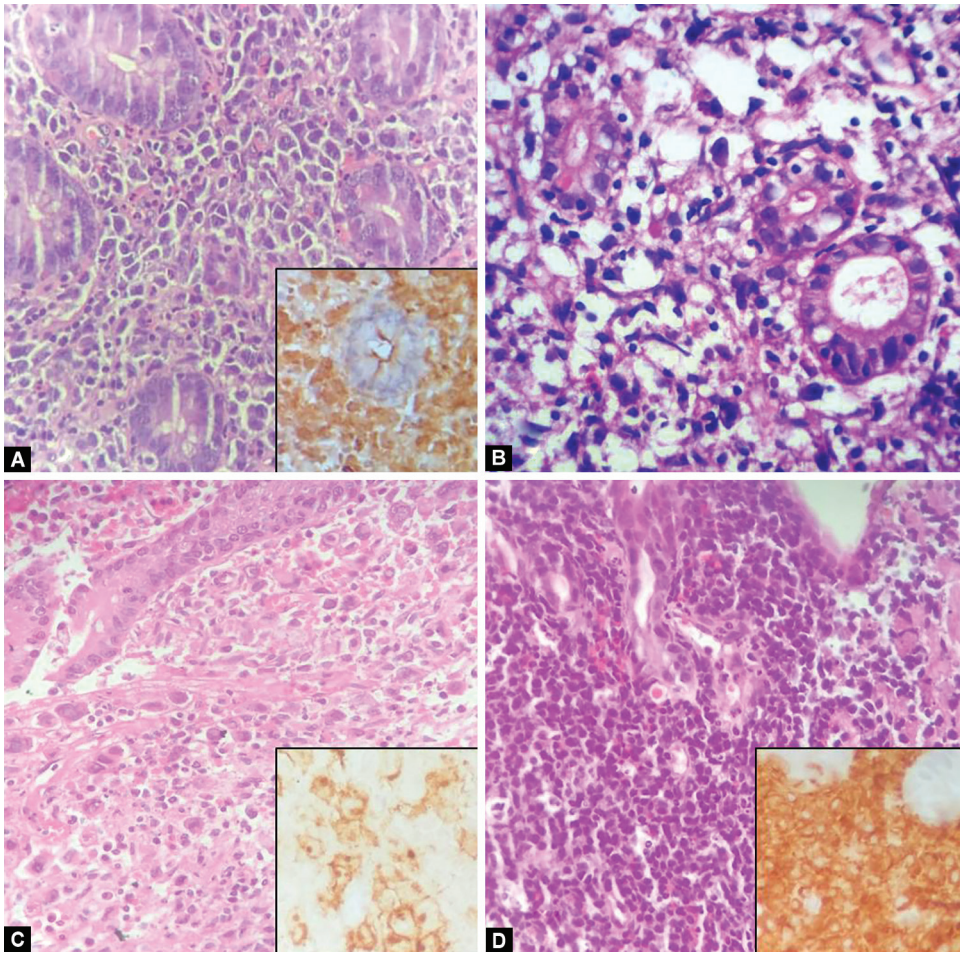
The PIL was seen predominantly in males (M:F of 5.8:1) as observed in other studies.[6,15,16] The age of onset of PIL varied from 45–70 years in the published studies. However, median age at diagnosis in our study was 44 years, which was one decade earlier as compared to the presentation of primary gastric lymphoma as reported by us in the previous studies and in concordance with other studies.[15,17]

The main presenting symptoms of PIL vary from abdominal pain, weight loss, and GI bleeding to intestinal obstruction/perforation requiring surgery. The B symptoms such as fever, weight loss, and night sweat were seen in 18–52% of patients.[18,19]

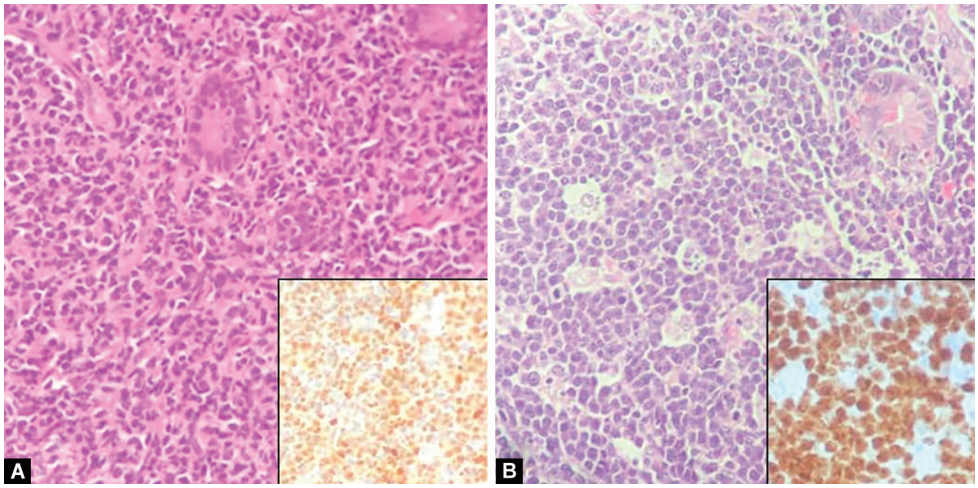
In our study, 40% of patients, presented with acute/subacute intestinal obstruction and 7% with intestinal perforation requiring surgical resection which was bit more in comparison with the previously published studies which could be due to late presentation.[18,20] Abdominal pain was present in 32% and B symptoms in 36% of the patients.

Ileum and ileocecal regions are commonly involved in PIL (6.9–37.1%) probably due to high density of lymphoid tissue in these areas.[21–24] Ileocecal region was the most common site involved in our study accounting for 27% of the cases followed by duodenum and colon 25% each and the rest in ileum, jejunum, and multiple sites. Majority of the patients who underwent surgery are those where ileum and ileocecal regions were involved. Multiple, noncontagious sites (stomach, small bowel, and colon) were involved in three patients, two with mantle cell lymphoma and one Burkitt lymphoma.

Majority of the GI lymphoma including PIL are NHL of B-cell lineage.[15,25] DLBCL and MALT lymphoma were the most common histological subtype (78%) seen as reported in other studies (Figs 2A and B).[6,22,26] Primary intestinal Hodgkin's lymphoma is rare, reported only in the form of case reports and small series.[27,28] However, two patients with primary intestinal Hodgkin's lymphoma involving jejunum and descending colon were seen in our study (Fig. 2C). Enteropathy-associated T-cell



Figs 2A to D: (A) DLBCL—Germinal center type: Sections from mucosal biopsy of ileocecal lesion/wall thickening showing diffuse sheets of medium-to-large monotonous lymphoid cells and CD10 positive (inset), ×400; (B) MALT lymphoma: lymphoepithelial lesions involving the intestinal crypts and intervening monocytoid cells with ample pale cytoplasm, ×400; (C) Classical Hodgkin's lymphoma: Sections from resected small intestine stricture showing mononuclear and multinucleated Reed–Sternberg cells in a reactive background and are CD15 immunostain membrane positive (inset), ×400; (D) T-cell-NHL: Sections from mucosal biopsy of duodenal ampullary lesion showing diffuse sheets of medium-sized atypical lymphoid cells with scant necrosis and are CD3 positive (inset), ×400



Figs 3A and B: (A) Mantle cell lymphoma: Sections from mucosal biopsy of colonic mass showing diffuse sheets of medium-sized monotonous atypical lymphoid cells that are cyclin D1 positive nuclear immunostain (inset), ×400; (B) Burkitt lymphoma: Sections from resected segment of jejunum with intussusception and polyps showing medium-to-large monotonous lymphoid cells with interspersed tingible body macrophages giving a starry sky pattern and high ki-67 proliferative index of 90% (inset), ×400

lymphoma (EATL) is a distinct type of intestinal lymphoma that occurs in refractory/untreated celiac disease, which is reported from the places where celiac disease is common.[29] However, we did not find single patient with EATL as celiac disease is uncommon in South India. Non-EATL was seen in three patients involving duodenum and ileum (Fig. 2D). Mantle cell lymphoma is a subtype of B-cell NHL that can present as PIL, commonly involves the colon although entire GI tract can be involved.[30,31] Lymphomatous polyposis is the characteristic endoscopic appearance.[30] Mantle cell lymphoma was seen in three patients, involving entire GI tract in two and ileocecal junctions in another patient (Fig. 3A). Characteristic endoscopic appearance of lymphomatous polyposis was seen in all three patients. Burkitt lymphoma is an aggressive B-cell NHL that is present in three distinct forms: endemic, sporadic, and immunodeficiency-related. Burkitt lymphoma of the GI tract commonly is seen in children and young adults and often involves the ileum and ileocecal regions.[32] Burkitt lymphoma was seen in three patients involving multiple segments of GI tract in one and ileum and ileocecal regions in the other two, respectively (Fig. 3B). The HIV infection increases the risk of developing NHL by 60–200-folds.[33,34] However, with the availability of highly active antiretroviral therapy (HAART) for HIV infection, the risk of developing lymphoma has reduced significantly.[35,36] GI tract is involved in 30–50% of the HIV-associated extranodal NHL and usually of high-grade B-cell histology with involvement of multiple sites in the GI tract.[37] Overall, eight patients with PIL had associated HIV infection in our study. Patients with HIV infection were younger (median age 35 years) and had extensive involvement of GI tract as compared to patients without HIV infection.

In conclusion, our study demonstrates the pattern of distribution and various histological subtypes of PIL including the rare variants like primary intestinal Hodgkin's lymphoma. We did not encounter patients with IPSID and EATL in our study. Relatively more number of patients presented with intestinal obstruction/perforation requiring surgery in comparison with other studies.

References

1. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 1992;52(19):5432s–5440s.
2. Zheng T, Mayne ST, Boyle P, et al. Epidemiology of non-Hodgkin's lymphoma in Connecticut. Cancer 1992;70(4):840–849. DOI: 10.1002/1097-0142(19920815)70:4<840::aid-cncr2820700420>3.0.co;2-i.
3. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29(1):252–260. DOI: 10.1002/1097-0142(197201)29:1<252::aid-cncr2820290138>3.0.co;2-#.
4. Herrmann R, Panahon AM, Barcos MP, et al. Gastrointestinal involvement in non-Hodgkin's lymphoma. Cancer 1980;46(1):215–222. DOI: 10.1002/1097-0142(19800701)46:1<215::aid-cncr2820460136>3.0.co;2-6.
5. Bautista-Quach MA, Ake CD, Chen M, et al. Gastrointestinal lymphomas: morphology, immunophenotype and molecular features. J Gastrointest Oncol 2012;3(3):209–225. DOI: 10.3978/j.issn.2078-6891.2012.024.
6. Koch P, del Valle F, Berdel WE, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol 2001;19(18):3861–3873. DOI: 10.1200/JCO.2001.19.18.3861.
7. Gurney KA, Cartwright RA, Gilman EA. Descriptive epidemiology of gastrointestinal non-Hodgkin's lymphoma in a population-based registry. Br J Cancer 1999;79(11–12):1929–1934. DOI: 10.1038/sj.bjc.6690307.
8. Warrick J, Luo J, Robirds D, et al. Gastrointestinal lymphomas in a North American population: clinicopathologic features from one major Central-Midwestern United States tertiary medical center. Diagn Pathol 2012;7:76. DOI: 10.1186/1746-1596-7-76.
9. Papaxoinis G, Papageorgiou S, Rontogianni D, et al. Primary gastrointestinal non-Hodgkin's lymphoma: a clinicopathologic study of 128 cases in Greece. A Hellenic Cooperative Oncology Group study (HeCOG). Leuk Lymphoma 2006;47(10):2140. DOI: 10.1080/10428190600709226.
10. Salem P, El-Hashimi L, Anaissie E, et al. Primary small intestinal lymphoma in adults – a comparative study of IPSID versus non-IPSID in the Middle East. Cancer 1987;59(9):1670–1676. DOI: 10.1002/1097-0142(19870501)59:9<1670::aid-cncr2820590925>3.0.co;2-d.

11. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. Blood 2005;105(6):2274–2280. DOI: 10.1182/blood-2004-07-2755.
12. Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. Cancer 1978;42(2):693–707. DOI: 10.1002/1097-0142(197808)42:2<693::aid-cncr2820420241>3.0.co;2-j.
13. Musshoff K, Schmidt-Vollmer H. Prognosis of non-Hodgkin's lymphomas with special emphasis on the staging classification. ZKrebsforsch Klin Onkol Cancer Res Clin Oncol 1975;83(4):323–341. DOI: 10.1007/BF00573019.
14. Swerdlow SH, Campo E, Harris NL, et al. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon, France: IARC; 2017.
15. Amer MH, ei-Akkad S. Gastrointestinal lymphoma in adults: clinical features and management of 300 cases. Gastroenterology 1994;106(4):846–858. DOI: 10.1016/0016-5085(94)90742-0.
16. Chandran R, Hemanth R, Harit KC. Primary gastrointestinal lymphoma: 30 years experience at the Cancer Institute, Madras, India. J Surg Oncol 1995;60(1):41–49. DOI: 10.1002/jso.2930600109.
17. Malipatel R, Patil M, Pritilata Rout P, et al. Primary gastric lymphoma: clinicopathological profile. Eurosian J Hepatogastroenterol 2018;8(1):6–10. DOI: 10.5005/jp-journals-10018-1250.
18. Raina V, Sharma A, Vora A, et al. Primary gastrointestinal non-Hodgkin's lymphoma chemotherapy alone an effective treatment modality: experience from a single centre in India. Indian J Cancer 2006;43(1):30–35. DOI: 10.4103/0019-509x.25773.
19. Morgan DR, Holgate CS, Dixon MF, et al. Primary small intestinal lymphoma: a study of 39 cases. J Pathol 1985;147(3):211–221. DOI: 10.1002/path.1711470309.
20. Kim SJ, Choi CW, Mun YC, et al. Multicenter retrospective analysis of 581 patients with primary intestinal non-Hodgkin lymphoma from the Consortium for Improving Survival of Lymphoma (CISL). BMC Cancer 2011;11:321. DOI: 10.1186/1471-2407-11-321.
21. Sweetenham JW, Mead GM, Wright DH, et al. Involvement of the ileocecal region by non-Hodgkin's lymphoma in adults: clinical features and results of treatment. Br J Cancer 1989;60(3):366–369. DOI: 10.1038/bjc.1989.286.
22. Kohno S, Ohshima K, Yoneda S, et al. Clinicopathological analysis of 143 primary malignant lymphomas in the small and large intestines based on the new WHO classification. Histopathology 2003;43(2):135–143. DOI: 10.1046/j.1365-2559.2003.01659.x.
23. Wang SL, Liao ZX, Liu XF, et al. Primary early-stage intestinal and colonic non-Hodgkin's lymphoma: clinical features, management, and outcome of 37 patients. World J Gastroenterol. 2005 Oct 7;11(37):5905–5909. DOI: 10.3748/wjg.v11.i37.5905.
24. Wang GB, Xu GL, Luo GY, et al. Primary intestinal non-Hodgkin's lymphoma: a clinicopathologic analysis of 81 patients. World J Gastroenterol 2011; 17:4625–4631. DOI: 10.3748/wjg.v17.i41.4625.
25. Nakamura S, Matsumoto T, Iida M, et al. Primary gastrointestinal lymphoma in Japan: a clinicopathologic analysis of 455 patients with special reference to its time trends. Cancer 2003;97(10):2462–2473. DOI: 10.1002/cncr.11415.
26. Nakamura S, Matsumoto T, Takeshita M, et al. Clinicopathologic study of primary small intestine lymphoma: prognostic significance of mucosa-associated lymphoid tissue-derived lymphoma. Cancer 2000;88(2):286–294. DOI: 10.1002/(sici)1097-0142(20000115)88:2<286::aid-cncr7>3.0.co;2-z.
27. Sharma S, Rana S, Kapur S, et al. Primary intestinal Hodgkin's lymphoma: an uncommon presentation. J Lab Physicians 2012;5(2):124–126. DOI: 10.4103/0974-2727.119866.
28. Morgan PB, Kessel IL, Xiao SY, et al. Uncommon presentations of Hodgkin's disease. Case 1. Hodgkin's disease of the jejunum. J Clin Oncol 2004;22(1):193–195. DOI: 10.1200/JCO.2004.04.072.
29. Delabie J, Holte H, Vose JM, et al. Enteropathy associated T-cell lymphoma: Clinical and histological findings from the international peripheral T- cell lymphoma project. Blood 2011;118(1):148–155. DOI: 10.1182/blood-2011-02-335216.
30. Lee HH, Cho SG, Lee IS, et al. Mantle cell lymphoma with gastrointestinal involvement and the role of endoscopic examinations. PLoS One 2020;15(9):e0239740. DOI: 10.1371/journal.pone.0239740.
31. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer 2003;97(3):586–591. DOI: 10.1002/cncr.11096.
32. Ferry JA. Burkitt lymphoma: clinicopathological features and differential diagnosis. Oncologist 2006;11(4):375–383. DOI: 10.1634/theoncologist.11-4-375.
33. Rabkin C. Epidemiology of AIDS related malignancies. Curr Opin Oncol 1994;6(5):492–496. DOI: 10.1097/00001622-199409000-00008.
34. Berel V, Peterman T, Berkelman R, et al. AIDS associated non-Hodgkin's lymphoma. Lancet 1991;33;7(8745):805–809. DOI: 10.1016/0140-6736(91)92513-2.
35. Clarke C. Changing incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among young men in San Francisco. AIDS 2001;15(14):1913–1915. DOI: 10.1097/00002030-200109280-00035.
36. Appleby P, Beral V, Newton R, et al. Highly active antiretroviral therapy and the incidence of cancer in human immunodeficiency virus-infected adults. J Natl Cancer Inst 2000;92(22):1823–1830. DOI: 10.1093/jnci/92.22.1823.
37. Heise W. GI-lymphomas in immunosuppressed patients. Best Pract Res Clin Gastroenterol 2010;24(1):57–69. DOI: 10.1016/j.bpg.2010.01.001.