ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 8, 2023

Online - 2455-3891
Print - 0974-2441

Case Series

DIAGNOSTIC PITFALLS IN THE INTERPRETATION OF EXTRANODAL LYMPHOMAS – A CASE SERIES

RONALD J BOSCO*, JEEVARAJ GIRIDHARAN, VIVITHA V

Deaprtment of Pathology, Srinivasan Medical College and Hospital, Samayapuram, Trichy, Tamil Nadu, India.
***Corresponding author: Ronald J Bosco; Email: ronaldaswathy@gmail.com**

Received: 05 May 2023, Revised and Accepted: 24 June 2023

ABSTRACT

Extranodal non-Hodgkin's lymphoma (ENNHL) by definition affects any organ or tissue excluding lymph node and spleen. Histopathological examination is the investigation of choice that further helps in deciding the advanced diagnostic panel of the immunohistochemistry (IHC) and molecular studies. Histopathological evaluation as such is not straight forward, since there is high probabilty of misdiagnosis and diagnostic pitfalls due to inadequate material, sampling and processing errors, inadequate clinical information, personal subjectivity of clinicians and pathologists, and IHC-related errors. This case series is reported at a tertiary care hospital. Total three cases of ENNHL are reported, where the process of diagnosis went through few pitfalls before the ultimate diagnosis was made. The first case was a jejunal mass clinically diagnosed as carcinoma, histopathologically found to be extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue transforming to diffuse large B-cell lymphoma in the mesenteric lymph node. Second case describes misinterpretation of small lymphocytic lymphoma as adenocarcinoma deposit in liver by clinical and radiological evaluation. Third case describes follicular dendritic cells of spleen where the first two biopsies showed chronic lymphocytic gastritis and reactive lymphadenitis and finally the third from spleen confirmed the diagnosis. The diagnosis of ENNHL in biopsies requires clinicopathological suspicion with discussion and repeat biopsies if inconclusive. Pathologist should be aware of the gross and microscopic features indicating high-grade NHL transformation in surgical specimens. During the initial clinical evaluation and follow-up of low-grade ENNHL, positron emission tomography scan findings can be used, to effectively target biopsy from areas or regional lymph nodes suspicious of high-grade transformation.

Keywords: Extranodal lymphoma, Non-Hodgkin lymphoma, High-grade transformation, Pitfalls of extranodal lymphoma.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i8.48596. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Lymphoma can be nodal or extranodal. Extranodal lymphomas are mainly of non-Hodgkin's type. The current WHO classification describes more than 40 different entities of lymphomas [1]. Diagnostic pitfalls in extranodal non-Hodgkin's lymphoma (ENNHL) are commonly due to inadequate material, sampling and processing errors, inadequate clinical information, personal subjectivity of clinicians and pathologists, and immunohistochemistry (IHC)-related errors [2]. Even with the advent of advanced IHC and molecular studies, histopathological examination remains the primary investigation that helps in deciding the IHC diagnostic panel. Histopathology as such is not free from diagnostic pitfalls. Some of the misdiagnosis and difficulties/diagnostic pitfalls faced by the pathologists during the initial histopathological evaluation in arriving at a preliminary diagnosis are discussed in this study.

CASE REPORTS

Case 1

A 51-year-old female presented with vague abdominal symptoms and loss of weight. Computed tomography (CT) scan showed ill-defined ulceroproliferative jejunal mass along with multiple enlarged lymph nodes, suggestive of adenocarcinoma. Biopsy was reported as chronic inflammatory changes and advised for repeat representative biopsy, which was not done. Resection of jejunum followed, which on histopathology and IHC, was confirmed as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). Surprisingly mesenteric lymph node showed high-grade features with IHC revealing transformation to diffuse large B-cell lymphoma (DLBCL) (Fig. 1).

Case 2

A 58-year-old male presented with vague abdominal symptoms. Positron emission tomography (PET) scan revealed hypermetabolic mass completely encasing the gall bladder with infiltration of liver, pylorus, omentum, and multiple lymphnodes, suggestive of a locally advanced gall bladder malignancy. Biopsies from liver reported elsewhere were reported as metastatic adenocarcinoma, probably from gallbladder and planned for chemotherapy. A week later, the patient presented with enlarged axillary lymph node, which on histopathological examination and IHC studies revealed small lymphocytic lymphoma (SLL). The liver biopsy was again reviewed with the help of IHC, which showed monotonous lymphoid infiltrate and reactive biliary ductular proliferation. This confirmed that the primary diagnosis was extra nodal SLL in liver and gallbladder rather than adenocarcinoma (Fig. 2).

Case 3

A 37-year-old male presented with abdominal symptoms and loss of weight. CT and PET scan revealed nodular thickening of gastric mucosa, multiple lymphadenopathy, pleural effusion with pancreatic, and splenic nodules, suggestive of gastric adenocarcinoma/lymphoma. Gastric biopsy followed, which showed chronic lymphocytic gastritis. Two weeks later, patient developed axillary lymphadenopathy and biopsy revealed follicular hyperplasia. With no definitive diagnosis attained, finally splenic core biopsy was done. Histopathology and IHC revealed follicular dendritic cell sarcoma (Fig. 3).

DISCUSSION

ENNHL by definition affects any organ or tissue excluding lymph node and spleen. The symptoms should be specific pertaining to the extranodal site and be the dominant lesion during staging [3]. Dawson's 5-point criteria define primary gastrointestinal lymphoma [4]. GIT is the most common site for ENNHL, with stomach followed by intestine as the most common sites. DLBCL and MZL of MALT are the most common high-grade and low-grade type, respectively [3,4]. The diagnosis of ENNHL usually has a high probability of misdiagnosis and diagnostic pitfalls both to the clinicians and pathologists.

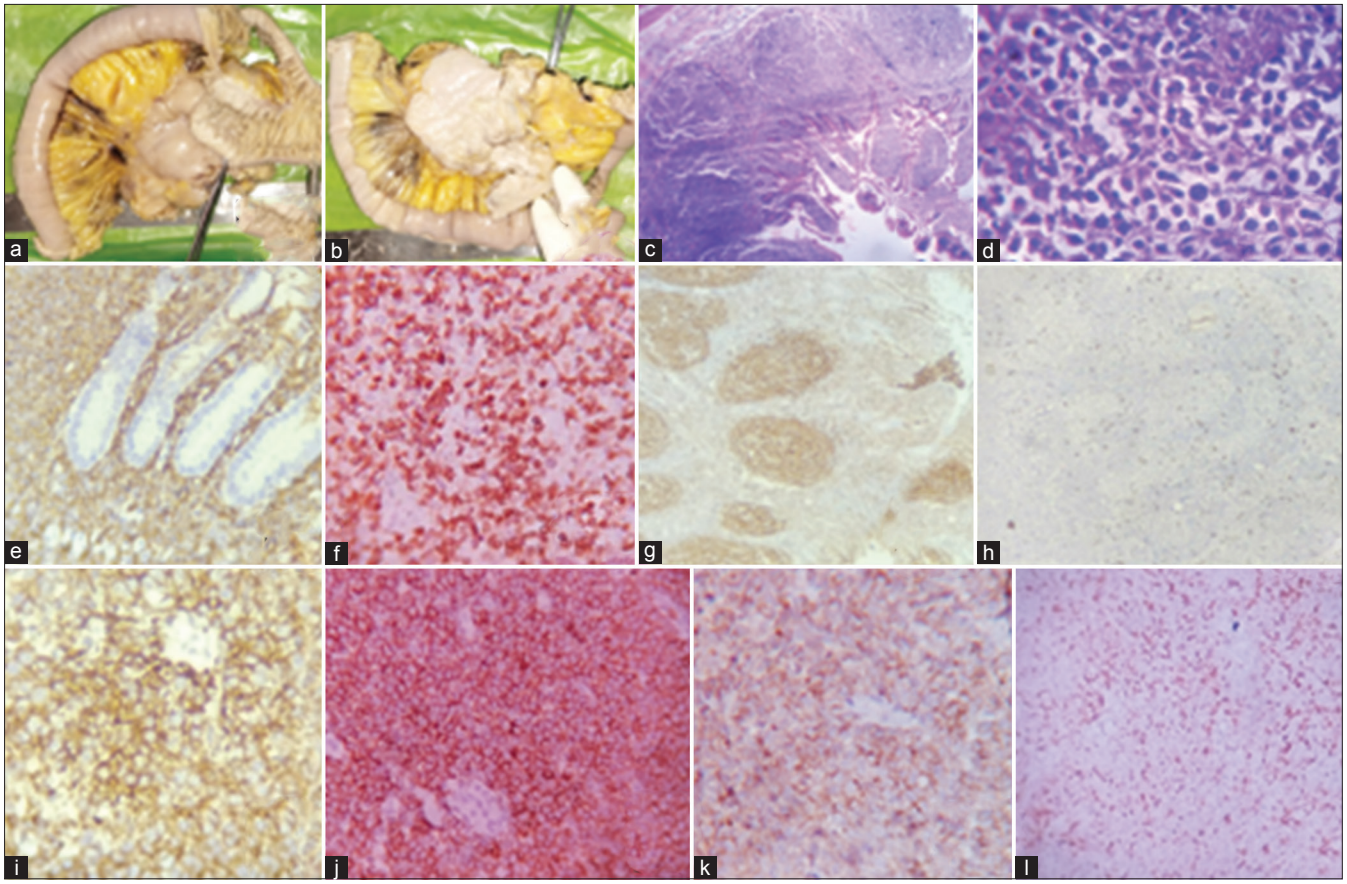

Fig. 1: Case 1 - (a) Grossly, dilated segment with thickened bowel wall measuring 4 cm with nodular cut surface. (b) A grey-white mass noted in the mesentery measuring 7×5 cm. (c) Transmural atypical lymphoid infiltrates composed of centrocyte like cells, centroblasts, and monocytoid B cells. (d) Mesenteric mass composed of diffuse large sized atypical lymphoid cells with vesicular chromatin and prominent nucleoli. (e) Intestinal lesion – CD20 diffuse positive, (f) BCL2 positive, (g) CD21 showed residual dendritic meshwork, and (h) Ki67 index – 10%. CD5, CD23, CD10, Cyclin D1, BCL6-negative (not shown in figure). (i) IHC of the mesenteric mass shows – CD45 positive, (j) CD20 diffuse positivity, (k) CD10 positive, and (l) Ki67 index 90%

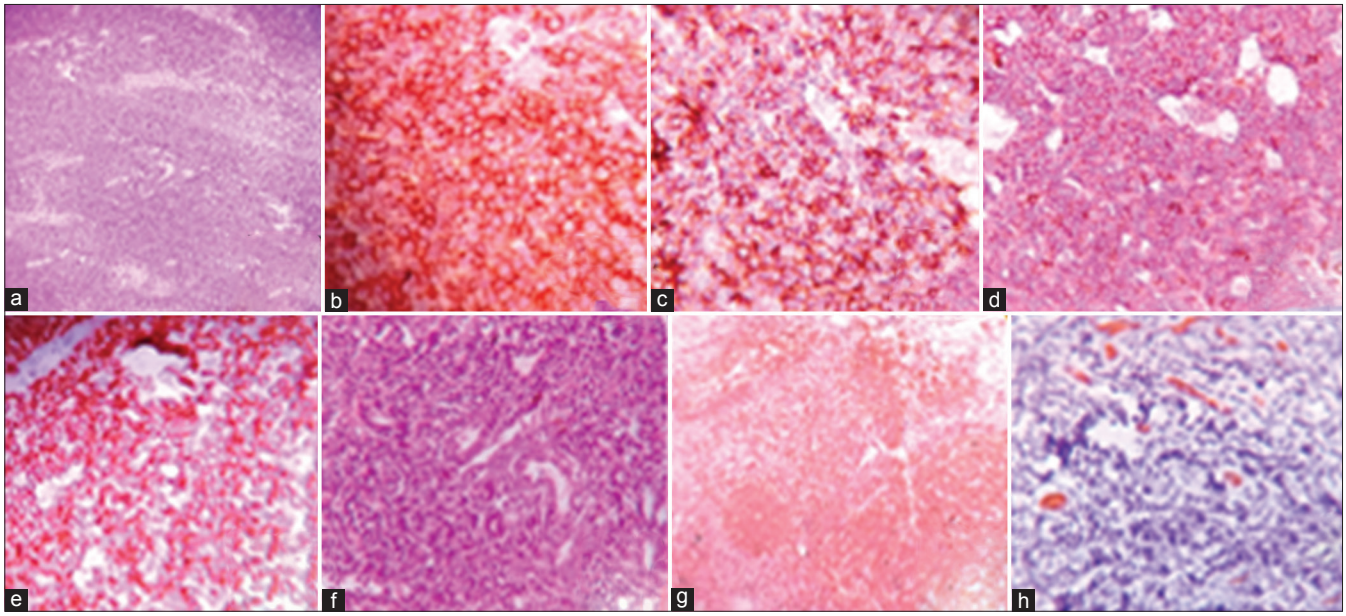

Fig. 2: Case 2 - (a) Axillary lymph node showing monotonous diffuse infiltration of small sized lymphocytes. (b) Axillary lymph node shows – CD20 positive, (c) CD23 positive, (d) CD5 positive, (e) BCL2 positive. CD10, Cyclin D, Bcl6-negative (not shown in the figure). (f) Liver biopsy showed monotonous lymphocytes and few reactive ductular proliferation. (g) Monotonous CD20 positive lymphoid cells in liver. (h) The scant reactive ductular population showed CK7 positive

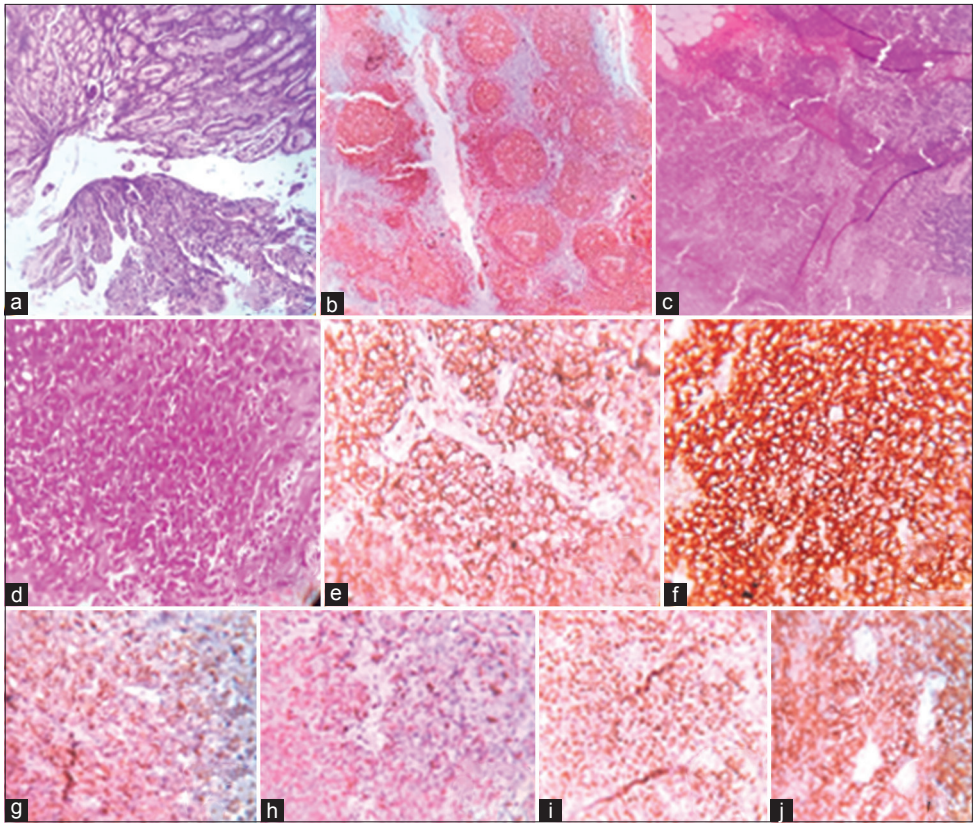

Fig. 3: Case 3 - (a) Gastric biopsy showed ulceration, mucosal atrophy, reactive follicles, and dense lymphoplasmacytic infiltration in the lamina propria. (b) CD20 in gastric biopsy showing reactive follicles. (c) Axillary lymph node shows follicular hyperplasia. (d) Splenic biopsy showing sheets of oval to spindled cells. (e) Splenic biopsy shows CD45 positive, (f) CD20 positive, (g) CD10 positive, (h) BCL2 positive, (i) BCL6 positive, and (j) CD21 positive. MUM1, CD15, and CD30 – negative (not shown in the figure)

ENNHL patients usually are asymptomatic, do not have B symptoms, or may present with vague GI symptoms [4] Endoscopy also mostly shows non-specific findings such as gastritis and ulcer, few may show ulceroproliferative and nodular lesions similar to carcinoma [3,4]. Under these circumstances, usually, the clinicians do not consider the possibility of lymphoma, and even if any features of malignancy were observed, they usually point toward an epithelial malignancy, thereby needing histopathology for a definitive opinion. With no clinical suspicion of lymphoma, sometimes not even suspicious of malignancy due to non-specific findings on endoscopy, the pathologist may get an impression of non-specific inflammation due to the low grade and mature looking lymphoid cells on biopsy. The architecture also could not be assessed in small biopsies and is not easy as seen in a nodal NHL. Unless the pathologist is aware enough about the possibility of lymphoma and proceeds with IHC, the diagnosis would be missed. In this scenario, many GI lymphomas are subjected to surgical management on the assumption of carcinoma only to be diagnosed incidentally as lymphoma [4].

In our study, Case 1 was a low-grade ENNHL with nodal high-grade transformation presenting as ulceroproliferative jejunal mass, misdiagnosed as adenocarcinoma, and surgically treated without repeating the previous inconclusive biopsy. This insists the importance of keeping low-grade ENNHL in differential diagnosis and also substantiates the opinion of repeat endoscopy biopsy if the findings are inconclusive [4]. Few indicators for high-grade transformation are high LDH, B symptoms, rapidly enlarging regional lymph node and PET scan that can pick high-grade lesions specifically [3,5-7]. FL is more prone for high-grade transformation to DLBCL [5,7]. Frequent follow-up endoscopy and biopsy with histopathological evaluation using the criteria for high-grade transformation should be done in all cases of low-grade ENNHL [3,6].

Case 2 was a SLL in gall bladder infiltrating into adjacent liver and later to lymphnodes, misdiagnosed as adenocarcinoma secondary deposits, due to the reactive ductular proliferation, and small mature lymphocytes resembling inflammation on liver biopsy. Diagnosis could be made only when axillary lymphnode was involved later. Misdiagnosis of ENNHL as adenocarcinoma is frequently reported [8]. In biopsies for malignancy, if the histopathology shows lymphoid infiltrate, pathologist should carefully look for features like lymphoepithelial lesion and consider the possibility of low-grade ENNHL, which must be evaluated by IHC [3].

Case 3, though clinically suspicious of NHL, proved to be follicular dendritic cells of spleenonly on the third biopsy after previous two biopsies showed chronic gastritis and reactive lymphadenitis. This insists the importance of selecting the appropriate site for biopsy using PET scan findings and doing repeat biopsy in evaluating cases suspicious of ENNHL. This is because reactive hyperplasia and paraneoplastic syndromes like autoimmune processes are common in NHL including dendritic cell neoplasm [9,10].

CONCLUSION

The diagnosis of ENNHL in biopsies requires clinicopathological suspicion with discussion, and repeat biopsies if inconclusive. There is an inclination for clinicians and pathologists toward adenocarcinoma in diagnosing malignant lesions of GIT. Pathologists should also be aware of the gross and microscopic features that indicate high-grade NHL transformation in surgical specimens. During the initial clinical evaluation and follow-up of low-grade ENNHL, PET scan findings should be used, to effectively target biopsy from areas or regional lymphnodes suspicious of high-grade transformation.

ACKNOWLEDGMENT

The authors are thankful to the Department of Pathology and Institutional ethical committee for the approval to conduct the study at

Srinivasan Medical College and Hospital, Samayapuram, Trichy, Tamil Nadu, India.

AUTHORS' CONTRIBUTION

Conceptualization, drafting - Ronald J Bosco, Jeevaraj Giridharan. Editing- Vivitha V

CONFLICTS OF INTEREST

Nil.

SOURCE OF FUNDING

Self.

ETHICAL COMMITTEE CLEARANCE

Obtained.

REFERENCES

1. Alaggio R, Amador C, Anagnostopoulos L, Attygalle AD, Araujo IB, Berti E, *et al*. The 5th edition of the World Health Organization Classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-48.
2. Li X. Pitfalls in the pathological diagnosis of lymphoma. Chin Clin Oncol 2015;4:3. doi: 10.3978/j.issn.2304-3865.2014.11.04. PMID: 25841710
3. Psyrri A, Papageorgiou S, Economopoulos T. Primary extranodal lymphomas of stomach: Clinical presentation, diagnostic pitfalls and management. Ann Oncol 2008;19:1992-9. doi: 10.1093/annonc/mdn525. PMID: 18647965; PMCID: PMC2733120
4. Bayramov R, Abdullayeva R. Primary gastrointestinal lymphoma. In: Lymphoma. London: IntechOpen; 2022. Available from: http://dx.doi.org/10.5772/intechopen.101424
5. Conconi A, Franceschetti S, von Hohenstaufen KA, Margiotta-Casaluci G, Stathis A, Moccia AA, *et al*. Histologic transformation in marginal zone lymphomas. Ann Oncol 2015;26:2329-35. doi: 10.1093/annonc/mdv368. PMID: 26400898
6. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, *et al*. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:17-29. doi: 10.1016/j.annonc.2019.10.010. Erratum in: Ann Oncol 2023;34:325. PMID: 31912792
7. Gbadamosi B, Pang Y, Ezekwudo D, Macari D, Khoury J, Konde A, *et al*. Clinical characteristics, treatment pattern and outcome of histologic transformed lymphoma, a single institution experience. J Cancer Sci Clin Ther 2019;3:114-30.
8. Ding D, Pei W, Chen W, Zuo Y, Ren S. Analysis of clinical characteristics, diagnosis, treatment and prognosis of 46 patients with primary gastrointestinal non-Hodgkin lymphoma. Mol Clin Oncol 2014;2:259-64. doi: 10.3892/mco.2013.224. PMID: 24649343; PMCID: PMC3917777
9. Su Z, Liu G, Liu J, Fang T, Zeng Y, Zhang H, *et al*. Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma: Report of a case and review of literature. Int J Clin Exp Pathol 2015;8:11983-94. PMID: 26722384; PMCID: PMC4680329
10. Walters M, Pittelkow MR, Hasserjian RP, Harris NL, Macon WR, Kurtin PJ, *et al*. Follicular dendritic cell sarcoma with indolent T-lymphoblastic proliferation is associated with paraneoplastic autoimmune multiorgan syndrome. Am J Surg Pathol 2018;42:1647-52. doi: 10.1097/PAS.0000000000001158. PMID: 30222603