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 straightforward, since there is a high probability 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 the 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 clinicalopathological 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.

Case 1
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 2
A 37-year-old male presented with 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 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 monocyteid 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 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
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 histology for a definitive opinion. With no clinical suspicion of lymphoma, sometimes 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 repeated 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 lymph node 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 spleen only 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.

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