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Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Original Research Article

Diagnostic evaluation of microscopic enteritis in duodenal biopsies of suspected malabsorption cases with clinico-immunohistological correlation

Ritika Gupta[1], Sarojini Raman[1,*], Bipad Bhanjan Mallick[2], Urmila Senapati[1]

[1]*Dept. of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India*
[2]*Dept. of Gastroenterology, Kalinga Institute of Medical Sciences & PBMH, Bhubaneswar, Odisha, India*

ARTICLE INFO

Article history:
Received 01-10-2021
Accepted 04-11-2021
Available online 14-02-2022

Keywords:
Biopsy
Intestinal mucosa
Intraepithelial lymphocytes
Malabsorption syndromes

ABSTRACT

Background: Microscopic Enteritis (ME) is characterized by increase in intraepithelial lymphocytes (IEL) in intestinal mucosa. It represents a common feature of broad group of diseases including gluten mediated and non gluten related diseases. Duodenal biopsies play an important role in diagnosing these group of disorders.
Aim: To compare IEL counts in Hematoxylin and eosin (H & E) stain and CD3 immunohistochemical (IHC) stain in duodenal biopsies of suspected malabsorption cases and compare them with clinical, immunological and biochemical parameters.
Setting & Design: This was a prospective study of two years.
Materials and Methods: 164 patients were studied. IEL counted at villous tip and base in H&E sections and IHC were compared in duodenal biopsy. Data of clinical history, other parameters were collected and correlated whenever available.
Statistical Analysis: To compare any two variables, Chi - square test and independent T test was used. Statistical significance was defined as $p < 0.05$.
Results: Out of 164 cases,105 cases had increased IEL. The age range was 4 to 94 years with mean age of 43.29 ± 17.96 years. Males (56, 53.3%) were affected more than females (49, 46.6%). The clinical and histological parameters showing statistical significance with raised IEL were pallor, dyspepsia, loss of appetite, crypt architecture, blunting, ulcer, villous crypt ratio, exudates, reactive atypia and edema with P< 0.05. IEL at villous tip in CD3 had highest sensitivity (100%) and specificity (92.20%) in our study.
Conclusion: ME should be investigated and diagnosed in correlation with a detail clinical history, complete haematological, biochemical and serological findings.

1. Introduction

Microscopic enteritis (ME) is a multifactorial inflammatory process including a broad group of diseases. It is characterised by microscopic and submicroscopic changes in intestinal mucosa associated with malabsorption syndromes.[1,2] Raised intraepithelial lymphocytes (IELs) is considered to be one of the sensitive histopathological indicator of ME according to Bucharest concensus 2015.[1–4] In evaluation of biopsies, immunohistochemical (IHC) marker like CD3 is very useful for highlighting the IELs. Correlating these histopathological features with clinicoserological parameters is helpful not only in arriving at a specific diagnosis, also helps in further work up of patients, avoiding the mimickers of ME.[4]

* *Corresponding author*.
E-mail address: sraman10371@gmail.com (S. Raman).

https://doi.org/10.18231/j.ijpo.2022.002

2. Aim & Objectives

To compare IEL counts in Hematoxylin and eosin (H & E) stain and CD3 immunohistochemical (IHC) stain in duodenal biopsies of suspected malabsorption cases and compare them with other clinical, histological, immunological and biochemical parameters.

3. Materials and Methods

The present study was conducted in the Department of Pathology of our institute from September 2018 to August 2020. During the period, patients who presented to medical gastroenterology outpatient with complaints of malabsorption like chronic diarrhea, dyspepsia, fever, vomiting, loss of appetite, nutritional deficiencies (iron, folate, vitamin D) etc underwent subsequent endoscopic biopsy. Endoscopic doudenal biopsies of various non neoplastic aetiologies were included in this study. Polyps, neoplastic conditions, inadequate biopsies, unoriented tissues and tissue sections lost during processing were excluded. Multiple filter paper mounted duodenal specimens fixed in 10% buffered formalin were embedded in paraffin blocks. 4-5μm thick sections were cut and stained with hematoxylin and eosin stain.

The different histological parameters studied in the biopsies were number and site of biopsy fragments, villous and crypt architecture, degree and types of inflammatory cells in lamina propria, IEL count, presence or absence of surface ulceration, exudate, reactive atypia, cryptitis, crypt abscess, lymphoid aggregates or granuloma, any microorganisms like parasite (strongyloides, giadia), tuberculosis etc. Special stains like PAS(periodic Schiff), ZN (ziel-neelsen) were used when needed. IELs were counted from five consequetive villous tips and bases of villi (total 100 enterocytes with 20 enterocytes at each villous tip or base). The upper limit of normal range for IEL in villous tip was 20 IEL/100 enterocytes and at the base of villi it was 18 IEL/100 enterocytes.[5] IHC CD3 was done for all cases. The antibodies and chemicals were procured from Dako, Denmark (Rabbit Anti-CD3 Monoclonal Antibody (Clone EP41). Positive internal control was normal small intestinal tissue in resection specimens.[5] CD3 T lymphocytes take membranous positivity. Counting was done similar to H and E study. Other supportive tests were correlated whenever possible like complete blood count, serological antitissue transglutaminase (tTG) IgA, tTG IgG tests, liver function test, iron profile, vitamin B12, folate assay etc.

3.1. Statistical analysis

All the categorical variables were expressed as frequency and percentage whereas the quantitative variables with symmetrical distribution were expressed as mean ± SD. To compare any two categorical variables, either Chi - square test or Fisher's exact test was used. To compare the quantitative variables, either independent T test or Wilcoxon Ranksum test was used based on the distribution of data. Statistical significance was defined as $p < 0.05$. All the analyses were carried out using standard statistical software Stata 18.0.

4. Results

Out of total 164 cases, 105 cases had increased IEL i.e Microscopic enteritis. In the rest of the cases IEL were within normal limit. The age range in the study group was 4 to 94 years with mean age of 43.29 ± 17.96. The maximum number of cases (39, 37.14%) belonged to age group of 21-40 years. Overall males (56, 53.3%) were affected more than females (49, 46.6%).

The most common presenting symptom with raised IEL cases was diarrhea in 41 (39.04%) cases. The clinical parameters showing statistical significance with raised IEL compared to normal IEL were pallor (P~ 0.001), dyspepsia (P~ 0.002) and loss of appetite (P~ 0.046). Fever had least correlation with raised IEL with (P~ 0.190) (Table 1).

Cases having raised IEL in duodenal mucosa revealed anemia in 30(28.57%) cases with Hb value ranging from 5 to 11gm/dl and a mean of 8.95 ± 1.32gm/dl. Hypoalbuminemia was present in 9 (8.57%) cases. Serology (anti-Ttg, IgA, IgG) was available in total 14 suspected cases of celiac disease out of which 11(10.47%) cases had increased value. Raised anti-Ttg was present in 7(0.50%) cases with a mean of 27.3±2.23 U/ml. Raised IgA noted in one case (443 mg/dl) and IgG level was raised in 3(21.4%) cases with a mean of 2024.66 ± 272.39 mg/dl. The serological tests were positive only in raised IEL cases (Table 2). Normal IEL had significant correlation with albumin (P ~0.003).

Out of 105 cases with raised IEL, 15(14.28%) cases had nodular appearance and 24 (22.85%) cases had ulcer. In H & E stain in villous tip 79 (48.17%) cases revealed raised IEL whereas in 100 (60.9%) cases IHC showed raised IEL. Thus IEL at villous tip in CD3 had highest sensitivity (100%), specificity (92.20%) in our study. IEL count in H & E and CD3 stain in base also revealed same finding (Table 3).

More than half of cases, 39.02% at tip and 50.31% at base did not show raised IEL in IHC even in presence of symptoms in patients. The orientation of duodenal mucosa was normal in 58 (57.43%) of raised IEL cases and is statistically significant.(p~0.026). Abnormal architecture was seen in 21(72.41%) cases and crypt hyperplasia seen in 13 (7.93%) cases with raised IEL. Eight cases of CD shows crypt hyperplasia (Figure 1 A). Blunting is seen in 28(80%) cases and (Figure 1 B,C) ulcer (granulation tissue) was found in 4 (28.57%) cases of raised IEL.(Figure 1 D).

Duodenal mucosa with normal villous to crypt ratio noted in 77 (59.69%) cases. Lamina propria inflammation was mild in 15(53.57%), moderate in 74(66.07%) and severe in 16(66.67%) of raised IEL cases. Plasma cells and

Table 1: Correlation of clinical parameters in cases showing ME and normal IEL in duodenal mucosa

Clinical parameters			ME	Normal IEL	P value
1.	Pallor	Present	24(92.31%)	2(7.69%)	**0.001**
		Absent	81(58.7%)	57(41.3%)	
2.	Diarrhoea	Present	41(73.21%)	15(26.79%)	0.077
		Absent	64(59.265%)	44(40.74%)	
3	Abdominal pain	Present	29(60.42%)	19(39.58%)	0.536
		Absent	76(65.52%)	40(34.48%)	
4	Loss of weight(LOW)	Present	19(55.88%)	15(44.12%)	0.267
		Absent	86(66.15%)	44(33.85%)	
5	Dyspepsia	Present	11(39.29%)	17(60.71%)	**0.002**
		Absent	94(70.77%)	42(29.23%)	
6	Loss of appetite (LOA)	Present	2(28.57%)	5(71.43%)	**0.046**
		Absent	103(65.61%)	54(34.39%)	
7	Fever	Present	3(100%)	0	0.190
		Absent	102(63.35%)	59(36.65%)	

Table 2: Correlation of laboratory parameters in cases showing raised IEL and normal IEL in duodenal mucosa

Laboratory Parameters			ME	Normal IEL	P value
1	Hb	Reduced	30(66.67%)	15(33.33%)	0.665
		Normal	75(63.03%)	44(36.97%)	
2	ESR	Raised	14(70%)	6(30%)	0.552
		Normal	91(63.19%)	53(36.81%)	
3	LFT	Raised	10(83.33%)	2(16.67%)	0.148
		Normal	95(62.5%)	57(37.5%)	
4	Albumin	Reduced	9(37.5%)	15(62.5%)	**0.003**
		Normal	96(68.57%)	44(31.43%)	
5	Nutrition Deficiency	Present	11(68.75%)	5(31.25%)	0.678
		Absent	94(63.75%)	54(36.49%)	
6	Anti Ttg, IgA, IgG	Raised	11(78.57%)	Not available	
		Normal	3(21.4%)	Not available	

Table 3: Cases with IEL count at villous tip & base in H & E and IHC, CD3

IEL	Tip	Tip	Base	Base
	H & E	CD3	H & E	CD3
Raised	79(48.17%)	100(60.9%)	58(35.58%)	81(49.69%)
Normal	85(51.83%)	64(39.02%)	105(64.4%)	82(50.31%)
Mean(±SD)	24±15.73	34.6±22.9	17±12.3	24.87±20.72
Sensitivity	97.50%	100%	98.30%	93.80%
Specificity	67.10%	92.20%	54.30%	64.60%
PPV	73.30%	95.20%	54.30%	72.40%
NPV	96.60%	100%	98.30%	91.40%

lymphocytes were the predominant cells in most of the cases along with few eosinophils and polymorphs in few cases. Eosinophils in excess in lamina propria were seen in strongyloides parasitic infection and eosinophilic enteritis. Exudate was a feature in 10(83.33%) cases without raised IEL. The parasite (larvae of Strongyloides and trophozoite of Giardiasis) were seen in 6(85.71%) cases with raised IEL. Reactive atypia was seen in lining epithelium of crypts in 7 (41.18%) cases with raised IEL and absent in 98(66.67%) cases with raised IEL. Crypt abscess was seen only in 5(100%) cases with raised IEL. Edema in lamina propria was seen in 29(70.73%) cases of duodenum along with raised IEL. Epithelioid granulomas along with caseous necrosis was seen in only 2(100%) cases one with ZN stain positive diagnosed as intestinal tuberculosis. The histomorphological parameters showing statistical significant correlation with raised IEL in comparison to normal IEL cases were crypt architecture(P~0.038), blunting(P~0.026), ulcer (P~0.004), villous crypt ratio(P~ 0.008), exudates (P~ 0.000), reactive atypia (P~ 0.038), edema (P~ 0.001)(Tables 4 and 5).

Out of 105 cases of raised IEL in 78(47.5%) cases no definite pathology could be identified except the increased count of IEL. Celiac disease were diagnosed in 11 (6.6%)

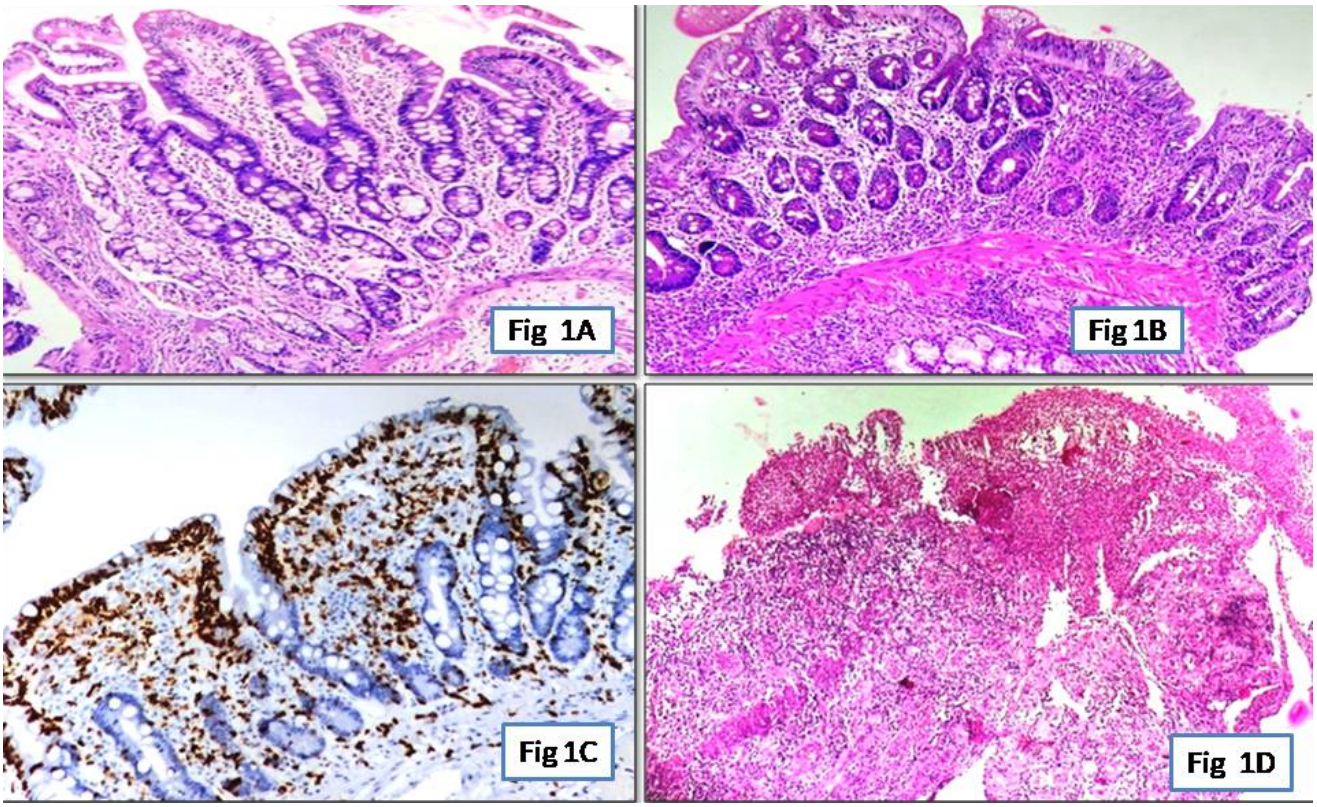

Fig. 1: A: Crypt hyperplasia inraised IEL cases, (H &E, X 100); **B:** Villous blunting, v:c ratio <1, (H &E, X 200; **C:** Corresponding section of duodenum with IHC CD3 highlighting the IEL s, (X200); **D:** Surface ulceration with loss of architecture, (H & E, X40)

Table 4: Correlation of histological features with ME and normal IELin duodenal mucosa

	Histological Features		Raised IEL(ME)	Normal IEL	P value
1.	Architecture	Normal	84(62.22%)	51(37.78%)	0.299
		Abnormal	21(72.41%)	8(27.59%)	
2.	**Crypt architecture**				
a	Normal		36(58.06%)	26(41.94%)	
b	Branching		49(63.64%)	28(36.36%)	0.038
c	Distortion		7(58.33%)	5(41.67%)	
d	Hyperplasia		13(100%)	0	
3	Blunting	Present	28(80)%	7(20%)	0.026
		Absent	77(59.69%)	52(40.31%)	
4	Ulcer	Present	4(28.57%)	10(71.43%)	0.004
		Absent	101(67.76%)	49(32.67%)	
	V/C Ratio				
	03:01		77(59.69%)	52(40.31%)	
5	02:01		21(80.77%)	5(19.23%)	0.008
	01:01		7(100%)	0	
	Flat		0	2(100%)	
	Lamina propria inflammation				
	Mild		15(53.57%)	13(46.43%)	
6	Moderate		74(66.07%)	38(33.93%)	0.448
	Severe		16(66.67%)	8(33.33%)	

Table 5: Correlation of other histological features with IEL

Other histological features			Raised IEL(ME)	Normal IEL	P value
7	Exudate	Present	2(16.67%)	10(83.33%)	**0.000**
		Absent	103(67.76%)	49(32.24%)	
8	Parasite	Present	6(85.71%)	1(14.29%)	0.222
		Absent	99(63.06%)	58(36.94%)	
9	Reactive atypia	Present	7(41.18%)	10(58.82%)	**0.038**
		Absent	98(66.67%)	49(33.33%)	
10	Cryptitis	Present	21(55.26%)	17(44.74%)	0.199
		Absent	84(66.67%)	42(33.33%)	
11	Crypt abscess	Present	5(100%)	0	0.089
		Absent	100(62.89%)	59(37.11%)	
12	Edema	Present	29(70.73%)	12(29.27%)	0.001
		Absent	73(67.59%)	35(32.41%)	
13	Fibrosis	Present	10(58.82%)	7(41.18%)	0.652
		Absent	94(64.38%)	52(35.62%)	
14	Lymphoid Aggregate	Present	63(63.64%)	36(36.36%)	0.898
		Absent	42(64.62%)	23(35.385)	
15	Granuloma	Present	2(100%)	0	0.286
		Absent	103(63.58%)	59(36.42%)	
16	Muscle disarray	Present	12(48%)	13(52%)	0.070

cases.

5. Discussion

Increase in villous epithelial lymphocytes in duodenum when present whether carries significance or not is a matter of debate since last two decades. According to a few authors it is a nonspecific finding contradictory to others. Though, increased IEL with normal villous architecture consistently corresponds to grade 1 (Marsh classification), there are many other disease conditions that are reported with similar histologic pattern. ME is a diagnostic dilemma, so a careful algorithm is applied in such cases to reach at a final diagnosis.[1,2]

In present study 105 were found to be with raised IELs. Balasubramanian et al have studied 101 cases and Mahadev et al in their study found 502(80.2%) cases.[5,6] The mean age in our study was 43.29± 17.96 years which was higher from other studies in which mean age was 19.5 ± 15.7 years and 21.8 years respectively.[7,8] Maximum cases of raised IEL in the present study were seen in age group 21-40 year (39,37.14%) similar to Balasubramanian et al study of 20-59 years.[5] In our study males (56,53.3%) were affected more than females (49,46.6%) with raised IEL similar to Yadav P. et al [(M=59) > (F= 35)].[8]

Our study revealed out of 105 cases with raised IEL, 7 (4.2%) cases were of parasitic infestation and no specific pathology was found in 59 (35.9%). Balasubramanian et al in their study observed infectious duodenitis in 5 (5%) cases (Giardia, Entamoeba and cryptosporidium) and non-specific duodenitis was observed in 41(40.6%) patients.[5]

5.1. Clinical presentations and laboratory data

In the present study, diarrhoea was the most common symptom in raised IEL cases (41, 39.04% cases) which correlate with that of different authors with 87.5% and 55% findings respectively.[5,7] Our study shows clinical features like pallor (P~ 0.001), dyspepsia (P~ 0.002), loss of appetite (P~0.046) having statistical significance with raised IEL cases. Similar observations were found by Mokhtar et al.[7] Mahadev et al did not report any significant difference between raised IEL with normal IEL cases regarding major clinical symptoms like diarrhoea or weight loss.[6] Contrary to them we have observed pallor to be significant clinical presentation in raised IEL cases.

5.2. Endoscopy

In current study, endoscopy in 60(61.86%) cases with raised IEL showed normal mucosa almost similar to Balasubramanian et al study (50%).[5] A little higher percentage (66%) was observed by Chellat et al.[9] H.pylori induced peptic ulcer was found in total 4 cases. Similar observations have been noted by other authors.[10,11] In present study we have got one case of Crohns and one case of IBD each. Endoscopically nodular appearance was seen in both and cobblestone appearance was seen in case of IBD. Three cases of giardiasis were diagnosed in our study, all showing nodular appearance in endoscopy.[5,8]

5.3. IEL and other histological features

In our study 79 (48.17%) cases had raised IEL at villous tip in H &E which on CD3 IHC was still higher in 100(60.9%) cases. Similar finding was observed by various

authors.[5,12–14] In their study also there was high correlation of IEL counts between H&E and CD3. This highlights the significance of CD3 application which can detect raised IEL even in near normal biopsy.[12–14]

In our study 77(59.69%) cases had raised IEL with normal villous architecture similar to Mahadeva and Shmidt et al.[6,13] The mean of IEL count was 24 ±15.7, which was nearer to Mahadev et al(38 ± 6.2) and higher than M Hayat et al. study (11± 6.8).[6,15]

In the current study the sensitivity of raised IEL group was 97.50% in H & E and 100% in CD3. Pellegrino et al have observed the sensitivity to be lower i.e. 93% both in H&E and CD3-staining. Comparing the specificity our study had 67.10% in H&E and 92.20% in CD3 which was lower than Pellegrino et al study where it was 100% both in H&E and CD 3.[12]

Present study had a significant correlation (p~0.00) between villous crypt ratio with raised IEL compared to normal IEL cases. But in Hayat et al study, there was no correlation between raised IEL cases and villous crypt ratio.[15] In current study lamina propria inflammation was of moderate degree in 74(70.47%) no of cases. Sixteen (15.23%) cases showed severe inflammation in raised IEL cases. Serra et al also have reported increase in lamina propria inflammation.[16]

Parasites were detected in 7 (4.2%) cases (Giardiasis and S.stercoralis) in present study which is more in number than other studies.[5] This could be due to more prevalence of parasitic infestation in tropical costal regions. Eosinophils were found to be the predominant constituent amongst the inflammatory cells in lamina propria. Similar findings were observed by various authors.[17–19] In our cases of giardiasis, villi were almost normal in all the cases. Contrary to ours, Obenhuber et al. found mild villous flattening, however similar to ours in their study also infiltration of the lamina propria were with plasma cells and eosinophils. The role of eosinophils involves the release of toxic cationic proteins, the reason for more severe histologic findings.[19]

In present study one case of Crohns and one case of IBD had raised IEL, villous blunting and moderate to marked lamina propria inflammation. As number of cases in our study was very less we are unable to compare with other studies.[3]

Similar to Balasubramanian et al. study we also found one case of confirmed tuberculosis with ZN stain positive with granuloma in two of our cases.[5] Raised IEL was seen in two cases of eosinophilic enteritis (EE) in our study which is a new finding not found in literature. Various authors have described about excess eosinophils in duodenal mucosa and intraepithelially not associated with raised IEL. Rather they have described about villous blunting. One of our case of EE had mild villous blunting also.[20–22] We could not find any case of H. pylori in our study though it is a common entity of ME. This is due to lack of duodenal samples received along with gastric biopsies which are diagnosed as H. pylori induced gastritis. Hammer et al have reported 6(6%) patients with H. pylori. Balasubramanian et al have also diagnosed one case of H. pylori whereas Kakar et aldid not report any, similar to our study.[4,5] Fifty nine (35.9%) cases in our study had normal IEL with no specific pathology. Mahadeva et al. and Balasubramanian et al have observed 502 cases (82%) and 41 cases (40.6%) without any specific histopathology.[5,6]

6. Limitations

Majority of our ME cases could not be confirmed because of unavailability of proper biochemical and serological investigations. Number of cases in each disease category were less, so hampering our effort to derive a significant conclusion. Multiple biopsies and follow up of cases after treatment is lacking in our patients. As the study was done in a tertiary care hospital referral bias was unavoidable, so it cannot be compared with general population.

7. Conclusion

ME is a histopathological entity that affects small bowel with microscopic and submicroscopic changes and may be associated with significant symptoms. The cause of raised IEL remains unknown in atleast half of the cases. Finding of a raised IEL count with normal villous architecture is of sufficient clinical importance so it should be highlighted in routine histopathological report of duodenal biopsies for further evaluation. Use of IHC is the most specific and sensitive method for demonstration of raised IEL. ME should be investigated and correlated with a detail clinical history, complete hematological, biochemical investigations.

8. Conflict of Interest

None.

9. Source of Funding

None.

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Author biography

Ritika Gupta, PG Resident

Sarojini Raman, Associate Professor https://orcid.org/0000-0002-9691-8486

Bipad Bhanjan Mallick, Assistant Professor

Urmila Senapati, Professor & HOD

Cite this article: Gupta R, Raman S, Mallick BB, Senapati U. Diagnostic evaluation of microscopic enteritis in duodenal biopsies of suspected malabsorption cases with clinico-immunohistological correlation. *Indian J Pathol Oncol* 2022;9(1):3-9.