Section: Pathology

Original Research Article

A STUDY TO EVALUATE CLINICAL PROFILE AND HISTOPATHOLOGY OF SMALL INTESTINAL BIOPSIES IN SUSPECTED CASES OF MALABSORPTION SYNDROME IN ADULTS

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Abstract

Background: Malabsorption is the reduced absorption of one or more nutrients from food. Important causes of malabsorption are gluten sensitive enteropathy, auto immune enteropathy, infections like tropical sprue, bacterial overgrowth, protein allergy, eosinophilic gastroenteritis, primary intestinal lymphangiectasia, chronic granulomatous disease, infiltrative diseases like amyloidosis, inherited disorders like microvillous inclusion disease, abetalipoproteinemia and neoplastic disorders like waldenstrom's macroglobulinemia and lymphoma. Often, we miss important diagnosis like celiac disease presuming its low prevalence in adults and in developing countries like India. The objective is to study the clinical profile and the current spectrum of histopathology using Modified Marsh Criteria in patients clinically suspected with malabsorption at a tertiary care centre. **Materials and Methods:** Study Design is a prospective hospital based cross-sectional study. Study area: Department of Pathology. Study Period is 18 months. Study population is all the samples sent as clinically suspicious of malabsorption syndrome from Gastroenterology department. Sample size of the study consisted of 41 cases. Sampling method is simple random technique. Sample collection began after obtaining clearance from the ethical committee. Brief clinical history of the patient including name, age, sex and complaints were noted. The specimens were received in a labelled container containing 10% formalin. The biopsies were processed in 10% formalin and paraffin embedded. 4-5-micron thick sections were cut from the paraffin blocks and then taken onto labelled slides for routine Hematoxylin and Eosin staining. **Result:** Out of 41 cases studied, 8(19.5%) were type 0, 5(12.2%) cases type I, 3(7.3%) cases type 2, 7 (17%) cases type 3a, 9(22.0%) cases type 3b and 4 (9.8%) cases were type 3c. No case of type 4 was reported. 5 (12.2%) cases showed crypt hyperplasia and moderate to severe villous atrophy without significant IELs. **Conclusion:** The study concludes that histopathological studies of duodenal biopsies are valuable in diagnosing malabsorption syndrome. Correlation with serology and other investigations are necessary to arrive at definitive cause of malabsorption.

INTRODUCTION

Malabsorption is the reduced absorption of one or more nutrients from food. Important causes of malabsorption are gluten sensitive enteropathy, auto immune enteropathy, Infections like tropical sprue, bacterial overgrowth, protein allergy, eosinophilic gastroenteritis, primary intestinal lymphangiectasia, chronic granulomatous disease, infiltrative diseases like amyloidosis, inherited conditions like microvillous inclusion disease, abetalipoproteinemia, and neoplastic conditions like Waldenstrom's macroglobulinemia and lymphoma are all significant causes of malabsorption.[1]

Malabsorption syndrome has a variety of aetiologies that change with time, place, and age. While intestinal lymphangiectasia, intestinal tuberculosis, cystic fibrosis, and Crohn's disease are the most

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frequent causes of malabsorption syndrome in the west, tropical sprue, parasitic infections, primary immunodeficiency syndromes, and intestinal TB have been reported to be the most frequent causes of malabsorption syndrome in developing nations.[2]

The most significant cause of malabsorption brought on by an intolerance to the stored protein gluten, which is present in wheat, barley, and rice, is celiac disease. Initially thought to be a childhood condition, it is now increasing and frequently detected in adults and the elderly population. It is described as an exacerbated immunological reaction to consumed gluten exhibited in people who are genetically predisposed. It affects around 1% of the world's population and 1.44% of Indians; its prevalence is rising in various geographic locations, in part because of improved diagnostic methods and increased public awareness.[3]

In several tropical nations, tropical sprue continues to be a substantial contributor to malabsorption. When other known causes of malabsorption had been ruled out, it is referred to as an intestinal mucosal illness that is characterised by the malabsorption of two or more unrelated nutrient groups.[4]

A wide diversity of morphology is seen histologically. Because of the unsanitary living circumstances in impoverished nations like India, gastrointestinal tract diseases are more prevalent, yet specific infections like giardiasis or tuberculosis are not more common. Pathologists frequently state that nonspecific inflammation may be brought on by gastrointestinal tract infections, chronic stomach mucosal irritation brought on by medications, or even a modest case of duodenitis. This diagnosis is made even if there are only a few lymphocytes or plasma cells present in the lamina propria. We frequently fail to diagnose serious conditions like celiac disease because we assume that they are uncommon in adults and in underdeveloped nations like India.[2]

Hence the present study was undertaken to study clinical profile and the current spectrum of histopathology in patients with malabsorption at a tertiary care centre.

Objectives

To study the clinical profile and the current spectrum of histopathology using Modified Marsh in patients clinically suspected with malabsorption at a tertiary care centre.

MATERIALS AND METHODS

Study Design: A prospective hospital based cross-sectional study.

Study area: Department of Pathology.

Study Period: 18 months.

Study population: All the samples sent as clinically suspicious of malabsorption syndrome from Gastroenterology department.

Sample size: The study consisted of 41 cases.

Sampling method: Simple random technique.

Inclusion Criteria

1. All small intestinal biopsies that were performed in the evaluation of clinically suspected cases of malabsorption syndrome.
2. Small intestinal specimens obtained in previously confirmed cases of Malabsorption syndrome.

Exclusion Criteria

1. Small intestinal biopsies in case of other morbidities other than Malabsorption syndrome.
2. Age less than 14 years.

Ethical Consideration: Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure: Sample collection began after obtaining clearance from the ethical committee. Brief clinical history of the patient including name, age, sex and complaints were noted. The specimens were received in a labelled container containing 10% formalin. The biopsies were processed in 10% formalin and paraffin embedded. 4-5-micron thick sections were cut from the paraffin blocks and then taken onto labelled slides for routine Hematoxylin and Eosin staining.

Hematoxylin and Eosin Staining Procedure

1. After the first change in xylene, the slides were placed in the rack and then put in the automatic slide stainer.
2. The slides were put in xylene container for 2 changes of 1 minute each.
3. The racks were automatically then shifted in to 60% alcohol for 2 minutes.
4. Then into 70% alcohol for 2 minutes.
5. Then rinsed in water for 2 minutes.
6. Then in hematoxylin for 12 minutes.
7. Then rinsed in water for 2 minutes.
8. Then in 1% acid alcohol for 5 seconds.
9. Then rinsed in water for 2 minutes.
10. This marked the end of the staining procedure and slide racks were then removed out of the machine.

Slides were air dried, cleared in xylene and then mounted and viewed under light microscope at different magnifications. The sections were studied for morphological changes according to modified marsh criteria.

Statistical Analysis

Data was collected using Questionnaire & compiled it on MS Excel and it has been analysed for various parameters and relevant frequencies and percentages were drawn in descriptive statistics and inferential statistics is used for quantitative & qualitative data. Chi- square test, sensitivity, specificity, positive predictive values, negative predictive values, Accuracy were calculated when required (by using SPSS software version 22) at 95% confidence interval, 5% level of significance, when P value ≤ 0.05 is considered significant.

RESULTS

42 duodenal biopsy samples were received in the department of pathology, clinically diagnosed as

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malabsorption syndrome. Patients presenting with complaints of chronic diarrhoea for more than 4 weeks and anaemic patients (hb<10gm/dl) not responding to oral iron therapy were included in the study. Adult population above 15 years of age were included. 41 cases showed duodenal histology while one case was rejected as it showed gastric histology. Microscopic examinations of duodenal biopsies were carried out. Counting of IELs/100 enterocytes was done and cases were classified into cases with <30IEL and >30 IELs/100 enterocytes. Cases that showed >30 IELs/100 enterocytes were considered significant according to Modified Marsh criteria (type 1 and above). Villous atrophy was looked for and graded into mild, moderate and severe atrophy. Crypt hyperplasia/ hypoplasia, presence and distribution of goblet cells, granulomas, parasites, cryptitis, crypt abscess, eosinophils and plasmacytosis of lamina propria were studied. Of this 41 cases, 28 cases showed significant IELs (>30/ 100 enterocytes) on H&E. While 13 cases had less than 30 IELs/ 100 enterocytes.

Table 1: Distribution of cases according to IEL- Modified Marsh Criteria

No of iel/100 enterocytes	No of cases	Percentage
<30	13	31.7
>30	28	68.3
Total	41	100.0

28 (68.3%) cases had more than 30 intra epithelial lymphocytes/ 100 enterocytes and 13 (31.7%) cases had less than 30. Of these 13 cases that had <30 IELs, the IELs were in the range of 5-10 IELs/ 100 enterocytes.

Table 2: Age distribution

Age(years)	No of cases		Total
	<30 IELs	>30 IELs	
15-30	3	9	12
31-50	8	10	18
51-70	2	7	9
>71	0	2	2
Total	13	28	41

Age group distribution of cases with >30 IELs showed most of the cases below 50 years of age with 35.7% cases in the age group of 31-50 years, followed by 32.1% cases in the age group of 15-30 years. There were 25% cases in the group of 51-70 years and 7% cases were above 70 years. Most of the cases were below 50 years of age, even in the overall study sample.

Table 3: Sex distribution

Sex	No of cases		Total
	<30IELs	>30 IELs	
Male	10	11	21
Female	3	17	20
Total	13	28	41

We infer that among 28 cases that showed significant IELs, 11 (39.2%) were male and 17 (60.7%) were female. Females were more in the study group having >30 IELs. However, number of male and female were almost equal in the overall study sample.

Table 4: Distribution of cases according to Clinical presentation

IELs/100 enterocytes	Anemia	Diarrhoea	Total
<30	8	5	13
>30	18	10	28
Total	26	15	41

Most of the cases 26(63.4%) presented with complaints of Refractory anaemia, while 15 (36.6%) cases presented with chronic diarrhoea. Anaemia was the major presenting feature in both the groups with and without significant IELs.

Table 5: Distribution of cases according to number of duodenal biopsy fragments received.

No of fragments	<30 IEL	>30 IEL	Total
2	4	2	6
3	1	14	15
4	8	11	19
5	0	1	1
Total	13	28	41

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Of the 6 cases that had 2 duodenal biopsy fragments, 2(33.3%) cases showed >30 IELs. while in cases with more than 3 fragments (35 cases) 26(74.2%) cases showed >30 IELs. The number of fragments submitted for histopathology evaluation has significance with pathology being identified more in cases having more than 3 fragments.

Table 6: Pattern of distribution of IEL

POD	<30IEL	>30 IEL	Total
Decrescendo	13	0	13
Crescendo	0	28	28
Total	13	28	41

Crescendo pattern of distribution of lymphocytes in all the cases with more than 30 intraepithelial lymphocytes/ 100 enterocytes and decresendo pattern of distribution in cases with less than 30 intraepithelial lymphocytes/ 100 enterocytes.

Out of 13 cases with <30 IEL, 5 (38.5%) cases showed crypt hyperplasia, while 23(82.1%) cases out of 28 cases with >30 IEL showed crypt hyperplasia. According to Modified Marsh classification, cases that have crypt hyperplasia should also have IELs count of more than 25-30. In our study, 5 cases showed crypt hyperplasia without significant IELs.

Table 7: Distribution of cases with villous atrophy according to IEL

Villous Atrophy	<30 IEL	>30 IEL	Total
Absent	8	8	16
Mild	3	7	10
Moderate	2	9	11
Severe	0	4	4
Total	13	28	41

Out of 13 cases with <30 IEL, 3(23%) cases showed moderate and 2 (15.5%)cases showed mild villous atrophy, while absent in 8(61.5%) cases. In cases with >30 IEL, 4(14.2%) cases showed severe villous atrophy, 9(32.3%) cases showed moderate and 7(25%) cases showed mild villous atrophy, while absent in 8(28.5%) cases. As discussed previously cases that had crypt hyperplasia, without significant IELs, also showed moderate to severe villous atrophy, which can be seen in Non-celiac enteropathy but serology to rule out celiac disease is necessary.

Table 8: Distribution of cases according to Marsh classification

Marsh classification	No of cases	Percentage
Type 0	8	19.5
Type 1	5	12.2
Type 2	3	7.3
Type 3a	7	17
Type 3b	9	22.0
Type 3c	4	9.8
Type 4	0	0
? Non celiac enteropathy	5	12.2%
Total	41	100%

Out of 41 cases studied, 8(19.5%) were type 0, 5(12.2%) cases type I ,3(7.3%)cases type 2, 7 (17%)cases type 3a, 9(22.0%) cases type 3b and 4 (9.8%)cases were type 3c. No cases type 4 were reported. 5 (12.2%) cases showed crypt hyperplasia and moderate to severe villous atrophy without significant IELs. Serology is necessary to rule out celiac disease as this finding can also be seen in non-celiac enteropathy.

DISCUSSION

In our study, on H&E evaluation of the duodenal biopsies sent as clinically suspicious of malabsorption, 28 (68.3%) cases had more than 30 intra epithelial lymphocytes/ 100 enterocytes while 13 (31.7%) cases had less than 30 epithelial lymphocytes/ 100 enterocytes.

Study by Hammo et al,[5] showed 79% cases having more than 30 intra epithelial lymphocytes/ 100 enterocytes while study by Karegar et al,[1] showed 48% cases having significant increase in IELs. Less sample size could be the reason for reduced percentage of cases showing >30 IELs in our study as Hammo et al,[5] studied 100 cases.

The clinical indication for duodenal biopsy evaluation in our study was refractory anaemia in 26(63.4%) cases, followed by chronic diarrhoea in 15 cases with 36.6%. Refractory anaemia with hb<10g/dl even with multiple courses of supplementary intake and patients presenting with chronic diarrhoea of more than 4 weeks were suspected clinically to have malabsorption syndrome. Refractory anaemia was the chief indication for evaluation of cases with and without significant IELs. There was no significant correlation of clinical indication with increase in IELs.

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Various studies conducted by kaur et al,[2] Iftikhar et al[3] and Karegar et al[1] had diarrhoea as major presenting complaint for evaluation with 52.3%, % and 84% respectively. Where as in our study, refractory anaemia (63.4%) was the major clinical indication. This difference could be due to anaemia being the common manifestation of various other chronic illness and nutritional deficiency associated with low socioeconomic status.

The age group of cases in our study ranged from 18 years to 73 years with mean age group of 45 years, similar to the Study by kaur et al,[2] with mean age of presentation at 40.02 years. whereas it was 32.5 years in the study by Karegar et al.[1]

Of the 28 cases that showed significant IELs, most of the cases were below 50 years of age with 35.7% cases in the age group of 31-50 years, followed by 32.1% cases in the age group of 15-30 years. There were 25% cases in the group of 51-70 years and 7% cases were above 70 years. This is in concordance with the study by Iftikhar et al,[3] showing maximum patients in the age group below 50 years with 86%. With advancing age, risk for other GI diseases like malignancy increases which becomes primary disease for evaluation. This could be the cause for less samples in the age group of more than 50 years.

21 cases were male and 20 were female out of 41 cases with almost equal distribution. However, of the 28 cases that showed significant IELs, 11 (39.2%) were male and 17 (60.7%) were female. This finding is in agreement with other studies showing female preponderance conducted by Karegar et al,[1] Hammo et al[5] and shihab et al.[6]

On evaluation with H&E stain, 6 cases that had 2 duodenal biopsy fragments, 2(33.3%) cases showed >30 IELs. while in cases with more than 3 fragments (35 cases) 26(74.2%) cases showed >30 IELs. The number of fragments submitted for histopathology evaluation has significance with pathology being identified more in cases having more than 3 fragments in our study, with 4 and above being recommended number of mucosal biopsies.

In the study by Iftikhar et al[3] 84% cases had more than 4 mucosal fragments, whereas average of 2 biopsies were obtained in the study by Mubarak et al.[7]

Our study showed crescendo pattern of distribution of lymphocytes (i.e. higher number of lymphocytes from the base to the tip of the villous) in all the 28 cases with more than 30 intraepithelial lymphocytes/ 100 enterocytes and decresendo pattern of distribution in all the 13 cases with less than 30 intraepithelial lymphocytes/ 100 enterocytes. Comparable to the study by Iftikhar et al,[3] showing similar pattern of distribution.

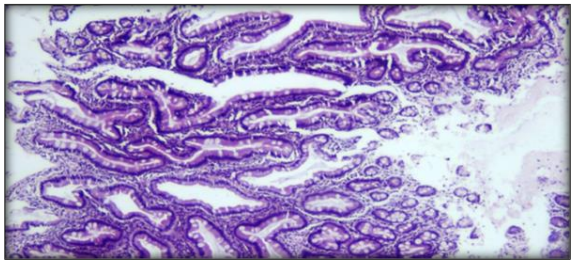

Figure 1: Marsh Type 0, H&E

In this study, according to modified marsh criteria, out of 41 cases studied, 8(19.5%) were type 0 without significant IELs, crypt hyperplasia and villous atrophy as shown in [Figure 1]. While it was 8% in study conducted by Hammo et al.[5] Another study conducted by sezgin et al,[8] showed 50% cases in this type, while study by Shihab and Enaya showed 0% cases.[9]

Marsh type 1 was observed in 5 cases (12.2%) in our study as shown in Fig 2, which is in the range of that observed by Brown et al,[10] and Lawers et al,[11] studies in which Marsh 1 was noted in 9-40 % cases. However, it is higher than those noted by Hammer and Greeson et al,[12] in which it was 1-3%. In a developing country like India, people usually don't present early to the health care system with minor symptoms which could explain less cases in early stage.

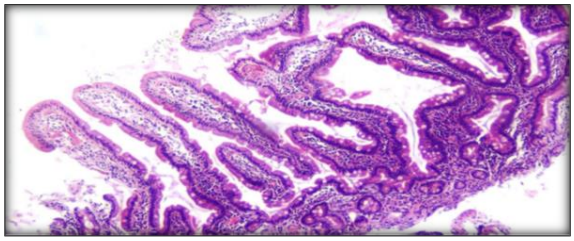

Figure 2: Marsh Type 1, H&E

Marsh type 2 was observed in 3 cases 7.3%) in our study, while it was 4% in the study by Iftikhar et al[3] and 10% in the study by Hammo et al[5]. This is a difficult type to identify as diagnosing crypt hyperplasia without villous atrophy needs expertise.

Marsh type 3 was observed in 20(48.7%) cases with 7 (17%) cases being type 3a as shown in Fig 3, 9(22.0%) cases being type 3b as shown in Fig 4 and 4 (9.8%) cases in type 3c as shown in Fig 5. This is somewhat similar to the study done by Hammo et al[5] in which Marsh type 3 was observed in 52% of cases. However, the study by Iftikhar et al,[3] showed 74% of the cases in this type. This is the most common type of Modified Marsh classification in many of the studies. As discussed earlier, in a developing country like India, people tend to present late in the course of disease and conditions like malabsorption are not usually considered in the differentials until other causes are evaluated and ruled out.

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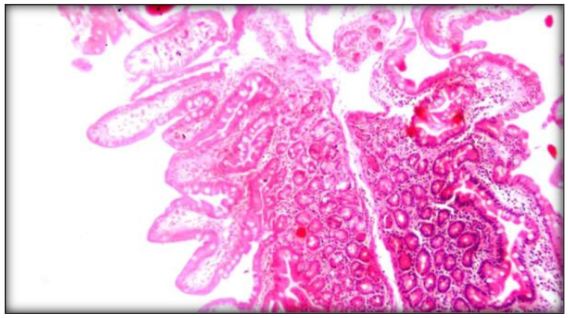

Figure 3: Marsh Type 3A, H&E

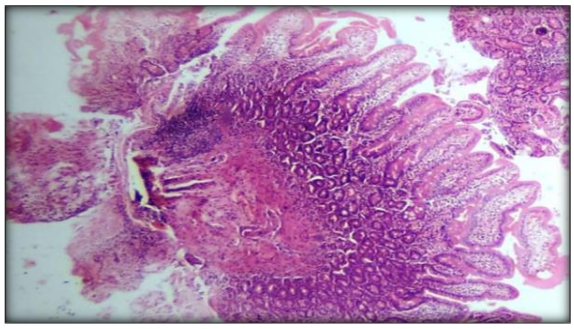

Figure 4: Marsh Type 3B, H&E

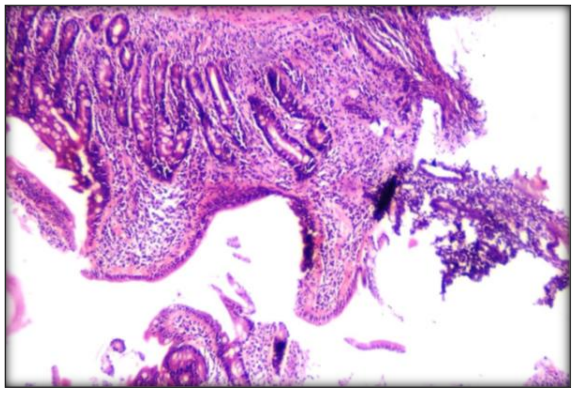

Figure 5: marsh type 3c, h&e. Villous atrophy with goblet cell depletion

Marsh type 4 was not detected in this study. This finding is in agreement with that observed by Hammo et al,[5] and Dickson et al,[13] who consider this as a rare stage of the disease. 5 (12.1%) cases showed moderate to severe villous atrophy and crypt hyperplasia without significant increase of IELs on H&E as shown in [Figure 6]. This group of cases were not fitting in any of the type of Modified Marsh classification. A Study by Pallav K et al,[14] shows that villous atrophy with lack of IELs and normal tTG is suggestive of non-celiac enteropathy (NCE). Since serology was not done in our study, we could not classify these cases any further.

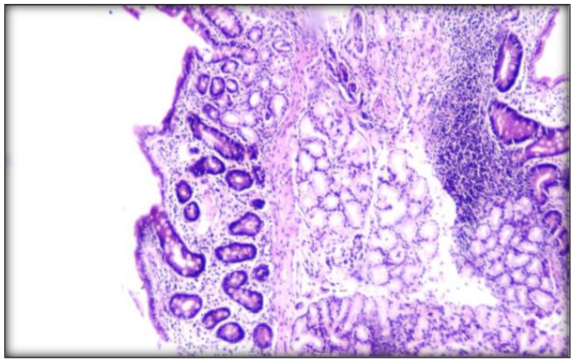

Figure 6: Villous Atrophy Without Increased IELs, H&E.

Another finding in our study was that 8 (72.7%) out of 11 cases showing moderate villous atrophy and all the 4 (100%)cases showing severe villous atrophy showed goblet cell depletion as shown in Fig 5. The degree of depletion was proportional to the villous atrophy. This is similar to the studies conducted by Iftikhar et al[3] and Svajdler et al[15] which also found goblet cell depletion in cases with villous atrophy. Goblet cell destruction by immunological mechanisms with progression of the disease could explain this.

We also looked for other histological findings associated with malabsorption syndrome which includes cryptitis and crypt abscess, basal plasmacytosis and granulomas in the lamina propria-seen in IBD, eosinophils in lamina propria (Tropical sprue) and parasites (giardiasis, etc.,). However, none of these histological findings were noted. The 8 cases that were typed under type 0 showed normal duodenal histology.

Duodenal biopsies in patients with bacterial overgrowth can have intra epithelial lymphocytosis but definitive diagnosis is made by culture of small intestine aspirates. Also anti-tTG antibodies are not elevated in bacterial overgrowth syndrome. Parasites like Giardia lamblia, Entamoeba histolytica also show significant IELs, but require stool examination for demonstration of the pathogen.

CONCLUSION

The study concludes that histopathological studies of duodenal biopsies are valuable in diagnosing malabsorption syndrome. Correlation with serology and other investigations are necessary to arrive at definitive cause of malabsorption.

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