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Outcomes of Seropositive Patients with Marsh 1 Histology in Clinical Practice

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Abstract

Goals—We retrospectively studied all seropositive Marsh 1 patients seen at two tertiary care hospitals in the last 15 years to determine their clinical, serological and histological outcomes.

Background—Patients with positive celiac serologies and Marsh 1 histology represent an understudied subgroup of patients, and it is unclear whether they should be advised to adopt a gluten-free diet (GFD).

Study—Subjects were identified based on positive celiac serologies and Marsh 1 histology while on a full-gluten diet. Clinical presentation and baseline laboratory data were noted. Clinical course, repeat serologies, and histology were determined.

Results—Of 620 patients with positive celiac serologies and abnormal duodenal histology, we identified 36 (5.8%) with positive tissue transglutaminase and/or anti-endomysial antibodies and Marsh 1 lesions who had adequate follow-up. Abdominal pain was the commonest (47.2%) presenting symptom. Twenty-eight patients were advised to adopt GFD, while eight were not. Among patients treated with GFD, 88.9% improved symptomatically, and 95% normalized serology. In contrast, among patients who continued to consume gluten, 85.7% remained symptomatic, and 80% had persistently positive serologies. Among the eight patients on normal diet, five underwent repeat biopsy, and four of them had the same or worse histology, with three patients progressing to Marsh 3c. Among the 28 patients on GFD, five underwent repeat biopsy and all improved to normal histology.

Conclusions—Most patients with positive celiac serology and Marsh 1 lesions benefit from GFD and, if not treated, a majority will continue to be symptomatic and remain at risk of progressing to villous atrophy.

Keywords

celiac disease; Marsh 1; duodenal lymphocytosis; minimal enteropathy

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Introduction

Celiac disease (CD) is an immune-mediated enteropathy that results from exposure to dietary gluten in genetically susceptible individuals.¹ In 1990, the European Society of Gastroenterology and Hepatology (ESPGHAN) reviewed the criteria for the diagnosis of CD and described it as “hyperplastic villous atrophy” on a gluten-containing diet with unequivocal response to gluten free diet (GFD).² In 1992, Marsh suggested a histological classification system for the diagnosis of CD,³ which was later modified by Oberhuber in 1999.⁴ The modified Marsh classification has been the most widely used histological classification for the diagnosis of CD and encompasses a spectrum of duodenal histology ranging from normal biopsy in Marsh 0 and increased intraepithelial lymphocytes (IELs) in Marsh 1, to increased IELs with crypt hyperplasia in Marsh 2 and increased IELs with crypt hyperplasia and villous atrophy in Marsh 3 lesions. According to the 1990 ESPGHAN criteria, the presence of Marsh 3 histology on a gluten-containing diet was considered the hallmark of CD.² In 2012, the guidelines were expanded to include the combination of a Marsh 2 lesion and the presence of positive serology as diagnostic for CD.⁵ The 2012 ESPGHAN revision also acknowledged that the natural history of infiltrative or Marsh 1 lesions is poorly understood, and that the need for GFD in these subjects is therefore an important area of uncertainty.

Previous studies attempting to address the natural history of Marsh 1 histology have had important limitations. The two largest studies to date of potential CD combined subjects with Marsh 0 and Marsh 1 lesions, and did not separately analyze patients with Marsh 1 histology in terms of progression to more advanced histology or symptomatic response to gluten-free diet.^{6, 7} It is important to note that asymptomatic patients with a positive celiac serology and Marsh 0 biopsy would be essentially indistinguishable from non-celiac patients with a false positive serology.⁸ Moreover, even in presence of a true positive serology, there is no active inflammation in Marsh 0 lesions while there is histologic evidence of inflammation in Marsh 1, which could be reasonably expected to influence the rate or risk of progression to villous atrophy as well as clinical response to GFD.⁹ Thus, there is a paucity of data on the clinical profile, natural history and response to GFD in patients with positive celiac serology and Marsh 1 histology.

We retrospectively studied all patients found to have positive celiac serology and Marsh 1 histology at two tertiary care hospitals in the last 15 years to determine their clinical profile along with clinical, serological and histological outcomes on follow-up.

Materials and Methods

This was a retrospective study including patients from two tertiary referral hospitals—Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH)—that serve over 3 million patients in the Greater Boston area and neighboring states in the Northeastern United States.

Cases were identified through a query of the Partners Healthcare Research Practice Data Registry (RPDR), an electronic database of all patients seen at MGH, BWH, and affiliated

institutions within the Partners Healthcare system. The RPDR is a centralized clinical data repository and query system initiated in 1996. It is automatically and continuously populated with patient data from a variety of data sources including billing, encounter scheduling, medications, laboratory, radiology, endoscopy, and surgery databases. A broad search was performed using terms CD, celiac serology, tissue-transglutaminase (tTG) antibodies, anti-endomysium antibodies (EMA), anti-gliadin antibodies (AGA).

All patients who were tested for these celiac-specific serologies and had an esophagogastroduodenoscopy (EGD) between 2000 and 2014 were screened to be included in this study. Duodenal biopsy results were reviewed for all individuals with positive celiac serologies. Details of the small bowel histology are given below.

Histology

As part of standard of care at our institution, at least four to six biopsy specimens were taken from the third part of the duodenum and duodenal bulb and fixed in 10% formalin. Mucosal biopsy was performed and multistep sections of the biopsy fragment were taken. A biopsy fragment was considered to be oriented when at least three crypts were oriented perpendicularly on the underlying muscularis mucosae, and the most oriented fragment was selected for interpretation. The specimens were analyzed for mucosal changes by pathologists with a special interest in gastrointestinal pathology. A modified Marsh grading system was used for grading mucosal changes: grade 0, normal histology (a crypt to villous ratio of 1:3 was taken as normal); grade 1, increase of intraepithelial lymphocytes (IELs) >40 per 100 enterocytes; grade 2, increased IELs along with crypt hyperplasia; grade 3, increased IELs along with crypt hyperplasia and variable degrees of villous atrophy. All the biopsies which were initially labeled as Marsh 1 in our database were further reviewed by a histopathologist with special interest in gastrointestinal pathology (G.Y.L.). The pathologist graded these samples according to the modified Marsh scoring system. Other than the fact that each subject had a positive TTG or EMA, the pathologist was otherwise blinded to titers of the celiac serologies, as well as demographic data, details of the clinical presentation, decisions regarding whether a patient was advised to adopt a GFD, as well as the clinical outcomes in terms of improvement in symptoms and, in cases where a follow-up biopsy was performed, whether the subject's histology was improved, worsened or unchanged. The study pathologist's histological grading was considered as final.

Inclusion and exclusion criteria

A patient was included in our study if he/she had a positive anti-tTG ab and/or EMA along with Marsh 1 histology on duodenal biopsy. Patients who were AGA positive were included only if one of the other celiac serologies (anti-tTG ab or EMA) were positive. Patients who were on GFD or gluten-restricted diet at the time of EGD were not included in the analysis. Similarly, patients with IgA deficiency were not included in this study.

Study variables and outcomes

A chart review of electronic medical record was then performed for patients with positive celiac serology and Marsh 1 lesion on histology. The following details were obtained at the time of presentation: chief complaint, clinical manifestations, family history, laboratory

values including hemoglobin level, albumin, transaminases, assay-specific cutoff values for celiac serologies (anti-tTG, EMA, AGA) and duodenal biopsy. Anemia was diagnosed using World Health Organization (WHO) age- and gender-specific hemoglobin cutoffs (<http://www.who.int/vmnis/indicators/haemoglobin>).

Patients were said to have adequate follow-up if they had at least 2 clinical visits with a gastroenterologist, with one being at least 6 months after diagnosis. Results of follow-up celiac serologies and duodenal biopsies (after at least 6 months from initiation of GFD) were also noted for these patients. In addition, a detailed chart review was done to assess whether initial symptoms persisted, improved or worsened after at least 6 months of follow-up. Patient adherence to GFD as reported in case files was also noted.

Results

Of 620 patients with one or more positive celiac serology and abnormal duodenal biopsy (i.e. modified Marsh criteria 1 or higher), 57 patients (9.2%) had Marsh 1 histology. The remaining patients had Marsh 2 or 3 lesions and thus were diagnosed with CD as per ESPGHAN criteria. Of these 57 patients, five patients were on gluten free or gluten-restricted diet at the time of biopsy and thus were excluded from this study. Another nine patients were excluded as they were positive for AGA alone. The remaining 43 biopsies were reviewed by a single expert histopathologist with special interest in gastrointestinal pathology (G.Y.L) and four patients were found to have various degrees of villous atrophy. These four patients were excluded from our study and the remaining 39 patients were found to have Marsh 1 histology after the independent review by single histopathologist. Of these 39 patients, 3 were lost to follow-up and thus, a total of 36 patients with positive anti-tTG ab and/or EMA along with Marsh 1 lesion on duodenal biopsy were included in our study.

Presenting complaints

Seventeen of 36 patients (47.2%) presented with a chief complaint of abdominal pain. Only three patients (8.3%) had diarrhea as their primary complaint. The next most common modes of presentation were for screening among first-degree relatives of patients diagnosed with CD (4 patients, 11.1%), followed by anemia, screening among children with type 1 diabetes mellitus, short stature and transaminitis (two patients, 5.5% each). The remaining five patients presented with weight loss, dermatitis herpetiformis, dyspepsia, multiple food allergies and very high levothyroxine requirements for hypothyroid state.

Clinical manifestations

Abdominal pain was the most common symptom, with approximately 66.7% of patients (24 patients) endorsing it at the time of initial visit. Surprisingly, constipation appeared to be more common than diarrhea, with 38.9% of patients (14 patients) presenting with constipation and 25% of patients (9 patients) with diarrhea (Table 1). A quarter of patients (9 patients) had at least one first- or second-degree relative diagnosed with CD at the time of initial presentation.

Laboratory Parameters

Four of 30 patients (13.3%) who had their hemoglobin checked at the time of initial presentation had anemia. Only 1 of 29 patients (3.4%) had hypoalbuminemia at the time of presentation. Transaminitis was present in two of 22 patients who had liver enzymes checked at the time of initial presentation (Table 1).

Serology

Thirty-four patients (94.4%) underwent tTG serology while two patients did not have anti-tTG antibodies checked. Of these 34 patients, 31 (91.2%) were positive for anti-tTG antibodies and the remaining two (5.5%) were negative for anti-tTG. Among the 17 patients who had EMA checked at the time of initial presentation, 13 patients (76.5%) had positive EMA and the remaining four patients (23.5%) were EMA negative. EMA serology was not done in the remaining 19 patients. Eight patients had AGA checked at the time of initial presentation; 5 patients (62.5%) had positive AGA and the remaining 3 patients (33.3%) had negative AGA. AGA serology was not done in the remaining 28 patients. All four patients who either had negative anti-tTG antibodies or did not have anti-tTG serology checked initially (two patients each) were EMA positive.

Duodenal Biopsy

All 36 patients had increased IELs without evidence of crypt hyperplasia or villous atrophy, confirming Marsh grade 1 histology.

Clinical follow up

Three patients (7.7 %) did not have a follow up clinic appointment with their clinical provider after EGD and thus were not included in this part of analysis (Figure 1). Of the remaining 36 patients, eight patients (22.2%) were not recommended to start GFD by their gastroenterologists (group A) while the other 28 patients were started on GFD (group B). All eight patients in group A continued on their normal diet as recommended.

Among patients who continued to consume gluten (group A), six of seven patients who were symptomatic at initial presentation (85.7%) continued to have symptoms, while one patient improved with symptomatic management. This patient presented with diarrhea and abdominal pain and improved with amitriptyline. One patient who was asymptomatic at the time of initial presentation was detected due to screening for family history. He remained asymptomatic after 1 year of follow-up.

Among patients who were started on a GFD, one patient was asymptomatic at the time of presentation and remained asymptomatic on GFD. Of the remaining 27 symptomatic patients, three (11.1%) had persistent symptoms after at least 6 months of GFD. Notably, of these three patients who were persistently symptomatic, two were non-compliant with the GFD. The remaining one patient was on strict GFD and had negative follow-up serology but continued to have symptoms (abdominal pain/constipation). The remaining 24/27 patients (88.9%) improved clinically on GFD (Table 2).

Follow up serology

Five patients (62.5%) in group A had follow-up serology and four of these (80%) had persistently positive serologies, while serologies spontaneously normalized in the other one patient who continued a normal diet (Table 2). All these patients continued to have symptoms on normal diet. In group B, 20 of 28 patients (71.4%) had follow-up serology. Of these 20 patients, 19 patients (95%) had negative serology at follow-up and one patient continued to have positive serology after 2 years of follow-up but the patient was non-complaint with GFD (Table 2).

Follow-up biopsy

In group A, five patients underwent a repeat biopsy after a median follow up of 46.9 months (interquartile range 36.2 months). Of these, three patients (60%) worsened to Marsh 3c histology, one patient persisted to have Marsh 1 histology and one spontaneously normalized to Marsh 0 on normal diet (Figure 1). All three patients with Marsh 3 histology, and one patient with Marsh 1 histology, continued to have positive repeat serologies on normal diet. The other one patient did not have repeat serology checked.

In group B, five patients (17.9%) underwent a repeat biopsy after a median follow up of 25 months (interquartile range 25.5 months). All five patients improved to Marsh 0 histology on GFD (Figure 1).

Discussion

In this study, we identified a cohort of 36 patients with positive celiac serology and Marsh 1 histological lesions. The majority of these patients presented with atypical manifestations, and abdominal pain was the most common presenting complaint in 47.2% of patients. Nearly 89% of patients treated with a GFD experienced symptom improvement compared to 14.3% of patients who continued on their usual diet. Among patients treated with GFD who had repeat serologies, 95% had normalized, compared to 20% among patients who continued to ingest gluten. Most strikingly, among patients who had repeat duodenal biopsies, the majority of patients with Marsh 1 lesions who continued their usual diets either continued to have Marsh 1 histology (20%) or worsened to Marsh 3c histology (60%), whereas all of the patients on GFD improved their histological classification from Marsh 1 to Marsh 0 over a median follow-up interval of just over two years.

The term “potential CD” is often used with different meanings in the literature. In some cases, potential CD is used to describe patients with positive CD serology but normal mucosa (including both Marsh 0 and 1)^{6, 7} and in other cases it refers to seropositive patients with an increased number of IELs, but no villous blunting (Marsh 1).¹⁰ Others have used the term to describe anyone with a first-degree relative who has CD.¹¹ To date, the largest series of seropositive patients with Marsh 1 duodenal histology included 23 patients reported by Tortora et al.¹² In this study, all 23 patients were advised to adopt a GFD, and the majority (22/23) had improvement in serology titers and symptoms. However, repeat biopsies were not reported, and this group was not compared to a matched group of seropositive Marsh 1 patients that continued on a gluten-containing diet. It is not possible to conclude from this

study whether the recommendation for GFD modified the risk of progression to more advanced Marsh lesions or worsening of symptoms in this subset of patients.

Although it has been proposed that patients with Marsh 1 histology may evolve into active CD,¹³⁻¹⁵ the question of whether to recommend a GFD in seropositive patients with increased duodenal IELs remains unanswered in part due to the relative infrequency of this presentation and lower interobserver reproducibility for Marsh 1 and 2 lesions.¹⁶ Historically, many patients who underwent endoscopy for symptoms had overt changes of inflammation and villous atrophy and the indication for a GFD was clear.^{17, 18} However, with increasing awareness of CD and more widespread adoption of screening tests,⁸ the numbers of seropositive patients with infiltrative, mild enteropathy is likely to increase, and understanding the natural history of this finding will be critical for guiding dietary recommendations in this group of patients.

We found that across multiple measures, including symptom improvement, serologic measures and repeat biopsy histology, patients who adopted a GFD did better than patients who continued on a regular diet. Similar results with gluten free diet were observed in a randomized controlled trial where 23 seropositive patients with grade 1 and 2 Marsh lesions were randomized to gluten-free or normal diet and among those on normal diet, the small-bowel mucosal villous architecture deteriorated in all participants, and the symptoms and abnormal antibody titers persisted.¹⁴ However, this study analyzed patients with both Marsh 1 and Marsh 2 lesions together, and they did not mention the exact numbers of patients with Marsh 1 lesions in their study. The high rate of progression to Marsh 3c histology (60% after a median of 46.9 months) among our patients on gluten containing diet is in contrast to a series recently published by Auricchio et al, in which the rate of progression to villous atrophy among potential celiac patients who continued on a gluten-containing diet was 13% after 3 years, 26% by 6 years, and 32% by 9 years.⁶ However, as noted above, this study analyzed patients with Marsh 0 and Marsh 1 histology together, potentially underestimating the rate of progression among the patients with Marsh 1 biopsies.

Another interesting finding of this study is the mode of presentation of these patients. Only 8.3% of patients presented with a chief complaint of diarrhea and the majority presented with atypical celiac symptoms¹⁹ such as abdominal pain, or were discovered during screening in the setting of CD family history or coexistence of type 1 diabetes mellitus. In addition, constipation was more common than diarrhea in our cohort. It is possible that because of low grade enteropathy in these patients, malabsorption and hence diarrhea is not as common as in classic CD. It is also possible that increased awareness about non-classical manifestations of CD and easy availability of celiac serological testing could have resulted in early detection of Marsh 1 lesions in these patients before the onset of classical symptoms.

Our study has several important strengths. First, this study focuses on clinical outcomes of a very specific population of individuals who are clinically symptomatic, have positive celiac serology and Marsh 1 lesion on histology. With increasing awareness of CD among clinicians, widespread use of serology, including point of care tests, and increased screening among at-risk groups, there would be a significant number of patients such as ours.¹⁴

However, most of the previous studies on this group are limited to relatively small numbers, and this study describes the largest cohort of seropositive Marsh 1 lesions to date. Moreover, there is no consensus among clinicians whether to put these patients on GFD or not, and this study provides perspective on what happens to these patients in clinical practice. An additional strength of this study is the inclusion of 10 patients who underwent repeat duodenal biopsies and those on gluten containing diet had worsened histology when compared with those on GFD.

Our study has a several limitations. First, not all patients underwent follow-up serology and biopsy, and there could have been selection bias with more symptomatic patients having higher chances of undergoing repeat serology and biopsy. This could have not been avoided given the retrospective design of the study. However, such a selection bias should be applicable to both the groups and yet, we observed improved duodenal histology in the majority of group B patients who adopted a GFD. Second, not all patients underwent repeat serology and biopsy at the same follow-up period. Patients on GFD underwent a second biopsy after a median interval of 25 months, whereas the median time between biopsies in patients on normal diet was 46.9 months. The longer interval between biopsies makes it possible that some patients on gluten containing diet may have been found to have stable histology if they had been biopsied earlier. Third, our findings are based on a small number of patients and relatively short period of follow-up. However, as mentioned above, the study population was derived from a much larger cohort of celiac patients seen at our institutions over 15 years, and represents the largest cohort of seropositive Marsh 1 patients described to date.

It is acknowledged that there is a lack of consensus on the management of patients with positive celiac serology and Marsh 1 histology. While GFD is recommended in seropositive patients with Marsh 2 and above,⁵ no such recommendations exist for seropositive Marsh 1 patients that we have described in this study. This is in large part due to a paucity of data on this subset of patients, and there is a need for prospective studies of the outcomes of these patients on GFD when compared with normal diet. Although based on a small number of available patients, our study suggests that seropositive Marsh 1 patients remain symptomatic if untreated and many progress to Marsh 3 lesions. However, we identified a small subset of patients who improve symptomatically with normal diet. Future studies will be necessary to identify this subset of patients who are at low risk of evolving to more advanced small bowel lesions and can thus avoid having to adopt a long term GFD. In conclusion, most patients with positive celiac serology and Marsh 1 lesions appear to benefit from GFD and, if not treated, a majority continues to be symptomatic and remain at risk of progressing to classic CD.

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Abbreviations

CD	celiac disease
GFD	gluten free diet
TTG	tissue-transglutaminase
EMA	anti-endomysium antibodies

AGA anti-gliadin antibodies
IEL intraepithelial lymphocyte

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Figure 1. Study Flowchart

Table 1
Baseline Characteristics of 36 Seropositive Marsh 1 Patients

Age, median (range) (y)	10.6 (3.0-62.5)
Sex	
Female	26 (72.2%)
Male	10 (27.8%)
Race	
White	33 (91.7%)
Non-white ^a	3 (8.3%)
Reason for testing	
Abdominal pain	17 (47.1%)
1st degree relative with CD	4 (11.1%)
Diarrhea	3 (8.3%)
Screening for hx of T1DM	2 (5.5%)
Clinical manifestations	
Abdominal pain	24 (66.7%)
Diarrhea	9 (25%)
Constipation	14 (38.9%)
Family history	
Celiac disease	9 (25%)
Autoimmune	7 (19.4%)
Celiac serologies	
EMA positive	13/17 (76.5%)
TTG positive	34/36 (94.4%)
Laboratory studies	
Anemia	4/30 (13.3%)
Hypoalbuminemia	1/29 (3.4%)
Abnormal LFTs	2/22 (9.1%)

^aNon-white race includes Black, Hispanic, Asian, Native American, unknown and not documented.

Table 2
Clinical Outcomes of Seropositive Marsh 1 Patients Based on Dietary Recommendations

	Group A Regular Diet (n=8)	Group B Gluten-free diet (n=28)	P value
Age, median (range) (y)	8.0 (3.7-59.9)	12.4 (3.0-62.5)	0.50
Sex			
Female	6 (75.0%)	20 (71.4%)	0.78
Male	2 (25.0%)	8 (28.6%)	
Clinical manifestations			
Abdominal pain	5 (62.5%)	19 (67.9%)	0.78
Diarrhea	0 (0.0%)	9 (32.1%)	0.07
Constipation	2 (25.0%)	11 (39.3%)	0.47
Laboratory studies			
Anemia	0/7 (0.0%)	4/22 (18.2%)	0.24
Hypoalbuminemia	0/7 (0.0%)	1/22 (4.5%)	0.50
Abnormal LFTs	2/5 (40.0%)	0/16 (0.0%)	0.01
TTG median, (range)	16.5 (3-29)	32.5 (4.5->300)	0.03
Symptomatic at diagnosis	7 (87.5%)	27 (96.4%)	0.83
Persistent symptoms	6/7 (85.7%)	3/27 (11.1%)*	<0.01
Improved	1/7 (14.3%)	24/27 (88.9%)	<0.01
Repeat serology (EMA or TTG)	5 (62.5%)	20 (71.4%)	
Persistently positive	4/5 (80%)	1/20 (5.0%)	<0.01
Normalized	1/5 (20%)	19/20 (95.0%)	<0.01

*
 2 non-compliant with GFD