Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2019 February ; 68(2): 251–255. doi:10.1097/MPG.0000000000002158.

Red spot lesions in the duodenal bulb are a highly specific endoscopic sign of celiac disease: A prospective study

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Abstract

We have recognized Red Spot Lesions (RSLs) in the duodenal bulb in children with celiac disease (CD) and believe they may represent an underappreciated and distinct endoscopic sign of CD. A total of 171 pediatric patients undergoing esophagogastroduodenoscopy with duodenal biopsy for symptoms consistent with CD were prospectively recruited. There were 75 patients who met criteria for CD and the remaining 96 patients served as symptomatic controls. As compared to endoscopic markers frequently mentioned in literature, RSLs had comparable sensitivity, specificity, positive predictive value, and negative predictive value of 31%, 94%, 80%, and 64%, respectively. If RSLs are noted during endoscopy in a patient with gastrointestinal symptoms that might be the result of CD, then sufficient duodenal biopsies to make the diagnosis of CD should be obtained.

Keywords

Celiac disease; intestinal biopsy; duodenum; diagnosis

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Author Contributions:

Conception and design of study: AML, EAF; Data acquisition: EAF, JDG, AK, AML, CEM, DCW; Analysis and interpretation of data: EAF, JDG, AML, PDM, JAS, DCW. Drafting manuscript: EAF, AML, JAS, ZJH. All authors critically reviewed and approved the final version of the manuscript.

Conflict of Interest: The authors declare no conflicts of interest.

Introduction:

Celiac disease (CD) is an immune enteropathy characterized by small intestinal villous atrophy perpetuated by gluten exposure in genetically susceptible individuals¹. CD may present with classical symptoms of malabsorption, such as diarrhea, bloating and weight loss, or non-classical symptoms such as anemia, chronic fatigue, delayed puberty, dermatitis herpetiformis, or low bone density². Despite greater awareness of CD and availability of serum tissue transglutaminase antibody (tTG) screening tests, most children with CD are undiagnosed³. Among adults, the interval between symptom onset and diagnosis remains nearly a decade^{4,5}.

Recognition of features in the duodenum at the time of endoscopy may lead to diagnosis of otherwise unsuspected CD^{6,7}. Frequently cited endoscopic signs of CD include nodular or mosaic patterned mucosa, and scalloping, flattening or absence of Kerkring's folds in the distal duodenum⁷. Other signs include deep mucosal grooves, visible submucosal vessels, and duodenal erosions^{7,8}. Although many of these findings are common to villous atrophy and may not be specific for CD⁹, they have been reported to have moderate sensitivity (40–70%) and high specificity (>90%) in populations where CD is a common cause of villous atrophy^{10,11}.

Enhanced imaging techniques can improve accuracy of endoscopic diagnosis. High resolution endoscopy and water immersion techniques enable visualization of individual villi¹². Narrow band imaging (NBI) is a system that equips an endoscope with a narrow band filter that selects blue and green light¹³. These wavelengths are highly absorbed by hemoglobin, thus facilitating visualization of vascular features more readily than with white light.

The present study evaluates a rarely noted endoscopic finding that may be associated with CD. Red Spot Lesions (RSLs) appear as small, discrete “red spots”, without obvious damage to the overlying mucosa. We hypothesize that the presence of RSLs in the duodenal bulb is associated with CD. The aim of this study was to examine the sensitivity and specificity of RSLs in the duodenum as an endoscopic sign of CD, and to compare the diagnostic utility of RSLs with other previously described mucosal findings, including flattened folds, scalloped folds, nodularity, ulceration, and decreased or absent villi.

Methods:

Study design.

This prospective blinded endoscopy-histology association study included children 18 years old undergoing esophagogastroduodenoscopy (EGD) with duodenal biopsy for gastrointestinal symptoms compatible with CD at Boston Children's Hospital between November 2007 and October 2008. Symptoms of CD were broadly defined to include abdominal pain, cramps or distension, diarrhea, constipation, nausea or vomiting, loss of appetite, weight loss or poor weight gain, gastroesophageal reflux, dairy intolerance, and mouth ulcers. Visual endoscopic findings associated with CD (nodularity, ulceration, flattened folds, scalloped folds, loss of villi beyond the duodenal bulb on macroscopic

examination and RSLs in the duodenal bulb) were systematically recorded on a scoring sheet by the endoscopist immediately following the procedure. RSLs were defined as two or more 1–3 mm pleomorphic red lesions in the absence of ulceration. Pathologists had access to all clinical and laboratory data, but were blinded to the endoscopist interpretation of visual findings. Ethics approval was provided by the Boston Children's Hospital Institutional Review Board.

Endoscopy procedures.

Before undergoing endoscopy, all patients were sedated with general anesthesia or Midazolam and Fentanyl per physician preference. All endoscopic procedures were performed by experienced endoscopists with high resolution endoscopes (GIF 160, GIF H180, or GIF Q180; Olympus Corporation, Tokyo, Japan). Endoscopists with training and experience in the use of NBI used this technique as well as white light to visualize the mucosa. A minimum of six biopsies were obtained with cold forceps, two from the duodenal bulb and four from the distal duodenum. Duodenal biopsies were specified as to whether they were taken from the duodenal bulb or the distal duodenum.

Blood for serology (tTG IgA and endomysial antibodies) was obtained from all patients at the time of intravenous catheter placement.

Histologic procedures.

All biopsies were fixed in formalin, paraffin embedded, cut into 5- μ m-thick sections and stained with hematoxylin and eosin by the Pathology Department according to standard operating procedures for clinical specimens. All specimens were examined by pathologists with expertise in pediatric gastrointestinal pathology who reported the presence or absence of diagnostic findings of CD according to the criteria outlined in the Marsh classification system¹⁴.

Celiac disease diagnosis.

Celiac disease diagnosis was confirmed in patients with Marsh II or III lesions plus either celiac associated antibodies (tTG IgA antibody level above the upper limit of normal and/or endomysial antibody titer > 1:2.5) or clinical response to a gluten-free diet by 6 months in sero-negative patients¹⁵.

Statistical Analysis.

Data were entered into a secure database and reviewed for errors prior to analysis. Summary statistics were calculated with SPSS 23.0 (SPSS Inc, Chicago). Association between categorical variables was tested using Pearson chi-square test (or exact chi-square test as appropriate). Age is reported as median with interquartile range (IQR). Diagnostic utility of various endoscopic markers of CD was evaluated using positive and negative predictive values, sensitivity and specificity. All tests were 2-sided at 0.05 significance level.

Results:

Patients.

A total of 171 children (53% female) median age 9 years (interquartile range 5–13) were enrolled in the study. There were 75 participants who met the criteria for CD, all of whom had Marsh III lesions. The 96 patients who did not have CD served as controls. The CD group and control group were similar with respect to age and clinical presentation, except for a higher prevalence of gastroesophageal reflux symptoms in control patients and a higher prevalence of diabetes mellitus in patients with celiac disease (Table 1). No biopsy evidence of erosions was noted in CD patients with RSLs and only one had ulceration, which was in the distal duodenum.

Endoscopic Features.

The gross endoscopic appearance of the duodenal bulb was abnormal in celiac patients more often than in control patients (72% vs 12%; odds ratio (OR) 17, 95% CI 7.7–37). Among CD patients, nodularity (40%), RSLs (31%) and ulceration (3%) were the most common findings in the duodenal bulb (Table 2). Nodularity [OR 15 (95% CI 5.1–46)] and RSLs [OR 6.6 (95% CI 2.5–17)] were each significantly more commonly found in the duodenal bulb in the CD group than the control group. Though qualitatively different, findings in the distal duodenum were also significantly more common among CD patients than controls. In this region, scalloping (OR 12, 95% CI 5–31), lack of villi (OR 11, 95% CI 3–32), nodularity (OR 29, 95% CI 4–226), and flattened folds (OR 3.6, 95% CI 1.4–9), were the most common findings.

When utilized, viewing with NBI enhanced all red spot lesions initially identified with white light (n=10).

Sensitivity and specificity of endoscopic signs of celiac disease.

All endoscopic signs had comparably low sensitivity and high specificity for CD (Table 2). Although RSLs were highly specific for CD, 6 patients with RSLs in their duodenum did not have histopathologic findings of CD. Of these, 2 had Crohn's disease, 1 had a resolution of symptoms on a gluten-free diet despite not meeting histopathologic criteria for CD, and 3 did not have a definitive diagnosis. The latter 4 may have had patchy CD which was missed on biopsy.

Association of RSLs with serum tTG IgA.

RSLs were significantly associated with abnormal tTG IgA (7% for tTG IgA <20 vs. 33% for tTG IgA > 20; P<0.0001). In practical terms, an elevated tTG IgA had an odds ratio of 6.5 (95% CI 2.7–17.8) for presence of RSLs on endoscopy compared to a tTG IgA <20 (upper limit of normal). The odds ratios of tTG IgA 20–100 and tTG IgA >100 were 9.4 (95% CI 2.7–32) and 5.9 (95% CI 2.2–16), respectively, compared to a tTG IgA <20.

Discussion:

Our single center prospective study identifies Red Spot Lesions in the duodenal bulb to be a distinct endoscopic sign of celiac disease that has comparable sensitivity and specificity to other previously described features, including nodularity, mosaic patterns, scalloping, and flattening of mucosal folds. We believe that RSLs observed in the duodenal bulb should prompt consideration of celiac disease, and duodenal biopsies should be obtained per celiac tissue sampling protocols. In this way, RSLs may aid in the diagnosis of CD in patients who undergo EGD for other indications.

RSLs are distinct from both visible submucosal vasculature, which has been used as an endoscopic marker of CD⁷, and erosions in the distal duodenum, which were described by Dickey and Hughes⁸. RSLs were located in areas of intact mucosa and were not associated with the presence of superficial erosions. The enhanced appearance of RSLs under NBI suggests that RSLs may represent submucosal blood, possibly within dilated vascular structures¹³. Notably, presence of RSLs was significantly associated with a very high serum tTG IgA antibody level. In CD, antibodies are most commonly directed towards the tTG-2 isotype and modulate tTG-2 activity¹⁶. Vascular wall components, including vimentin, are known substrates of tTG-2¹⁷. In a murine model, inhibition of tTG-2 caused mesenteric vasodilation¹⁸. tTG-2 is also a regulator of capillary sprouting and angiogenesis¹⁹. More studies are needed to explore the vascular effects of tTG-2 antibodies in CD.

Greater awareness of endoscopic signs of CD may lead to targeted biopsy of patients with these findings and improve recognition of CD among patients undergoing upper endoscopy in whom the diagnosis is unsuspected. While it is difficult to quantify “missed” CD, the average interval between symptom onset and diagnosis in adults is nearly a decade^{4,5}. These symptoms often prompt endoscopy for indications such as IBS or GERD for which duodenal biopsy may not be routine or cost effective. In a multicenter study in the United States, duodenal biopsies were obtained during upper endoscopy for anemia, iron deficiency or weight loss less than 50% of the time²⁰. When duodenal biopsies were submitted to a national pathology laboratory, the average number was two²¹, which is inadequate to exclude CD².

There are some limitations to this study. Only pediatric patients with symptoms compatible with celiac disease were included; therefore, it is unknown whether these findings may apply in asymptomatic children or in older populations. As well, EGDs were performed by many physicians and, similar to other endoscopic findings, RSL quantification is somewhat subjective. The use of a standardized data collection form in which the presence or absence of findings was recorded may have reduced ascertainment bias. As well, the consistent association between presence of RSLs and CD suggests that endoscopists were consistent in how they reported this finding.

Red Spot Lesions in the duodenal bulb may be an underappreciated, yet comparably specific endoscopic sign of CD to other more recognized features, such as nodularity, mosaic patterns, scalloping, and flattening of mucosal folds. In patients undergoing upper endoscopy for gastrointestinal symptoms, RSLs may prompt the endoscopist to consider the

diagnosis of CD and procure adequate biopsies from both the duodenal bulb and the distal duodenum to enable evaluation for CD. Routine use of NBI may assist the endoscopist in identifying the lesions. Greater awareness of endoscopic signs of CD and targeted biopsy of patients may increase identification of CD among symptomatic patients undergoing upper endoscopy in whom the diagnosis is not suspected prior to endoscopy.

Acknowledgments

Source of Funding:

This research was supported by Boston Children's Hospital. Jocelyn A. Silvester, MD is supported by NIH/NIDDK T32 DK 07760. All other authors report no financial disclosures.

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What is Known

- Although gross endoscopic appearance of the duodenum is not considered diagnostic of CD, commonly cited endoscopic findings have moderate sensitivity and high specificity in populations with suspected celiac disease (CD).
- Recognition of key duodenal signs during endoscopy may facilitate diagnosis of otherwise unsuspected CD.

What is New

- The presence of small, discrete “red spots” (Red Spot Lesions or RSLs) may represent a distinct endoscopic finding of CD in the duodenal bulb.
- Patients with elevated serum tTG IgA antibodies may be more likely to have RSLs.

Figure 1. RSLs in the duodenal bulb of 5-year-old male diagnosed with CD presenting with constipation, encopresis, and elevated tTG IgA (A is white light and B is NBI). (C, inset) RSLs in the duodenal bulb of 10-year-old female diagnosed with CD presenting with abdominal pain, elevated tTG IgA, and Type 1 diabetes.

Table 1.

Comparison of study population with and without CD

	Celiac disease (n=75)	No celiac disease (n=96)	P value
<i>Demographic Characteristics</i>			
Median age [IQR], years	8.7 [4.5–13.3]	8.8 [5–13.1]	1
Male:female ratio	28:47	52:44	0.04
<i>Serology</i>			<0.0001
tTG IgA < 20	16% (12)	93% (89)	
tTG IgA 20 – 100	20% (15)	2% (2)	
tTG IgA > 100	63% (47)	2% (2)	
Unknown	1% (1)	3% (3)	
<i>Histologic findings</i>			<0.0001
Marsh 0 (normal)	--	91% (87)	
Marsh 1	--	9% (9)	
Marsh 2	4% (3)	--	
Marsh 3a	27% (20)	--	
Marsh 3b	41% (31)	--	
Marsh 3c	28% (21)	--	
<i>Symptoms at Presentation (%(n))</i>			
Abdominal pain/cramps	53% (40)	59% (58)	0.44
Diarrhea	39% (29)	34% (33)	0.68
Constipation	36% (27)	30% (29)	0.52
Abdominal distension	21% (16)	10% (10)	0.08
Nausea/vomiting	29% (22)	38% (36)	0.34
Loss of appetite	17% (13)	23% (22)	0.48
Weight loss/poor weight gain	36% (27)	28% (27)	0.35
Short stature/poor growth	16% (12)	16% (15)	1
Increased fatigability	19% (14)	17% (16)	0.89
Joint problems	8% (6)	8% (8)	1
Severe mouth ulcers	3% (2)	6% (6)	0.46
Itchy rash	3% (2)	3% (3)	1
Dairy Intolerance	5% (4)	6% (6)	1
Gastroesophageal reflux	9% (7)	27% (26)	0.006
Gassiness	15% (11)	18% (17)	0.75
Headache	17% (13)	15% (14)	0.78
<i>Associated Diseases (%(n))</i>			
Diabetes Mellitus	12% (9)	2% (2)	0.02
Thyroid Disease	4% (3)	1% (1)	0.45
Down Syndrome	3% (2)	1% (1)	0.84

Table 2.

Prevalence and diagnostic accuracy of gross endoscopic findings in celiac disease

	Celiac disease (n=75)	No celiac disease (n=96)	Sensitivity	Specificity	Positive Predictive Value(PPV)	Negative Predictive Value(NPV)
<i>Duodenal Bulb</i>						
Normal	28% (22)	88% (84)	-	-	-	-
RSLs	31% (23)	6% (6)	31%	94%	80%	63%
Nodularity	40% (30)	4% (4)	40%	96%	88%	67%
Ulceration	3% (2)	2% (2)	3%	98%	50%	56%
<i>Distal Duodenum</i>						
Normal	33% (25)	86% (82)	-	-	-	-
Flattened Folds	22% (15)	7% (7)	22%	93%	68%	60%
Scalloped Folds	44% (32)	6% (6)	44%	94%	84%	68%
Nodularity	23% (17)	1% (1)	23%	99%	94%	62%
Ulceration	1% (1)	2% (2)	1%	98%	33%	56%
Lack of Villi	31% (23)	4% (4)	31%	96%	85%	64%