Implications of Positive Anti-Gliadin Antibody with Negative Tissue Transglutaminase Antibody Titers While Consuming Gluten

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Introduction

Celiac disease is a well-known small bowel enteropathy resulting in intestinal inflammation and atrophy in the setting of genetically predisposed gluten sensitivity. After ingestion, gluten is broken down along the small bowel brush border most notably resulting in gliadin. Gliadin is then broken down by tissue transglutaminase (tTG) resulting in deaminated gliadin. About 1% of the general population has developed antibodies to various enzymes and products along this pathway resulting in clinical manifestations of celiac disease [1,4]. Celiac disease most often presents in childhood with nonspecific symptoms including vomiting, diarrhea, abdominal pain and distension; though malabsorption may be severe enough to cause malnutrition and failure to thrive.

Due to its protean manifestations, celiac serology is often requested for chronic non-febrile ailments for which there is no obvious cause. Though small bowel biopsy remains the gold standard for confirmatory diagnosis, initial screening for antibodies targeted at enzymes and products along the gluten metabolism pathway in symptomatic patients that continue gluten consumption is recommended. The American Gastroenterology Association identifies anti-tissue transglutaminase antibody (tTG IgA) testing as the preferred and proficient single screening test for patients over 2 years old [1]. Tricore Laboratories, utilized by the University of New Mexico, routinely performs total serum IgA levels, anti-deamidated gliadin IgA antibody (AGA IgA), and tissue transglutaminase IgA antibody (tTG) levels when a celiac serology is requested. Though this combination of tests is performed to increase the overall sensitivity of the screening, positive AGA in the setting of negative tTG has often been considered a false positive result requiring additional workup [1,2].

Of note, an additional immune-mediated enteropathy that often presents with nonspecific symptomatology is Eosinophilic Esophagitis (EoE). EoE is a chronic inflammatory process in which the esophageal epithelia is believed to lose its barrier function ultimately resulting in esophageal inflammation, most notably eosinophilic infiltration. Patients often present with signs and symptoms of esophageal dysfunction, some of which may overlap many of the presenting symptoms of celiac disease. To date, diagnosis relies on clinical suspicion after ruling out other potential causes with ultimate confirmation by biopsy [3].

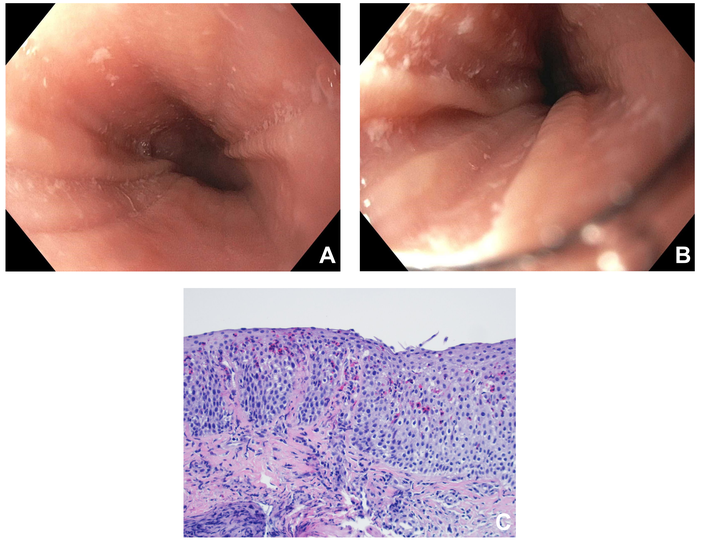
The purpose of our evaluation is to understand the diagnostic implications of negative tTG IgA in the setting of positive AGA IgA in pediatric patients who are consuming gluten at the first evaluation. Through recent observation it has been shown that this result pattern suggests that the likelihood of celiac disease is in fact very low, though may be indicative of other conditions, most consistently eosinophilic esophagitis. Therefore, in the presence of a negative tTG, a positive anti-gliadin antibody should be considered a false positive test for celiac disease, though still suggests notable enteropathy such as EoE.

Cases

Over the last 18 months, the UNM Division of Pediatric Gastroenterology has identified 8 children with a positive AGA and negative tTG, all with an initial presentation of persistent gastrointestinal distress and all while continuing to consume gluten. The patients range in age from 2 to 17 years old. Most are considered otherwise healthy, though few have notable comorbidities including one with cystic fibrosis and another with notable depression and anxiety. As noted in Table 1, 4 patients have undergone diagnostic endoscopy with the other 4 currently pending endoscopy scheduling. Of the 4 children status post endoscopy, 3 have confirmed eosinophilic esophagitis per endoscopy with confirmatory histologic evaluation (Image A-C) and 1 had overall normal endoscopic results, all without evidence of celiac disease.

Table 1. Serologic and EGD Results for 8 Patients With GI Distress, Celiac Screening

Patient	tTG (Ref 0-14.9)	AGA (Ref 0-14.9)	EGD Results
A	<0.5	19.8	EoE
B	<0.5	239	EoE
C	<0.5	28.2	EoE
D	<0.5	>250	No inflammatory changes
E	5.9	47	pending
F	<0.5	21.4	pending
G	<0.5	153	pending
H	<0.5	24.8	pending



Images A-C: Images A through C were obtained during EGD of patient B. Image A and B are gross visual representations of the esophagus with evidence of eosinophilic esophagitis including mucosal changes with white plaques and linear furrowing. Image C is a histological sample obtained from the same EGD with pathology report noting reactive squamous mucosa with increased eosinophilic infiltration also consistent with eosinophilic esophagitis.

Discussion

Many gastroenteropathies present with similar and overall nonspecific symptoms, oftentimes requiring empiric treatment in conjunction with a wide array of screening. Celiac serology is a common screening test performed for this specific purpose. Though tTG positivity has long been considered the standard for initial diagnosis of celiac disease, many laboratories have added at least one additional serologic test to the celiac screen with the intention of increasing screening sensitivity. The University of New Mexico relies on Tricore Laboratories for the majority of the laboratory testing. Tricore's celiac screen includes baseline IgA levels, tTG IgA, and AGA IgA levels. It has often been thought that negative tTG in the setting of positive AGA has been representative of a false positive, which poses the question of the validity and necessity of AGA testing in screening for celiac disease.

The results of this analysis suggest that, though negative tTG in conjunction with positive AGA doesn't necessarily point to celiac disease, this result pattern may point to something else useful. Positive AGA in the presence of negative tTG suggests that the likelihood of celiac disease is very low, though may be indicative of other conditions such as eosinophilic esophagitis.

We recognize the limitations of this analysis given the small sample size, though a more comprehensive 10-year retrospective study is planned.

Conclusion

Positive tTG is still believed to be the single best diagnostic test for celiac disease alone. Common serologic screening often involves at least one additional test that may include AGA as it does at Tricore Laboratories. Based on the preliminary results of this ongoing analysis, the presence of a negative tTG with a positive anti-gliadin antibody is likely representative of false positivity for celiac disease, though has been consistently found with eosinophilic esophagitis.

References

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