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Cow's Milk Protein-Induced Villous Atrophy and Elevated Celiac Autoimmunity in Children with Celiac Disease on a Glutten-Free Diet: A Report of Three Cases

Kristin Capone

Naire Sansotta

Pankaj Vohra

Stefano Guandalini

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Kristin Capone, MD[1]; Naire Sansotta, MD[2]; Pankaj Vohra, MD[3]; Stefano Guandalini, MD[1]

[1]Department of Pediatric GI, Hepatology & Nutrition, University of Chicago - Comer Children's Hospital, Chicago, IL; [2]Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy; [3]Division of Pediatric Gastroenterology, University of New Mexico, Albuquerque, NM

Section of Pediatric GI, Hepatology & Nutrition, The University of Chicago - Comer Children's Hospital

BACKGROUND

- The vast majority of children with celiac disease (CD) respond to a gluten-free diet (GFD). Rarely elevation of tissue transglutaminase IgA (TTG), endomysial antibodies (EMA) or villous atrophy (VA) persists.
- In most cases this is related to ongoing incidental gluten ingestion, yet some patients remain refractory despite the strictest GFD.
- Cow's milk protein allergy (CMPA) can cause enteropathy and a recent case report also described an associated elevated TTG.[1]

OBJECTIVES

- To describe the serologic and histologic response of three patients with CD who had persistent autoimmunity and VA despite a strict GFD, to the elimination of cow's milk protein.

PATIENT 1

- Patient 1 (female) initially presented to an outside gastroenterologist at 20 months with vomiting, diarrhea, weight loss, and irritability. TTG was >100U (nml <20U) which led to an esophagogastroduodenoscopy (EGD) 3 months later. No family history of CD.
- Duodenal histology demonstrated VA and increased intraepithelial lymphocytes (IELs) consistent with CD.
- She began a GFD with complete resolution of symptoms; however, her TTG rechecked 6, 12, and 17 months later remained >100U despite careful dietary review by a dietician.
- Repeat EGD done 18 months on the GFD was again consistent with CD.
- She was then referred to our center where her diet was also reviewed.
- Two years into a GFD, she started a gluten contamination elimination diet comprised of only unprocessed foods, and 4 months later her TTG was 790U and EMA 1:80. Repeat EGD remained consistent with CD.
- Immunophenotyping was performed and the majority of the IELs were CD3+/CD8+ and thus not supportive of type 2 refractory CD.
- Work-up was negative for other etiologies of elevated TTG including thyroid, autoimmune, and inflammatory conditions.
- She was followed conservatively for the next 18 months as she was asymptomatic with normal growth.
- Four years into a GFD, we started a strict cow's milk protein-free diet (CM-GFD) hypothesizing that CMPA could cause the persistent VA and elevated serology. Six months into the diet her TTG was 22U.
- Twelve months later her serologies (TTG of 14U and negative EMA) were completely normal for the first time since diagnosis. Repeat EGD showed, again for the first time, completely normal duodenal histology.

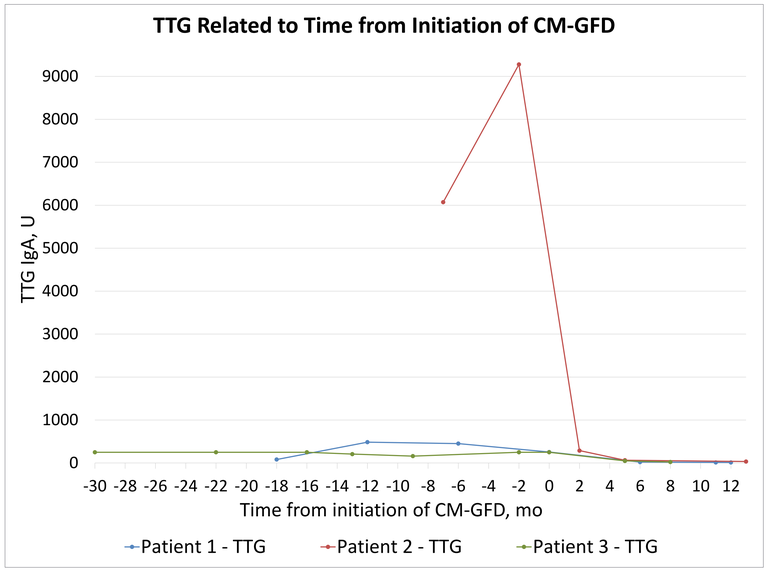
PATIENT 2

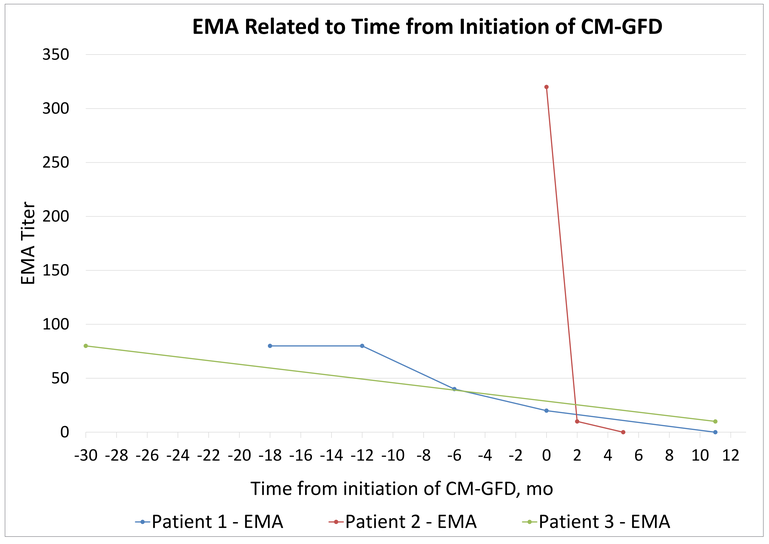
- Patient 2 (female) first presented to an outside gastroenterologist at 13 months with diarrhea, abdominal distention, and poor mood. Her TTG was >100U (nml <4U) with a positive EMA. No family history of CD.
- An EGD done 3 months later was consistent with CD.
- She started a GFD with resolution of her symptoms and normal growth.
- Her TTG 13 months into the GFD remained >100U, so oats were also eliminated to exclude possible cross-contamination.
- She was referred to our clinic 2 months later when her TTG was quantified at 6072U (nml <20U). Our dietician reviewed her diet and judged it as strictly GF.
- Five months later her TTG had increased to 9278U and EMA was 1:320. Repeat EGD 2 months later showed persistent VA and increased IELs.
- Extensive workup for other causes of elevated TTG was also negative.
- After our experience with patient 1, we started patient 2 on a CM-GFD and 2.5 months later her TTG had dropped to 289U and EMA 1:10.
- Another 5 months later her TTG was 65U and EMA became negative. After 13 months on the CM-GFD her TTG is 35U. Repeat EGD is pending.

PATIENT 3

- Patient 3 (female) presented to University of New Mexico at 17 months with 2 months of vomiting, diarrhea, weight loss, weakness, irritability, and lethargy and refusal to walk for 3 weeks. No family history of CD.
- Her albumin was 1.9 and TTG was >225U (nml <15U). Thyroid studies were normal. DQ2 positive.
- EGD at 20 months showed increased IELs, VA, and crypt hyperplasia.
- Symptoms resolved on a strict GFD excluding any processed foods or foods containing more than 4 ingredients.
- After starting the GFD, TTG was elevated to 132U at 3 months, >225U at 10 months, and >250U at 12 months with an EMA of 1:80.
- Two years after diagnosis, she underwent a 2nd EGD which again demonstrated increased IELs and VA. Immunophenotyping was normal with the majority of IELs CD3+/CD8+.
- TTG remained elevated >250U so a 3rd EGD was done 20 months into the GFD which demonstrated increased IELs and mild villous blunting.
- After a 3 month trial of oral steroids, the TTG decreased to 161U but increased again to >250U 6 months after steroids were discontinued.
- A 4th EGD done 4 years after diagnosis again demonstrated increased IEL's and moderate villous blunting. Based on the experience at our center, she was also placed on a CM-GFD.
- After starting the CM-GFD, TTG reduced to 49U at 5 months and reduced to 24.8U at 8 months with EMA of <1:10. Awaiting repeat EGD.

FIGURE 1. TTG AND EMA RELATED TO TIME FROM INITIATION OF CM-GFD





CONCLUSIONS

- We present, for the first time, three cases of asymptomatic pediatric celiac disease with persistently elevated TTG, EMA, and VA despite a strict GFD who responded promptly to the elimination of milk protein with full normalization of serology and - in one case so far - documented histologic recovery.
- This suggests a concomitant cow's milk allergic enteropathy may be responsible for some CD patients who do not respond to a strict GFD, and that in such pediatric patients a CM-GFD should be tried prior to labeling a patient refractory.

[1]Merikas E, Grapsa D, Syrigos K, et al. Cow's Milk Protein Allergy Causing Persistent Elevation of Antitissue Transglutaminase Antibodies in a Child With Celiac Disease. J Clin Gastroenterol. 2015 Sep;49(8):714-5.