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Introduction

- Seronegative enteropathy=
 - Negative celiac disease (CeD) serology [tissue transglutaminase (tTG), deaminated gliadin peptide (DGP) +/- anti-endomysial antibody (EMA)] in patients with small bowel villous atrophy
 - Many common medications have been implicated in causing a reversible enteropathy
 - mainly Olmesartan
- We describe the first case of a patient who developed severe diarrhea and subsequent diagnosis of seronegative enteropathy following initiation of ethacrynic acid

Case Presentation

- 78-year-old male with a history of hypertension, hyperlipidemia, and chronic kidney disease
- Presented for outpatient gastroenterology consultation with a complaint of 16 days of moderate volume, watery stools occurring 3-5 times per day
- He was started on ethacrynic acid by his nephrologist for volume overload ~6 weeks prior to presentation
- Other medications/supplements:
 - Magnesium, vitamin E and vitamin C supplements, which he stopped, without improvement in diarrhea
 - Continued to take losartan for high blood pressure, which he had been on for many years

Workup

- Infectious and chronic diarrhea workup returned negative except for an elevated calprotectin level:
 - 753 ug/g (normal < 49 ug/g)
- Colonoscopy with terminal ileum intubation was normal
 - negative random biopsies for microscopic colitis
- Upper endoscopy visually normal
 - duodenal biopsies: mild to moderate villous blunting (Figure 1a) and increased intraepithelial lymphocytes (Figure 1b), consistent with a Marsh 3a-3b lesion
- CeD serological testing was normal
- Absent celiac genes (HLA DQ2.2, DQ 2.5, and DQ8)

Clinical Course

- After stopping ethacrynic acid, the patient's diarrhea resolved within 2 days
- Repeat duodenal biopsies 5 months later showed resolution of his enteropathy

Discussion

- Seronegative enteropathy is a clinical challenge as many conditions and medications may cause severe small intestinal damage
- Seronegative CeD was excluded in this patient with absent celiac genes and enteropathy resolution without a gluten-free diet
- Other causes of seronegative enteropathy:
 - Autoimmune: Crohn's disease, autoimmune enteropathy
 - Infectious: HIV enteropathy, tropical sprue, mycobacterium avium complex, Whipple's disease, giardiasis, tuberculosis, SIBO
 - Infiltrative: amyloidosis, collagenous sprue, eosinophilic enteritis
 - Other: lymphoma, common variable immune deficiency, abetalipoproteinemia, peptic duodenopathy, Zollinger-Ellison syndrome, small bowel ischemia, malnutrition, radiation enteritis, graft-versus-host disease
 - Medications: angiotensin-receptor blockers (Olmesartan, losartan), NSAIDs (sulindac), alcohol, chemotherapy/ immunosuppressive (azathioprine, mycophenolate mofetil, methotrexate, colchicine), anti-CTLA4 antibody (ipilimumab), antibiotics (neomycin)
- First case to our knowledge of seronegative enteropathy due to ethacrynic acid
 - With clinical and histological remission upon drug discontinuation

Conclusions

- It is important for clinicians to recognize each potential drug associated with seronegative enteropathy, in order to properly diagnose and manage an easily reversible condition
- Incorrect interpretation of the duodenal biopsies could have led to a misdiagnosis of CeD and a subsequent unnecessary gluten free diet

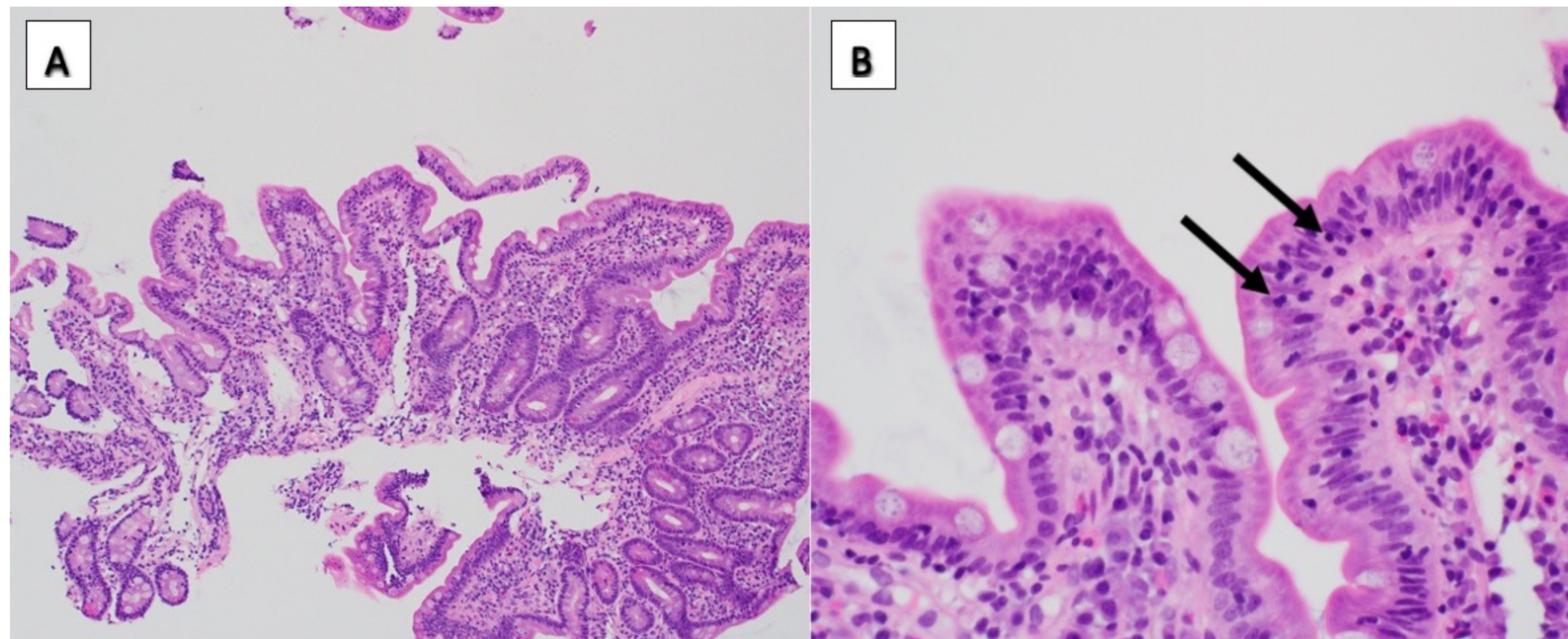


Figure 1: A: Duodenal biopsies showing villous blunting (H&E stain,100x magnification); B: Duodenal biopsies with arrows pointing to increased intraepithelial lymphocytes (H&E stain, 400x magnification)

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