

Preexposition Prophylaxis With Truvada (Tenofovir/Emtricitabine) as Potential Cause of Celiac Disease-Like Enteropathy

Präexpositionsprophylaxe mit Truvada (Tenofovir/Emtricitabin) als eine mögliche Ursache Zöliakie-ähnlicher Enteropathie



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ABSTRACT

We present here a case of a 39-year-old patient who presented with celiac-disease-like symptoms and MARSH 3a histology in duodenal biopsies under normal diet. Interestingly, HLA

genotyping and celiac-specific serology were negative, primarily leading to exclusion of celiac disease. However, biopsies from a second endoscopy a couple of months later (still under normal diet) showed histologic progression of the disease to MARSH 3b and led to the re-evaluation of the out-of-hospital-obtained histological samples by a pathologist experienced in celiac disease. The second biopsy described previously as MARSH 3b turned out to be non-specific and was therefore re-classified as MARSH 0. After all known causes of duodenal villous atrophy were excluded by a thorough evaluation, a correlation between the first biopsy (MARSH 3a) and Truvada intake could be established. After Truvada discontinuation and under normal diet, normalisation of duodenal mucosa was observed, leading to the assumption that Truvada could lead to celiac-like enteropathy.

ZUSAMMENFASSUNG

Wir präsentieren den Fall eines 39-jährigen Patienten, der unsere Klinik aufgrund von Zöliakie-ähnlichen Symptomen und einem histologischen Befund von MARSH 3a aufgesucht hat. Die Zöliakie-spezifische Serologie sowie HLA-Genotypisierung waren jedoch negativ, wodurch Zöliakie ausgeschlossen wurde. Sechs Monate später wurden erneut intestinale Biopsien entnommen, die die Progression der Erkrankung von MARSH 3a auf MARSH 3b zeigten. Infolgedessen wurden die histologischen Schnitte noch einmal, von einem in Zöliakie erfahrenen Pathologen befundet. Die zweite Biopsie – ursprünglich MARSH 3b – stellte sich als unspezifisch heraus und wurde auf MARSH 0 heruntergestuft. Wir konnten alle bekannten Ursachen von Zottenatrophie ausschließen und letztlich eine Korrelation zwischen der ersten Biopsie (MARSH 3a) und Einnahme von Truvada feststellen. Nachdem der Patient das Medikament abgesetzt und dabei eine normale Diät gehalten hatte, normalisierte sich die duodenale Mucosa, was zur Annahme führte, dass Truvada eine Zöliakie-ähnliche Enteropathie verursachen kann.

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Truvada (tenofovir/emtricitabine) is a commonly prescribed drug for pre-exposition prophylaxis (PrEP) of human immunodeficiency virus (HIV)¹. The adherence to the regimen of once-daily dosing may almost completely reduce the risk of HIV acquisition [1]. Here, we present a case of celiac-disease-like enteropathy caused by Truvada. To the best of our knowledge, tenofovir/emtricitabine-induced celiac-disease-like enteropathy has not been previously described in the literature.

A 39-year-old male patient presented in December 2019 to our outpatient clinic for further evaluation and treatment of the MARSH 3A celiac disease (CD) revealed by duodenal biopsies (► **Fig. 1a**) obtained by upper gastrointestinal (GI) endoscopy in an out-of-hospital office. He was under normal diet at initial presentation. Celiac disease serology (IgA tissue transglutaminase (TG2) antibodies) was, however, negative (total IgA was normal). External stool cultures had been negative for bacterial or protozoal infection. Faecal calprotectin and routine lab values were normal except for folic acid deficiency. Abdominal ultrasound and upper abdominal MRI, performed because of exocrine pancreatic insufficiency (reduced stool elastase), were also unremarkable. At the time of presentation in our clinic, the patient complained of abdominal discomfort with the point of maximal intensity in the right upper quadrant and fluid-loose stools three times a day. He was 175 cm tall, had a stable weight of 75 kg and did not complain of weight loss. His family history was negative for celiac disease.

EMA- and TG2-antibodies were also negative at our laboratory, HLA genotype testing for HLA DQ2 and HLA DQ8 were negative as well. Consequently, celiac disease was primarily excluded, and a review of the pathology specimen was recommended. The patient remained on a normal diet.

However, he returned to our department only 6 months later, with a follow-up upper GI endoscopy performed in another GI out-of-hospital office with duodenal histology showing progression to MARSH 3B histology, according to the out-of-hospital pathologist. A sucrose–lactulose–mannitol (SLM) test demonstrated increased intestinal permeability, and thus, a gluten-free diet (GFD) was initiated for the first time. It resulted in complete resolution of the symptoms. Although seronegative CD or CD without HLA-

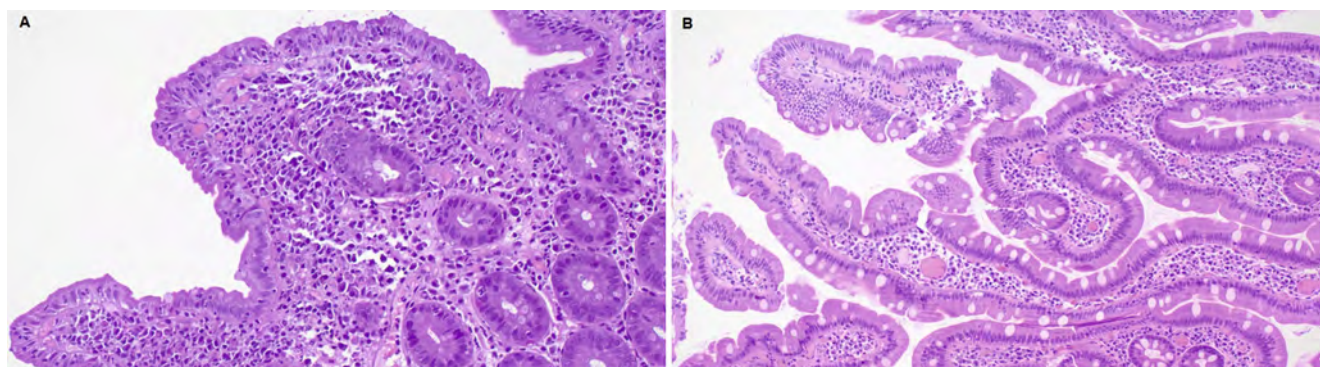
DQ2/DQ8 positivity are exceptions [2], the progression of histopathology from MARSH 3a to 3b and the patient's symptoms led to the decision of starting a GFD pending further clarification. Despite the fact that an SLM test reports on altered mucosal permeability and has been used in screening for CD [3, 4], it is not sufficiently specific.

Meanwhile, we initiated an extensive search for other possible causes of villous atrophy according to the current guidelines [5]. HIV serology testing was negative. IgG, IgM, IgA levels were normal, which excluded common variable immunodeficiency (CVID) as a possible cause. The patient had never visited tropical regions, making tropical sprue rather unlikely. Inflammatory bowel disease (IBD) was considered unlikely because of normal calprotectin. Stool examination for giardia was negative and a normal glucose H2-test ruled out small intestinal bacterial overgrowth (SIBO).

Furthermore, both histology specimens obtained outside the hospital were requested and re-examined by our hospital pathologists experienced in celiac disease, whereby no signs of collagenous sprue, amyloidosis, eosinophilic gastroenteritis, Whipple's disease, giardiasis, or tropical sprue and autoimmune enteropathy were found.

MARSH classification for the initial biopsy obtained in mid-October 2019 (► **Fig. 1a**) was re-evaluated, revealing MARSH 3a histology as previously described. However, the re-assessment of the biopsies from June 2020 showed only non-specific lesions that could not be unambiguously ascribed to celiac disease and were therefore classified as MARSH 0. The incorrect orientation of a biopsy specimen leading to tangential cuttings and faulty interpretations has been previously described [6].

A detailed medication history revealed no medication-associated causes of villous atrophy other than Truvada. The patient reported having taken Truvada from July 2019 till the beginning of October 2019 and further from July 2020 onwards. Thus, the second duodenal biopsies were obtained without Truvada and first duodenal biopsies only shortly after stopping the exposure. Consequently, Truvada-associated celiac-disease-like enteropathy was suspected. The patient was advised to discontinue PrEP medication and resume normal diet. A follow-up upper GI endoscopy 6 months later in September 2021 (6 months without Truva-



► **Fig. 1** The duodenal biopsies obtained in the upper gastrointestinal tract endoscopy. **A** – Biopsy from October 2019 showing villous blunting, crypt hyperplasia, goblet cell depletion, patchy intraepithelial lymphocytosis and increased lymphoplasmacytic cell content within the lamina propria, classified as MARSH 3a. **B** – Biopsy from September 2021 showing normal duodenal mucosa after Truvada discontinuation, assessed as MARSH 0. For **A** and **B**: original magnification 200x, hematoxyllin and eosin staining.



► **Fig. 2 Timeline summarizing patient's history.** Red triangles symbolise dates of gastroscopies. Time when the patient was under Truvada is shown in green, when under gluten-free diet in blue. GFD – gluten-free diet, PrEP – preexposure prophylaxis.

da and under normal diet) showed a histopathological resolution and no villous atrophy (► **Fig. 1b**, ► **Fig. 2**).

PrEP is associated with an increased risk of gastrointestinal adverse events, according to a recent meta-analysis (gastrointestinal adverse events (12 trials; RR, 1.63 [95% CI, 1.26–2.11];)) [7], but the pivotal trials on tenofovir/emtricitabine reported only on gastroenteritis, gastritis, abdominal pain and nausea.

Tenofovir is a nucleoside reverse transcriptase inhibitor (NRTI) available in two forms, of which tenofovir disoproxil fumarate (TDF) is a component of tenofovir/emtricitabine PrEP medication [8]. Among potential side effects, nephrotoxicity probably elicited by mitochondrial damage is best known [9]. Combination with emtricitabine – another NRTI agent [8] – may increase mitochondrial toxicity. Although these mechanisms are poorly understood [10] and not evaluated in intestinal tissues, this might be a possible explanation in our case. However, these speculations require further investigation. Activation of leucocytes in the intestines owing to tenofovir/emtricitabine administration has already been described in a rare case of eosinophilic colitis [11]. Whereas there was an eosinophilic infiltration in the aforementioned case, which made it easier to assume an allergic drug reaction, its absence in our case made the differentiation more complicated. Only did a thorough history taking and step-by-step exclusion enable the association between the symptoms and medication intake. Finally, Truvada should be added to the compendium of drugs linked to celiac-like enteropathy, similarly to the olmesartan medoxomil that has recently attracted the highest attention [12].

In summary, this case should raise clinicians' awareness for considering potential adverse effects of different medications such as tenofovir/emtricitabine in cases of duodenal atrophy mimicking celiac disease.

Conflict of Interest

JP: no conflicts of interest MW: no conflicts of interest HV: no conflicts of interest MT: speaker for Falk Foundation, Gilead, Intercept and MSD; advised for Albireo, BiomX, Boehringer Ingelheim, Falk Pharma GmbH,

Genfit, Gilead, Intercept, Janssen, MSD, Novartis, Phenex, Regulus and Shire. Travel grants from Abbvie, Falk, Gilead and Intercept and research grants from Albireo, Alnylam, Cymabay, Falk, Gilead, Intercept, MSD Takeda and UltraGenyx. He is also co-inventor of patents on the medical use of NorUDCA filed by the Medical Universities of Graz and Vienna. LKS: has been a principal investigator for studies sponsored by Sigma-Tau, Sanofi, Tigenix and FALK; has received lecture fees from MSD, AbbVie, Ferring, MerckSerono/Dr Falk, Chiesi, Novartis, Roche, Abbott, Phadia Austria/Thermo Fisher Scientific, CSL-Behring, Janssen-Cilag Pharma, Vertex; has received non-financial support from Mylan, Abbott, MSD, Gilead, MerckSerono/Dr Falk, Novartis, Pfizer, Janssen-Cilag Pharma, Chiesi, Shire, Abbvie, Takeda, Vertex, Astropharma; has been a consultant for MSD and Takeda MHK: no conflicts of interest

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