DR BENCE KŐVÁRI (Orcid ID : 0000-0002-4498-8781)

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Teriflunomide, a potential novel cause of chronic active colitis

Bence Kővári[1,2], Jeffrey Zachs [3], Brent Murchie [4], Gregory Y Lauwers[2]

1. Department of Pathology, University of Szeged, Albert Szent-Györgyi Health Center, Szeged, Hungary.
2. H. Lee Moffitt Cancer Center & Research Institute and Departments of Pathology & Cell Biology and Oncologic Sciences, University of South Florida, Tampa, FL, USA.
3. SaraPath Diagnostics & Sarasota Memorial Hospital Department of Pathology, Sarasota, FL, USA.
4. Florida Digestive Health Specialists & Florida State University College of Medicine at Sarasota Memorial Hospital, Sarasota, FL, USA.

Correspondence:

Bence Kővári

Full address: Department of Pathology, University of Szeged, Állomás u. 1, 6720 Szeged, Hungary.

E-mail: kovari.bence.p@gmail.com

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Teriflunomide is a novel pyrimidine synthesis inhibitor which limits immune response by selectively blocking dihydroorotate dehydrogenase, required by rapidly dividing B and T lymphocytes [1]. It is indicated as a first-line treatment for relapsing-remitting multiple sclerosis (RRMS). The most common adverse reactions reported in patients receiving either 7 or 14 mg daily include headache (18% and 16%), elevated alanine aminotransferase (13% and 15%), diarrhea (13% and 14%), alopecia (10% and 13%), and nausea (8% and 11%), respectively [2].

Although diarrhea is a frequent side effect, there is little known about the pathogenesis or the microscopic alterations. In a series of 100 patients treated with teriflunomide, 14 developed mild-to-moderate diarrhea, which resolved within a month; however, 4 experienced prolonged diarrhea related to lactose intolerance confirmed by a positive lactose breath test and associated with the lactose present in the capsule [3]. A recent manuscript proposed the possibility of teriflunomide promoting a lymphocytic colitis pattern [4]. Finally, Duquette et al. also described a case of histologically acute and subacute colitis related to high teriflunomide blood concentration after 2 years of treatment [5].

We report a case of colitis for which the pathology implicates teriflunomide therapy, despite the puzzling patient's history.

A 39-year-old female patient diagnosed with relapsing-remitting multiple sclerosis was treated with 14 mg *per os* teriflunomide per day. The patient has not received other immunosuppressant or immunomodulatory drugs. Three years after the initiation of the therapy, the patient developed prolonged watery diarrhea with cramping abdominal pain. Clostridioides difficile (C. diff) was detected from a stool sample one month after the start of the symptoms. The symptomology stopped after the cassation of teriflunomide and appropriate antibiotherapy.

The colonoscopy showed few scattered non-bleeding aphthous ulcers in the ileum. The colonic mucosa was diffusely congested, erythematous and friable. Shallow ulcerations, up to 15 mm

diameter, were detected in a confluent and circumferential pattern from the rectum to the ascending colon.

Terminal ileum and multistep colon biopsies were taken. Microscopically, there was no evidence of pseudomembranes, erupting “volcano” crypts, increased intraepithelial lymphocytosis, subepithelial collagen band, granuloma, microorganisms or vasculitis. The microscopy was very much suggestive of drug-induced colitis with multifocal crypt apoptosis and crypt withering combined with diffuse active inflammation and surface epithelial damage, minimal erosions, and reactive changes as well as cryptitis and crypt abscesses. Lamina propria lymphocytes, plasma cells, and eosinophil granulocytes were respectively moderately increased. Evidence of mild chronicity, including crypt architectural disarray, basal plasmacytosis with shortened crypts, and crypt dropout was also present (Figure 1, 2). Immunohistochemistry for cytomegalovirus (CMV) and adenovirus performed on multiple blocks yielded a negative result.

This case is challenging on several fronts. Based on the morphologic changes, we suggest that teriflunomide, a pyrimidine synthesis inhibitor, may initiate mucosal injury in a way similar to the purine synthesis inhibitor mycophenolate by altering DNA synthesis that is not only required by rapidly dividing B and T lymphocytes but also to a certain extend by intestinal epithelium [1]. However, while neither the endoscopic nor the microscopic appearance was consistent with C. diff colitis, it raises the question of whether teriflunomide could synergistically promote C difficile infection.

References

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Figure 1. Histological image of descending colon biopsy. Note the active inflammation with crypt abscesses, and apoptosis of crypt epithelial cells (asterisk).

Figure 2. Histological image of sigmoid colon biopsy. Note the active inflammation with mild crypt architectural distortion, basal plasmacytosis, and the withering crypts.

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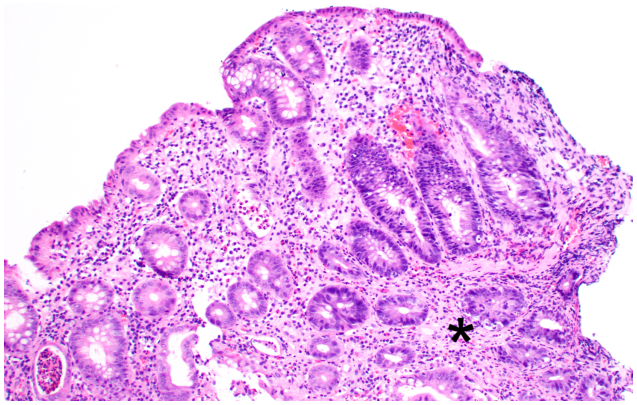

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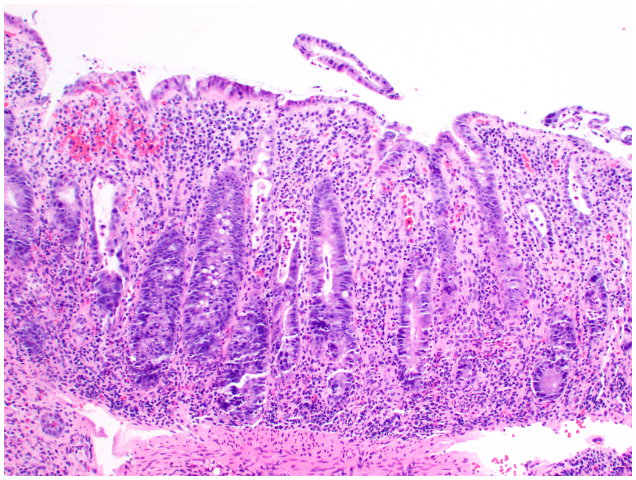

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