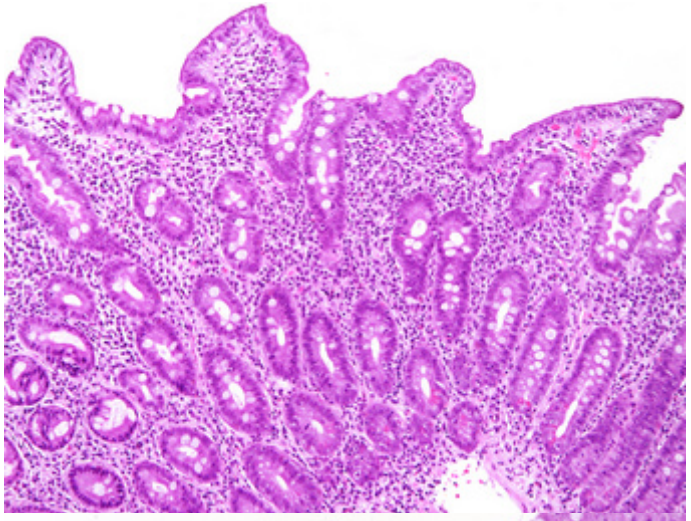
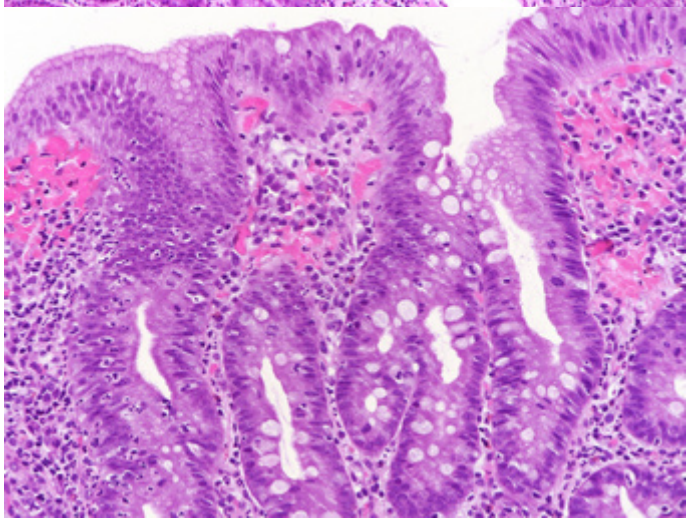
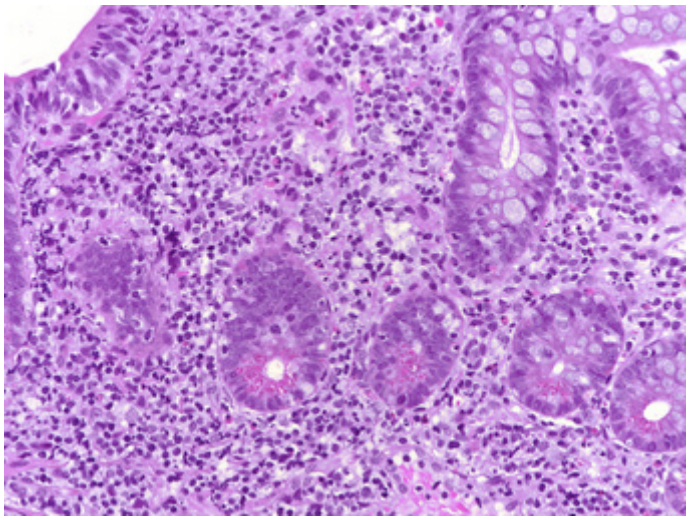
November 2020

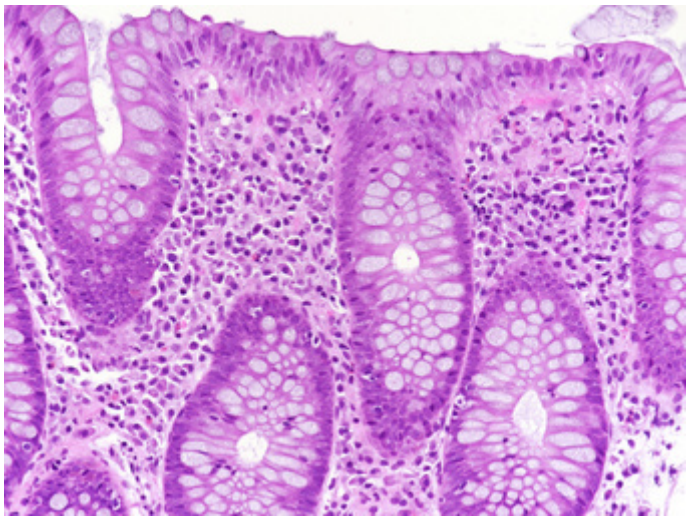
Small and large bowel biopsies from a 37-year old male with chronic diarrhoea.

What is your diagnosis?









Diagnosis:

Drug-related enterocolitis (emtricitabine/tenofovir).

Comment:

A 37-year old male underwent endoscopic evaluation of upper and lower gastrointestinal tract for “chronic diarrhoea” (lasting for months). The mucosa of stomach, duodenum, ileum and large bowel was unremarkable on gross inspection. Biopsies were taken from all sites.

While stomach biopsies (antrum and corpus) were normal, the duodenal mucosa showed villous blunting and crypt hyperplasia with increased apoptosis, up to 5 apoptotic bodies per biopsy specimen per investigated level (Panel A). There was increased inflammatory cell content within the lamina propria, but no intraepithelial lymphocytosis. Focal active inflammation was seen together with gastric/foveolar metaplasia (Panel B). Ileum biopsies likewise showed chronic active inflammation, increased apoptosis, up to 10 apoptotic bodies per biopsy specimen per investigated level, as well as eosinophilic infiltration and degranulation (Panel C). Biopsies sampled from different areas of the colon showed preserved architecture and slightly increased mononuclear infiltration without decreasing gradient from right to left colon/rectum. Apoptotic count within the crypt epithelium exceeded normal values (up to 7 apoptotic bodies per biopsy specimen per investigated level). The number of eosinophils was increased (without decreasing gradient to left colon/rectum; eosinophils were sometimes found deep below crypts and/or within the muscularis mucosae), with degranulation proven in biopsies lacking crush artefacts (Panels D-F).

This case is presented to illustrate potential impact of histological diagnosis but also limitations in the evaluation of patients with chronic diarrhoea. It is evident that firm diagnosis is not possible due to lack of specific histologic changes. Still, I would like to share some ideas regarding the work-up of this “everyday routine case”.

First, is this normal small and large bowel mucosa? No, it is definitively not, though changes are subtle.

Is this “unspecific mildly chronic, mildly active enterocolitis”? In general, use of the Sydney System (developed for diagnosis of gastritis) is discouraged for bowel biopsies, because “cells of chronicity” are normally present within the mucosa. In addition, a diagnosis like this is of no help for clinicians and patients.

Could this be chronic inflammatory bowel disease? The macroscopic appearance of the mucosa is entirely normal throughout, which would be very unusual, if not impossible, at first diagnosis of Crohn’s disease or ulcerative colitis. Although there is increased cell content within the lamina propria, we miss clear-cut features of chronicity, such as architectural distortion, metaplasia or basal plasmacytosis.

Could this be “microscopic colitis”? The normal endoscopic appearance would fit into this diagnostic category, though a 37-year-old male would not be the typical patient. Increased mononuclear inflammation would also fit; however, we miss intraepithelial lymphocytosis (for diagnosis of lymphocytic colitis) or subepithelial collagen deposition (for diagnosis of collagenous colitis).

There is increased mononuclear inflammation within the lamina propria (with lack of decreasing gradient from right colon to left colon/rectum), which is a rather unspecific finding and may simply indicate “resolving colitis”, that is, residual histologic changes after an infectious episode. However, the patient’s history indicates long-lasting, that is, chronic diarrhoea, and not (sub)acute symptoms.

Which are the most striking features in addition to increased mononuclear infiltration? These are increased apoptosis and eosinophilic infiltration and degranulation. Should this case therefore be signed out as “eosinophilic colitis”? In addition to the fact that definition of normal value differs within the literature, use of this term cannot generally be recommended, since clinicians do believe this to be a clear-cut entity, which in most cases, however, is not the case. There are many different scenarios, in which eosinophil counts may be increased, starting from parasitic infestation. The combination with increased apoptosis (and focal active inflammation) should in fact raise suspicion for drug-related disease, with NSAIDs being first choice. Depending on the clinical setting, mast cell staining (DD mast cell activation syndrome) may additionally be performed (e.g. CD117, mast cell tryptase) in this setting. In our patient, CD117 staining rendered normal values.

Finally, a phone call with the responsible clinician rendered the following information: celiac disease serology negative, stool testing (including parasites) negative, and no blood eosinophilia. The patient was having sex with men and was chronically using an antiretroviral combination drug (emtricitabine and tenofovir), which is used to treat or prevent HIV/AIDS before exposure in individuals who are at high risk. No other drugs were reported.

A quick literature search disclosed a recent case report on “eosinophilic colitis associated with emtricitabine/tenofovir”. Hence, the observed histologic changes are most probably related to the use of this combination drug. Since the patient denied discontinuation of his medication definitive proof is lacking.

For further reading:

- Langner C. Colorectal normal histology and histopathologic findings in patients with chronic diarrhea. Gastroenterol Clin North Am. 2012; 41: 561-80.
- McCarthy AJ, Lauwers GY, Sheahan K. Iatrogenic pathology of the intestines. Histopathology. 2015; 66: 15-28.
- Patil DT, Odze RD. Biopsy diagnosis of colitis: an algorithmic approach. Virchows Arch. 2018; 472: 67-80.
- Lozier MR, Sanchez AM, Reyes R. Eosinophilic Colitis Associated with Emtricitabine/Tenofovir. Cureus. 2018; 10: e3498.

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