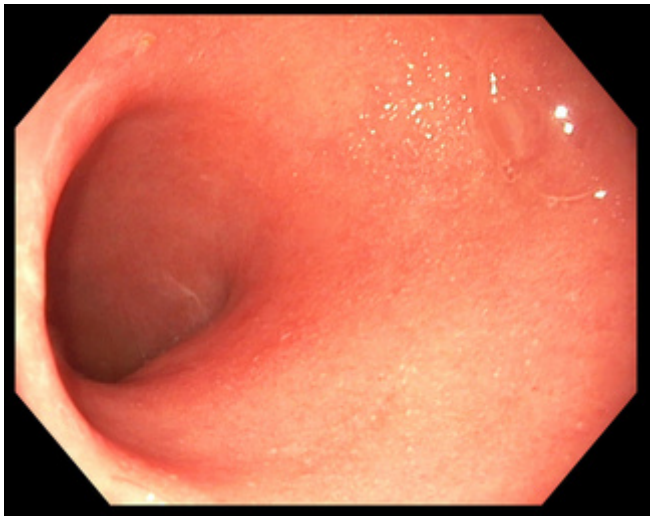
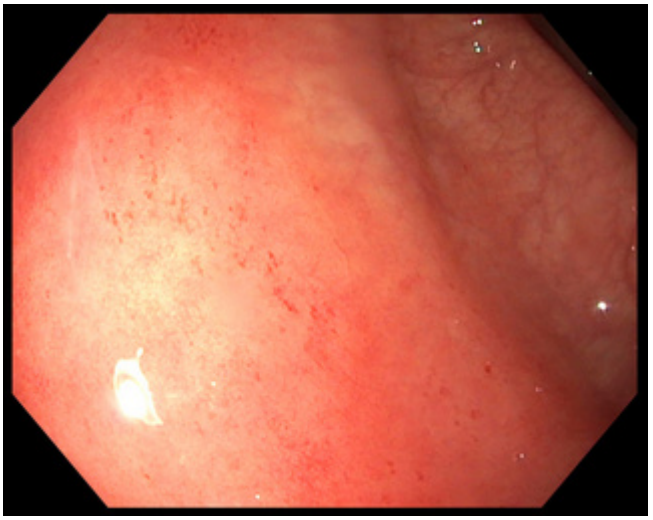
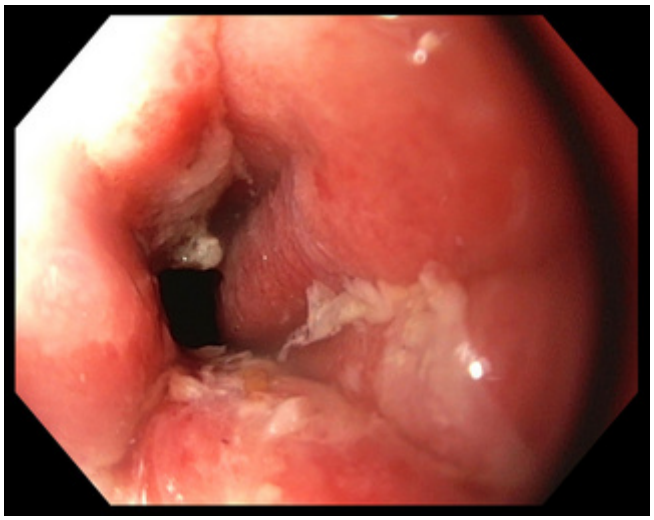
January 2021

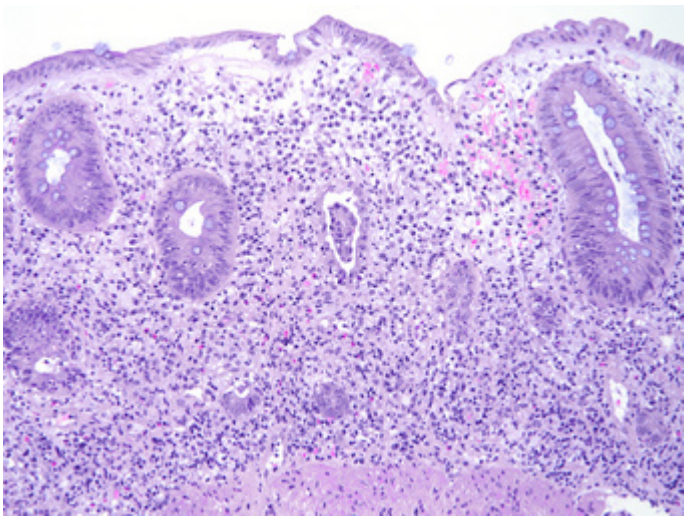
Large bowel biopsies in a 53-year-old male with history of prostate cancer.

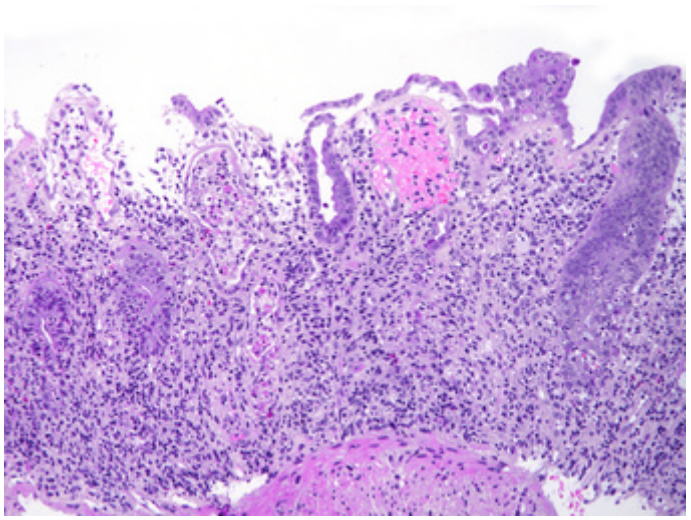
What is your diagnosis?

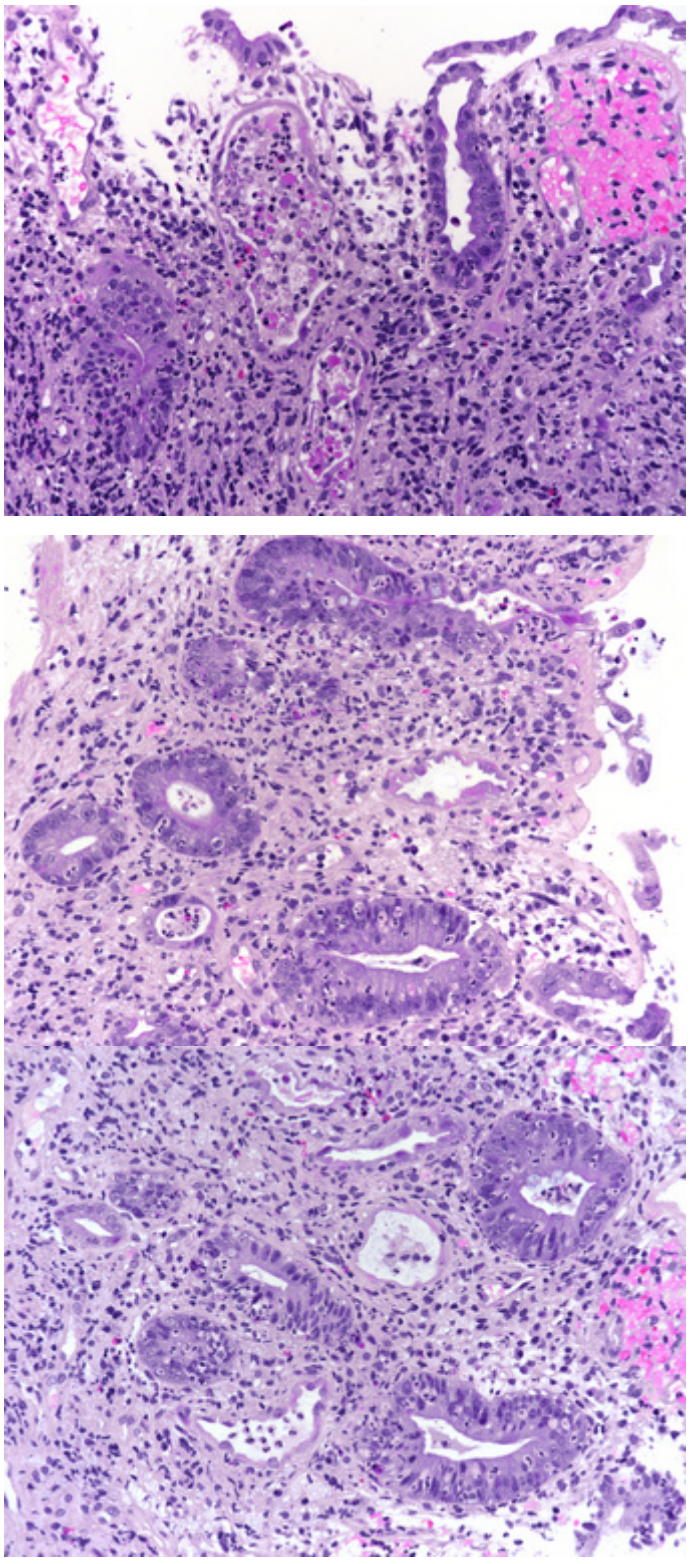












Diagnosis:

Immune checkpoint inhibitor colitis.

Comment:

The patient had undergone radical prostatectomy for Gleason 4+5=9 prostate cancer (pT3 N1 (4/26) L1 V1 Pn1) six years before colonoscopy, followed by postoperative radiotherapy due to positive margins. During the disease course, distant lymph node and widespread bone metastasis occurred and the patient received different chemotherapy regimens since then. During the last four months, he was on pembrolizumab/olaparib combination therapy. The endoscopic procedure was prompted by complaints about diarrhoea and haematochezia.

Endoscopy revealed mild diffuse colitis with obliterated vascular pattern and petechial haemorrhage (Panels A-B). The mucosa of the distal rectum was covered by fibrinous exudate, raising suspicion for radiation proctitis (Panel C). Biopsies were taken from this area.

Histology showed slightly altered mucosal architecture with expanded lamina propria, containing a mixed inflammatory infiltrate, characterized by lymphocytes and plasma cells (with mild basal plasmacytosis), macrophages, but also neutrophils and eosinophils (Panel D). Surface erosions and mucosal haemorrhage could easily be identified (Panel E). On larger magnification, neutrophilic cryptitis with increased crypt cell apoptosis and crypt abscess formation as well as crypts lined by flattened eosinophilic epithelium and/or containing apoptotic debris were seen (Panels F-H).

In summary, while there were some features of chronic injury (architectural distortion, basal plasmactosis), severe acute inflammation and signs of immediate epithelial injury, such as degenerative crypt epithelial changes and increased apoptosis dominated the histological picture.

This morphology is highly suggestive of drug-induced (“toxic”) colitis and is most probably caused by pembrolizumab. This drug belongs to the group of immune checkpoint inhibitors (ICI) which are used in oncology. Specifically, this humanized antibody targets the programmed cell death protein 1 (PD-1) receptor of lymphocytes, thereby preventing it from binding to ligands that deactivate the anti-tumour immune response. With regard to side effects that can be seen in the colon, ICIs are known to induce different types of mucosal injury. Some patients show active colitis with neutrophilic crypt microabscesses with prominent crypt epithelial cell apoptosis and crypt atrophy/dropout. These latter features are reminiscent of other colitides with prominent apoptosis such as acute graft-versus-host disease or certain drug-induced colitides. Other patients show a lymphocytic colitis-like pattern, characterized by increased intraepithelial lymphocytes and surface epithelial injury. Apoptosis is only mildly increased in these latter cases.

Depending on the duration of mucosal injury, features of chronic disease, such as architectural distortion and/or basal plasmactosis may be observed. This notion caused very recent subclassification into “acute colitis”, “chronic active colitis” and “microscopic colitis” phenotypes. Notably, histological activity was identified as independent predictor of adverse colitis outcome in that study (Pai et al. 2021).

Olaparib is a PARP inhibitor, inhibiting poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair. This drug is fairly new, and, to the best of our knowledge, colonic side effects have not yet been described (but can naturally not be ruled out at this time point).

For further reading:

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