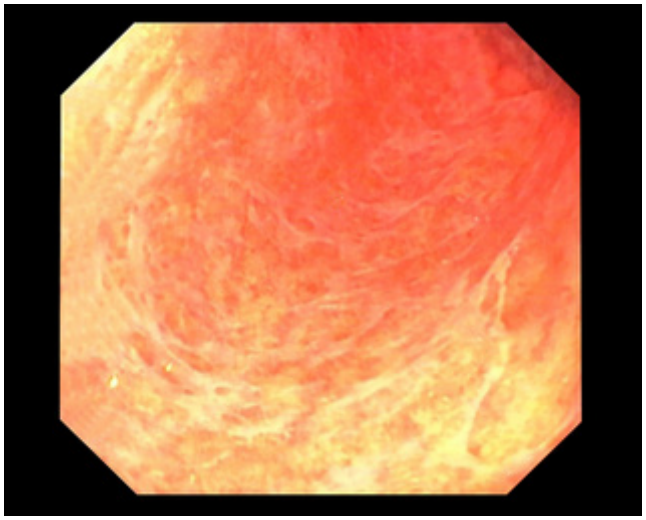
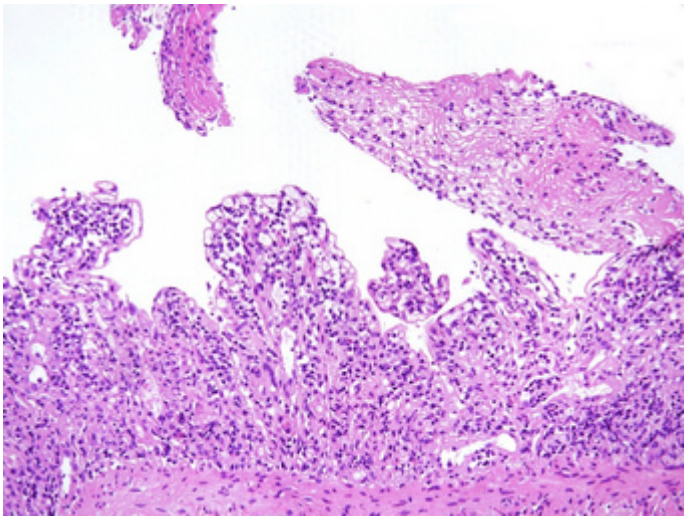
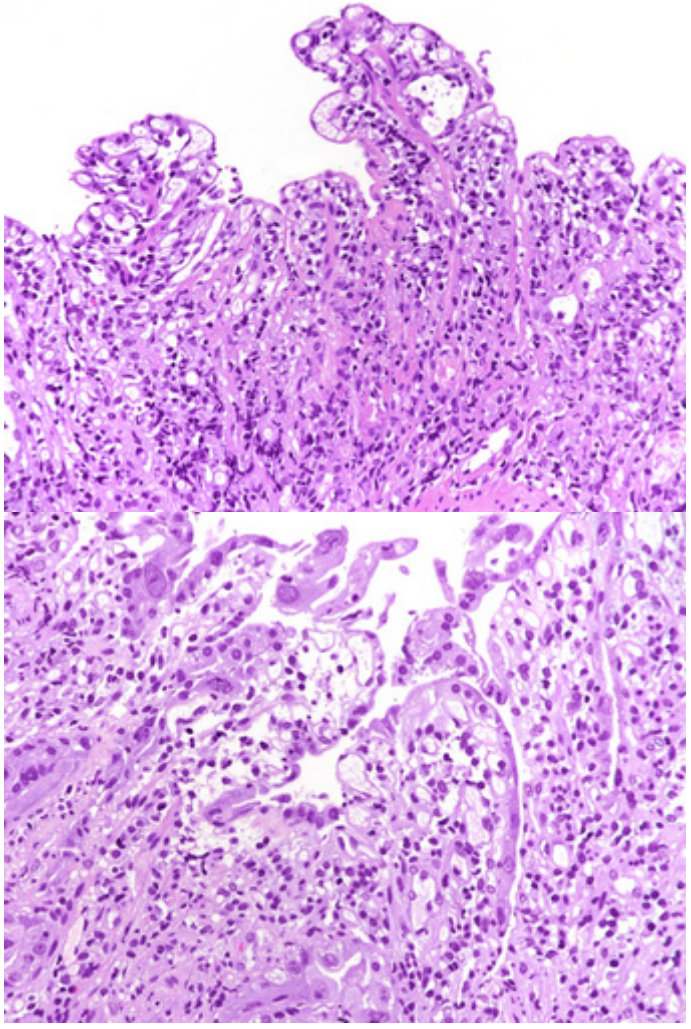
June 2019

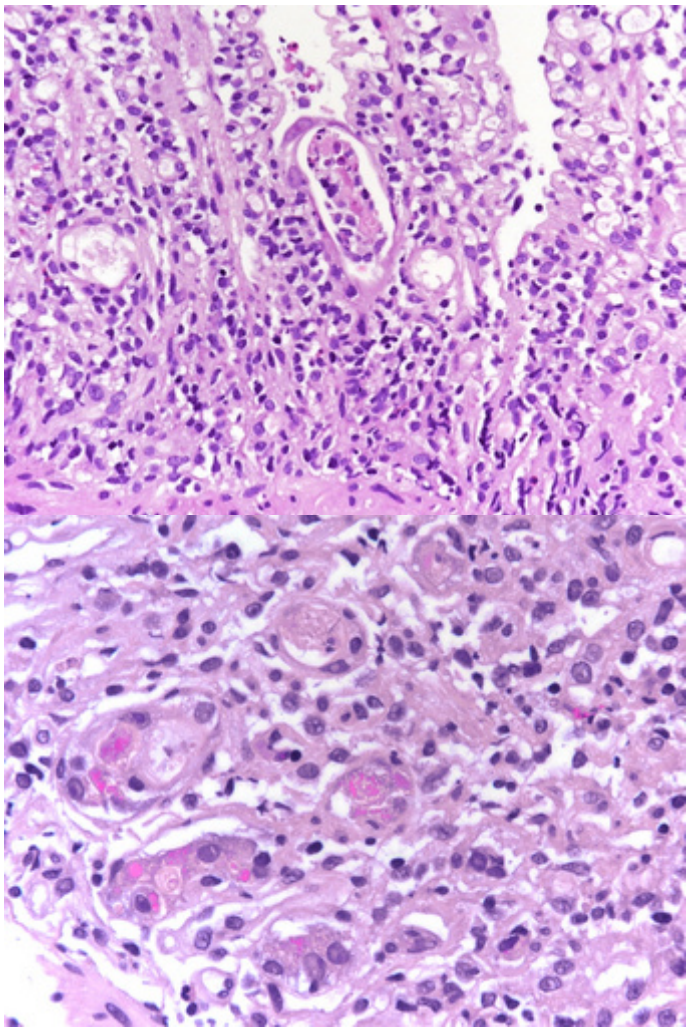
Duodenal biopsy from a 59-year-old female with history of allogeneic (hematopoietic) stem cell transplantation for acute myeloid leukaemia (AML).

What is your diagnosis?









Diagnosis:

Acute intestinal graft-versus-host disease (GvHD).

Comment:

Endoscopically, the duodenal mucosa demonstrated oedema along with erythema and erosions, partly covered by fibrinous exudate (Panel A). Upon histology, the lamina propria is expanded by a mixed inflammatory infiltrate. There is frank epithelial destruction with total necrosis / loss of individual / contiguous crypts and severe villous atrophy. A fibrinous exudate is seen on the mucosal surface (Panels B and C). On higher power, large areas of erosion are seen, the recovering epithelium showing mitotic figures and bizarre nuclei, which were negative for cytomegalovirus (CMV) upon immunohistochemistry (Panel D). Apoptotic cells are observed at the bottom of the remaining crypts within the lining and also within the crypt lumen (Panel E and F), ultimately qualifying for diagnosis of severe graft-versus-host disease (GvHD).

GvHD is a severe complication of allogeneic hematopoietic stem cell transplantation (HSCT).The disorder frequently involves the gastrointestinal tract, but may also affect skin, liver and more rarely other organs, such as lung. Historically, GvHD has been classified into “acute GvHD” (occurring within 100 days of HSCT); “persistent, recurrent, or late acute GvHD” (occurring more than 100 day after HSCT, without diagnostic or distinctive manifestations of chronic GvHD); “chronic GvHD”, no time limit, with at least one diagnostic or distinctive manifestation of chronic GVHD, without features characteristic of acute GvHD. Overlap pictures may exist.

The histologic hallmark of acute GVHD in the gastrointestinal tract is apoptosis of individual epithelial cells, originally described as crypt cell degeneration. Of note, apoptosis, ranging from focal to extensive, is prominent in the regenerative compartment of the gland or crypt, that is, within the small and large bowel at

the base of the crypts. Minimal thresholds have not been fully established, but most pathologists require the finding of at least one apoptotic body per biopsy (per investigated level) to suggest diagnosis of GvHD on histologic grounds. In more severe disease, there may be crypt destruction with apoptotic debris admixed with neutrophils within crypt lumina, and ultimately total crypt loss. In 1974, Lerner et al. suggested a grading system, which nicely illustrates the progressive mucosal damage. Due to limited clinical implications this system is no longer applied. Features of chronic GvHD in the gastrointestinal tract include web and/or stricture formation (concentric rings).

Differential diagnosis mainly include effects of chemotherapeutic conditioning regimens (may lead to false-positive reporting in the first 20 days after HSCT) and infections, such as viral infections (most commonly CMV). The latter may induce reactive nuclear changes in crypt epithelial cells along with increased mitotic activity. Of note, certain drugs may also induce apoptosis within the gastrointestinal tract, and ultimately a GvHD-like picture. Most important in this group is mycophenolate mofetil (MMF), as this drug may be used after HSCT to prevent graft rejection.

Accurate pathological work-up is necessary, which includes analysis of several levels (at least 8 serial / step sections are recommended to avoid false-negative reporting). Detection of apoptotic bodies may be facilitated by immunohistochemical staining with activated caspase 3, but interpretation of staining results may be challenging. Testing for CMV infection should be done in all cases, that is, including cases with no suspicion on H&E. Please note that that CMV and GvHD may simultaneously affect the gastrointestinal tract. The pathologist’s report should be made in accordance with the NIH consensus, including the categories “not GvHD” (histologically no evidence for GVHD), “possible GvHD” (evidence of GvHD but other possible explanations), and “likely GvHD” (clear evidence of GVHD without a competing cause of injury).

For further reading:

- Lerner KG, Kao GF, Storb R, Buckner CD, Clift RA, Thomas ED. Histopathology of graft-vs.-host reaction (GvHR) in human recipients of marrow from HL-A-matched sibling donors. Transplant Proc. 1974; 6: 367-371.
- Washington K, Jagasia M. Pathology of graft-versus-host disease in the gastrointestinal tract. Hum Pathol. 2009; 40: 909-917.
- Shulman HM, Cardona DM, Greenson JK, et al. NIH Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. The 2014 Pathology Working Group Report. Biol Blood Marrow Transplant. 2015; 21: 589-603.

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