Case History:

A 59-year-old woman presented with polyps nearly “carpeting” the entire body and fundus of the stomach. Several of these polyps were biopsied. These biopsy and endoscopic findings prompted a total gastrectomy. Her most recent colonoscopy was approximately 3 years ago and showed only external and internal hemorrhoids with one adenoma in the sigmoid colon.

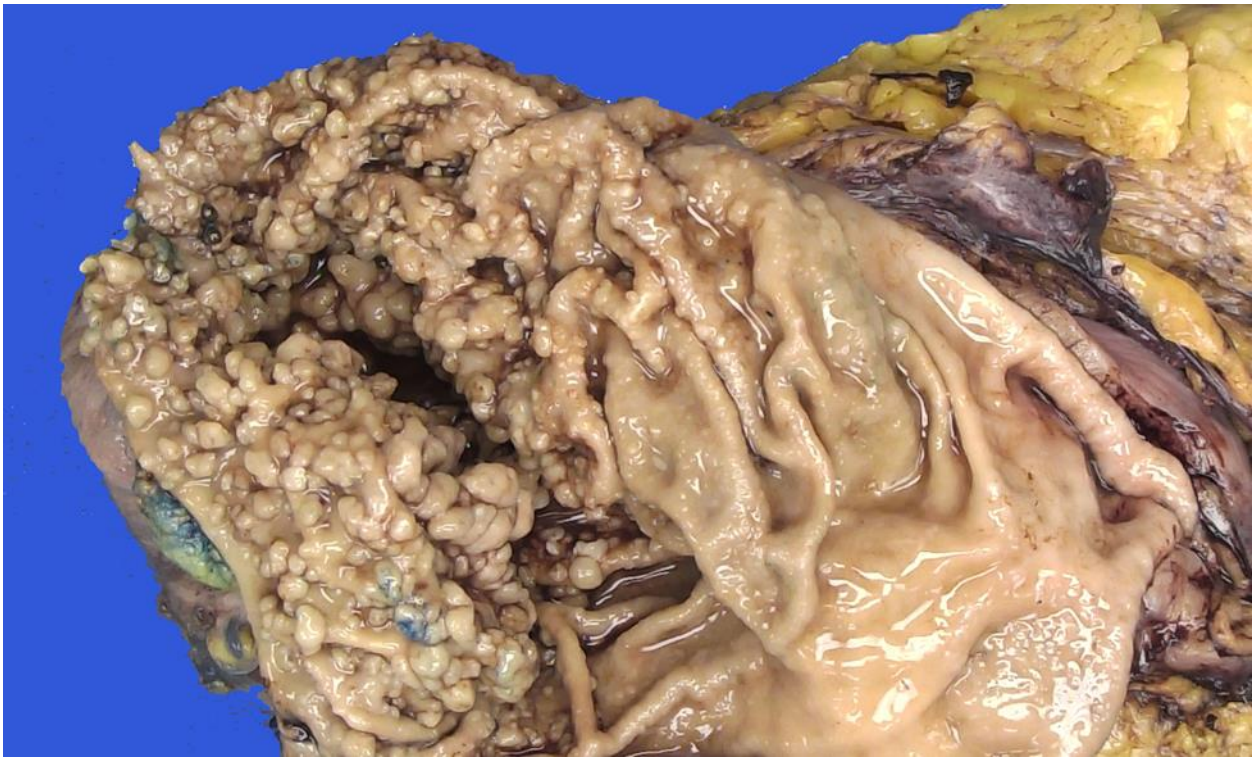

Figure 1. Polyps carpet the proximal stomach with sparing of the antrum.

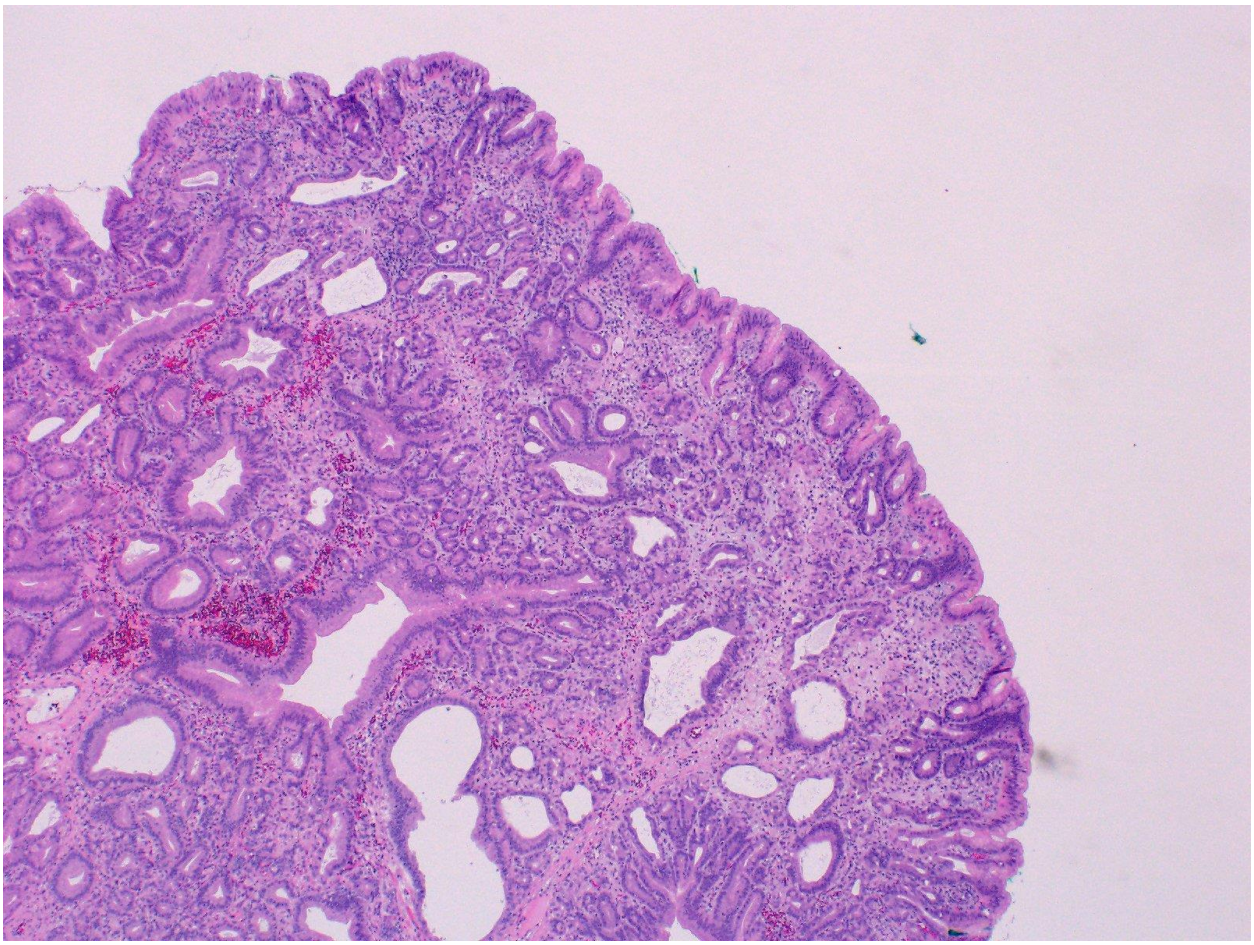

Figure 2. The biopsies from all sites in the body and fundus showed multiple polyps with the above features. H&E, 4x.

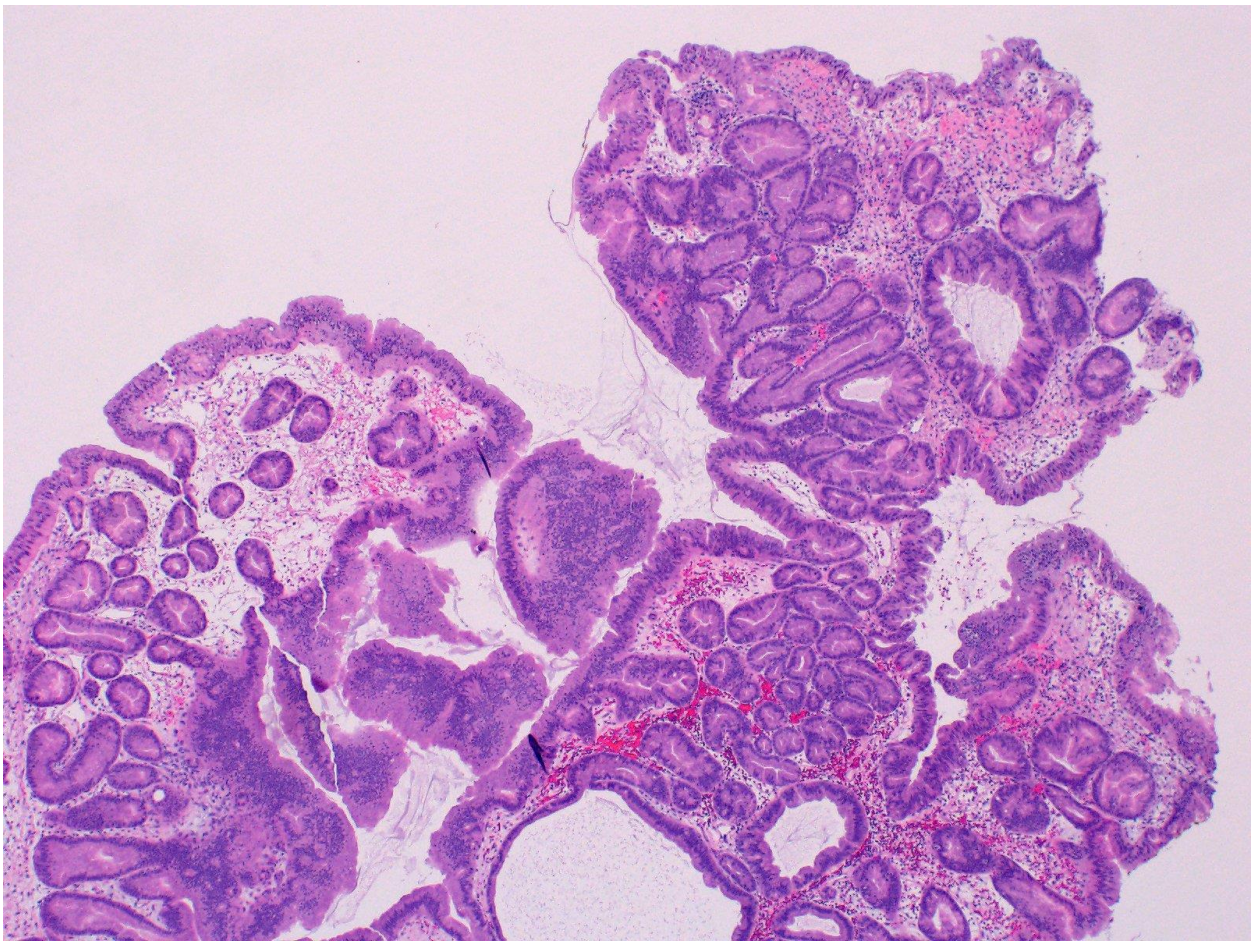

Figure 3. There were a few polyps with the above features. H&E, 4x.

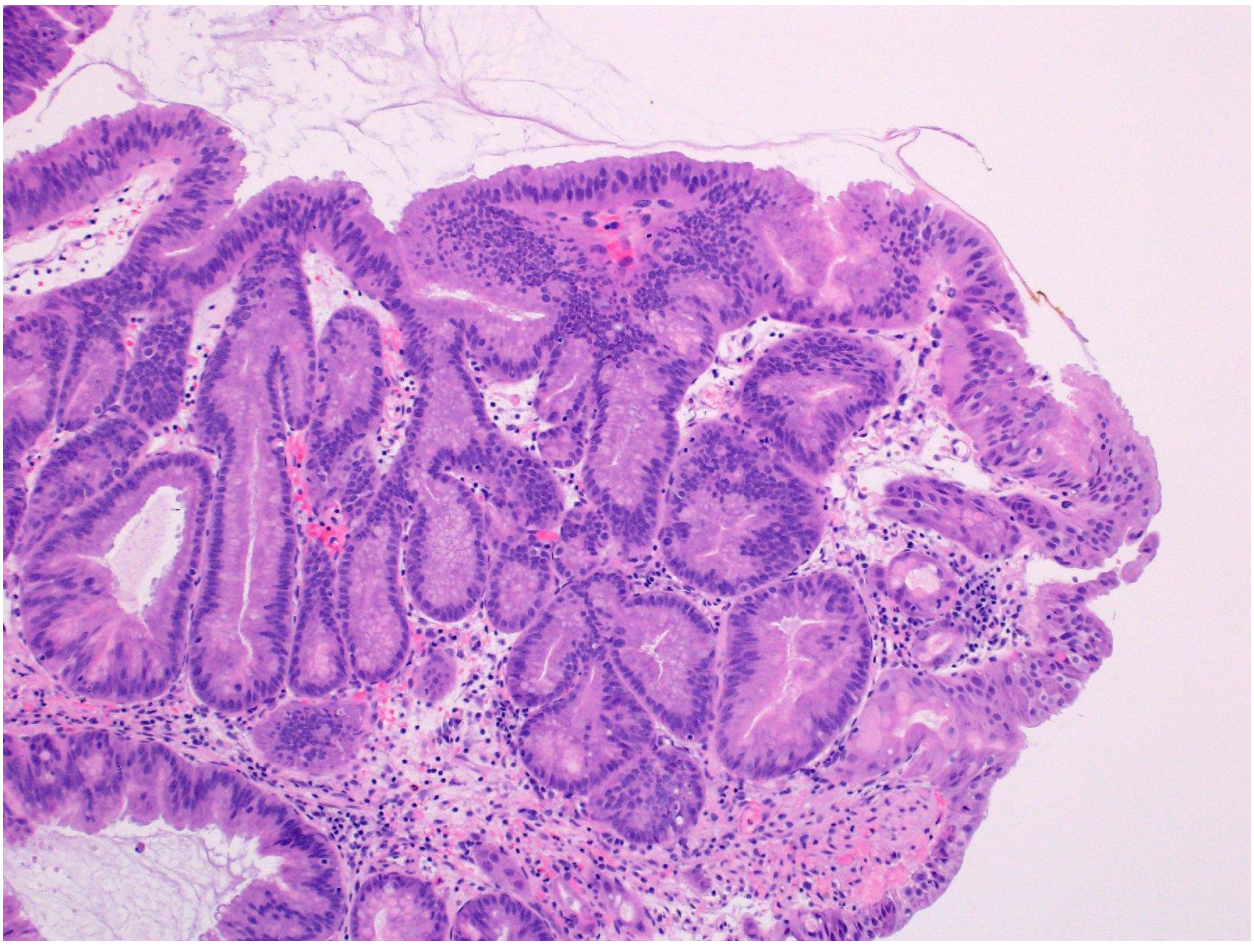

Figure 4. Closer view of polyp in figure 3. H&E, 10x.

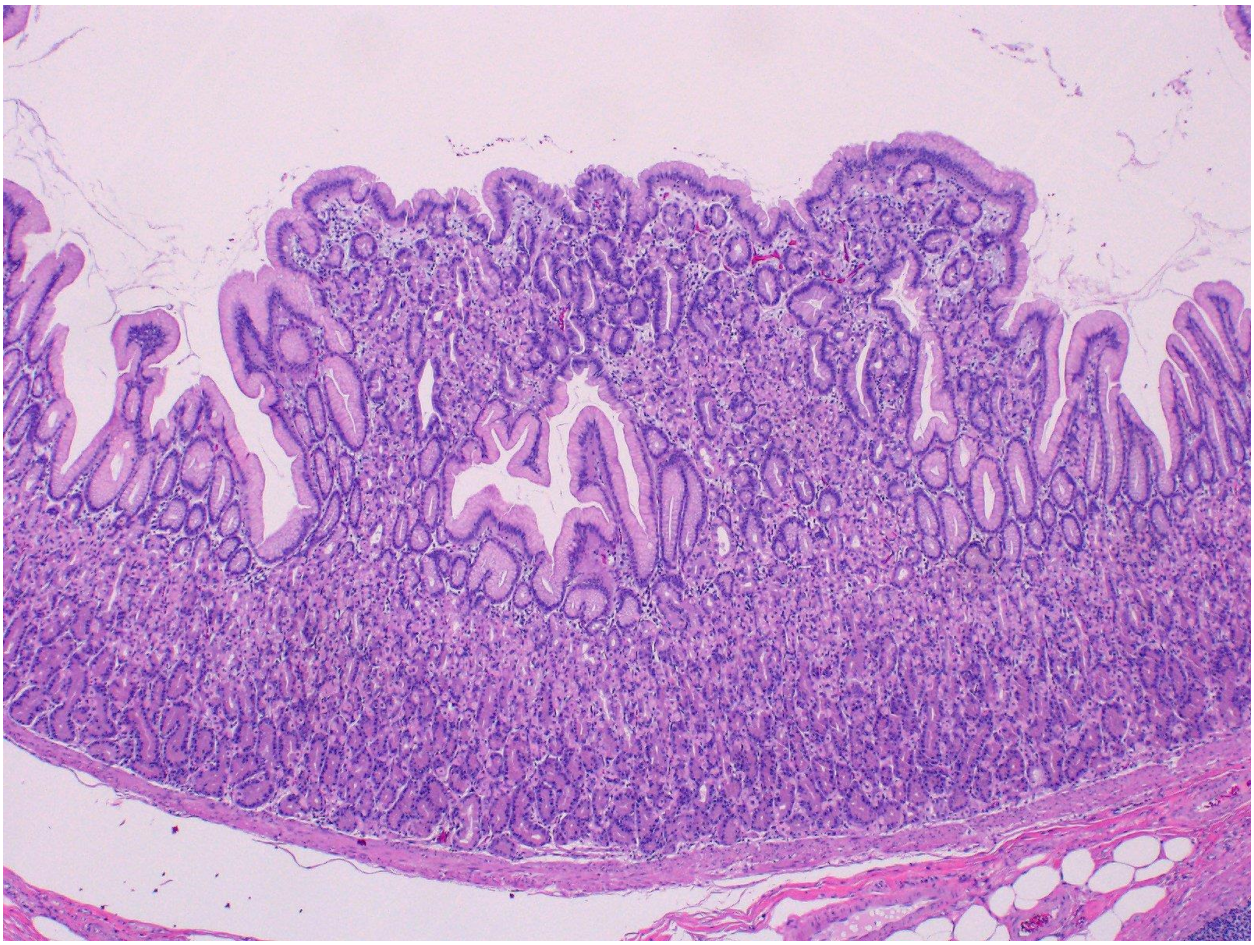

Figure 5. In addition to well-developed polypoid areas, the grossly flat mucosa had numerous lesions as shown. H&E, 4x

Which condition does this patient most likely have?

A. Familial adenomatous polyposis
B. Cronkhite-Canada syndrome
C. Cowden syndrome
D. Juvenile polyposis syndrome
E. Gastric adenocarcinoma and proximal polyposis of the stomach

Answer: E. Gastric adenocarcinoma and proximal polyposis of the stomach

Discussion:

Figure 1 shows the resection specimen with proximal (body and fundus) polyposis with sparing of the antrum. There were multiple polyps with microcysts lined by oxyntic epithelium, identical to fundic gland polyps (FGPs) (figure 2). Figures 3-4 demonstrate a polyp with foveolar-type low grade dysplasia. Small lesions with disorganized oxyntic glands arising at the level of the gastric pits (figure 5) have been described as "hyperproliferative aberrant pits" (HPAP). Taking into account lack of colonic polyposis, the features are suggestive of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).

First described in 2012 by Worthley et al, GAPPS is an autosomal dominant syndrome characterized by numerous polyps covering the body and fundus of the stomach and sparing the antrum and since described in 10 families prior to the case described here.[1-5] No colorectal or duodenal polyposis is present in these patients, although McDuffie et al. studied families affected by the syndrome and showed that patients with GAPPS have more colorectal polyps than patients without GAPPS in these families.[6] The initial description by Worthley et al. covered patients presenting with the syndrome at a wide age range from 10 to 75 years of age, and the youngest patient diagnosed with gastric adenocarcinoma developed the malignancy at the age of 33 years.

Worthley et al. proposed four criteria for this syndrome, in addition to ruling out other heritable gastric polyposis syndromes and proton pump inhibitor (PPI) effect:

1) Gastric polyps restricted to the body and fundus with no colorectal or duodenal polyposis.
2) >100 polyps carpeting the proximal stomach if an index case in a family, or >30 polyps with similar distribution in a first-degree relative of a patient with known GAPPS.
3) Predominantly FGP-like polyps, and, if an index case, then some should have dysplasia.
4) Autosomal dominant inheritance.

In a subsequent study by de Boer et al. of one of the families reported in the initial study, most patients affected by the syndrome had well-developed polyps morphologically identical to FGPs.[7] The most common polypoid lesion, which the authors described as an HPAP, had disorganized oxyntic glands arising from the foveolar region at the level of gastric pits. This compares to FGPs where the aberrant oxyntic glands are present in the basal half of body mucosa, with normal overlying foveolar epithelium.

In addition to FGPs and HPAPs, neoplastic lesions including discrete gastric adenomas, FGP-like lesions or HPAPs with dysplasia, and gastric adenocarcinoma were also described. The adenomas had foveolar-type dysplasia, and the lone adenocarcinoma in the study was associated with a foveolar adenoma and had a gastric tubular morphology. The gastric phenotype of the dysplasia was confirmed by a strong MUC5AC staining pattern with absent MUC2.

The presence of multiple FGPs including some with dysplasia is reminiscent of familial adenomatous polyposis (FAP) syndrome which is characterized by an adenomatous polyposis coli (APC) gene mutation and aberrant signaling leading to nuclear beta-catenin expression. McDuffie et al demonstrated nuclear beta-catenin expression in both gastric and colonic polyps in GAPPS patients.[6] Hence it is interesting that while the coding region of the APC gene itself is not mutated, Li et al found that GAPPS syndrome is associated with point mutations in the Ying Yang 1 (YY1) binding motif of APC promoter 1B. Overall 8 of the 10 known families with this syndrome have been tested for APC promoter 1B mutations, and each

has had an APC promoter 1B point mutation.[3-5] In the clinical workup for our patient, genetic testing had been done for FAP and showed negative result, however typical FAP assay would not test for the promoter 1B mutations.

Other answer choices:

A. Familial adenomatous polyposis (FAP) is also associated with a gastric polyposis characterized by fundic gland polyps with or without low-grade dysplasia. However, this patient had no colorectal polyposis. Of note, APC promoter mutations including APC 1B promoter mutations have rarely been identified in FAP patients.[8]

B. Cronkhite-Canada syndrome is a protein-losing enteropathy with diffuse gastric, small intestinal and colorectal polyposis.[9] Unlike the polyps of GAPPS syndrome, these polyps are generally considered to be non-neoplastic, although gastric and colorectal carcinomas have been reported in patients with this syndrome.[10] The polyps have dilated glands set in an expanded and edematous stroma, with often scant and predominantly mononuclear inflammation.[9]

C. Cowden syndrome is an autosomal dominant genetic syndrome with increased risk of breast, thyroid and other extra-gastrointestinal cancers, but no increase in gastric cancer. PTEN germline mutations is reported in 80% of patients. The polyposis in this syndrome is mostly colorectal, although 12% of polyps were gastric in a recent large series; these polyps are mostly hamartomatous with an expanded, fibrotic lamina propria and distorted glands.[11]

D. Juvenile polyposis syndrome is characterized by juvenile polyps in the gastrointestinal tract and predisposition to both colon and gastric cancer. Juvenile polyps in the stomach are less common than in the colon, and carpeting of the stomach is quite rare in this syndrome; those cases with carpeting of the stomach are most often associated with loss of SMAD4.[12] In addition, the polyps are hamartomatous with dilated glands and edematous, inflamed stroma unlike the FGP-like polyps seen in GAPPS syndrome.

References

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