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Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis

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Abstract

Fundic gland polyps are now commonly recognized during endoscopy. These polyps are benign, often multiple and usually detected in the gastric body and fundus. In the past, these polyps were sometimes associated with familial adenomatous polyposis. In recent years, it has become evident that increasing numbers of these polyps are being detected during endoscopic studies, particularly in patients treated with proton pump inhibitors for prolonged periods. In some, dysplastic changes in these polyps have also been reported. Recent studies have suggested that there may be no increase in risk of colon cancer with long-term proton pump inhibitor therapy. While temporarily reassuring, ongoing vigilance, particularly in those genetically predisposed to colon cancer, is still warranted.

Key words: Gastric polyps; Fundic gland polyposis; Gastric dysplasia; Gastric cancer; Colon polyps; Familial polyposis coli; Adenomatous polyposis coli gene mutation

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GASTRIC POLYPS

Gastric polyps and tumors have been classified into mucosal, lymphoid, mesenchymal and stromal types[1]. Both neoplastic (adenoma, carcinoma, carcinoids) and non-neoplastic mucosal types occur. Most neoplastic epithelial polyps are asymptomatic and, usually, occur in the gastric antrum. Occasionally, these polyps bleed or present with an iron deficiency anemia. Rarely, gastric adenomas, particularly if large and pedunculated, cause symptoms from intermittent gastric outlet obstruction due to duodenal prolapse. Carcinoma may also complicate such adenomas. But, even these complex malignant polyps have been amenable to endoscopic resection[2].

FUNDIC GLAND POLYPOSIS

One of the most common types of gastric polyps, generally classified as non-neoplastic, is the sporadic fundic gland polyp. Usually, these are confined to the gastric body and fundus and rarely cause symptoms. Fundic gland polyps are typically detected during investigation for abdominal pain, dyspepsia or chronic reflux. Historically, it has been estimated that these polyps occur in up to 2% of all endoscopic studies. Although quite characteristic, they were only first described as a distinct pathological type in 1977[3]. Previously, these were reported to occur most often in females and were thought to be derived from the parietal cell- and chief cell-bearing region of the gastric mucosa[1]. Cystic dilation of pits deep in the mucous neck cells was observed with mucous cells, chief cells and parietal cells lining these mucosal cysts. Inflammatory changes in these polyps is usually minimal or absent. It has been reported that these polyps may resolve spontaneously[4].

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Gastric polyps also occur in the majority of patients with FAP, screened with endoscopy[5-7]. FAP results from inherited germline mutations in the adenomatous polyposis coli (*APC*) gene, coupled with second somatic mutations. This leads to inactivation of both copies of the *APC* tumor suppressor gene[8,9]. Importantly, the most common gastric lesion in FAP is the syndromic fundic gland polyp, histologically similar to sporadic fundic gland polyps. Gastric and duodenal adenomas also occur in FAP, but are much less common. Fundic gland polyps are most often not associated with FAP and have little or no potential for malignant transformation[5,10]. However,

high-grade dysplasia and gastric adenocarcinoma have both been associated with fundic gland polyps in FAP[7,11-15]. As a result, colonoscopic surveillance has been suggested to determine if FAP or an attenuated form of FAP is present when fundic gland polyps are first detected[16]. Evidence strongly supporting this approach is not available. As fundic gland polyps are being increasingly recognized during endoscopic evaluations, added colonoscopic studies might be best reserved for those with concomitant gastric or duodenal adenomas.

MOLECULAR GENETIC MARKERS

Since both sporadic and syndromic FAP-associated fundic gland polyps have similar histological appearances, genetic markers have been explored to determine if there are additional similarities or differences. Distinct disruptions in the Wnt signaling pathway with activating beta-catenin mutations occur with sporadic polyps, while FAP-associated polyps showed second, somatic mutations of the *APC* gene[17]. With chronic acid suppression therapy, multiple fundic gland polyps develop that are also histologically and genetically identical to single sporadic polyps[18]. In these, beta-catenin mutations were detected in most polyps. In addition, distinct mutations in different polyps from the same individual indicated a multifocal origin for the polyps[18]. Separate studies on fundic gland polyps in the absence of FAP have also failed to show *APC* gene deletions[19]. Interestingly, a very low prevalence of *H pylori* infection was also noted with these polyps[19]. In contrast, *APC* gene mutations were found in FAP with both syndromic fundic gland polyps and high grade dysplasia in gastric epithelium[20]. While these studies have served to elucidate molecular changes in sporadic and syndromic (FAP) gastric fundic gland polyps, more information is needed to determine if these markers could be used cost-effectively to predict risk in fundic gland polyps for eventual development of gastric cancer.

PROTON PUMP INHIBITOR-ASSOCIATED GASTRIC POLYPS

Omeprazole was first introduced for clinical use as a proton pump inhibitor in 1988. Since then, worldwide sales figures for proton pump inhibitors have dramatically risen with estimated sales now totaling over $10 billion and rising. Over 720 million prescriptions for proton pump inhibitors have been written worldwide, largely for long-term use, while large randomized clinical trials have confirmed the high efficacy and safety profile of long-term treatment[21]. In addition, however, substantial physiological changes occur with chronic acid suppression therapy. Increased levels of circulating gastrin occur. This hormone stimulates increased cell proliferation. Chronic ECL cell stimulation also results as reflected by increased levels of chromogranin A, an endocrine cell product[22]. In recent years, gastric fundic gland polyps have become increasingly detected in patients on long-term proton pump inhibitor therapy[23-26]. These fundic gland polyps are often multiple in this setting and localized in the gastric body and fundus. No definite sex predilection has been defined. They appear to have similar histologic and genetic features to those developing without proton pump inhibitor use. Recent studies have defined a relationship between the length of drug use, especially after 12 mo, and increased polyp risk[26]. In addition, most patients with fundic gland polyps on proton pump inhibitors are *H pylori*-negative[26], consistent with a previous report of fundic gland polyp regression following acquisition of *H pylori*[27]. Of concern, multiple fundic gland polyps have also been noted in some children on long-term omeprazole therapy[28,29]. Moreover, in a pediatric FAP population on proton pump inhibitors for more than 6 mo, dysplasia was reported in fundic gland polyps[29]. These studies imply that with increasing use of long-term proton pump inhibitors, an epidemic of fundic gland polyposis will be defined. Studies are needed to determine if further follow-up of patients on long-term therapy with proton pump inhibitors and fundic gland polyps is warranted. In spite of an early record of safety with long-term use, there remain concerns regarding the potential risk of cancer with long-term exposure, not only in those with FAP, but also in those genetically predisposed to cancer. This concern is reflected in the recently published studies on colon cancer risk with long-term proton pump inhibitor exposure. In these studies, no increased risk was shown[30,31]. While temporarily reassuring, ongoing vigilance will be required before the final chapter is written.

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