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CASE REPORT

Filling in the "GAPPS": an unusual presentation of a child with gastric adenocarcinoma and proximal polyposis of the stomach

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Abstract

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS) is a very rare gastric polyposis syndrome characterized by numerous polyps of the gastric fundus and body. We present the unusual case of a 10-year-old Polish-American male with history of eosinophilic esophagitis, who was found to have multiple fundic gland polyps (FGP) with low grade dysplasia on esophagogastroduodenoscopy. Subsequent evaluation including genetic testing confirmed the diagnosis of GAPPS, and after exhaustive multidisciplinary consultation the decision was made to proceed with prophylactic total gastrectomy given the markedly increased risk of gastric adenocarcinoma in GAPPS patients. To our knowledge, this represents the youngest patient diagnosed with GAPPS and the youngest patient who has undergone prophylactic gastrectomy for this disease at age 8 and 10 years, respectively. The pathophysiology, presentation, and treatment of GAPPS in a pediatric patient are discussed.

Keywords Fundic gland polyp · Gastric cancer · Eosinophilic esophagitis

Introduction

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS) is a rare autosomal dominant gastric polyposis syndrome [1]. First described in 2012 [1], GAPPS is diagnosed via the following clinical and pathologic criteria: (1) gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; (2) > 100 polyps carpeting the proximal stomach in the index case or > 30 polyps in a first-degree relative of another case; (3) predominantly fundic gland polyps (FGPs), some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma); and (4) an autosomal dominant pattern of inheritance [2]. Other causes of FGPs including proton pump inhibitor (PPI) effect and heritable gastric polyposis syndromes must be excluded [2]. Genetically distinct from classical familial adenomatous polyposis (FAP) and attenuated FAP [3], GAPPS is characterized by a unique point mutation in the promoter 1B region of the *APC* gene [4]. Expression of promoter 1B is based on epigenetics. A mutation results in a loss of function which leads to activation of secondary signaling pathways that promote the development of polyps [4]. In contrast to FAP, the polyposis in patients with GAPPS is characteristically in the stomach only [2], and while patients with GAPPS may have an increased frequency of colorectal polyps, they do not have extensive colorectal polyposis as described in patients with FAP [5]. GAPPS follows an autosomal dominant pattern of inheritance and is variably penetrant; genetic testing of immediate families is advised following diagnosis in the index case [1]. While sporadic and PPI-associated FGPs tend to stud the gastric mucosa and show no propensity towards the development of dysplasia [6], the FGPs in GAPPS progress to carpet the gastric body and fundus, and advance along the dysplasia-carcinoma sequence toward frank invasive adenocarcinoma [4]. As a result, endoscopic surveillance can be inadequate and prophylactic gastrectomy should be offered to these patients.

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Case report

A 7-year-old Polish-American male initially presented with vomiting and was found to have eosinophilic esophagitis (EoE) by esophagogastroduodenoscopy (EGD) and biopsy. Clinical and histologic resolution was achieved with high dose PPI therapy (1.6 mg/kg/day) and swallowed topical budesonide. At age 8 years, a follow-up EGD revealed new-onset polyps in the gastric body and fundus, and biopsy of the polyps was diagnostic of FGPs (Fig. 1). The FGPs were thought to be related to PPI usage over the previous 11 months, therefore his PPI was weaned off. An EGD 5 months later demonstrated persistent innumerable gastric polyps, carpeting the gastric body and fundus, consistent in shape and size. Random biopsies were taken and multiple biopsy fragments showed FGPs with several foci of low-grade dysplasia (Figs. 2 and 3). Capsule endoscopy and colonoscopy were performed and revealed no other polyps in the gastrointestinal tract, thereby excluding many of the most common polyposis syndromes, including classical FAP. The family was referred to Medical Genetics for comprehensive testing, and the patient was found to have a pathogenic missense point mutation in the 1B promoter region of the *APC* gene (c.-195A > C) consistent with the GAPPS phenotype. His mother was also found to have the mutation and referred to adult gastroenterology, while his father and younger sister tested negative. Due to the potential for rapid progression from dysplasia to invasive gastric adenocarcinoma in patients with GAPPS, our patient was referred for PET MRI, which was negative for metastatic disease. After extensive multidisciplinary discussion, including referral to the National Institutes of Health (NIH), the patient underwent complete gastrectomy (Fig. 4), roux-en-Y esophagojejunostomy, and jejunostomy tube placement. Intraoperative frozen section analysis of the gastroesophageal junction confirmed complete resection of the gastric tissue. The surgical specimen contained a carpeting of homogeneous appearing polypoid lesions in the gastric body and fundus, sparing the antrum, ranging from 0.3 to 0.6 cm in size. Histology demonstrated FGPs with multiple foci of low grade dysplasia and without neoplasia.

Discussion

We report this case of GAPPS to draw attention both to this rare, newly-described genetic disease and discuss the management strategies in a pediatric patient. To our knowledge, our patient represents the earliest diagnosis of GAPPS and youngest patient who has undergone prophylactic gastrectomy for this disease at age 8 and 10 years, respectively. Prior case reports have not focused on pediatric patients, likely because they are not typically the index case and due to the overall rarity of the disease.

Published reports have described the first cases of known GAPPS in families from North America, Europe, and Asia

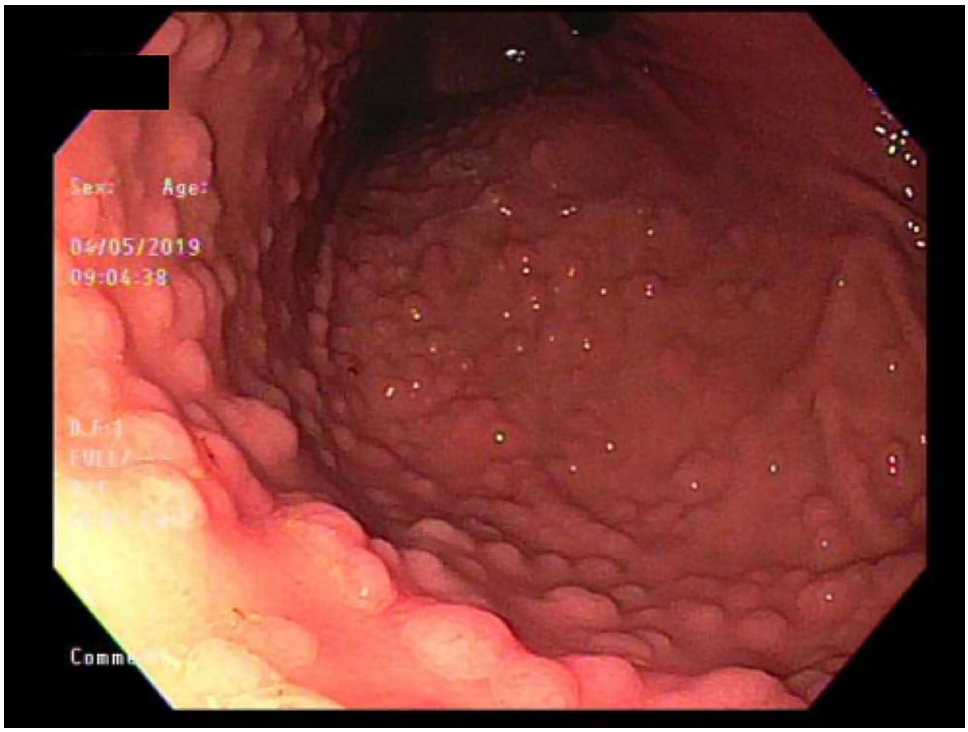

Fig. 1 Endoscopy image demonstrating numerous gastric polyps

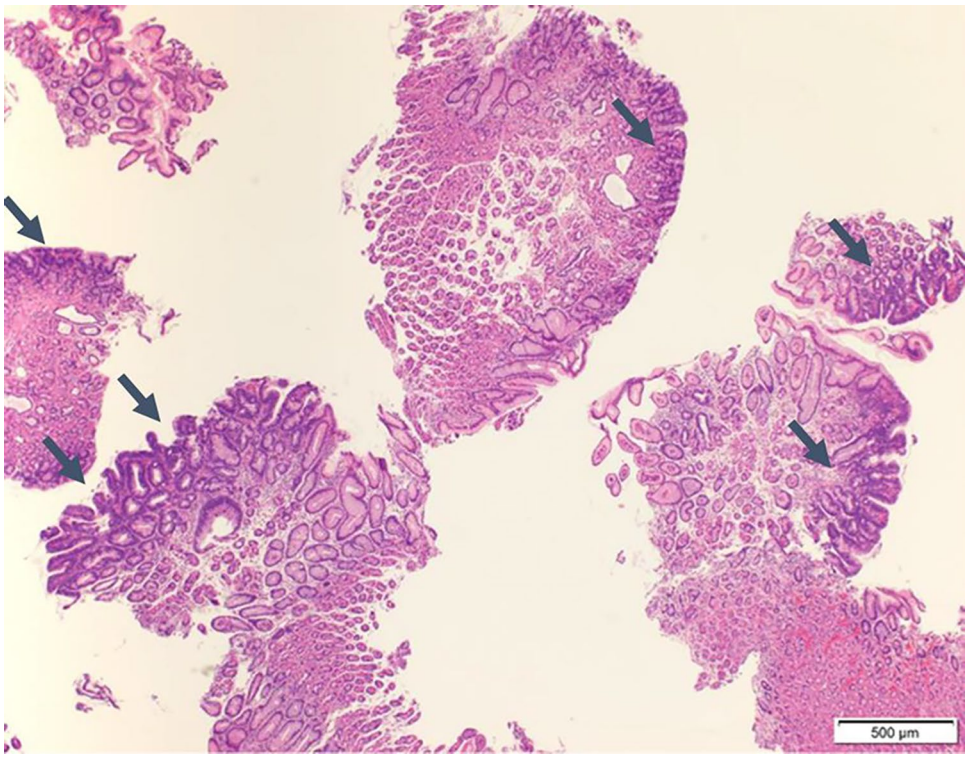

Fig. 2 Low-power histopathology from fundic gland polyps demonstrating multiple areas of low grade dysplasia (arrows)

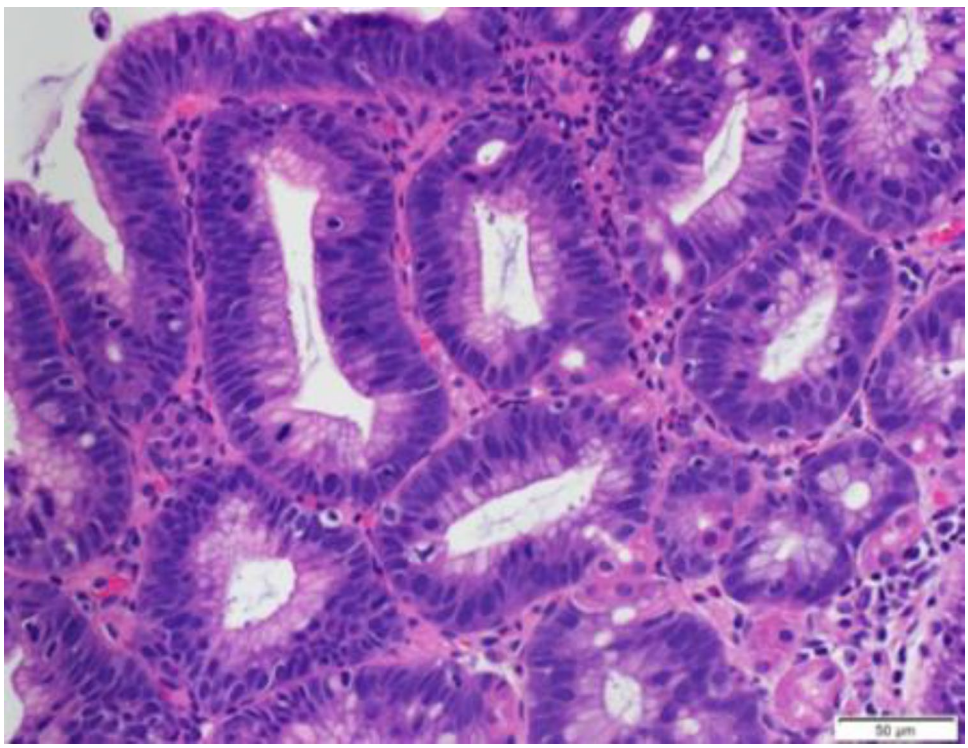

Fig. 3 High-power histopathology from fundic gland polyp demonstrating low grade dysplasia

[1, 4, 5, 7–10]. The index patients in these cases have been of adult age. The youngest patient previously diagnosed with GAPPS is a 10-year-old Australian patient [1]. This patient underwent EGD after a parent was diagnosed with GAPPS and histological examination of the stomach showed innumerable FGPs with multifocal dysplasia. At the time of the published paper, that patient had not undergone prophylactic gastrectomy and their clinical status is unknown.

Fig. 4 Gastrectomy specimen demonstrating carpet-like gastric polyps in the fundus and body; sparing the antrum

The youngest reported case of gastric adenocarcinoma from GAPPS is 23 years old [7]. This patient was initially diagnosed with GAPPS at 19 years of age following detection of GAPPS in first degree relative. At the time of diagnosis, she had fundic gland polyps, but no dysplasia. After her sibling died from GAPPS-related adenocarcinoma at 26 years of age, the patient opted for prophylactic gastrectomy at 23 years of age, which demonstrated gastric adenocarcinoma.

Regardless of age at presentation, the GAPPS phenotype of fundic gland polyposis of the proximal stomach is unique and should prompt genetic evaluation for the specific APC promoter 1B mutation. This mutation interferes with binding of the YinYang-I transcription factor resulting in overall decreased APC expression. [4] In non-gastric tissue, promoter 1A is generally able to compensate for altered 1B function in order to salvage APC expression; however epigenetic silencing of 1A in the stomach via methylation leads to complete dependence on 1B. As a result, promoter 1B mutations in the gastric mucosa results in insufficient APC expression and, by extension, B-catenin disinhibition. Over-activation of the B-catenin pathway then promotes uncontrolled acceleration through the cell cycle polyposis and progression along the dysplasia-carcinoma sequence [4]. Our patient was found to have the promotor IB variants c.-195A > C. This specific variant was identified in the previously youngest described case of GAPPS [2], at 10 years of age, raising the possibility that this variant may be associated with early age of onset of disease.

Timeliness is paramount in the diagnosis and management of GAPPS due to the aggressive nature of the disease. Prior management strategies have included surveillance EGDs and prophylactic gastrectomy [1–5, 7–10]. While surveillance EGDs are less invasive, no optimal time interval between EGDs has been established. One case report describes a 26-year-old female diagnosed with GAPPS, with surveillance EGD every 18–24 months [7]. Five years after the initial diagnosis, she progressed to low-grade dysplasia. Shortly before a planned prophylactic gastrectomy, she was admitted to the hospital with abdominal pain, diagnosed with metastatic adenocarcinoma, and died 19 days later. This case demonstrates the rapid progression that can occur with GAPPS. Another problem with surveillance EGD is that there is no established number of biopsies for GAPPS surveillance. Since GAPPS patients have > 100 polyps, many biopsies would be required to detect a potential area of focal dysplasia. Finally, while there have been patients as young as 10 years of age diagnosed with GAPPS [1], we do not know how quickly these young patients can progress to adenocarcinoma. After interdisciplinary discussions, including with the NIH and our institutional tumor board, we recommended prophylactic gastrectomy for our patient. While a prophylactic gastrectomy is an invasive procedure requiring long-term nutritional management, particularly in a pediatric patient,

the surgery prevents the advancement of the disease towards gastric adenocarcinoma and death.

It is unknown how long our patient would have remained undiagnosed with GAPPS without the EGD surveillance he was receiving for his EoE. The development of gastric polyps/polyposis is often a silent process with little to no symptomatology. The patient theoretically could have progressed from dysplasia to frank adenocarcinoma before coming to clinical attention, again underscoring the importance of early recognition. Although the patient's polyps were initially thought to be secondary to PPI use, persistence and progression even 5 months after PPI discontinuation was considered atypical for FGPs developing in the setting of PPI use. Furthermore, it is postulated that PPI-associated FGPs arise as a result of hypergastrinemia in the setting of acid suppression, and typically occur after prolonged use of PPI, particularly > 12 months [6]. Our patient was treated with PPI for 11 months, which makes PPI-associated FGPs less likely. Additionally, there have been no studies that has shown an unequivocal link between PPI-induced dysplasia and gastric cancer [6]. Instead, dysplasia within FGPs is more characteristic of inherited polyposis syndromes. Long-term strategies for continued surveillance for GAPPS remain unclear and will likely be influenced by advancements in the understanding of the natural history and extra-gastrointestinal manifestations of GAPPS as more patients with the disease are identified.

This patient case represents a very rare and serious diagnosis. Here we presented the pathophysiology, presentation, and treatment of GAPPS in a pediatric patient with the confounding factors of EoE and PPI use.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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