Barrett Esophagus with Progression to Adenocarcinoma in Multiple Family Members with Attenuated Familial Polyposis

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Attenuated familial polyposis (AFAP) is a subset of familial adenomatous polyposis (FAP) that has a relatively benign disease course. AFAP is characterized by no more than 100 colorectal polyps and has a tendency toward rectal sparing, a 20–25-year delay in the onset of adenomatosis and bowel symptoms, a 10–15-year delay in the development of colorectal cancer, and death caused by colorectal cancer in 15–20 years. Extracolonic involvement is limited. Although gastric polyps and duodenal adenomas are frequent, esophageal involvement has not been reported in the literature, to our knowledge. We report a case of AFAP with esophageal mucosal disease that progressed from metaplasia to malignancy.

Case Report

A 41-year-old white male with a family history of FAP presented for gastroenterologic evaluation. Multiple family members had tested positive for exon 4 deletions in the 5' end of the adenomatous polyposis coli (APC) gene. The patient's colonoscopic examination revealed multiple polyps (<100) ranging in size from 2 mm to 1 cm throughout the entire colon. Biopsies of the polyps revealed tubular adenomas. A diagnosis of AFAP was made. Surveillance esophagogastroduodenoscopy showed a distal esophageal lesion 37 cm from the incisors, overlying an area suspicious for Barrett esophagus. An endoscopic ultrasound confirmed a T2N1aMx lesion. The patient underwent a transhiatal esophagectomy and colectomy. Pathology of the resected esophageal lesion revealed an invasive, well-differentiated T2N1aMx adenocarcinoma in the background of Barrett esophagus.

The patient likely inherited this mutation from his 65-year-old father, who tested positive for it, as did the patient's 2 brothers: a 43-year-old with 10–20 polyps on colonoscopy, and a 33-year-old with 70–80 polyps on colonoscopy.

A biopsy of the patient's father revealed Barrett mucosa with extensive low-grade dysplasia. Barrett esophagus was found during an endoscopic examination of the patient's younger brother and was confirmed via biopsies. The patient's older brother had endoscopic findings suggestive of Barrett esophagus, although biopsies revealed severe esophagitis with no metaplastic changes.

Discussion

AFAP is an autosomal dominant, genetically transmitted disease characterized by no more than 100 colorectal adenomas with a predisposition for colorectal cancer. AFAP has a predilection for right-sided colonic adenomas with delayed adenoma expression and limited extracolonic involvement.1 Because AFAP is not a well-defined disease entity, diagnostic criteria and methods of investigation vary; therefore, the true incidence and prevalence of the disease are unknown.1 In AFAP, polyps are detected at a mean age of 40–45 years, and colorectal carcinoma develops at a mean age of 55–57 years; in contrast, bowel involvement is delayed by 20–25 years in AFAP.2,4 Although gastric and duodenal adenomas are frequently encountered, involvement of esophageal mucosa is especially rare.2,5,8 To the best of our knowledge, our case is the first report of esophageal adenocarcinoma in a patient with AFAP; however, even more intriguing is the manifes-
tation of Barrett esophagus in multiple family members of the patient.

Standard clinical diagnosis of typical or classical FAP is based on the identification of more than 100 colorectal adenomatous polyps. Extraprofessional features of FAP are summarized in Table 1.9

Clinical diagnosis of AFAP is more difficult. Recently, diagnostic criteria for AFAP have been proposed by 2 groups: Nielsen and associates and Knudsen and colleagues.10,11 According to Nielsen and coworkers, AFAP should meet at least 1 of the following criteria: 2 patients in the same family with 10–99 adenomas who are older than 30 years of age; or 1 patient with 10–99 adenomas who is older than 30 years of age and has a first-degree relative with colorectal cancer and several adenomas.10 Knudsen and coworkers proposed the following criteria for AFAP: a dominant mode of inheritance and 3–99 colorectal adenomas in a patient 20 years of age or older.11 In both sets of criteria, family members should not have more than 100 adenomas before 30 years of age. Our patient fulfilled both sets of criteria for AFAP.

Hereditary forms of colorectal cancer are characterized by family history, young age at disease onset, and the presence of other tumors. Given the incidence of de novo mutations, however, AFAP cannot be ruled out in the absence of a positive family history, which is particularly important when assessing a patient with a low polyp burden.

Tumor suppressor genes produce proteins that inhibit tumor formation by regulating mitotic activity and providing inhibitory cell cycle control. The APC gene is a tumor suppressor gene located on chromosome 5q31.12,13 APC produces a 2,843 amino acid protein that forms a cytoplasmic complex with glycogen synthase kinase-3 β, β-catenin, and axin. β-catenin activates transcription of genes that regulate cellular growth and proliferation, such as c-myc. Wnt signaling proteins are extracellular signaling molecules that help to regulate tissue development throughout the organism. These signaling proteins are closely associated with the APC-β-catenin pathway. Reduced levels of β-catenin inhibit Wnt expression. When APC is mutated, β-catenin levels rise, activating Wnt. Overexpression of Wnt leads to activation of genes that drive cell proliferation and tumor formation. APC gene mutations associated with AFAP have mainly been detected in 3 regions: the 5’ end (the first 5 exons), exon 9, and the distal 3’ end of the gene. A germline APC truncation mutation is responsible for autosomal dominant inheritance; however, de novo germline mutations occur in 20–30% of cases.

Although AFAP is usually characterized by fewer than 100 colorectal polyps, several researchers have described kindred in whom the number of polyps far exceeds this criterion.3,5,6,14 The penetrance of colorectal cancer remains high in patients with AFAP, but the exact incidence and lifetime risk remain unknown. Extracolonic involvement is usually limited to the upper gastrointestinal tract in the form of gastric fundic polyps and duodenal adenomas.12,5,6,15 As with FAP, upper gastrointestinal cancers do not appear to be a prominent feature in AFAP. This finding was documented in a study by Soravia and associates, who reported only 1 case of duodenal cancer among 79 patients.2 Another series reported 2 cases of periampullary or duodenal cancers among 132 patients, 1 case of periampullary carcinoma among 16 patients, and 1 case of adenocarcinoma of the stomach (in a 71-year-old patient) among 9 patients.7,16 Desmoid tumors have been described in the literature, particularly in patients with mutations at the 3’ end of the gene. Congenital hypertrophy of the retinal pigment epithelium has not been reported until now. Osteomas, epidermoid cysts, and papillary thyroid carcinomas have been reported only sporadically.

Table 1. Extraprofessional Features in Familial Adenomatous Polyposis

<table>
<thead>
<tr>
<th>Benign lesions</th>
<th>Malignant lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypertrophy of the retinal pigment epithelium (70–80%)</td>
<td>Thyroid cancer (2–3%)</td>
</tr>
<tr>
<td>Epidermoid cysts (50%)</td>
<td>Brain tumors (&lt;1%)</td>
</tr>
<tr>
<td>Osteomas (50–90%)</td>
<td>Hepatoblastomas (~1%)</td>
</tr>
<tr>
<td>Desmoid tumors (10–15%)</td>
<td></td>
</tr>
<tr>
<td>Supernumerary teeth (11–27%)</td>
<td></td>
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<tr>
<td>Adenval gland adenomas (7–13%)</td>
<td></td>
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</tbody>
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Conclusion

To date, AFAP remains a poorly understood entity, and no specific guidelines have been established for its surveillance and treatment.15 There is a general consensus that yearly colonoscopies comprise standard-of-care treatment, given the development of polyps proximal to the splenic flexure.17 Endoscopy is recommended starting at 20–25 years of age. Due to the late onset of polyposis in AFAP—contrary to classic FAP—no upper age limit has been set for surveillance.17,18 Dye spraying during colonoscopy is recommended to differentiate AFAP from FAP.19,20 AFAP is somewhat difficult to classify as a separate entity due
to varied disease expression in individuals with identical mutations. Unlike classic FAP mutations, mutations causing AFAP have reduced or variable penetrance, which may be the reason for this variable expression.\textsuperscript{12,21} External factors, such as hormones, growth factors, and environmental exposure, could also be vital factors determining the phenotypic expression of AFAP.

It would be interesting to determine whether our patient's kindred actually have a unique mutation that accounts for their unusual esophageal involvement. It is also likely that they had similar exposure to the previously mentioned external factors. Close follow-up of the patient's siblings is required to monitor development of esophageal neoplasms; in fact, 1 sibling already had Barrett epithelium. Further research is needed to provide more substantiated evidence of AFAP's potential direct association with Barrett epithelium, the progression to adenocarcinoma, and whether prophylactic resection is warranted. We hope that our case helps to provide insight into understanding AFAP, an uncommon and intriguing disease.

References


Review

Germline APC Mutation and Familial Barrett Esophagus: Causal or Coincidence?

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There has been a striking increase in the incidence of esophageal adenocarcinoma in Western populations over the past several decades. In most cases, esophageal adenocarcinoma is thought to derive from a precursor lesion—Barrett esophagus—through a multistep progression: metaplasia, dysplasia, early adenocarcinoma, and, finally, invasive cancer. Parallel to this histologic progression is a stepwise accumulation of genetic alterations and chromosomal changes. In addition, familial Barrett esophagus has been described when Barrett esophagus, esophageal adenocarcinoma, and/or adenocarcinoma of the gastroesophageal junction occur in multiple family members, purportedly through an autosomal dominant, polygenic inheritance pattern.\textsuperscript{1} Familial adenomatous...
polyposis (FAP) and attenuated FAP (AFAP), a more recently described variant of FAP, are caused by germline mutations in the adenomatous polyposis coli (APC) gene. Tumor development in FAP and AFAP occurs after a somatically acquired "second hit"—according to Knudson's "2-hit" hypothesis—resulting in the loss of the remaining normal APC allele. Gupta and colleagues present an interesting family with AFAP who have gastroesophageal reflux disease, Barrett esophagus, and/or esophageal adenocarcinoma. Although the simultaneous occurrence of these 2 potentially inherited disorders in the same family may be a chance event, this case report raises the possibility that the disorders could be linked.

The increase in esophageal adenocarcinoma over the past several decades implicates 1 or more major environmental factors in its pathogenesis (ie, obesity, gastroesophageal reflux disease). It is possible that changes in environmental factors, together with existing genetic susceptibility factors, contribute to the rising incidence in esophageal adenocarcinoma, as has been suggested with the obesity epidemic in the United States. There have been multiple reports of familial clustering of patients with hiatal hernia, esophagitis, Barrett esophagus, and esophageal adenocarcinoma. These findings have led some investigators to propose a subgroup of patients with familial Barrett esophagus (individuals with more than 1 first- or second-degree relative with long-segment Barrett esophagus or adenocarcinoma of the esophagus or gastroesophageal junction). In these reports of familial clustering, the prevalence of gastroesophageal reflux disease in relatives of familial Barrett esophagus patients was approximately 40% (vs 20% in sporadic Barrett esophagus). In a recent study of 20 families, the risk of Barrett esophagus in familial Barrett esophagus patients was estimated to be 20% (vs 10% in sporadic Barrett esophagus patients), with an adenocarcinoma risk of 31% (vs 5% in sporadic Barrett esophagus patients). Another study found familial Barrett esophagus in 7.3% of patients presenting with Barrett esophagus, esophageal adenocarcinoma, or gastroesophageal junction adenocarcinoma. Romero and associates found a significantly higher incidence of reflux symptoms and esophagitis in first-degree relatives of Barrett esophagus patients. Twin studies have consistently shown a higher incidence of reflux symptoms in monozygotic twins compared to dizygotic twins. A recent segregation analysis of 881 singly ascertained pedigrees provided epidemiologic evidence in support of 1 or more rare, autosomal dominant susceptibility alleles in familial Barrett esophagus families. The above findings suggest either Mendelian inheritance with markedly reduced penetrance, or a complex disorder with multiple genetic and environmental factors.

If these 2 conditions are linked in the family discussed in the case report by Gupta and coworkers, what is the possible pathogenetic mechanism? As Gupta and colleagues note, APC gene mutations in FAP lead to increased β-catenin levels and activation of the Wnt pathway. Activation and alteration of the Wnt signaling pathway has been implicated in a broad range of cancers. A recent model of Barrett esophagus and esophageal adenocarcinoma proposed that multiple alterations in Wnt pathway components lead to nuclear accumulation of β-catenin and activation of target genes in Barrett esophagus, which promote progression to esophageal adenocarcinoma. APC promoter hypermethylation is also observed in a high percentage of esophageal adenocarcinoma patients. Although this model proposes a different mechanism of Wnt activation in esophageal adenocarcinoma compared to AFAP/FAP, both conditions lead to increased nuclear β-catenin, with activation of target genes in carcinogenesis.

It appears that some, but not all, extracolonic manifestations of FAP, as well as the AFAP phenotype itself, correlate with specific mutation sites in the APC gene. Although upper gastrointestinal cancers occur in less than 10% of individuals with FAP or AFAP and have not been found to correlate with specific mutation sites in classic FAP, the AFAP phenotype still has not been fully characterized, and relatively rare associations may not have been noted as of yet. It is possible that the specific mutation in this AFAP family is linked to genetic alterations present in familial Barrett esophagus that have yet to be identified. It has been proposed, although not widely accepted, that genotype-phenotype correlations be used in the management of FAP. Because specific mutations have been associated with the risk of rectal cancer and/or poor prognosis in rectum retention, it has been suggested that the results of genetic testing should be added to the clinical phenotype to assist surgical decision making in FAP.

In conclusion, Gupta and associates present an intriguing family with AFAP, gastroesophageal reflux disease, Barrett esophagus, and/or esophageal adenocarcinoma. An association has not been previously noted between either FAP or AFAP and esophageal reflux, Barrett esophagus, or esophageal adenocarcinoma. There appears to be a subgroup of patients with Barrett esophagus or esophageal adenocarcinoma who have an inherited susceptibility termed “familial Barrett esophagus.” The family in this case report certainly fulfills criteria for familial Barrett esophagus, as defined in the literature. Although it is biologically plausible that the esophageal mucosal disease in this family is related to AFAP, it is more likely that the occurrence of 2 rare conditions in the same family is a sheer coincidence. The important clinical message is to ascertain whether other cancers, particularly...
gastrointestinal cancers or their precursor lesions, are present in family members of patients with colonic polyposis, Barrett esophagus, or esophageal adenocarcinoma to determine whether there is an increased inherited risk and whether screening of other family members is warranted. In the future, different screening recommendations, surveillance regimens, and/or treatments may be based on specific genetic alterations identified as being associated with inherited susceptibility to gastrointestinal cancers. This customization awaits more complete characterization of the natural history of these inherited conditions and identification of the genetic abnormalities present.

References


