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Diagnosis, surveillance, and treatment strategies for familial adenomatous polyposis: rationale and update

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Abstract

Familial adenomatous polyposis is characterized by the development of multiple (>100) colorectal adenomas throughout the colorectum. This disorder can be caused by a germline mutation in the adenomatous polyposis coli gene and can be diagnosed either clinically or genetically. After diagnosis with the condition, patients should undergo prophylactic proctocolectomy with a neoreservoir, usually an ileoanal pouch, at an appropriate time. Individuals with a family history of this disease who have not been diagnosed should be advised to attend genetic counseling and to enroll in appropriate clinical and genetic surveillance programs. Recent progress in endoscopic technology, including high-resolution endoscopy, capsule endoscopy, and double-balloon endoscopy, has made possible more detailed and wide-ranging investigation of the gastrointestinal tract. Although there has been limited evidence, further studies on these new endoscopic technologies might alter the surveillance strategies for familial adenomatous polyposis.

Keywords

adenomatous polyposis coli gene; attenuated familial adenomatous polyposis; familial adenomatous polyposis; genetic testing; human MutY homolog-associated polyposis

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder [1] that can be caused by a germline mutation in the adenomatous polyposis coli (*APC*) gene [2–4]. FAP is characterized by the development of multiple (> 100) colorectal adenomas throughout the colorectum. This disorder affects both sexes equally and is estimated to occur in 1/8300–1/14 025 live births [5]. Approximately 50% of FAP patients develop adenomas by the age of 15 years, which increases to 95% by the age of 35 years. The lifetime risk of colorectal cancer (CRC) approaches 100% if patients are not treated by prophylactic colectomy [6]. Patients with FAP can also have a variety of extraintestinal disorders, which include adenomas of the duodenum, papilla [7], small intestine, and stomach; gastric fundic gland polyps [8]; desmoid tumors [9]; osteomas [10]; skin lesions (lipoma, fibroma, and

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Conflicts of interest

There are no conflicts of interest.

epidermoid cysts) [10]; dental abnormalities [11]; congenital hypertrophy of the retinal pigment epithelium (CHRPE) [12]; hepatoblastoma [13]; and cancers in the thyroid gland, biliary system, pancreas [14], and brain [15]. On the basis of these factors, patients with FAP should be enrolled in a lifetime surveillance program to detect these disorders. In this article, we have reviewed the significant scientific results for current FAP diagnostic, surveillance, and treatment strategies. We have focused on gastrointestinal disorders and investigated their trends in accordance with recent advances in endoscopic technology.

Clinical diagnosis of familial adenomatous polyposis

The diagnosis of FAP relies primarily on clinical findings on the number and history of colorectal adenomatous polyps. Individuals with 100 or more polyps, or with fewer than 100 polyps but with a family history of FAP, are clinically diagnosed with FAP (Fig. 1). Attenuated FAP (AFAP) is a recognized variant of FAP and is characterized by a later onset of disease compared with classical FAP and fewer adenomatous polyps, typically between 10 and 99 [16,17]. These adenomatous polyps are more prone to occur in the right colon and phenotypic expression is often variable within families. The presence and incidence of extraintestinal disorders such as gastric polyps and thyroid and duodenal cancers are similar to those of classical FAP and are potentially helpful in the clinical diagnosis of AFAP.

Genetic diagnosis of familial adenomatous polyposis

Genetic defect

Germline mutations in the *APC* gene on chromosome 5q21 account for almost all cases of FAP [2–4]. The *APC* gene has 15 exons and encodes a gene product of 2843 amino acids with a molecular weight of ~309 000 Da. *APC* is a tumor suppressor gene or ‘gatekeeping’ gene [18]. *APC* suppresses canonical Wnt signaling, which is essential for tumorigenesis and development and homeostasis of a variety of cell types, such as epithelial and lymphoid cells [19]. In addition, *APC* plays roles in several other fundamental cellular processes. These include cell adhesion and migration, organization of the actin and microtubule networks, spindle formation, and chromosome segregation. Deregulation of these processes caused by mutations in *APC* is implicated in the initiation and expansion of colon cancer [20]. Approximately 33% of *APC* mutations occur between amino acids 1061 and 1309 [21], which lead to a high number of colonic adenomas at a younger age [22,23]. Moreover, the location of the mutation is related to the average age at onset. Patients with a mutation at codon 1309 have an average age at onset of 20 years; a mutation between codons 168 and 1580 (excluding 1309) results in an average age at onset of 30 years; mutations at the 5′ end of codon 168 and 3′ end of codon 1580 result in an average at onset of 52 years [22]. *APC* gene mutations between codons 169 and 1393 result in FAP, whereas more 3′ and 5′ mutations and somatic mosaicism for *APC* mutations predispose to AFAP [24–27]. Other correlations between the mutation site and the phenotype include profuse colorectal polyposis on mutations between codons 1250 and 1464 [28]; desmoid tumors, osteomas, and epidermoid cysts on mutations in codons 1395–1493 [29]; desmoid tumors on mutations distal to codon 1444 [30]; and CHRPE on mutations between codons 311 and 1444 [30].

Although there may be an average correlation between a specific genotype and phenotype, there is vast heterogeneity in expression, even between patients with identical mutations.

Recently, it was clarified that loss of *APC* causes upregulation of a DNA demethylase system and the concomitant hypomethylation of key intestinal cell fating genes. *APC* seems to control intestinal cell fating through a switch in DNA methylation dynamics. Wild-type *APC* and retinoic acid downregulate demethylase components, thereby promoting DNA methylation of key genes and helping progenitors commit to differentiation [31].

Molecular genetic testing

Genetic testing should be performed for certain indications including confirmation of the diagnosis of FAP and presymptomatic diagnosis of individuals 10 years of age or older who are at risk for FAP [32]. The likelihood of detecting an *APC* mutation is highly related to the severity of polyposis and the family history. Patients with an FAP phenotype are significantly more likely to have an *APC* mutation than patients with an AFAP phenotype [33,34]. Fewer than 30% of individuals with attenuated phenotypes are expected to have an identifiable *APC* mutation [35].

Several methods for *APC* gene testing are currently available. Full gene sequencing of all *APC* exons and intron–exon boundaries shows the highest sensitivity in detecting *APC* mutations but is labor intensive and is not cost effective [36]. Alternatively, the protein truncation test has the advantage of being cost effective when compared with full gene sequencing, despite having a lower detection rate for *APC* gene mutations of ~80% [37]. Southern blot analysis can be used to detect partial and whole-gene deletions or other large rearrangements, although partial or whole *APC* gene deletion has been identified in only ~8–12% of individuals with FAP [38]. Linkage studies can be carried out to provide an accurate diagnosis of *APC*-associated polyposis in affected family members and should be performed with the consent of the family members to be tested [39]. These studies should be carried out on families with more than one affected family member belonging to different generations to detect individuals with the disease-related mutation who cannot be identified by any other gene-testing method. The markers used for linkage studies are very tightly linked to the *APC* locus, and this method has 98% accuracy in detecting *APC* mutations in more than 95% of families with an *APC*-associated polyposis condition [40].

Surveillance

Colorectal advanced adenoma and cancer

Genetic testing for the *APC* gene mutation is one of the screening strategies for FAP. Individuals with a family history of FAP (first-degree relatives of FAP patients) should undergo genetic counseling and screening for FAP between the ages of 10 and 12 years to identify carriers of the *APC* gene mutation [41,42]. Surveillance and treatment strategies should be determined on the basis of each patient's personal history. (i) Patients with a personal history of classical FAP should undergo prophylactic proctocolectomy or colectomy at the appropriate time (details in the Surgical options section). (ii) Unaffected patients with a family history of mutation and with a known *APC* disease-causing mutation

should be recommended for flexible sigmoidoscopy or colonoscopy every 12 months beginning at 10–15 years of age. (iii) Unaffected patients with family history of mutation with negative molecular genetic testing results should be recommended for the same surveillance schedule as that for patients with average risk. (iv) Unaffected patients with a family history of mutation who have not undergone molecular genetic testing should be recommended for the following surveillance strategy: colonoscopy screening should start at 10–15 years of age, and the screening frequency should reduce with each subsequent decade. After the age of 50 years, patients should be advised to follow the American Gastroenterology Association guidelines for screening average-risk patients [41].

Gastric neoplasia

Numerous fundic gland polyps, often numbering in the hundreds, are observed in 12.5–84% of patients with FAP (Fig. 2) [43]. The polyps may cover the entire surface of the acid-secreting epithelium and even coalesce to give the mucosal surface a ‘matted’ appearance [44]. Gastric cancer can arise from fundic gland polyps in FAP patients [45,46], although the lifetime risk of gastric cancer in FAP patients is estimated to be only 0.6% [47].

Gastric adenomatous polyps can develop into gastric adenocarcinoma and are the second most prevalent gastric lesions in individuals with FAP. Gastric adenomatous polyps are usually detected within the gastric antrum [48]. Although the risk for gastric cancer among individuals with FAP living in Western countries is low, the risk among Japanese and Korean individuals with FAP may be 10-fold higher than that in the general population [8]. Esophagogastroduodenoscopy (EGD) should be advised for individuals with FAP either by the age of 25 years or before colectomy and EGD should be repeated every 1–3 years.

Neoplasia in the small intestine

Adenomatous polyps of the duodenum are observed in 50–90% of individuals with FAP and are commonly found in the second and third portions of the duodenum, and less frequently in the distal small bowel [49]. Duodenal adenomas are distributed throughout the duodenum with the majority being found in clusters around and distal to the ampulla of Vater. Adenomatous polyps of the periampullary region, which includes the duodenal papilla and ampulla of Vater, are seen in at least 50% of individuals with classic FAP. Polyps in this area can cause obstruction of the pancreatic duct, which results in pancreatitis or biliary obstruction, both of which occur at increased frequency in individuals with FAP. Periampullary carcinoma occurs in ~4% of individuals with FAP and is the leading cause of cancer death among FAP patients who have undergone a colectomy [50]. Very few adenomas are found proximal to the ampulla compared with the number found in the second part of the duodenum and they typically present as multiple discrete adenomas (1–10 mm in diameter) or as flat confluent plaques (Fig. 3) [51]. The average age at diagnosis of duodenal cancer is 50 years (range, 18–78 years) [49], which is ~10 years after the expected development of colonic cancer in untreated individuals with FAP [1]. The estimated relative risks for duodenal adenocarcinoma and ampullary carcinoma compared with the general population are 331 and 124, respectively [51].

The frequency of EGD depends on the severity of the duodenal adenoma, which can be determined using the Spigelman staging criteria (Table 1) [51]. This classification system comprises five stages (0–IV) depending on the number of points that have been accumulated for number, size, histology, and degree of dysplasia of the duodenal adenomas. In a previous 10-year follow-up case series, the stages of this classification system were correlated with the risk of developing duodenal cancer. Stage II, III, and IV disease were associated with a 2.3, 2.4, and 36% risk for duodenal cancer, respectively [51]. Thus, surveillance intervals can be adjusted or treatment initiated in patients with FAP and duodenal adenomatosis according to the Spigelman stage. A side-viewing endoscope should be used to visualize the duodenal papilla, and a tissue biopsy specimen should be dissected even if no polyps can be visualized but the papilla is enlarged. Endoscopic retrograde cholangiopancreatography may be necessary to evaluate for adenomas of the common bile duct.

Small-bowel cancer distal to the duodenum occurs rarely, with only 17 cases of jejunal carcinoma and three cases of ileal carcinoma in individuals with FAP reported [52]; hence, the clinical relevance of small-bowel polyps beyond the duodenum appears to be limited. Push enteroscopy (PE) has been commonly used for endoscopic screening in FAP patients to identify high-risk individuals. However, PE commonly results in insufficient screening of the small intestine, and the best screening method for small-bowel polyps in FAP patients is yet to be established [53].

Human MutY homolog-associated polyposis

Human MutY homolog (*MUTYH*)-associated polyposis (MAP) is a recently described adenomatous polyposis syndrome related to mutations in the base excision repair (*BER*) gene, *MUTYH* (formerly known as *MYH*) [54]. Patients with MAP typically present with clinical manifestations similar to that of AFAP, and the risk for CRC is estimated to be as high as 80% for biallelic *MUTYH* mutation carriers [55]. The exact incidence of MAP is unknown, but mutations in *MUTYH* likely account for 28% of cases of adenomatous polyposis syndrome [56]. In addition, biallelic mutations in *MUTYH* are related to early onset CRC without polyposis or defective DNA mismatch repair (*MMR*) genes. Patients who exhibit features of (A)FAP and have a family history of adenomas or CRC compatible with a recessive pattern of inheritance are appropriate candidates for *MUTYH* mutation analysis [57]. Screening for *APC* and *MUTYH* gene mutations may be performed in parallel in some patients, such as in those with isolated cases of multiple adenomas [58].

Biallelic mutation carriers should be managed in a manner similar to FAP patients, but because of the later age of polyposis onset, commencement of surveillance with colonoscopy is recommended at 25 years, followed by repeat colonoscopies every 1–2 years. In monoallelic *MUTYH* mutation carriers, baseline colonoscopy is suggested at 25 years of age; however, in the absence of adenomatous polyps, repeat screening should be performed every 3–5 years [58].

Gardner syndrome

Gardner syndrome (GS) is characterized by inherited colonic adenomatous polyposis together with a number of extracolonic lesions [10]. This syndrome arises from a mutation in the *APC* gene, and the number of colonic polyps is related to the locus of the mutation in the *APC* gene [23]. The common extraintestinal manifestations including osteomas [59] and dental abnormalities [60], cutaneous lesions [61], desmoid tumors [62,63], CHRPE [64], adrenal adenomas [65], and nasal angiofibromas [66] have been described in ~20% of patients with FAP. However, more patients with FAP show these features if they undergo detailed physical and radiologic examinations [67]. Thus, the difference between FAP and GS is somewhat semantic, and GS is usually considered to be a subset of FAP. In contrast, the term GS continues to be commonly applied, particularly in families that exhibit frequent and obvious extraintestinal lesions.

Turcot syndrome

Turcot syndrome (TS) was originally described by Turcot in 1959 [68,69]. It is characterized by the development of primary tumors of the central nervous system, such as glioblastoma multiforme and medulloblastoma, along with numerous adenomatous colorectal polyps and colonic adenocarcinoma. TS type I is characterized by the presence of glial tumors, relatively few colonic polyps, and cancer. TS type II is characterized by thousands of colonic polyps and increased risk for medulloblastoma [70]. The association between brain tumors and multiple colorectal adenomas can result from two distinct types of germline defects: mutation of the *APC* gene or mutation of a mismatch-repair gene [71]. However, the term ‘TS’ is no longer clinically meaningful because with the definition of the genetics of the familial colon cancers it became clear that brain tumors were associated with both FAP and Lynch syndrome.

Surgical options

For patients with known classical FAP, prophylactic proctocolectomy or colectomy is recommended [43,72]. The timing of surgery in patients less than 18 years of age is not yet established. In those patients with mild polyposis without a family history of early cancer or severe genotype, the timing of surgery can be individualized. Generally, total abdominal colectomy with ileorectal anastomosis (IRA) is preferred for AFAP and total proctocolectomy with ileal pouch-anal anastomosis (TPC/ IPAA) is recommended for FAR.

Total abdominal colectomy with ileorectal anastomosis

This surgical approach is indicated when the polyps in the rectum are amenable to endoscopic surveillance and resection. This also has advantages such as a low complication rate, good functional outcome, and lower risks for sexual or bladder dysfunction.

Total proctocolectomy with ileal pouch-anal anastomosis

TPC/IPAA is usually indicated for classical FAP patients with severe disease in the colon and/or rectum and patients with an unstable rectum after total abdominal colectomy with

IRA. Patients with low adherence to follow-up would be indicated for this surgical option as well.

Total proctocolectomy with end ileostomy

This option can be indicated when IPAA is not feasible because of either tumor location or lack of technical skill. This procedure will lead to permanent stoma; hence, its indication should be carefully determined.

Treatment options for the patients with AFAP should be determined according to patient age and severity of disease. Patients younger than 21 years with small adenoma burden (fewer than 20 adenomas, all less than 1 cm in diameter, and none with advanced histology) can be followed up by colonoscopy and polypectomy every 1–2 years. Patients who are 21 or older with small adenoma burden can be followed up under the same strategies as the younger patients; however, colectomy with IRA may be considered. Patients with significant polyposis that is not considered manageable with polypectomy should be referred for colectomy with IRA; however, TPC/IPAA could be also indicated on the basis of the burden of disease in the rectum.

Chemoprevention of familial adenomatous polyposis

Prostaglandin plays a key role in the adenoma–carcinoma sequence by altering cell adhesion, inhibiting apoptosis, and promoting angiogenesis [73,74]. NSAIDs inhibit cyclooxygenase (COX), a key enzyme in the conversion of arachidonic acid to prostaglandins. Many drugs have been studied as potential agents for chemoprevention in FAP patients. Treatment with 150 mg sulindac [75–77] (an NSAID) twice daily resulted in a statistically significant reduction in polyp count and diameter compared with treatment with placebo [78]. In FAP patients who had undergone colectomy with IRA, the use of sulindac significantly reduced rectal polyp number, as well as led to a higher grade of adenoma recurrence [79].

Celecoxib, a selective COX-2 inhibitor, also caused a reduction in the mean number of polyps and polyp burden at a high dose compared with placebo [80]. However, the use of a COX-2 inhibitor for chemoprevention in FAP patients is limited because of potential cardiovascular toxicity [81–83].

Aspirin has not only a favorable cardiovascular profile but is used as primary pharmacotherapy in patients with cardiovascular risk factors. A dose of 600 mg/day aspirin for a mean of 25 months substantially reduced cancer incidence after 55.7 months in carriers of hereditary CRC. However, further studies are needed to establish the optimum dose and duration of aspirin treatment [84].

Recently reported studies on the surveillance for familial adenomatous polyposis patients

Progress in endoscopic technology in the current decade has provided more detailed and broad-ranging information on the extent of comorbidities related to FAP.

Colorectal screening

Colorectal screening with high-resolution (HR) chromo-endoscopy for FAP patients was reported to result in significantly better adenomatous lesion detection compared with conventional white light endoscopy [85]. Colorectal screening with HR chromoendoscopy may facilitate earlier and more effective detection of disease development in patients with AFAP, which might lead to prompt decision making on salvage surgery, although further prospective study is needed.

Screening for gastric and duodenal adenomas

HR upper endoscopy combined with chromoendoscopy improves the detection of duodenal adenomas compared with conventional white light endoscopy [86,87]. In addition, a combination of forward-viewing HR endoscopy for the duodenal region and side-viewing endoscopy for the periampullary region is useful for surveillance of duodenal adenomatosis in FAP patients [87]. The use of narrow-band imaging did not improve the detection rate of gastric polyps, but resulted in detection of more duodenal adenomas. Although this resulted in upgrades of the Spigelman stage, it was not clinically relevant partly because of the limited number of cases. Further study is needed to validate these results [88].

Screening for small-bowel lesions

Visualization of the ampulla using capsule endoscopy (CE) is apparently not sufficient [89]; however, CE is reported to be useful for the surveillance of jejunal–ileal polyps in high-risk patients with FAP [90–95]. Compared with PE or ileoscopy, CE results in a higher completion rate for small-bowel screening with less invasiveness [96]. The use of double-balloon enteroscopy-assisted chromoendoscopy of the small bowel also improves the detection rate of small intestine polyps in patients with FAP [97].

Although adenomas in the small intestine are reported to be rare, these two modalities should be performed complementarily to each other to provide the best outcome.

Conclusion

We reviewed the literature on the strategies for the diagnosis, surveillance, and treatment of FAP. Recent progress in endoscopic technology, including HR endoscopy, capsule endoscopy, and double-balloon endoscopy, has facilitated more detailed and wide-ranging investigation of the gastrointestinal tract. Further study will elucidate the potential of these new endoscopic technologies to enhance surveillance strategies for FAP.

Biography

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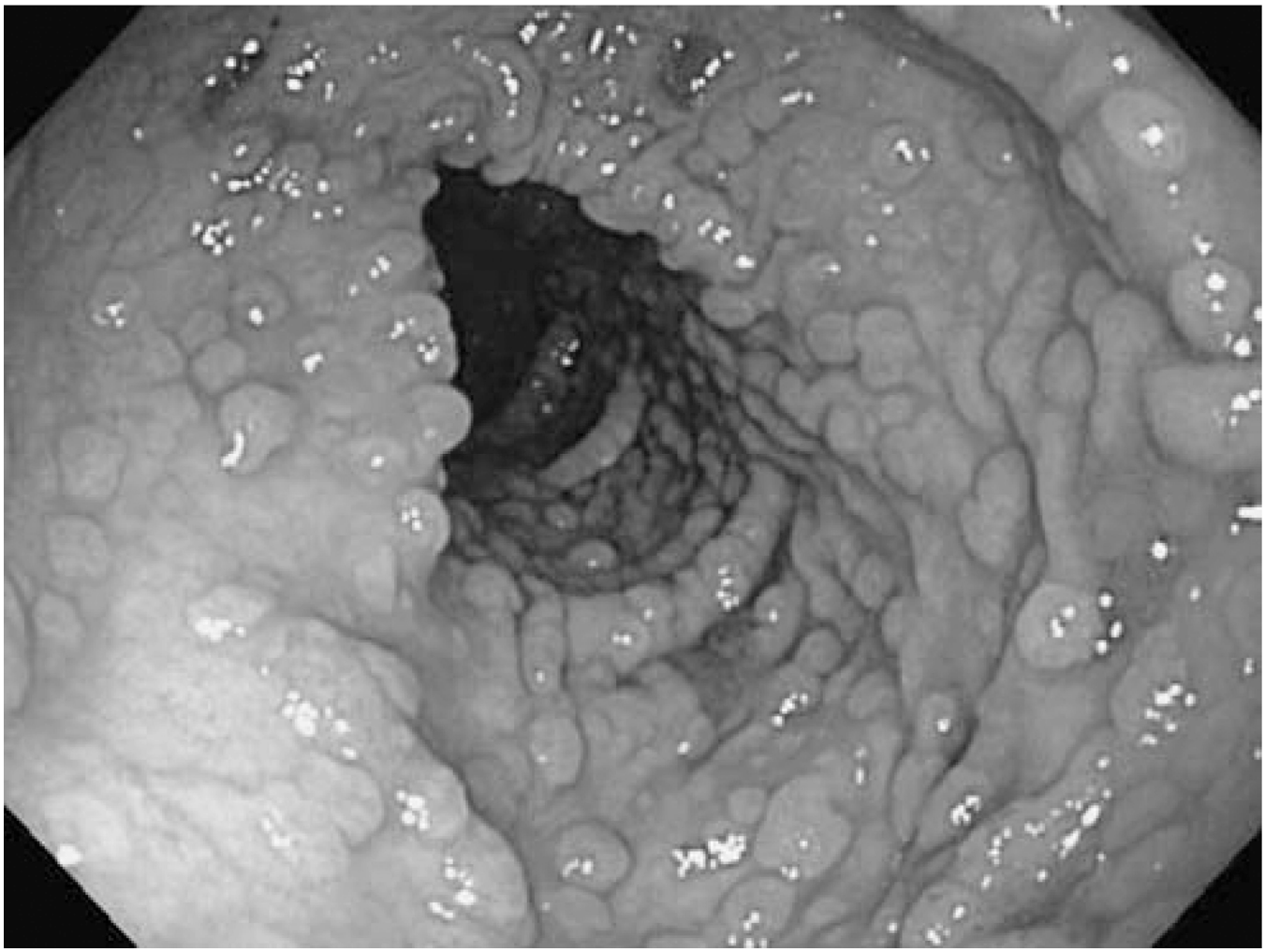

Fig. 1.
Colonoscopic findings of familial adenomatous polyposis.

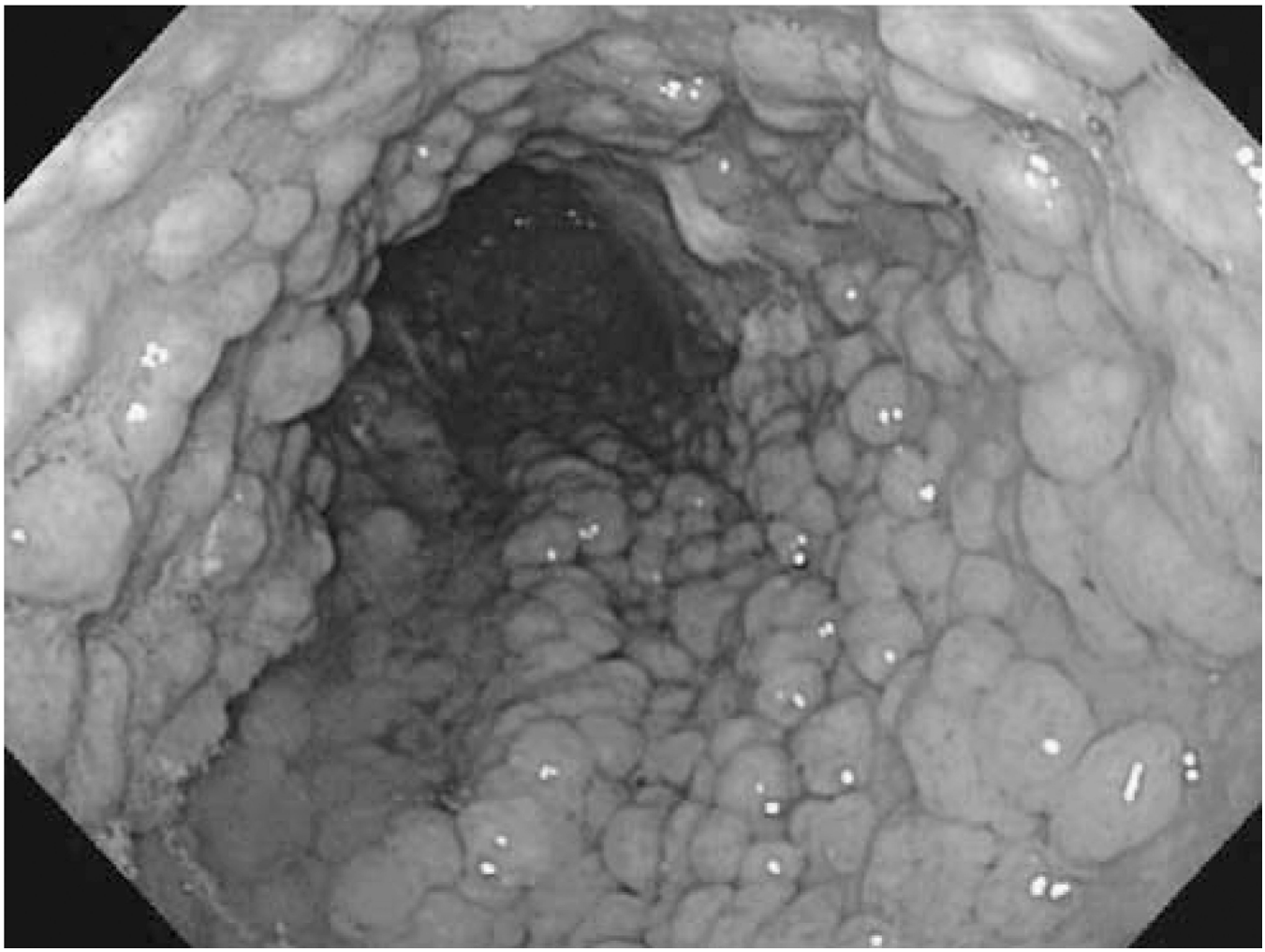

Fig. 2.
Gastric fundic gland polyps in a familial adenomatous polyposis patient.

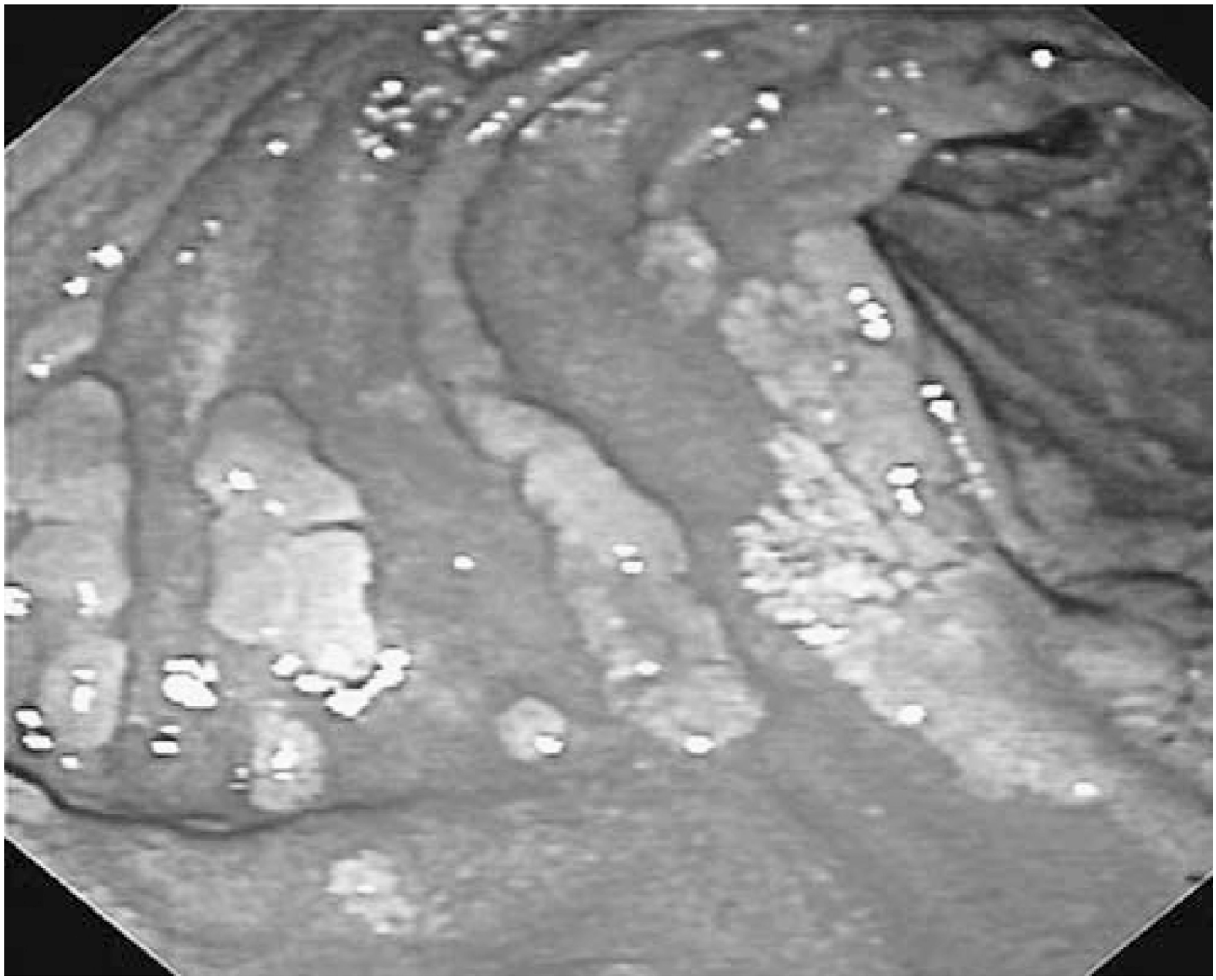

Fig. 3.
Endoscopic view of the duodenum in a familial adenomatous polyposis patient showing confluent adenomatous plaques.

Table 1

Classification of the severity of duodenal polyposis [51]

	No. of points		
	1	**2**	**3**
No. of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–1 2 points.