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Review Article

Gastroduodenal Lesions in Familial Adenomatous Polyposis

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Abstract Prophylactic colectomy is generally recommended for patients with familial adenomatous polyposis (FAP) who are inevitably affected with large bowel cancer. After prophylactic colectomy has been performed, gastrointestinal malignancy is the leading cause of death. Duodenal adenomas are found in patients with FAP and the adenoma–carcinoma sequence exists in the FAP duodenum, suggesting that treatment of duodenal polyps might be beneficial. Several methods of treatment for duodenal lesions in patients with FAP have been reported, but the current treatment options are not ideal. The nonsteroid anti-inflammatory drugs, sulindac and aspirin, are used for chemoprevention, while recently developed cyclooxygenase-2 inhibitors may be of some use in the future. Endoscopic polypectomy has been attempted for duodenal polyps and open surgical polypectomy has proven to be effective for selected patients. Photodynamic therapy and Argon plasma coagulation may be suitable to treat carpeted polyposis. New methods of duodenal resection, such as pancreas-preserving duodenectomy and pylorus-preserving pancreaticoduodenectomy, might be considered for severe duodenal polyposis; however, because prophylactic duodenal surgery has been considered too aggressive, surveillance duodenoscopy is usually performed to detect duodenal cancer at an early stage.

Key words Familial adenomatous polyposis · Duodenal polyp · Duodenal cancer · Surveillance

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by numerous, of up to hundreds or even thousands, of adenomas in the large bowel. Without effective treatment, patients are inevitably affected with large bowel cancer.[1] Thus, to prevent cancer death, prophylactic colectomy is generally recommended, which has significantly improved the survival of these patients. Nevertheless, the life expectancy of patients with FAP falls short of that of the general population.[2] After prophylactic colectomy has been performed, upper gastrointestinal malignancy is the leading cause of death for these patients.[3,4] Duodenal polyps are found in most patients with FAP. The adenoma–carcinoma sequence exists in the FAP duodenum, suggesting that treatment of duodenal polyps might be beneficial.[5] However, as prophylactic duodenal surgery is considered to be too aggressive, surveillance duodenoscopy is usually performed to detect duodenal cancer at an early stage.

History

Gastric polyps in patients with FAP were initially described in 1895[6] and the first report of duodenal polyps was documented in 1904.[7] Duodenal and gastric cancer occurring in association with FAP were first described in 1935[8] and 1962,[9] respectively. Consequently, concern was expressed about the risk of duodenal cancer, and careful surveillance of the upper gastrointestinal tract was recommended in the 1960s. Although it was known that involvement of the upper gastrointestinal tract could occur, examination of the stomach and duodenum was performed only if the patients presented symptoms such as abdominal pain, jaundice, or unexplained anemia. Utsunomiya et al. reported a high incidence of gastric polyps (66.7%) in patients with FAP in 1974,[10] then in 1977, Yao et al. reported a remarkably high incidence of duodenal adenomas in patients with FAP.[11] In the following decade, several centers published the results of studies investigating the incidence of duode-

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nal adenomas which was revealed to be approximately 50% with a range of 20%–66%. In 1989, Spigelman et al. reported the results of a prospective study that revealed approximately 90% of FAP patients carried duodenal adenomas.[12] Since the adenoma–carcinoma sequence also exists in the duodenum of patients with FAP,[5] this high incidence of precursor lesions alerted clinicians to the possible importance of prevention in the duodenum. Gastric polyps, being predominantly nonadenomatous, were not thought to be subject to the same risk of malignant change.

Frequency of Duodenal Cancer

Duodenal cancer is rare in the general population, the incidence having been reported to range between 0.01% and 0.04%.[13] In 1977, Jones and Nance reviewed the reported cases of periampullary cancer developing in association with FAP and suggested that the upper gastrointestinal tract be examined in patients with this disorder.[14] In a surveillance series of 20 patients with FAP documented by Iida et al., one duodenal cancer was diagnosed.[15] In 1988, Jagelman et al. reported the results of a survey of ten polyposis registries, coordinated by the Leeds Castle Polyposis Group, being an international cluster of registries dealing with FAP.[3] According to this survey, 57 of 1255 patients with FAP had an extracolonic intestinal malignancy, which occurred in the duodenum in 39 (3.1%) patients. The duodenal cancers were diagnosed in these patients at an average age of 52 years. Bulow et al. reported the results of a multicenter study, namely, the "DAF" study in Denmark, Finland, Holland, Norway, and Sweden, which have national polyposis registers with almost complete registration.[16] The data from this series, conducted from 1990 to 1998, showed that a gastroduodenoscopy performed every 2 years in several hundred patients yielded eight patients with duodenal cancer diagnosed at an average age of 47 years. Iwama et al. reported the results from a Japanese register involving 1050 patients, 11 (1%) of whom died as a result of duodenal cancer, showing a 250-fold increased in risk.[4] Offerhaus et al. estimated that the relative risk of duodenal cancer developing in patients with FAP was 331 and that of ampullary cancer developing was 124.[17] Thus, duodenal cancer has been reported to occur in 1%–5% of patients with FAP, demonstrating a relative risk 100–300-fold greater than that in the general population.

Although duodenal adenomatous polyps are rare in the general population, duodenal adenomas are found in between 20% and 100% with an average incidence of 61% of patients with FAP (Table 1).[11,12,15,16,18–29] The estimated prevalence of duodenal adenomas depends in part on the methods used for surveillance, including the type of equipment used, whether or not dye spray and magnifying endoscopy is used, and the number of biopsies taken to detect microadenomas. Thus, since duodenal polyps tend to develop around and at the ampulla or more distal part of the duodenum, the use of side-viewing duodenoscopy with multiple biopsies leads to reports at the higher end of the range.[12] Histopathological examination is essential since random biopsies from mucosa that appears normal, especially that from the ampulla, often reveals adenomatous change. Of interest

Table 1. Upper gastrointestinal polyps in familial adenomatous polyposis

First author[Ref.]	Year	Country	No. of patients	G-Ad (%)	D-Ad (%)
Yao[11]	1977	Japan	14	—	100
Ranzi[24]	1981	Italy	9	44	66
Jarvinen[25]	1983	Finland	34	12	48
Burt[21]	1984	USA	11	9	63
Bulow[19]	1985	Denmark	26	3	46
Tonelli[18]	1985	Italy	24	12	58
Kurts[20]	1987	USA	41	0	20
Sarre[23]	1987	USA	100	2	33
Alexander[22]	1989	USA	18	—	50
Spigelman[12]	1989	UK	102	5	92
Iida[15]	1989	Japan	20	—	90
Seow-Choen[72]	1992	Singapore	25	4	20
Church[73]	1992	USA	240	7	66
Goedde[74]	1992	USA	30	17	67
Bulow[16]	1995	Scandinavia	310	—	64
Sawada[26]	1995	Japan	35	26	40
Iida[28]	1996	Japan	23	—	91
Bertoni[29]	1996	Italy	25	—	72
Marcello[27]	1996	USA	42	14	73

G-Ad, gastric adenoma; D-Ad, duodenal adenoma

Table 2. Stages of severity in duodenal polyposis (Spigelman's stage)

	Grade (points)		
	1	2	3
No. of polyps	1–4	5–20	>20
Size of polyps (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Modererate	Severe

Stage 0, 0 points; Stage I, 1–4 points; Stage II, 5–6 points; Stage III, 7–8 points; Stage IV, 9–12 points

is the staging of duodenal polyposis, which may provide more information to assess the risk of malignant transformation.[12,30,31] Duodenal polyposis can be staged by a classification based on scoring the size and number of polyps, the degree of dysplasia, and the polyp architecture (Table 2). A prospective study from St. Mark's hospital in London reported that 90% or more of the patients are affected with duodenal polyposis, 10% having stage IV polyposis, while 20% had stage I, and the remainder had stage II or III.[12,31] Patients with stage IV duodenal polyposis tended to be older, with an average age of 50.4 years, than those with other stages, suggesting that duodenal polyposis progresses over time. The afore mentioned DAF study from Scandinavia reported a duodenal adenoma prevalence rate of around 70%, with 13% of patients having stage IV disease.[16]

Although the risk of gastric cancer developing in association with FAP is not increased in patients from Western countries, it is higher in these from east Asia. Thus, the incidence of gastric cancer in patients with FAP from Korea was found to be 4.2% while that in those from Japan was found to be 2.1%, being higher than that in those from Western countries or that in the general Asian population.[4,32] The observed/expected morbidity ratio for gastric cancer was 3.4 in Japan.[4]

Gastric polyps are found in 0.15%–2.5% of the general population; however, gastric fundic gland polyposis is found in approximately half of all patients with FAP. The histopathologic picture of fundic gland polyposis is characterized by dilatation and cystic change of the fundic gland.[30,33] Fundic gland polyps may increase in number but they do not have great potential for malignant change,[34] although a rare case of an attenuated type of FAP in which gastric cancer developed from fundic gland polyposis was recently reported.[35] Gastric adenomas occur infrequently, and are usually located in the antrum of the stomach. They were found in 6% of the patients with FAP in the St. Mark's study. Although the natural history of gastric adenoma is not known, it may be a precursor of malignancy. Iida et al. reported a case in which mucosal cancer developed after 4 years of observation.[36]

Since duodenal lesions cluster around the ampulla in patients with FAP, it is hypothesized that the bile in these patients carries carcinogens.[12] In fact, the risk of periampullary cancer developing in patients with FAP was estimated to be approximately 100 times higher than that of the general population. The high incidence of duodenal adenomas and cancers in these patients, coupled with evidence of their clustering around the ampulla of Vater, suggests the presence of carcinogens in the bile of patients with FAP. A high level of DNA adduct formation in the FAP duodenum and the carcinogenic effect of bile taken from patients with FAP on rat intestinal mucosa support this supposition.[37,38]

Natural History

Gastric fundic gland polyposis may appear as early as in the first decade of life, and while it can increase in number and size gradually, it does not significantly increase the risk of gastric cancer,[34,39] although one such case report exists.[35] On the other hand, gastric adenomas may be precursors of malignancy. Iida et al. reported the results of a prospective observation of the natural history of gastric adenomas which revealed that gastric adenomas did not increase in size or in the degree of atypia over a mean period of 7 years.[36] However, one gastric mucosal cancer was revealed by the histopathological examination of biopsy samples developed during the observation period of 4 years, suggesting that gastric adenomas have a potential for malignant transformation.[36]

The natural history of duodenal adenomas has been described by several centers. Iida et al. reported that cancer developed in 1 of 18 patients with duodenal adenomas, while the remainder did not progress during 7 years of observation.[15] Tonelli et al. observed an increase in the size and number of duodenal polyps over 33 months in 2 of 10 patients.[18] At St. Mark's hospital, 70 patients underwent repeat duodenoscopies over a mean period of 40 months. During this period, duodenal cancer developed in 3 patients, 1 case being definite and 2 probable, and the stage of polyposis worsened in 7.[40] An advanced stage of polyposis, advanced age, and the duration after colectomy seem to be risk factors predisposing to the progression of duodenal polyposis over time. The DAF study is planned to cease in the year 2000 after 10 years; however the 1998 data indicate that there are significant increases in the number and size of polyps, and the degree of dysplasia, with a resultant significant worsening in overall stage with time.

As the periampullary area is particularly at risk, the observation that 14% of ampullary adenomas in a total of 76 patients studied progressed over 44 months causes concern, as is the finding that 41% of "major" ampullary

adenomas, defined as those with a diameter of 10 mm or greater having moderate to severe dysplasia or villous histology, progressed.[41] On the other hand, Noda et al. reported that the histopathology of 17 ampullary adenomas did not change during an observation period of 7.7 years.[42] A recent case report described the malignant transformation of duodenal adenoma in a 44-year-old Japanese man with an observation period of 5 years.[43] Another case report described a 30-year-old women who underwent annual duodenoscopies for 10 years, in whom unresectable ampullary cancer developed, highlighting the limitations of current surveillance and treatment methods.

Genetics

The detection of genetic events associated with duodenal lesions may be helpful for selecting patients at high risk of developing duodenal cancers. Patients with FAP carry germ line mutations in one allele of the *Adenomatous Polyposis Coli (APC)* tumor suppresser gene on chromosome 5q21. In the colonic tumors of patients with FAP, another allele of *APC* gene is altered which leads to a loss of APC function. A loss of heterozygosity (LOH) of the locus of the *APC* gene is detected in 15% of adenomas with severe dysplasia and 26%–44% of colonic cancers in patients with FAP.[44] Somatic *APC* gene mutation is found in 53% of adenomas with moderate dysplasia, 64% of those with severe dysplasia, and 33%–52% of all colonic cancers.[45] K-*ras* mutation and *p53* mutation are reported to occur in 7%–25%[46] and 3%–5%,[47,48] respectively, of colonic adenomas in patients with FAP.

The genetic alterations in the duodenal tumors of patients with FAP are poorly characterized when compared with those in colorectal tumorigenesis. Toyooka et al. reported that a somatic *APC* gene mutation was found in 46% of duodenal adenomas, 67% of ampullary adenomas, and 50% of ampullary cancers.[49] A somatic *APC* gene mutation was commonly found in small adenomas with mild dysplasia, suggesting that the *APC* gene alters at an early stage of duodenal tumor development.[49] In this series, K-*ras* mutation was not detected and was considered to play a minimal role in duodenal tumor development. In contrast, Gallinger et al. found *APC* mutations in only 3 of 48 (6%) periampullary adenomas.[50] Of interest was that the K-*ras* mutation was found in 37% of periampullary adenomas in their series.[50] The *p53* gene mutation was not often found in duodenal adenomas.[51,52]

The association of a particular genotype with severe duodenal disease might be used to select with patients should undergo duodenal surgery; however, there is conflicting evidence to support the presence of a genotype–phenotype correlation in duodenal lesions associated with FAP. Sanabria et al. reported that familial segregation determined the severity of periampullary neoplasms while age was also a significant variable.[53] Specific *APC* germ-line mutations did not correlate with the severity of periampullary polyps. Duodenal polyposis clusters in particular families. In fact, at St. Mark's hospital, two or more members of some families suffered from severe duodenal polyposis and cancer; however, no particular site of mutation in the *APC* gene was found to be associated with the severity of duodenal polyposis. An attenuated type of FAP characterized by sparse colonic polyps with late onset has been reported to be correlated with a specific site of mutation in the *APC* gene.[54,55] It has also been suggested that attenuated APC could be associated with severe duodenal disease;[54,56] however, further research is needed in the area of the genotype–phenotype correlation in duodenal disease.

Other possible factors contributing to the development of severe duodenal polyposis include the action of modifier genes and environmental influences. For example, a modifier gene on chromosome 1p35–36 has been reported to influence the severity of duodenal polyposis.[57,58] The effect of environmental factors might be modulated by abnormalities in hepatic metabolism, leading to changes in the constitution of bile in these patients with resulting variation in the duodenal phenotype.[59]

Treatment

Several methods of treatment for duodenal lesions in patients with FAP have been reported, but the current options are not ideal. Patients who have undergone a subtotal colectomy and ileorectal anastomosis may have rectal polyposis treated by snare polypectomy and coagulation therapy.[60] However, duodenal polyps are often sessile and there may be carpeting,[61,62] which makes endoscopic polypectomy and hot biopsy difficult,[34] as does the position of many polyps around the entry of the bile duct in the ampulla. Iwama et al. described the efficacy of the local excision of ampullary lesions for selected patients;[63] however, some European surgeons reported that surgical polypectomy including local excision was followed by high morbidity and frequent recurrence.[64] In the European series, all of the 12 patients undergoing surgical polypectomy suffered recurrent duodenal polyposis within 13 months of surgery. The differences between the reports may be attributed to the severity of the disease as well as the surgical procedures. It is most important to carefully select patients whose polyposis is suitable for such treatment; that is, those with only one or a few polyps, which can be

large but not carpeted, the histopathology of which shows moderate/severe dysplasia or mucosal cancer.[63] To assess the extent of duodenal lesions, endoscopic ultrasound and spiral computed tomography are useful.[34,65] Although endoscopic ultrasound is an invasive procedure, it may contribute to the accuracy of staging and to determining the extent of the duodenal polyposis, thereby being beneficial for clinical decision-making.[34]

New methods for performing duodenal resection have recently been developed, such as pancreas-preserving duodenectomy[66] and pylorus-preserving pancreaticoduodenectomy. Penna et al. reported the results of surgically treating duodenal polyposis in 18 patients with FAP.[67] In consideration of the findings that recurrence developed after local excision in all of six patients who underwent this procedure, a high incidence of postoperative complications was seen after surgical polypectomy, and pancreaticoduodenectomy resulted in acceptable morbidity and eliminated the risk of cancer, prophylactic duodenal resection might be a reasonable option for patients with severe duodenal polyposis.[67]

Photodynamic therapy is a method used to destroy the superficial layer of mucosa by light delivered by laser after the administration of photosensitizing agents.[68] Since localized necrosis is limited to within the surface of the mucosa, the risk of perforation is low. Therefore, this method may be effective for treating patients with carpeted polyposis. Argon plasma coagulation is a method of noncontact electrocoagulation involving the application of an electric current to tissue by ionized argon gas, which has been used to control hematemesis. It coagulates to a depth of 2–3 mm, which reduces the risk of duodenal perforation, and is currently being trialled.

At St. Mark's hospital, a prospective study was performed to test the effect of nonsteroid anti-inflammatory drugs (NSAIDs), such as sulindac, on rectal and duodenal polyps. Sulindac was effective in suppressing cell proliferation and macroscopic development in rectal polyps.[69] In the duodenum, NSAIDs also reduced cell proliferation, although the effect was not statistically significant.[19,69] Cyclooxygenase (COX) converts arachidonic acid to prostaglandins which may affect cell proliferation and tumor growth.[70] NSAIDs inhibit COX and are supposed to inhibit cell proliferation through this effect. One form of COX, COX-2, is considered to play a key role in tumorigenesis in FAP. COX-2 inhibitors have recently been developed and may be of use in the future.[71] Aspirin was expected to be worth examining for its efficacy following reports of a significant reduction in the number of deaths from colon cancer in patients taking aspirin for a long time; however, studies subsequently showed that low-dose aspirin was not effective for duodenal polyposis (St. Mark's hospital, unpublished data).

The administration of gene therapy by supplying normal copies of the *APC* gene via an enema to the rectal stump and orally to the duodenum is being canvassed and may also prove to be beneficial.

Recommendations for the Follow-Up and Management of Duodenal Lesions in Patients with FAP (Table 3)

In the absence of symptoms, the first endoscopy in patients with FAP should be performed at around 20 years of age, and repeated after 1 year. It is important that the periampullary area is visualized and if the patient has mild duodenal polyposis of stage I or II, the next duodenoscopy should be carried out in another 3 years. If no progression is observed after 3 years, the next endoscopy could be done in another 5 years. Patients with moderate or severe duodenal polyposis of stage III or IV should have an endoscopy done every year. Endoscopic ultrasound could be considered if it is available, and chemoprevention is also recommended. Patients

Table 3. Recommendations for follow-up and management

The first endoscopy should be performed at around 20 years of age. The periampullary area should be visualized and biopsies taken.

1. Mild duodenal polyposis (stage I or II)
   Endoscopy every 3–5 years
2. Moderate polyposis (stage III)
   NSAID, chemoprevention
   Endoscopy every year. Endoscopic ultrasound is recommended
3. Severe polyposis (stage IV)
   NSAID, chemoprevention
   More frequent examinations are needed and surgical intervention must be considered
   Endoscopic ultrasound

If polyposis comprises:

(1) One or a few polyps that can be large but not carpeted with moderate/severe dysplasia
   → Surgical or endoscopic local resection
(2) Multiple, carpeted polyps with mild or moderate dysplasia
   → Argon plasma coagulation, photodynamic therapy
(3) Multiple, carpeted polyps with severe dysplasia showing rapid growth, or polyps greater than 1 cm in diameter with severe dysplasia showing rapid growth
   → Prophylactic duodenal surgery (pylorus-preserving pancreaticoduodenectomy or duodenectomy)
(4) Polyps greater than 1 cm in diameter with induration, ulceration, consistently severe dysplastic pathology, or rapid growth predisposing to a risk of cancer
   → Pancreaticoduodenectomy

NSAID, nonsteroidal anti-inflammatory drug

with severe polyposis need more frequent examinations and consideration for surgical intervention.

Polyps greater than 1 cm in diameter, induration, ulceration, consistently severe dysplastic pathology, or rapid growth alert the risk of cancer and may determine early surgical intervention. Due to the frequency of recurrence after local excision, coupled with advanced techniques of duodenal surgery such as pylorus-preserving pancreaticoduodenectomy or duodenectomy, prophylactic duodenal resection might be a reasonable option for patients with severe duodenal polyposis.

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