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REVIEW

The Pancreas in Familial Adenomatous Polyposis

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Summary

Familial adenomatous polyposis is an archetypal disease illustrating the genetic basis of human cancer. The adenomatous polyposis coli gene functions as a tumor suppressor with hundreds of known mutations that result in a defective adenomatous polyposis coli protein. In addition to the certain fate of colon cancer without colectomy, patients with familial adenomatous polyposis are also at increased risk for other types of neoplasms, including those which affect the pancreas. This review focuses on periampullary and ampullary tumors, benign and malignant pancreatic neoplasms that are associated with familial adenomatous polyposis and Gardner syndrome and pancreatitis in these patients. An individualized surveillance regimen is suggested which for certain patients could include endoscopic ultrasound.

Background

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by hundreds and thousands colonic adenomatous polyps that most often emerge in the second and third decades of life. Colon cancer is inevitable if the colon is not resected, fortunately this condition accounts for only one percent of all colorectal cancers. Gardner syndrome (GS) is a variant of FAP with the addition of extracolonic lesions. Though the extraintestinal growths do not define a genetically separate syndrome from FAP, the term GS is used quite often by patients and physicians when the extraintestinal lesions represent a dominant part of the clinical picture.

FAP was first linked to extracolonic manifestations in 1923 by Nichols, when he described the association of FAP and desmoid tumors [1]. In 1951, Gardner described FAP associated with a number of extracolonic growths, including fibromas, osteomas, and epidermoid cysts [2]. Additional manifestations of the underlying genetic defect such as dental abnormalities, desmoid tumors and other lesions were later recognized. A variation of FAP, attenuated FAP, is characterized by fewer polyps, later onset of cancer and lower penetrance (not all individuals with the gene defect will develop cancer). Extracolonic manifestations in FAP/GS directly involve the pancreas in approximately one percent of cases [3]. Lesions reported have been benign, precancerous and cancerous. Furthermore, pancreatic duct obstruction with or without pancreatitis caused by benign or malignant tumors is not observed infrequently.

Both FAP and GS arise from adenomatous polyposis coli (APC) gene mutations [4, 5]. Inheritance is autosomal dominant with near complete penetrance of the colonic phenotype but variable penetrance of the extraintestinal manifestations of the disease. It is important to note that many of the different extraintestinal lesions correlate with mutations at specific locations of the APC gene [6]. Colonic adenomatosis, duodenal polyposis, colon and gastric cancer risk

associated with GS were shown to be identical to FAP; and if affected patients are examined thoroughly, extraintestinal growths can be found in many FAP families [7].
GS also cannot be separated from FAP when considering its overall prevalence. Estimates for the combined syndromes vary from 1 in 6,850 to 1 in 31,250 (2.29 to 3.2 cases per 100,000 persons) [8, 9]. The incidence of FAP is 1 case in 7,500 live births and is due to congenital inheritance in a Mendelian dominant fashion in 80% of patients. The remaining 20% represent spontaneous mutations, with no family history reported [8]. One person per million population is diagnosed with GS.
GS is associated with several benign extraintestinal growths and patients are at increased risk for several extracolonic malignancies. Benign extraintestinal growths include osteomas and dental abnormalities, cutaneous lesions, desmoid tumors, congenital hypertrophy of the retinal pigment epithelium, adrenal adenomas, and nasal angiofibroma. The following malignancies have been described in various studies: duodenal and periampullary (3 to 5% of patients with GS), thyroid (2%), pancreatic (2%), hepatoblastoma (1.6%), central nervous system (less than 1%), gastric (0.6%), small bowel distal to the duodenum and adrenal.

Involvement of the Pancreas in FAP/GS

Pancreatic lesions linked or associated with FAP/GS are scarce. The following section will review and discuss the various types of pancreatic lesions that were reported in linkage or association to FAP/GS including benign, precancerous, cancerous and other lesions.

FAP/GS and Periampullary Lesions

Though data suggest that many if not most ampullary/periampullary tumors are more analogous to intestinal than pancreatic neoplasms [3, 10, 11, 12], we think the review of ampullary/periampullary tumors in association with FAP/GS should be included here based on clinical presentation. Furthermore, tumors can develop in deeper parts of the ampulla, which are lined by pancreaticobiliary duct mucosa. Intestinal-type adenocarcinoma and pancreaticobiliary-type adenocarcinoma represent the main histological types of ampullary carcinoma. Interestingly, molecular alterations in ampullary carcinomas are similar to those of colorectal as well as pancreatic carcinomas, although they have different frequencies. In addition, it can be difficult to distinguish a primary ampullary lesion such as carcinoma from other periampullary tumors pre-operatively [13] (Figure 1).
Benign neoplasms of the ampulla of Vater are rare, representing less than 10% of periampullary neoplasms [14, 15]. FAP/GS patients often develop periampullary adenomas that may progress to periampullary cancer, a common cause of death in this population. The most common benign lesions are villous and tubulovillous adenomas. With the extensive availability of flexible endoscopy and the widespread application of screening and surveillance programs for high-risk patients with FAP, ampullary adenomas are being increasingly recognized [16, 17, 18, 19, 20]. In autopsy series the prevalence of ampullary adenomas was

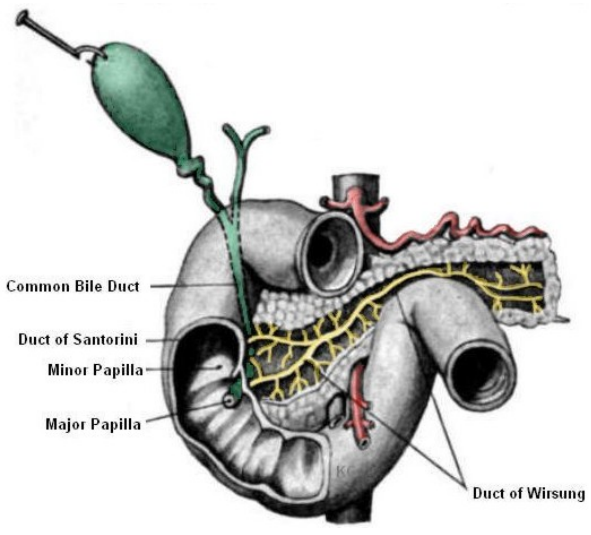

Figure 1. In FAP the pancreas may be affected by ampullary and periampullary neoplasms, pancreatitis, pancreatic adenocarcinoma and a variety of rarer neoplasms. [From: Arthur William Mayo Robson, Percy John Cammidge. The Pancreas, Its Surgery and Pathology. Philadelphia, PA, USA: Saunders, 1907, p. 35.]

estimated to be ranging from 0.04 to 0.12% [21, 22, 23].

The adenoma-to-carcinoma sequence described elsewhere in the gastrointestinal tract appears to also apply to the progression of ampullary adenomas to carcinoma [14, 24]. The adenoma-carcinoma sequence was morphologically recognized in a minute carcinoma in an adenoma of the papilla of Vater [21]. Nevertheless, these studies [14, 21, 24] were not designed to examine the progression to carcinoma in FAP patients specifically. In contrast, Mizumoto *et al*. studied the role of telomerase in periampullary tumor progression in patients with FAP [25]. Telomerase was found to be activated even in normal mucosa of FAP patients and the telomerase activation level was thought to reflect the malignant potential of these periampullary neoplasms.

The risk of periampullary cancer in FAP is unclear, and variables that predict the occurrence and biological behavior of periampullary tumors are not well understood. Sanabria *et al*. have postulated that occurrence and severity of periampullary neoplasms in patients with FAP segregates in families [26]. This familial association may be related to as yet unidentified modifier genes or perhaps common environmental factors.

Individuals with FAP/GS may have a 100- to 200-fold increased risk of developing periampullary carcinoma when compared to the general population [27]. The incidence of ampullary tumors is increased 200- to 300-fold among patients with hereditary polyposis syndromes, such as FAP and hereditary non-polyposis colorectal cancer [28, 29]. The impact of FAP on the tumorigenesis and mortality involving several organs was studied by Iwama *et al*. [30]. In this Japanese study the organ-specific morbidity and mortality rates of malignant tumor in FAP patients were compared with those of the general population. The observed/expected mortality ratio was 250:1 (95% confidence interval: 112-447) for periampullary and small intestinal carcinomas.

Periampullary malignancies of the intestinal type have a worse prognosis than true ampullary cancers of pancreatic origin. In contrast, in ampullary cancers of pancreatic origin, resectability rates are higher (over 90% in contemporary series), and 5-year survival rates are approximately 30 to 50%, even in patients with lymph node involvement [13, 31, 32].

Other pancreatic precancerous lesions that have been reported in association with FAP/GS include three cases of intraductal papillary mucinous pancreatic neoplasms [33, 34, 35], two pancreatic duct adenomas [36], and one high-grade pancreatic intraepithelial neoplasia (PanIN-3) [37]. However, in the latter report it was not very clear if adenomatous changes of the pancreatic duct epithelium represented adenomatous transformation (nonmucinous) of the major pancreatic ducts or mere extension from the adjacent adenomatous duodenal epithelium. The authors cautioned that more studies and reports are needed to establish a clear link.

A possible genetic link between FAP/GS and intraductal papillary mucinous pancreatic neoplasms was investigated by Maire *et al*. [33]. A patient with FAP presented with an intraductal papillary mucinous pancreatic tumor (IPMT). Histological examination of the resected specimen confirmed IPMT with in situ carcinoma. Genetic analysis showed loss of the wild allele of the APC gene in IPMT, causing inactivation of both alleles demonstrating that IPMT was probably not incidental in this patient. Twelve months after resection, the patient remained free of recurrent tumor.

Another report of IPMT involves a 67-year-old man with a clinical diagnosis of attenuated FAP and a past history of synchronous colon cancers in the transverse colon. Additionally, several foci of heterotopic gastric oxyntic mucosa were noted in the duodenum, interspersed with flat and polypoid adenomas. The duodenal adenomas showed low grade dysplasia and loss of APC protein expression, but retention of beta catenin staining localized to the nucleus and cytoplasm. The IPMN in the

pancreas showed an identical immuno-histochemical profile to the duodenal adenomas. Although the patient did not show germ line truncating APC mutations or mutations in the MYH gene, the authors were of the opinion that the past history, clinical features, and immunohistochemical profile of the various lesions established a strong link between IPMN and FAP/GS [34].

Komorowski *et al*. [36] present a patient with FAP/GS who developed polyps with carcinoma in situ of the common bile duct and ampulla of Vater, along with extensive adenomatous changes in the duodenum, gallbladder, extrahepatic bile ducts, and main pancreatic duct.

Pancreatic Malignancies, Germline Mutations and Linkage to FAP/GS

Reports of malignancies of the pancreas in association with FAP/GS are rare and involve a variety of cell lines. Exocrine, endocrine, and stromal pancreatic tissues have all been reported as sites for malignancies in association with FAP/GS. Whether there is a true linkage or association by coincidence is unclear. However, pancreatic adenocarcinoma has been described in a variety cancer susceptibility syndromes associated with germline mutations in p16, BRCA1, BRCA2, and APC [38]. Needless to say, more reports and studies are considered necessary to support linkage and or association. Due to the rarity of these and other types of malignancies reported in association to FAP, true linkage will be difficult to prove.

The risk of pancreatic adenocarcinoma in FAP/GS has been estimated to be increased more than four-fold compared to the general population (RR: 4.46; 95% CI: 1.2 to 11.4). The absolute lifetime risk is still low at about 2%, however [39]. FAP is caused by mutations in the 5q21 gene locus, but most pancreatic carcinomas are associated with other mutations such as K-*ras* (12p12), 17p, 18q (*DCC* locus), *p53* (17p13), etc. [40, 41, 42, 43, 44, 45].

Unfortunately, reports on mutations of the APC gene in human pancreatic cancers are limited and have conflicting findings. For example, Neuman *et al*. [46] suggest that inactivation of the APC gene on chromosome 5 may be an initiating step for carcinomas of the stomach and pancreas as well as of the colon, but that the genes involved in tumor progression events may be tissue- or tumor-specific [46]. Chromosome 5 allele loss occurred at the same frequency in all three gastrointestinal tumors (approximately 30%). Horii *et al*. reported somatic mutations of the APC gene in 4 of 10 pancreatic cancers in their series [47], Yashima *et al*., however, reported the mutation in only 1 of 39 pancreatic cancers [48]. Gupta and Mazzara [37] noted that the variant results of these two studies can be explained in part by the fact that Horii *et al*. examined a much more extensive region of the 5q gene and used an RNase detection method as opposed to the polymerase chain reaction-single-strand conformation polymorphism method used by Yashima *et al*.. Furthermore, the studies reporting the contribution of the APC gene in human pancreatic cancers have involved Japanese patients, and it may be possible that there are differences in the molecular pathogenesis of pancreatic cancers in that population group [49].

Seymour *et al*., McKie *et al*., and Ding *et al*. found no APC mutations in pancreatic carcinomas [44, 49, 50]. Gupta and Mazzara emphasize that pancreatic cancers usually have abundant desmoplastic stroma surrounding malignant glands and they suggest that disproportionate sampling of this reactive stroma could cause a false-negative result [37].

Another example of exocrine tissue tumor in association with FAP/GS is acinar cell carcinoma. The pancreas is composed predominantly of acinar cells but, curiously, acinar cell carcinoma accounts for only 1% of all primary pancreatic neoplasms. The first description of the association of FAP/GS with acinar cell carcinoma of the pancreas was reported by Seket *et al*. [51]. A 65-year-old patient with a history of FAP/GS developed advanced duodenal polyposis and a synchronous 25 mm tumor of the pancreatic neck. The patient had a total pancreatectomy

and antrectomy. Histological examination revealed an acinar cell carcinoma of the pancreas and duodenal adenomas showed low- and high-grade dysplasia but not cancer. To date, this is the only reported case showing histology of this nature. Stewart *et al*. reported a pancreatic glucagonoma in association with FAP [52].

Pancreatoblastomas are unusual malignant neoplasms typically encountered in the pediatric age group that may also rarely affect adults. Pancreatoblastomas are clinicopathologically distinct from adult pancreatic ductal carcinomas and resemble other infantile embryonal tumors. Abraham *et al*. described molecular alterations in the APC/beta-catenin pathway in 6 of 9 patients with pancreatoblastomas, one of which had the FAP mutation [53]. They concluded that pancreatoblastomas may represent an extracolonic manifestation of FAP.

We are reporting the case of a 66-year-old woman with GS who had an unusually fast growing adenocarcinoma of the pancreatic tail following a Whipple procedure years earlier for an ampullary carcinoma (unpublished manuscript).

FAP/GS and Other Neoplastic Lesions of the Pancreas

Benign lesions of the pancreas directly related to FAP/GS are very rare. Desmoid tumors (also referred to as desmoid fibromatosis) are histologically benign fibrous neoplasms originating from the musculoaponeurotic structures. They are rarely encountered in the abdomen, and if they are, tend to be associated with FAP/GS. Pho *et al*. report a cystic pancreatic lesion involving the distal pancreas in a 17-year-old male with known FAP [54]. Histopathological examination of the resected specimen showed a benign pancreatic cyst and fibrous plaque with desmoid fibromatosis adherent to the surface of the pancreas, serosa of the stomach, and colon. The fibrous plaque was histologically identical to the fibrous mesenteric plaque known to occur in FAP and associated mesenteric fibromatosis.

Desmoid tumors may represent a somewhat different disease in FAP/GS than in patients without an APC gene mutation. They are rare in the general population (5 to 6 per million per year) [55] but in FAP affect from 4 to 20% of patients [56, 57, 58]. When present in any member of an FAP family, the family has traditionally been said to have GS, since all members of the family exhibit the same APC mutation. Desmoid tumors may be the first manifestation of GS, and some families have been reported to have desmoids as the only manifestation of an APC mutation [59, 60]. Desmoid tumors in GS are monoclonal growths, implying that they are true neoplasms [61]. Desmoids in FAP also arise from APC inactivation and subsequent accumulation of beta-catenin in cells [62]. In contrast, APC mutations are uncommon in sporadic desmoids [63]. It has also been reported that the high rate of postoperative recurrence for intra-abdominal desmoids in genetically predisposed cases differed markedly from the low rate of recurrence after resection of sporadic tumors [64].

A periampullary carcinoid tumor was reported in a patient with FAP several years after total colostomy [65]. Only two previous case reports exist describing carcinoid tumors in association with FAP. No known genetic basis exists explaining the link between FAP and carcinoid tumors, however the presence of two rare entities in the same patient might suggest an association.

Pancreatitis in FAP/GS

Pancreatitis can be a severe and potentially lethal complication associated with FAP/GS. Though acute pancreatitis is a rare event, with an estimated incidence of around 5 to10 per 100,000 inhabitants in Western Europe [66], the incidence of acute pancreatitis may be higher in the FAP patient population. In one series [67], the frequency of pancreatitis in FAP was 3.5% (5/141). In a review by van Esch *et al*., more than the half of the patients had several episodes of pancreatitis with the first episode occurring at a mean of 45 years (range: 23-72 years) [68]. Causes of pancreatitis

in FAP patients include endoscopic instrumentation and obstruction of the pancreatic or common bile duct because of ampullary/periampullary tumors, most commonly adenomas. A number of instances of apparently idiopathic pancreatitis were also reported. Also in the review by Van Esch *et al*., the cause of pancreatitis in 5 of 7 patients could not be determined, as none of the patients had obstruction of the ampulla and other common risk factors for pancreatitis were absent [68]. Furthermore, other risk factors for pancreatitis such as pancreatic serine protease inhibitor Kazal type I (SPINK1) gene mutations were ruled out. Although this does not exclude the possibility that SPINK1 plays a role in FAP-associated pancreatitis, it appears less likely. In that report, it was suggested that pancreatitis may be a manifestation of FAP although the actual mechanism was unclear. In most cases the clinical course of the pancreatitis was benign, although one fatality was described.

Surveillance for Pancreatic Lesions in FAP/GS Patients

Symptoms of pancreatic cancer are vague and often are nonspecific. Consequently, vigilance, awareness and increased suspicion by the clinician represents the most critical approach for detecting pancreatic lesions in FAP/GS patients. Pancreatic cancer should be suspected in patients with adult onset diabetes who have no predisposing features or family history of diabetes; or in patients who have had an unexplained episode of acute pancreatitis. Alarming symptoms and signs such as persistent back pain, marked and rapid weight loss, abdominal mass, ascites, and supraclavicular lymphadenopathy always raise a high suspicion for pancreatic cancer. When the diagnosis of pancreatic malignancy is suspected from clinical symptoms and/or abdominal ultrasound findings, the selective use of multidetector CT scan with pancreatic protocol and EUS/FNA will accurately delineate tumor size, infiltration, and the presence of metastatic disease in the majority of cases.

Cancer risk is one of the greatest challenges facing clinicians involved in the care of patients with FAP/GS, and with improved survival following prophylactic colectomy, the burden of associated extracolonic lesions will increase. Until recently, the value of upper gastrointestinal surveillance in FAP/GS populations has been contentious, but with improved understanding of the natural history coupled with developments in surgery, interventional endoscopy and medical therapy, treatment algorithms for gastrointestinal lesions in FAP are becoming more available [69]. Furthermore, variable endoscopic surveillance protocols and treatment strategies have been proposed with upper endoscopy for gastric and duodenal polyps [17, 70, 71, 72] and ampullary/periampullary neoplasia in FAP/GS [35, 36]. Obtaining routine biopsies of the papilla, even if it appears grossly normal is recommended by some. For patients with periampullary adenomas, surveillance endoscopy and biopsy should be performed at intervals based on the stage of disease. If excision is complete, one approach is for follow-up endoscopy and multiple biopsies every six months for a minimum of two years, with endoscopy thereafter at three-year intervals [72]. Adenomas identified in the papilla of Vater should be removed endoscopically if possible, and follow-up examination should be carried out yearly [73]. Surgical consultation should be obtained for those patients with high risk, according to the Spigelman *et al*. [74] classification for example, duodenal polyposis, or pancreatic lesions.

Given the rarity of pancreatic involvement in FAP/GS aggressive surveillance protocols for these patients is hard to justify and a compromise should be struck. The authors of this paper recommend incorporating surveillance for pancreatic lesions along with surveillance for upper gastrointestinal and ampullary/periampullary neoplasia (Table 1). Surveillance recommendations might be stratified in FAP/GS patients according to coexisting risk factors for pancreatic cancer. Tailoring surveillance according to the presence

or absence of additional risk factors such as smoking, pancreatitis, diabetes and family history of pancreatic cancer in such patients might be appropriate. In patients with additional risk factors we recommend a single-session upper endoscopy and endoscopic ultrasound. This would allow a screening examination of the luminal gastrointestinal tract together with a look at the pancreas, biliary tract, gallbladder and a significant part of the liver. The difference in cost between using one modality of surveillance (upper endoscopy) *versus* standard upper endoscopy followed by EUS at the same session is small in the United States. The use of surveillance for pancreatic along with ampullary/periampullary and upper gastrointestinal neoplasia might alter management decisions but more studies are needed to study the efficacy and benefits of such surveillance. The choice of EUS over CT scans for surveillance of pancreatic and biliary neoplasia would save the patient frequent exposure to radiation and contrast if CT was to be used repeatedly. In addition, the use of EUS would allow for sampling of suspicious abnormalities at the time of the surveillance exam.

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Abbreviations APC: adenomatous polyposis coli; FAP: familial adenomatous polyposis; GS: Gardner syndrome

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Table 1. Recommended surveillance for upper GI, ampullary/periampullary and pancreatic lesions in familial adenomatous polyposis (FAP).

FAP patients with one of the following risk factors: - Family history of pancreatic cancer - Smoking - History of pancreatitis - Diabetes - History of surgery to the upper digestive tract	Upper endoscopy with both end-viewing and side-viewing instruments and endoscopic ultrasound, if possible in a single session, every 3-5 years starting at the time of considering colectomy or early in the third decade of life, whichever is earlier.
FAP patients without any of the above risk factors:	Upper endoscopy with both end-viewing and side-viewing instruments with or without endoscopic ultrasound every 3-5 years starting at the time of considering colectomy or early in the third decade of life whichever is earlier.

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