Familial adenomatous polyposis (FAP) is characterised by the development of numerous colorectal adenomatous polyps. Other extracolonic benign or malignant lesions have been reported previously in association with FAP but precancerous lesions in the pancreas have never been described. We report the first case of intraductal papillary and mucinous pancreatic tumour (IPMT) in a patient with FAP. A 48-year-old man with a well-documented past history of FAP was admitted for epigastric pain, weight loss, and new onset diabetes mellitus. Spiral computed tomography scan revealed a large tumour in the pancreatic head with upstream main pancreatic duct dilatation. Endoscopic ultrasonography confirmed these data. Mucous secretion was seen at duodenoscopy and a lesion in the main pancreatic duct was confirmed by retrograde pancreatography. The patient underwent a pancreaticoduodenectomy for suspected IPMT. Histological examination of the resected specimen confirmed an IPMT with in situ carcinoma. Twelve months after resection, the patient remained free of tumour relapse. Genetic analysis showed loss of the wild allele of the adenomatous polyposis coli gene in IPMT, causing inactivation of both alleles and demonstrating that IPMT was not incidental in this patient. IPMT should be included in the extracolonic localisation of FAP.

**CASE REPORT**

A 48-year-old man was admitted in March 2000 for investigation of recent epigastric pain with dorsal irradiation associated with weight loss of 17 kg and new onset diabetes mellitus. He had previously undergone a colectomy with ileorectal anastomosis in 1974 for FAP (six cases described in his family) and an abdominoperineal resection with preoperative radiotherapy in 1985 for rectal adenocarcinoma (stage B1 in the Astler-Coller classification).

Clinical examination was normal as were serum pancreatic enzymes and biochemical hepatic tests. At upper gastrointestinal endoscopy, mucous protrusion through the major papilla was observed, as well as a 20 mm ampullary tumour, with no other duodenal polyp. Histological examination of ampullar biopsies demonstrated a papillary adenoma with low grade dysplasia. Abdominal ultrasonography showed dilatation of the main pancreatic duct above a tumour located in the pancreatic head. Spiral computed tomography scan found pancreatic calcifications in the body and tail and confirmed a heterogeneous mass in the head of the pancreas measuring 60×35 mm, with proximal main pancreatic duct dilatation, a 20 mm ampullary lesion, and a mass (50×35 mm) in the left adrenal gland (fig 1). At endoscopic ultrasonography, the pancreatic tumour was seen to develop in the cephalic part of the main pancreatic duct, which was markedly enlarged, both distal and proximal. The common bile duct was partially stenosed by the lesion. The surrounding vessels seemed to be respected and there were no lymph nodes. Finally, lateral duodenoscopy with endoscopic retrograde cholangiopancreatography (ERCP) was performed and showed: (a) mucous spreading through the major papilla, (b) a polypoid lesion of the major papilla, (c) a large intraductal friable mass of the pancreatic head extending through the papilla after sphincterotomy, and (d) stenosis of the common bile duct (fig 2A, B).

**Abbreviations:** APC, adenomatous polyposis coli; ERCP, endoscopic retrograde cholangiopancreatography; FAP, familial adenomatous polyposis; IPMT, intraductal papillary and mucinous tumour.
An adenomatous proliferation with high grade dysplasia was
demonstrated by transpapillary biopsies. Pancreatic magnetic
resonance imaging confirmed these data (fig 3). Serum carci-
noembryonic antigen and carbohydrate antigen 19.9 values
were normal.

The diagnosis of IPMT localised in the pancreatic head with
possible malignant transformation (suggested by the large
intraductal vegetation) was suspected. Pancreatic metastasis
from colorectal cancer was reasonably excluded as: (1) rectal
adenocarcinoma was a stage B1 Astler-Coller, (2) there was a
long delay between the two events (15 years), (3) intraductal
location of the pancreatic tumour, (4) absence of other meta-
static lesions, and (5) presence of mucous, pathognomonic of
IPMT.

As no vascular or lymph node involvement was found at the
preoperative investigations, the patient underwent a duoden-
pancreatectomy with pancreaticogastric anastomosis. No
postoperative complications occurred. Complete histological
examination of the resected specimen demonstrated: (a)
IPMT with severe atypia corresponding to high grade
dysplasia/carcinoma in situ in the cephalic part of the main
pancreatic duct (figs 4, 5A, B), (b) absence of tumour and cal-
cified chronic pancreatitis at the section cut, (c) an ampullary
tumour with low grade dysplasia, which was independent of
the IPMT (these entities were separated by 10 mm of normal
main pancreatic duct), and (d) a microscopic duodenal
adenoma with low grade dysplasia. The adrenal biopsy
showed a benign adenoma. Twelve months after surgery, the
patient was asymptomatic and there was no evidence of
tumour relapse.

Genetic analysis showed that the germline mutation was a
3921del5 mutation in exon 15 of the APC gene. Loss of
heterozygosity was evidenced in the pancreatic tumour, caus-
ing inactivation of both alleles in the APC gene.

DISCUSSION
Extracolonic malignant tumours have previously been re-
ported in patients with FAP. Malignant transformation of
duodenal adenomas is the best known. The frequency of duo-
denal adenomas is approximately 90% with a malignant
than five years of age (1.6%).

Adenocarcinoma (0.5%), and hepatoblastoma in children less than five years of age (1.6%).

The lifetime risk of other extracolonic tumours has been estimated as follows: pancreatic adenocarcinoma (2%), thyroid cancer (2%), gastric adenocarcinoma (0.5%), and hepatoblastoma in children less than five years of age (1.6%).

In a cohort study of 1391 patients with FAP, the relative risks of pancreatic and thyroid cancers, respectively, were 4.5 (95% confidence interval (CI) 1.2–11.4) and 7.6 (95% CI 2.5–17.7). Two cases of gastric adenocarcinoma occurring in patients with fundic gland polyps have also been reported. Finally, one case each of pancreatic cystic and pseudopapillary tumour, pancreatic glucagonoma, and duodenal endocrine tumour have been described.

This is the first observation of an association between FAP and IPMT. IPMT is a rare type of pancreatic tumour, first described by Ohhashi and colleagues. This disease is defined by adenomatous proliferation of the epithelium lining of the pancreatic ducts, with excessive mucous production. All gradations from benign appearing epithelium to in situ or invasive carcinoma may be encountered. Because of its well known malignant potential, surgical resection is warranted whenever possible.

Carcinogenesis of IPMT and colorectal adenomatous polyps are strikingly similar: (1) epithelial hyperplasia precedes the development of adenomas with increasing grades of dysplasia and then invasive cancer and metastases, and (2) common genetic alterations including p53 and K-ras mutations (with gradual increase from normal pancreatic duct to adenoma and adenocarcinoma in IPMT). APC somatic mutations have previously been reported in extracolonic tumours associated with FAP. Toyooka and colleagues found a somatic mutation of the second copy of the APC gene in 69% of duodenal, periampullary, or gastric tumours in 21 patients with FAP. In addition, somatic mutations in the APC gene have been described in 30–47% of sporadic pancreatic cancers. To our knowledge, such mutations have never been reported in IPMT. In the case described here, we showed loss of heterozygosity of the APC gene in pancreatic IPMT. This result implicates the APC gene in the development of this tumour.

Screening for duodenal cancer (upper gastrointestinal endoscopy, including side viewing examinations, every 1–3 years, starting from age 20–25 years) is warranted in patients with FAP because of a well documented increased risk. In contrast, screening for pancreatic tumours seems unwarranted as pancreatic tumours are rare (2%) and often difficult to diagnose with non-invasive techniques. However, IPMT diagnosis should be considered in cases of acute pancreatitis, diabetes, or steatorrhoea in patients with FAP.

In conclusion, IMPT should be added to the list of extracolonic premalignant tumours that can occur in patients with FAP. The presence of a mutation in the second allele of the APC gene in IPMT in our case argues in favour of a common carcinogenic process in both IPMT and colic adenomas.

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Intraductal papillary and mucinous pancreatic tumour in FAP


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