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 ampullary 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 carcinoembryonic 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 metastatic 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 duodenopancreatectomy 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 calcified 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, causing inactivation of both alleles in the APC gene.

DISCUSSION
Extracolonic malignant tumours have previously been reported in patients with FAP. Malignant transformation of duodenal adenomas is the best known. The frequency of duodenal adenomas is approximately 90% with a malignant pancreatic duct (figs 4, 5A, B), (b) absence of tumour and calcified 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.
than five years of age (1.6%).
adenocarcinoma (0.5%), and hepatoblastoma in children less
atic adenocarcinoma (2%), thyroid cancer (2%), gastric
extracolonic tumours has been estimated as follows: pancre-
posis have also been reported.
adenocarcinoma occurring in patients with fundic gland poly-
potential between 1% and 5%. The lifetime risk of other
extracolonic tumours has been estimated as follows: pancre-
atic ducts, pancreas and duodenum in a single patient with familial
this disease is defined by adenomatous proliferation of the epithelium lining of the
the pancreas ducts, with excessive mucous production. All
of 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
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 muta-
tions 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 unwar-
anted 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, IPMT should be added to the list of extra-
colonic 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 carci-
ngenetic process in both IPMT and colic adenomas.

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F Maire, P Hammel, B Terris, S Olschwang, D O'Toole, A Sauvanet, L Palazzo, P Ponsot, B Laplane, P Lévy and P Ruszniewski

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