Hospital Practice

UPPER GASTROINTESTINAL CANCER IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS

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Summary 102 patients with familial adenomatous polyposis underwent upper gastrointestinal endoscopy as a screening test for gastroduodenal adenomas. 100 had duodenal abnormalities (dysplasia in 94, and hyperplasia in 6), usually in the second and third parts of the duodenum (91%). The periampullary area was abnormal in 87 of 97 patients who had a biopsy specimen taken from this site (dysplasia 72, hyperplasia 13, and inflammation 2). By contrast, gastric dysplasia was found in only 6 patients. Classification of duodenal polyposis on a 5-grade scale (stages 0–IV), based on polyp number, size, histology, and severity of dysplasia, showed that 11 had stage IV disease: these patients are at greatest risk of malignant change and require close surveillance. The pattern of dysplasia observed in the upper gastrointestinal tract resembled the pattern of mucosal exposure to bile.

INTRODUCTION

IN a multicentre study, 1255 patients with familial adenomatous polyposis were found to be at high risk of duodenal or ampullary cancer (39 patients, periampullary in 36) whereas only 7 had gastric cancer.[1] By contrast, a 10-fold greater incidence of gastric cancer would have been expected in the general population (from US figures). In patients with familial adenomatous polyposis treated routinely by colectomy, it seems that upper gastrointestinal cancer has overtaken large-bowel cancer as a cause of death. Our results in 197 such patients treated by colectomy and ileorectal anastomosis between 1948 and 1987 support this view: only 4 have died from rectal cancer, whereas 9 have died from upper gastrointestinal cancer (duodenum 5, pancreas 2, bileduct 1, and jejunum 1).

Upper gastrointestinal polyps in familial adenomatous polyposis include non-adenomatous gastric fundic gland polyps (common), gastric adenomas (rare), and duodenal adenomas (common), but the reported prevalence of these different types of polyp varies widely, from 28% to 100%.[2-18] Since adenomas are likely precursors of cancer,[19,20] we set up a screening programme to record polyp prevalence and natural history, and to identify patients at particular risk of duodenal cancer.

PATIENTS AND METHODS

Retrospective Study

Between 1974 and 1988, 94 patients with familial adenomatous polyposis had had 163 endoscopies (61 families; 59 M, 35 F; mean age at first endoscopy 39 years, range 15–73; for screening in 70, for symptoms in 24). These investigations did not follow a standard protocol and were not all done by the same endoscopist. A forward-viewing endoscope was used in 98% of examinations. In 1988, results were collected and reviewed retrospectively.

Prospective Study

Throughout 1988, 102 patients (69 families: 59 M, 43 F; mean age 41 years, range 14–66) with known familial adenomatous polyposis underwent upper gastrointestinal endoscopy to a set protocol by a single endoscopist (C. B. W.) as part of a screening programme. (47 of these patients had had an earlier endoscopy and therefore also had data included in the retrospective study.) A forward-viewing endoscope ('GIFXQ10' Olympus, Keymed, Southend) was used for the first 6 patients, but subsequently a side-viewing video-endoscope (Olympus 'JFV10', Keymed) was used. The site, number, and size of polyps seen were noted. The appearance of the duodenum was recorded on videotape and a map of the periampullary region was drawn for comparison at follow-up endoscopies. Biopsy specimens were taken from representative gastric and duodenal polyps, and the papilla of Vater and peripapillary area; where duodenal polyps were not seen multiple random duodenal biopsy specimens were taken. All patients were questioned about their smoking habits.

Duodenal polyposis was staged according to polyp number (1–4 polyps = 1 point, 5–20 polyps = 2, > 20 polyps = 3); polyp size (1–4 mm = 1 point, 5–10 mm = 2, > 10 mm = 3); histological type (tubular polyp/hyperplasia/inflammation = 1, tubulovillous = 2, villous = 3); and dysplasia (mild = 1, moderate = 2, severe = 3). An overall score of 0 points = stage 0, 1–4 = I, 5–6 = II, 7–8 = III, and 9–12 = IV.

RESULTS

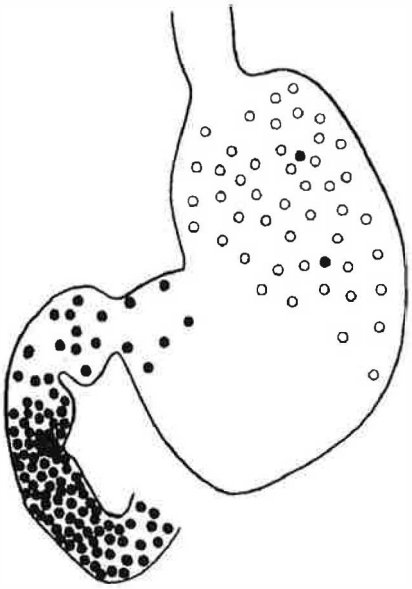
Of the 102 patients screened prospectively, 56 had gastric polyps (4 had less than 5, 20 had 5–20, 32 had more than 20), and 88 had duodenal polyps (12 had less than 5, 39 had 5–20, 37 had more than 20). Gastric fundus polyps were small (mean diameter 4·7 mm, range 1–30) and multiple, whereas antral polyps, when present, were larger (mean diameter 6·4 mm, range 1–15) and less numerous. Duodenal polyps were larger still (mean diameter 9·4 mm, range 1–50) and usually multiple. In the 88 patients with duodenal polyps, the distribution was predominantly distal: none had involvement of the duodenal bulb alone, 8 had involvement of the bulb and the 2nd and 3rd parts of the duodenum, and 80 had involvement of the 2nd and 3rd parts of the duodenum only.

Histological examination of biopsy specimens revealed adenoma in only 6 of 73 patients who had gastric biopsy specimens taken, whereas duodenal adenomas, which were predominantly mildly dysplastic and tubular, were almost inevitable—found in 94 of 102 patients. (1 gastric adenoma and 8 duodenal adenomas were found in random biopsy specimens taken in the absence of polyps.) Periampullary biopsy detected adenomas in 11 patients in whom endoscopy and biopsy elsewhere in the duodenum were normal: periampullary specimens were available for 97 patients, and showed adenoma in 72, hyperplasia in 13, inflammation in 2, and normal histological appearances in 10. In the 80 patients for whom a biopsy specimen was obtained from both the peripapillary area and the papilla

SEVERITY OF DUODENAL POLYPOSIS

Stage	n	M, F	Age (yr)*	Smokers
0	2	1, 1	33·5 (33–34)	0
I	19	14, 5	38 (14–64)	6
II	35	17, 18	38 (26–65)	14
III	35	22, 13	42 (20–67)	13
IV	11	5, 6	51 (28–66)	3

*Shown as mean (range).



Overall representation of sites affected by upper gastrointestinal polyposis.

For the 102 patients in this study, ○ represents 1 patient with fundic gland polyp(s); ● represents 1 patient with adenoma(s).

itself, the papilla was twice as likely to show adenomatous change (81% *vs* 41%).

Fewer polyps were seen in the retrospective series, and fewer biopsy specimens were taken. For the 47 patients who were included on both series the prospective study showed greater yields of gastric fundic gland polyposis (540%), gastric adenomas (200%), and duodenal adenomas (190%).

In the prospective study, most patients showed small duodenal adenomas (under 10 mm diameter), but larger villous or more severely dysplastic lesions were seen in some. The classification described above allowed estimation of the severity of duodenal polyposis based on known adenoma/cancer risk factors (see table). Most patients had stage II or stage III polyposis; 11 of 102 had stage IV duodenal polyposis, which occurred more often in the elderly. Gender and cigarette smoking were not related to severity of duodenal polyposis.

Of the 6 patients in the prospective study who had gastric adenomas, 5 had stage III or IV duodenal disease. Gastric adenomas were antral in all 6 patients, 2 of whom also had adenomas in the body or fundus of the stomach (see figure).

DISCUSSION

Duodenal adenomas occur in most patients with familial adenomatous polyposis, and to group patients into colonic and non-colonic subtypes[21] is unnecessary. The foregut adenomas can be small, and concentrated in the second and third parts of the duodenum. Careful examination of the distal duodenum, with multiple biopsies (even where the mucosa seemed macroscopically normal) and the use of a side-viewing endoscope doubled the yield of adenomas in the prospective series compared with our earlier results in the same patients. Similar technical differences may account for the variation in prevalence reported from other centres.[2-18] Foregut adenomas therefore seem almost as common a feature of familial adenomatous polyposis as colonic polyps, and are probably equally important as indicators of long-term cancer risk.[19,20] However, the distribution of adenomas within the foregut differs from the more uniform pattern seen in the colon and rectum. Adenomas are relatively infrequent in the stomach and the duodenal bulb, and when gastric adenomas occur, they usually do so in the antrum and in association with more severe duodenal disease. Nevertheless, non-adenomatous fundic gland polyps are often seen in the stomach,[18] and indicate a general tendency to gastrointestinal mucosa overgrowth, with a predominance of adenomas in the duodenum and large intestine.

Within the duodenum, the greatest concentration of adenomas is on or around the papilla. This distribution raises the possibility that adenoma formation is partly bile-dependent: a genetically determined mucosal growth abnormality may interact with an environmental factor (or factors) in bile that determines the type of growth abnormality. This sequence is consistent with Knudson's "two-hit" hypothesis of carcinogenesis,[22] the mutation on chromosome 5 in patients with familial adenomatous polyposis[23] and sporadic colon cancer,[24] and the experimental[25-27] and epidemiological evidence[28] that have linked bile to intestinal cancer growth. However, upper gastrointestinal cancer appears to develop slowly in patients with familial adenomatous polyposis, with a median interval of 22 years after colectomy reported in 37 patients.[1]

What are the clinical implications of these observations for the management of patients with familial adenomatous polyposis? Our patients now have regular upper gastrointestinal endoscopy, at which periampullary maps are drawn and videotapes and still photographs are taken to record the natural history of their gastroduodenal polyps. For most of our patients, with mild or moderate polyposis, an interval of 3 years between endoscopies seems appropriate, but for patients with severe (stage IV) polyposis endoscopy must be repeated at least yearly. The role of colectomy in the treatment of lower gastroduodenal polyps is well-established in these patients, but treatment of their upper gastrointestinal polyps remains open to debate. Endoscopic removal is often impractical because sessile polyps cannot be snared and perforation may occur, whereas endoscopic electrocoagulation may cause periampullary scarring and bileduct obstruction. Endoscopic photodynamic laser therapy[29] and chemoprevention with agents such as vitamin C[30] are unproven in practice, and a treatable abnormality in the bile of patients with familial adenomatous polyposis has not yet been identified. Preventive surgery may be indicated for patients with severe duodenal polyposis who have rapid polyp growth, polyp induration, or consistently severe dysplasia. The usual techniques involve duodenotomy or pancreaticoduodenectomy: duodenotomy (used in 8 of the patients in our retrospective series) involves polyp removal by a technique of submucosal infiltration and local incision analogous to that used for rectal tumours,[31] but is usually of only temporary benefit and makes subsequent attempts to remove polyps more difficult; pancreaticoduodenectomy (used in 5 patients in our retrospective series) is a major operation with considerable potential morbidity, and a mortality rate that must be weighed against the largely unknown natural history of these polyps.

It is now clear that upper gastrointestinal cancer, related to adenomatous polyps, is a major cause of death in patients with familial adenomatous polyposis. Careful screening of the upper gastrointestinal tract of these patients will improve our knowledge of the natural history of these polyps and of the most appropriate treatment at various stages of the disease. As the distribution of gastroduodenal polyposis in

these patients appears to be related to bile exposure, these observations may enable identification of a tumour-promoter in bile, which may have implications for other patients with gastrointestinal cancer.

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Cell Biology

CELL-SURFACE PEPTIDASES AS MODULATORS OF GROWTH AND DIFFERENTIATION

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Summary Some of the many cell-surface antigens defined by the CD (cluster differentiation) nomenclature have lately emerged as proteins with well-characterised enzymic activities. One important example is CD10 or CALLA (common acute lymphoblastic leukaemia antigen), which is identical to endopeptidase-24.11, an enzyme with an important role in the hydrolysis of biologically active peptides. CD13 and CD26 are also surface peptidases. These enzymes, which have a wide distribution on the surfaces of various cell types, may have specific roles in the control of growth and differentiation in both haemopoietic and epithelial cell systems.

INTRODUCTION

MUCH effort has been expended on the identification of cell-surface antigens that can act as markers of specific cell types within related lineages, and in raising antibodies to such markers. Many individual antigens of this type are, however, present on cells of very different phenotypes (so-called "jumping" antigens). Thus, although they may be restricted to specific phenotypes within a particular related cell lineage, they are found in widely different tissues. It is now easier, with the aid of specific antibodies, to clone and sequence the cDNA that codes for such molecules than to establish their functions directly. Screening of data bases for published sequences can reveal unexpected identities and thus suggest the biological role of cell-type-specific markers. One example of such a serendipitous correlation involves some haemopoietic markers and a group of enzymes collectively called cell-surface peptidases.[1]

Cell-surface peptidases are ectoenzymes (ie, plasma membrane proteins with the active domain exposed at the extracellular surface); other ectoenzymes include 5'-nucleotidase, acetylcholinesterase, and alkaline phosphatase.[2] These enzymes have a wide, but by no means ubiquitous, distribution among mammalian organs and tissues and, by virtue of their topology, can hydrolyse substrates in the extracellular space. Renal and intestinal brush border membranes are very abundant sources of membrane peptidases, but these enzymes are found in lower amounts on the surfaces of many other cell types.[3] Their functions probably differ according to the cellular location. In the intestine they are associated with the final steps of digestion (peptide scavenging) but elsewhere they may have more purposeful roles in the inactivation of peptide signals. Their role at other locations is, however, only now becoming apparent. In-vitro studies have clearly shown that endopeptidase-24.11 (EC 3.4.24.11) has a key role in initiating the degradation of a wide range of active peptides,