Leading article

Colorectal neoplasia in acromegaly

Since its original description by Pierre Marie in 1886, acromegaly has been known to be associated with an increased morbidity and mortality.¹ Early epidemiological reviews showed this was due largely to diabetes mellitus and cardiovascular, cerebrovascular, and respiratory disease.^{1–4} In two early studies,^{3, 4} the mean age of death was 57 years with 26% and 64%, respectively, of patients in one of these studies dying before the ages of 50 and 60 years.³ Recent reviews have suggested that these patients are also at increased risk of developing neoplasia, particularly colorectal cancer and tubulovillous adenomas,^{5–22} with one small prospective study reporting carcinomas in three of 12 patients (table 1).²³ This is probably because more effective and aggressive treatment of both the underlying acromegaly and its metabolic and vascular complications has meant that patients are now surviving long enough to develop malignant complications of the disease.

We have recently confirmed that acromegaly predisposes to colonic neoplasia by performing a prospective colonoscopic evaluation of 155 patients.²⁴ Colorectal carcinomas were present in 5% (eight patients) and at least one tubular adenoma in 25% (39 patients). Interestingly, only one patient with a carcinoma had gastrointestinal symptoms. Furthermore, three of the cancers occurred at the caecum, an unusual site for sporadic cancers in the non-acromegalic population. Two cancers were Dukes' A, three Dukes' B, two Dukes' C, and one Dukes' D. Although a number of factors were compared between those patients with neoplasia and those without, the only significant difference

was that the former group were older than the unaffected patients (62 *v* 54 years) with the age of those with a carcinoma ranging from 58 to 74 years (median 64). Although there are no perfect control groups of age and sex matched asymptomatic non-acromegalic patients, by using such surveys as are available, these findings suggest an increased risk of colorectal cancer with the relative risk being at least 13-fold and possibly as high as 92-fold.^{25, 26} The prevalence of left-sided tubular adenomas was also significantly increased, particularly in patients over 50 years of age. These results, together with the previously published studies, provide evidence that patients with acromegaly are a high risk group for the development of colorectal neoplasia and should undergo regular surveillance colonoscopy, as for other high risk populations.

What age should this begin and how often should it be repeated? In the non-acromegalic population, it has been suggested that a single sigmoidoscopic screening at the age of 55 years may be a cost effective way of reducing mortality from colorectal cancer.²⁷ We believe a more aggressive policy is warranted in acromegaly. As our youngest acromegalic patient with an adenoma was 39 years old, we screen all patients with acromegaly over the age of 40. In addition, as 25% of adenomas and 50% of carcinomas in the acromegalic patients occurred in the ascending or transverse colon, only total colonoscopy is adequate. In order to define the interval between screening examinations, we have looked at the incidence of new colorectal neoplasia in patients who have had a second colonoscopy at varying intervals after their original screening examination, at which all visualised lesions were removed. Of the patients who had colorectal polyps at this original screening, 25% had developed new adenomas within a mean of 24 months, compared with none of the patients in whom the original screening examination was normal.²⁸ Based on this preliminary data, we suggest that patients with an adenoma should undergo colonoscopy every two to three years whereas in patients with a normal colonoscopy, it is probably safe to repeat this at five yearly intervals.

Practical issues

There are several practical issues that affect the success of colonoscopy in acromegalic patients:

- The patient has colomegaly with a significant increase in the total length of the colon, in addition to an

Table 1 Reports of patients with acromegaly and colonic lesions

Reference	No of patients studied	Mean age (y)	No with tubular adenomas	No with hyperplastic polyps	No with cancer
<i>Retrospective studies</i>					
Klein and colleagues ⁵	26	53			2 (8)
Ziel and colleagues ⁸	3	57			2 (66)
Brunner and colleagues ⁹	13	NR			0 (0)
Pines and colleagues ¹³	48	61			3 (6)
Ron and colleagues ¹⁴	1041	61			13 (1.3)
<i>Prospective studies</i>					
Klein and colleagues ⁵	17	49	5 (29)	3 (18)	2 (12)
Brunner and colleagues ⁹	29	NR	4 (14)		2 (7)
Ezzat and colleagues ^{11, 12}	23	47	8 (35)	1 (4)	0 (0)
Vasen and colleagues ¹⁶	49	54	11 (22)	5 (10)	0 (0)
Terzolo and colleagues ¹⁷	31	52	12 (38)	8 (26)	0 (0)
Ladas and colleagues ¹⁹	54	47	5 (9)	11 (20)	0 (0)
Delhougène and colleagues ²⁰	103	51	23 (22)	25 (24)	0 (0)
Colao and colleagues ²¹	50	NR	11 (22)	12 (24)	1 (2)
Archambeaud-Mouvier and colleagues ²²	16	53	4 (25)	NR	2 (12.5)
Iruarte and colleagues ²³	12	56	2 (15)	1 (8)	3 (20)
Jenkins and colleagues ²⁴	155	57	39 (25)	42 (27)	8 (5)

Values in parentheses are percentages of the total number of patients studied. NR, not recorded.

Abbreviations used in this paper: FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; RER, replication error; IGF-I, insulin-like growth factor I; GH, growth hormone; DCA, deoxycholic acid.

increased circumference.²⁹ This frequently results in an enormous colon with large folds of redundant mucosa. Good colonoscopic technique is therefore essential, minimising loops whenever possible. An overtube is more frequently needed than in non-acromegalic subjects.

- The patient has a prolonged large bowel transit time compared with a non-acromegalic patient (37 v 17 hours respectively) which renders standard bowel preparation almost invariably inadequate.³⁰ We have found that twice the "standard" amount of the osmotic purgative Klean-Prep (Norgine Ltd, Harefield, UK) provides good results. Two litres are given at six, four and two hours before the procedure with a liquid-only diet for the preceding 24 hours. Oral iron must be stopped at least one week before the start of the preparation. Despite this rigorous preparation, inadequate bowel clearance still occurs occasionally, necessitating further prolonged preparation. Admission to hospital for bowel preparation is often required.
- The experience and persistence of the endoscopist is crucial. Inexperienced operators reach the caecum in only about 75% of patients with acromegaly.

Despite these problems, it is essential to see the entire colon. Failure to reach the caecum should be regarded as an unsuccessful and incomplete examination, and a repeat attempt by an experienced operator is mandatory. Failing this, a barium enema or virtual computed tomography colonography are recommended.

Possible mechanisms

The mechanisms for the development of colorectal neoplasia in acromegaly are unclear, although they are likely to be multifactorial. These patients may offer a unique model for the study of sporadic colorectal cancer in the non-acromegalic population. Previous models have relied upon hereditary familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). One of the first steps will be to evaluate whether there is a similar prevalence and accumulation of mutations in the oncogenes (K-ras, c-myc) and tumour suppressor genes (APC, MCC, DCC, p53) in the acromegalic tumours as in sporadic and FAP tumours. Similarly, we are currently assessing the DNA replication error (RER) status of these tumours by studying DNA microsatellite instability at a variety of loci that are affected in HNPCC and in 20% of sporadic tumours.³¹ The increased tendency for caecal lesions in acromegaly makes this of particular interest as RER positivity has been associated with a right sided location.

Insulin-like growth factor I (IGF-I), the tissue biomarker of growth hormone (GH), and the concentrations of which are by definition elevated in acromegaly, is an obvious candidate for involvement in the neoplastic process. IGF-I is a known mitogen which stimulates the growth of several colon cancer cell lines in vitro.³² In the non-acromegalic population, expression of IGF-I mRNA is increased in colon cancers. Furthermore, IGF-I receptors are present on the surfaces of colon cancer cells and of normal gastrointestinal cells.³³ Our preliminary findings also suggest a role for IGF-I in adenoma formation in acromegaly. All patients in whom a new tubular adenoma was detected at follow up colonoscopy had raised IGF-I concentrations that were significantly higher than in patients without new adenomas ($p < 0.001$).²⁸ In support of this, a previous study of colorectal mucosal cellular proliferation in acromegalic patients showed that biopsy samples from the sigmoid colon had a significantly increased cellular proliferation index compared with non-acromegalic mucosa.³⁴ Such

proliferation is thought to be the initial step in the adenoma to carcinoma sequence, and in these patients correlated with IGF-I concentrations.

Although it seems probable that GH/IGF-I is, in some way, involved in the pathogenesis, it is unlikely to be the initiating carcinogen; other intraluminal local environmental influences may be important. For example, bile acids have long been implicated in the pathogenesis of colorectal cancer. The unconjugated secondary bile acid, deoxycholic acid (DCA), is formed in the caecum by anaerobic bacterial deconjugation and dehydroxylation of the primary bile acid, cholic acid. Serum concentrations of fasting unconjugated DCA have been shown to reflect intracolonic concentrations.³⁵ Serum DCA concentrations are significantly raised in non-acromegalic patients with colorectal neoplasia.³⁶⁻³⁷ Such a difference also exists in acromegaly; not only do patients with neoplasia have significantly elevated concentrations compared with those without neoplasia, but DCA concentrations in the latter group are also significantly increased compared with non-acromegalic patients.³⁸ Although, at present the evidence is only circumstantial, this possible role of bile acids requires further clarification, not least because of the effects upon them by somatostatin analogues. These substances, available for about 15 years, are extremely effective at reducing circulating GH and IGF-I concentrations and are the medical treatment of choice for acromegaly. However, in vivo they notably prolong intestinal transit and subsequent to the resultant changes in bacterial flora, increase the conversion of conjugated DCA, which leads to increased intraluminal and serum concentrations of unconjugated DCA.³⁵⁻³⁹ Conversely, somatostatin analogues can inhibit the growth of colonic cancer cell lines in vitro.⁴⁰ Furthermore, colorectal neoplasia in acromegaly occurs just as often in patients on other medical therapy as on somatostatin analogues.²⁴ The outcome of these competing effects is unclear at present.

In summary, there is now good evidence that acromegaly predisposes to colorectal neoplasia. Although the mechanisms may be multifactorial, the study of these patients may be a useful model for understanding the pathogenesis of sporadic colorectal carcinoma. As with other high risk groups, regular, total colonoscopic screening is required.

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