Carcinomas and carcinoid tumours of the appendix in a district general hospital

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SYNOPSIS In a retrospective series of 40 appendiceal tumours occurring over a 10-year period, 30 were carcinoid tumours of classical histological pattern, five were adenocarcinomas, and two were tumours intermediate in pattern between carcinoid and carcinoma. The remaining three tumours were secondaries from primary colonic tumours. The implications of the findings are discussed.

Primary epithelial tumours of the appendix are relatively uncommon, and adenocarcinoma arising in the appendix is generally regarded as a lesion of considerable rarity. The true incidence of carcinoma is difficult to estimate owing to confusion with argentaffin carcinoid tumours, reactive epithelial conditions following episodes of obstruction, and secondary spread from primary tumours of the gastrointestinal tract and other organs (Latchis and Canter, 1966). Recent publications (Klein, 1974; Subbuswamy *et al*, 1974) have described forms intermediate between carcinoid and carcinoma. The present study was carried out to assess the relative frequency and clinical importance of such tumours in a district general hospital.

Material and methods

Material was taken from the surgical pathology files of King's Mill Hospital, Sutton-in-Ashfield. The laboratory serves a population of approximately 250 000. During the 10-year period 1965-75 the total number of appendicectomy specimens examined histologically was 4107. Appendices were routinely received unopened from the operating theatres and were examined macroscopically by making several transverse sections through the base and middle of the appendix and a longitudinal section through the tip. In each appendix, one half of the longitudinal tip section and two or more of the transverse sections were embedded and examined histologically. Sections were stained routinely with haematoxylin and eosin; those containing tumour were stained with diazo method for enterochromaffin granules and the periodic acid Schiff method. Selected sections

were also stained with alcian blue, the buffered silver nitrate method of Grimelius (1968), the lead haematoxylin technique (Solcia *et al*, 1969), and Singh's technique for argentaffin granules (Singh, 1964).

Results

Forty of the 4107 appendices contained tumour. The tumours fell into four categories:

(A) Thirty (0.75% of appendices examined) were carcinoid tumours of classical pattern, consisting of infiltrating cords and rosettes of cells, the majority of which stained positively with diazo, argentaffin or argyrophil techniques (fig 1). In 14 of these cases, the tumour cells formed occasional acini containing PAS positive mucin. Table I shows the clinical and pathological features of these tumours, and table II shows their staining reactions.

The mode of presentation of the classical carcinoid tumours was variable. Tumours in the middle third and base of the appendix predominated among the 19 cases presenting with symptoms of a classical attack of acute appendicitis. Fifteen of these cases showed acute inflammation on histological examination. There was no correlation between the size and site of the tumours and none of the cases showed any systemic or remote gastrointestinal symptoms indicative of a carcinoid syndrome.

(B) Two tumours (0.05%) resembled carcinoids in their histological pattern but contained mucin-secreting cells in numbers that equalled or exceeded those of the argentaffin and argyrophil cells (fig 2). Table III gives the clinical and pathological details of these cases.

(C) Five tumours (0.12%) were adenocarcinomas forming tubules or cystic structures containing mucin (figs 3 and 4). One tumour contained small

Fig 1 A diazo positive carcinoid of classical pattern forming interlacing cords and masses in the lamina propria. (Haematoxylin and eosin $\times 120$)

Presentation	Total number	Site of tumour			Size of tumour (cm)		
		Tip	Middle third	Base	0.5	0.5-1	1-2
Surgical diagnosis of acute appendicitis	19	5	11	3	5	9	5
Removed for recurrent abdominal pain	4	3	1	0	2	1	1
Incidental removal at laparotomy for other reasons	7 ¹	6	0	0	5	0	2

Table I Presenting features and macroscopic pathology of carcinoid tumours of classical pattern

¹One removed incidentally at cholecystectomy involved the whole length of the appendix

PAS	Argentaffin and diazo positive	Argyrophil positive argentaffin negative	Argentaffin and argyrophil negative
Positive	12	2	0
Negative	14	1	1

Table II Staining reactions of carcinoid tumours of classical pattern

numbers of diazo positive cells as an integral part of the tumour. The primary appendiceal origin of these tumours was established either at necropsy or by laparotomy and colectomy. Table IV gives clinical and pathological details.

(D) Three other adenocarcinomas were shown to be secondary carcinomas from primary tumours in the colon. Two were instances of transcoelomic

spread; one was direct spread from a caecal carcinoma which was not obvious at appendicectomy. All showed acute inflammation of the appendix.

Discussion

The overall incidence of carcinoid tumours in this series is 0.75%. This figure is comparable to that of Collins (1963), who found an incidence of 0.689%. Dische (1968) reported an incidence of 1.3% in a series of 1426 appendices in which both halves of the longitudinally divided terminal 1.5 cm were embedded and sectioned; more proximal areas were sectioned only where there was a definite indication to do so. We have embedded and sectioned only one half of the tip but have routinely embedded transverse sections from more proximal areas. The 48%

Case	Presentation	Pathology	Operation	Follow-up
Female 60 yr	Acute abdominal pain	Tumour invading submucosa of appendix for 1.5 cm near the tip. Diazo positive cords, numerous acini with pools of mucin (fig 2), and Paneth cells in moderate numbers. Excision appeared complete. Acute inflammation present elsewhere	Appendicectomy	Alive and well 1 yr later
Male 38 yr	Acute abdominal pain	Appendix diffusely thickened by tumour. Goblet cells and acini with occasional diazo positive cells and Paneth cells. Invasion extended to serosal surface and fat of mesoappendix	Appendicectomy; hemicolecotomy 1 mth later	Alive and well 6 mth later. Residual tumour present in serosa of hemicolecotomy specimen

Table III Carcinoid-like tumours with predominant mucoid element

Fig 2 A mucinous carcinoid tumour with both solid diazo positive cords and acini containing darkly staining mucin. (Periodic acid Schiff $\times 315$)

of carcinoids showing small numbers of mucin-secreting cells is comparable with that of other series (Dische, 1968; Soga and Tazawa, 1971).

In our series, 14 out of the 30 classical carcinoid tumours occurred at the tip, 12 in the middle third of the appendix, and three at the base; one involved almost the whole length of the organ. Most textbooks emphasize that the tip is the commonest site, but in this series only half of the carcinoids were at the tip and many of these were of microscopic dimensions and unassociated with abdominal pain (see table I). We feel that the emphasis on tumours at the tip may lead to tumours in other regions of the appendix being overlooked. Despite the fact that

most of even the small carcinoids showed extensive invasion to the serosa and often into the meso-appendix, all were treated by simple appendicectomy and none has returned with recurrence or metastasis. The area has a stable population and any instances of recurrence would tend to return to the hospital group. This bears out the view that only in the very largest carcinoids is incomplete removal an indication for hemicolecotomy.

The two cases in which diazo positive cells were equalled or outnumbered by mucin-secreting cells with an acinar and goblet-cell pattern correspond with tumours described by Subbuswamy *et al* (1974) as goblet-cell carcinoid, and by Klein (1974) as

Fig 3

Fig 4

Fig 3 *Mucooid cystadenocarcinoma invading the submucosa and forming mucous lakes in the wall of an appendix distended by tumour. (H and E $\times$ 50)*

Fig 4 *Colonic-pattern adenocarcinoma forming tubules in an invaded area of muscularis. (H and E $\times$ 247)*

Case	History	Pathology	Operation	Follow-up
Male 70 yr	Abdominal mass palpated during an admission for acute retention	Mucoid cystadenocarcinoma distending lumen of appendix and invading serosa. Colon and other viscera free of tumour but peritoneum covered by small metastases (fig 3)	Colectomy	Died 1 yr later, no necropsy
Female 76 yr	6 mth abdominal pain; 24 h guarding and tenderness in right iliac fossa	Well-differentiated adenocarcinoma of colonic pattern invading to the serosal surface. Appendix also acutely inflamed (fig 4)	Appendicectomy; subsequent laparotomy showed multiple peritoneal metastases	Died 2 mth later. Necropsy: multiple peritoneal metastases but no primary tumour elsewhere
Female 84 yr	2 mth spasmodic pain in right iliac fossa and intermittent diarrhoea	Mucoid cystadenocarcinoma distending appendix and invading the wall. Colon and other viscera free of tumour	Colectomy	Alive and well 9 mth later
Male 51 yr	Acute abdominal pain	Well-differentiated tubular adenocarcinoma invading to serosal surface. Appendix acutely inflamed and perforated. Occasional diazo positive cells present in tumour	Appendicectomy; hemicolectomy 1 mth later	Alive and well 18 mth later. No tumour in hemicolectomy specimen
Male 61 yr	3 days abdominal pain, later developing rebound tenderness in right iliac fossa	Gangrenous appendix with adenocarcinoma of colonic pattern arising from mucosa close to base. Colectomy specimen: tumour in caecal wall adjacent to stump of appendix but no mucosal tumour present in caecum	Appendicectomy and colectomy 1 wk later	Alive and well 18 mth later

Table IV Primary adenocarcinomas of the appendix

mucinous carcinoid tumour. Like the tumours described by these authors they also contain numbers of Paneth cells. In one of these cases the tumour invaded the serosal aspect of the resected colon as well. A further two cases of this condition occurred at this hospital outside the period under review, one of whom developed widespread peritoneal metastases after appendicectomy; the other died from myocardial infarction 18 months after appendicectomy and was free from tumour at necropsy. Our experience of this condition suggests that it is more aggressive in behaviour than the classical carcinoid tumour and that adequate histological examination of the excised appendix is necessary to assess completeness of excision and the need for further surgery.

The five cases of apparent primary adenocarcinoma of the appendix represent an incidence of 0.12% of appendicectomy specimens. This figure is unexpectedly high, but we feel that the findings at necropsy or at laparotomy and colectomy justify the view that these are true primary tumours of the appendix. Of the five tumours in this group, two are examples of the mucinous cystadenocarcinoma described by Higa *et al* (1973). The other three are adenocarcinomas of tubular structure resembling adenocarcinoma of the colon. In one of these colonic pattern adenocarcinomas, a small proportion of the tumour cells were diazo positive; this is also occasionally seen in primary adenocarcinomas of the stomach and colon.

A range of patterns is seen among primary appendiceal tumours, from carcinoids to well-differentiated cystadenocarcinomas, through

tumours containing varying proportions of enterochromaffin and mucin-producing cells. Traditionally, the two cell types have been held to arise from a common endodermal precursor, and neoplastic change in such a precursor could produce a tumour containing both types of cell. Pearse (1969) and Weichert (1970) have postulated a neural crest origin for cells of the enterochromaffin and APUD series. If the concept is accepted, tumours containing both mucinous and enterochromaffin cells could arise in two ways: first, by metaplasia of tumour cells of either neural crest or endodermal origin; secondly, by simultaneous neoplastic change in a field containing cells of both origins. Recent observations on lower animals may support the traditional view of a common precursor cell. Melmed *et al* (1972) confirm the existence of 'intermediate' cells in the pancreas of the goat, rat, and monkey. Such 'intermediate' cells have ultrastructural features of both exocrine mucin secretion and endocrine polypeptide secretion. If similar intermediate forms exist in the mid-gut and contain enterochromaffin granules, they could give rise to neoplasms containing both enterochromaffin and mucinous elements. Further studies of carcinoid and mucinous carcinoid tumours by electron microscopy would be needed to clarify this point.

All the secondary tumours, and three of the primary tumours, presented with symptoms of acute appendicitis and were macroscopically inflamed. Only on microscopy was it apparent that both acute appendicitis and malignant infiltration were present. In the other two primary tumours, the appendix was

macroscopically infiltrated by tumour. In some laboratories it appears to be the practice to examine histologically only those appendices in which the operative findings are inconclusive (Gilmore *et al*, 1975). In our experience, the routine histological examination of all appendices has resulted in the discovery of a small number of potentially curable primary carcinomas of the appendix the presence of which was not apparent at operation.

The routine histopathological examination of appendectomy specimens serves two purposes. If examination of the appendix at operation is inconclusive, histology may confirm or refute the diagnosis. In both inflamed and apparently normal appendices, histology may disclose additional pathology which may affect the subsequent clinical management of the patient. It is likely that in future the cost-effectiveness of many routine procedures may be more closely examined. We would submit that the additional findings on histological examination of the inflamed appendix may be of greater importance than those on the macroscopically normal or inconclusively inflamed appendix.

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