INTRAESOPHAGEAL ADENOCARCINOMA

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A study of 87 cases of carcinoma involving the gastro-oesophageal region included seven cases of adenocarcinoma confined to the anatomical limits of the oesophagus. Six of these intra-oesophageal adenocarcinomas appear to have arisen in "oesophagi lined by columnar epithelium". The seventh, a carcinoma of double histological pattern associated with a sliding hiatus hernia, showed a complex mixture of epithelial structures in the lower oesophagus. The histogenesis of intraoesophageal adenocarcinoma is discussed, and it is stressed that its prognosis may be relatively favourable.

Adenocarcinoma of the oesophagus, once thought to be a very rare lesion, has been reported more frequently in recent years. Smithers (1956) recorded a total of 21 cases. There has been much controversy as to the histogenesis of these tumours, as there has also been with regard to the glandular epithelium sometimes found in the oesophagus.

In the course of a study of 87 cases of gastro-oesophageal carcinoma, 11 adenocarcinomas situated mainly or entirely within the oesophagus were encountered, and it is with some of these that this communication mainly deals. The results of the investigation of the series of gastro-oesophageal carcinomas will first be summarized.

The study comprised 87 surgically-excised carcinomas of the gastro-oesophageal region. The anatomical and histological features of the tumours are shown in Table I. Adenocarcinomas are the largest histological group in each anatomical category; they outnumber squamous carcinomas even in the mainly intraoesophageal group. No squamous carcinomas were found in the group astride the junction or in the mainly intragastric tumours. It is clear that the tissues of the oesophageal wall offer a favourable pathway for the spread of gastric carcinoma; the gastric wall,

however, is evidently not a favourable environment for oesophageal carcinoma. Anaplastic carcinomas occurred on both sides of the junction. The mixed carcinomas, a heterogeneous group, are being fully described elsewhere (Dodge, 1961). They included two adenocarcinomas showing squamous metaplasia, two muco-epidermoid carcinomas (probably arising in oesophageal mucous glands), two carcinomas, probably of double histogenesis, and one "collision carcinoma" arising from the meeting of two separate invasive growths. The tumour was localized in 14 of the 66 adenocarcinomas, two of the mixed carcinomas, but in none of the anaplastic or squamous carcinomas. Twenty cases came to necropsy, and in 15 there was no evidence of metastasis. Metastases are known to have occurred in 15 cases (10 adenocarcinomas, one squamous, one anaplastic, and three mixed carcinomas). Metastases were confined to the regional lymph nodes, ribs and chest wall, liver, adrenals, and lungs. Twenty-one patients died within one month of operation; 16 are known to have survived one year. Only one patient (with a squamous carcinoma) had so far survived five years.

Of the 11 adenocarcinomas situated mainly or entirely within the oesophagus, four were situated

TABLE I
SITUATION AND HISTOLOGICAL TYPES OF GASTRO-OESOPHAGEAL CARCINOMA

Histological Type	Anatomical Situation			Total
	Mainly Intraoesophageal	Astride Gastro-oesophageal Junction	Mainly Intragastric	
Adenocarcinoma	11	16	39	66
Squamous carcinoma	7	0	0	7
Anaplastic carcinoma	2	0	5	7
Mixed carcinoma	5	1	1	7

TABLE II
INTRAESOPHAGEAL ADENOCARCINOMA

Case	Sex	Age	Area Involved by Tumour	Post-operative Course
1	M	66	7.5 cm. of lower oesophagus	Died 16 months later of pneumonia. No recurrence or metastasis
2	M	60	Lower third of oesophagus	Died 1 yr. later. No recurrence or metastasis
3	M	54	Lower third of oesophagus	Well 1½ yr. later
4	M	?	3 cm. of lower oesophagus	Post-operative death. No metastasis
5	M	41	5 cm. of middle third of oesophagus	Recurrence 13 months later. Died 19 months later.
6	M	59	7.5 cm. of lower oesophagus	Well 2½ yr. later
7	M	65	Mass in lower third of oesophagus	Post-operative death (pulmonary embolism). No metastases

partly within the proximal part of the stomach, and there is little doubt that these were gastric adenocarcinomas which had spread almost entirely upward into the oesophagus. Seven cases of intra-oesophageal adenocarcinoma were found, and it is with these that the present study is mainly concerned. In these cases, the tumour was limited to the anatomical oesophagus, and the stomach was intact. Details of these cases are summarized in Table II.

The extent to which the oesophagus may be invaded by gastric carcinoma is well recognized. In two of the partly intragastric neoplasms the tumour extended from the stomach to the level of the aortic arch. If an oesophageal biopsy from a case of suspected oesophageal cancer reveals adenocarcinoma, it is sometimes assumed that this indicates that a gastric carcinoma has invaded the oesophagus, and that the patient is therefore probably beyond surgical aid. One of the purposes of the present paper, however, is to reiterate the fact that adenocarcinomas limited to the oesophagus do occur, and that, as Barrett (1957) has pointed out, the prognosis of adenocarcinoma within the oesophagus need not be hopeless.

Details of the seven cases are shown in Table II. The following points are stressed: (1) In each of these cases the tumour, as seen at operation and in the gross specimen, lay entirely within the oesophagus. (2) In Cases 1-6 inclusive, the tumours were bounded at their lower ends by columnar epithelium (Case 7 is discussed in more detail below). (3) In

these six cases, the columnar cell glandular epithelium extended from the stomach in a continuous sheet into the oesophagus up to the tumour margin. (4) In six of the seven cases the tumours were situated in the lower third of the oesophagus. The most proximally-placed adenocarcinoma (Case 5) had its lower margin 4 cm. above the diaphragm. (5) In Case 5 the tumour extended to the proximal margin of resection; in the other six cases the upper margin of the tumour was bounded by squamous epithelium. (6) In Cases 1-6 inclusive, there was no evidence of a diaphragmatic defect or hiatus hernia, and the gross topography of the gastro-oesophageal region appeared to be normal at the time of operation. Several of these features are seen in Fig. 1. These findings lead to the conclusion that Cases 1-6 are each an example of an adenocarcinoma that has arisen in a "lower oesophagus lined by columnar epithelium", as described by Barrett (1958).

Case 7 revealed a more involved state of affairs, with a hiatus hernia, a complex mixture of epithelial structures below the tumour margin, and a carcinoma showing two distinct structural patterns. This case will be described in more detail.

CASE HISTORY

A man of 65 complained of retrosternal pain, worse on eating, for two months. He had no difficulty in swallowing. A barium swallow revealed a filling defect in the lower third of the oesophagus, and below this a reducible, sliding hiatus hernia, with evidence of reflux.

FIG. 1.—Diagram of a longitudinal whole-tumour section of an adenocarcinoma lying within the lower third of the oesophagus (Case 3). Squamous epithelium shaded black, columnar epithelium vertically hatched, tumour unshaded. Muscularis diagonally hatched, other tissue stippled. Extensive ulcerated carcinoma, with an outlying "satellite" nodule of tumour at the proximal margin of resection (A). $\times 2.5$.

FIG. 3.—Case 7. Diagram of longitudinal section of the specimen. Oesophageal squamous epithelium and oesophageal mucous glands are shaded black, fundal mucosa horizontally, and cardial mucosa vertically hatched. Tumour unshaded, and other tissues as in Fig. 1. Mucous glands are embedded in the cardial mucosa and in the submucosa below it. Squamous epithelium at both margins of tumour.

FIG. 2.—Case 7. Polypoid carcinoma of oesophagus. Specimen removed by gastro-oesophageal resection, seen from the outside (right) and in longitudinal section (left). At the right, the tumour protrudes through the upper everted end of the specimen, and there is a rim of gastric mucosa at the lower end. At the left, the tumour is seen to lie in the submucosa of the oesophagus.

Oesophagoscopy showed a tumour at 37 cm. from the incisors. At operation a tumour was found in the lower oesophagus; it was described as lying about 4.5 cm. above the gastro-oesophageal junction. The tumour was excised, with a margin of normal-looking tissue above and below, including a cuff of cardial mucosa, and a gastro-oesophageal anastomosis was performed. Three weeks later the patient died suddenly. Necropsy revealed ilio-femoral venous thrombosis and a massive pulmonary embolus. There was no evidence of residual tumour or of secondary deposits.

The outer and cut surfaces of the operation specimen are shown in Fig. 2. The large fungating tumour lies well within the oesophageal tube. Figs. 3 and 4 show diagrammatically the state of affairs revealed by microscopy. The important features are: (1) A short length of gastric mucosa of fundal type at the distal

margin; (2) a strip of gastric mucosa of cardial type extending upwards along the oesophageal tube, almost to the distal margin of the tumour, but separated from it by a short zone of squamous epithelium; (3) several glands within the strip of cardial mucosa showing intestinal metaplasia (Fig. 5); (4) islands of squamous epithelium also embedded in the same strip (Fig. 5); (5) numerous oesophageal mucous glands in the submucosa beneath the cardial-type epithelium (Fig. 6); (6) an adenocarcinoma, bounded above and below by squamous epithelium, showing two distinct and quite sharply separated types of growth: (a) a well-differentiated adenocarcinoma, confined to the surface, at both upper and lower margins of growth (Fig. 7), (b) a much less differentiated adenocarcinoma (Fig. 8), forming the main bulk of the tumour, and penetrating the oesophageal submucosa more deeply.

FIG. 4.—Case 7. A more detailed diagram of the distal part of the specimen. Shading as before. The letters A, B, C, D indicate the areas shown in Figs. 5-8 respectively.

FIG. 5.—Case 7. Area A of Fig. 4. An island of squamous epithelium in the cardiac mucosa. Many of the glands (L.) show intestinal metaplasia. Haematoxylin and eosin $\times 100$.

FIG. 6.—Case 7. Area B of Fig. 4. Oesophageal mucous gland in submucosa below cardiac mucosa. Haematoxylin and eosin $\times 100$.

FIG. 7.—Case 7. Area C of Fig. 4. Well-differentiated adenocarcinomatous pattern in superficial, peripheral part of tumour. Haematoxylin and eosin $\times 330$.

FIG. 8.—Case 7. Area D of Fig. 4. Poorly-differentiated carcinoma forming central, deeper part of tumour. Haematoxylin and eosin $\times 330$.

The cardiac mucosa here is evidently of a different origin from the mucosa seen in the "oesophagus lined by columnar epithelium". Oesophageal mucous glands and islands of squamous epithelium were not seen in the glandular epithelium below the tumours in Cases 1-6. The intestinal metaplasia in this area is also unusual. The dual histological structure of the carcinoma suggests the possibility of a double origin. The superficial marginal zone of well-differentiated adenocarcinoma may have arisen from another area of glandular epithelium (either of cardiac or perhaps of intestinal type). The situation of the more deeply-placed central mass of less differentiated carcinoma suggests that it may have arisen from deeper structures, possibly from mucous glands in the submucosa. The mucous glands, abundant more distally, are absent around the tumour area, and the possibility that this component of the tumour has arisen in oesophageal mucous glands cannot be excluded.

DISCUSSION

All these tumours lay within the confines of the oesophagus, as seen at operation, *i.e.*, within the tube-shaped structure, devoid of a serosal coat, leading from the pharynx to the sac of the stomach.

In Cases 1-6 there was no evidence of a diaphragmatic defect or of any downward extensions of the peritoneal cavity. In each of these cases, however, the tumour was found to be bordered below by columnar epithelium, which extended in an apparently unbroken sheet distally from the tumour edge. Proximally, the tumours were bordered by oesophageal squamous epithelium. The tumours in Cases 1-4 and Case 6 lay in the lower third of the oesophagus and in Case 5 in the middle third. These findings indicate that each of these six carcinomas has arisen in what Barrett (1958) calls "the lower oesophagus lined by columnar epithelium". In this condition, which is probably a malformation rather than an acquired defect, columnar epithelium extends upwards from the stomach in a continuous sheet into an oesophagus which is in all other respects normal. This malformation differs from a sliding hiatus hernia in that the anatomy of the peritoneal sac and the local arteries remains normal. It is therefore easy to understand how its existence may be overlooked both by surgeons and pathologists.

The remaining case (Case 7) shows a more complicated pattern. This was the only case in which a sliding hiatus hernia was reported. The situation revealed here (Figs. 2-8) may be interpreted as follows:

(1) The strip of gastric mucosa at the lower end of the specimen represents the upper limit of the herniated stomach. (2) The strip of cardiac-type mucosa above this, in which were embedded islands of squamous epithelium and below which lay oesophageal mucous glands, has come about as a consequence of reflux oesophagitis. This mixture of epithelial types was not seen in any of the other cases, and it is suggested that in this case, where there was reflux of gastric contents, the original squamous epithelium had been largely destroyed and replaced by upward-growing columnar epithelium, and had survived only in isolated patches. The protected mucous glands have, however, remained intact, and they label this segment as "oesophagus". (3) The carcinoma, bounded at its lower (as well as upper) margin by a narrow zone of squamous epithelium, may have arisen from a further island of proliferating columnar epithelium, but could also be of mucous gland origin. (4) The double histological structure of the carcinoma indeed raises the possibility of a double histogenesis. The well-differentiated, superficial, peripheral component may have arisen from columnar epithelium lining the lumen of the oesophagus. The poorly-differentiated, deeply placed, central component may have arisen from mucous glands in the sub-mucosa. It may be significant that oesophageal mucous glands are numerous both above and below the tumour, but are absent along its deep border.

One other possible origin of intraoesophageal adenocarcinoma should be mentioned, namely, the islands of so-called heterotopic gastric mucosa in the oesophagus, described by Schridde (1904), Taylor (1927), and Rector and Connerley (1941). The work of Johns (1952) on the development of the oesophageal lining has made it clear that these islands represent, not ectopic gastric mucosa, but the persistent remains of the normal oesophageal lining of the foetus. He showed that squamous transformation begins at the mid-oesophagus and that the extremities of the organ are the last to lose

their columnar epithelium. This explains why these "heterotopic" islands appear at the upper and lower ends of the oesophagus. No ulceration has been described in connexion with these islands of glandular mucosa (Barrett, 1950), and only one well-documented case of adenocarcinoma of the upper oesophagus has been reported (Carrie, 1950). These islands are clearly a different abnormality from the lower oesophagus lined by columnar epithelium and from the state of affairs shown by Case 7.

Adenocarcinomas confined to the oesophagus are clearly an entity to be reckoned with. The post-operative course of the seven cases reported here justifies their separation from those of gastric carcinoma invading the oesophagus. None of the patients has shown evidence of metastasis. In six of the seven cases complete surgical excision appears to have been achieved; five patients survived the operation for a year, and the two who died within a year of operation had no evidence of local recurrence or metastasis at necropsy. These results suggest that when a patient is found by biopsy to have adenocarcinoma in the oesophagus, it may be well worth while to try to determine whether this is an oesophageal extension of a gastric carcinoma, with a very poor prognosis, or whether it represents an intraoesophageal adenocarcinoma. In the latter case, surgical excision may well be feasible. As more of these lesions become available for study, further information on their histogenesis and behaviour may come to light.

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