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*Case report*

# Adenocarcinoma of the cervical oesophagus arising from ectopic gastric mucosa

## The histochemical determination of its origin

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**Summary.** A case of adenocarcinoma of the cervical oesophagus was examined by employing a battery of histochemical techniques and was demonstrated to arise from ectopic gastric mucosa. The patient was a 66-year-old Japanese male. Endoscopy revealed an ulcerated tumour on the right anterior wall of the cervical oesophagus, approximately 16 cm from the incisor teeth. Pathological examination of surgically removed specimens showed well-differentiated tubular adenocarcinoma. Ectopic gastric mucosa was found in the oesophageal mucosa adjoining the carcinoma. Histochemical stains for characterizing mucosubstances and immunostains for various antigens were used. In addition to this carcinoma, ectopic gastric mucosa in the oesophagus and normal oesophageal, cardiac, tracheal and bronchial mucosa were also examined. The results showed that the carcinoma contained mucins, which showed reactivities characteristic of the gastric surface mucous cell (galactose oxidase-cold thionin Schiff reactive) and gland mucous cell (paradoxical concanavalin A staining reactive). Ectopic gastric mucosa consistently contained these mucins, but other tissue sites lacked them.

**Key words:** Oesophageal adenocarcinoma – Ectopic gastric mucosa – Mucosubstance – Immunohistochemistry

## Introduction

Adenocarcinoma of the oesophagus occurs only rarely in the cervical region, and until recently its existence as a distinct entity was doubted. Ectopic gastric mucosa is often referred to as a possible source in such cases, although actual cases have seldom been reported. This paper reports a case of adenocarcinoma of the cervical oesophagus, reviews the literature and discusses the histochemical features suggesting the probable histogenesis of adenocarcinoma. Histochemical comparisons of the oesophageal mucosa, ectopic gastric mucosa, gastric cardiac mucosa and tracheal and bronchial mucosa are also reported.

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## Case report

### *Clinical history*

The patient was a 66-year-old Japanese man, who presented in August 1988 with a history of difficulty in swallowing medicine for hypertension. He visited the Department of Otorhinolaryngology, Shinshu University Hospital in February 1989. Oesophagoscopy revealed a hard, rough-surfaced, partially ulcerated tumour located 16 cm distal to the incisor teeth. There were no abnormalities of the distal oesophagus. Biopsy specimens from the lesion revealed adenocarcinoma, and metastasis from other organs was suggested by pathologists – but no primary tumour was found in the digestive organs or lungs. In May 1989 the patient underwent oesophagectomy with the gastric pull-up method and a left-neck exploration in the Department of Surgery, Shinshu University Hospital. The patient is well 20 months after surgery.

## Results

The resected specimen consisted of the oesophagus, 15 cm in length, with the upper trachea, larynx, lower pharynx and bilateral lobes of the thyroid. An ulcerated nodular lesion at the proximal end of the right anterior wall of the oesophagus, approximately 2 cm below the

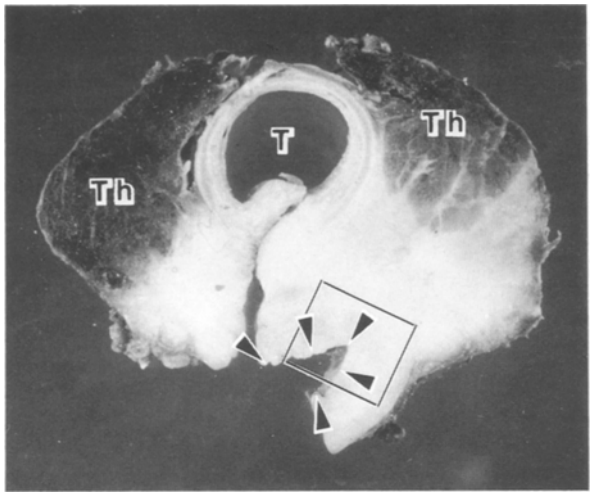


**Fig. 1.** A horizontally sliced section of the removed specimen. *Arrowheads* indicate the cut surfaces of the oesophageal mucosa. Carcinoma tissues infiltrate diffusely the oesophageal mucosa and the surrounding tissues of the trachea (*T*) and the bilateral thyroids (*Th*). A *rectangle* in the picture indicates the area shown in Fig. 2. The scale at the bottom is divided in 5 mm

cricoid cartilage was slightly elevated and measured 2 × 1 cm. On cut section, the tumour appeared to infiltrate deeply into the muscular wall of the oesophagus and adhered to the trachea and thyroid (Fig. 1). The whole tumour measured 3.0 × 4.5 × 5.0 cm. The oesophageal mucosa adjacent to the lesion and tracheal mucosa appeared intact.

Microscopic examination was carried out by slicing the cervical oesophagus horizontally approximately 5 mm in thickness. The tumour revealed a well-differentiated tubular adenocarcinoma with abundant fibrous stroma, infiltrating beyond the muscular wall of the oesophagus to the adventitia of the trachea (Figs. 2, 3). The tracheal mucosa and thyroid were not invaded. The tumour cells had relatively clear apical cytoplasm and oval or polygonal nuclei (Fig. 4).

Ectopic gastric mucosa was found in the lamina propria and submucosa (Fig. 5), where carcinoma was also found. It consisted of surface mucous cells and mucous glands, resembling cardiac glands. Intestinal metaplasia was not found. Other parts of the oesophagus were lined

**Table 1.** Lectins, peroxidase and antibodies used

| Reagents | Sources | Dilutions |
|---|---|---|
| Concanavalin A | Sigma, type V | 1 mg/ml |
| Horseradish peroxidase | Toyobo | 1 mg/100 ml |
| Anti-lysozyme | Dakopatts | × 300 |
| Anti-lactoferrin | Dakopatts | × 500 |
| Anti-chromogranin A | Dakopatts | × 500 |
| Anti-S-100 protein | Dakopatts | × 1000 |
| Anti-muscle actin | Enzo Diagnostics | × 1 |
| Peroxidase-conjugated goat anti-rabbit IgG | MBL | × 200 |

Sigma: St. Louis, Mo., USA; Toyobo: Osaka, Japan; Dakopatts: Copenhagen, Denmark; Enzo Diagnostics: New York, USA; MBL: Nagoya, Japan

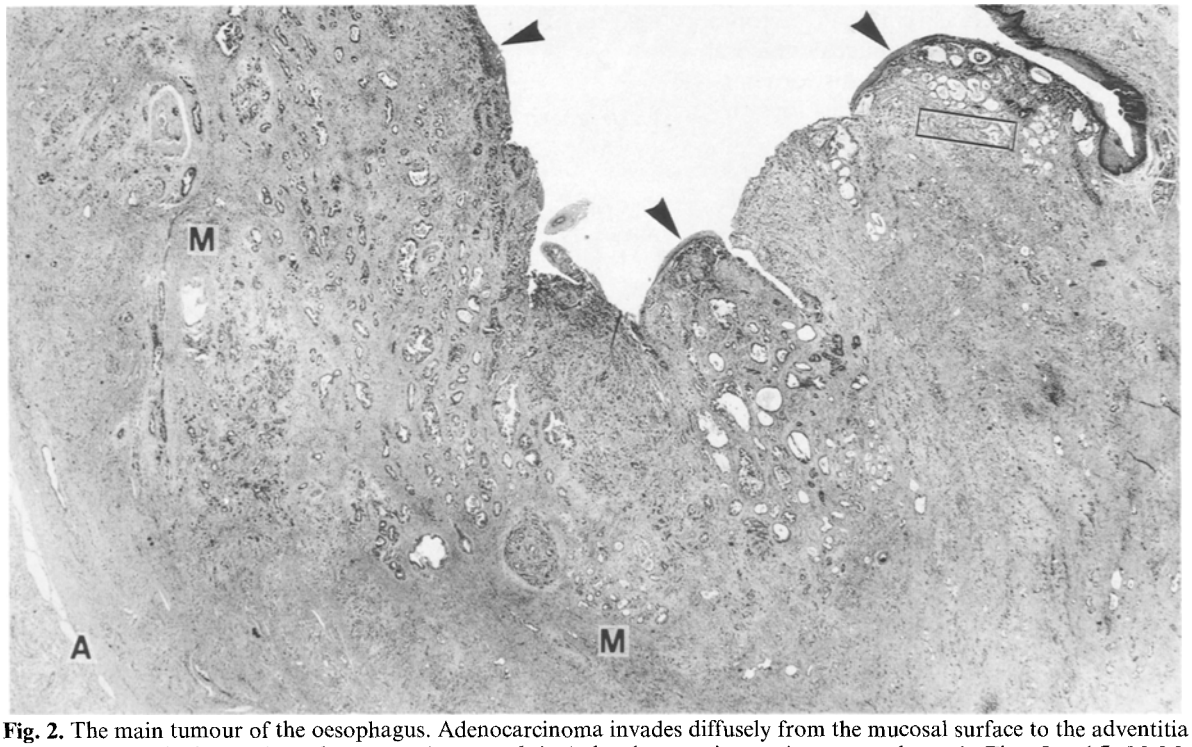


**Fig. 2.** The main tumour of the oesophagus. Adenocarcinoma invades diffusely from the mucosal surface to the adventitia (*A*). *Arrowheads* indicate the residual oesophageal mucosa. A *rectangle* includes the ectopic gastric mucosa shown in Figs. 5 and 7. *M*, Muscularis propria. × 12.5

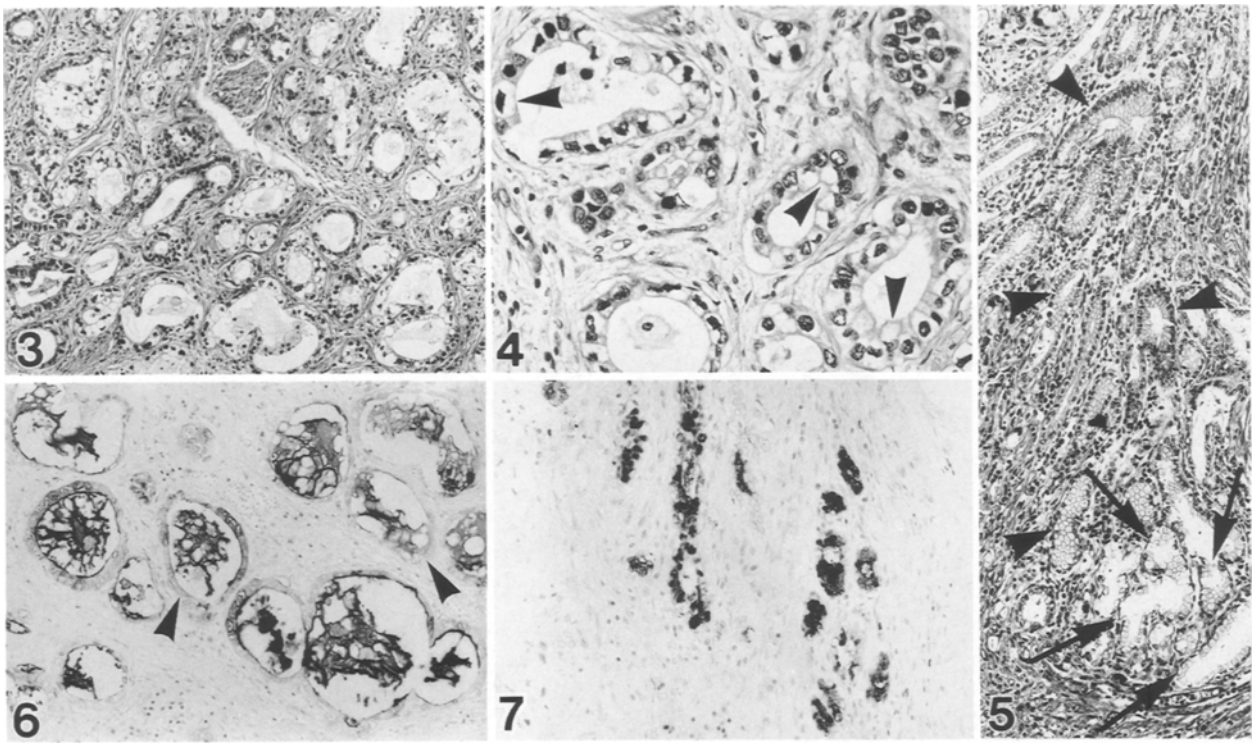


**Fig. 3.** The carcinoma reveals the pattern of well-differentiated tubular adenocarcinoma. ×100

**Fig. 4.** Higher magnification of the carcinoma. The cells have clear apical cytoplasm (*arrowheads*). ×250

**Fig. 5.** Higher magnification of the rectangle in Fig. 2. The ectopic gastric mucosa consists of surface mucous cells (*arrowheads*) and gland mucous cells (*arrows*). ×100

**Fig. 6.** With GOCTS-PCS sequence, most of the carcinoma cells show either class III Con A reactivity or GOCTS reactivity. In this black and white figure, class III mucins appear darker than lightly stained GOCTS-reactive mucins (*arrow heads*). GOCTS-PCS, ×150

**Fig. 7.** Gland mucous cells in the ectopic gastric mucosa of the present case show class III Con A reactivity. PCS, ×150

**Table 2.** Comparison of mucins and antigens in the carcinoma tissues and three tissue sites

| | Oesophageal gland | | | | | | Trachea and bronchus | | | | | | Cardia | | | | | Carcinoma |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sqc | Dtc | Mcc | Sec | Onc | Mec | Cic | Goc | Dtc | Sec | Mcc | Mec | Smc | Cgc | Mnc | Chc | Prc | |
| Mucosubstances[a] | | | | | | | | | | | | | | | | | | |
| Acidity | − | − | u/i | u/i | − | − | u/i | u/i | − | u/i | i/u | − | − | − | −/u | − | − | i/u |
| PA-SB-PH-PAS | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| GOCTS | − | − | + | − | − | − | − | − | − | − | ± | − | +++ | ± | ± | − | − | ++~+ |
| PCS | − | − | − | − | − | − | − | − | − | − | − | − | − | +++ | +++ | − | − | +++~+ |
| N-GOCTS | − | − | +++ | − | − | − | − | ± | − | − | + | − | +++ | ± | ± | − | − | +++~+ |
| Antigens | | | | | | | | | | | | | | | | | | |
| Lysozyme | − | − | ± | + | − | − | − | − | − | + | − | − | − | + | + | − | − | +/− |
| Lactoferrin | − | − | − | + | − | − | − | − | − | + | − | − | − | ± | − | − | − | − |
| S-100 protein | − | − | − | + | + | + | − | − | − | + | − | + | − | − | − | − | − | − |
| Actin | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − | − | − | − |
| Chromograinin A[b] | | | | − | | | | | | + | | | | | + | | | − |

Sqc, Squamous cell; Dtc, ductal cell; Mcc, mucous cell; Sec, serous cell; Onc, oncocyte; Mec, myoepithelial cell; Cic, ciliated cell; Goc, goblet cell; Smc, surface mucous cell; Cgc, cardiac gland cell; Mnc, mucous neck cell; Chc, chief cell; Prc, parietal cell; u, sulphomucin, i, sialomucin; u/i, sulphomucin predominates sialomucin; i/u, vice versa.
Number of + indicates the relative intensity of the reaction, where +++ is the strongest reaction. Ectopic gastric mucosa shows the same histochemical reactivities as does the cardiac mucosa, so does not show in this table.

[a] The results obtained with methods characterizing mucosubstances are evaluated by the reactivities of the cytoplasm
[b] + or − on the line of chromogranin A indicates the presence or absence of positive endocrine cells

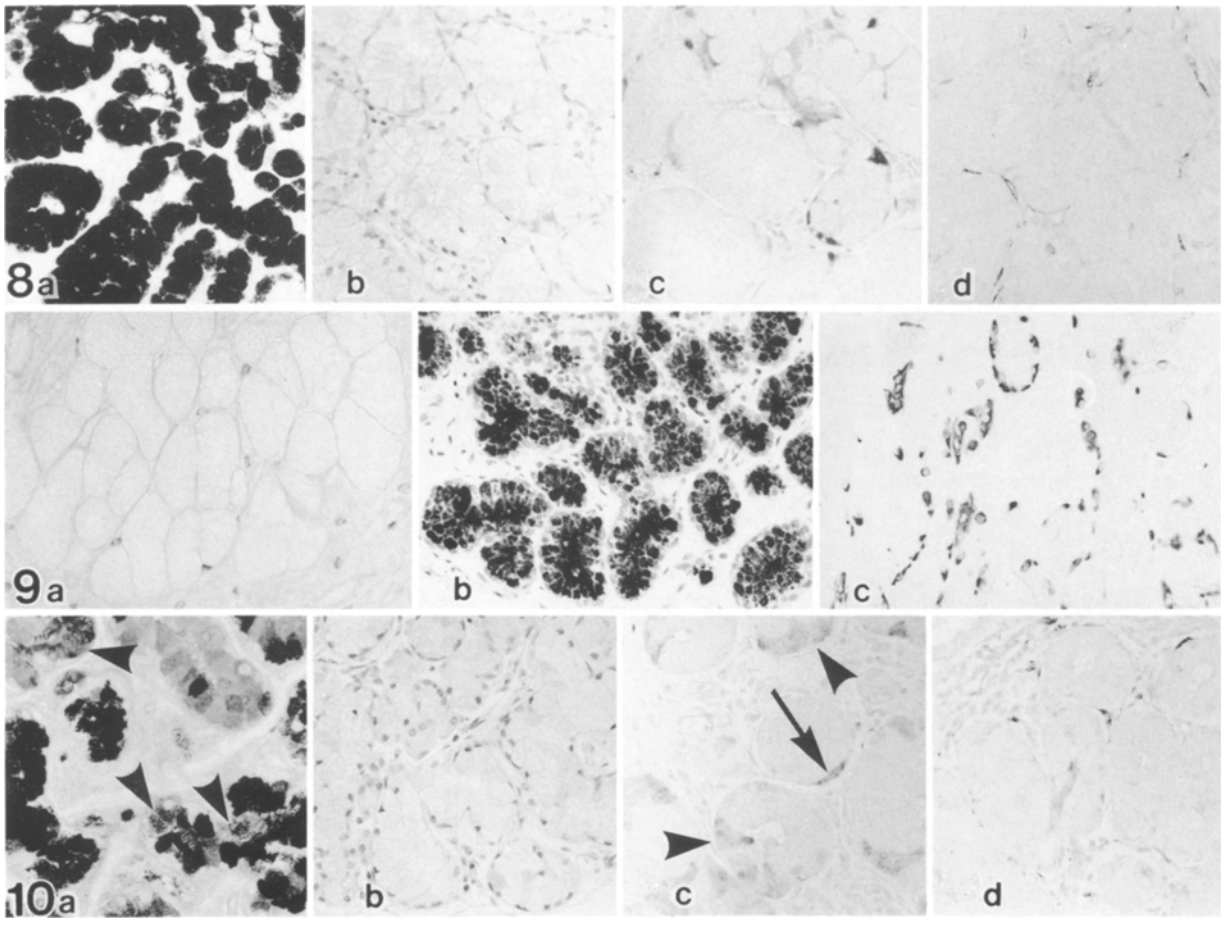


**Fig. 8. a** Both mucous cells and serous cells in an oesophageal gland contain acid mucins. In this figure, most gland cells stain intensely, indicating the predominance of sulphomucins. HID-AB, ×200. **b** The oesophageal gland cells lack class III Con A reactivity. Compare with Fig. 9b. PCS, ×200. **c, d** Myoepithelial cells contain S-100 protein (**c**) and actin (**d**). Indirect immunostaining with anti-S-100 protein antibody and anti-actin antibody. ×250

**Fig. 9. a** Cardiac glands lack acid mucins. Compare with Figs. 8a and 10a. HID-AB, ×200. **b** Cardiac glands contain class III mucins. PCS, ×200. **c** Chromogranin A-containing cells scatter among cardiac gland cells. Indirect immunostaining with anti-chromogranin A antibody. ×250

**Fig. 10. a** Bronchial gland mucous cells contain sulpho- or sialomucins. In this figure sulphomucins appear more darkly stained compared with lightly stained sialomucins. Serous cells contain only sulphomucins (*arrowheads*). HID-AB stain, ×200. **b** The bronchial gland lacks class III mucin. Compare with Fig. 9b. PCS, ×200. **c** Serous cells (*arrowheads*) and myoepithelial cells (*arrow*) contain S-100 protein. Indirect immunostaining with anti-S-100 protein antibody. ×250. **d** Myoepithelial cells contain actin. Indirect immunostaining with anti-muscle actin antibody. ×250

by normal squamous mucosa. A tracheoesophageal lymph node contained metastatic adenocarcinoma.

*Histochemistry*

A battery of histochemical stains were carried out to compare the carcinoma in the present case with the mucosa of adjacent organs. In addition to the tumour ten cases of histologically normal cardiac, oesophageal and tracheal mucosa, were selected from the pathology files of Shinshu University Hospital. Five cases of ectopic gastric mucosa removed incidentally by endoscopy were also examined.

The histochemical methods for characterizing mucosubstances included alcian blue pH 2.5-periodic acid-Schiff (Spicer et al. 1967) (AB-PAS, to detect mucosubstances), high iron diamine-alcian blue pH 2.5 (Spicer et al. 1967) (HID-AB, to differentiate sialomucins from sulphomucins), periodic acid-sodium borohydride-potassium hydroxide-PAS (Culling et al. 1974) (PA-SB-PH-PAS, to identify 8-*O*-acetyl-*N*-acetylneuraminic acid) galactose oxidase-cold thionin Schiff-paradoxical Concanavalin A steining (Ota et al. 1991) (GOCTS-PCS, to detect gastric surface mucous cell-type mucin and gland mucous cell-type mucin respectively) and neuraminidase-GOCTS (Katsuyama et al. 1985) (N-GOCTS, to detect sialic acid binding penultimate β-galactose or β-*N*-acetylgalactosamine). Among variations of the paradoxical Concanavalin A (Con A) staining, only the sequence to detect class III mucins was performed in this study. In addition, the distribution of various antigens – actin, lysozyme, lactoferrin, chromogranin A and S-100 protein – was also examined by the indirect immunoperoxidase method. As the control for

immunostaining, hydrated and rinsed tissue sections were first incubated with a phosphate-buffered saline solution containing only normal bovine albumin. Sources of antibodies and conditions for staining were listed in Table 1.

Results obtained with histochemical stains were summarized in Table 2. The cells of the tumour contained abundant mucins, which were stained for neutral- sialo- or sulphomucins. With GOCTS-PCS, most of the carcinoma cells showed either class III Con A reactivity or GOCTS reactivity (Fig. 6). 8-*O*-Acetyl-*N*-acetylneuraminic acid was consistently absent. The carcinoma cells occasionally contained lysozyme but lacked reactivities for actin, lactoferrin, chromogranin A and S-100 protein.

In the ectopic gastric mucosa in the present case and other biopsy specimens, surface mucous cells showed intense GOCTS reactivity, whereas gland mucous cells possessed class III Con A reactivity (Fig. 7). Endocrine cells stained for chromogranin A were scattered among gland cells, which also stained weakly for lysozyme.

In the oesophageal glands and ducts, both mucous and serous cells contained sulpho- or sialomucins, although the serous cells stained only faintly. Sulphomucins predominated in both (Fig. 8a). Mucous cells showed only a faint GOCTS reactivity, which was markedly enhanced by prior neuraminidase digestion. Class III Con A reactive mucins (Fig. 8b) were absent. Among the antigens examined, lysozyme, lactoferrin and S-100 protein were demonstrated in the serous cells. Oncocytes contained little mucin but stained for S-100 protein. This gland had myoepithelial cells positive for S-100 protein (Fig. 8c) and actin (Fig. 8d) but lacked endocrine cells containing chromogranin A. Examined ductal epithelia contained neither mucins nor antigens.

In the cardiac mucosa mucous cells contained neutral mucins almost exclusively (Fig. 9a). The surface mucous cells showed GOCTS reactivity and so did cardiac gland cells class III Con A reactivity (Fig. 9b). The latter also stained for lysozyme and lactoferrin. Chromogranin A containing endocrine cells were scattered in the glands (Fig. 9c).

In the tracheal and bronchial mucosa, goblet cells and mucous cells of the glands contained sialo- and/or sulphomucins. Serous cells of the glands consistently stained for sulphomucins (Fig. 10a). They never showed class III Con A reactivity (Fig. 10b) and stained only faintly with GOCTS. Amongst the antigens examined, serous cells contained lysozyme, lactoferrin and S-100 protein. These glands had myoepithelial cells identified by S-100 protein (Fig. 10 c) and actin (Fig. 10d). Chromogranin A-containing endocrine cells were only occasionally found among tracheal and bronchial covering epithelia but not in the glands. Ductal epithelia contained neither mucins nor antigens.

## Discussion

The most common malignant tumour of the oesophagus is squamous cell carcinoma, and adenocarcinoma accounts for only 0.8–10% of oesophageal malignancies (Fujita et al. 1979; Puestow et al. 1955; Raphael et al. 1966; Smithers 1956). The majority of adenocarcinomas originate in the lower segment, where this pattern represents close to 20% of malignancies (Goldman and Antonioli 1982). Gastric carcinoma extending into the lower oesophagus might contribute to this percentage.

Adenocarcinoma of the upper oesophagus is exceptionally rare, and we found 38 cases in the literatures (Christensen and Sternberg 1987; Ellis et al. 1959; Nakayama et al. 1964; Sakamoto et al. 1970; Setoguchi et al. 1990). Among these cases, 8 cases were reported to have originated from ectopic gastric mucosa (Christensen and Sternberg 1987) and 1 case from an oesophageal gland (Setoguchi et al. 1990). The histological grounds of such assumptions were based on the fact that the carcinomas were located in the respective tissues or in their vicinity. The histogenesis of 29 other cases was not described in these reports.

The histogenesis of adenocarcinoma of the oesophagus has been interpreted in three ways (Morson and Belcher 1953): as an upward extension of carcinoma of the stomach, as malignant change in the oesophageal mucous glands and from ectopic gastric mucosa. In addition, the possible invasion of adenocarcinoma from surrounding organs such as the lung and trachea has to be taken into consideration. The determination of the origin of oesophageal adenocarcinoma, therefore, is not always possible. Location of a carcinoma in ectopic gastric mucosa, the oesophageal glands or in the vicinity of these sites does not necessarily mean that the carcinoma rises from these tissues. Histological markers are required to determine the histogenesis of the oesophageal adenocarcinoma.

The histochemical staining carried out in this report indicated that the adenocarcinoma of the present case probably originated from the ectopic gastric mucosa. As reported previously and further confirmed here, gastric surface or gland mucous cells are characterized by their intense galactose oxidase-Schiff (Katsuyama et al. 1985; Ota et al. 1991; Tatematsu et al. 1986) or class III Con A reactivity (Katsuyama et al. 1978; Suganuma et al. 1981; Tatematsu et al. 1986) respectively. In addition, gastric mucous cells elaborate neutral mucins almost exclusively. These histochemical properties may be applied to identifying gastric type epithelia in the oesophageal mucosa and carcinoma tissues derived from them. Employing the same histochemical method used in this study, the present authors have examined 30 cases of squamous cell carcinoma and 3 cases of adenoid cystic carcinoma of the oesophagus. None of these cases produced mucins stained with the GOCTS reaction or the paradoxical Con A staining (unpublished data).

The present study also revealed that oesophageal glands and tracheal and bronchial glands resembled each other not only in their histochemical properties but also in having the myoepithelial cell, the latter feature corresponding with the occurrence of adenoid cystic carcinoma in both tissues. The oesophageal mucosa, however, lacked those endocrine cells which contain chromogranin A.

Ectopic gastric mucosa was most frequently found in the upper oesophagus or in the oesophageal inlet. On endoscopy it was found in 3.8% of patients examined (Jabbari et al. 1985) and in autopsy cases in up to 70% (Schridde 1951). It is conceivable, therefore, that the cervical oesophagus could be the site where the adenocarcinoma arises from the ectopic gastric mucosa. Histochemical stains are useful to confirm its origin.

## References


Christensen WN, Sternberg SS (1987) Adenocarcinoma of the upper esophagus arising in ectopic gastric mucosa; two case reports and review of the literature. Am J Surg Pathol 11:397–402

Culling CFA, Reid PE, Clay MG, Dunn WL (1974) The histochemical demonstration of *O*-acetylated sialic acid in gastrointestinal mucins: their association with the potassium hydroxide-periodic acid-Schiff effect. J Histochem Cytochem 22:826–831

Ellis FH, Jackson RC, Krueger JT, Moersch HJ, Clagett OT, Gage RP (1959) Carcinoma of the esophagus and cardia; result of treatment, 1946 to 1956. N Engl J Med 260:351–358

Fujita H, Kakegawa T, Kumagaya Y (1979) Adenoid cystic carcinoma arising from esophagus (in Japanese). Gan No Rinsho 25:235–241

Goldman H, Antonioli DA (1982) Mucosal biopsy of the esophagus, stomach, and proximal duodenum. Hum Pathol 13:423–448

Jabbari M, Goresky CA, Lough J, Yaffe C, Daly D, Cote C (1985) The inlet patch: heterotopic gastric mucosa in the upper esophagus. Gastroenterology 89:352–356

Katsuyama T, Ono K, Nakayama J, Kanai M (1985) Recent advances in mucosubstance histochemistry. In: Kawai K (ed) Gastric mucus secreting cells. Excerpta Medica, Amsterdam, pp 3–18

Morson BC, Belcher JR (1953) Adenocarcinoma of the oesophagus and ectopic gastric mucosa. Br J Cancer 6:127–132

Nakayama K, Yanagisawa F, Suzuki K, Nakano K, Hoshino K, Onodera M, Yokoyama T, Mochizuki N (1964) Primary esophageal adenocarcinoma (in Japanese). Gan No Rinsho 10:8–16

Ota H, Katsuyama T, Ishii K, Nakayama J, Shiozawa T, Tsukahara Y (1991) A dual staining method for identifying mucins of different gastric epithelial mucous cells. Histochem J 23:22–28

Puestow CB, Gillesby WJ, Guznon VL (1955) Carcinoma of the esophagus. Arch Surg 70:662–666

Raphael HA, Ellis FH, Dockerty MB (1966) Primary adenocarcinoma of the esophagus; 18-year review and review of literature. Ann Surg 164:785–796

Sakamoto G, Nakamura K, Saito K, Sato M, Sugahara T (1970) Primary adenocarcinoma arising from heterotopic gastric glands of the esophagus (in Japanese). Gan No Rinsho 16:1105–1110

Schridde H (1951) Heterotopic gastric mucosa in esophagus with ulceration and stricture formation. J Thorac Surg 21:306–312

Setoguchi M, Harada T, Nagao N, Hirata K, Ayabe K, Kajiwara Y, Matsuo T (1990) A case of esophageal carcinoma arising in esophageal gland that appeared as submucosal tumor (in Japanese) [abstract] (in Japanese). In: Abstracts of the 39th Annual Meeting of Gastroenterological Endoscopy. Japanese Society of Gastroenterological Endoscopy, Tokyo, p 344

Smithers DW (1956) Adenocarcinoma of the esophagus. Thorax 11:257–261

Spicer SS, Horn RG, Leppi TJ (1967) Histochemistry of connective tissue mucopolysaccharides. In: Wagner BW, Smith DE (eds) The connective tissue. Williams and Wilkins, Baltimore, pp 251–303

Suganuma T, Katsuyama T, Tsukahara M, Tatematsu M, Sakakura Y, Murata F (1981) Comparative histochemical study of alimentary tract with special reference to the mucous neck cells of the stomach. Am J Anat 161:219–238

Tatematsu M, Furihata C, Katsuyama T, Miki K, Honda H, Konishi Y, Ito N (1986) Gastric and intestinal phenotypic expressions of human signet ring cell carcinomas revealed by their biochemistry, mucin histochemistry and ultrastructure. Cancer Res 46:4866–4872