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CASE REPORT

Teiichi Motoyama · Masami Higuchi · Jun Taguchi

Combined choriocarcinoma, hepatoid adenocarcinoma, small cell carcinoma and tubular adenocarcinoma in the oesophagus

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Abstract We describe an oesophageal tumour composed of choriocarcinoma, hepatoid adenocarcinoma, small cell carcinoma and tubular adenocarcinoma. The choriocarcinomatous areas and hepatoid adenocarcinomatous areas contained beta human chorionic gonadotropin-positive cells and alpha fetoprotein-positive cells, respectively. The small cell carcinomatous areas contained cells positive for serotonin or adrenocorticotrophic hormone, while the tubular adenocarcinomatous areas contained cells positive for carcinoembryonic antigen. Non-neoplastic gastric type columnar epithelium was found directly adjoing the tumour at the oral side. This tumour, with its unprecedented histology combination of tissues may have originated in Barrett's oesophagus, although we could not confirm a history of chronic gastro-oesophageal reflux.

Key words Choriocarcinoma · Hepatoid adenocarcinoma · Small cell carcinoma · Tubular adenocarcinoma · Oesophagus

Introduction

Primary carcinoma of the oesophagus is almost always squamous cell carcinoma. Although there are a few reports of choriocarcinoma or small cell carcinoma of the oesophagus, the presence of hepatoid adenocarcinoma has not been reported. We report a patient with choriocarcinoma, hepatoid adenocarcinoma, small cell carcinoma and tubular adenocarcinoma and discuss the possible histogenesis of this combined tumour.

T. Motoyama (✉)
Department of Pathology,
Yamagata University of School of Medicine,
Yamagata 990-23, Japan

M. Higuchi
Department of Pathology, Kaetsu Hospital,
Niitsu 956, Japan

J. Taguchi
Department of Internal Medicine, Kaetsu Hospital,
Niitsu 956, Japan

Case report

A 80-year-old woman (gravida 6, para 6) was admitted to Kaetsu Hospital because of appitite loss and general weakness. The menopause had occurred when she was 48 years of age. She had a history of cerebral infarction 6 years earlier. Radiographic and endoscopic examinations revealed a tumour with an ulcer in the lower oesophagus, which on biopsy showed features of undifferentiated carcinoma. Since radiographic examination disclosed distant metastases to the liver and lungs the patient underwent anti-cancer chemotherapy with bleomycin. However, she died of multiple liver and lung metastases approximately 2 months after admission. Serum levels of human chorionic gonadotropin (hCG) and alpha fetoprotein (AFP) were not assayed during life.

Pathological observations

Gross autopsy description

The ulcerative localized tumour in the lower intra-thoracic and abdominal oesophagus measured 6×3 cm. Cut surfaces showed two different features, a haemorrhagic brown area and a whitish yellow area (Fig. 1). Submucosal tumours with occasional luminal exposure were also observed in the stomach. There were multiple haemorrhagic masses in the liver, which were up to 8 cm in diameter, and in the lungs, which were up to 2 cm in diameter. It was confirmed that there were no tumours in the uterus, ovaries, or retroperitoneal or mediastinal areas.

Microscopic findings

The haemorrhagic brown area was composed of choriocarcinoma (Fig. 2A). The whitish yellow area contained hepatoid adenocarcinoma (Fig. 2B), small cell carcinoma (Fig. 2C) and tubular adenocarcinoma (Fig. 2D). Argyro-

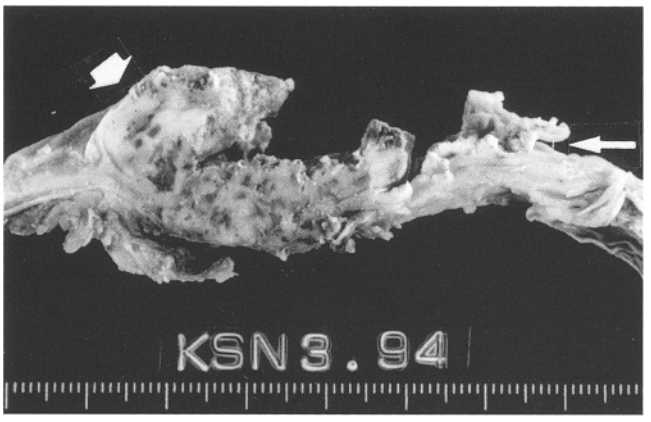

Fig. 1 Cut surface of the oesophageal tumour showed two different macroscopic features, a, haemorrhagic brown area and a whitish yellow area. The *short arrow* indicates the oesophagogastric junction, and the *long arrow* indicates site of epithelium shown in Fig. 3

philic cells were detected by Grimelius' method in the small cell carcinomatous foci. Non-neoplastic gastric-type columnar epithelium with intestinal metaplasia was found on the oral side of the tumour (Fig. 3). There were no features of typical yolk sac tumour in any area. All lesions in the stomach, liver and lungs showed the features of pure choriocarcinoma.

Immunohistochemical findings

The results of immunohistochemical examinations are summarized in Table 1. The choriocarcinomatous foci contained cells positive for β-hCG, human placental lactogen (hPL), pregnancy-specific β1-glycoprotein (SP1) and placental alkaline phosphatase (PLAP). Although β-hCG was detected in both syncytiotrophoblastic cells and cytotrophoblastic cells, the former were more frequently positive for the antigen than the latter (Fig. 4A). The hepatoid adenocarcinomatous foci contained not only AFP-positive cells (Fig. B), but also alpha-1 antitrypsin (AAT)-, albumin (ALB)-, prealbumin (PLAB)- and transferrin (TF)-positive cells. The small cell carcinomatous foci contained occasional chromogranin-positive cells (Fig. 4C) or synaptophysin-positive cells. A few small cell carcinoma cells reacted with anti-serotonin mouse monoclonal antibody or anti-adrenocorticotrophic hormone (ACTH) rabbit polyclonal antibody (both from Dakopatts) (Fig. 4D). Neuron-specific enolase (NSE) was not detected. Carcinoembryonic antigen

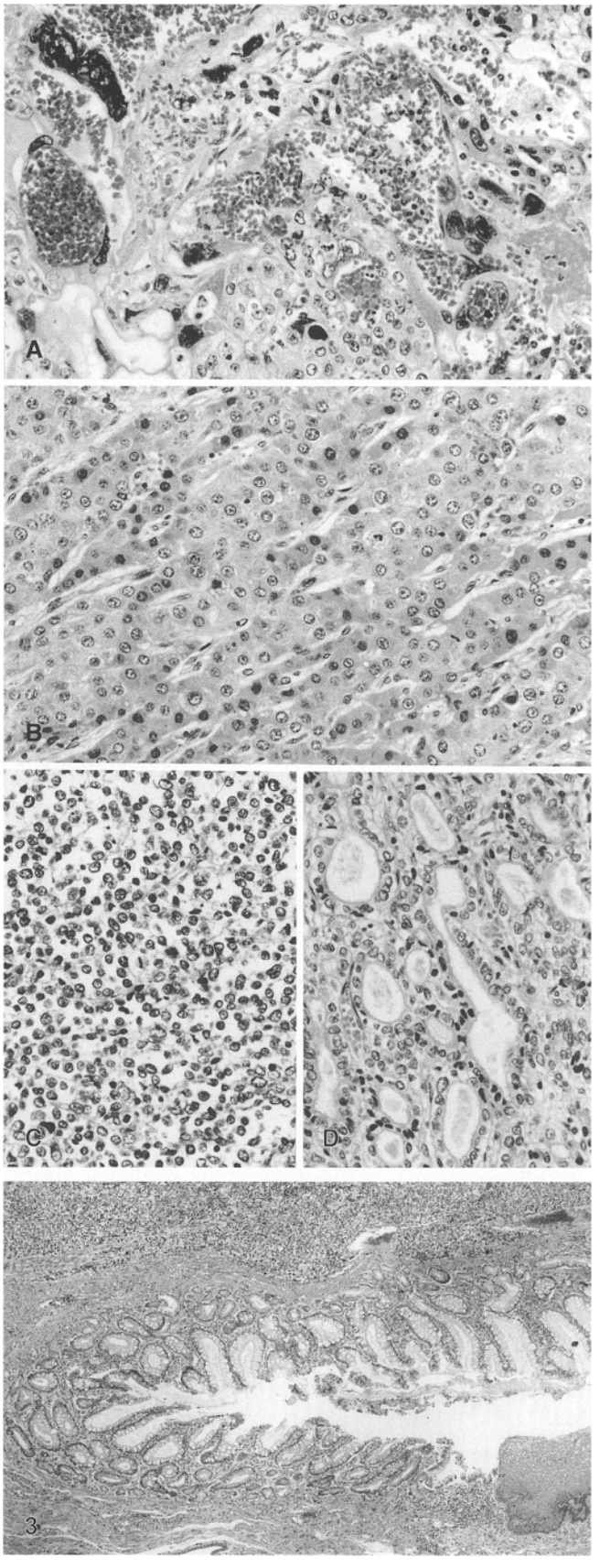

Fig. 2 **A** Choriocarcinomatous focus composed of cytotrophoblastic and syncytiotrophoblastic cells. **B** Hepatoid adenocarcinomatous focus showing trabecular arrangement. **C** Small cell carcinomatous focus with solid glowth. **D** Tubular adenocarcinomatous focus. ×175

Fig. 3 Gastric-type columnar epithelium found at the oral side of the tumour indicated by the long arrow in Fig. 1. ×30

Table 1 Immunohistochemical findings for placental, hepatic and neuroendocrine markers and carcinoembryonic antigen[a] (*β-hCG* β-human chorionic gonadotropin, *hPL* human placental lactogen, *SP1* pregnancy-specific β_1-glycoprotein, *PLAP* placental alkaline phosphatase, *AFP* α-fetoprotein, *AAT* α_1-antitrypsin, *ALB* albumin, *PALB* prealbumin, *TF* transferrin, *CHR* chromogranin, *SYN* synaptophysin, *NSE* neuron-specific enolase, *CEA* carcinoembryonic antigen, – no positive cells, + a few positive, <1% of cells, ++ occasional positive, 1–10% of cells, +++ frequently positive, >10% of cells)

Foci of:	Placental marker				Hepatic marker					Neuroendocrine marker			CEA
	β-hCG	hPL	SP1	PLAP	AFP	AAT	ALB	PLAB	TF	CHR	SYN	NSE	
Choriocarcinoma	+++	+	+	++	–	–	–	–	–	–	–	–	–
Hepatoid adenocarcinoma	–	–	–	–	++	+	+	+	+	–	–	–	–
Small cell carcinoma	–	–	–	+	–	–	–	–	–	++	+	–	–
Tubular adenocarcinoma	–	–	–	+	–	–	–	–	–	–	–	–	++

[a] Anti-β-hCG mouse monoclonal antibody, anti-CHR rabbit polyclonal antibody and anti-CEA mouse monoclonal antibody were obtained from Nichirei (Tokyo, Japan), ICN (Stillwater, MN) and Mochida (Tokyo, Japan), respectively. Anti-hPL, SP1, PLAP, AAT, ALB, PLAB, TF and SYN rabbit polyclonal antibodies and anti-AFP goat polyclonal antibody were obtained from Dakopatts (Copenhagen, Denmark). All immunoperoxidase studies were performed using streptavidin biotin-peroxidase complex system (Nichirei)

(CEA) was detected only in the tubular adenocarcinomatous foci. A few PLAP-positive cells were also detected in the small cell carcinomatous and tubular adenocarcinomatous foci.

Discussion

Primary tumours of the upper gastrointestinal tract showing trophoblastic differentiation or hepatoid differentiation are rare. Most have been reported as arising in the stomach [5, 6, 11, 15]. To the best of our knowledge, only five choriocarcinomas have been documented as arising in the oesophagus [7, 10, 16, 17, 19], but primary hepatoid adenocarcinoma of the oesophagus has not been reported. Primary small cell carcinomas are known to arise in either the stomach or the oesophagus, although they are also rare [8, 9]. It is well known that the choriocarcinomas, hepatoid adenocarcinomas and small cell carcinomas readily metastasize to distant organs and usually carry a poor prognosis. Recently, we reported the first case of combined choriocarcinoma and hepatoid adenocarcinoma in the stomach [12]. Such a combination has not previously been found in the oesophagus.

Some authors suggest that primary oesophageal choriocarcinomas arise in an adenocarcinoma in Barrett's oesophagus [10, 19]. Two of the previously reported cases of primary oesophageal choriocarcinoma were the pure type [7, 17]. In such pure cases, the common adenocarcinomatous components may have been expelled by the more aggressive choriocarcinomatous components. We must also pay attention to the cardia or the oesophageal glands as possible origin for the present tumour. However, only gastric foveolar and intestinal metaplastic epithelia were seen directly adjacent to the tumour, and the tubular adenocarcinomatous foci contained cells positive for alcian blue stain. These findings suggest that the tubular adenocarcinomatous component is related to intestinal metaplasia. Our previous investigations also suggested that hepatoid adenocarcinomas and choriocarcinomas represent aberrant differentiation in common adenocarcinomas in the stomach [11, 12]. Moreover, our experimental study using cultured small cell carcinoma cell lines suggest that some gastrointestinal small cell carcinomas derive from aberrant differentiation of common adenocarcinoma [2]. Such small cell carcinomas usually express low levels of NSE [2]. In our case, small cell carcinomatous foci bordered on adenocarcinomatous foci, and, we consider that the present small cell carcinoma was also derived from an adenoarcinoma.

Garcia and Ghali [3] speculated on the possibility of retrodifferentiation of neoplastic mucosal epithelial cells in their case of coexistent choriocarcinoma and yolk sac tumour in the stomach. However, yolk sac tumours are known to show hepatoid differentiation occasionally [14, 18]. The complete absence of the common features of yolk sac tumour suggests that in the present case hepatoid tumour tissues were not derived from differentiation of a yolk sac tumour.

Since non-neoplastic gastrointestinal-type columnar epithelium was directly adjacent to the lesion in the present case, it is likely that our patient had a combined choriocarcinoma, hepatoid adenocarcinoma and small cell carcinoma arising in an adenocarcinoma, which may have complicated long-standing Barrett's oesophagus. Barrett's oesophagus is implicated as a precursor of oesophageal adenocarcinoma [1, 13].

Although effective regimens have not yet been established for hepatoid adenocarcinomas, choriocarcinomas and small cell carcinomas each demand a specific regimen [4, 19]. Multiple site sampling during biopsy examination is important for selection of therapy.

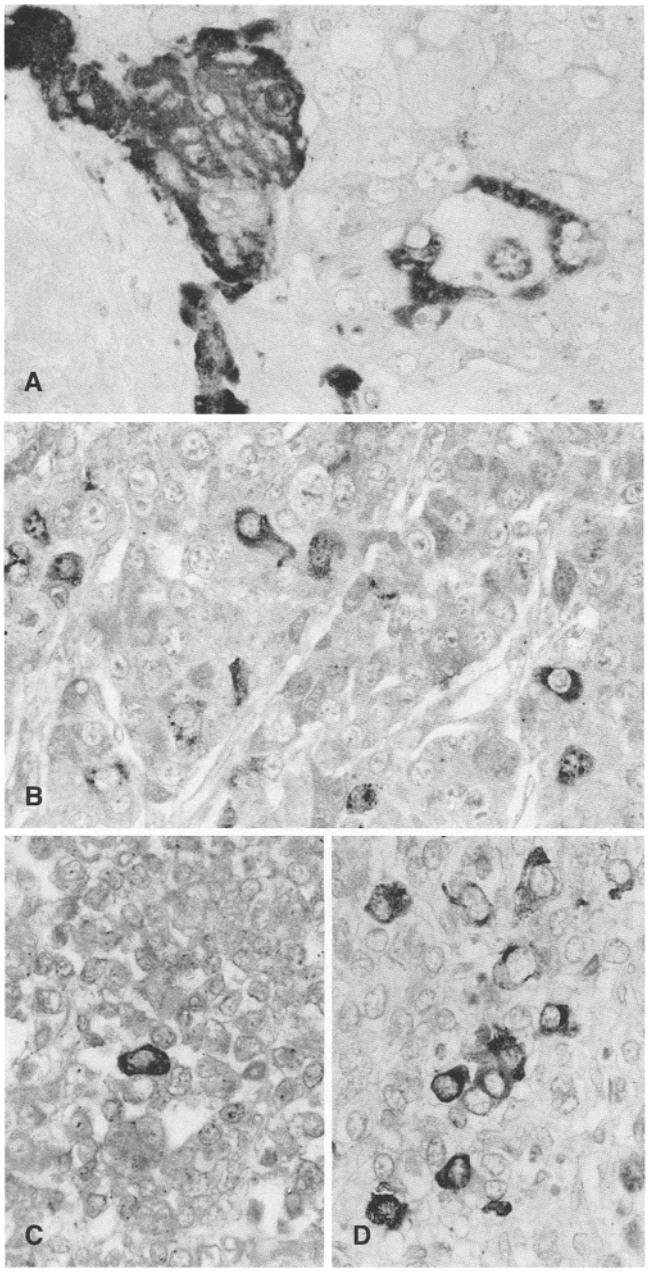

Fig. 4A–D Immunohistochemical staining. **A** Choriocarcinomatous focus stained with anti-β-hCG antibody; **B** hepatoid adenocarcinomatous focus stained with anti-AFP antibody. **C, D** Small cell carcinomatous foci stained with **C** anti-chromogranin or **D** anti-ACTH antibody. Methylgreen counterstain, ×350

References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr (1991) Rising incidence of adenocarcinoma of the eosphagus and gastric cardia. JAMA 265:1287–1289
2. Fujiwara T, Motoyama T, Ishihara N, Watanabe H, Kumanishi T, Kato K, Ichinose H, Nagatsu T (1993) Characterization of four new cell lines derived from small-cell gastrointestinal carcinoma. Int J Cancer 54:965–971
3. Garcia RL, Ghali VS (1985) Gastric choriocarcinoma and yolk sac tumor in a man. Observation about its possible origin. Hum Pathol 16:955–958
4. Hussein AM, Feun LG, Sridhar KS, Benedetto P, Waldman S, Otrakji CL (1990) Combination chemotherapy and radiotherapy for small-cell carcinoma of the esophagus. A case report of long-term survival and review of the literature. Am J Clin Oncol 13:369–373
5. Ishikura H, Kurimoto K, Shamoto M, Miyamoto Y, Yamagiwa H, Ito T, Aizawa M (1986) Hepatoid adenocarcinoma of the stomach. An analysis of seven cases. Cancer 58:119–126
6. Jindrak K, Bochetto JF, Alpert LI (1976) Primary gastric choriocarcinoma: case report with review of world literature. Hum Pathol 7:595–604
7. Kikuchi Y, Tsuneta Y, Kawai T, Aizawa M (1988) Choriocarcinoma of the esophagus producing chorionic gonadotropin. Acta Pathol Jpn 38:489–499
8. Law S Y-K, Fok M, Lam K-Y, Loke S-L, Ma LT, Wong J (1994) Small cell carcinoma of the esophagus. Cancer 73:2894–2899
9. Matsui K, Kitagawa M, Miwa A, Kuroda Y, Tsuji M (1991) Small cell carcinoma of the stomach: a clinicopathologic study of 17 cases. Am J Gastroenterol 86:1167–11775
10. McKechnie JC, Fechner RE (1971) Choriocarcinoma and adenocarcinoma of the esophagus with gonadotropin secretion. Cancer 27:694–7021
11. Motoyama T, Aizawa K, Watanabe H, Fukase M, Saito K (1993) Alpha-fetoprotein-producing gastric carcinomas: a comparative study of three different subtypes. Acta Pathol Jpn 43:654–661
12. Motoyama T, Aizawa K, Fujiwara T, Endoh Y, Watanabe H (1994) Coexistence of choriocarcinoma and hepatoid adenocarcinoma in the stomach. Pathol Int 44:716–721
13. Potet F, Flejou JE, Gervaz H, Paraf F (1991) Adenocarcinoma of the lower esophagus and the esophagogastric junction. Semin Diagn Pathol 8:126–136
14. Prat J, Bhan AK, Dickersin GR, Robboy SJ, Scully RE (1982) Hepatoid yolk sac tumor of the ovary (endodermal sinus tumor with hepatoid differentiation). A light microscopic, ultrastructural and immunohistochemical study of seven cases. Cancer 50:2355–2368
15. Saigo PE, Brigati DJ, Sternberg SS, Rosen PP, Turnbull AD (1981) Primary gastric choriocarcinoma. An immunohistological study. Am J Surg Pathol 5:333–342
16. Sasano N, Abe S, Satake O, Endo K, Satoh M, Yamazaki M (1970) Choriocarcinoma mimicry of an esophageal carcinoma with urinary gonadotropic activities. Tohoku J Exp Med 100:153–163
17. Trillo AA, Accettullo LM, Yeiter TL (1979) Choriocarcinoma of the esophagus: histologic and cytologic findings. A case report. Acta Cytol 23:69–74
18. Ulbright TM, Roth LM, Brodhecker CA (1986) Yolk sac differentiation in germ cell tumors. A morphologic study of 50 cases with emphasis on hepatic tissue, enteric, and parietal yolk sac features. Am J Surg Pathol 10:151–164
19. Wasan HS, Schofield JB, Krausz T, Sikora K, Waxman J (1994) Combined choriocarcinoma and yolk sac tumor arising in Barrett's esophagus. Cancer 73:514–517