Resection of a Submucosal Tumor-Like Superficial Carcinoma in Middle Thoracic Esophagus Concomitant with Mucosal Adenocarcinoma and Submucosal Squamous Cell Carcinoma: A Case Report and Review of Literature

Soichiro YAMAMOTO[*1], Nobue KUMAKI[*2], Hiroyasu MAKUUCHI[*1], Soji OZAWA[*1], Hideo SHIMADA[*1], Osamu CHINO[*1], Akihito KAZUNO[*1], Seiei YASUDA[*1], Takaaki TAMAYAMA[*3] and Izumi SAKAI[*3]

[*1]*Department of Surgery, Tokai University School of Medicine*
[*2]*Department of Pathology, Tokai University School of Medicine*
[*3]*PL Tokyo Health Care Center*

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A 67-year-old man was pointed out mucosal irregularity on health check-up and was referred to our institution. Diagnostic examinations were performed and an aggregated type 0-IIa lesion having 3 small protrusions was recognized in the middle thoracic esophagus. Endoscopic biopsy led to diagnosis of esophageal cancer concomitant with adenocarcinoma and squamous cell carcinoma. Thoracic esophagectomy with 3-fields lymph node dissection was performed via a right thoracoabdominal approach and reconstructed with stomach roll. Three submucosal tumors like small protrusions were recognized in resected specimen. One of them was well differentiated tubular adenocarcinoma which occupied in mucosal layer. The other two were moderately differentiated squamous cell carcinoma. They existed very near but no connection was recognized by serial section. The adenocarcinoma existing in middle esophagus is very rare. Almost all of them were submucosal or advanced cancers. When we searched with the ICHUSHI database (a domestic medical literature database service provided by the NPO Japan Medical Abstracts Society) and the PubMed database, there was no report of mucosal adenocarcinoma occurred in middle thoracic esophagus in the past 10 years. Then this report was thought to be the first report of mucosal adenocarcinoma in middle thoracic esophagus in the world.

Key words: Primary esophageal adenocarcinoma, thoracic esophagus, esophageal gland duct, mucosal adenocarcinoma

INTRODUCTION

Squamous cell carcinomas are the most common esophageal cancers found in Japanese patients, and adenocarcinomas account for only 5.0% of cases. With the exception of Barrett esophageal cancer, which has attracted attention recently and other esophageal adenocarcinoma occurred in middle and upper thoracic esophagus is very rare [1].

Here we report a case of mucosal adenocarcinoma occurred in middle thoracic esophagus, comprised of coexisting submucosal squamous cell carcinoma.

CASE REPORT

A 67-year-old man was pointed out an esophageal mucosal irregularity in middle thoracic esophagus on health check-up in July 2008. Endoscopic examination was performed, and an aggregation of three submucosal tumors like nodes of about 5 mm in size was identified in the middle thoracic esophagus. The patient was diagnosed with squamous cell carcinoma by biopsy, and referred to TOKAI University Hospital.

Past medical history: Not particular.

Physiological findings on admission: Not particular.

Blood test findings: No remarkable findings, including tumor markers such as CEA, SCC, and CYFRA (Table 1), were observed.

Esophagographic findings: One small protruding lesion (5 mm in size) and two small protruding lesions (4 mm in size) were identified in the middle thoracic esophagus. The surface was smooth with a mild depression in the center (Fig. 1a and 1b, arrows).

Endoscopic findings: An aggregation of three small protrusion resembling type 0-IIa cancer was found in the left wall, at 35 to 37 cm from the incisors [2]. The elevation showed partial erosion at the top of an elevated lesion and resembled a sub-epithelial growth (Fig. 2a). Double staining with toluidine blue and iodine was performed, and the eroded surface was stained with toluidine blue. Slight depression was also observed in the region between the elevations (Fig. 2b). Neither Barrett mucosa nor ectopic gastric mucosa was found in the surrounding of the protruded lesions. Histopathological view of biopsy from lesion c was arranged in tubular pattern (Fig. 2c), and lesion d was arranged in sheet like pattern (Fig. 2d).

Thoraco-abdominal CT findings: No mediastinal lymph node swelling or distant metastasis was observed.

Based on these findings, the patient was diagnosed

Soichiro YAMAMOTO, Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-93-2659 E-mail: soichiro@is.icc.u-tokai.ac.jp

Table 1 Laboratory data

WBC	6300 mm^3	T-Cho	229 mg/dl
RBC	4.19 $x10^4$ mm^3	BUN	12 mg/dl
Hb	14.3 g/dl	Cre	0.9 mg/dl
Ht	42.7 %	Na	142 mEq/l
Plt	18.2 $x10^6$ mm^3	K	4.0 mEq/l
		Cl	106 mEq/l
TP	7.9 g/dl		
Alb	4.7 g/dl		
T-Bil	0.7 mg/dl		
GOT	13 IU/l		
GPT	6 IU/l	CEA	3.4 ng/ml
LDH	191 IU/l	SCC	1.9 ng/ml
γ-GTP	21 IU/l	CYFRA	< 1.0 ng/ml

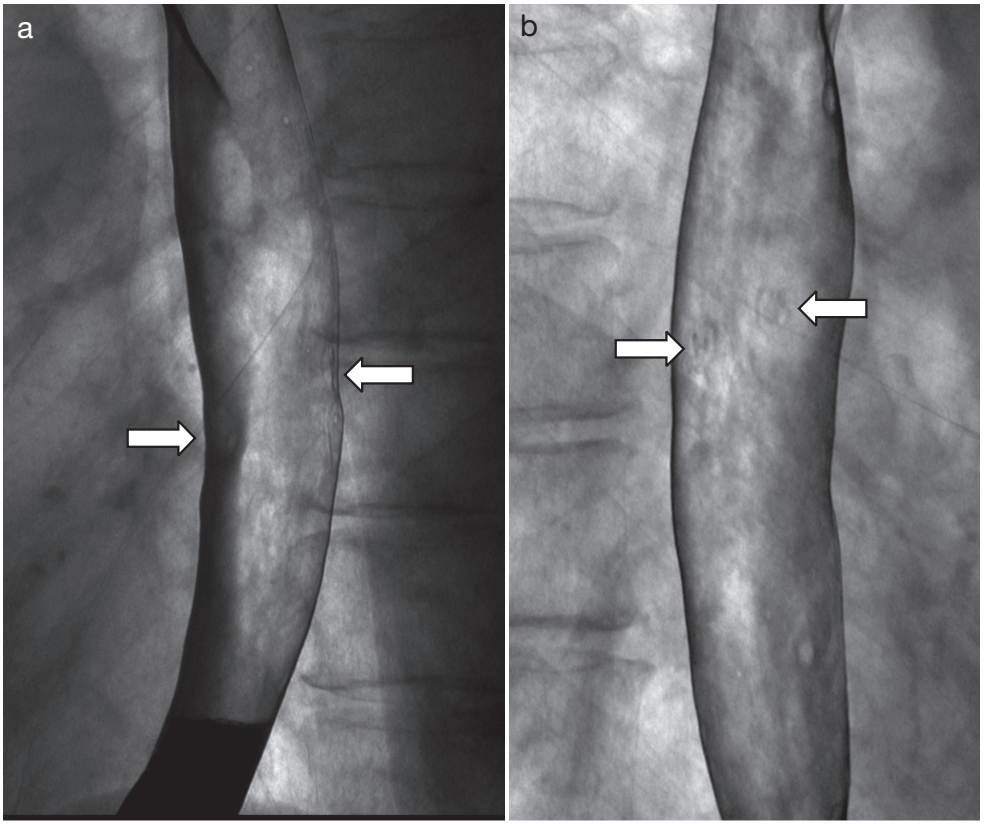

Fig. 1 Barium double contrast study.
a: Profile view. The irregular line was demonstrated in thoracic esophagus.
b: Enface view. A protruding tumor with a smooth surface and central depression was observed.

with esophageal cancer (adenocarcinoma and squamous cell carcinoma) with a macroscopic type of 0-IIa, cT1b-SM1, N0, M0, clinical stage I [2]. In October 2008, the patient underwent surgical treatment consisting of right transthoracic subtotal esophagectomy, three-field lymph node dissection from cervix, mediastinum and abdomen, and reconstruction of esophagus using stomach roll. The patient had a good postoperative course without complications, and he was discharged on hospital day 23.

Pathological diagnosis: The resected esophagus was cut into approximately every 5-mm width; an examination of these pieces found adenocarcinoma and squamous cell carcinoma (Fig. 3a, b). For evaluation of the extent of the cancer and the continuity of the adenocarcinoma and squamous cell carcinoma, we examined HE (Hematoxylin Eosin) serial sections every 40-μm-point. Examination of the sections confirmed fibrous scar tissue between the adenocarcinoma and squamous cell carcinoma, indication the absence of continuity (Fig 3d–g). The moderate differentiated squamous cell carcinoma was present with an invasion depth of pT1b-

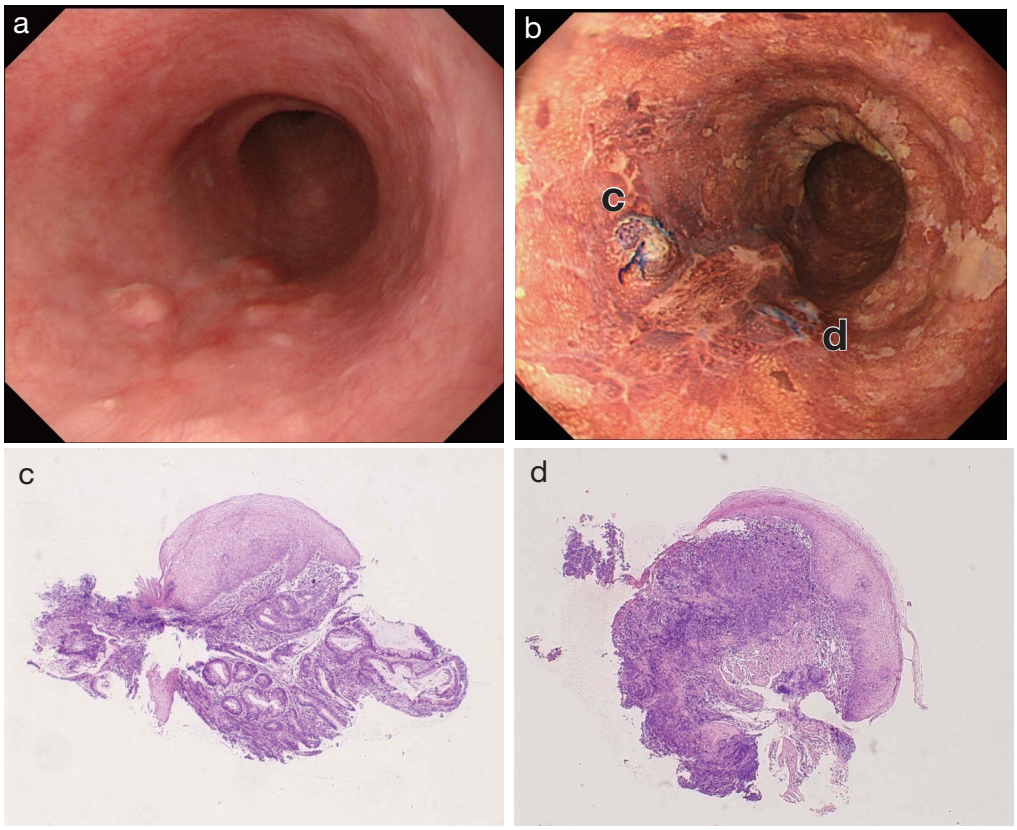

Fig. 2 Endoscopic findings and histopathological findings of biopsy specimens.
a: Conventional endoscopic view. The three slightly elevated protruding lesion were noted.
b: Double staining view. The top of protruding lesion was stained by toluidine.
c: Histopathological view of biopsy from lesion c. Carcinoma cells arranged in tubular pattern were noted in lamina propria.
d: Histopathological view of biopsy from lesion d. Carcinoma cells arranged in sheet-like pattern were seen.

SM2 (Fig. 3d). The well differentiated adenocarcinoma was covered by non-neoplastic stratified squamous epithelium. The adenocarcinoma cells grew mainly in the lamina propria and partly extended to the muscularis mucosa (Fig 3g). Regional lymph node metastasis was identified in 2 of 76 dissected specimens (No.106rR and No.108 lymph node), and the node metastasis stage was pN1. Both nodes contained squamous cell carcinoma and no metastasis of adenocarcinoma. Final findings were recorded as the coexistence of mucosal adenocarcinoma pT1a-MM and, superficial squamous cell carcinoma pT1b-SM2, N1a, M0, pathological stage II [2].

Post-operative adjuvant chemotherapy with 2 courses of cisplatin and 5-fluorouracil was administered. The patient is alive now, 6 years and 10 months after surgery without recurrence.

DISCUSSION

The patient had coexisting, multiple esophageal cancers; mucosal esophageal adenocarcinoma and squamous cell carcinoma of a sub-epithelial growth. According to the comprehensive registry of esophageal cancer in Japan, adenocarcinoma and Barrett esophageal cancer were pathologically identified in 3.3% and 1.7%, respectively, of resected specimens [1].

Reports of adenocarcinoma occurred in esophagus were searched in the ICHUSHI database from 2005 to 2014. About 450 reports were investigated and almost all of them were about Barrett adenocarcinoma. Reports of primary adenocarcinoma occurred in middle thoracic and upper esophagus were only 16 reports and 16 cases. Furthermore, 9 cases were superficial cancer and remain 7 cases were advanced. Seven cases were existed in middle thoracic esophagus, which were considered to be derived from proper esophageal gland. Within them superficial cancer were three cases [3–5] and advanced cancer were four cases [6–9]. There were 9 cases existed upper esophagus, which were considered to be chiefly derived from ectopic gastric mucosa, superficial cancer were six cases [10–15], and advanced cancer were three cases [16–18]. No report of mucosal adenocarcinoma occurred in middle and upper thoracic esophagus could be discovered in the PubMed database going back to 10 years.

Adenocarcinomas in middle esophagus tend to show sub-epithelial growth, because the adenocarcinomas are considered to develop from the esophageal glands and its ducts [19]. Esophageal adenocarcinoma may originate from 1) ectopic gastric mucosa, 2) proper esophageal gland, 3) cardiac gland of the esophagus, and 4) Barrett esophagus. Ectopic gastric mucosa is frequently found in the cervical esophagus immediately below the esophageal orifice, while the esophageal cardiac gland and Barrett esophagus are often present in the abdominal esophagus and distal part of lower thoracic esophagus. Therefore, these types of adenocarcinomas can be diagnosed based on the location

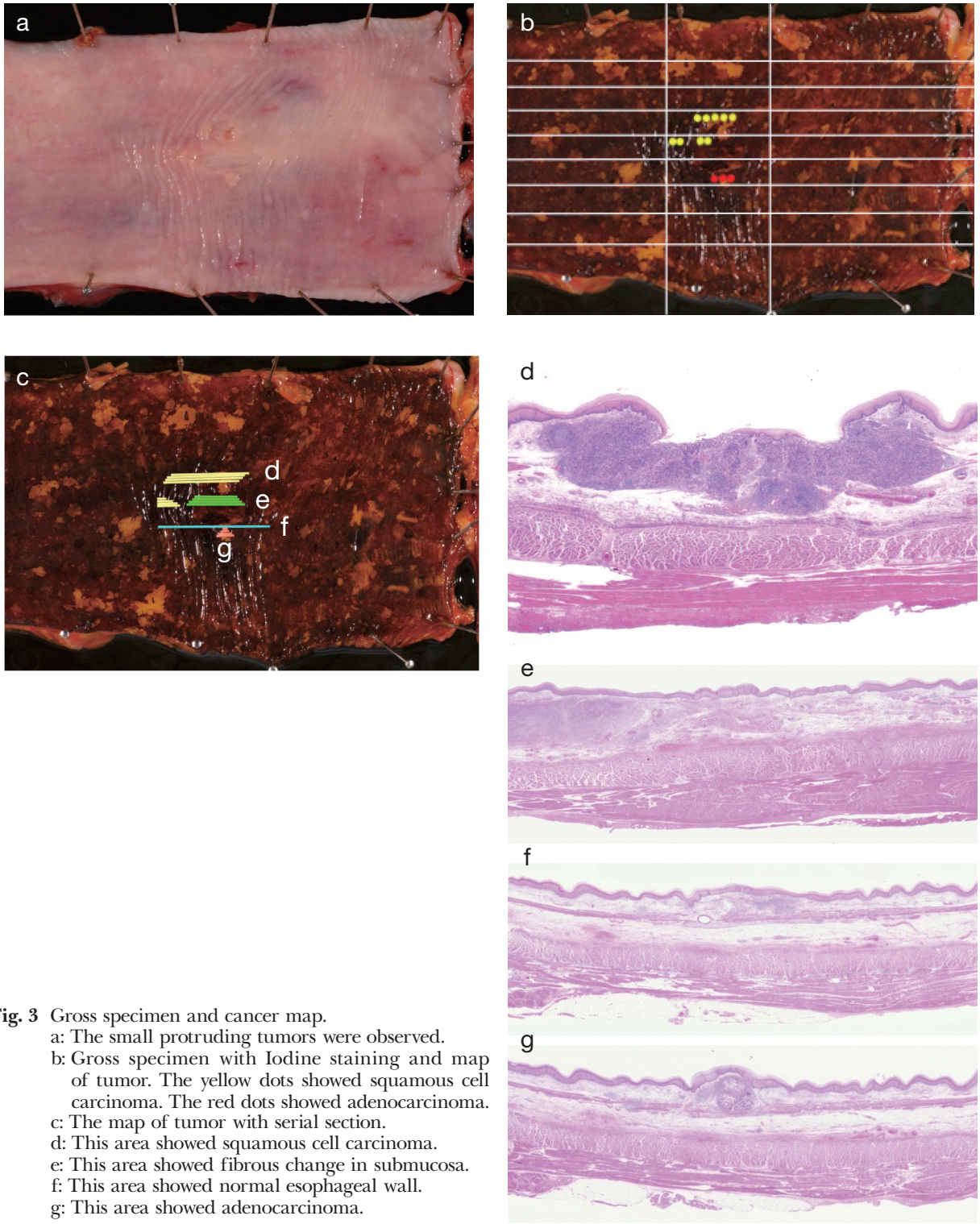

Fig. 3 Gross specimen and cancer map.
a: The small protruding tumors were observed.
b: Gross specimen with Iodine staining and map of tumor. The yellow dots showed squamous cell carcinoma. The red dots showed adenocarcinoma.
c: The map of tumor with serial section.
d: This area showed squamous cell carcinoma.
e: This area showed fibrous change in submucosa.
f: This area showed normal esophageal wall.
g: This area showed adenocarcinoma.

and surrounding mucosa [16]. The adenocarcinoma of this case was chiefly occupied the proper mucosal layer. The tumor attached to muscularis mucosa and mucosae epithelium partly. Then we considered that this adenocarcinoma occurred from duct of proper esophageal gland which passed through proper mucosal layer, or malignant transformation of basal cells of esophageal epithelium.

We performed a histopathological examination of the resected specimens to identify their origin. The adenocarcinoma was present mainly in the lamina propria and was covered by non-neoplastic squamous epithelium (Fig. 4a). There was no adenosquamous carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. No proper esophageal gland was observed around the periphery of the adenocarcinoma, and a gland duct was present slightly apart from the adenocarcinoma (Fig. 4a, arrowhead). In addition, only a small portion of the adenocarcinoma was in contact with the squamous basal layer; however, the continuity was not clear (Fig. 4b, arrow).

The adenocarcinoma specimen was immunohisto-

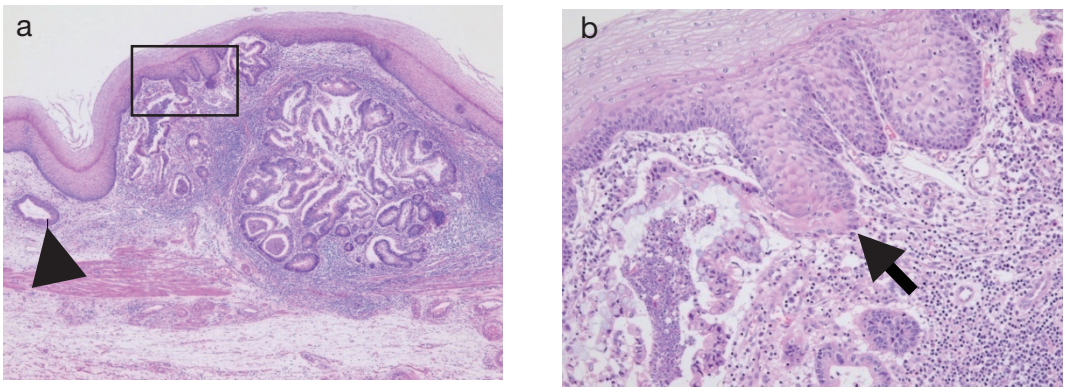

Fig. 4 Histopathological section of adenocarcinoma.
a: Middle power view of adenocarcinoma located lamina propria mucosa. The esophageal gland duct was observed near adenocarcinoma (Arrowhead).
b: The adenocarcinoma was in slightly contacted with squamous basal layer (Arrow).

Table 2 Immunohistochemical expression patterns of squamous epithelium, duct and adenocarcinoma.

	Squamous epithelium	Duct		Adenocarcinoma
		Basal cells	Luminal cells	
MUC2	-	-	-	+
MUC5AC	-	-	-	+
MUC6	-	-	-	-
CDX2	-	-	+	+
PAS	+	-	+	+
CK18	-	-	+	+
CAM5.2	-	-	+	+
CK19	-	-	+	+
CK14	+	+	-	+
p63	+	+	-	+
CK5/6	+	+	+	+
CK34βE12	+	+	+	-
CK7	-	-	+	+
CK20	-	-	-	+

chemical stained for mucin (MUC) and PAS-stained for phenotypic comparison of the squamous epithelium over the adenocarcinoma with the duct located near the cancer (Table 2). The squamous epithelium and all of the layers of the duct were negative for all phenotypes of mucins. The adenocarcinoma was positive for MUC2 and MUC5AC and negative for MUC6. The adenocarcinoma and the duct lumen were positive for CDX2. PAS was positive in squamous epithelium, the duct lumen, and the adenocarcinoma (Fig. 5). Based on these results, the adenocarcinoma seemed to have both gastric and intestinal phenotypes [20]. Using cytokeratin staining, we determined that CK18, CAM5.2 and CK19, the markers of columnar epithelium, were negative in the duct basal layer but positive in the duct lumen and the adenocarcinoma (Fig. 6). In addition, CK14 and p63 staining, which are markers for the squamous epithelium basal layer, were negative in duct lumen, but positive in duct basal cells, squamous epithelium and adenocarcinoma [21]. The markers for squamous epithelium, CK5/6, were positive in all specimens, while CK34ßE12 was negative only in the adenocarcinoma. CK7 was positive in the adenocarcinoma and the duct lumen, and CK20 was positive only in the adenocarcinoma (Fig. 7). The staining pattern of the adenocarcinoma was different from that of the squamous epithelium basal layer, was similar to the pattern found in the duct lumen (Table 2). These findings suggest that the adenocarcinoma was not likely to have originated from glandular metaplasia of the squamous epithelium.

There is a report of close histological examination of duct-derived esophageal adenoma that was present in the submucosal layer with cytokeratin and mucin phenotypes resembling those of a non-neoplastic duct [22]. The esophageal gland duct was positive for CK14, CK19, CK7, CK8, CK18 and CK20 immunohistochemical staining, resembling the patterns in the normal squamous epithelium and multilayered epithelium [23]. The presence of multilayered epithelium is considered an early-stage feature of Barrett mucosa [24].

On the basis of results of the immunohistochemical staining, the adenocarcinoma in our patient likely developed from a duct of proper esophageal gland.

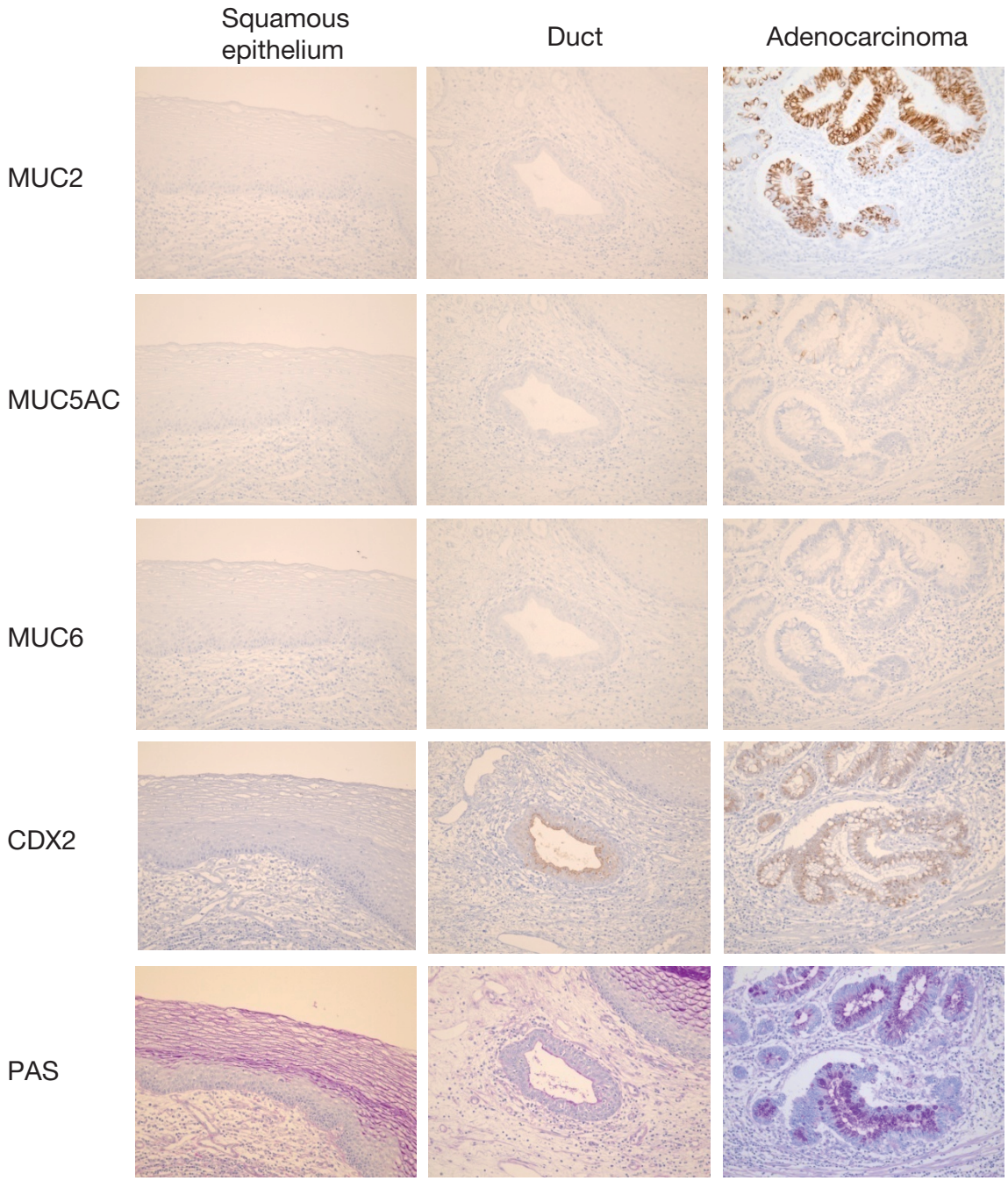

Fig. 5 Immunohistochemical expression of MUCs, CDX2 and PAS staining.
High-power view of immunohistochemical expressions (MUC2, MUC5AC, MUC6, CDX2) and PAS staining with squamous epithelium, adenocarcinoma and esophageal gland duct.

Another possibility includes the malignant transformation of undifferentiated pluripotent basal cells that reside in the normal esophageal epithelium, but we could not find sufficient evidence for this possibility in the present study.

CONCLUSION

We encountered the very rare case which developed mucosal adenocarcinoma and superficial squamous cell carcinoma next to each other in middle thoracic esophagus. No report of mucosal adenocarcinoma occurred in middle thoracic esophagus could be searched in neither the ICHUSHI database nor the PubMed database. Although histopathological and immunohistochemical examinations were performed, the origin of the carcinogenesis of the adenocarcinoma could not be clarified.

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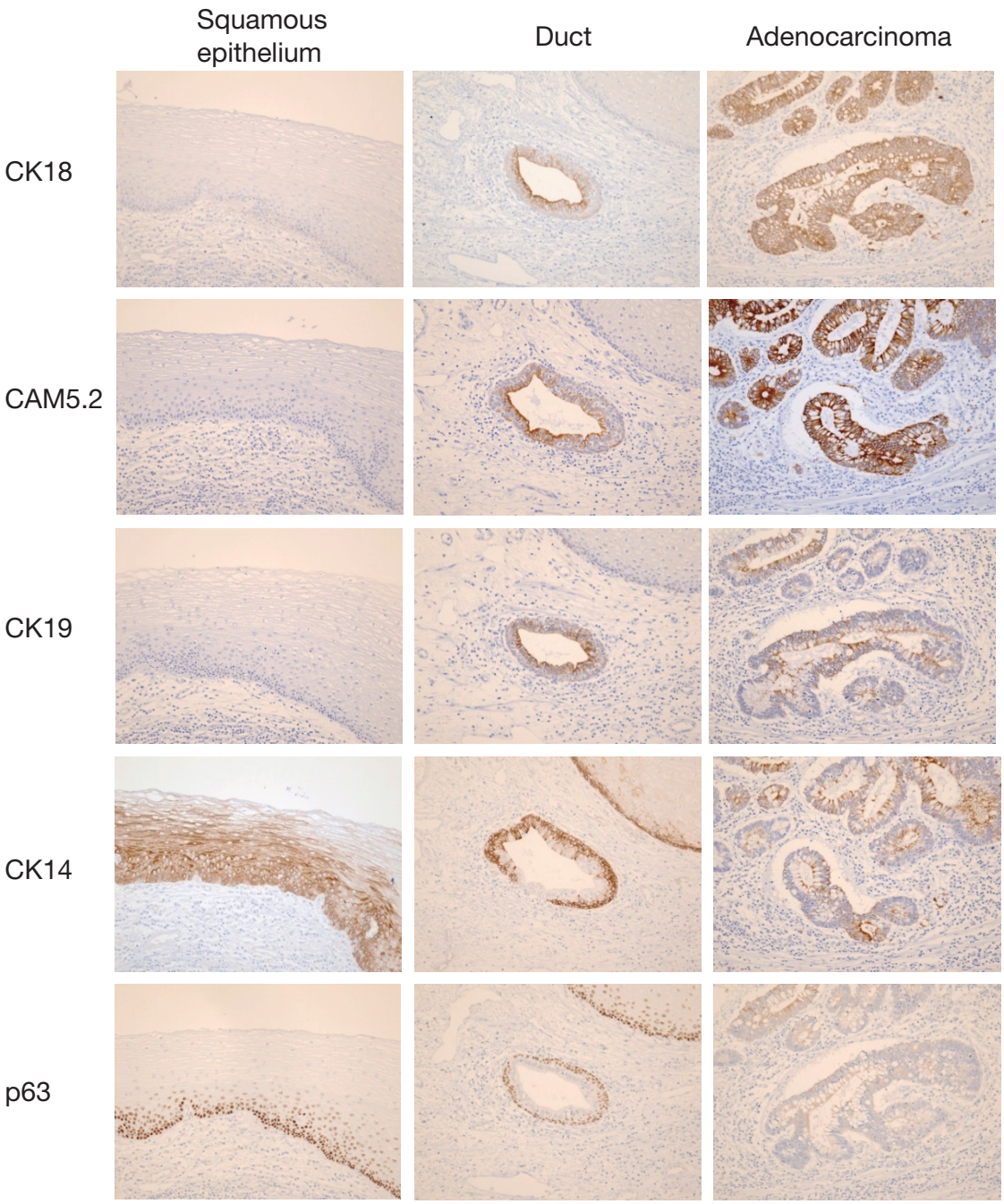

Fig. 6 Immunohistochemical expression of cytokeratins and p63.
High-power view of immunohistochemical expression (CK18, CAM5.2, CK19, CK14, p63) in squamous epithelium, adenocarcinoma and esophageal gland duct.

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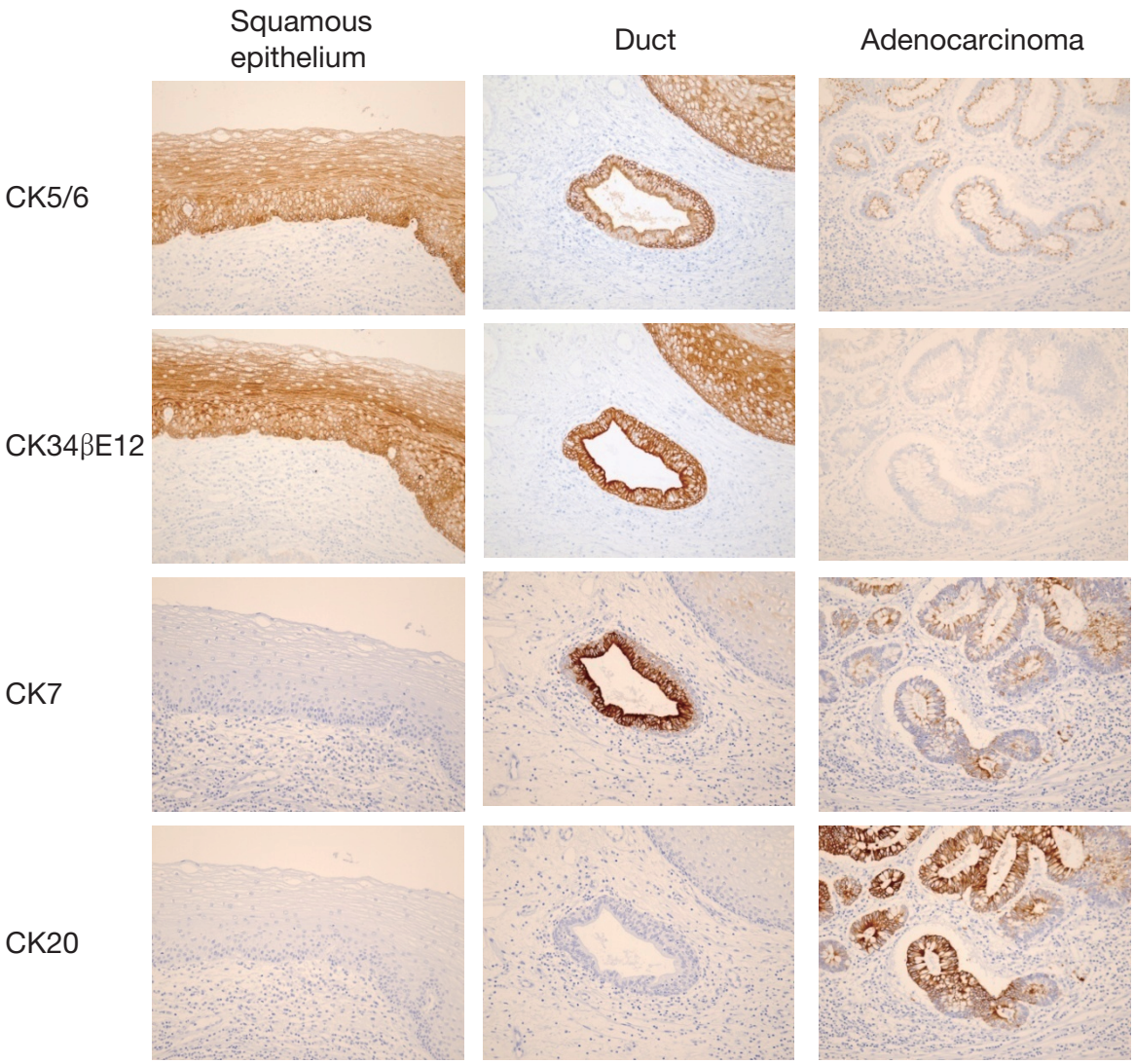

Fig. 7 Immunohistochemical expression of cytokeratins.
High-power view of immunohistochemical expressions (CK5/6, CK34βE12, CK7, CK20) in squamous epithelium, adenocarcinoma and esophageal gland duct.

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