We describe a rare case of cervical esophageal adenocarcinoma originating from the esophageal gland. A 63-year-old man underwent endoscopic screening during a medical checkup, during which a type 2 tumor was incidentally detected in the cervical esophagus, which was confirmed as adenocarcinoma on biopsy. Endoscopic ultrasonography indicated that the tumor had invaded the muscularis propria layer. Computed tomography and 18F-fluorodeoxyglucose positron emission tomography imaging revealed neither lymphadenopathy nor distant metastasis. He was clinically diagnosed with T2N0M0, Stage II disease. He preoperatively received 2 courses of chemotherapy consisting of cisplatin (90mg/m²) on day 1 and 5-fluorouracil (900mg/m²) on days 1‒5. Esophagectomy with lymph node dissection was performed. Histopathological diagnosis showed well-differentiated tubular adenocarcinoma that probably originated from the ducts of the esophageal glands. The final diagnosis was T1bN0M0, Stage I disease. The postoperative course was uneventful. He was healthy without any recurrence 27 months after the surgery.

**Key words:** cervical esophagus, adenocarcinoma, esophageal gland

**Introduction**

Most primary adenocarcinomas of the esophagus are derived from Barrett’s epithelium and ectopic gastric mucosa [1,2]. Adenocarcinomas developing in the esophagus that were derived from other sources were rarely noted. Esophageal adenomas or adenocarcinomas originating from the esophageal glands have been reported in the literature [3‒5]. The esophageal glands are present in the submucosal layer, and their ducts penetrate the muscularis mucosae. These glands are also presumed to be the site for the origin of esophageal cancer. In the present report, we described a case of cervical esophageal adenocarcinoma that originated in the ducts of the esophageal glands.

**Case Report**

A 63-year-old man without any evident symptoms was found to have a tumor in his cervical esophagus, which was incidentally detected during esophageographic screening. He had no history of smoking or alcohol consumption, and was receiving treatment for hyperlipidemia and diabetes in an outpatient clinic. He was admitted to Shiga University of Medicine Science Hospital, Shiga, Japan, for further examination and treatment of the esophageal tumor. On physical examination, his physique was average (height, 160cm; weight, 56.9kg). No superficial lymph nodes were palpable. On laboratory blood examination, his carbohydrate antigen 19–9 level was elevated (65U/mL; normal range, 0–37U/mL), but his other biochemical data and blood counts were within normal range. Moreover, his squamous cell carcinoma antigen level and carcinoembryonic antigen were within normal ranges.
Upper gastrointestinal endoscopy indicated a type 2 tumor at a site 18 to 20 cm distal from the incisors (Fig. 1a). Barium esophagography revealed an elevated lesion with a diameter of approximately 2.3 cm on the left wall of the cervical esophagus (Fig. 2a). On histological examination of the biopsy specimens, this tumor was diagnosed as well-differentiated adenocarcinoma. An endoscopic ultrasonography indicated that the proximal lesion invaded the muscularis propria layer. On a computed tomography (CT) scan, a tumor displaying contrast enhancement was detected in the cervical esophagus, but no lymph node swelling was noted (Fig. 3a). On a positron emission tomography scan, a slight uptake with a standardized uptake value of 2.0 was detected in the cervical esophagus. We diagnosed the tumor as T2N0M0, Stage Ⅱ disease, according to the TNM staging system issued by the International Union Against Cancer.

Chemotherapy with 5-fluorouracil and cisplatin (FP) therapy was initiated preoperatively. The FP regimen consisted of cisplatin (90 mg/m²), administered as a 2-h continuous intravenous infusion on day 1, and 5-fluorouracil (900 mg/m²), administered as a continuous intravenous infusion on days 1-5 of a 28-day cycle. The patient developed Grade 2 hematological toxicity (neutrophil count, 600/m³), Grade 1 anorexia, and Grade 1 constipation, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Two courses of FP therapy were administered as scheduled. Responses were evaluated 2 courses after the initial administration of FP therapy using the response evaluation criteria in solid tumors guidelines. Upper gastrointestinal endoscopy showed that the tumor became a slightly depressed lesion (Fig. 1b). On esophagography, we noted that the tumor had become flat (Fig. 2b). A CT scan also confirmed the shrinkage of the tumor (Fig. 3b). The changes noted on these examinations after chemotherapy represented a partial response. Surgery was performed 38 days after administration of FP therapy. Subtotal esophagectomy and lymphadenectomy of the neck and upper mediastinum were performed with reconstruction by using a gastric tube for esophageal replacement through the posterior mediastinal route.

On macroscopic examination, the presence of a type 2 tumor (18 mm × 16 mm) adjacent to the proximal surgical margin was confirmed in the esophagus (Fig. 4a). Following microscopic examination, the tumor in the cervical esophagus was diagnosed as well-differentiated tubular adenocarcinoma invading the muscularis mucosa (m3) (Fig. 4b, c). The submucosal layer that the tumor existed in was replaced fibrosis (Fig. 4d). The tumor had a negative proximal surgical margin, and no evidence of lymphatic/venous invasion or lymph node metastases was noted. Table 1 shows the immunohistochemical staining characteristics for a normal esophagus and cancer tissue using cytokeratin (CK) antibodies, to evaluate tumor origin as described previously. These findings showed that this cancer tissue had the features of the ducts of the esophageal glands,
which is consistent with a previous case\(^3\). The postoperative course was uneventful, and the patient is currently healthy without any recurrence at 27 months after the surgery.

**Discussion**

We experienced a rare case of primary esophageal adenocarcinoma originating from the esophageal glands in the cervical esophagus. In Japan, approximately 90\% of cases of esophageal cancer are squamous cell carcinoma, and the incidence of adenocarcinoma is approximately 5\%\(^8\). Most esophageal adenocarcinomas originate from Barrett’s epithelium, and a case wherein the origin is not the Barrett’s epithelium were rarely noted\(^9\). The origins of primary adenocarcinoma of the esophagus include the true esophageal gland (deep gland), the esophagofundic gland (superficial gland), and heterotopic gastric mucosa\(^10\).

Endoh et al\(^3\) reported that anticytokeratin antibodies with selective reactivity can be used to define the origin of carcinomas. CK1, CK5, CK10,
CK14, and epithelial membrane antigen (EMA) are distributed in the duct of the esophageal gland, squamous epithelium, squamous cell carcinoma, and tumors originating from the duct of the esophageal gland, but negative reactivity is observed in the acinar gland\textsuperscript{11,12}. In previous cases, the immunophenotype of the duct of the esophageal gland was determined based on the reactivity with several antibodies. In the present case, similar reactivity expression patterns were noted between the cancerous gland and the duct of the esophageal gland, consistent with the findings from a previous report\textsuperscript{3}. No esophageal cardiac gland or ectopic gastric mucosa was observed surrounding the main tumor, and only the duct of the esophageal gland was observed. In addition, the tumor was shrunk, thus resulting in a change of the muscularis propria layer to m3 after chemotherapy. The main lesion of this tumor was in the m3 layer, although the acinus of the esophageal gland was present in the submucosal layer. It is difficult to evaluate the specimen after chemotherapy, and the depth of residual main tumor is not always identical with the layer that cells of tumor origin tumor exist in. The possibility of other origin cannot be ruled out only for this reason. However, this evidence along with the findings of histological evaluation can support the result of immunohistochemical stain that the present adenocarcinoma originated from the duct of the esophageal gland rather than acinus. Cervical esophageal adenocarcinoma is very rare, and most cases are reported to be derived from ectopic gastric mucosa\textsuperscript{1}.

Fig. 4 Histopathological examination.
(a) Macroscopic appearance of the lesion: a 0–Ip–type tumor (18mm × 16mm) adjacent to the proximal surgical margin.
(b) A loupe view of the cervical esophagus noted a fibrosis, which probably replaced to cancerous lesion was remarkable in the submucosal layer.
(c) The tumor is a well-differentiated tubular adenocarcinoma that had invaded the muscularis mucosa.
(d) Most of submucosal layer that the tumor existed in was replaced fibrosis.
To the best of our knowledge, in cervical esophagus, this is the first report of esophageal adenocarcinoma probably originated from esophageal gland.

The standard treatment for cervical esophageal adenocarcinoma has not yet been established because it is a rare tumor. In most cases, the treatments administered were the same as those used for squamous cell carcinoma. The current treatment strategy was also based on the treatment of locally advanced cervical squamous cell carcinoma of the esophagus. These patients may also be treated with high-dose chemotherapy or chemoradiotherapy. In most cases, the treatment for cervical esophageal cancer was cervical esophagectomy and lymphadenectomy of the neck. In the present case, neoadjuvant chemotherapy administered were the same as those used for squamous cell carcinoma according to the Japan Clinical Oncology Group 9,907 trial. And subtotal esophagectomy with lymphadenectomy followed by neoadjuvant chemotherapy were performed, because the distal end of the tumor was in upper thoracic esophagus. The patient is doing well 27 months after the surgery.

We described a rare case of primary cervical esophageal adenocarcinoma probably originating from the ducts of the esophageal gland. Accumulation of similar cases will help to elucidate its epidemiology and biology.

References

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Table 1 Immunohistochemical findings for the normal esophageal tissue and cancer tissue

<table>
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CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; Duct, esophageal gland duct; Acinus, esophageal gland (chief cell). (-) Negative; (+) Positive.