Human Epidermal Growth Factor Receptor 2-positive Primary Adenocarcinoma in the Cervical Oesophagus: A Case Report

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Abstract. *Background/Aim:* Cervical oesophageal adenocarcinoma (COA) is extremely rare. We present a case of human epidermal growth factor receptor 2 (HER2)-positive COA that showed repeated recurrences despite multidisciplinary treatments. *Case Report:* A 49-year-old male was diagnosed with clinical stage IVA COA that originated from ectopic gastric mucosa. He initially underwent definitive chemoradiotherapy (CRT) (60.0 Gy/30 fractions, 5-fluorouracil, and cisplatin). Two months after CRT, the right supraclavicular lymph node (LN) reenlarged and salvage lymphadenectomy was performed. Immunohistochemical staining revealed a HER2-positive adenocarcinoma. Four months after lymphadenectomy, multiple metastases in the mediastinal LNs and lungs were detected, and S-1, oxaliplatin and trastuzumab were administered. Four months after chemotherapy, the patient presented with new liver metastasis. Further metastasis was prevented by Nivolumab treatment for four months. *Conclusion:* HER2-positive COA may be more aggressive and may require further intensive treatments. This literature review may be helpful in determining treatment strategies for COA.

The main histological types of oesophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (1). Oesophageal adenocarcinoma generally occurs in the lower oesophagus and arises from Barrett's epithelium associated with reflux oesophagitis (1). However, oesophageal

adenocarcinoma in the cervical oesophagus is extremely rare. Thus, a treatment strategy has not been established. Here, we present a case of human epidermal growth factor receptor 2 (HER2)-positive cervical oesophageal adenocarcinoma that showed repeated recurrences despite multidisciplinary treatments. In addition, we review reported cases to develop a treatment strategy for this rare form of cancer.

Case Report

A 49-year-old male visited a clinic due to sore throat. Esophagoscopy revealed a tumour in the cervical oesophagus, and he was referred to our hospital for scrutiny and subsequent treatment. He had no history of major illness or family history of cancer. He had inveterate habits of drinking seven bottles of beer per week and smoking 1 pack-per-day for 29 years.

Esophagoscopy revealed a half-circumferential tumour at the left wall in the cervical oesophagus, 17-25 cm from the incisors (Figure 1A). Histopathological examination of the biopsy samples showed adenocarcinoma (Figure 1B). Computed tomography (CT) suggested a tumour in the cervical oesophagus that may invade the trachea and metastases to the right supraclavicular and right recurrent laryngeal nerve lymph nodes (LNs) (Figure 1C and D) but no distant metastases. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT showed high FDG uptake with maximum standardized uptake values (SUV_{max}) of 34.6, 11.9, and 6.8 in the primary lesion, right supraclavicular LN, and right recurrent laryngeal nerve LN, respectively (Figure 1E and F). Oesophagography revealed a wall irregularity in the cervical oesophagus (Figure 1G). Finally, the tumour was diagnosed as clinical T4b, N2, M0, stage IVA adenocarcinoma in the cervical oesophagus [Union for International Cancer Control (UICC) 8th Ed].

The patient underwent definitive chemoradiotherapy (CRT) consisting of a total radiation dose of 60.0 Gy/30 fractions for the primary lesion and LN metastasis, and 40.0 Gy/20 fractions for the regional LNs, and concurrent

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Figure 1. Preliminary evaluations. Esophagoscopy shows a half-circumferential tumour at the left wall of the cervical oesophagus, 17-25 cm from the incisors (A). Histopathological examination of biopsy samples shows adenocarcinoma (B). Computed tomography (CT) suggests a tumour in the cervical oesophagus that is likely to invade the trachea, and metastases to the right supraclavicular and right recurrent laryngeal nerve lymph nodes (LNs) (C and D, yellow arrowheads). Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography/CT shows high FDG uptake with a maximum standardized uptake value (SUV_{max}) of 34.6, 11.9, and 6.8 in the primary lesion, right supraclavicular LN, and right recurrent laryngeal nerve LN, respectively (E and F). Oesophagography reveals a wall irregularity in the cervical oesophagus (G, yellow arrowheads).

administration of 5-fluorouracil and cisplatin (FP) regimen chemotherapy. The FP regimen consisted of cisplatin 80 mg/m²/day, administered intravenously (IV) on day 1, followed by 5-fluorouracil 800 mg/m²/day, administered continuously IV during the period from day 1 to day 5. Two courses were administered at 4-week intervals during CRT. PET/CT two weeks after CRT showed a remarkable decrease in FDG accumulation in both the primary tumour and metastatic LNs. The patient underwent two additional courses of FP regimen chemotherapy. However, PET/CT two months after CRT showed a re-enlargement of the right supraclavicular LN with FDG accumulation with an SUV_{max} of 11.2 (Figure 2A). Thus, salvage lymphadenectomy was performed as a curative measure. Immunohistochemical staining of the resected LN revealed a HER2 (3+) oesophageal adenocarcinoma metastasis (Figure 2B and C).

Four months after salvage lymphadenectomy, multiple novel metastases were detected on CT in the mediastinal LNs and lungs (Figure 3). Based on the pathological HER-2 status, the patient underwent S-1 and oxaliplatin (SOX) regimen chemotherapy plus trastuzumab as the second regimen (2). Four months after the chemotherapy, new liver metastasis appeared and Nivolumab was administered as the third regimen. The metastasis did not worsen, and the patient survived for 4 months after Nivolumab treatment.

Discussion

In Japan, SCC has long been the dominant histological type of oesophageal cancer, representing over 85% of these cancers (3). However, in recent years, the prevalence of oesophageal adenocarcinoma has increased rapidly from 1.7% to 10% (4) as the prevalence of reflux esophagitis increased, possibly due to the increase in obesity. Meanwhile, oesophageal adenocarcinoma in the cervical oesophagus is extremely rare. To the best of our knowledge, only 24 cases of adenocarcinoma in the cervical oesophagus, including our case, have been reported (Table I). Based on our review of this literature, the median age of the patients was 65.5 years, and 83.3% were male. Most of the cases were ectopic and originated from the gastric mucosa, and only 16.7% were associated with extensive Barrett's oesophagus. Our case did not have extensive Barrett's oesophagus, suggesting that it was ectopic and originated from the gastric mucosa in the cervical oesophagus.

Treatment strategies for cervical oesophageal adenocarcinoma have not been established due to the rarity of this condition. In the present case, CRT with the FP regimen was initially administered to preserve the voice, and the tumour seemed to disappear temporally. However, LN metastasis was revealed only 2 months after CRT. Although salvage

Figure 2. Post-treatment evaluations. Positron emission tomography/computed tomography (PET/CT) two months after chemoradiotherapy shows re-enlargement of the right supraclavicular lymph node with fluorodeoxyglucose accumulation and a maximum standardized uptake value of 11.2 (A, yellow arrowhead). There are no enlargement of the cervical oesophagus and right recurrent laryngeal nerve lymph nodes (B). Immunohistochemical staining after salvage lymphadenectomy indicates HER2-positive (3+) oesophageal adenocarcinoma metastasis (C and D).

lymphadenectomy and adjuvant chemotherapy were performed for cure, multiple metastases occurred shortly after the treatments. Immunohistochemistry revealed that the recurrent lesions were HER2-positive, predicting a cancer with a highly malignant potential and a high risk of recurrence (5). Our case suggested that cervical adenocarcinoma with a positive HER2 status may be more aggressive than that with a negative HER2 status even in cervical oesophageal adenocarcinoma. Notably, subsequent chemotherapy with SOX and trastuzumab could not prevent further progression, and treatment with an immune-checkpoint inhibitor is ongoing.

The literature review may help determine a treatment strategy (4, 6-25). Most of the reported patients with stage 0 and I adenocarcinomas underwent endoscopic treatment or surgery and had considerably good results without any recurrences (4, 8, 11, 12, 14, 20-25). For patients with stage II, surgery alone without adjuvant treatment was adequate (9, 18, 22). In contrast, patients with stage III and higher advanced cancer underwent various treatments, including CRT and surgery (10, 13, 15, 16, 20). However, recurrence was observed in 43% of these patients, and the median survival was only 19 months, which suggested that further

Table I. Cases of cervical esophageal adenocarcinoma.

Author, year	Age	Gender	Size (mm)	Shape	Stage	Treatment	Regimen	Radiotherapy (Gy)	Outcome (month)	Dead/Alive	Recurrence	Origin
Goodwin <i>et al.</i> 1983 (6)	73	F	30	0-Ip	-	S+RT	-	50	5	Dead	No	Extensive Barrett's esophagus
Ishii <i>et al.</i> 1991 (7)	66	M	30×45×50	-	-	S	-	-	20	Alive	-	Ectopic gastric mucosa
Takagi <i>et al.</i> 1995 (8)	70	M	19×16	I	I	S	-	-	-	-	-	Ectopic gastric mucosa
Lauwers <i>et al.</i> 1998 (9)	57	F	20×40	0-Ip	II	S+RT	-	45	8	Alive	-	Ectopic gastric mucosa
Noguchi <i>et al.</i> 2001 (4)	73	M	25×20	0-IIa	I	S	-	-	60	Alive	No	Ectopic gastric mucosa
Klaase <i>et al.</i> 2001 (10)	43	M	40	-	III	S+RT	-	-	8	Dead	Yes	Ectopic gastric mucosa
Hirayama <i>et al.</i> 2003 (11)	77	F	21×8	0-Ip	I	EMR	-	-	31	Alive	No	Ectopic gastric mucosa
Abe <i>et al.</i> 2004 (12)	50	M	24×18	0-Is	I	S	-	-	18	Alive	No	Ectopic gastric mucosa
von Rahden <i>et al.</i> 2005 (13)	50	M	40	-	III	CRT+S	5FU, CDDP	48,6	36	Alive	No	Ectopic gastric mucosa
Yoshida <i>et al.</i> 2010 (14)	79	M	40×35	0-Is	I	EMR	-	-	24	Alive	No	Ectopic gastric mucosa
Bard <i>et al.</i> 2011 (15)	87	M	-	-	III	CRT	CDDP	42	17	Dead	Yes	Ectopic gastric mucosa
Akanuma <i>et al.</i> 2013 (16)	57	M	-	2	III	CRT+S+CRT	5FU, CDDP	38, 30	48	Alive	No	Ectopic gastric mucosa
Tanaka <i>et al.</i> 2014 (17)	76	M	35	2	-	S	-	-	19	Alive	No	Extensive Barrett's esophagus
Ajmal <i>et al.</i> 2015 (18)	57	M	30	2	II	S	-	-	-	-	-	Ectopic gastric mucosa
Sundriyal <i>et al.</i> 2015 (19)	61	M	30	2	-	CRT	-	-	-	-	No	Extensive Barrett's esophagus
Nomura <i>et al.</i> 2015 (20)	62	M	49×31	0-IIb	I	ESD	-	-	12	Alive	No	Ectopic gastric mucosa
Nomura <i>et al.</i> 2015 (20)	57	M	40	2	III	CRT+S	DTX, 5FU, CDDP	60	15	Alive	No	Ectopic gastric mucosa
Hudspeth <i>et al.</i> 2016 (21)	77	M	15	0-I	I	EMR+APC	-	-	12	Alive	No	Extensive Barrett's esophagus
Kadota <i>et al.</i> 2016 (22)	78	M	20×25	0-Is+IIc	I	ESD	-	-	-	-	No	Ectopic gastric mucosa
Kadota <i>et al.</i> 2016 (22)	70	M	42×20	2	cII, pIII	S	-	-	180	Dead (heart failure)	No	Ectopic gastric mucosa
Gushima <i>et al.</i> 2017 (23)	65	F	16×10	0-Ip	I	ESD	-	-	40	Alive	No	Ectopic gastric mucosa
Tanaka <i>et al.</i> 2019 (24)	72	M	8	0-Is	I	ESD	-	-	24	Alive	No	Ectopic gastric mucosa
Oono <i>et al.</i> 2019 (25)	58	M	32×27	1	0	ESD	-	-	-	-	-	Ectopic gastric mucosa
Our case	49	M	80	2	IVa	CRT+S	5FU, CDDP	60	19	Alive	Yes	Ectopic gastric mucosa

–: Undescribe; S: surgery; RT: radiotherapy; CRT: chemoradiation therapy; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; APC: argon-plasma coagulation; 5FU: 5-fluorouracil; CDDP: cisplatin; DTX: docetaxel.

Figure 3. Computed tomography four months after salvage lymphadenectomy. Multiple new metastases are seen in the mediastinal lymph nodes (A, yellow arrowhead) and the lungs (B, C and D, yellow arrowheads). There are no tumours in the cervical oesophagus, and no metastases to the right supraclavicular and right recurrent laryngeal nerve LNs (E and F).

advances in the treatment strategy are necessary for advanced cervical oesophageal adenocarcinoma.

To our knowledge, this is the first report of a case of HER2-positive primary cervical oesophageal adenocarcinoma. Our experience suggests that a HER2-positive tumors have a highly malignant potential, and further intensive treatments are recommended. Recently, a novel regimen with trastuzumab deruxtecan was reported to improve survival of patients with HER2-positive gastric cancer (26). In addition, novel agents such as immune-checkpoint inhibitors and multi-kinase inhibitors have proven effective against gastric and esophagogastric adenocarcinoma (27-29). Further progress in treatment strategies, including those agents, is necessary to improve the treatment outcomes of advanced adenocarcinoma in the cervical oesophagus.

Conclusion

Our case suggests the existence of an aggressive cervical oesophageal adenocarcinoma. It is necessary to accumulate the data on treatment outcomes and progress treatment strategy for cervical oesophageal adenocarcinoma to further improve survival outcome.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

TH described and designed the article. NY edited the article. HB supervised the editing of the manuscript. NY, MI and YB were

involved in the operation of the patient. CM, YH and TT collected the data. All Authors read and approved the final manuscript.

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