Case Report

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Esophageal Adenocarcinomas in Heterotopic Gastric Mucosa: Review and Report of a Case with Complete Response to Neoadjuvant Radiochemotherapy

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Key Words

Cervical esophageal adenocarcinoma · Heterotopic gastric mucosa · Inlet patch

Abstract

Adenocarcinomas are exceedingly rare in the cervical esophagus (26 reported cases), where squamous cell cancer (SCC) is the predominant tumor type. Esophageal heterotopic gastric mucosa (HGM) – a frequent remnant of incomplete replacement of the original columnar epithelium during the embryonic period – is suspected as cellular origin of cervical esophageal adenocarcinomas. As in any rare tumor entity, no standard treatment strategy is available for cervical esophageal adenocarcinomas. We herein report about the case of a 52-year-old man with a locally advanced, irresectable cervical esophageal adenocarcinoma originating in HGM. We decided on a neoadjuvant therapy (48.6 Gy + 5-FU/cisplatin) derived from experiences with SCC. Restaging showed an extraordinary good clinical response of the previously irresectable tumor. Subsequently the patient underwent limited cervical esophageal resection, lymphadenectomy and interposition of a free jejunal loop for reconstruction. Postoperative histopathological work-up of the specimen showed no residual tumor tissue, but unchanged HGM. This is the first case with complete response of a rare cervical esophageal adenocarcinoma to a neoadjuvant protocol. On 3-year follow-up the patient is doing fine with no complaints of dysphagia and no evidence of local or systemic recurrence.

Introduction

Histopathological examination of cervical esophageal cancers mostly reveals squamous cell carcinomas (SCCs). Esophageal adenocarcinomas – in Western countries frequently and increasingly found in the distal third of the thoracic esophagus [1] – are an absolute rarity in the cervical esophagus. Only 26 cases (and 4 cases of high-grade dysplasia/intraepithelial neoplasia) have so far been reported in the published literature (see table 1) with heterotopic (ectopic) gastric mucosa (HGM) in the cervical esophagus associated with adenocarcinoma.

HGM is a lesion occurring throughout the entire gastrointestinal tract, but is frequently found near the upper esophageal sphincter [2]: The macroscopic appearance is a red or salmon-colored velvety patch which is – due to its localization – also called 'inlet patch'. Although most patients are asymptomatic, some develop symptoms based on acid secretion from the inlet patch, which may be responsible for symptoms (e.g. dysphagia/odynophagia), or may even cause further pathophysiological changes (e.g. stenoses, strictures, webs, fistulas). The rare event of malignant transformation and progression towards cancer may be regarded as the maximum complication [2].

We herein report about the first case of a cervical esophageal adenocarcinoma in HGM which was successfully treated with a multimodal concept.

Case Report

Clinical Presentation

A 50-year-old white male with a histologically proven, locally advanced adenocarcinoma of the cervical esophagus was admitted to our University hospital for further staging and oncological treatment. A 3-month history of dysphagia had led to clinical investigation with endoscopy, biopsy and subsequent histopathological diagnosis of the rare tumor entity.

Flexible endoscopy of the esophagus showed the almost circular growth pattern of the tumor with subtotal stenosis of the esophageal lumen. The tumor localization close to the upper esophageal sphincter (20–24 cm from the incisors) was also demonstrated on the pharyngoesophagogram (barium swallow, fig. 1). The tumor was staged a T3 N+ category by endoscopic ultrasound. CT scan of neck, thorax and abdomen showed an extensive wall thickening in the cervical esophagus but no signs of systemic tumor spread.

Pretreatment Biopsies

Repeated biopsies of the tumor consistently showed a moderately differentiated tubulo-papillary adenocarcinoma (G2) in the neighborhood of normal esophageal squamous-cell epithelium, originating in HGM of the fundic type (fig. 2).

Treatment Strategy: Neoadjuvant Radiochemotherapy and Limited Cervical Esophageal Resection with Jejunum Interposition

The locally advanced tumor growth with displacement of the trachea suggested irresectability of the tumor. Thus a neoadjuvant treatment strategy was chosen and preoperative radiochemotherapy was initiated. The patient received a total dose of 48.6 Gy radiation and

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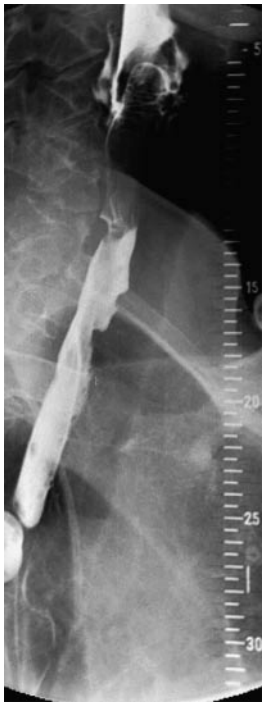
Table 1. Chronological list of publications about cases with malignant progression (26 adenocarcinoma and 4 high-grade dysplasia) of heterotopic gastric mucosa

Cases	Authors	Year	Lesion and treatment	Patient's course[1]
1	Carrie [28]	1950	adenocarcinoma (pT2): resection of the upper esophagus	no recurrence (>1 year)
2	Morson and Belcher [29]	1952	adenocarcinoma (pT3): esophagectomy	n. a.
3	Raphael et al. [30]	1966	advanced adenocarcinoma: radiotherapy	died (suicide) (2 months)
4	Davis et al. [31]	1969	adenocarcinoma (pT1sm): esophagectomy	no recurrence (7 months)
5	Sakamoto et al. [32]	1970	adenocarcinoma (pT2): esophagectomy	died after 10 months
6	Clemente [33]	1974	adenocarcinoma (pT3): esophagectomy	recurrence (10 months)
7	Danhoff [34]	1978	advanced adenocarcinoma: radiotherapy	died (9 months)
8	Goeau-Brissonniere et al. [35]	1985	adenocarcinoma (pT3): esophagectomy	no recurrence (31 months)
9	Kamiya et al. [36]	1983	adenocarcinoma (pT3): esophagectomy	died (pneumonia) (7 months)
10 + 11	Schmidt et al. [22]	1985	case 1: adenocarcinoma (pT3): esophagectomy case 2: high-grade dysplasia: surgical local excision	died (4 months) no recurrence (1 year)
12 + 13	Christensen and Sternberg [13]	1987	case 1: adenocarcinoma (pT2): esophagectomy case 2: adenocarcinoma (pT3): esophagectomy	recurrence (25 months) not available
14	Ishii et al. [37]	1991	adenocarcinoma (pT3): esophagectomy	no recurrence (20 months)
15	Sperling and Grendell [38]	1995	adenocarcinoma (cT3/4): surgical exploration and excisional biopsy, radiotherapy	n. a.
16	Takagi et al. [39]	1995	adenocarcinoma (pT1sm): esophagectomy	n.a.
17	Mion et al. [20]	1996	high-grade dysplasia in an adenoma: endoscopically guided local excision of the tumor through a cervical incision	n.a.
18	Kammori et al. [40]	1996	early adenocarcinoma (pT1): esophagectomy	n.a.
19	Pai et al. [41]	1997	adenocarcinoma (pT2): surgery/radiochemotherapy	recurrence (24 months)
20	Berkelhammer et al. [42]	1997	early adenocarcinoma (pT1sm): transthoracic esophagectomy	no recurrence (2 years)
21	Lauwers et al. [43]	1998	advanced adenocarcinoma (pT3): esophagectomy, laryngectomy, partial pharyngectomy, adjuvant radiotherapy	no recurrence (8 months)
22 + 23	Klaase et al. [14]	2001	case 1: high-grade dysplasia: argon plasma coagulation case 2: locally advanced adenocarcinoma (pT4): esophagectomy, laryngectomy, additional postoperative radiotherapy	no recurrence (16 months) died (4 months)
24	Pech et al. [44]	2001	early adenocarcinoma (pT1): endoscopic mucosa resection	no recurrence (1 year)
25	Noguchi et al. [27]	2001	adenocarcinoma (pT1sm): resection of the cervical esophagus, pharyngectomy, laryngectomy, bilateral lymphadenectomy	no recurrence (5 years)
26	Sauve et al. [21]	2001	high-grade dysplasia: argon plasma coagulation	no recurrence (2 years)
27	Chatelain et al. [45]	2002	adenocarcinoma (pT3): transthoracic esophagectomy; radiochemotherapy of local and systemic recurrence	died (15 months)
28	Hirayama et al. [46]	2003	adenocarcinoma (pT1m): endoscopic mucosa resection	no recurrence (31 months)
29 + 30	Balon et al. [47]	2003	case 1: adenocarcinoma (pT3): transhiatal esophagectomy case 2: adenocarcinoma (pT1): transhiatal esophagectomy; radiochemotherapy of recurrence	died (21 months) died (16 months)

[1] n.a. = Not available.

simultaneously 2 cycles of chemotherapy with cisplatin 50 mg/m^2 and 5-FU 750 mg/m^2 per continuous infusion (days 1–5 and 28–33).

Clinical restaging (repeated endoscopy and CT scan 1 week after completion of the protocol) showed a very good response to radiochemotherapy. Thus it was decided to proceed with surgical treatment. The patient received a limited resection of the cervical esophagus with reconstruction by interposition of a free-transplanted jejunal loop [3, 4]. The procedure was performed via a left-sided cervical approach with resection of the cervical esophagus from the upper esophageal sphincter to the thoracic inlet including a central cervical lymphadenectomy. Gastrointestinal continuity was restored by interposition of a short proximal jejunal segment (anastomosed proximal-



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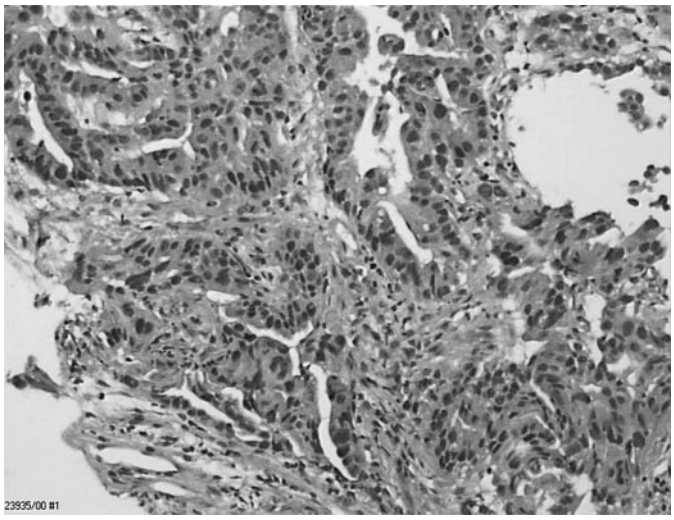

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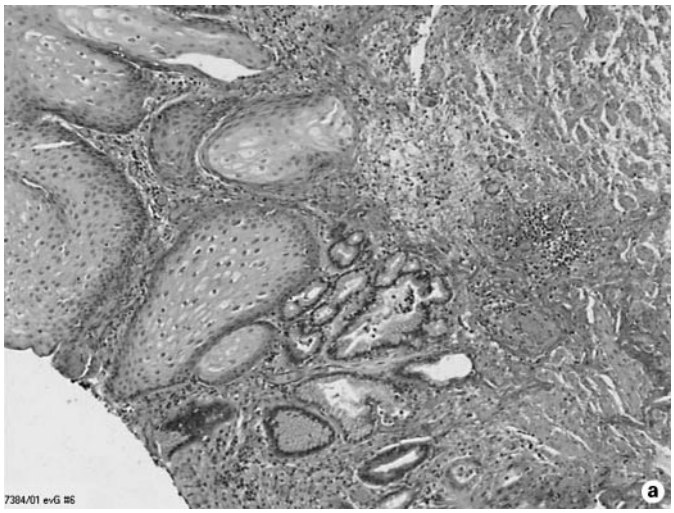
Fig. 1. The swallow examination (pharyngoesophagography) with soluble contrast medium shows irregularities of the wall of the cervical esophagus, demonstrating localization of the cancer in the cervical esophagus.

Fig. 2. Pretreatment biopsy (HE, 200×) shows the well-differentiated adenocarcinoma originating in heterotopic gastric mucosa.



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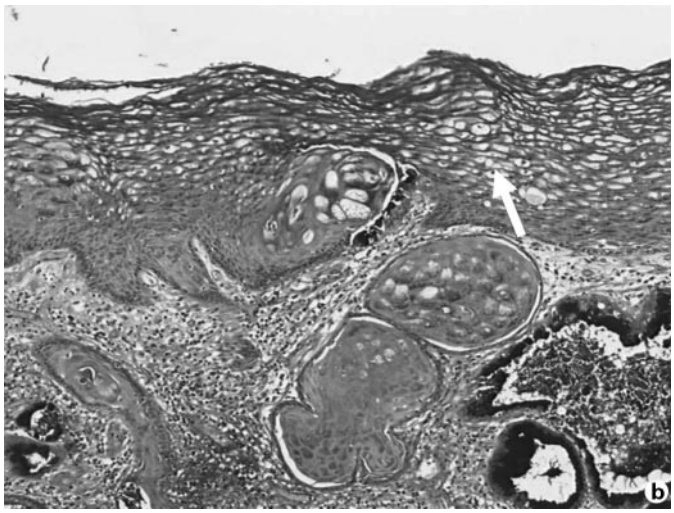

b

Fig. 3. a Elastica-van Gieson stain (200×) demonstrating HGM besides normal esophageal squamous cell epithelium. **b** Postoperative histopathological evaluation of the specimen shows foci of heterotopic gastric mucosa underneath partially regenerating esophageal squamous cell epithelium (PAS stained, 400×). No residual tumor cells were found, indicating a complete response to the neoadjuvant treatment.

ly end-to-side and distally end-to-end to the remaining esophagus) with microvascular anastomosis of the jejunal segment to the inferior thyroid artery and the internal jugular vein (microsurgical technique).

The patient's postoperative clinical course was uneventful with no surgical complications. He was discharged on the 12th postoperative day eating a regular diet.

Histopathological Examination

The surgical specimen was examined completely (25 blocks, histological staining with HE, Elastica-van-Gieson and PAS, fig. 3a, b). Special staining for *Helicobacter pylori* was negative. Histopathological examination revealed a complete response to the neoadjuvant radiochemotherapy as there was no residual tumor tissue found in the specimen (grade of regression 1 according to Mandard [5]). In

contrast, the HGM of the fundic type was consistently detectable at the margins of the tumor bed ulcer. Histopathological classification according to the TNM staging system of the UICC [6] was ypT0 ypN0 (0/12) ypM R0.

Follow-Up

Repeated follow-up with endoscopies and CT scans at 6-month intervals did not show evidence of recurrence of tumor, neither locally, locoregionally nor systemically. Disease-free survival of the patient is 36 months at time of this publication.

Discussion

Adenocarcinomas in the Esophagus

Adenocarcinomas originate from glandular differentiated tissues. In the squamous-cell-lined esophagus (where SCC is the predominant histological tumor type), three glandular differentiated tissues can give rise to adenocarcinomas:

(1) intestinal metaplasia (Barrett's epithelium)

(2) mucosal and submucosal esophageal glands

(3) HGM.

ad (1) Intestinal metaplasia (Barrett's mucosa) develops due to severe mucosal injury by chronic gastroesophageal reflux. These metaplastic changes are common (15% of patients with reflux and 1% in an unselected patient population; [1]) and the risk for malignant transformation and development of an adenocarcinoma is well understood [1]: Barrett's mucosa is considered a precancerous lesion and carcinogenesis follows a dysplasia-carcinoma sequence [7].

Naturally these cancers are localized in the distal esophagus, the region of predominant acid exposition. Rare conditions can lead to more proximally localized Barrett's epithelium, i.e. in extensive (long-segment) Barrett [8] or rare cases with recurrence of Barrett's epithelium in the cervical esophageal stump after subtotal esophagectomy and gastric pull-up [9].

ad (2) Mucosal and submucosal esophageal glands are regarded as the cellular origin when esophageal adenocarcinomas develop without Barrett's metaplasia. This has been reported to be the case in up to 40% of patients with adenocarcinoma of the distal esophagus. A recent study by Theisen et al. [10] showed that chemotherapy can unmask Barrett's epithelium previously overgrown by the tumor, suggesting that the vast majority of distal esophageal adenocarcinoma indeed develop from underlying Barrett's mucosa.

True esophageal adenocarcinomas originating from mucosal or submucosal glands frequently present as mucoepidermoid and adenoid-cystic carcinomas.

ad (3) HGM has been found in association with cervical adenocarcinomas. But in contrast to Barrett's mucosa, HGM is not regarded as a precancerous lesion. Similar to other tissues, initiation of cancer occurs as a sporadic event, without a special precancerous predisposition. This is suggested by incidence figures: the prevalence of HGM is high (up to 70% microscopic foci [11, 12]), but it rarely gives rise to adenocarcinoma (26 reported cases, table 1).

Thus a reliable estimate of the frequency of cervical esophageal adenocarcinoma development is impossible [13, 14]. Jabbari et al. [15] call the ectopic gastric mucosa an 'occasional substratum' for the evolution of the relatively uncommon cervical esophageal adenocarcinoma.

This can happen, not only in the inlet patch of the esophagus, but also in HGM at other localizations. HGM has been described in localizations throughout the entire gastrointestinal tract – from the mouth to the rectum [16]. In the cervical esophagus it is a frequent but – due to the localization – underdiagnosed lesion. The typical localization is the area immediately below the upper esophageal sphincter, where it's macroscopically visible form is also called 'inlet patch'. Although often clearly visible – it presents as velvety red patch with a distinct border [15] – it is easily missed by flexible endoscopy. The region is quickly passed protruding the scope having overcome the resistance of the upper esophageal sphincter. Only by careful withdrawal of the endoscope, the area of interest can be examined [14].

The origin of the inlet patch is discussed controversially; however, it is almost generally accepted that the inlet patch is a congenital condition, resulting from the embryologic epithelization process. It appears to result from incomplete replacement of the original columnar epithelium by squamous epithelium during the embryonic period [2, 12, 17].

In addition to the exceedingly rare event of malignant progression, HGM bears further clinical impact. The variable presentation of HGM in terms of clinical and pathological features led to proposal of a new clinicopathological classification (HGM I–V) which was recently published [2]. In the majority of cases the carriers of HGM are asymptomatic (HGM I), but rarely HGM is associated with symptoms (HGM II) [18, 19]. Most of these belong to the group of peptic disorders [16] due to acid secretion [18] by parietal cells [15] in the gastric inlet patch. Therapeutic intervention is only required when the patient harboring HGM in the cervical esophagus is symptomatic. Symptoms may occur with (HGM II) or without (HGM III) additional morphological changes (i.e. benign strictures, stenoses, webs, fistula).

The region below the upper esophageal sphincter should be inspected for existence of an inlet patch during routine flexible endoscopy and suspect lesions should be biopsied. Development of an adenocarcinoma in HGM presumably is a rare sporadic event, unlike Barrett's cancer originating from precancerous Barrett's mucosa. Nevertheless it possibly has a dysplasia-carcinoma sequence in common with other epithelia (e.g. Barrett's esophagus [1, 7]). In rare reports, dysplastic changes have been described [14, 20–22] The demonstration of dysplasia ('intraepithelial neoplasia' according to the new nomenclature recently introduced by the WHO [23]) should lead to further therapeutic considerations. In the published classification [2] preneoplastic changes are defined as HGM IV, whereas HGM V is suggested for the exceedingly rare cases of invasive carcinoma within HGM.

Treatment of Cervical Esophageal Adenocarcinoma

The importance of distinguishing esophageal cancers according to the histological tumor type (adenocarcinoma/SCC) and localization (cervical/supracarinal, infracarinal) [24] is nowadays almost generally accepted. Histological tumor type as well as localization are major parameters for the selection of the therapeutic strategy. No standard treatment is available for rare tumors like cervical esophageal adenocarcinomas. The treatment strategy applied in the presented case was derived from our experience with treatment of locally advanced SCCs of the cervical esophagus. Due to the close anatomical relationship to the trachea, larynx and hypopharynx, a radical resection of such tumors usually can only be performed by a radical esophagopharyngolaryngectomy. This mutilating procedure is often not accepted by patients in the Western hemisphere [3, 4]. In our experience with locally advanced cervical SCC, a substantial 'down-

sizing' of the tumor extent can be achieved by neoadjuvant radiochemotherapy [25]. A limited resection of the cervical esophagus with preservation of the larynx thus becomes possible without a loss in prognosis [3, 4]. Since preoperative radiochemotherapy has also been shown effective for esophageal adenocarcinoma the decision for a neoadjuvant strategy was made.

In our case the neoadjuvant treatment lead to a complete response: no residual tumor cells were found during final histopathological examination. 'Complete responders' are the group of patients who have maximum benefit from preoperative treatment and the following resection. There are some data in the literature suggesting that esophageal adenocarcinomas arising in Barrett's esophagus are clinically and biologically different from non-Barrett adenocarcinomas [26]. Tumors in patients with Barrett's esophagus have been shown to be less likely to have a complete response to preoperative chemoradiation.

In our case there was no need to perform pharyngectomy or laryngectomy [27] because neither of these structures was infiltrated by the tumor after radiochemotherapy. The tumor could be resected in total by a limited cervical esophageal resection. Reconstruction of alimentary passage with a free jejunal transplant resulted in a good swallowing function.

Conclusion

Adenocarcinomas are rare in the cervical esophagus where SCCs are predominant. HGM can be the precursor tissue, but may not be regarded as a precancerous lesion – in sharp contrast to Barrett's epithelium. Naturally no standard treatment strategies exist for rare tumors. Our neoadjuvant concept with radiochemotherapy followed by cervical esophageal resection – derived from our experiences with cervical SCCs – was successfully applied, resulting in long-term survival of the patient.

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