Esophageal Adenocarcinoma with Enteroblastic Differentiation Arising in Ectopic Gastric Mucosa in the Cervical Esophagus: a Case Report and Literature Review

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INTRODUCTION

Alfa-fetoprotein (AFP)-producing gastrointestinal carcinomas have been mostly reported as arising in the stomach [1-3]; there were few cases reported with esophageal cancers [4-14]. Adenocarcinoma with enteroblastic differentiation is a subtype of AFP-producing adenocarcinoma. This type of tumor is rare and reported as a case and a series of cases in the stomach [15, 16]. Enteroblastic type of adenocarcinoma was reported as histologically cuboidal or as columnar cells with clear cell cytoplasm combined with tubular adenocarcinoma [3, 15, 16]. Immunohistochemical stain was characteristically positive for AFP, glypican 3, or Sall-like protein 4 (SALL4) [16].

We report a rare case of esophageal adenocarcinoma with enteroblastic differentiation from ectopic gastric mucosa in the cervical esophagus, treated successfully with endoscopic submucosal dissection (ESD). We also review a series of published cases.

CASE REPORT

A 65-year-old woman was referred to our hospital with a complaint of dysphagia. She had no past and family medical history of relevant disorders. She did not smoke and consumed alcohol occasionally. The laboratory analysis showed no remarkable abnormalities, including serum tumor markers such as squamous cell carcinoma antigen (SCC), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) levels. Alfa-fetoprotein was not studied before treatment. An upper gastrointestinal endoscopy revealed a 5-mm area of ectopic gastric mucosa at 16cm from the incisors and 15-mm reddish elevated lesions at the distal side of the ectopic gastric mucosa.
There was a demarcation line between the elevated lesion and the background ectopic gastric mucosa by magnifying the endoscopy (ME) with narrow-band imaging (NBI) (Fig. 1b, arrows). The epithelial irregular microsurface pattern and irregular microvascular pattern were visualized (Fig. 1b). The endoscopic biopsies taken from the elevated lesion and the orange area exhibited moderately differentiated tubular adenocarcinoma and ectopic gastric mucosa, respectively. There was no evidence of a deep submucosal invasion of the tumor on endoscopic ultrasound (EUS) (data not shown). Computed tomography (CT) revealed an absence of swollen lymph nodes in the neck and mediastinum (data not shown). [18F] fluorodeoxyglucose - positron emission tomography (FDG-PET) did not show abnormal uptake in the upper esophagus, regional lymph node and distant organs (data not shown). Pretreatment diagnosis was esophageal adenocarcinoma, Ce type 0-I T1 N0 M0 stage I according to the TNM classification.

After the informed consent of the patient was obtained, endoscopic submucosal dissection (ESD) was performed. The resected specimen measured 34 x 30mm and contained a 16 x 10mm tumor. The oral side of the tumor was surrounded by ectopic gastric mucosa (Fig. 2). Histopathological examination showed a moderately differentiated tubular adenocarcinoma, composed of cuboidal cells with clear cell cytoplasm. The tumors were spread into the submucosal layer (Fig 3a, b). Vascular and lymphatic invasion was not identified. The specimens on immunohistochemical staining were positive for MUC2, MUC5AC, and MUC6, but negative for CD10. AFP and glypican 3 were weakly positive and SALL4 was strongly positive (Fig 3c-e). Based on these results, we finally diagnosed the tumor as adenocarcinoma with enteroblastic differentiation arising from ectopic gastric mucosa in the cervical esophagus.

After diagnosis, we checked the serum level of AFP of the patient and it was consequently normal. After 40 months, the patient was followed up with no evidence of recurrence.

**DISCUSSION**

Generally, AFP is considered to function in the human fetus and is synthesized in the fetal liver and the yolk sac [17]. Therefore, the serum level of AFP is a useful marker for the diagnosis and detection of hepatocellular carcinoma (HCC) or yolk sac tumor. On the other hand, AFP-producing carcinoma has been reported in a variety of organs, such as stomach, papilla of Vater, colon, pancreas, lung, and ovary [1-3, 18-22]. Many cases of AFP-producing carcinoma have been reported in the stomach. There have been few cases reported in the hepatoid adenocarcinoma of esophagus, since AFP-producing esophageal carcinoma was first reported in 1993 by Sawada et al. Motoyama et al. classified AFP-producing carcinomas of the stomach into three types: hepatoid type, yolk sac tumor-like type, and fetal gastrointestinal type [23]. Meanwhile, Kinjo et al. classified them, according to the characteristic of tumor, as a common adenocarcinoma type, enteroblastic type, hepatoid type, and yolk sac tumor type [3]. The fetal gastrointestinal type and enteroblastic type were considered to be equivalent to carcinoma with enteroblastic differentiation [15]. However, AFP-producing esophageal carcinoma, including adenocarcinoma with enteroblastic differentiation, has not been categorized by the World Health Organization (WHO) classification.

Histologically, adenocarcinoma with enteroblastic differentiation has a primitive intestinal-like structure, composed of cuboidal or columnar cells with clear cytoplasm [1, 3, 15]. In case of stomach location, the gastric mucosal
epithelium was covered with tubular adenocarcinoma, and the deeper part of the mucosal layer and the submucosa were composed of tubular adenocarcinoma and adenocarcinoma with enteroblastic differentiation [24]. Kinjo et al. suggested that AFP-producing carcinoma developed from tubular adenocarcinoma and invaded into deeper layers [3]. Our case is compatible with the case of the stomach location. Therefore, it is likely that we could not diagnose it properly from the biopsy samples, which prelevated only the surface layer.

Immunohistochemically, recent reports have demonstrated that AFP, glypican3, and SALL4 were sensitive markers for the enteroblastic type of tumor [16, 25-27]. In our patient, the tumor more strongly expressed SALL4 than AFP and glypican 3. In the study by Murakami et al., glypican 3, SALL4, and AFP were expressed in 83%, 72%, and 45%, respectively, in gastric carcinoma [16]. Glypican 3 is a cell surface heparin sulfate proteoglycan considered to be an oncofetal protein because of its presence in the fetal liver and the cells of liver tumors. SALL4 is a zinc finger transcription factor. Recent studies have revealed that SALL4 is expressed not only in primitive germ cell tumors but also in gastric carcinoma with fetal gut differentiation [25, 26]. Hishinuma et al. suggested that glypican 3 and AFP could be sensitive markers for AFP-producing gastric cancer [27]. Ushiku et al. indicated that SALL4 is a sensitive marker for AFP-producing gastric carcinoma as well [25]. It remains uncertain how to diagnose AFP-producing carcinoma, including adenocarcinoma with enteroblastic differentiation. Recent reports have suggested that the diagnostic criterion for gastric adenocarcinomas with enteroblastic differentiation should be positivity in one out of the three enteroblastic markers (AFP, glypican 3, and SALL4) [16].

In the previous literature, only eleven cases of AFP-producing esophageal adenocarcinoma were reported (Table I). Most of these types were of the hepatoid type. Nine of the patients were males with a wide range of age groups. The majority of cases occurred in Asians. The lesions were frequently located in the lower third of the esophagus and some cases were related to Barrett’s epithelium. These results were similar to cases of conventional esophageal adenocarcinoma. Interestingly, an AFP-producing esophageal adenocarcinoma arising in ectopic gastric mucosa has never been reported before. The serum levels of AFP are not elevated in all cases. However, the high levels of AFP suggest that the tumor metastasized to other organs. In such case, pre-operative or post-operative serum level of AFP may be a useful marker for predicting and monitoring prognosis and recurrence. In our case, it is difficult to prove the tumor producing AFP before treatment. However, it may be expected to have a good prognosis, because serum AFP was not elevated after ESD. In fact, the patient survived 40 months with no recurrence after the endoscopic treatment.

Many reported cases of AFP-producing esophageal carcinoma were treated with esophagectomy or chemotherapy.
For adjuvant chemotherapy, most cases were treated with cisplatin plus 5-fluorouracil as first line therapy. However, this regimen is controversial. In spite of multimodal therapy, the survival rate of the tumors has been very low. AFP-producing esophageal carcinoma has a poor prognosis and has been found at an advanced stage of disease with metastasis in lymph nodes and liver at the time of diagnosis, as is the case of gastric adenocarcinoma with enteroblastic differentiation. Only two of all the reported cases were still alive at the time of the last follow up. Both these cases had been treated with esophagectomy and had no evidence of metastasis. However, median follow-up time was very short (4.5 months). In our case, there is no recurrence after 40 months. If we can detect this type of tumor at an early stage by endoscopic examination, a long-term prognosis can be expected by a minimally invasive treatment, such as ESD. The number of reported patients is very small and further investigations are required.

CONCLUSION

We presented a case of AFP-producing esophageal carcinoma arising from ectopic gastric mucosa in the cervical esophagus. To the best of our knowledge, this is the first report of a patient who underwent ESD for adenocarcinoma with enteroblastic differentiation in the esophagus. It is difficult to diagnose the histological type based on preoperative biopsy specimens and endoscopic features. Regardless of the serum level of AFP, the diagnosis of this type of carcinoma should be based on pathological features, such as a hepatoid pattern and a clear cell tubular pattern, and on immunohistochemistry.

Conflicts of interest: None to declare.

Authors’ contribution: R.G.: manuscript writing and pathological diagnosis; R.N. and T.S.: endoscopic examinations and management of the patient; T.Y.: pathological diagnosis and manuscript revision; H.N. manuscript revision; Y.S.: manuscript writing and revision. All authors read and approved the final manuscript.

REFERENCES


