CASE REPORT

Alpha-fetoprotein-producing esophageal adenocarcinoma: a mimicker of hepatocellular carcinoma

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Abstract Alpha-fetoprotein (AFP)-producing esophageal adenocarcinoma (EAC) is a rare occurrence. Elevation of serum AFP is commonly associated with hepatocellular carcinoma and yolk sac tumors, but rarely with esophageal carcinoma. Here, we report a rare case of AFP-producing EAC. A 51-year-old man presented with two weeks of acid reflux and a 35-lb weight loss. Laboratory data were notable for transaminitis and AFP was 2524 ng/mL. Computed tomography of the abdomen revealed abnormal thickening of the esophagus and multiple metastatic masses throughout the liver. Biopsy of one of the masses revealed adenocarcinoma of gastrointestinal origin. Subsequent upper endoscopy revealed an esophageal mass with biopsy notable for ulcerated dysplastic glandular mucosa with likely underlying malignancy. The patient underwent palliative esophageal stent placement but died two months later. Elevated AFP levels are an unusual occurrence in EAC. Prognosis is poor given its advanced presenting stage and high metastatic potential. Most cases are unsuccessfully treated with surgery and chemotherapy. Serial measurement of serum AFP may be useful for monitoring clinical status and treatment response. Clinicians should consider AFP-producing EAC in their differential diagnosis in the work-up of a liver mass in the setting of elevated AFP or liver function impairment, especially in the absence of chronic liver disease.

Keywords Esophageal adenocarcinoma • Alpha-fetoprotein • Hepatocellular carcinoma • Liver mass

Introduction

Alpha-fetoprotein (AFP) is a glycoprotein normally produced by the fetal liver and yolk sac, beginning the sixth week of gestation. Although elevated at birth, the AFP level decreases to the normal adult range of 10–15 ng/mL over the first year of life. Tissues may regain the ability to produce AFP if they undergo malignant transformation [1]. As a result, elevation of serum AFP is commonly associated with hepatocellular carcinoma (HCC) and yolk sac tumors, and has also been reported in patients with other malignancies, most notably those of gastrointestinal origin. However, the organs of origin typically include gastric, pancreatic, and biliary, but rarely esophageal. McIntire et al., in their study of gastrointestinal neoplasms, reported elevation of serum AFP in 70% of 73 patients with HCC, 25% of 8 patients with biliary tract carcinoma, 24% of 45 patients with pancreatic carcinoma, 15% of 95 patients with gastric carcinoma, 3% of 191 patients with colorectal carcinoma, and 0% of 14 patients with esophageal or small intestine carcinoma [2]. To our knowledge, our case is only the 15th case of AFP-producing esophageal adenocarcinoma to be reported in the literature. Here, we report an interesting case of AFP-producing esophageal adenocarcinoma in the setting of transaminitis.
Case report

A 51-year-old previously healthy man presented with new-onset severe acid reflux triggered by solid foods of 2 weeks’ duration. In an effort to alleviate his symptoms, he restricted himself to a diet consisting of soft and liquid foods. He also endorsed a weight loss of 35 lb over the same period of time, right flank pain of 3 weeks’ duration, and non-bloody emesis in the two days leading up to presentation. He denied dysphagia or regurgitation of undigested food. He worked as a drywall mechanic, and denied any history of smoking, drinking, or illicit drug use. The patient’s vitals were within normal limits and physical examination was only remarkable for mild right upper quadrant tenderness without rebound or guarding.

Initial laboratory data were notable for hemoglobin 12.8 g/dL, AST 66 U/L, ALT 81 U/L, CEA 6.4 ug/L, CA 19–9 317,443 U/mL, and AFP 2524 ng/mL. Hepatitis B surface antigen and hepatitis C antibody were non-reactive. Computed tomography (CT) of the abdomen and pelvis revealed abnormal thickening of the esophagus (Fig. 1), numerous large retroperitoneal lymph nodes, and multiple masses throughout the liver consistent with metastatic disease (Fig. 2), but no evidence of pancreatic, biliary, or colonic masses and irregularities. CT-guided biopsy of one of the liver masses revealed CDX-2 positive (Fig. 3) and TTF-1 negative adenocarcinoma, suggesting gastrointestinal or pancreatobiliary origin. The combination of these imaging and immunohistochemical findings prompted a subsequent upper endoscopy, which revealed the presumed primary source, i.e., a large, fungating, partially obstructing mass with no stigmata of recent bleeding in the lower third of the esophagus situated 32–37 cm from the incisors (Fig. 4). There was no evidence of a gastric tumor. Cold forceps biopsy of the mass revealed ulcerated glandular mucosa with high-grade dysplasia (Fig. 5), with likely underlying malignancy.

One month later, the patient presented to the transfusion center to begin his first cycle of FOLFOX/Herceptin® therapy, but was subsequently admitted for dehydration in the setting of repeated vomiting. Given his poor functional status, he was no longer deemed a candidate for further chemotherapy. He underwent palliative esophageal stent placement and was discharged on home hospice where he died a week later.

Discussion

Esophageal adenocarcinoma is typically found in the lower third of the esophagus, and most commonly occurs in Caucasian males. Most, if not all, arise from a region of Barrett’s esophagus, a metaplastic response to chronic gastroesophageal reflux disease. Other risk factors for esophageal adenocarcinoma include smoking, obesity, and certain epidermal growth factor polymorphisms [3]. While elevations in CEA, CA 19–9, and β-HCG can be seen in esophageal carcinoma, few cases have reported elevations of AFP in the setting of esophageal adenocarcinoma [4, 5]. Wahren et al., in an attempt to identify possible tumor markers in patients with esophagus cancer, reported serum AFP levels >5 ng/mL in 18% of 33 cases of esophageal adenocarcinoma, although the highest reported AFP level was only 320 ng/mL [6]. Thus, elevated AFP levels in the setting of transaminitis and a liver mass usually prompt clinicians to consider HCC rather than esophageal cancer as the most likely diagnosis.
This diagnostic dilemma is further complicated since some AFP-producing esophageal adenocarcinomas can actually resemble HCC on pathology. A review of the literature suggests that AFP-producing esophageal adenocarcinomas can be categorized into two histological subtypes. If the adenocarcinoma contains cells resembling hepatic cells, they are classified as hepatoid adenocarcinoma. Hepatoid adenocarcinoma is a general term used to define any adenocarcinoma of extrahepatic origin that exhibits histologic characteristics resembling hepatic cells or hepatocellular carcinoma [7]. It most commonly arises from gastric epithelium, but can also arise from a variety of sites, including the gallbladder, lung, renal pelvis, ovaries, or esophagus. In contrast, AFP-producing esophageal adenocarcinomas exhibiting no hepatic characteristics on histologic examination are simply termed AFP-producing adenocarcinomas. Examination of our biopsy specimens revealed no evidence of hepatic features, suggesting that our patient’s malignancy can be categorized as AFP-producing esophageal adenocarcinoma. To be clear, however, we would like to note that both these subtypes are grouped under the umbrella term of AFP-producing esophageal adenocarcinoma in the literature and throughout this discussion for the sake of simplicity. Despite our patient’s markedly elevated serum AFP level, the AFP stain of his esophageal specimen was negative. This apparent incongruence is likely due to inadequate biopsy of the esophageal lesion, as histological analysis of the specimen revealed ulcerated glandular mucosa with high-grade dysplasia suggestive of underlying malignancy. Discussion
with a pathologist revealed that this finding is indicative of only a superficial sampling of the malignancy, suggesting that an inadequate specimen was obtained to detect AFP-positive cells. Unfortunately, the biopsy was obtained via cold forceps and the adequacy of the specimen could not be determined at the time of the procedure. Other less likely explanations for the negative AFP stain include tumor heterogeneity or the serum AFP being secondary to a paraneoplastic phenomenon. Given the marked elevation of serum AFP and the exclusion of a possible secondary malignancy, we believed the elevated serum AFP must be due to the esophageal adenocarcinoma, and that AFP staining of this lesion would have been positive if a more adequate specimen had been obtained.

Although our esophageal biopsy specimen did not detect the presence of concurrent Barrett’s esophagus, the majority, if not all, esophageal adenocarcinoma arises from Barrett’s metaplasia, making it highly likely that this AFP-producing esophageal adenocarcinoma is the sequela of Barrett’s. We also felt confident that the esophageal tumor was not a metastatic lesion. Immunohistochemical staining of liver mass biopsy suggested adenocarcinoma of gastrointestinal or pancreatobiliary origin. However, CT imaging did not note any masses or irregularities involving the colon, pancreas, or biliary system, and upper endoscopy only noted the presence of an esophageal mass, but not the presence of any gastric tumor. Furthermore, the fungating nature of the esophageal mass suggests outgrowth from the original esophageal mucosa.

Unfortunately, AFP-producing esophageal adenocarcinoma exhibits a poor clinical trajectory, and closely mirrors the clinical course of AFP-producing gastric adenocarcinoma. Both are characterized by a more advanced stage at presentation, higher liver metastatic potential, and poorer prognosis when compared to their non-AFP counterparts [8]. The hepatoid adenocarcinoma histological subtype of AFP-producing esophageal adenocarcinoma has traditionally been associated with increased hepatic metastatic potential and poorer prognosis when compared to its non-hepatoid counterpart [9, 10]. However, a review of all cases of AFP-producing esophageal adenocarcinoma suggests that both histologic types possess high liver metastatic potential and poor prognosis (Table 1), although the small number of cases makes it difficult to determine definite trends. The majority of cases were treated with a combination of surgery and a chemotherapy regimen involving fluorouracil-related and platinum-based agents. However, the overall results remain

Table 1 Summary of AFP-producing esophageal adenocarcinomas

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Histology subtype</th>
<th>AFP (ng/mL)</th>
<th>Survival (months)</th>
<th>Metastasis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>Female</td>
<td>Hepatoid</td>
<td>N/A</td>
<td>2</td>
<td>Liver, lung</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>44</td>
<td>Female</td>
<td>Hepatoid</td>
<td>WNL</td>
<td>4</td>
<td>Liver</td>
<td>Surgery, CTX</td>
</tr>
<tr>
<td>47</td>
<td>Male</td>
<td>Hepatoid</td>
<td>326,400</td>
<td>14</td>
<td>Liver</td>
<td>Paclitaxel, cisplatin</td>
</tr>
<tr>
<td>56</td>
<td>Male</td>
<td>Hepatoid</td>
<td>&gt;3000</td>
<td>N/A</td>
<td>Liver</td>
<td>N/A</td>
</tr>
<tr>
<td>55</td>
<td>Male</td>
<td>Hepatoid</td>
<td>&gt;300,000</td>
<td>4</td>
<td>Liver, LN, lung, mediastinum</td>
<td>None</td>
</tr>
<tr>
<td>55</td>
<td>Male</td>
<td>Hepatoid</td>
<td>47,800</td>
<td>9</td>
<td>Lung, LN, bone</td>
<td>Surgery, CTX</td>
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<tr>
<td>62</td>
<td>Male</td>
<td>Hepatoid</td>
<td>N/A</td>
<td>24 (alive)</td>
<td>Liver</td>
<td>Surgery, cisplatin, S-1</td>
</tr>
<tr>
<td>76</td>
<td>Male</td>
<td>Hepatoid</td>
<td>N/A</td>
<td>2 (alive)</td>
<td>N/A</td>
<td>Surgery</td>
</tr>
<tr>
<td>58</td>
<td>Male</td>
<td>Hepatoid</td>
<td>3788</td>
<td>22 (alive)</td>
<td>None</td>
<td>Surgery, S-1</td>
</tr>
<tr>
<td>80</td>
<td>Male</td>
<td>AFP-producing</td>
<td>351.5</td>
<td>4</td>
<td>Liver, lung, spleen, LN</td>
<td>Surgery, tegafur, lentinan, XRT</td>
</tr>
<tr>
<td>59</td>
<td>Male</td>
<td>AFP-producing</td>
<td>1500</td>
<td>2</td>
<td>Liver, LN</td>
<td>CTX</td>
</tr>
<tr>
<td>45</td>
<td>Male</td>
<td>AFP-producing</td>
<td>28.6</td>
<td>19</td>
<td>Liver, LN, pleural, peritoneal</td>
<td>Surgery, cisplatin, 5-FU, oxaliplatin, XRT</td>
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<tr>
<td>51</td>
<td>Male</td>
<td>AFP-producing</td>
<td>52.4</td>
<td>67</td>
<td>Pleura, LN</td>
<td>Surgery, cisplatin, 5-FU</td>
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<td>69</td>
<td>Male</td>
<td>AFP-producing</td>
<td>76.9</td>
<td>6 (alive)</td>
<td>N/A</td>
<td>Surgery</td>
</tr>
<tr>
<td>51</td>
<td>Male</td>
<td>AFP-producing</td>
<td>2524</td>
<td>2</td>
<td>Liver, LN</td>
<td>None</td>
</tr>
</tbody>
</table>

*AFP* alpha-fetoprotein, *CTX* chemotherapy (not specified), *LN* lymph nodes, *WNL* not elevated in serum but positive on biopsy immunohistochemistry, *XRT* radiotherapy
disappointing. Only four of the reported cases were still alive at the time of last follow-up—one had no evidence of metastasis and two did not specify. The fourth case involved a 62-year-old man with esophagogastric junction cancer and liver metastasis who was still alive at 2-year follow-up [11]. He was treated with total gastrectomy and lower esophageal resection, followed by 6 cycles of chemotherapy with S-1 and cisplatin, suggesting that combined surgery and chemotherapy may offer the best chance of prolonging survival.

As is the case with AFP-producing gastric adenocarcinoma, serial measurement of serum AFP levels in AFP-producing esophageal adenocarcinoma may be useful for monitoring clinical status and response to treatment. Chen et al. noted an abrupt decrease in their patient’s AFP post esophagectomy, but a subsequent increase with tumor recurrence and new metastases [12]. Similarly, Chiba et al. noted a significant decrease in AFP levels after the initiation of paclitaxel and cisplatin, with a corresponding regression in the size of their patient’s metastatic liver lesions [13]. Kobayashi et al. reported a case where serum AFP levels responded well initially to cisplatin and 5-fluorouracil (5-FU) [14]. However, a rapid rise in AFP levels several months later prompted a CT scan, which revealed a new pleural effusion and mediastinal lymph node swelling. Recurrent adenocarcinoma cells were detected by aspiration cytology in the effusion, and the patient eventually died a few months later. These findings suggest that measurement of the serum AFP level may be useful in assessing response to treatment or evaluating for recurrence and new metastases.

We believe prompt diagnosis of AFP-producing esophageal adenocarcinoma remains a challenge given its rarity. This may be due to the lack of routine testing for serum AFP in patients with esophageal adenocarcinoma, resulting in its under-reporting. A review of previous reports in the literature revealed a predominance of these cases originating from Japan. This may be attributed to the higher incidence of esophageal cancer in eastern countries, but is unlikely to be the only factor given that the predominant histological subtype in these regions is squamous cell carcinoma rather than adenocarcinoma [15]. Another contributing factor may be that clinicians from eastern countries routinely check a wider range of tumor markers in a malignancy work-up, thereby resulting in increased reporting of this phenomenon.

A few characteristics about our case distinguish it from previous reports. To our knowledge, our patient is only the third case of AFP-producing esophageal adenocarcinoma to be described in the Western world, as nearly all other cases occurred in Asia. Our case also exhibited the highest serum AFP level when compared to previously reported AFP-producing histological subtypes. Furthermore, while our patient did endorse symptoms of acid reflux, he had no complaints of dysphagia to suggest the presence of a mass or obstructing lesion in the esophagus. Instead, he endorsed right flank pain, which localized his symptoms to the liver, the site of his metastases, rather than that of his primary malignancy. This presentation differs markedly from prior reports in which the patient complained primarily of dysphagia, thereby suggesting a primary process in the esophagus. These unusual presenting symptoms made determining the site of origin of the primary malignancy particularly challenging and emphasize the importance of keeping a broad differential when evaluating a patient with an elevated AFP. Although HCC was the highest on our differential due to the markedly elevated AFP, the lack of cirrhosis, other risk factors for chronic liver disease, and multiple masses eventually led us to consider alternative etiologies. A review of prior imaging revealed an abnormal thickening of the esophagus on CT scan, which ultimately led us to the correct diagnosis. Despite discovering the primary source of malignancy, it did not prolong our patient’s survival as he died only two months after his diagnosis, further illustrating the poor prognosis and aggressive nature of this malignancy. Future clinicians should consider AFP-producing esophageal adenocarcinoma in their differential diagnosis when liver mass(es) are found without a clear liver-based etiology. We also recommend seeking out and investigating esophageal symptoms in any patient found to have an elevated AFP without a history of liver disease given the possibility of an esophageal primary cancer. Timely diagnosis is crucial since AFP-producing esophageal adenocarcinoma is aggressive and its management differs from that of HCC. The absence of cirrhosis or signs of chronic liver disease should raise the possibility of metastatic disease from an extrahepatic source. Clinicians should carefully examine any imaging findings for alternative sources of malignancy, and consider the use of further imaging, endoscopy, biopsy, and immunohistochemistry when appropriate to guide diagnostic work-up.

Compliance with ethical standards

Conflict of Interest: Jeremy Wang, Wendy Liu, and Keyur Parikh declare that they have no conflict of interest. Anthony B. Post serves on the speakers’ bureau and advisory panels for Gilead Pharmaceuticals.

Human/Animal Rights: All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Multiple attempts were made to contact the patient’s family for informed consent. However, they could not be reached with the phone numbers listed in the medical chart. The information in this case report has been sufficiently anonymized to protect patient confidentiality.
References
