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Foamy Histiocyte-like Esophageal Adenocarcinoma: Unusual Morphology and Diagnostic Pitfalls

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Abstract. *In the United States and other western countries, the vast majority of primary esophageal malignancies are adenocarcinomas arising in the lower esophagus within a background of Barrett's esophagus. The microscopic feature of esophageal adenocarcinoma varies, with the tubular or papillary adenocarcinoma of intestinal pattern being the most common, and other less common morphological patterns include adenosquamous, signet ring cell, mucinous, mucoepidermoid, and adenoid cystic carcinoma. This is a case report of esophageal adenocarcinoma with foamy histiocyte-like feature in a 71-year-old male with a history of smoking and Barrett's esophagus who presented with dysphagia and weight loss. The tumor cells showed an abundant foamy cytoplasm, low N/C ratio and irregular nuclear contour. They were arranged in single, trabecular and glandular patterns and deeply invaded adventitia. Lymphovascular invasion and perineural invasion were present. The foamy histiocyte like–tumor cells were negative for CD68, but strongly and diffusely positive for CK7. E-Cadherin was maintained in the tumor cells, and p53 immunostaining revealed a wild-type staining pattern. To the best of our knowledge, this is the first documented case of primary esophageal adenocarcinoma with foamy-histiocyte-like phenotype. The clinical course, diagnosis and prognosis of this entity are discussed.*

The prevalence, incidence and associated mortality of esophageal adenocarcinoma have been increasing over the past several decades (1, 2). In the United States, the vast majority of primary esophageal malignancies are adenocarcinomas arising in the lower esophagus or esophagogastric junction within a background of Barrett's esophagus (BE), although many new diagnostic cancer patients have no reported history of BE or heartburn (2, 3).

Clinically the signs and symptoms of esophageal adenocarcinoma include dysphagia, weight loss, chest pain, heartburn, and coughing/hoarseness. The microscopic feature of esophageal adenocarcinoma varies, with the tubular or papillary adenocarcinoma of intestinal pattern being the most common, and other less common morphological patterns include adenosquamous, signet ring cell, mucinous, mucoepidermoid, and adenoid cystic carcinoma. Carcinomas with foamy histiocyte-like features have been reported in the prostate, pancreas, breast and liver cancers, but not in esophagus adenocarcinomas (4).

In this paper we present a case of an unusual esophageal adenocarcinoma with foamy histiocyte-like feature of the distal esophagus in a 71-year-old male who had a history of smoking, Barrett's esophagus and neoadjuvant chemoradiation therapy, and discuss the diagnosis and its potential pitfall. To the best of our knowledge, this is the first documented case of primary esophageal adenocarcinoma with foamy-histiocyte-like phenotype. The clinical course, diagnostic pitfalls and prognosis of this entity are discussed.

Case Presentation

The patient was a 71-year-old male former heavy smoker with a past medical history of hypertension, diabetes mellitus type 2, coronary artery disease status post coronary artery bypass grafting, and Barrett's esophagus. He received esophageal dilation in 2011 due to dysphagia. Over the past 2 months he again developed dysphagia for solid food and had lost about 5 pounds of body weight. Esophagogastroduodenoscopy revealed an ulcerated lesion extended from 34 cm to 39 cm just beyond the gastroesophageal junction. The biopsy revealed an invasive adenocarcinoma. The patient underwent

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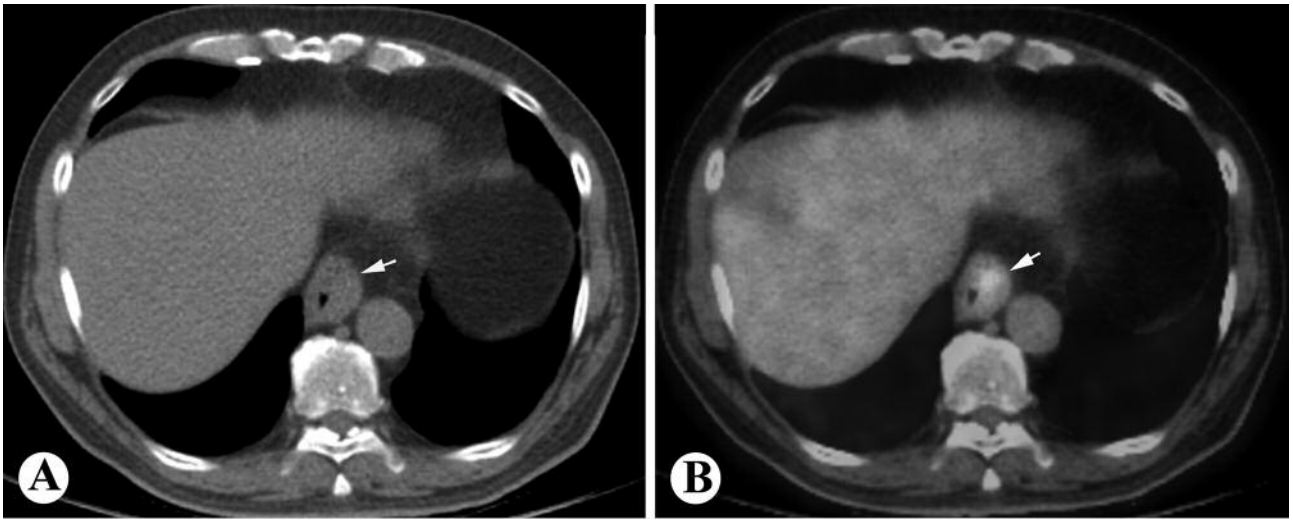

Figure 1. *Imaging findings of esophageal carcinoma. A: Computed tomography (CT) scan showing distal esophageal wall thickening (arrow); B: The PET/CT scan similarly showing distal esophageal thickening with increased ^{18}F-Fluorodeoxyglucose (FDG) avidity (arrow).*

a course of neoadjuvant chemoradiation therapy. His computed tomography (CT) scan showed distal esophageal thickening with no signs of metastasis (Figure 1A). The PET/CT scan similarly showed distal esophageal thickening with increased ^{18}F-Fluorodeoxyglucose (FDG) avidity (Figure 1B). There was no extra esophageal FDG avidity suggestive of metastatic disease. The endoscopic ultrasound revealed a stricture at 38 cm that the scope could not be passed beyond. Esophagogastrectomy was performed and the specimen was submitted for pathological evaluation.

In pathology, grossly the specimen consisted of a limited resection of 9.2 cm-segment including distal esophagus, cardia, and proximal stomach (Figure 2A). The length of the esophagus portion was 5.2 cm with a circumference of 3.5 cm. The stomach portion measured 4.0 cm in length and 7.5 cm in circumference. There was an ulcerated lesion (2.5 x 1.5 cm) in the gastroesophageal junction (GEJ), which measured 0.4 cm in depth and was 0.8 cm from the adventitial margin.

Microscopically there were focal residual tumor cells in a fibrotic stroma, consistent with response to the chemoradiation therapy. The tumor cells had low nuclear to cytoplasmic ratio and foamy cytoplasm (foamy histiocyte-like or "fried-egg" appearance), few tumor cells had large cytoplasmic vacuole (Figure 2B). Nuclear atypia was present. Cords and glandular arrangement of the foamy tumor cells were also present (Figure 2C). During intraoperative consultation, tumor cells involved both proximal and distal resection margins. Residual foamy tumor cells also deeply invaded the adventitia. Final resection margins were negative for carcinoma on additionally taken tissue. Lymphovascular invasion and perineural invasion were present. Uninvolved gastric and esophageal mucosa revealed changes consistent with reactive gastropathy and radiation esophagitis with ulceration.

Fourteen regional lymph nodes were identified, and two of them were positive for rare tumor cells morphologically mimicking foamy histiocytes (Figure 2D), cytokeratin AE1/AE3 immunostaining highlighted these tumor cells in the small lymph node. The foamy histiocyte like-tumor cells were negative for CD68, but they were strongly and diffusely positive for CK7. E-cadherin was maintained in the tumor cells with histocyte-like features. Immunostaining for p53 revealed a wild-type staining pattern. The final diagnosis was invasive adenocarcinoma with histiocyte-like features (yrpT3N1). Post-surgery, his subsequent clinical course was complicated by respiratory failure, tracheoesophageal fistula development and multiple episodes of aspiration pneumonia. On one year follow-up, he was appropriately treated and stayed in a stable condition without recurrence or metastasis identified in imaging findings.

Discussion

Esophageal adenocarcinoma is one of the most lethal malignancies in the gastrointestinal system and its incidence has increased approximately 600% during the past 40 years (1, 2). The American Cancer Society's estimates, in the United States for 2018, about 17,290 new diagnoses of esophageal cancer cases, and about 15,850 deaths from esophageal cancer (https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html). Barrett's esophagus is the major risk fact for esophageal adenocarcinoma with dysplasia

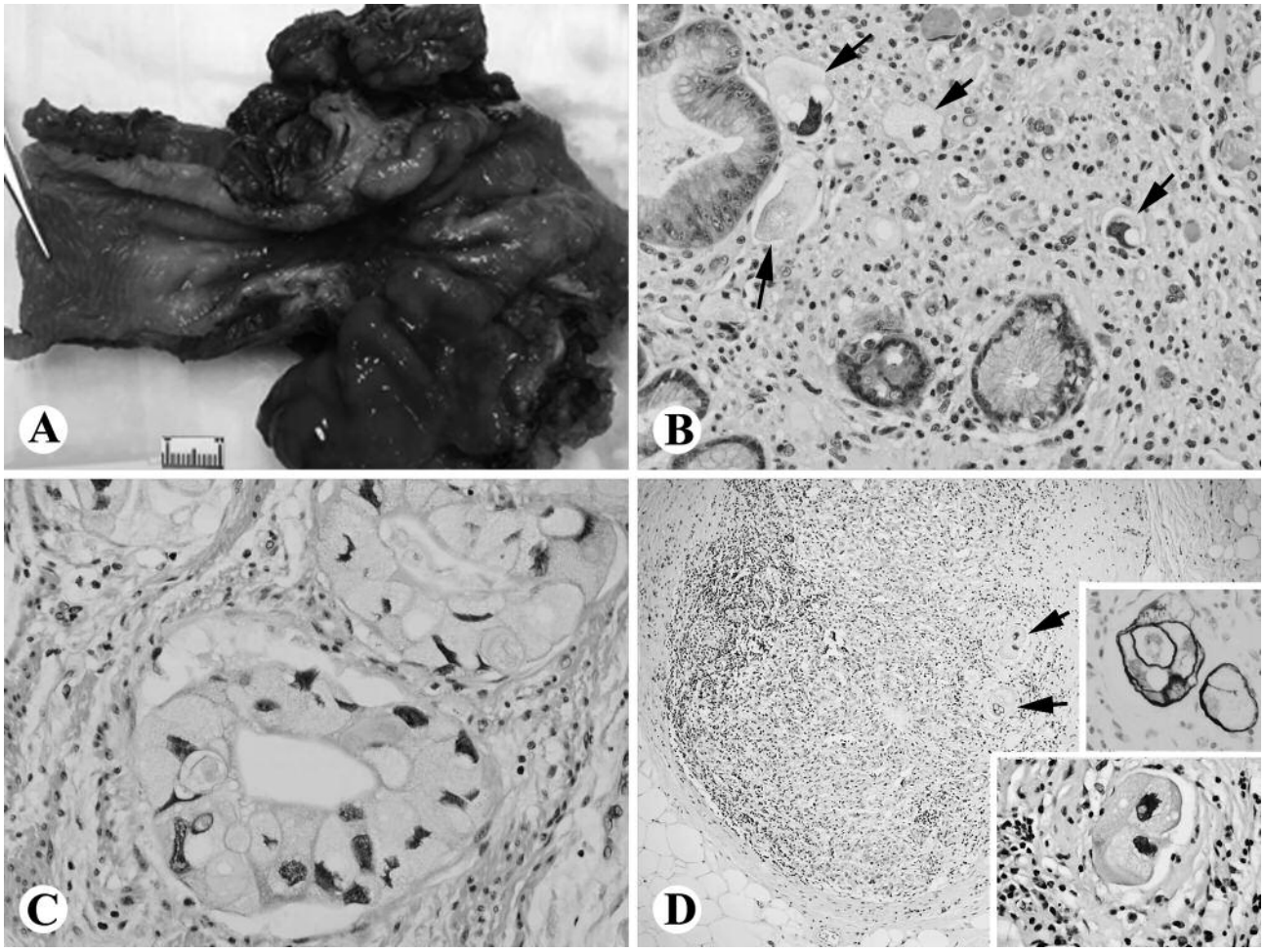

Figure 2. *Foamy histiocyte-like esophageal adenocarcinoma. A: Grossly, the esophagogastrectomy specimen showing an ulcerated lesion at the GE junction; B-D: Microscopically, single tumor cells (arrows) (B) and tumor glands with foamy cytoplasm (C) present in the stroma and small clusters of tumor cells (arrows) present in the lymph node (D) with AE1/AE3 immunoreactivity (D, inset upper 400×). (H&E stain, B, 100×; C, 400×; D, 40×, inset lower, 400×).*

being the most recognized factor for cancer risk stratification (5). Other risk factors include smoking, alcohol, gastroesophageal reflux disease, obesity, and history of radiation therapy. Currently esophagogastrectomy is the standard therapy, sometime with the preoperative neoadjuvant chemoradiation therapy for locally advanced esophageal cancer. The prognosis of esophageal adenocarcinoma is poor, and its 5-year survival rate is about 20%. Histological evidence of residue tumor cells after neoadjuvant therapy is an important prognostic factor. Sarcopenia may also worsen the long-term survival of patients with unresectable locally advanced esophageal cancer (6).

Microscopically esophageal adenocarcinoma has a wide range of glandular differentiation, with intestinal phenotype being the most common, and signet ring carcinoma is much less common than its gastric counterpart. Foamy histiocyte-like esophageal adenocarcinoma has not been reported in literature through PubMed search, and it may represent a diagnostic pitfall for pathologists. In the tumor bed, xanthogranuloma and infection may need to be ruled out for certain difficult cases, particularly in cases who received preoperative chemoradiation therapy as xanthogranulmatous response to extravasated mucin may occur after treatment. Metastatic foamy histiocyte-like tumor cells in the lymph nodes, as in our case, could be difficult to differentiate from reactive sinusoid histiocytes, and immunohistochemical staining for cytokeratin would be indicated in these situations.

Foamy histiocyte-like feature has been reported in different cancer types including prostatic adenocarcinoma, hepatocellular carcinoma, pancreatic intraepithelial neoplasia, pancreatic ductal adenocarcinoma, and breast adenocarcinoma (4, 7-11). Their clinical outcome is not clear due to the paucity of available information. In our case, the esophageal adenocarcinoma with foamy histiocyte-like feature had an aggressive pathological feature, with extensive involvement of adventitia, proximal and distal resection margins. Lymphovascular invasion and perineural invasion were present. Two lymph nodes were also positive for metastatic carcinoma. In the previous reports, hepatocellular carcinoma with foamy histiocyte-like feature had varied clinical outcome, and two out of three patients had a relatively better outcome as compared with conventional hepatocellular carcinoma (4, 8). However, the foamy histiocyte-like appearance of the tumor cells in our case may be due to therapy effect. Unfortunately, preoperative biopsy material was not available for review.

In summary, we report the first case of esophageal adenocarcinoma with histiocyte-like phenotype in a patient that received preoperative chemoradiation. The tumor morphology was unusual. The singly arranged or small cluster of tumor cells present in the lymph node could be misdiagnosed as reactive histiocyte post-radiation therapy. This may be the potential diagnostic pitfall for lymph node metastasis and, therefore, immunostaining for pancytokeratin is recommended. Further classification with a larger number of cases will be helpful to understand this rare and unique variant.

References

1 Brown LM, Devesa SS and Chow WH: Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. J Natl Cancer Inst *100*: 1184-1187, 2008.

2 Rubenstein JH and Shaheen NJ: Epidemiology, diagnosis, and management of esophageal adenocarcinoma. Gastroenterology *149*: 302-317, 2015.

3 Cooper SC, El-Agib A, Dar S, Mohammed I, Nightingale P, Murray IA, Cooper BT and Trudgill NJ: Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. Eur J Gastroenterol Hepatol *21*: 850-854, 2009.

4 Dunn R, Zhang W, Lai J, Litton T, Zhou Y and Lai JP: Foamy histiocyte-like hepatocellular carcinoma (HCC): A new variant of HCC? Ann Hepatol *16*: 304-307, 2017.

5 Quante M, Graham TA and Jansen M: Insights into the pathophysiology of esophageal adenocarcinoma. Gastroenterology *154*: 406-420, 2018.

6 Sato S, Kunisaki C, Suematsu H, Tanaka Y, Miyamoto H, Kosaka T, Yukawa N, Tanaka K, Sato K, Akiyama H and Endo I: Impact of sarcopenia in patients with unresectable locally advanced esophageal cancer receiving chemoradiotherapy. In Vivo *32*: 603-610, 2018.

7 Humphrey PA: Variants of acinar adenocarcinoma of the prostate mimicking benign conditions. Mod Pathol 31: S64-70, 2018.

8 Noro T, Gotohda N, Kojima M, Konishi M, Nakaghori T, Takahashi S, Hasebe T and Kinoshita T: Hepatocellular carcinoma with foamy histiocyte-like appearance: a deceptively clear cell carcinoma appearing variant. Case Rep Gastroenterol *4*: 286-292, 2010.

9 Albores-Saavedra J, Weimersheimer-Sandoval M, Chable-Montero F, Montante-Montes de Oca D, Hruban RH and Henson DE: The foamy variant of pancreatic intraepithelial neoplasia. Ann Diagn Pathol *12*: 252-259, 2008.

10 Adsay V, Logani S, Sarkar F, Crissman J and Vaitkevicius V: Foamy gland pattern of pancreatic ductal adenocarcinoma: a deceptively benign-appearing variant. Am J Surg Pathol *24*: 493-504, 2000.

11 Kimura A, Miki H, Yuri T, Hatano T and Tsubura A: A case report of lipid-rich carcinoma of the breast including histological characteristics and intrinsic subtype profile. Case Rep Oncol *4*: 275-80, 2011.

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