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Reviewer Comments

Reviewer 1 comments:

Title: The title needs modification. Abstract: Describes the case well. Introduction:Well written. Gives a clear idea of the disease process. Case report: Has been written very well and gives a clear picture of the case. Discussion: It is a very interesting case and highlights a very relevant issue which any clinician can face. It has very important message. Conclusion: Useful information for the practicing surgeon.

Author Comments: The title has been modified to: Metastatic pancreatic adenocarcinoma manifesting as dysphagia prior to localization of primary lesion: A case report and literature review.

The title has been modified in the manuscript and highlighted in red.

Reviewer 2 comments:

One concern is the submucosal adenocarcinoma may derived from ectopic gastric epithelium. Address this possibilities and cite some references.

Author comments:

An area of the discussion has been added with relevant references discussing this interesting possibility. The added text and references are below. It has been placed in the manuscript and highlighted in red text.

Adenocarcinoma found in the upper esophagus is an uncommon occurrence seldom encountered. While the esophageal carcinoma in the present case is likely an early manifestation of metastatic disease arising from an initially radiographically absent pancreatic primary, other etiologies must be considered. Another possible differential diagnosis with the rare but documented potential to result in the formation of an upper esophageal adenocarcinoma is a focus of gastric heterotopia. Ectopic gastric mucosa is typically an asymptomatic finding that is incidentally diagnosed during endoscopic biopsies, and has an estimated incidence ranging from 3.6-10%[27,28]. If visualized

endoscopically, gastric heterotopia is often a salmon colored round patch that is well demarcated from surrounding esophageal stratified squamous mucosa[29]. Histologically, gastric heterotopia has fundic type gastric mucosa with chief and parietal cells commonly in the absence of clinically evident reflux symptoms[28]. It is thought that ectopic gastric tissue stems from incomplete replacement of columnar epithelium with squamous epithelium during fetal development, or it is acquired later in life from chronic reflux, like the pathophysiologic development of Barrett's esophagus[30-33].

Gastric heterotopia resulting in proximal esophageal adenocarcinoma is a rare occurrence, with less than 5 dozen cases reported. While the mechanism of invasive carcinoma arising from gastric heterotopia is unknown, it is possible that it occurs through a metaplasia-dysplasia cascade in a similar fashion invasive carcinoma arises from Barret's esophagus[33]. In the setting of Barrett's esophagus, intestinal metaplasia replaces the stratified squamous epithelial layer that normally lines the esophagus with mucin containing goblet cells scattered amongst a background of foveolar columnar epithelium[34]. In the rare occurrence of histologic progression to a neoplastic process, dysplasia of gastric mucosa or intestinal metaplasia may be present[29]. Interestingly, in adenocarcinomas attributed to proximal esophageal gastric heterotopia, intestinal metaplasia associated with BE is reported in approximately 5% of cases and only sporadically through case reports [35]. In the present case, esophageal biopsy demonstrated glandular epithelium, high grade columnar dysplasia with papillary architecture, and nuclear crowding and hyperchromasia with overlying squamous epithelium consistent with the esophageal mucosa. Histology consistent with gastric heterotropia was not found, making this possibility a less likely cause of the proximal esophageal carcinoma.

27. Poyrazoglu OK, Bahcecioglu IH, Dagli AF, Ataseven H, Celebi S, Yalniz M. Heterotopic gastric mucosa (inlet patch): endoscopic prevalence,

histopathological, demographical and clinical characteristics. Int J Clin Pract. 2009;63(2):287-91. [PMID: 17535303; DOI:10.1111/j.1742-1241.2006.01215.x.]

28. Borhan-Manesh F and Farnum JB. Incidence of heterotopic gastric mucosa in the upper oesophagus. Gut. 1991; 32(9): 968–972. [PMID: 1916499; doi: 10.1136/gut.32.9.968]
29. Chong VH. Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus. World J Gastroenterol. 2013 Jan 21; 19(3): 331–338. [PMID: 23372354; doi: 10.3748/wjg.v19.i3.331]
30. Tanaka M., Ushiku T., Ikemura M., Shibahara J., Seto Y., Fukayama M. Esophageal adenocarcinoma arising in cervical inlet patch with synchronous Barrett's esophagus-related dysplasia. Pathol. Int. 2014;64(August (8)):397–401. [PMID: 25143128; doi: 10.1111/pin.12181]
31. Von Rahden BHA, Stein HJ, Becker K, Liebermann-Meffert D, Siewert JR. Heterotopic gastric mucosa of the esophagus: literature-review and proposal of a clinicopathologic classification. Am. J. Gastroenterol. Nature Publishing Group (2004) 99 (March (3)) 543–551. [PMID: 15056100; DOI: 10.1111/j.1572-0241.2004.04082.x]
32. Avidan B, Sonnenberg A, Chejfec G, Schnell TG, Sontag SJ. Is there a link between cervical inlet patch and Barrett's esophagus?, Gastrointest. Endosc., Elsevier, (2001) 53 (June (7)) 717–721. PMID: 11375577; DOI: 10.1067/mge.2001.114782]
33. Riddiough GE, Hornby ST, Asadi K, Aly A. Gastric adenocarinoma of the upper oesophagus: A literature review and case report. Int J Surg Case Rep. 2017;30:205-214. PMID: 28086198; DOI:10.1016/j.ijscr.2016.11.014]
34. Jain S and Dhingra S. Pathology of esophageal cancer and Barrett's esophagus. Ann Cardiothorac Surg. 2017 Mar; 6(2): 99–109. [PMID: 28446998; doi: 10.21037/acs.2017.03.06]
35. Peitz U, Vieth M, Evert M, Arand J, Roessner A, Malfertheiner P. The prevalence of gastric heterotopia of the proximal esophagus is underestimated, but

preneoplasia is rare - correlation with Barrett's esophagus. BMC Gastroenterol. 2017 Jul 12;17(1):87. [PMID: 28701149; doi: 10.1186/s12876-017-0644-3]