

Peer Review File

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Reviewer A

Comment 1) This paper was written on the assumption that heterotopic pancreas in Meckel's diverticulum (MD) caused lower GI bleeding. However, it has not been proved and it may not be true. The authors should discuss how the heterotopic pancreas in MD caused the lower GI bleeding.

Reply 1) Thanks for your comment. We've done a thorough literature review related to the etiology of bleeding in MD. Abundant evidence supported heterotopic pancreas in MD did cause the lower GI bleeding and mechanism is stated as follows.

Changes in the text 1 (page 7, line 134-page 8, line 135-140, highlight in yellow):

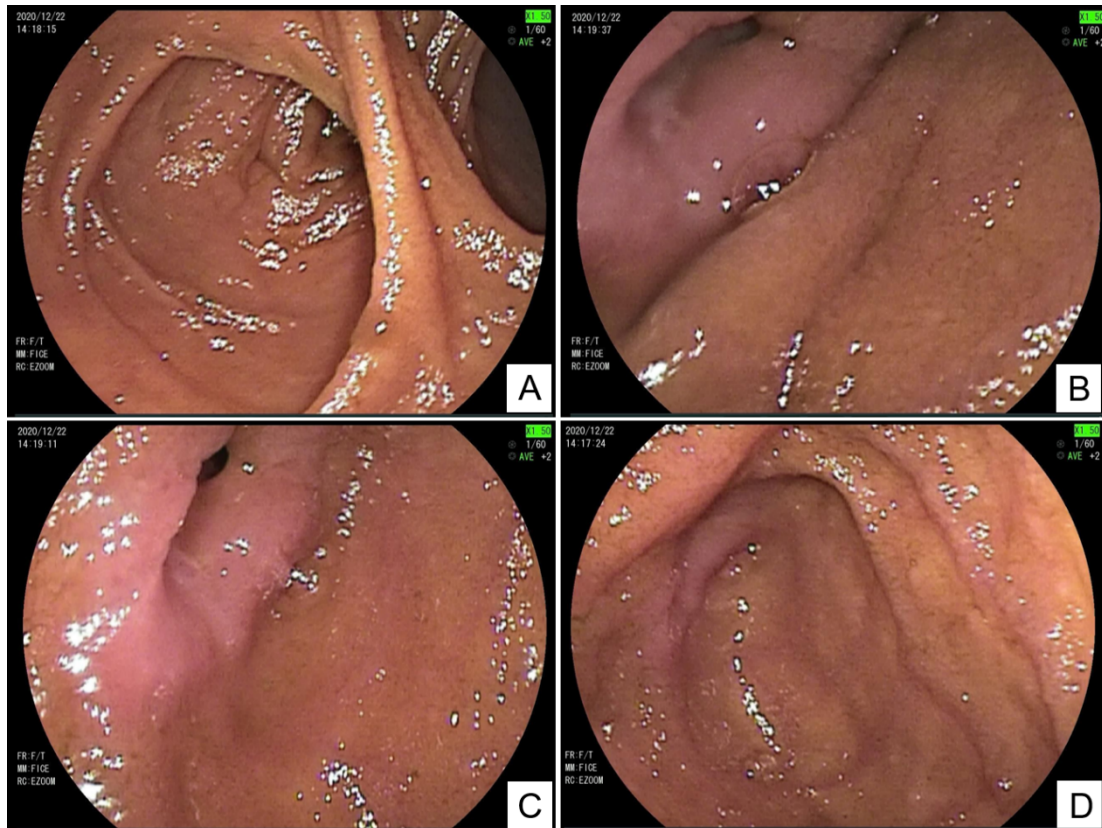
GI bleeding is an associated complication of heterotopic pancreas. The etiology of bleeding in patients with heterotopic pancreas is believed to be related to ulceration of the mucosa overlying the aberrant lesion(15). As described previously, chemical irritation and inflammation can lead to disruption of the mucosal barrier while pancreatic enzymes, such as elastase, may cause thinning and erosion into the walls of underlying vasculature(15). Ulceration as the cause of GI bleeding is supported by the series put forward by Pang which reported ulcerated mucosa in pathologic specimens from patients with evidence of bleeding(16).

Comment 2) Although the ulcer in MD was the most important lesion in this case, it was poorly mentioned. The size and depth of the ulcer must be described. Figure 1B is not enough. Figures for the histological findings of the ulcer are also needed.

Reply 2) Thanks for your comment. The diverticulo-like mass was 3*2cm in size, and the ulcer was 0.5*0.6cm in size and 0.3cm in depth. We also added two more pictures of double balloon enteroscopy in figure 1. And the histological findings of the ulcer are

shown in figure 3.

Changes in the text (page 5, line 85-86; page 7, line 234):



Comment 3) Recent report indicated that the cause of bleeding in MD is not a peptic ulcer, but Dieulafoy's lesion (*). Therefore, the authors should re-examine the presence of vascular lesion pathologically. The heterotopic pancreas may be innocent.

(*). Takeyama J. *Fetal Pediatr Pathol.* 2022; 41: 865-70)

Reply 3) Thanks for your comment. We have read Takeyama J's report carefully which is enlightening and re-examined the cause of bleeding in MD in our case. We added a separate paragraph in the Discussion and also some references. It is worth mentioning that DL was not found in our case through histological examination and the ulceration was evident, so we believe it was the heterotopic pancreas that caused GI bleeding.

Changes in the text (page 8, line 141-151, highlight in yellow):

It has been widely accepted that GI bleeding resulted from a peptic ulcer is caused by the ectopic gastric mucosa or pancreatic tissue in MD (17,18). This is supported by a

study reporting that the frequency of symptoms in all MD is approximately 2%-4%, whereas those in MD with ectopic tissue is as high as 60% (18). However, Takeyama J pointed out that Dieulafoy's Lesion (DL), a vascular abnormality, is the actual cause of GI bleeding in MD, with 100% detection rate of DL in 10 cases, and no ectopic tissue was found in one of the cases (19). This finding suggests that ectopic tissue may not be the only reason of GI bleeding in MD. However, DL was not found in our case and the ulceration was evident, so we believe it was the heterotopic pancreas that caused GI bleeding. But for those cases with GI bleeding in MD in which no ectopic tissue is found or ulceration is not evident, DL has to be considered and special examinations like pieces of step sections or angiography are needed to distinguish if GI bleeding is caused by DL.

Reviewer B

Comment This is a case report of a rather uncommon abnormality.

Interesting case report of an uncommon entity.

Reply Thanks for your comment.