Double heterotopic pancreas and Meckel's diverticulum in a child: do they have a common origin?

Gökhan Baysoy[1], Necati Balamtekin[1], Nuray Uslu[1], Afra Karavelioğlu[2], Beril Talim[3], Hasan Özen[1]

Units of [1]Pediatric Gastroenterology, Hepatology and Nutrition, and [3]Pathology, Department of Pediatrics, and [2]Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Heterotopic pancreatic tissue consists of normally differentiated pancreatic tissue without a real anatomic and vascular connection to the pancreas, whereas Meckel's diverticulum is one of the most important cause of lower gastrointestinal bleeding in children. Although heterotopic pancreatic tissue is related to various gastrointestinal diseases/malformations in both humans and animals, it is rarely associated with Meckel's diverticulum. Herein, we report a five-year old boy who presented with melena and hematochezia, which were discovered to be the result of Meckel's diverticulum. He also had multiple heterotopic pancreatic tissues in various parts of the gastrointestinal tract. The reason for this association is not known, but might involve some abnormalities of signaling molecules expressed in the development of the gastrointestinal tract and associated organs. In clinical practice, it is important to remember that Meckel's diverticulum and heterotopic pancreatic tissue might occur together or accompany various other gastrointestinal anomalies.

Key words: child, heterotopic pancreas, Meckel's diverticulum, embryology.

Heterotopic pancreatic tissue consists of normally differentiated pancreatic tissue without a real anatomic and vascular connection to the pancreas[1]. Ectopic tissue is usually discovered in the submucosa of the upper gastrointestinal (GI) tract, including the stomach, duodenum and jejunum, or within a Meckel's diverticulum.

Meckel's diverticulum is one of the most important cause of lower GI bleeding in children. It may contain ectopic gastric, intestinal or pancreatic tissues. Multiple heterotopic pancreatic tissues and Meckel's diverticulum have rarely been reported[2]. We report a five-year-old boy with double heterotopic pancreatic tissue and Meckel's diverticulum.

Case Report

A five-year-old boy was admitted to our hospital with the complaints of hematochezia and melena. Past medical history revealed that he had melena one month before. During the first episode, he was hospitalized in another center and an upper GI endoscopy had been performed. The endoscopy showed an ectopic pancreatic tissue with central umbilication in the prepyloric antrum and normal esophagus, duodenum and gastric mucosa. Urease test and histopathological examination of the stomach did not reveal *Helicobacter pylori*. Meckel's scan was found to be negative. That episode lasted five days and the patient required multiple blood transfusions. A second bleeding episode had started three days before the admission to our hospital. He was transfused multiple times before admission to our unit. On admission, physical examination and vital signs of the patient were normal. Laboratory tests revealed normal liver enzymes, liver function tests (activated partial thromboplastin time [aPTT]/ international normalized ratio [INR], albumin), hemoglobin, and thrombocyte count. Upper GI endoscopy was normal except for a prepyloric ectopic pancreatic tissue. Colonoscopy, carried out in the same session, was suboptimal because of blood covering the mucosa. No

mucosal lesions could be seen within the colon up to the cecum. Terminal ileum could not be intubated. Tc-99m–labeled red blood cell scintigraphy showed an active bleeding site in the right lower quadrant around the terminal ileum.

On the suspicion of Meckel's diverticulum, he was operated. During the operation, a Meckel's diverticulum, 35 cm proximal to the ileocecal valve, was localized and dissected. Histopathological examination showed ectopic gastric tissue within the diverticulum. During abdominal exploration, a nodular mass was palpated 15 cm distal to the Treitz ligament within the intestinal wall. The bowel segment containing this mass was resected and an anastomosis was performed between the two bowel segments. Histopathological evaluation of this resected bowel segment revealed pancreatic tissue in the submucosa, lined by intestinal mucosa (Fig. 1). The postoperative course was uneventful, and he was discharged symptom-free.

Discussion

Heterotopic pancreatic tissue is usually asymptomatic and submucosally located, and is usually discovered incidentally in the upper GI tract during endoscopy, surgery or autopsy[1]. It may sometimes cause symptoms such as inflammation (pancreatitis), bleeding, malignant transformation in adults, and intussusception in children, leading to the diagnosis[3-6]. Occasionally, heterotopic pancreatic tissue may be subserosal[4,7].

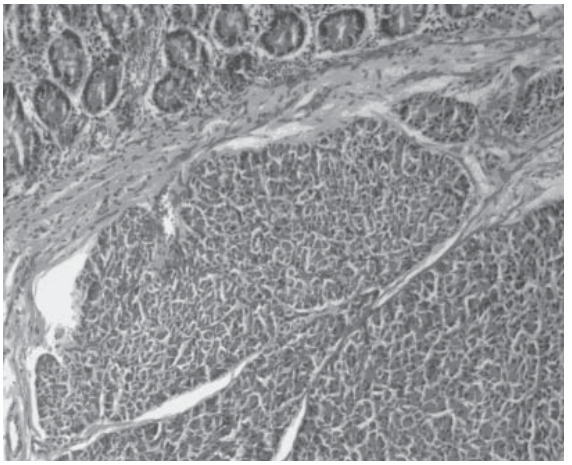

Figure 1. Submucosal pancreatic acini beneath intestinal mucosa represented in upper part (hematoxylin & eosin stain, original magnification x 10).

Heterotopic pancreatic tissue is usually solitary; however, it may be multiple in some cases[2,3]. In a report by Ogata et al.[3], the authors stated that 2 out of 12 patients had more than one heterotopic pancreatic tissue. Four patients had heterotopic tissue within Meckel's diverticulum, and one of them also had extra-diverticular pancreatic tissue. Our patient had double heterotopic pancreatic tissue apart from Meckel's diverticulum. They did not cause any symptoms in our patient and were detected during the investigation for GI bleeding.

Heterotopic pancreatic tissue is related to various GI diseases/malformations in both humans and animals[3]. Congenital diaphragmatic hernia, hypertrophic pyloric stenosis, malrotation, jejunal atresia, choledochal cysts, biliary atresia, and Meckel's diverticulum were reported to occur with Heterotopic pancreas in humans[3]. Presence of heterotopic pancreatic tissue with other GI system malformations may indicate a common embryological origin.

Meckel's diverticulum is the most common omphalomesenteric abnormality and is said to occur in 2-3% of the population[8]. It occurs after the 10th week of embryogenesis after the returning of the midgut into the abdominal cavity[8]. Painless and profuse bleeding and intussusceptions are important complications of Meckel's diverticulum. Although diverticulum is in connection with the intestines, it mostly contains non-intestinal cells such as gastric, pancreatic, and/or hepatic cells. Bossard et al.[9] suggested that these cells might have escaped from the normal restriction of the intestinal programming, causing the formation of other endodermal cells. Although the concurrence of Meckel's diverticulum and pancreatic heterotopia was previously reported either as heterotopic tissue within the diverticulum or outside the diverticulum[10], the link between pancreatic heterotopia and Meckel's diverticulum is not known. It is not known if this coexistence is coincidental or an associated condition. Improper molecular signaling throughout the GI tract might underlie the concurrent appearance of these anomalies.

The GI tract is mainly formed from endoderm and mesoderm. Development of accessory organs, such as the pancreas, involves close interaction of these two layers via the hedgehog signaling[11]. Pancreatic development requires complex signaling molecules under genetic control[12]. Sonic hedgehog (Shh) is expressed throughout the GI tract. It has been shown in mice that Shh is required for the growth and differentiation of the foregut, and homozygous Shh-null mutant mice show esophageal atresia/stenosis, tracheoesophageal fistula and tracheal and lung anomalies, features similar to those observed in humans with foregut defects[13]. On the contrary, loss of Shh expression is necessary for proper pancreatic development. This path also creates a way to the formation of pancreatic heterotopia. The absence of normally occurring Shh in the stomach is the cause of ectopic pancreatic tissue development in these regions[14]. Complete loss of Shh was shown to cause GI system anomalies in mice[11,15]. Expression of home domain transcription factor Pdx1 is also necessary for appropriate pancreatic development[16]. It was proposed that pancreatic heterotopia occurs mainly in regions where Pdx1 expression and inactive Shh signaling concur[14]. Pancreatic heterotopia was believed to result from buds of embryonic pancreatic tissue penetrating into the gut wall and consequently separated from the pancreas. In the present case, loss of Shh in a different part of the GI tract might cause both multiple heterotopic pancreas tissues and Meckel's diverticulum.

In conclusion, the cause of concurrent heterotopic pancreatic tissue and Meckel's diverticulum is not known but might involve abnormalities of signaling molecules expressed in the development of the GI tract and associated organs. In clinical practice, it is important to remember that Meckel's diverticulum or heterotopic pancreatic tissue might accompany each other or various other GI anomalies.

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