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Possible link between ectopic pancreas and holoprosencephaly

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Abbreviations: HPE, holoprosencephaly; PP, pancreatic polypeptide

We report on the incidental observation of ectopic pancreas in a donor for islet cell transplantation. The donor's clinical and imaging presentation was definitive for holoprosencephaly. This case report discusses a possible link between ectopic pancreas and holoprosencephaly.

Case Presentation

A 22-y-old male became a multiple-organ donor after diagnosis of brain death and obtaining a legal consent. His past medical history included hydrocephalus necessitating ventriculo-peritoneal shunt placement at birth and seizure disorder since 2 y of age, with a clinical diagnosis of holoprosencephaly (HPE), but was unremarkable for pancreatic disease. Laboratory tests revealed serum lipase level of 115 U/L and hemoglobin A_{1c} of 4.6%. His body weight was 35 kg and height 160 cm. His pancreas was retrieved en bloc with the spleen and duodenum at a local hospital and transported to the Clinical Islet Laboratory at the University of Alberta for the purpose of islet isolation and transplantation. When the spleen and duodenum were dissected from the pancreas, it was noted that a small yellowish nodule presented at the posterior aspect of proximal duodenum, just below the pyloric ring (**Fig. 1**). This solid nodule, apparently not connected with the pancreas, could be easily dissected from the duodenal wall. The nodule was not subjected to islet isolation process, but was preserved for histological examination. During intraductal perfusion of the pancreas as a first step of islet isolation procedure, it was further noted that there was no communication between the ventral and dorsal ducts, leading to a diagnosis of pancreas divisum. The isolation procedure from this small pancreas (55 g) failed to yield enough islet mass for clinical transplantation. Histopathologic examination of the nodule revealed ectopic pancreas consisting of pancreatic acini, ducts and islets (**Fig. 2**). Immunohistologically islets stained positive for both insulin and glucagon, but we could not detect islets containing abundant pancreatic polypeptide (PP) positive cells.

Discussion

HPE is a genetically and phenotypically heterogenous disorder involving the development of brain and face. Sonic hedgehog (*Shh*) is one of genes for responsible for HPE. Dominant and recessive mutations of *Shh* in humans lead to HPE.[1] *Shh* is broadly expressed throughout embryonic development but is excluded from the pancreas during development. Thus increased *Shh* signaling can suppress the development of the pancreas[2] while inhibition of *Shh* leads to ectopic development of the pancreatic tissue.[3] Although we did not investigate the mutation of *Shh* and chromosomal abnormality, the present case suggests a link between HPE and development of ectopic pancreas.

Tsugu et al. have reported a young Japanese female with congenital brain malformation associated with intracranial ectopic pancreas.[4] The patient underwent ventriculo-peritoneal shunt placement for hydrocephalus at birth, suggesting HPE. At age of 11, her brain tumor was resected and pathological examination revealed a non-functioning pancreatic tumor arising from intracranial ectopic pancreas. Interestingly a further detailed analysis showed pancreatic duodenal homebox 1 was not expressed in the ectopic pancreatic tissue.[5]

A review described by Lemire indicates that there is one case of HPE associated with ectopic pancreas,[6] but we note that the term "ectopic pancreas" was used to describe pancreas located caudally[7] in the Lemire's review.

The histogenetic mechanism of ectopic pancreas development remains unknown. One hypothesis postulates trans-commitment of non-pancreatic tissue progenitors to pancreatic lineage. Another theory proposes that pancreas fragments are separated from the original pancreas into the different sites during development of the pancreas. If the latter is the case, a question arises as to which anlage is the origin of the ectopic pancreas. To answer this question we examined the presence of PP-rich islets in the ectopic pancreas and found that very few PP-expressing cells were detected. Because it is well known that islets in the ventral pancreas contain abundant PP-cells in contrast to PP-poor islets in the dorsal panceras,[8] the present case suggests that the origin is not likely to be the ventral pancreas.

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There are several reported cases, including the present case, with ectopic pancreas accompanied with pancreas divisum.[9] Considering an incidence of 1.3–22%,[10] pancreas divisum may be now regarded as a normal variant rather than a true malformation. We believe that co-existence of the two entities in our case is just incidental and insignificant.

In summary, we report a case of ectopic pancreas in association with HPE. This case report is a valuable starting point for further investigation regarding a genetic link between the two conditions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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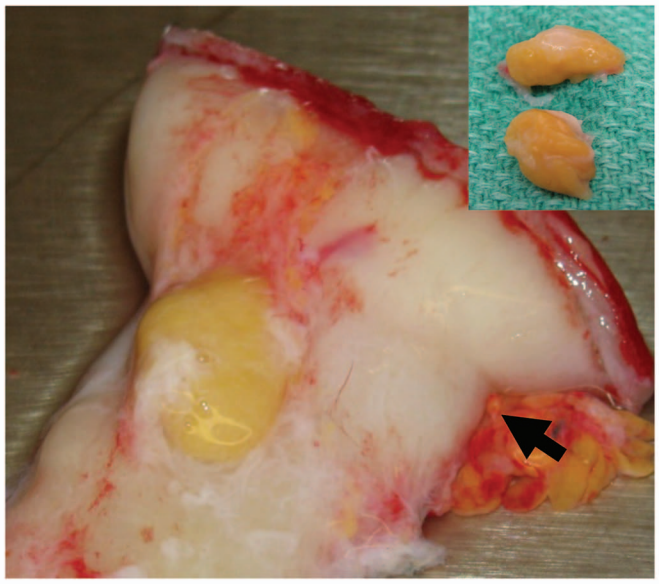

Figure 1. Ectopic pancreas is located on the posterior duodenum, just near the pyloric ring (arrow). Inset: A cut surface of resected ectopic pancreas shows no cystic lesions.

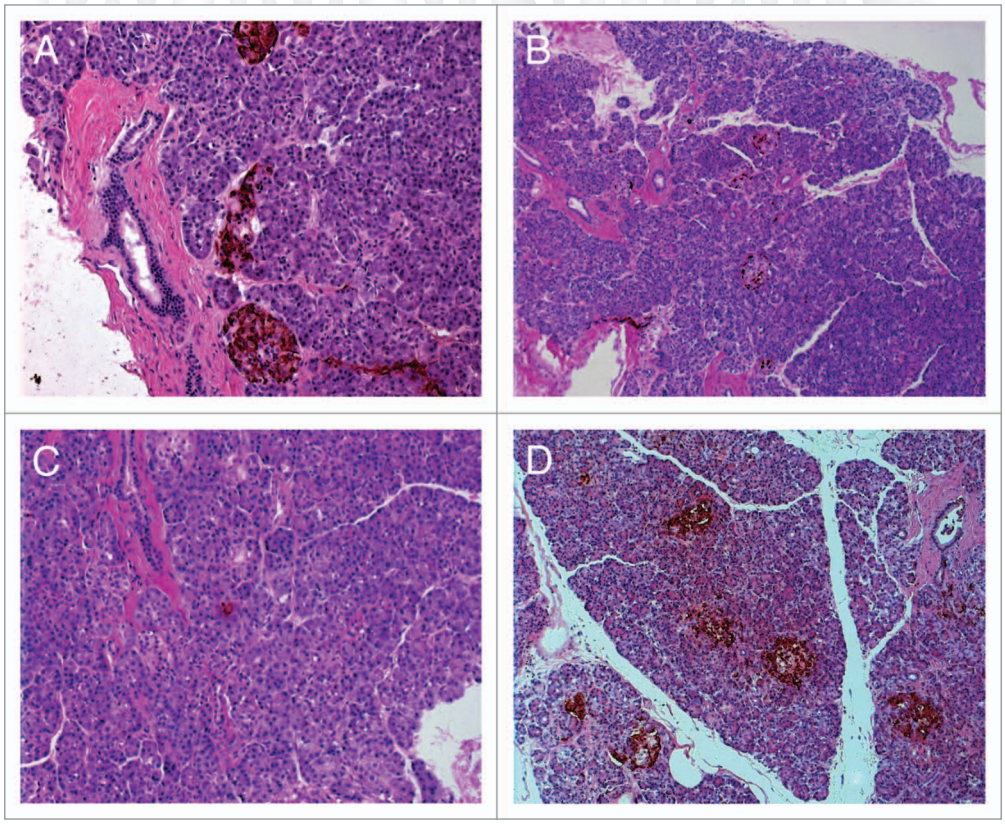

Figure 2. Ectopic pancreas stained for insulin (A), glucagon (B) and pancreatic polypeptide (C). Normal ventral pancreas from a different donor stained for pancreatic polypeptide shows pancreatic polypeptide enriched islets (D).

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