Abdominal hamartoma with pancreatic and hepatic differentiation in a sow

Nanako USHIO1), James K. CHAMBERS1)*, Kennichi WATANABE1), Takuya E. KISHIMOTO1), Jun-You LI2), Hiroyuki NAKAYAMA1) and Kazuyuki UCHIDA1)

1)Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113–8657, Japan
2)Animal Resource Science Center, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113–8657, Japan

(Received 31 March 2016/Accepted 20 April 2016/Published online in J-STAGE 1 May 2016)

ABSTRACT. A 7-year-old Duroc sow exhibited emaciation, loss of appetite and rapid breathing, and was euthanized. Histopathological examination revealed mild to moderate fibrosis of the heart, cystic kidneys and ulcerative enteritis associated with Balantidium infection. Additionally, a small nodule was incidentally found in the peripancreatic fat tissue. The nodule consisted of disarranged cellular components: pancreatic islet cells (either insulin-, glucagon- or somatostatin-positive), pancreatic acinar cells, hepatocytes (human hepatocyte-positive) and ductal cells (cytokeratin 19-positive). Some of the human hepatocyte-positive cells were also positive for chromogranin A and cytokeratin 7, indicating that they were hepatic progenitor cells. The nodule was therefore diagnosed as hamartoma, probably originating from a fragment of the caudal verge of the liver bud, which contains hepatic and pancreatic progenitors.

KEY WORDS: abdominal hamartoma, liver, pancreas, sow

Hamartoma is a focal overgrowth of endogenous mature cells in an organ [2, 4]. Pancreatic hamartoma in humans was divided into solid, and solid and cystic hamartoma in a previous report [6]. Solid pancreatic hamartoma is composed of three disarranged cellular components (acinar, islet and ductal cells) in the sclerotic stroma [6, 9]. Solid and cystic pancreatic hamartoma is a solid hamartoma with cystic lesions [6, 8]. Animal cases of pancreatic hamartoma, however, have not been reported. We observed a unique hamartoma lesion consisting of pancreatic and hepatic cells in a sow.

A 7-year-old Duroc sow exhibited emaciation, loss of appetite and rapid breathing, and was euthanized because of a poor prognosis. At necropsy, enlargement of the heart (right ventricular dilation and left ventricular hypertrophy) and polycystic kidneys was observed. Tissues from the heart, trachea, thyroid glands, lung, liver, spleen, pancreas, small intestines, large intestines and brain were fixed in 10% neutral-buffered formalin. The tissues were routinely embedded in paraffin, sectioned 4-µm thick and stained with periodic acid Schiff (PAS) as well as hematoxylin and eosin (HE).

Microscopically, mild to moderate fibrosis was found in the ventricular wall of the heart. In the small and large intestines, ulcerative enteritis associated with Balantidium infection was observed. A small nodule was incidentally found in the peripancreatic fat tissue (Fig. 1) composed of (i) cuboidal endocrine cells with an eosinophilic cytoplasm, a pale round nucleus and prominent nucleoli forming islet structures surrounded by thin connective tissue (Fig. 2, black arrows), (ii) columnar epithelial cells forming the duct (Fig. 2, green arrows), (iii) polygonal cells with an eosinophilic granular cytoplasm and an oval-shaped nucleus arranged in a trabecular pattern or a pseudo acinar structure (Fig. 3, arrows) and (iv) pancreatic exocrine cells with a hyperchromatic nucleus and PAS-positive zymogen granules in the cytoplasm forming the acinus (Figs. 2 and 3, arrowheads). All types of cells were mature and showed no nuclear or cytological atypia.

Immunohistochemistry was performed using the primary antibodies listed in Table 1. Reaction products were visualized using the EnVision+ System (Dako, Kyoto, Japan). The cuboidal cells (i) were positive for glucagon (Fig. 4), somatostatin (Fig. 5) or insulin (Fig. 6). The glucagon- or somatostatin-positive cells were located in the periphery of the islet structure (Figs. 4 and 5), and the insulin-positive cells were in the center (Fig. 6). Duct-forming columnar cells (ii) were immunopositive for cytokeratin (CK) 19 (Fig. 7). The large polygonal cells with eosinophilic granules (iii) were moderately to strongly immunopositive for human hepatocyte and chromogranin A, and partly immunopositive for CK 7 (Figs. 8–10), but negative for synaptophysin. Hepatocytes in the liver were positive for human hepatocyte and chromogranin A, and partly positive for CK 7, while ductal cells in the pancreas and liver were positive for CK 19. Islet cells in the pancreas were positive for glucagon, somatostatin, insulin and/or synaptophysin. Immunohistochemistry results are summarized in Table 2.

In the present study, the cellular components of the peripancreatic nodule indicated its pancreatic and hepatic differentiation. Differential diagnosis of the nodule included hamartoma, transdifferentiation of pancreatic cells to hepatic cells and ectopic liver tissue in the pancreas. Transdifferentiation, known as metaplasia of pancreatic exocrine cells into hepatocytes, has been observed in vitro and in experiments during regeneration after massive injury [3, 5, 10–13, 15]. Glucocorticoid adminis-
tration or copper deficiency can also induce transdifferentiation of the pancreas to the liver [11, 12, 15]. In the present case, however, glucocorticoid administration was not conducted, and regeneration of the pancreas was not observed. Immunohistochemical examinations revealed that insulin-, glucagon- and somatostatin-positive cells were arranged in the same pattern observed in the pancreatic islets of a pig [14]. However, some of the endocrine cells were scattered in the tissues without forming islets. Large polygonal cells were positive for human hepatocyte, and some of these cells were also positive for chromogranin A and CK 7 (Figs. 8–10). This staining pattern was consistent with that of he-
Table 1. Primary antibodies used in the present study

| Antibody                        | Clone   | Dilution | Antigen retrieval | Source                          |
|--------------------------------|---------|----------|-------------------|---------------------------------|
| Mouse monoclonal anti-human Hepatocyte | OCH1E5  | 1:200    | Auto clave (pH 6.0) | Dako, Kyoto, Japan               |
| Rabbit polyclonal anti-chromogranin A |         | 1:2,000  | None              | Yanaihara, Fujinomiya, Japan     |
| Mouse monoclonal anti-CK 7      | OV-TL 12/30 | 1:100   | Protease K        | Dako, Kyoto, Japan               |
| Mouse monoclonal anti-synaptophysin | SY38    | 1:50     | Auto clave (pH 9.0) | Dako, Kyoto, Japan               |
| Mouse monoclonal anti-CK 19     | b170    | Ready to use | Protease K | Leica Biosystems, Newcastle, U.K. |
| Rabbit polyclonal anti-glucagon |         | 1:100    | None              | Dako, Kyoto, Japan               |
| Rabbit polyclonal anti-somatostatin |       | 1:500    | None              | Dako, Kyoto, Japan               |
| Genia Pig polyclonal anti-insulin |       | 1:200    | Auto clave (pH 9.0) | Dako, Kyoto, Japan               |

Table 2. Results of immunohistochemistry

| Marker                  | Nodule                  | Islet cells in the pancreas | Duocal cells in the pancreas and liver | Hepatocytes in the liver |
|-------------------------|-------------------------|----------------------------|----------------------------------------|--------------------------|
|                         | Cuboidal endocrine cells (i) | Duct-forming columnar cells (ii) | Large polygonal cells (iii) | Pyramidal exocrine cells (iv) |
| Human Hepatocyte        | –                       | –                          | +                                      | –                        |
| Chromogranin A          | –                       | –                          | +                                      | –                        |
| CK 7                    | –                       | +                          | –                                      | +                        |
| Synaptophysin           | –                       | –                          | –                                      | –                        |
| CK 19                   | –                       | +                          | –                                      | +                        |
| Glucagon                | ±                       | –                          | –                                      | ±                        |
| Somatostatin            | ±                       | –                          | –                                      | –                        |
| Insulin                 | ±                       | –                          | –                                      | –                        |

+ : Positive, ± : Partly positive, – : Negative.

ABDOMINAL HAMARTOMA IN A SOW

Table 2. Results of immunohistochemistry

| Marker                  | Nodule                  | Islet cells in the pancreas | Duocal cells in the pancreas and liver | Hepatocytes in the liver |
|-------------------------|-------------------------|----------------------------|----------------------------------------|--------------------------|
|                         | Cuboidal endocrine cells (i) | Duct-forming columnar cells (ii) | Large polygonal cells (iii) | Pyramidal exocrine cells (iv) |
| Human Hepatocyte        | –                       | –                          | +                                      | –                        |
| Chromogranin A          | –                       | –                          | +                                      | –                        |
| CK 7                    | –                       | +                          | –                                      | +                        |
| Synaptophysin           | –                       | –                          | –                                      | –                        |
| CK 19                   | –                       | +                          | –                                      | +                        |
| Glucagon                | ±                       | –                          | –                                      | ±                        |
| Somatostatin            | ±                       | –                          | –                                      | –                        |
| Insulin                 | ±                       | –                          | –                                      | –                        |

+ : Positive, ± : Partly positive, – : Negative.

REFERENCES

1. Angelo, J. R., Guerrero-Zayas, M. I. and Tremblay, K. D. 2012. A fate map of the murine pancreas buds reveals a multipotent ventral foregut organ progenitor. PLoS ONE 7: e40707. [Medline] [CrossRef]
2. Cantile, C. and Youssef, S. 2015. Nervous system. p.404. In: Jubb, Kennedy, and Palmer’s Pathology of Domestic Animals, 6th ed., vol. 1. (Grant Maxie, M. ed.), Elsevier, Philadelphia.
3. Corbett, J. L. and Tosh, D. 2014. Conversion of one cell type into another: implications for understanding organ development, pathogenesis of cancer and generating cells for therapy. Biochem. Soc. Trans. 42: 609–616. [Medline] [CrossRef]
4. Gardner, D. G. 1978. The concept of hamartomas: its relevance to the pathogenesis of odontogenic lesions. Oral Surg. Oral Med. Oral Pathol. 45: 884–886. [Medline] [CrossRef]
5. Jubb, K. V. F. and Stent, A. W. Pancreas. p. 356. In: Jubb, Kennedy, and Palmer’s Pathology of Domestic Animals, 6th ed., vol. 2. (Grant Maxie, M. ed.), Elsevier, Philadelphia.
6. Kim, H. H., Cho, C. K., Hur, Y. H., Koh, Y. S., Kim, J. C., Kim, H. J., Kim, J. W., Kim, Y. and Lee, J. H. 2012. Pancreatic hamartoma diagnosed after surgical resection. J. Korean Surg. Soc. 83: 330–334. [Medline] [CrossRef]
7. Libbrecht, L. and Roskams, T. 2002. Hepatic progenitor cells in human liver diseases. Semin. Cell Dev. Biol. 13: 389–396. [Medline] [CrossRef]
8. Matsushita, D., Kurahara, H., Matakis, Y., Maemura, K., Higashi, M., Iino, S., Sakoda, M., Shinchi, H., Ueno, S. and Natsugoe, S. 2016. Pancreatic hamartoma: a case report and literature review. BMC gastroenterol. 16: 3. [Medline] [CrossRef]
9. Nagata, S., Yamaguchi, K., Inoue, T., Yamaguchi, H., Ito, T., Gibo, J., Tanaka, M. and Tsuneyoshi, M. 2007. Solid pancreatic hamartoma. Pathol. Int. 57: 276–280. [Medline] [CrossRef]
10. Reddy, J. K., Rao, M. S., Yeldandi, A. V., Tan, X. D. and Dwivedi, R. S. 1991. Pancreatic hepatocytes. An in vivo model for cell lineage in pancreas of adult rat. Dis. Dig. Sci. 36: 502–509. [Medline] [CrossRef]
11. Shen, C. N., Horb, M. E., Slack, J. M. and Tosh, D. 2003. Transdifferentiation of pancreas to liver. Mech. Dev. 120: 107–116. [Medline] [CrossRef]
12. Shen, C. N. and Tosh, D. 2010. Transdifferentiation of pancreatic cells to hepatocytes. Methods Mol. Biol. 640: 273–280. [Medline] [CrossRef]
13. Slack, J. M. 2009. Metaplasia and somatic cell reprogramming. J. Pathol. 217: 161–168. [Medline] [CrossRef]
14. Steiner, D. J., Kim, A., Miller, K. and Hara, M. 2010. Pancreatic islet plasticity: interspecies comparison of islet architecture and composition. Islets 2: 135–145. [Medline] [CrossRef]
15. Wallace, K., Marek, C. J., Currie, R. A. and Wright, M. C. 2009. Exocrine pancreas trans-differentiation to hepatocytes—a physiological response to elevated glucocorticoid in vivo. J. Steroid Biochem. Mol. Biol. 116: 76–85. [Medline] [CrossRef]