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LETTER TO THE EDITOR

A Retrospective Case Control Study of Ductal Plate Malformation-like Features in Consecutive 200 Autopsies

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To the Editor:

Human ductal plate (DP) and ductal plate malformations (DPM) was first coined by Jorgenson MJ [1]. DP and DPM in humans have been investigated by Summerfield JA et al. [2], by Desmet VJ group [3–6], Gerber MA group [7–9], and the author [10–29]. Although there have been several mouse studies of DP, it is obvious that results of mouse DP cannot be applied to human DP. Therefore, to investigate human DP and DPM, one must use only human materials. According to DP hypothesis, embryonic DP gives rise to human intrahepatic bile ducts (IBD). Intrahepatic peribiliary glands (IPG) [30–36] and pancreatic acinar cells are also derived from DP. Human DP is a biliary structure located in the interface between hepatoblasts (HB) and portal mesenchyme (PM). DP probably develop from periportal HB probably through induction by PM, although it has been not investigated. Human DP undergoes remodeling (RM) and remodeled to lead to IBD. The persistence of DP in postnatal livers is called DP malformation (DPM) due to abnormal DP RM. DPM was first coined by Jorgensen MJ [1] in congenital hepatic fibrosis (CHF), but recent studies expanded DPM to those seen in cholangiocarcinoma (CC) and ductular reaction (DR) [37–41], which is apparently wrong because DMP is defined as exuberant biliary elements derived from failure of DP RM.

Since these DPM-like structures (DPM-LS) in CC and DR is, by definition, not true DPM. The author briefly state herein a histological retrospective case control study of DPM-LS in consecutive 200 human autopsies, all of which have been carried out by the author in recent 13 years. The materials account for 114 males and 86 females. The age ranged from fetal 38 gestational weeks to 99 years, with a median of 67 years. Tissue samples were obtained from each liver, and the number was 3–16 blocks per liver (median = 5 blocks). Hilar liver and large portal tract were prepared in every case to check IPG and large bile dusts. In the current study, the DPM-LS was defined as having 2 or more of the following criteria: irregular abnormal biliary elements (BE), cystic dilation of BE, intraluminal projections in BE, intraluminal bridge formations in BE [37].

Normal DP (Controls) and DPM-LS in DP.

Histological and Immunohistochemical study was done in 32 fetal livers (gestational weeks (GW) 7–40). DP was present already in 7GW. DP was single or double-layered structures present in the interface between PM and HB (Fig. 1a and b). In later GW, a part of DP showed tubular structures (TS) which were frequently continuous with DP (Fig. 1c and d). In later GW, immature IBD was seen with partial deletion of DP (Fig. 1e and f). In further GW, mature IBD were seen with deletion of the interface DP. The process were seen to spread from hilus to periphery. DPM-LS were noted in DP (DMP in DP) in 3 cases (Fig. 1d and g). Based on DP hypothesis, the following scenario is possible: Induction of DP by PM, DP formation, parts of DP forms TS which is future IBD, TS transform into PM to form immature IBD with concomitant DP loss by apoptosis, mature IBD from immature IBD. DP is positive for cytokeratin (CK) 8 and 18 (Fig. 1c, f and g), but contrary to previous reports DP is negative for CK7 and CK19. However, the remodeling DP and IBD

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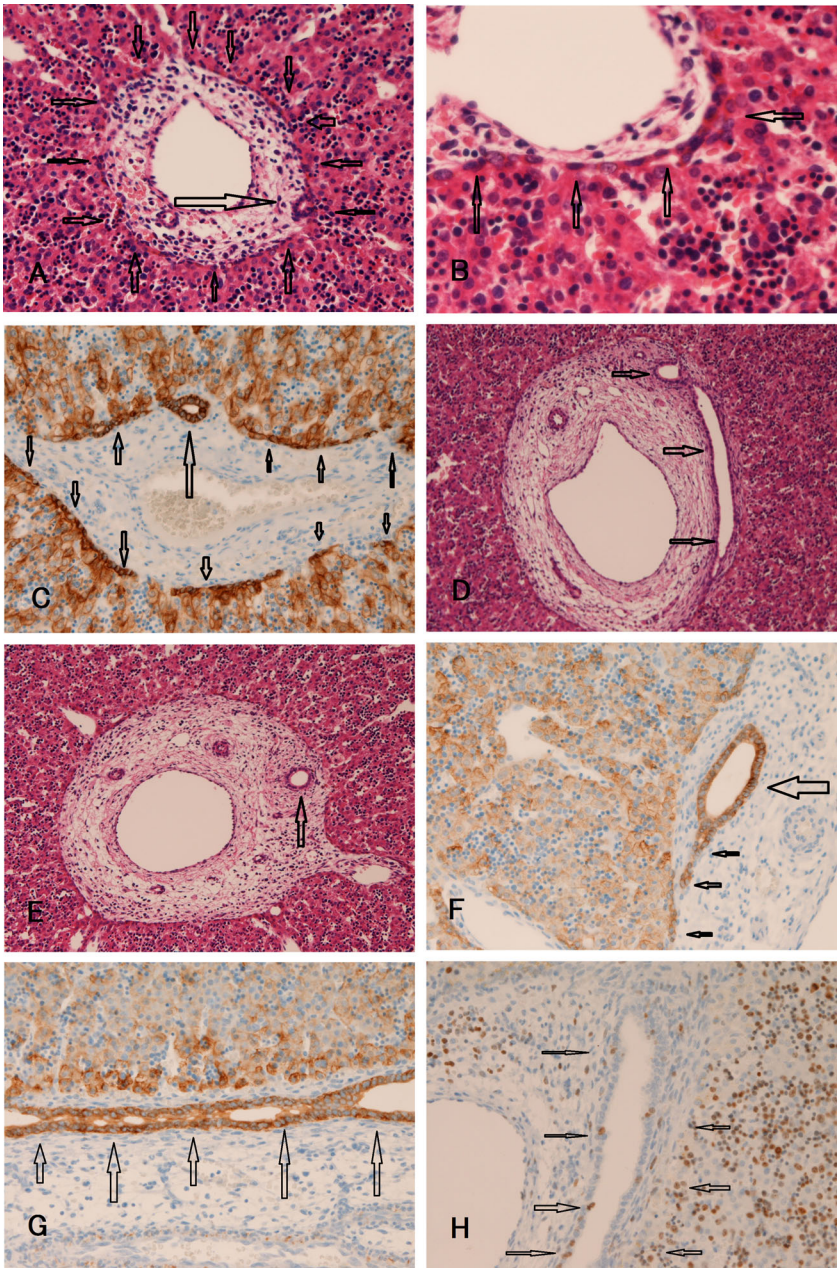

Fig. 1 Histological and Immunohistochemical features of ductal plate (DP) and its derivatives in human fetal livers. **a**: DP (*arrows*) is present in the interface between hepatoblasts and portal mesenchyme in a portal tract. Large arrow indicates duplicated DP that is a future intrahepatic bile duct. 8 gestational weeks (GW) HE, ×100. **b**: High power view of DP (*arrows*). The DP is composed of single or double layers of cuboidal epithelial cells apparently different from hepatoblasts. 7GW. HE, ×200. **c**: Cytokeratin (CK) 18 immunostaining highlights DP compared with hepatoblasts which are less intensely stained. Large arrow indicates a tubular structure detached from DP. It is a future intrahepatic bile duct. 11GW. X150. **d**: Abnormal tubular structures (arrows) detached from DP. It takes shape of ductal plate malformation (DPM) in DP: DPM in DM. 12GW. X100. **e**: Immature intrahepatic bile duct (arrow) originating from DP. DP is present in the interface between hepatoblasts and portal mesenchyme. 12GW. HE, ×100. **f**: CK18 immuhistochemistry reveals that immature bile duct (large arrows) is continuous with DP (small arrows), as if bile duct developed from DP. 13GW. X150. **g**: DPM in DP as seen with CK18 immunostaining. The DPM in DP is apparent. This phenomenon has not been described. 13GW. X150. **h**: Ki-67 immunostaing reveals Ki67-positive cells in DP (*arrows*) and immature bile duct. 15GW. X200

occasionally and frequently, respectively, positive for CK7 and CK19 in addition to CK8 and CK18. In addition, contrary to previous reported, DP and its derivatives are active structures and showed frequently apoptosis by TUNNEL methods and cell division evidenced by Ki-67 immunostainings (Fig. 1h). DP shows many other signal transduction receptor and others, but these are unwritten herein because they are beyond the aims.

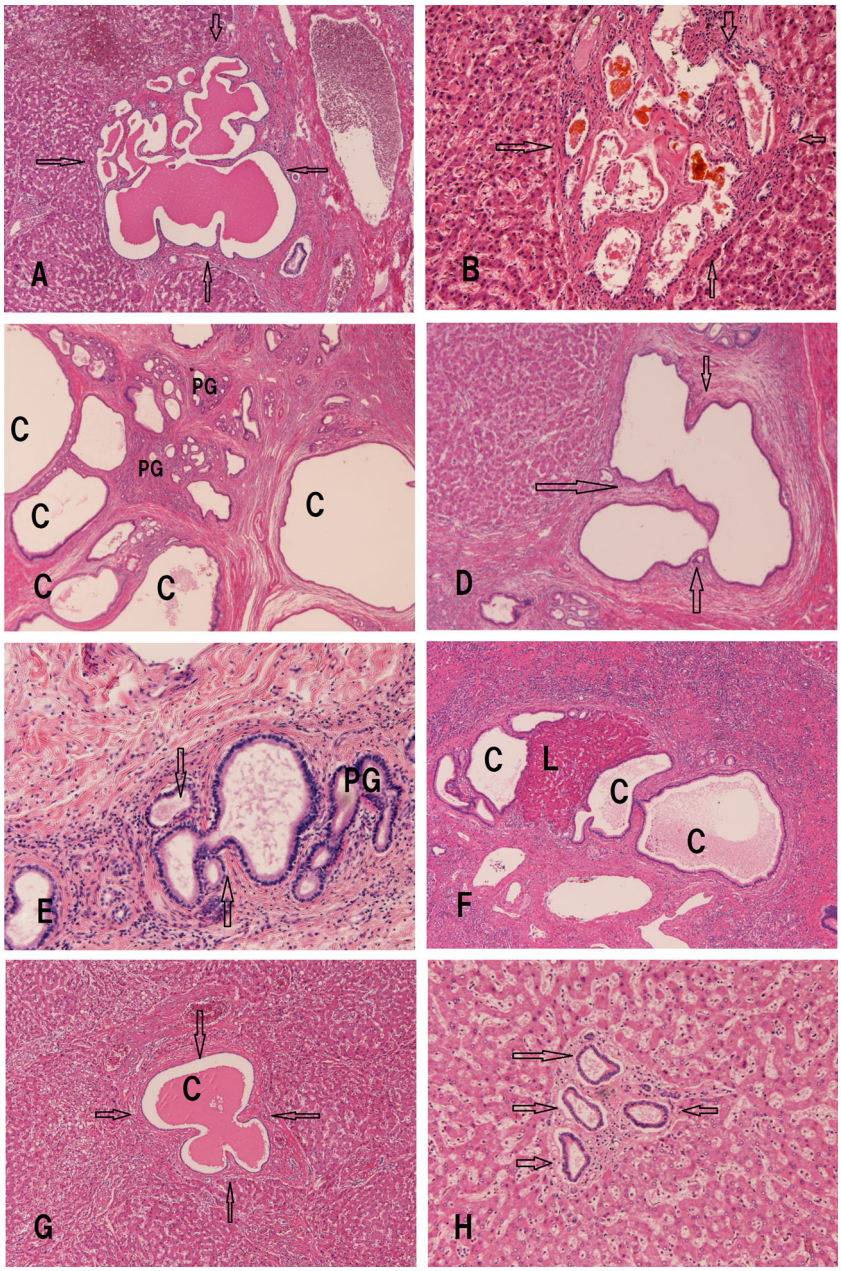

Fig. 2 Histological features of ductal plate malformation (DMP)-like structure (DPM-LS) in postnatal 200 autopsy livers. **a**: Typical von-Meyenburg complex (VMC)(arrows) without bile. HE, ×40. **b**: Typical VMC (arrows) with bile. HE, ×40. **c**: Cystic dilation (C) of intrahepatic peribiliary glands (PG). HE, ×40. **d**: DPM-LS in intrahepatic bile duct. Cystic dilations and intraluminal protrusions (arrows) are apparent. HE, ×40. **e**: DPM-LS in intrahepatic peribiliary glands (PG). Cystic dilations and intraluminal protrusions (arrows) are apparent. HE, ×40. **f**: Peculiar cystic dilations (C) next to liver parenchymal nodule (L) in cirrhosis. Although the histological appearances is very similar to congenital hepatic fibrosis, no typical festoon fibrosis was seen. This anomalous features are thought to derive from ductular reactions. They are not true DPM. HE, ×20. **g**: Small DPM-LS in liver parenchyma (arrows). Intraluminal protrusions are obvious (arrows). It is true DPM. HE, ×100 **h**: Mildly cystic abundant round abnormal biliary elements (arrows) within hepatic lobules. Although these are round, they are evidently abnormal and represent DPM. HE, ×100

DPM-LS in 200 Autopsies

The DPM-LS were seen in 86 livers (43%), and they were classifiable into the following seven: von-Meyenbrug complex (VMC) (46 cases, 23%), cystic dilation of IPG (5 cases, 2.5%), DPM-LS in IBD (12 cases 6%), DPM-LS in IPG (24 cases, 13%), peculiar cystic dilations next to liver parenchyma (3 cases, 1.5%), small DPM-LS in liver parenchyma (23 cases, 11.5%), mildly cystic abundant round abnormal IBD (26 cases 13%). Since there were overlap, the sum of individual cases does not equal the total numbers. There were no cases of Caroli's disease, congenital hepatic fibrosis (CHF), infantile and adult type polycystic kidney diseases (IPKD, APKD), monolobar Caroli's disease, congenital biliary atresia (CBA).

VMC was typical and classifiable into simple VMC (Fig. 2a) and VMC with bile (Fig. 2b). Most of the VMC were in the vicinity of portal tracts, but some were not. This fact and the histological features indicate that VMC of both types are true DPM, not DPM-LS.

Cystic dilation of IPG has been called peribiliary cysts or hepatic hilar cyst (Fig. 2c). This condition was seen in 5 cases three of which are associated with cirrhosis and two of which with otherwise normal liver (ONL). This abnormality seems not to reflect DPM but represent cystic dilations of IPG, as described previously [35].

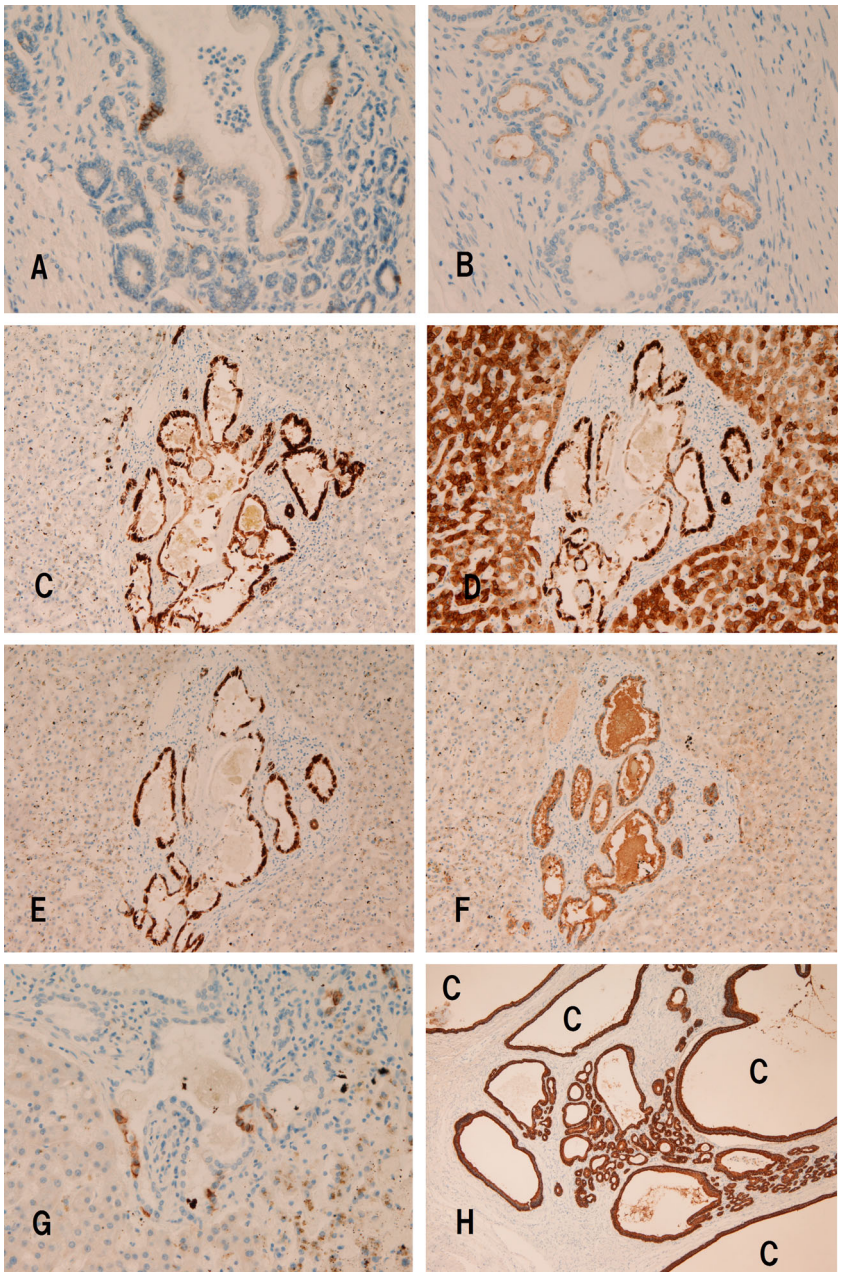

Fig. 3 Immunohistochemical features normal biliary elements and of ductal plate malformation (DPM) and DMP-like structures (DPM-LS). **a**: The normal intrahepatic bile duct (IBD)(upper) and intrahepatic peribiliary glands (IPG) express NCAM. X200. **b**: Normal IPG express MUC1. X200. **c**: von-Meyenburg complex (VMC) expresses cytokeratin (CK) 7. X100. **d**: VMC and hepatocytes express CK18. X100. **e**: VMC expresses CK19. X100. **f**: VMC expresses CA19–9. X100. **g**: VMC expresses NCAM. X200. **h**: Cystic dilation of IPG expresses CK7. X20

DPM-LS in IBD (Fig. 2d) was seen in 12 cases, all of which were associated with extrahepatic biliary obstruction by metastatic carcinoma. The changes are characteristic of DPM, but they appear not to be related with DP remodeling. Hence, it is not true DPM.

DLM-LS in IPG (Fig. 2e) was seen in 24 cases, 20 of which were associated with ONL and 4 of which were with metastatic carcinomas and various hepatobiliary disease. Although difficult, the changes no doubt indicate DPM-LS but they may not reflect true DPM (true DMP represents DPM derived from failure of DP DM).

Peculiar cystic dilations next to liver parenchyma (Fig. 2f) were seen in 3 cases, all of which had cirrhosis. Although the histological appearances is very similar to CHB, no typical festoon fibrosis was seen. Thus it is not CHF, but may represent DR that are prevail in perinodular areas. This type is not true DPM.

Small DPM-LS in liver parenchyma (Fig. 2f) was seen in 23 cases, 20 cases of which were ONL and 3 cases of which were fatty liver, hepatic fibrosis, and congestion. This type is true DPM.

Mildly cystic abundant round abnormal IBD (Fig. 2h) were seen in 26 cases, all of which are ONL. This type seems true DPM.

There are 2 cases of CC and 17 cases of chronic liver diseases, but no DPM-LS was seen in the livers except for 3

cases of peculiar cystic dilations next to liver parenchyma in cirrhosis. On the contrary, 5 out of 22 metastatic carcinoma to the liver showed DPM-LS

Immunohistochemical Features

Immunohistochemical investigation was done in selected 20 cases. The following antigens were investigated by Envision method and its variations [42, 43]: cytokeratin (CK) WSS, CKMNF16, CKCAM5,2, CKAE1/3, CK34BE12, CK5, CK6, CK7, CK8, CK14, CK18, CK19, CK20, CEA, CA19–9, p53, p63, Ki-67, vimentin, AFP, NSE, NCAM(CD56), EMA, VEGF, E-cadherin, B-catenin, MUC1, MUC2, MUC5AC, MUC6, CDX-2. TTF-1, KIT, PDGFRA, HepPar1, synaptophysin, and chromogranin. Normal IBD and IPG were positive for NCAM (Fig. 3a), MUC1 (Fig. 3b), CKWSS, CKAE1/3, CKCAM5.2, CKMNF16, CK7, CK8, CK18, CK19, EMA, CEA, CA19–9, E-Cadherin and B-catenin, but negative for CK34BE12, CK5, CK6, CK14, CK20, p53, p63, vimentin, AFP, NSE, VEGF, KIT, PDGFRA, MUC2, MUC5AC, MUC6, CDX-2,TTF-1, KIT, PDGFRA, HepPar1, synaptophysin and chromogranin. Ki-67 labeling index was circa 2%. The epithelial cells of VMC, small DPM-LS in liver parenchyma, and mildly cystic abundant round abnormal IBD were positive for CKWSS, CKAE1/3, CKCAM5.2, CKMNF16, CK7 (Fig. 3c), CK8, CK18 (Fig. 3d), CK19 (Fig. 3e), EMA, CEA, CA19–9 (Fig. 3f), MUC1, MUC6, NCAM (Fig. 3g), E-Cadherin and B-catenin, but negative for CK34BE12, CK5, CK6, CK14, CK20, p53, p63, vimentin, AFP, NSE, VEGF, KIT, PDGFRA, MUC2, MUC5AC, CDX-2, TTF-1, KIT, PDGFRA, HepPar1, synaptophysin, chromogranin, and NSE. KI-67-labeling index was circa 1%. The epithelium of cystic dilation of IPG was positive for CKWSS, CKAE1/3, CKCAM5.2, CKMNF16, CK7, CK8, CK18, CK19 (Fig. 3h), EMA, CEA, CA19–9, MUC1, MUC5AC, E-Cadherin and B-catenin, but negative for CK34BE12, CK5, CK6, CK14, CK20, p53, p63, vimentin, AFP, NSE, VEGF, KIT, PDGFRA, MUC2, MUC6, CDX-2, TTF-1, KIT, PDGFRA, HepPar1, synaptophysin, chromogranin, NSE and NCAM. KI-67-labeling index was circa 3%. The epithelium of DLM-LS in IPG, DPM-LS, and peculiar cystic dilations next to liver parenchyma in IBD was positive for CKWSS, CKAE1/3, CKCAM5.2, CKMNF16, CK7, CK8, CK18, CK19, EMA, CEA, CA19–9, MUC1, MUC6, E-Cadherin and B-catenin, but negative for CK34BE12, CK5, CK6, CK14, CK20, p53, p63, vimentin, AFP, NSE, VEGF, KIT, PDGFRA, MUC2, MUC5AC, CDX-2, TTF-1, KIT, PDGFRA, HepPar1, synaptophysin, chromogranin, NSE and NCAM. KI-67-labeling index was circa 2%. The data showed most of DMP and DPM-LS showed Pan-CK, CK7, CK8, CK18, CK19, CEA, CA19–9, EMA, Ki-67 labeling, E-cadherin, B-catenin, and some MUC1, MUC5AC and MUC6.

Summary The author reported the true DPM and DPM-LS in 200 consecutive autopsies, and reported the incidence, histopathology, and Immunohistochemical features of DPM and PDM-LS.

Compliance with Ethical Standards

Conflict of Interest The author has no conflict of interest.

Funding The author has no funds or sponsors. This work was performed only by the author's money and only by author's head and body.

Informed Consent The informed consent was obtained from each mother or relative. The publication was permitted by the Ethical Committee of the Hospital.

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