# Hepatocellular progenitor cell tumor of the gallbladder: a case report and review of the literature

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**A 75-year-old man presented to his physician with weakness, anorexia, and constant right upper quadrant pain. He underwent a laparoscopic cholecystectomy, which was converted to an open cholecystectomy due to presumed adhesions. Direct examination of the liver was negative for masses or lesions. A CT scan was negative for masses or nodules. The gallbladder was $8.5 \times 2.5\,cm^2$, with a diffusely thick wall measuring 2.5 cm. Microscopic examination showed a monomorphic tumor consisting of cells with increased nuclear:cytoplasmic ratio and occasional nucleoli, infiltrating the entire gallbladder uniformly. The tumor cells that reacted to antibodies directed against HepPar1, CAM 5.2, CK19 and scattered cells were immunoreactive for CD117, CD34, and CD56. This immunohistochemical profile suggested a 'hepatocellular progenitor cell tumor of the gall bladder'. This report is, to our knowledge, the first such case of a tumor of this cell type reported in the gallbladder. In addition, we present a review of the literature.**
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Primary malignant tumors of the gallbladder are predominantly adenocarcinomas; rarely, lymphoma or sarcoma occur. We recently studied a malignant tumor restricted to the gallbladder with light microscopic and immunohistochemical characteristics of hepatic progenitor cells.[1,2]

## Case report

A 75-year-old Caucasian man presented to his physician with weakness, anorexia, and constant right upper quadrant pain. Past medical history was significant for hypertension, type II diabetes mellitus, and remote appendectomy. He had a remote two packs per day smoking history (30 years prior). He was not jaundiced but was dehydrated and febrile (101⁰). Laboratory tests of comprehensive metabolic profile, including standard liver tests, were within normal limits. He was anemic (hemoglobin 12.4 g/dl, hematocrit 36.4%) and his white blood cell count was increased (10.8 th/mm³). Current medications included glucophage, glyburide, triamterene/ hydrochlorthiazide, lisinopril, and chlordiazepoxide.

Laparoscopic cholecystectomy was attempted, but because of the perception of adhesions, an open cholecystectomy was performed. Intraoperative cholangiogram was negative for gallstones. There were no liver lesions on direct visual examination. Neither perihepatic nor intra-abdominal adenopathy was noted.

There were no nodules or tumors in the thorax, abdomen, or pelvis with computerized tomographic (CT) scan performed on postoperative day 6.

## Pathology

### Gross Pathology (Figure 1)

The gallbladder measured $8.5 \times 2.5\,cm^2$; the wall was diffusely and uniformly thickened to 2.5 cm. A single dark green, $1.5 \times 1.5 \times 1\,cm^3$, granular, ovoid stone was present. The mucosa was focally hemorrhagic but was otherwise velvety and without lesions.

### Microscopic Pathology (Figure 2)

A monomorphic tumor infiltrated the lamina propria, submucosa, muscularis propria, and serosa.

Correspondence: Dr EM Brunt, MD, 4th Floor, FDT, SLUH, 3635 Vista Avenue, St Louis, MO 63110, USA.
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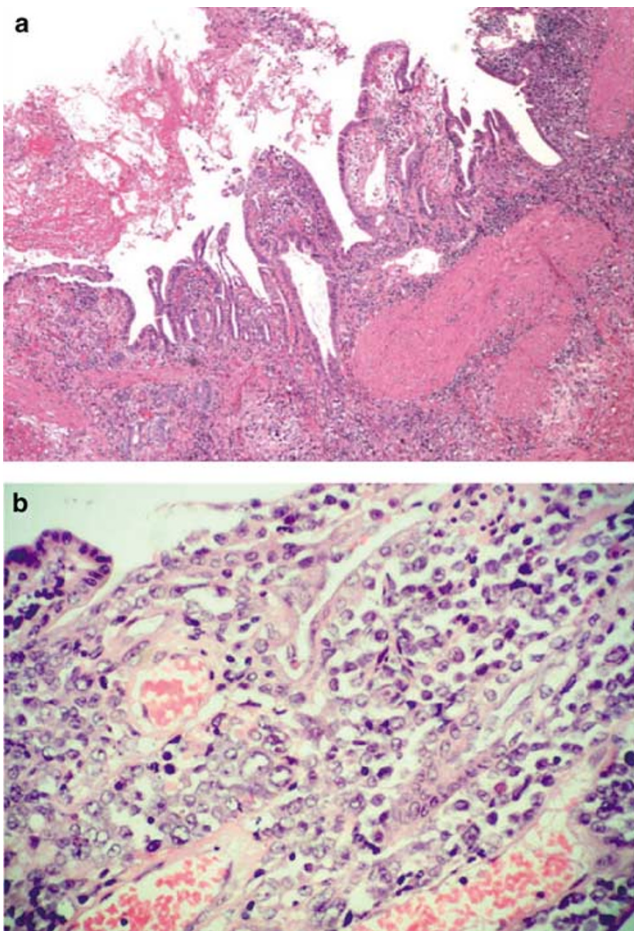**Figure 1** Gross photograph of the gallbladder shows a uniformly thickened wall.



**Figure 2** (**a**) This light microscopic photomicrograph illustrates the unremarkable surface mucosa with a monomorphic tumor within the lamina propria and the submucosa (H&E). (**b**) In this higher power field, the tumor cells are oval and show a high nuclear: cytoplasmic ratio, open chromatin, and occasional prominent nucleoli (H&E).

The surface mucosa was intact and unremarkable, without evidence of dysplasia or *in situ* carcinoma. The tumor was in sheets and small clusters around

vessels, but no evidence of gland or trabecular formation was seen; tumor necrosis was extensive. The tumor cells were round to oval, and showed mild nuclear pleomorphism, increased nuclear: cytoplasmic ratio, margination of chromatin, and occasional prominent nucleoli. Mitoses were rarely noted. Perineural invasion and lymphovascular invasion were seen. Additionally, a dense lympho-cytic infiltrate was in the lamina propria, with occasional follicles. The adhesions on the serosal surface were negative for tumor.

### Immunohistochemistry (Figure 3)

Table 1 lists the markers studied in the case. The initial impression of lymphoma was ruled out by a battery of lymphocyte immunohistochemical mar-kers. Immunostains for polyclonal CEA, HMB45, and S-100 were also nonreactive. Positive markers included pankeratin (>50%), CK7 (in a cluster of tumor cells, <1%), HepPar1 (positive in >90%), CK19 (focally positive in 25%), CD117 (scattered tumor cells, <1%), CD34 (scattered tumor cells, <1%), CD56 (scattered tumor cells, <1%), CD10 (<1%), EMA (positive in 50%), and CAM 5.2 (positive in >50%). The surface mucosa was diffusely positive for CK7 and CK19, but there were no single cells positive for CD34, CD117, or CD56 in the epithelium.

Based on the clinical observations and gross findings, the tumor was determined to be a primary gallbladder tumor. Light microscopy and immuno-histochemical profile indicated hepatic progenitor cell/intermediate cell origin.

## Discussion

Hepatic progenitor cells in the normal human liver are small round epithelial cells that reside in the most proximal branches of the biliary system, the Canal of Hering.[3] These cells have been identified as the precursors of the mature hepatocytic and biliary cells. Activated progenitor cells are present in the diseased and regenerating liver.[1] In rodent studies, these cells have been referred to in a variety of terms, including 'oval cells'.[4,5] In human tissue, subtypes of progenitor cells reflecting different stages of maturation identified by immunohisto-chemical markers are known to exist. These have been shown in a variety of liver diseases. The immunohistochemical profiles confirm both biliary and hepatocytic phenotypes: OV-6, CK19, CK7, HepPar 1, albumin, neural cell adhesion marker (NCAM-1)(CD56), and stem cell markers: c-kit (CD117) and CD34.[1,2,6] Similar cells have also been identified in rodent pancreas,[7] which is derived embryonically with the liver from a common anlage in the endoderm. After pancreatic injury, oval cells in the pancreas have been shown to differentiate
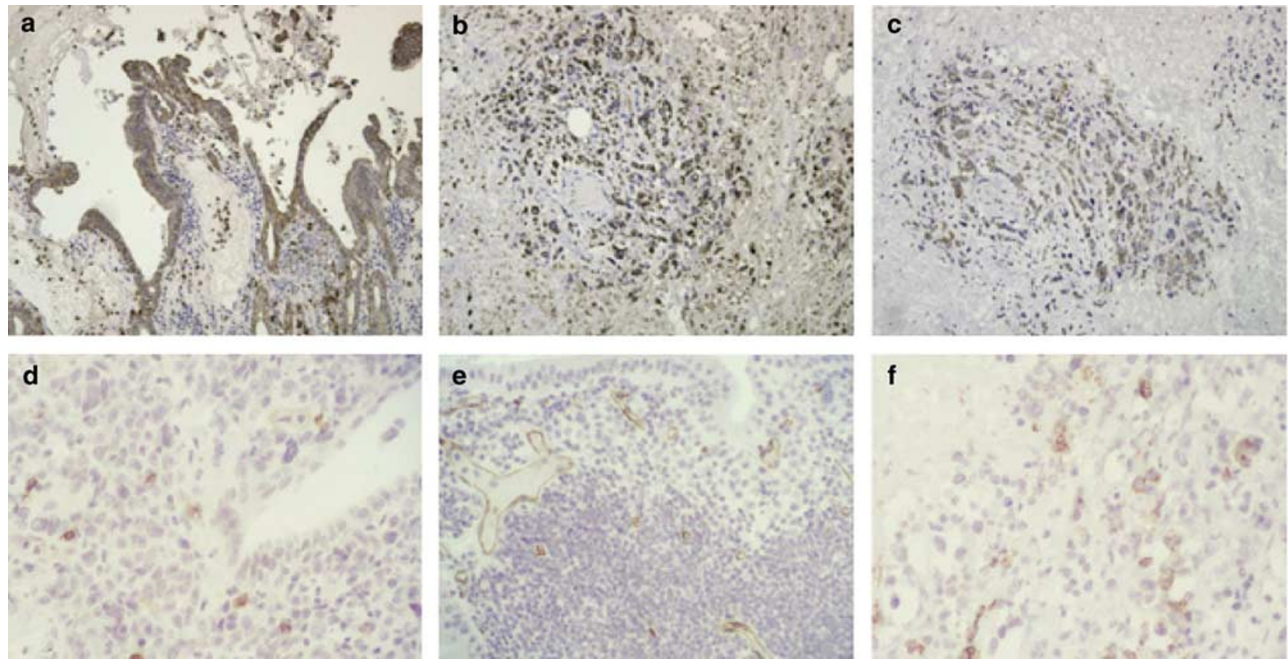
**Figure 3** (a–f) Immunohistochemistry panel. See results and Table 1. (**a**) Pankeratin, (**b**) CK19, (**c**) HepPar1, (**d**) CD117, (**e**) CD34, and (**f**) CD56.

into hepatocytes, as determined by expression of genes normally in hepatocytes, including alpha-fetoprotein, albumin, and alpha-1-antitrypsin.

'Intermediate cells' is the term that has been proposed by Roskams and Theise[1,2] for the epithelial cells with a morphologic and immunophenotype intermediate between hepatocytes and cholangiocytes that are seen in varying numbers in hepatic regenerative responses to toxic, metabolic, and inflammatory damage to the hepatic parenchyma. In contrast to small size and diffuse cytoplasmic reactivity with CK7 of progenitor cells, intermediate cells have submembranous reactivity of CK7 and lesser degree of CK19 reactivity. Intermediate cells are a component of the reparative and regenerative response of the liver termed the 'ductular reaction' and have been documented in a variety of disorders including alcoholic and nonalcoholic fatty liver disease, cholestatic liver disease, chronic hepatitis and submassive necrosis. The subject has been reviewed in two recent manuscripts.[1,2]

Neoplasms of progenitor cell origin have been proven in the chemical hepatocarcinogenesis models in rodents.[8–14] Several groups have reported cells with progenitor phenotype in humans with benign tumors (liver cell adenomas), and in malignant tumors in children (hepatoblastomas) and adults (hepatocellular carcinoma, cholangiocarcinoma and mixed phenotypes). Table 2 reviews the reported cases. In some reported cases, tumor cells were described as arranged in trabeculae, and surrounded by a delicate fibrous stroma,[15] whereas in others, tumors were arranged in strands with vague

gland-like structures.[16] Immunohistochemical reactions demonstrated expression of keratins, Hepatocyte-specific antigen (HepPar 1), albumin mRNA, biliary markers (CK7, CK19), stem cell markers (CK14, CD117, CD34) and a neural marker, NCAM (CD56). Ultrastructural examination has also shown features of both hepatocyte and cholangiocyte differentiation.[15] It has been postulated that these tumors arise from progenitor cells with a dual phenotype.[17]

Studies of hepatoblastoma have shown varying results. Ruck *et al*[18] showed ultrastructural characteristics of small epithelial cells, which expressed albumin, a hepatocytic marker, and CK7, a marker of biliary differentiation. OV-1 and OV-6, rodent markers of oval cells, were also positive in fetal and embryonal areas. Conversely, Badve *et al*[19] studied 10 hepatoblastomas and found that the oval cell 'like' areas were not positive for any progenitor cell markers (HepPar 1, CD34, bcl2, CK19, alpha-1-microglobulin); these authors concluded that the tumor cells were more of an undifferentiated phenotype. The variances in these studies may reflect the challenges of antigen reactivity in different tissue preparations, as Ruck *et al* utilized frozen tissue sections, while Badve *et al* utilized paraffin sections.[20,17]

Hearyoung *et al*[16] suggested three classifications of primary liver tumors with morphologic and immunohistochemically defined intermediate phenotype: (i) intermediate carcinomas, (ii) transitional combined hepatocellular and cholangiocarcinomas, (iii) hepatocellular carcinoma—small cell type. In

**Table 1** Immunohistochemical stains

| Antibody/Company | Dilution | Predicted reactivity | Findings in gallbladder tumor |
|---|---|---|---|
| CD 3/Dako Cytomation, CA, USA | 1:400 | Pan-T cell | Negative in tumor<br>Positive in inflammatory cells |
| CD 20/Dako Cytomation, CA, USA | 1:4000 | Mature B cell | Negative in tumor<br>Positive in inflammatory cells |
| CD30/Dako Cytomation, CA, USA | 1:200 | Anaplastic large cell lymphomas | Negative in tumor |
| KP-1/Dako Cytomation, CA, USA | 1:4000 | Histiocytic | Negative in tumor<br>Positive in the inflammatory infiltrate |
| Myeloperoxidase/Dako Cytomation, CA, USA | 1:2000 | Myeloid blasts | Negative in tumor<br>Positive in inflammatory cells |
| CD45/Dako Cytomation, CA, USA | 1:3000 | Leukocytes | Negative in tumor<br>Positive in inflammatory cells |
| CD 10/Novocastra, UK | 1:50 | Common ALL antigen | Rare positive tumor cells (<1%)<br>Positive in endothelial structures and luminal surface epithelium |
| CD 117/Dako Cytomation, CA, USA | 1:200 | C-kit protein in progenitor cells | Positive in less than 1% of tumor (occasional small cells)<br>Positive in smooth muscle cells |
| CD 34/Dako Cytomation, CA, USA | 1:400 | Human hematopoietic progenitor cell antigen | Positive in scattered tumor cells (<1%)<br><br>Positive in endothelial vessels |
| MAC 387/Dako Cytomation, CA, USA | 1:800 | Macrophages, sarcomas | Negative in tumor<br>Positive in inflammatory cells |
| S100/Dako Cytomation, CA, USA | 1:4000 | Melanocytic, neural, histiocytic | Negative |
| MelA/Biocare Medical, CA, USA | 1:50 | Melanoma | Negative |
| AE1/AE3<br>Biocare Medical/CA, USA | 1:800 | Pan keratin | Positive in <10% tumor<br>Positive in surface epithelium |
| CK7/Dako Cytomation, CA, USA | 1:400 | 54 kd simple keratin | Positive in rare cell <1% of the tumor<br>Positive in surface epithelium |
| Keratin/Dako Cytomation, CA, USA | 1:5000 | Epithelial | Positive in 50% tumor cells<br>Positive in surface epithelium |
| CEA polyclonal/Dako Cytomation, CA, USA | 1:10000 | Canalicular staining of HCC | Negative |
| CK 19/Dako Cytomation, CA, USA | 1:50 | Cholangiocytes, progenitor cells | Positive in 25% tumor cells<br><br>Positive in surface epithelium, biliary channels |
| EMA/Dako Cytomation, CA, USA | 1:1200 | Transmembrane glycoprotein on epithelium | Positive in 50% tumor cells<br><br><br>Positive in surface epithelium |
| Hep Par 1/Dako Cytomation, CA, USA | 1:1000 | Hepatocytes | Positive in >90% tumor cells |
| CAM 5.2/Becton Dickinson, CA, USA | — | Cytokeratins eight and 18 (hepatocytes and cholangiocytes) | Positive in >50% tumor cells<br><br><br>Positive in surface epithelium |
| CD 56/Biodesign International, ME, USA | 1:20 | Neural cell adhesion molecule | Positive in scattered (<1%) tumor cells<br><br>Positive in the nerves |

their study of 29 tumors, they demonstrated that survival rates for intermediate carcinomas (75%) were between that of hepatocellular carcinomas (62.5%) and transitional combined hepatocellular and cholangiocarcinoma (80%) with follow-up ranging from 14 to 18 months.

Our case is a primary tumor of the gallbladder. As a result of lack of gland formation or trabecular structures and the relatively monomorphic appearance of the tumor cells, we initially suspected lymphoma, or, less likely, melanoma. However, the markers for lymphoma and melanoma were negative and immunohistochemical marker positivity for HepPar 1, CK19, and CD117 led to a diagnosis of a tumor of hepatic progenitor cell/intermediate cell phenotype. The paucity of cells reactive for CK7, CD117, CD56, and CD34 may reflect poorly preserved antigenicity in the formalin-fixed specimen.[6,17,19]

The primitive endoderm grows into the mesoderm to develop into the liver and the gallbladder in embryogenesis.[21] We speculate that progenitor cells in the gallbladder share some or all of the features of hepatic progenitor cells.

**Table 2** Reported studies of tumors with progenitor cell components

| Reference Au/Jnl/Yr | Lesions studied (n) | Adults or pediatrics | Immunohistochemistry results | Tissue preparation |
|---|---|---|---|---|
| Roskams[23] Histopathology, 1995 | FNH (23) | N/A | CK19: decreasing gradient of positivity from periseptal to centrinodular areas (23/23 cases) CK7: positive, same as above (23/23 cases) OV6: membranous accentuation, same as above (23/23 cases) Chromogranin A: intense staining, with a decreasing gradient (23/23 cases) NCAM: negative | Frozen and paraffin; ultrastructural analysis |
| Ruck[18] Histopathology, 1997 | Hepatoblastoma (17) | Pediatrics | CK7: in small epithelial cells associated with the tonofilament bundle OV6: scattered cells in 5/7 fetal areas, 7/10 embryonal areas Albumin: diffuse cytoplasmic staining in small epithelial cells (coexpressed CK7) OV1: scattered cells in3/7 fetal areas, 6/10 embryonal areas | Frozen (12/17 cases) and paraffin; ultrastructural analysis (7/17 cases) |
| Robrechts[15] Liver, 1998 | Malignant primary liver tumor (1) | Adult | CK19: focally reactive in the small cells (F) CK7: diffuse but variable reactivity (P) CK 18: diffuse and strong (F) CK8: 50% of the tumor cells (F) CK20: negative (P) PthRP: negative in tumor cells, positive in reactive bile ductules (F) Neural cell adhesion molecule: negative (F) α-fetoprotein: negative (P) Chromogranin A: negative (P) | Frozen (F) and paraffin (P); ultrastructural analysis |
| Libbrecht[24] Am J Surg Pathol, 2001 | Hepatic adenomas (10) | Adults | CK19: strongly positive (5/10 cases ) CK7: diffuse strong cytoplasmic (5/10 cases) OV-6: strongly positive (5/10 cases) Chromogranin A: strongly positive (5/10 cases) CK8: more intense than in hepatocytes CK18: more intense than in hepatocytes | Frozen and paraffin; ultrastructural analysis (5/10 cases) |
| Uenshi[22] Hepatogastroenterology, 2002 | Malignant primary liver, tumors, dual phenotype (1) | Adult | CK19: diffuse (in the central cholangiocarcinoma-like areas) CK7: diffuse (same) HepPar 1: focal (in HCC-likeareas) | Paraffin |
| Tickoo[25] Am J Surg Pathol, 2002 | Malignant primary liver tumors 'CHCC' (27) HCC (12) Peripheral CC (7) | Adults | CK19: at least 6% or greater % positivity in the small cells transitional areas (22/24 cases) CK7: same as above (23/25 cases) AE1: same as above (21/22 cases) CK20: same as above (7/25 cases) EMA: same as above (24/25 cases) CAM 5.2: same as above (21/21 cases ) Albumin mRNA: cytoplasmic bluish-black staining in at least 6% or greater cells (22/23 cases) | Paraffin |
| Badve[19] Mod Pathol, 2003 | Hepatoblastoma (epithelial type) (10) | Pediatrics | CK19: negative in small cell component HepPar 1: negative in small cell component CD34: negative in small cell component Bcl-2: negative in small cell component $\alpha_1$ microglobulin: negative in small cell component | Paraffin |

**Table 2** Continued

| Reference Au/Jnl/Yr | Lesions studied (n) | Adults or pediatrics | Immunohistochemistry results | Tissue preparation |
|---|---|---|---|---|
| Haeryoung[16] J Hepatol, 2004 | Intermediate cell (13) combined HC (6) small cell HCC (10) | Adults | CK19: in IC cases—from 5 to >50% of the small cells (13/13 cases) <br>● Combined HC cases—in 5 to >50% of cells in transitional areas between the cholangiocytic and hepatocellular areas (6/6 cases) <br>● Small cell HCC—5–50% positive in small cells in a few cases (3/10 cases) <br>CK7: not carried out <br>HepPar 1: IC cases −5 to >50% of small cells coexpressed with CK19 intensity (7/13 cases) <br>● In CHC cases −5 to 10% strong in one case and >50% strong in the rest if the transitional areas expressed cholangiocytic and the hepatocyte markers (4/6 cases) <br>● small cell HCC cases −5 to >50% of small cells (9/10 cases) <br>CD117: 5 to >50% small cells in 6 tumors IC cases (10/13 cases) <br>● 5–50% small cells within the transitional zone in combined HC cases (in 5/6 cases) <br>● mostly 5% only in one case 50% small cells in small cell HCC cases (7/10 cases) and none of these cases expressed CK19 <br>CEA: cytoplasmic expression in small cells ranging from 5 to >50% in 8/13 IC cases and 4/6 CHC cases, and none in small cell HCC cases | Paraffin |
| Theise[17] Histopathology, 2003 | Malignant primary liver tumors (4) | Adults | CK19: positivity, ranging from faint to strong in small cells (4/4 cases) <br>HepPar 1: negative in small cells, positive in HCC components of tumors (4/4 cases) <br>CD34: negative in all tumor cells (4/4 cases) <br>CD117: negative in all tumor cells (4/4 cases) <br>AE1/AE3: positivity, ranging from faint to strong in small cells (4/4 cases) <br>$\alpha$-fetoprotein: focally positive in HCC components and a few small cells <br>$\alpha_1$-antitrypsin: focally positive in HCC and negative in small cells | Paraffin |
| Vadlamani, 2004 | Current case, malignant primary gallbladder tumor (1) | Adult | CK 19: positive in 25% of the tumor cells <br>CK 7: positive in a small cluster, <1% of tumor cells <br>HepPar 1: >90% of tumor cells <br>CD34: positive in <1% tumor cells <br>CD117: positive in <1% tumor cells <br>CD56: positive in <1% tumor cells <br>AE1/AE3: positive <10%of tumor cells <br>CAM5.2: positive in >50% of tumor cells | Paraffin |

CK19: cytokeratin 19; CK7: cytokeratin 7; HepPar 1: hepatocyte-specific antigen in paraffin-1; AE1/AE3: simple cytokeratins 8 and 18; CD117: *c-kit*; CD34: cluster determinant 34; CD56: cluster determinant 56 (neural cell adhesion molecule); CHC: combined hepatocellular cholangiocarcinoma; HCC: hepatocellular carcinoma; CCa: cholangiocarcinoma; FNH: focal nodular hyperplasia; N/A: not available.

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To our knowledge, this is the first report of a primary gallbladder tumor comprising cells with the phenotype of hepatic progenitor/intermediate cells.

## Acknowledgements

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