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Choledochal cyst with secondary cholangitis, choledochitis, duodenal papillitis, and pancreatitis in a young domestic shorthair cat

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Abstract. Choledochal cysts, congenital segmental dilations of the common bile duct, have been reported in few cats, and histologic characterization is lacking. A 20-mo-old spayed female domestic shorthair cat was presented because of vomiting and weight loss. There was progressive elevation of liver enzyme activity (ALT > ALP, GGT) and hyperbilirubinemia. Diagnostic imaging identified focal cystic dilation of the common bile duct, dilation and tortuosity of adjacent hepatic ducts, and a prominent duodenal papilla. A choledochal cyst was suspected, and the animal was euthanized. On postmortem examination, there was a 2-cm, firm, thickened, cystic dilation of the common bile duct, patent with adjacent ducts. Histologically, the cyst wall was expanded by fibroblasts, collagen, and lymphoplasmacytic inflammation. Adjacent bile ducts were markedly dilated and tortuous, with lymphoplasmacytic inflammation and papillary mucosal hyperplasia that extended to the major duodenal papilla. There was chronic neutrophilic cholangitis, suggesting bacterial infection and/or disturbed bile drainage, extrahepatic obstruction, and lymphoplasmacytic pancreatitis with ductular metaplasia. Prominent lymphoid follicles within biliary ducts and duodenum suggested chronic antigenic stimulation. Choledochal cysts can be associated with chronic neutrophilic cholangitis, extrahepatic obstruction, choledochitis, duodenal papillitis, and pancreatitis, and should be a differential for increased hepatic enzymes and hyperbilirubinemia in young cats.

Keywords: bile ducts; cats; cholangitis; choledochal cyst; congenital; liver; pancreatitis.

Hepatobiliary anomalies are relatively common in cats, with accessory gallbladder and biliary cysts the most prevalent.[11] There is a reported 12% frequency of accessory gallbladder in cats[11]; biliary cysts are most common in association with polycystic kidney disease, with affected cats having a 68% rate of concurrent polycystic liver disease.[3] Additionally, solitary biliary cysts, and so-called cystadenomas, are often incidental findings during postmortem examination of older cats.[1,11] These lesions, in our opinion, may represent long-standing congenital malformations.

In our experience with feline postmortem examinations at a tertiary care veterinary hospital, hepatobiliary malformations were present in 16 of 124 (12.9%) cases; most of these (10 of 124 cats, 63% of hepatobiliary malformations, or 8% of total cases) were ductal plate malformations (DPMs; unpublished data). DPMs are congenital anomalies of the biliary tree that arise from aberrant development of the embryonic ductal plate that normally develops into tubular biliary ducts.[12,20,21] These anomalies can affect different segments of the intrahepatic biliary tree, resulting in a variety of anomalies identified both in humans[20] and animals, including dogs, cats, horses, cattle, rodents, and non-human primates.[4,8,10,12,13,21]

Congenital choledochal cysts (CC) are dilations predominantly affecting extrahepatic bile ducts, and, in humans, multiple subtypes using different classification schemes have been described.[14,16,19] Multiple distinct theories exist regarding the pathomechanisms behind formation of CCs, with different pathogeneses often proposed for different subtypes of choledochal cysts. First, some believe that a subset of CCs represent a purely congenital biliary malformation, with speculated underlying causes including embryologic overproliferation of extrahepatic biliary epithelium, segmental lack of ganglion cells, interference of biliary mucosa cell-to-cell adhesion, or abnormal rotation and fusion of pancreatic buds during development.[15] Second, given the involvement of the intrahepatic biliary tree in some subtypes of CCs, some believe CCs are related to DPMs; however, the true link between these malformations is unclear given that the extrahepatic biliary tree is not embryologically derived directly from the ductal plate.[17,20] Third, others maintain that some subtypes of CCs form as sequela of congenital pancreatobiliary malunion or maljunction, a condition in which the common bile duct and pancreatic duct merge prior to the

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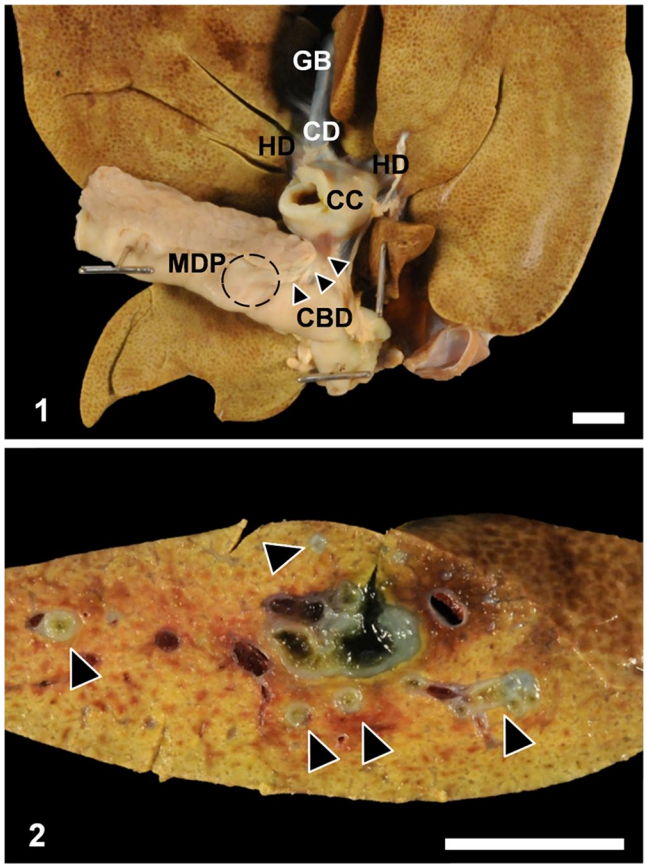
Table 1. Serum biochemistry panel indicates marked hepatocellular injury, mild cholestasis, and moderate hyperbilirubinemia in a young domestic shorthair cat.

	Day			
Clinicopathologic parameter	1	5	6	Reference interval
ALP	69	56	NA	12–59 IU/L
ALT	334	502	653	27–158 IU/L
GGT	8	11	NA	0–6 IU/L
Total bilirubin	89	103	118	0–5 µmol/L

ALT was markedly elevated in this patient; only mild cholestasis was present in spite of moderate hyperbilirubinemia. ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; NA = not available.



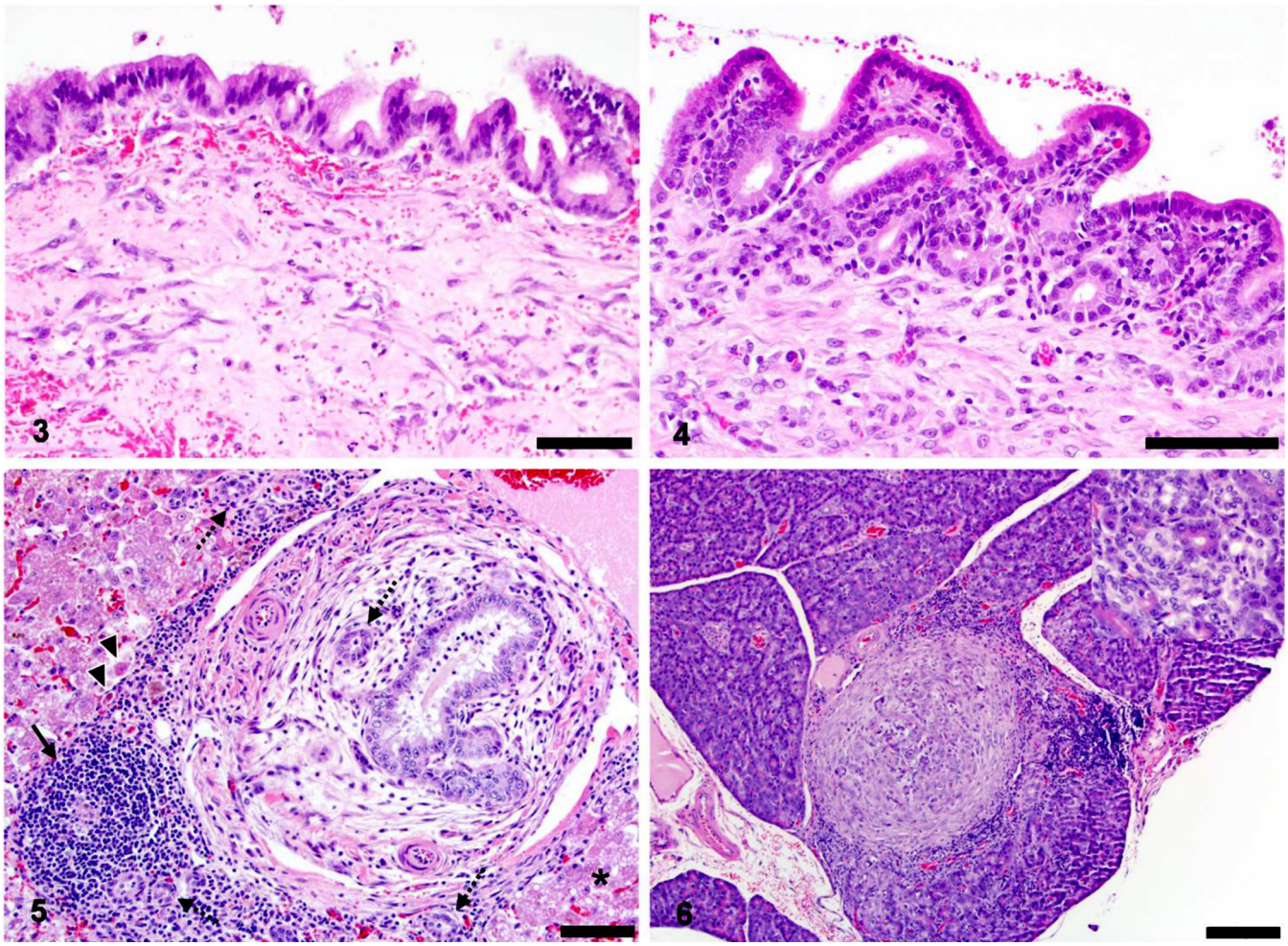
Figures 1 and 2. Gross features of choledochal cyst (CC) and associated liver in a young domestic shorthair cat. **Figure 1.** Midway along the common bile duct there is a thick-walled CC (incised open) patent with hepatic ducts (HD), common bile duct (CBD; arrowheads), and cystic duct (CD) leading to the gallbladder (GB). MDP = major duodenal papilla, indicated with dashed circle. Bar = 1 cm. **Figure 2.** The CC is associated with intrahepatic and extrahepatic bile duct dilation and inflammation. Fibrosis often accompanied intrahepatic duct dilation (arrowheads). Bar = 1 cm.

major duodenal papilla, leading to pancreatic enzyme reflux in the common bile duct and subsequent inflammation and dilation.[9,17,19,20] However, the lack of confirmed pancreatobiliary malunion in multiple subtypes of CCs, as well as the presence of pancreatobiliary malunion in patients without CCs, argues against this as an exclusive pathogenesis for all subtypes of CCs.[9,16,19] Last, adult-onset CCs have been associated with distal obstruction of extrahepatic ducts, resulting in acquired segmental dilation. Ultimately, given the different subtypes described in humans, it is likely that different pathomechanisms variably contribute to development of CCs in different scenarios.

CCs have been characterized sporadically in cats with variable clinical courses, including association with concurrent cholangitis, pancreatitis, and/or enteritis.[2,7,17] Despite these reports, a thorough histologic characterization of feline choledochal cysts as well as affected adjacent organs has not been reported. Here we describe the clinical, gross, and histologic findings in a case of a CC in a young cat.

A 20-mo-old spayed female cat was presented because of vomiting and weight loss. Serial serum biochemistry panels revealed progressive elevation of hepatic enzyme values, with hepatocellular enzymes (alanine aminotransferase, ALT) being more prominently elevated than cholestatic enzymes (alkaline phosphatase, ALP; gamma-glutamyl transferase, GGT; Table 1). Abdominal ultrasound and computed tomography identified focal cystic dilation of the common bile duct that was suspected to represent a CC, with accompanying dilation and tortuosity of adjacent hepatic ducts and a prominent duodenal papilla (Suppl. Figs. 1, 2). The animal was euthanized given the poor prognosis.

On postmortem examination, midway along the common bile duct, distal to the gallbladder, cystic duct, and hepatic ducts, but proximal to the major duodenal papilla, there was a thick-walled, 2-cm diameter cyst that was connected with hepatic ducts, common bile duct, and the cystic duct (Fig. 1). The wall of the cyst was 2–5 mm thick, firm, and pale-tan. The segment of common bile duct distal to the cyst could be traced to the major duodenal papilla and was considered to be of normal diameter, based on our experience; the relationship of this duct with the pancreatic duct was not observed. The liver had a diffuse, mildly enhanced reticular pattern, and, on cut surface, intrahepatic bile ducts, particularly those near the hilus, were multifocally dilated and surrounded by mildly thickened concentric rims of firm tan fibrous tissue (Fig. 2). Given these findings, a diagnosis of choledochal cyst was



Figures 3–6. Histologic features of choledochal cyst (CC) and associated liver and pancreas in a young domestic shorthair cat. **Figure 3.** The CC wall was comprised of mature fibroblasts, scattered mixed inflammatory cells, and patchy hemorrhage below a simple cuboidal-to-columnar mucosa. Bar = 50 µm. **Figure 4.** The CC was associated with intrahepatic and extrahepatic bile duct mucosal papillary hyperplasia and lymphoplasmacytic-to-neutrophilic inflammation. Bar = 50 µm. **Figure 5.** The CC was associated with chronic neutrophilic cholangitis, extra-hepatic obstruction, and hepatocellular injury. Intrahepatic bile ducts were tortuous and surrounded by neutrophils, lymphocytes, and fewer plasma cells and macrophages. De novo lymphoid follicles (arrow) and neutrophilic exocytosis were common. Periductular myofibroblasts, edema, and fibrosis indicated extrahepatic obstruction, which was accompanied by proliferation of small caliber bile ducts (ductular reaction; dashed arrows). Hepatocytes often had intracellular lipid (asterisk), and individual necrotic hepatocytes were identified uncommonly at the limiting plate, some of which contained golden brown pigment (lipofuscin; arrowheads). Bar = 50 µm. **Figure 6.** The CC was associated with lymphoplasmacytic pancreatitis, fibrosis, and ductular metaplasia. Inflammation often cuffed areas of discrete fibrosis, within which there was often loss of zymogen granules and replacement of acini with ductular structures (inset). Bar = 100 µm.

assigned, and secondary cholangitis and extrahepatic obstruction were suspected. The remainder of the postmortem examination was unremarkable. Samples of the CC, common bile duct, liver, pancreas, duodenum, jejunum, spleen, lymph node, lung, kidney, stomach, and urinary bladder were collected and processed routinely for microscopic evaluation.

Histologic evaluation of the CC revealed a wall comprised of mature spindle cells (presumed fibroblasts and myofibroblasts), collagenous stroma, mild scattered lymphoplasmacytic inflammation, and mild patchy hemorrhage overlain by a simple cuboidal to, less commonly, columnar epithelium (Fig. 3). Submucosal mucous glands were frequently absent. Branches of the cystic duct, hepatic ducts, and common bile duct extending from the cyst were moderately dilated and tortuous. The mucosa of these ducts was convoluted with papillary hyperplasia (Fig. 4), and, within the submucosa, there was mild-to-moderate lymphoplasmacytic inflammation with lymphoid follicle formation. These mucosal and submucosal changes extended to the level of the major duodenal papilla. Within the mucosa and submucosa of the duodenum at the major duodenal papilla, lymphoid follicles were prominent, suggesting chronic antigenic stimulation.

Histologic evaluation of the liver revealed marked dilation, tortuosity, and papillary hyperplasia of hilar intrahepatic bile ducts similar to that seen with extrahepatic bile ducts. Diffusely throughout the parenchyma, biliary ducts were cuffed by variably mild-to-marked numbers of neutrophils admixed with lymphocytes, plasma cells, and macrophages (Fig. 5). There was frequent exocytosis of neutrophils across the biliary epithelium with luminal accumulation of degenerate-to-intact neutrophils and necrotic cellular debris. Surrounding the bile ducts, lymphocytes often formed follicles, suggesting chronic antigenic stimulation. In addition, there was robust periductular proliferation of concentric spindloid cells (myofibroblasts) admixed with collagenous stroma and edema, which, given the antemortem hyperbilirubinemia, was considered most consistent with acute extrahepatic obstruction and cholestasis (Fig. 5).

Obstruction was suspected to be functional in nature and secondary to the extensive fibrosis and inflammation present in the extrahepatic biliary tree and CC. Cholangitis may have contributed directly to periductular edema and myofibroblast proliferation. Mild hemorrhage was also present multifocally in affected portal stroma. Changes in the hepatic parenchyma included mild multifocal random individual hepatocyte necrosis, moderate accumulation of microvesicular lipid within centrilobular hepatocytes (hepatic lipidosis), and moderate multifocal accumulation of golden granular pigment (lipofuscin) within hepatocytes and Kupffer cells. There was also moderate proliferation of small caliber bile ducts that was interpreted as a likely mix of type 1 and type 2A ductular reaction (biliary hyperplasia), secondary to presumed extrahepatic obstruction and chronic cholangitis and cholestasis, respectively.[5]

Histologic evaluation of the pancreas revealed moderate lymphoplasmacytic pancreatitis that was accompanied by unusual discrete areas of fibrosis admixed with proliferation of duct structures (Fig. 6), interpreted as reactive ductular metaplasia as a result of chronic inflammation. Additionally, there was occasional pancreatic duct tortuosity similar to that seen in the biliary tree with associated periductular fibrosis. Histologic evaluation of remaining tissues was unremarkable.

In summary, this cat had a thick-walled, fibrotic cyst of the common bile duct consistent with a CC. Further, this was associated with chronic choledochitis, neutrophilic cholangitis, extrahepatic obstruction, pancreatitis, and major duodenal papillitis, as well as hepatocellular injury and necrosis. Collectively, these changes likely contributed to the clinical decline of this animal.

CCs have been characterized sporadically in cats, but specific histologic features are not well described. In contrast, in humans, histologic features of CCs, as well the associated liver, have been characterized more extensively. Common histologic features described in humans include fibrosis of the cyst wall, lymphocytic inflammation, and absence of mucus-producing glands.[16] All of these features were also present in our feline case (Fig. 3). In addition, mucosal hyperplasia has also been described; this feature was generally absent from the CC mucosa but was prominent in the adjacent extrahepatic biliary tree to the level of duodenal papilla as well as some pancreatic ducts (Fig. 4). Lining of the cyst by columnar epithelium is also described[16] and was seen in some areas in our feline choledochal cyst (Fig. 3), although the mucosa more often maintained a typical simple columnar biliary epithelium. Other described features that were not seen in our case include metaplasia of the mucosa to that resembling pyloric and/or duodenal mucosa.[16]

In humans, CCs are classified using a variety of schemes, with the Todani classification scheme being the most widely accepted.[19] Using this system, the CC in our case is most consistent with type I, which is characterized by focal-to-segmental, fusiform-to-cystic dilation of the common bile duct.[19] In humans, this subtype has been described as histologically lacking biliary mucosa,[16] but this was not the case in our cat, given that the majority of the examined cyst maintained a simple cuboidal epithelium typical of biliary lining, with occasional transition to a more columnar appearance. However, the significance of this change reported in type I CCs in humans is unclear, given that more severe mucosal changes may simply reflect disease severity (i.e., response to inflammation, cholelithiasis, trauma, etc.). Of the 6 CCs reported previously in cats, 3 were classified as type I, 2 classified as type IV, and 1 was unclassified (suspected to be type I, II, or III).[2,7,17] Including our case, type I cysts are therefore the type encountered most commonly in cats (4 of 7, 57%), which is similar to humans, in which type I cysts comprise 60–90% of cases in both adults and children.[14,16] Additionally, in type I cysts, mild dilation or enlargement of intrahepatic biliary ducts is also often described.[16] This is consistent with changes seen in our feline case, and may also be considered a direct contributor to concurrent neutrophilic cholangitis and extrahepatic obstruction (i.e., biliary stasis predisposing to bactobilia). In humans with type I cysts, this intrahepatic duct dilation is speculated to occur secondary to biliary stasis.[16] However, as with the uncertainty of the pathogenesis of the CC itself, it is unclear whether these associated bile duct dilations represent a continuation of a congenital dilation or a change secondary to altered bile flow (i.e., as occurs with pancreaticobiliary malunion).

Type I CCs can be further subclassified into multiple subtypes; subtypes IA and IB are both characterized by focal dilations and are distinguished by the presence (IA) or absence (IB) of pancreatobiliary malunion.[19] In our case, definitive gross evaluation for the presence of pancreatobiliary malunion was precluded given the miniscule size of the ducts in cats. Furthermore, histologic identification of these individual ducts is also extremely challenging; in our experience, most cats (104 of 124, 84%) exhibit a complex network of conjoined ductal structures at the major duodenal papilla (unpublished data), and the identification of 2 distinct duct structures is rarely achieved in

cats that (presumably) do not have pancreatobiliary malunion. Despite this, the presence of pronounced histologic duct dilation at the major duodenal papilla, which we have not seen previously, and concurrent pancreatic lesions (dilated intrapancreatic ducts, pancreatitis, and atypical fibrosis and ductular metaplasia) support the possibility of pancreatobiliary malunion in our cat.

In human CCs, the presence of pancreatobiliary malunion and the risk of concurrent disease in adjacent organs are not mutually exclusive. In humans, CCs are associated with cholangitis, pancreatitis, and cholelithiasis.[16] In the previous reported CCs in cats, cholangitis was confirmed in 4 of 6 cases, and was most often neutrophilic in nature, with 2 animals having confirmed bactobilia; furthermore, enteritis and pancreatitis were noted in single cats.[2,7,17] In our case, cholangitis and pancreatitis were both present, in addition to choledochitis and major duodenal papillitis. Notably, in the general population of cats (i.e., those without CCs), concurrent cholangitis, pancreatitis, and enteritis are thought to be facilitated by feline duodenal papilla anatomy, resulting in a clinical syndrome dubbed "triaditis."[6] Based on our case and previously published cases of feline CCs and knowledge of feline duodenal papilla anatomy, we postulate that similar to humans, cats with a CC should be considered at elevated risk for not only cholangitis, but also pancreatitis and possibly enteritis.[17] Additionally, CCs predispose human patients to an increased risk of development of biliary and pancreatic neoplasia.[16] Although this progression has not been described in cats with CCs—likely given the low numbers of cases and often young age of patients in which this condition is described—this complication may also be possible in cats.

Interestingly, despite clear histologic evidence of extrahepatic obstruction and cholangitis in our cat, antemortem clinicopathologic evaluation of hepatocellular enzymes was dominated by a pattern of hepatocellular injury rather than cholestasis (Table 1). There was histologic evidence of hepatocellular injury (hepatocyte necrosis, excessive lipofuscin accumulation for the age of the cat, lipidosis) to support ALT elevation, but the lack of concordant ALP and GGT elevation in spite of bilirubin elevation was considered unusual. We hypothesize that this phenomenon may represent spontaneous normalization of cholestatic serum biochemistry values following a period of chronic cholangitis; this has been reported in humans with chronic sclerosing cholangitis, despite evidence of persistent gross lesions.[18] Alternatively, it is possible that the ALT elevation seen in our cat reflected injury of other tissues (e.g., skeletal muscle, thyroid); the cat did have concurrent mild AST elevation on initial presentation (AST 135 IU/L, reference interval: 16–67 IU/L). However, these tissues were not available for histologic evaluation, and this change could not be further evaluated. Ultimately, these theories are purely speculative; the significance of this antemortem finding is ultimately unknown.

Finally, diagnostic imaging (abdominal ultrasound and computed tomography) was helpful in diagnosis of choledochal cyst in our case. However, laparoscopic and/or postmortem examination may be required for definitive diagnosis of CCs in cats and other animals, and in tandem with histopathologic examination, is critical for evaluation of complications in adjacent organs.

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Supplemental material

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