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TOPIC HIGHLIGHT

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Endoscopic therapy in acute recurrent pancreatitis

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a largely diagnostic to a largely therapeutic modality. Cross-sectional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), and less invasive endoscopy, especially endoscopic ultrasound (EUS), have largely taken over from ERCP for diagnosis. However, ERCP remains the "first line" therapeutic tool in the management of mechanical causes of acute recurrent pancreatitis, including bile duct stones (choledocholithiasis), ampullary masses (benign and malignant), congenital variants of biliary and pancreatic anatomy (e.g. pancreas divisum, choledochoceles), sphincter of Oddi dysfunction (SOD), pancreatic stones and strictures, and parasitic disorders involving the biliary tree and/or pancreatic duct (e.g Ascariasis, Clonorchiasis).

Key words: Acute pancreatitis; Endoscopic retrograde cholangiopancreatography; Endoscopic Ultrasound; Choledocholithiasis; Ampullary lesions; Cystic tumors of the pancreas; Sphincter of Oddi dysfunction; Pancreas divisum; Choledochal cyst; Pancreatic stones

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INTRODUCTION

As endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a mainly diagnostic to a predominantly therapeutic modality, so have the indications for pancreatic endotherapy. ERCP is no longer a "first line" investigation but used selectively for patients identified by less- or non-invasive imaging techniques to have a problem that may benefit from endoscopic therapy. Idiopathic acute recurrent pancreatitis (ARP) is a frequent reason for referrals to ERCP endoscopists[1,2]. Conditions causing ARP amenable to endoscopic diagnosis and treatment include: (1) Choledocholithiasis, including microlithiasis ("biliary sludge"); (2) Congenital abnormalities of biliary and pancreatic anatomy (e.g. choledochocele, duodenal duplication/diverticulum, pancreas divisum); (3) Ampullary lesions, benign and malignant; (4) Mucin-secretin pancreatic tumors, including cystic neoplasms in communication with the pancreatic duct, and intrapancreatic mucin-secretin neoplasms (IPMNs); (5) Pancreatic duct strictures, stones and neoplasms; (6) Sphincter of Oddi dysfunction (biliary and pancreatic); (7) Biliary and pancreatic parasites.

CHOLEDOCHOLITHIASIS, INCLUDING BILIARY SLUDGE (MICROLITHIASIS)

In the West, bile duct stones (choledocholithiasis), including microlithiasis (biliary sludge), are by far the commonest cause of ARP. Cholecystectomy will usually take care of the problem. However, when ARP patients have apparently normal gallbladders without stones on cross-sectional imaging, the diagnosis is often questioned. Transabdominal ultrasound (TUS) provides useful information about gallbladder wall and the diameter of bile ducts, but lacks sensitivity for small stones (< 5 mm) and biliary sludge. Endoscopic ultrasound (EUS), a less invasive test than ERCP, is an excellent tool for diagnosing microlithiasis[3]. In my practice, we frequently schedule EUS with ERCP available immediately afterwards (under the same sedation) when we are looking for bile duct stones in patients with recent acute pancreatitis or biliary colic with transiently elevated liver tests, or assessing obstructive jaundice. If the EUS is negative for stones or ampullary lesions, we do not proceed to ERCP. Typically, small gallstones migrate spontaneously out into the small intestine within 24 h. If the liver tests (e.g. bilirubin, alkaline phosphatase, alanine and aspartate aminotransferase (ALT, AST) normalize quickly, and the bile duct resumes a normal diameter, it is very likely that the offending stone has passed. Patients with an intact gallbladder who can be shown by EUS to have microlithiasis should be offered cholecystectomy. Not all surgeons believe that microlithiasis is a satisfactory

explanation for gallstone-like symptoms, but the results of cholecystectomy are convincing to this author! Is there a role for "empiric" ("best guess") biliary sphincterotomy in patients with ARP who have an intact gallbladder but cannot be shown by EUS to have stones or biliary sludge? This intervention would also address biliary sphincter of Oddi dysfunction (SOD) (see below). Preserving the sphincter of Oddi is important in young patients. However, elderly patients with comorbidities that render them "high risk" for surgery may be safely managed by empiric sphincterotomy for symptomatic choledocholithiasis, whether or not the offending sludge or stones can be identified by other imaging[4]. Oral dissolution therapy (i.e. ursodeoxycholic acid) for suspected biliary sludge seems a logical alternative to endotherapy in ARP. However, as the sludge is rarely comprised of pure cholesterol the results are unpredictable and often disappointing.

CONGENITAL ABNORMALITIES OF BILIARY AND PANCREATIC ANATOMY

Choledochal cysts are congenital abnormalities of the biliary tree[5]. Five types are recognized by the Todani classification. Fusiform dilatation of the extrahepatic bile duct (Type Ⅰ) is the commonest choledochal cyst encountered by ERCP endoscopists. Choledochoceles (Type Ⅲ) involve the distal bile duct and protrude as a symmetrical, smooth-surfaced mass into the duodenum at the expected level of the main duodenal papilla. Choledochoceles often are associated with anomalous pancreatico-biliary ductal drainage, such that the patients are predisposed to develop ARP. Blind-ending choledochoceles drain poorly, accumulating sludge and stones, which cause a variety of problems, including cholangitis, obstructive jaundice and gallstone pancreatitis. All choledochal cysts carry some risk of malignant transformation (to cholangiocarcinoma), but this is considered minor for choledochoceles (Type Ⅲ cysts), which are effectively treated by exposing the cyst lumen (usually by needle knife papillotomy) and thereby improving bile flow. Another congenital defect that can interfere with bile and pancreatic juice flow is a duplication cyst of the descending duodenum. This is amenable to endoscopic therapy: a needle knife is used to incise the typical septum that is present. A unique form of duodenal diverticulum - the so-called "windsock" diverticulum, is also a risk factor for ARP. This "billowing" duodenal diverticulum can be managed endoscopically. The commonest abnormality of pancreatic duct anatomy seen in routine ERCP practice is pancreas divisum (P Div), in which the dominant drainage of the pancreas (the dorsal duct) is through the minor duodenal papilla[6]. The ventral pancreatic duct (PD) in P Div is typically small and may be "invisible" (the unsuspected presence of a tiny ventral duct is a common cause of a "failed pancreatogram". The P Div anomaly occurs in 7%-8% of American of European ("Causasian") descent. It is much rarer in African Americans, Asians, Hispanics and other non-Caucasian ethnic groups. P Div is certainly associated with ARP but why a few patients are affected while the majority are spared is unknown. Several studies have suggested that a heterozygous defect in the cystic fibrosis transmembrane regulator (CFTR) gene may predispose patients with P Div to ARP[7]. Improving the drainage of the dorsal PD by minor papillotomy stops the attacks in 70%-80% of cases if chronic pancreatitis (CP) is not already established. Once CP is present, minor papillotomy may only benefit 40%-50%. Patients with a "pancreatic pain syndrome" and P Div but no other objective evidence of pancreatitis do even worse, with symptomatic benefit in only 20% or so. Annular pancreas is a congenital defect resulting in an incomplete ring of pancreas encircling the descending duodenum. This is said to be a cause of ARP, but as annular pancreas is frequently associated with P Div, the predisposition to pancreatitis is more likely a manifestation of the latter. Patients with annular pancreas may exhibit partial gastric outlet obstruction (from constriction of the descending duodenum by a swollen pancreas) during attacks of pancreatitis.

AMPULLARY LESIONS, BENIGN AND MALIGNANT

Ampullary adenomas and carcinomas create an obstruction to pancreatic exocrine secretion and bile flow[8]. Duodenoscopy is mandatory in the investigation of ARP. This author believes that every trainee in gastroenterology should learn to use a side-viewing duodenoscope, not for ERCP but to be able to assess duodenal lesions, including those involving the major and minor papilla. For adenomas and cancers limited to the mucosa (T1 lesions) by endoscopic ultrasound (EUS) examination, endoscopic resection is an option[9]. The main duodenal papilla is a site of predilection for polyp formation in both sporadic and familial adenomatous polyposis (FAP). Polyps < 3 cm in diameter can be removed endoscopically without prior EUS. This is usually accomplished by hot snare cautery, followed by stenting of the pancreatic duct orifice to reduce the risk of procedure-related acute pancreatitis[10]. Piecemeal resection is also an option, but carries a higher risk of recurrence. Polyps ⩾ 3 cm should be assessed by EUS looking for extension of adenomatous tissue into the bile duct and/or pancreatic duct, and to determine the depth of invasion should tumor be present. Clearly malignant tumors of the duodenal papilla (ampullary cancers) are not suitable for endoscopic resection. Biliary and pancreatic drainage may be improved by papillotomy. However, biliary stenting without papillotomy is a safer way to treat obstructive jaundice in ampullary cancer, as these lesions are often quite vascular and bleed when incised. Polyps and tumors involving the minor duodenal papilla rarely cause ARP. However, a cystic dilatation of the distal (duodenal) end of dorsal pancreatic duct in pancreas divisum, called a Santorinicele, may indicate obstruction to flow in patients with P Div and ARP[11]. Incision of the Santorinicele with a re-establishes good flow and may resolve the clinical problem.

CYSTIC TUMORS OF THE PANCREAS, INCLUDING MUCIN-SECRETING CYSTADENOMAS AND IPMNS

Cystic tumors of the pancreas may present with ARP[12]. Serous cystic (or microcystic) tumors have a typical "honeycomb" appearance due to clusters of tiny

cysts. Microcystic adenomas rarely undergo malignant transformation. On the other hand, mucinous cystic tumors can undergo malignant transformation. These tumors may be difficult to distinguish from pancreatic pseudocysts on cross-sectional imaging, but EUS with fine needle aspiration (FNA) of the contents usually makes the diagnosis. About 50% of mucinous cysts of the pancreas have high levels of carcinoembryonic antigen (CEA), the fluid stains positive for the presence of mucin, viscosity is increased (> water) and amylase levels are generally normal or much lower than would be expected in a communicating pseudocyst. The cyst aspirate is also sent for cytologic examination to look for signs of malignant transformation (to cystadenocarcinoma). It used to be said that cystic tumors never communicated with the pancreatic duct (PD), but this is patently untrue. Mucinous cysts communicating with the duct may cause it to become quite dilated. Another source of mucinous distension of the PD is the presence of small tumors of the PD side branches (intrapancreatic mucin-secretin neoplasm, or IPMN)[13,14]. Typically, these present with ARP and imaging showing gross dilatation of the PD. EUS may also reveal nodules within the main PD or side branches. Pancreatoscopy using "mini-'scopes" may identify villous-looking tumors within the PD. At endoscopy with a side-viewing instrument, the main papilla may appear to "wink" open and discharge gelatinous material. Due to the malignant potential of mucinous tumors of the pancreas, surgery is the treatment of choice. In patients unfit for surgery, periodic aspiration of large cysts may reduce the frequency of ARP. Endoscopic stenting of PD is rarely helpful in IPMN as the stent lumen quickly becomes occluded with mucus. Other cystic tumors of the pancreas may occasionally present with ARP (e.g. neuroendocrine tumors which have undergone cystic degeneration, cystic metastases).

PANCREATIC DUCT STRICTURES, STONES AND NEOPLASMS

Pancreatic endotherapy is becoming important in the management of a number of mainly benign pancreatic disorders[15-17]. Strictures of the main PD may be benign or malignant. Benign strictures are usually seen in chronic pancreatitis, but may form after trauma (blunt or penetrating) or instrumentation (e.g. duct stenting). Benign strictures may be solitary or multiple, the latter creating the so-called "chain of lakes" or "string of pearls" appearance. Pancreatic stones frequently form in association with PD strictures, presumably reflecting poor drainage of exocrine secretions. Often these stones are an epiphenomenon, and not truly obstructing. Should pancreatic duct stones be removed? Certainly, it is tempting to try to clear the duct of stones in symptomatic patients, but the results are often disappointing. Pain in chronic pancreatitis is often multifactorial. Endotherapy of presumed obstructing stones and benign PD strictures may be considered a "trial of therapy": if the patient gets symptomatic relief, formal surgical drainage of the pancreas (e.g. by lateral pancreaticojejunostomy, or Puestow procedure) with or without parenchymal resection may help the patient long term. After pancreatic sphincterotomy, small pancreatic stones can usually be removed using a basket or balloon catheter. Large stones that completely obstruct the lumen cannot be recovered this way, and require contact or extracorporeal shockwave lithotripsy (ESWL) to fragment them first[18]. The Brussels group (Drs Deviere and Cremer) have reported excellent results using ESWL for PD stones. PD strictures are typically managed by endoscopic stenting. There are few data on metal mesh stenting in benign pancreatic disease, although several European studies have suggested benefit. At present, metal mesh stenting is not recommended in the US for the management of benign PD strictures[19]. Plastic pancreatic duct stents can induce focal pancreatitis and strictures by occluding small side branches. The recently-introduced "star-shaped" stents that facilitate flow of pancreatic secretions around them may address this problem. As migration of plastic stents into the PD creates a difficult management problem, non-flanged stents intended to spontaneously dislodge into the bowel are made with a curl - or "pigtail" - at their distal end. An interesting application of metal mesh stents in benign pancreatic disease has been tried by the ERCP group from Indiana University (Drs Lehman and Sherman), with some success. They had a group of P Div patients with ARP who failed to improve despite repeated minor papillotomes. As their dorsal PDs were not dilated, they were considered unsuitable for surgical drainage procedures. Drs Lehman and Sherman used expandable metal mesh stents inserted through the minor papilla to cause the dorsal PDs to progressively dilate over time[20]. After this treatment, surgeons were able to perform lateral pancreaticojejunostomies on these patients. Pancreatic cancer (adenocarcinoma) is an unusual cause of ARP, but it should always be considered in elderly patients with unexplained bouts of pancreatitis. EUS may identify small lesions in the PD before a mass is appreciated on CT or MRI scan. Pancreatic stents are rarely indicated in pancreatic cancer, but there have been reports of patients with intractable pain or steatorrhea benefiting from relief of malignant PD obstruction. As mentioned previously, cystic neoplasms, IPMNs and neuroendocrine tumors of the pancreas that can present with ARP.

SPHINCTER OF ODDI DYSFUNCTION (SOD)

When no other cause of ARP is identified in a patient with prior cholecystectomy, SOD should be considered[21,22]. At present, the only way to measure biliary and pancreatic sphincter pressures is perform ERCP using a manometry catheter[23]. Historically, this has been associated with increased risk of post-ERCP pancreatitis (compared to non-manometry ERCP). As Freeman has pointed out, it is not the manometry itself that is dangerous but the instrumentation of a hypersensitive sphincter and (typically) non-dilated bile duct and pancreatic ducts[24]. Prophylactic stenting of the PD after manometry in cases of suspected SOD has significantly reduced the risk of post-ERCP pancreatitis (PEP), and virtually abolished severe (necrotizing) PEP. Most experts now recommend same-session biliary and pancreatic sphincter pressure measurements in ARP patients, as 60%-70% of those

with elevated biliary sphincter pressure have concurrent pancreatic sphincter hypertension[25]. That is, if only biliary pressures are measured and sphincterotomy performed for sustained elevations in ARP, more than 1/2 of these patients will continue to have attacks of pancreatitis. The exact mechanism of ARP in sphincter of Oddi dysfunction (SOD) is unknown[26]. Pharmacologic maneuvers aimed at reducing sphincter of Oddi (SO) pressure, including nitrates and calcium channel blockers, have been disappointing. One small study using intersphincteric botulinum toxin injection claimed an 80% success rate (12 of 15 patients) for relief of ARP[27], but others have failed to reproduce this impressive outcome. Stenting the PD orifice alone (i.e. without sphincterotomy) is not helpful in SOD: it is likely to exacerbate rather than improve pancreatic pain in the setting of a hypertensive sphincter.

BILIARY AND PANCREATIC PARASITES

A rare cause of ARP, usually limited to tropical climates, is the presence of parasites within the bile ducts or pancreatic duct. Certain liver flukes (e.g. Fasciola hepatica[28], Clonorchis sinensis[29]) like to live and lay their eggs in the bile ducts, where they cause irritation and obstruction (especially when they die). Ascaris lumbricoides worms like to live in the pancreatic duct, where they obstruct flow of exocrine secretions[30]. In the North of India (Kashmir), Ascariasis is the commonest cause of acute pancreatitis. The treatment of these parasites is principally pharmacologic, but occasionally the ERCP endoscopist is called upon to decompress ducts obstructed by parasites, usually by sphincterotomy and trawling (by balloon or basket catheter).

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