

What Should Be Done with Idiopathic Recurrent Pancreatitis That Remains ‘Idiopathic’ after Standard Investigation?

John Baillie

Division of Gastroenterology, Duke University Medical Center. Durham, NC, USA

One of the most difficult areas of practice in the area of hepatobiliary and pancreatic disorders is the evaluation of patients who have recurrent attacks of acute pancreatitis without a clear etiology, as determined by “standard” work-up [1]. What constitutes a “standard” work-up is far from clear: every center evaluating patients with this problem seems to have evolved its own unique algorithm. The commonest cause of acute pancreatitis worldwide is gallbladder stones (cholelithiasis) [2]. Exhaustive evaluation of the gallbladder by serial transabdominal ultrasound examinations may fail to reveal gallstones, especially microlithiasis. However, the sensitivity of transabdominal ultrasound for detecting gallstones varies greatly, and depends considerably on the interest and expertise of the operator. At referral centers, repeat transabdominal ultrasound by experienced radiologists or radiology technicians may reveal gallstones. Although computed tomography (CT) has limited sensitivity for cholelithiasis, sometimes a CT scan of the abdomen performed to image the pancreas will reveal a stone, or stones, in the gallbladder or biliary tree. Endoscopic ultrasound (EUS) is a rapidly evolving technology that is proving helpful in evaluating both the gallbladder and extrahepatic biliary tree for the presence of stones. In expert hands, with care taken to obtain high quality “source” images, magnetic resonance cholangiopancreatography (MRCP) can detect stones in the biliary tree and gallbladder. However, small stones (i.e., those of 5 mm diameter or less) frequently elude

detection by MRCP. The finding of even a single stone in the gallbladder by any of the aforementioned imaging techniques justifies removal of the “offending” organ, usually by laparoscopic cholecystectomy (LC). In the early days of LC (i.e., 1990 onwards), intraoperative cholangiography was almost routinely performed to look for bile duct stones (choledocholithiasis). In current surgical practice, intraoperative cholangiography is used quite selectively: it is typically reserved for situations in which biliary dilatation and/or abnormal liver function tests (LFTs) suggest the presence of biliary calculi [3]. As a result, asymptomatic bile duct stones may remain undetected until episodes of biliary colic, jaundice or pancreatitis require further investigation. Patients with recurrent pancreatitis who still have a gallbladder, but whose imaging is negative for stones, are increasingly sent for LC as a “trial of therapy”: i.e., cholecystectomy is being used as a diagnostic test. Can this be justified? Given the very low morbidity and mortality of LC, I think it can, although care must be taken not to use this approach indiscriminately. Elderly patients with comorbidities (e.g., cardiac, respiratory and neurological) are less suitable candidates for “empiric” LC than otherwise fit young adults. The author has had a number of patients whose idiopathic recurrent pancreatitis has ceased after cholecystectomy, sometimes with the finding of cholelithiasis despite multiple prior negative imaging studies. One patient had a number of stones in the cystic duct: these were impossible to

identify when we went back and reviewed the endoscopic retrograde cholangiopancreatography (ERCP) films. Stones causing gallbladder “filling defects” on ultrasound examination may be impossible to distinguish from polyps: this distinction tends to be academic, because all such patients will be offered cholecystectomy and the resultant specimen will provide the answer. What if the patient has a dilated common bile duct (CBD) without obvious filling defects at the time of ERCP? Retrospective data from Duke University Medical Center suggest that biliary dilatation (>7 mm diameter) without abnormal LFTs is unlikely to be associated with choledocholithiasis. However, in the setting of recurrent pancreatitis with a dilated bile duct, it is tempting to cut the biliary sphincter for access to “trawl” for stones with a basket or balloon catheter. If the LFTs are elevated, the sensitivity of such intervention for identifying bile duct stones is considerably higher than if the LFTs are normal. The finding of a dilated bile duct brings the patient into the realm of sphincter of Oddi dysfunction (SOD). Whereas biliary SOD is defined by the so-called Milwaukee Criteria, pancreatic sphincter dysfunction is a more novel concept. I will return to the difficult area of SOD and its management shortly. Patients who have already had their gallbladder removed (post-cholecystectomy) require a different approach. Clearly, the gallbladder itself can no longer be implicated in causing recurrent pancreatitis. Could such patients be passing biliary stones? Do they have a hypertensive sphincter of Oddi? [4]. Is there another mechanical cause of biliary and/or pancreatic ductal obstruction, such as an ampullary adenoma [5] or carcinoma, a pancreatic duct stone or stricture, a congenital bile duct abnormality (e.g., choledochal cyst) or pancreatic ductal anomaly (e.g., pancreas divisum, anomalous pancreaticobiliary ductal union)? All of these questions justify a diagnostic ERCP, although some lesions may be detectable by other forms of imaging, including EUS and MRCP. Until the roles of EUS and MRCP in evaluating recurrent pancreatitis are more clearly defined, ERCP

will remain the “gold standard”. If diagnosis of a lesion causing recurrent pancreatitis is delayed by failure to perform side-viewing duodenoscopy and ERCP, malpractice could be alleged, so the physician managing such patients should carefully weigh the “pros” and “cons” of ERCP in each case. As many findings at ERCP require therapeutic intervention (e.g., sphincterotomy, stone removal, stricture dilation), there is no place for the solely diagnostic ERCP endoscopist in modern hepatobiliary and pancreatic practice. It is the author’s opinion that recurrent pancreatitis should be evaluated at specialist referral centers, where the necessary expertise in ERCP is available, and back-up in the form of percutaneous interventional radiology and surgery are easily accessible. Aspiration of bile for cholesterol crystal analysis should be part of ERCP in post-cholecystectomy patients being evaluated for recurrent pancreatitis. Care must be taken to avoid contaminating the “clean” bile aspirated from the bile duct with contrast media: the latter may crystallize into crystalline forms mimicking true cholesterol crystals. A dedicated microscope must be available in the Endoscopy Unit to view the aspirated bile while it is still warm. Bile samples that are stored in a refrigerator for later analysis may provide false positive tests. There should be no delay in bile microscopy, as a positive diagnosis of cholesterol crystals is an indication for biliary sphincterotomy in the post-cholecystectomy patient.

Biliary and pancreatic manometry are highly specialized tests that should only be performed in specialist centers. There are several reasons for this: 1) the equipment is expensive and requires frequent maintenance by personnel familiar with it; 2) the interpretation of manometry tracings requires practice and experience for consistent results, and 3) these procedures carry significantly higher morbidity in many centers than standard diagnostic and therapeutic ERCP. A frequently asked – and rarely answered – question regarding biliary and pancreatic manometry is: how reproducible is a positive or negative result? If one believes that

sphincter hypertension may be an episodic phenomenon, should one do series studies in the hope of “catching” sphincter hypertension “in the act”? Most investigators would say “no”, as the risk and cost of repeat ERCP for manometry is unjustifiable. If the original result was positive, and the offending sphincter was cut, should repeat manometry be performed to check for the “adequacy” of the sphincterotomy when patients continue to have attacks of pancreatitis? In the author’s experience, this is usually a fruitless effort, although occasionally sphincterotomy site stenosis (after a small “cut”) may be found and remedied.

Anatomical abnormalities, such as pancreas divisum, duodenal duplication cyst, choledochoceles, ampullary mass, etc., lead to specific managements, ranging from endotherapy to surgery. This author’s experience of minor papillotomy for pancreas divisum mirrors the best data in the literature [6]: only recurrent discrete attacks of pancreatitis (and not “pancreatic pain”) will respond consistently to this intervention.

So, what is left when patients continue to have recurrent episodes of pancreatitis despite the aforementioned interventions? If they have not been considered before, metabolic causes of pancreatitis, such as hypercalcemia and hypertriglyceridemia, should be carefully looked for. Even when a patient has had prior normal serum calcium levels, a calcium should be checked on each admission with pancreatitis, because the onset of hypercalcemia may be insidious. Hypercalcemia causing pancreatitis is almost always (>90%) due to hyperparathyroidism. Hypertriglyceridemia causing pancreatitis is rarely subtle: indeed, a triglyceride level greater than 1,000 mg/dL is usually necessary for this phenomenon to occur (and values in the 3,000-6,000 range are not uncommon). The serum of affected patients is clearly lipemic, and they may have external clues to their disorder, such as xanthelasma. Drug hypersensitivity as a cause of pancreatitis will usually have been considered early on. However, in truly obscure cases, it is worthwhile to repeat a careful drug history,

including questions about over-the-counter and homeopathic remedies. Most drug-induced pancreatitis is idiosyncratic and not dose-related. The use of illicit drugs is also relevant: intravenous drug abuse may result in microembolic phenomena, of which pancreatitis is one manifestation. Urine testing for drugs of abuse may reveal metabolites of cocaine and other “recreational” agents. In patients who abuse alcohol, recurrent attacks may be evidence of continued use, despite protestations to the contrary. Although checking blood or urine alcohol levels without the patient’s express permission may confirm such suspicions, this practice raises ethical issues and concerns about patient privacy that cannot be ignored. Collagen vascular disorders (e.g., systemic lupus erythematosus, polyarteritis) may cause microvascular ischemia of the pancreas, manifest as attacks of pancreatitis. There are usually other clues to the diagnosis, such as Raynaud’s phenomenon and peripheral manifestations of collagen disorders, but an anti-nuclear antibody (ANA) screen and an erythrocyte sedimentation rate (ESR) are important data. Rare infective (e.g. viral) and parasitic disorders (e.g., Ascariasis) causing pancreatitis are usually evident from other clinical manifestations.

Malignancy is an important consideration in idiopathic recurrent pancreatitis [7]. The youngest patient the author has diagnosed with adenocarcinoma of the pancreas was a 25-year old, and these days it is not unusual to make this diagnosis in patients in their 40s. So, this is no longer (and perhaps never was) a disease of “the elderly”. Recurrent pancreatitis may be caused by a small tumor encircling the pancreatic duct. An isolated, unexplained pancreatic duct stricture in a patient over 35 years without predisposing cause should be considered malignant until this is disproved or confirmed. EUS can be helpful in assessing such strictures, although sometimes “blind” resection of part or all of the gland is necessary to make a tissue diagnosis. Cytologic and biochemical methods of analyzing pancreatic juice and pancreatic stricture brushings (e.g.,

telomerase [8] assay, ploidy status) may add weight to the suspicion of malignancy. Whether or not pancreatic adenocarcinomas detected at a very early stage are truly curable by surgery remains to be seen. At present, the long term survival after pancreaticoduodenectomy (Whipple procedure) for cancer is abysmal. Endocrine tumors of the pancreas (e.g., islet cell tumors) rarely impinge on the ductal system and therefore rarely present with pancreatitis. On the other hand, cystic tumors of the pancreas not infrequently present with pancreatitis. Mucinous duct ectatic tumors [9] produce mucin which blocks the pancreatic duct, impeding outflow and encouraging bouts of pancreatitis. Cross-sectional imaging techniques (especially CT scanning) are useful in characterizing such lesions.

Finally, genetic predisposition needs to be considered in patients with idiopathic recurrent pancreatitis, especially teenagers and young adults. While cystic fibrosis, caused by a homozygous defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, usually progresses to pancreatic exocrine insufficiency without bouts of pancreatitis, the same cannot be said for patients with a heterozygous defect (i.e., partial loss of CFTR) or a defective cationic trypsinogen gene. Detailed discussion of this and other genetic predispositions to pancreatitis - including the protease inhibitor, Kazal type 1 (SPINK1) gene family - are beyond the scope of this review [10]. However, it should be said that patients being sent to have blood tests for these abnormalities should receive prior genetic counseling, as the implication of a positive test are considerable. American patients fear that genetic testing data may be used by insurance carriers to deny them medical coverage. There are also issues of paternity and maternity that may be uncovered by "routine" genetic testing of family members. These are best dealt with by professional genetic counselors.

In summary, idiopathic recurrent pancreatitis is a difficult clinical challenge that requires the skills of an experienced hepatobiliary and

pancreatic consultant. Much of the work-up is best performed in referral centers which are suitably equipped to carry out the tests and treat the abnormalities found.

Key words Cholangiopancreatography, Endoscopic Retrograde; Cholelithiasis; Endosonography; Genetic Predisposition to Disease; Magnetic Resonance Imaging; Oddi's Sphincter; Pancreatitis, Acute Necrotizing

Abbreviations ANA: anti-nuclear antibody; CBD: common bile duct; CFTR: cystic fibrosis transmembrane conductance regulator; CT: computed tomography; ERCP: endoscopic retrograde cholangiopancreatography; ESR: erythrocyte sedimentation rate; EUS: endoscopic ultrasound; LC: laparoscopic cholecystectomy; LFTs: liver function tests; MRCP: magnetic resonance cholangiopancreatography; SOD: sphincter of Oddi dysfunction; SPINK1: protease inhibitor, Kazal type 1

Correspondence

John Baillie
Division of Gastroenterology
Duke University Medical Center
Erwin Road
Durham
NC 27710
USA
Phone: +1-919-684-3894
Fax: +1-919-684-4695
E-mail address: baill001@mc.duke.edu

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