Acute idiopathic pancreatitis: Is it truly idiopathic?

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Abstract

Acute pancreatitis is a severe disease with considerable morbidity and mortality. A variety of causes have been cited, the commonest being alcoholic and gallstone pancreatitis. However in a few cases, no distinct etiology can be identified. These are termed acute idiopathic pancreatitis. In such patients, microlithiasis and sphincter of Oddi dysfunction have been attributed to the development of acute pancreatitis. The pathophysiology and management of acute idiopathic pancreatitis due to microlithiasis and sphincter of Oddi dysfunction are discussed in the paper.

Keywords: Idiopathic, pancreatitis, microlithiasis, sphincter of oddi, treatment

Introduction

Although there are innumerable causes of acute pancreatitis, a definitive etiology cannot be found in a few cases which are designated as acute idiopathic pancreatitis (AIP). Two potential pathological conditions have been postulated to explain the etiology of acute idiopathic pancreatitis [4]. These include microlithiasis and sphincter of Oddi dysfunction. Both these conditions are invariably missed on a conventional imaging thereby classifying the etiology of acute pancreatitis as idiopathic.

Pathophysiology

Microlithiasis is invariably confused with sludge. Sludge usually contains cholesterol monohydrate crystals, calcium bicarbonate granules, calcium carbonate salts embedded in strands of mucin, whereas, microlithiasis is best described as the presence of cholesterol crystals in bile, in the absence of macroscopic stones [5,6]. Rapid precipitation of crystals from bile which is supersaturated with cholesterol is the big factor in cholesterol microlithiasis. Patients with gallbladder microlithiasis have lower amount of phosphatidylcholine in the bile compared to patients with grossly visible gallbladder stones. Rapid cholesterol crystallisation in the hepatic bile is usually attributed to low biliary phosphatidylcholine concentration. The relative phosphatidylcholine deficiency is due to missense mutations in the multidrug resistant protein -3 gene (MDR-3) [7]. This phenomenon is related to rapid cholesterol crystallisation, microlithiasis and risk of acute pancreatitis. Hypersecretion of gallbladder mucin strongly adds to the cholesterol crystallisation, thereby, leading to microlithiasis. Mucin may enhance cholesterol crystallisation by offering low affinity binding sites for phosphatidylcholine and cholesterol. Mucin may also increase bile viscosity leading to formation of a gel matrix which may entrap cholesterol crystals in the gallbladder. In fact, various theories have been proposed for the development of acute pancreatitis once microlithiasis has developed [8].

Obstruction of pancreatic duct outflow is a primary event in the etiology of pancreatitis. Acute biliary pancreatitis is usually associated with both small stones, less than 5 mm, and sludge in the gallbladder and common bile duct. Microlithiasis causes functional obstruction at the Sphincter of Oddi, leading to pancreatitis, papillary spasm or papillary stenosis. These obstructive lesions leads to reflux of bile and pancreatic secretions into the pancreatic duct. This leads to high pressure at sphincter of Oddi. Cholesterol crystals and possibly, hydrophobic bile salts lead to pancreatic duct injury, extending into the acini. Release of activated pancreatic enzymes into the glandular interstitium of the pancreas leads to production and release of cytokines, thereby precipitating an attack of acute pancreatitis. Bile salts cause extensive damage in the functioning of pancreatic cells. Bile salts cause impairment in calcium signalling in
pancreatic acinar cells leading to the death of cells. Bile salts transport into the acinar cells by the transporter sodium taurocholate cotransporting polypeptide (NTCP) and organic anion transporting polypeptide 1 (OATP1) in the luminal basolateral membrane of the pancreatic cell. Under physiological conditions, these molecules function to clear small amounts of bile salts which reflux into the terminal acini [9]. However, in case of massive reflux, large amounts of bile salts are present in the lumen of the terminal acini that is in the pancreatic cells. The pancreatic acinar cell clearing mechanisms for bile salts is thereby overwhelmed. These chain of events leads to the final cascade terminating into cell death.

Diagnosis
Technically, cholesterol microlithiasis is defined by the presence of typical plate-like rectangular cholesterol monohydrate crystals or intermediate non-plate like anhydrous crystals such as needles, arcs, tubes or spirals in the bile. The gold standard for diagnosis for cholesterol microlithiasis is polarising light microscopic examination of bile obtained by ERCP. Polarising light microscopy of aspirated duodenal contents after intravenous CCK infusion is also an acceptable method for diagnosis. Several risk factors should raise the suspicion of microlithiasis or sludge [9]. These include:
1. Pregnancy
2. Rapid weight loss
3. Gastrectomy
4. Octreotide therapy and
5. Patients on long term Total Parenteral Nutrition (TPN)

Treatment
Acute pancreatitis once diagnosed needs to be managed by aggressive fluid resuscitation and meticulous prevention of infections. Once the patient attains hemodynamic stability devoid of sepsis, then definitive treatment of the cause can be commenced. If left untreated, acute pancreatitis induced by microlithiasis is likely to develop recurrent acute pancreatitis. The treatment for such patients is cholecystectomy. Cholecystectomy causes decrease in the residence time of bile in the biliary tree thereby leading to a reduction in the nucleation process of cholesterol crystals. Hepatic bile being less concentrated than gallbladder bile will have very slow crystallization. In patients who are high risk for cholecystectomy, endoscopic sphincterotomy can be proposed with significant benefit. Sphincterotomy promotes drainage of pancreatic juices and bile thereby reducing the severity of the inflammatory process in the pancreas as well as reduction in the nucleation process occurring in the biliary tree. Maintenance with ursodeoxycholic acid (UDCA) may be helpful in a few patients, who have already undergone cholecystectomy or in those patients wherein there are contraindications to surgical endoscopic interventions. Ursodeoxycholic acid decreases cholesterol secretion into bile and prolongs crystal nucleation. It is especially useful in patients with missense mutations in the MDR-3 gene [9].

Sphincter of Oddi dysfunction
In patients who have already undergone cholecystectomy, if acute pancreatitis develops without any cause, it is usually attributed to sphincter of Oddi dysfunction [10]. Sphincter of Oddi dysfunction is a benign non-calcus obstructive disorder which occurs at the level of sphincter of Oddi. It relates to passive obstruction at the Sphincter of Oddi due to inflammation, fibrosis or by spasm of sphincter muscle [11]. Sphincter of Oddi dysfunction can lead to three types of clinical scenarios:
1. Persistent or recurrent biliary pain following cholecystectomy in the absence of structural abnormalities
2. Acute idiopathic pancreatitis
3. Biliary pain in patients with intact gallbladder but without choledolithiasis.

Microlithiasis and biliary sludge can cause Sphincter of Oddi dysfunction. Diagnosis of Sphincter of Oddi dysfunction is a great challenge. Duodenal aspiration of bile after CCK or common bile duct aspiration of bile at ERCP after CCK administration is essential to ascertain the diagnosis of microlithiasis. Endoscopic ultrasonography (EUS) has a higher sensitivity in the diagnosis of microlithiasis and sludge [12]. It also confers an added advantage of ruling out other causes such as pancreatic divisum, neoplasms and undiagnosed chronic pancreatitis. Sphincter of Oddi manometry during ERCP for acute idiopathic pancreatitis reveals sphincter hypertension in 30-65% patients. A variety of medications have been proposed for treatment of sphincter of Oddi dysfunction [13]. However, none of these treatment modalities can deliver long lasting results. Endoscopic sphincterotomy is relatively the best option for managing sphincter of Oddi dysfunction [13, 14, 15]. Both biliary and pancreatic sphincterotomy have been done to achieve the best outcome.

Conclusion
Microlithiasis and sphincter of Oddi dysfunction are most likely causes for acute idiopathic pancreatitis. Arriving at a diagnosis by virtue of high index of suspicion is essential. Confirming the diagnosis by microscopic study of bile aspirated from the biliary tree at ERCP is diagnostic for microlithiasis. Once diagnosed with microlithiasis, cholecystectomy is the mainstay of treatment. However in a patient developing acute idiopathic pancreatitis despite having undergone cholecystectomy, one should strongly suspect sphincter of Oddi dysfunction. Manometry of the sphincter of Oddi will in majority of times confirm the diagnosis of sphincter of Oddi dysfunction as a cause of acute idiopathic pancreatitis. Endoscopic sphincterotomy in such cases is therapeutic.

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