Sclerosing Cholangitis – Primary, Secondary and More...

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Key words: sclerosing cholangitis, bile ducts, biliary cirrhosis, cholestasis, endoscopic retrograde cholangiopancreatography

IMAJ 2002;4:1141–1142

Sclerosing cholangitis, first described by Delbet in 1924 [1], refers to a pathologic condition of inflammation and fibrosis of the biliary tree that may result in diffuse bile duct strictures and dilatation [2]. This pathology is probably the end result of several insults. Primary SC, the most common type, may be divided into subclasses: SC with no apparent associated disease or condition, or SC associated with inflammatory bowel disease, systemic fibrosis, or collagen vascular diseases. Secondary SC is a broad category in which an underlying noxious insult to the biliary tree may be identifiable. The insult may be obstructive cholangitis secondary to choledocholithiasis, surgical damage, trauma, vascular insults, parasites, or congenital fibrocystic disorders. Additional causes of secondary SC are toxic, due to chemical agents or drugs.

The etiology of primary SC is unknown, but a few mechanisms have been proposed. In the context of inflammatory bowel disease, bacterial toxic products introduced through the diseased colon have been suggested and supported by animal studies [2]. There is, however, no correlation between the activity of the colitis and the biliary disease, and SC may even appear after the colon has been removed [3]. Infectious agents such as cytomegalovirus or *Cryptosporidium* have been implicated as a cause, especially in immune compromised patients [4].

The clinical presentation, complications and management tend to be the same in the various types of SC. Between 20% and 44% of patients in large series are asymptomatic [5]. When symptomatic, the clinical picture consists of cholestasis (jaundice, pruritus), right upper quadrant abdominal pain, weight loss, anorexia, and fatigue. Febrile episodes appear spontaneously or following biliary manipulation. Cholestasis may relapse and remit due to microlithiasis, sludge, or intermittent bacterial cholangitis [6]. Pigment gallstones occur in up to 30% of patients [7]. Nutritional deficiencies of fat-soluble vitamins may cause night blindness and osteoporosis. Disease progression is usually insidious but may be rapid, particularly in toxic SC [8]. Progressive liver damage caused by extension of the fibro-inflammatory process and toxic damage by bile salts and copper may lead to cirrhosis and its complications. Liver failure is the most common cause of death in these patients.

It is important to recognize that primary SC is a premalignant condition, with a 30–40% prevalence of cholangiocarcinoma in autopsies [3]. The diagnosis of cholangiocarcinoma in the context of SC may be extremely difficult.

Laboratory findings are dominated by cholestasis and its consequences: high alkaline phosphatase, gammaglutamyl transpeptidase and 5-nucleotidase, hypercholesterolemia and prolonged prothrombin time. Also present are hypergammaglobulinemia (especially immunoglobulin M) and autoantibodies (perinuclear antineutrophil cytoplasmic antibodies, antinuclear antibodies).

The management of SC consists of treating the biliary process as well as complications. Despite sporadic success with steroids [9], methotrexate or tacrolimus [10], immunosuppressive treatment has generally failed [11]. Ursodeoxycholic is the primary therapy but is less successful in SC than in primary biliary cirrhosis [12]. It improves liver enzymes and, less consistently, bilirubin levels. Its effect on liver histology and on symptoms is at best marginal, although recent reports suggest that higher doses may be more beneficial [13]. Episodes of cholangitis require prompt antibiotic treatment; a severely symptomatic patient may require intervention by endoscopy or invasive radiology for sphincterotomy, stricture dilatation, and stenting [14]. End-stage liver disease or refractory complications are indications for liver transplantation [15].

In the current issue of *IMAJ*, Morali et al. [16] describe a 16 year old girl who was operated on for an echinoccocal liver cyst. During surgery formaldehyde was injected for local sterilization and prevention of recurrence. A postoperative biliary-cutaneous fistula developed, with recurrent episodes of bacterial cholangitis. The clinical course was rapidly progressive, and within a year she developed secondary SC and decompensated biliary cirrhosis necessitating liver transplantation 4 years after the initial insult. The explanted liver revealed severe liver damage caused by the injection, calcifications and secondary impaction of gallstones and sludge.

Echinococcal liver cysts may be managed percutaneously by aspiration and injection of a scolicidal agent such as formaldehyde [17], but large cysts should be excised when possible, particularly in young patients. A scolicidal agent is often applied intraoperatively for cyst sterilization. Perioperative use of an antihelmintic agent such as albendazole has been advocated by some [18] to avoid contamination. Primary closure is preferred but is not always possible, and sometimes marsupialization or external drainage is needed but is accompanied by a high rate of complications. Hepatic resection may be necessary for large or multiple cysts [19]. The presence of a cysto-biliary communication is a predictor of postoperative morbidity such as cholangitis or intrabiliary rupture. In a recent case series, communication was seen in 21% and was associated with occult intrabiliary rupture in 13%, and with frank intrabiliary rupture in 8% [20]. Therefore, it has been suggested that when instillation of a sclerosing agent is planned a preoperative

SC = sclerosing cholangitis

cholangiogram should be performed. If a cysto-biliary connection is proven, endoscopic sphincterotomy should be performed to lower the pressure in the biliary system, and to prevent fistula formation. In a recent report [21], pre- and postoperative endoscopic retrograde cholangiopancreatography was compared in patients operated for liver hydatid cysts. Biliary fistulas and SC were more common among those who underwent ERCP after the operation. A recent report even suggests complete endoscopic treatment by internal trans-fistulary drainage without opening the cyst cavity, in cysts communicating with the biliary tree [22].

Based on the above, the present case [16] raises some important questions: Is any one of the scolicidal solutions less damaging than others, and should preventive measures such as cholangiography, sphicterotomy or specific surgical techniques be undertaken to decrease possible injury? Reported cases in the literature are often anecdotal with no available prospective data. Caustic damage has actually been described with all solutions: formaldehyde, hypertonic saline, as well as alcohol. Recently, albendazole sulfoxide was shown to be an effective scolicidal solution with no caustic effects in rabbits [23] or sheep [24], but no human data are yet available. It seems justifiable that a preoperative ERCP be performed to exclude cysto-biliary communication. If found, sphincterotomy should be performed and a scolicidal solution avoided to prevent exposure of the biliary tree to the caustic agent. Liver resection should be considered if cystectomy cannot be performed in these cases. Perioperative albendazole should also be administered. These precautions should reduce the prevalence of the devastating complication.

A particularly intruiging feature in the present case was the rapidity of progression to end-stage cirrhosis. This might be explained by a combination of unfortunate events: severe and diffuse bile strictures caused by the caustic agent at an anatomically central location, aggravated by gallstones and sludge. Moreover, a direct toxic effect on the liver cannot be excluded. In addition, one may speculate that the biliary damage may expose some antigenic sites that provoke an immunologic response, or enable antigenic factors that originate in the bowel to cause damage as described in primary SC. If true, it remains to be determined which patients are prone to develop this complication; for example, regarding HLA haplotype, which has been shown to play a role in determining the course of primary SC [25].

In summary, sclerosing cholangitis is a potentially fatal disease occurring in three different settings: in patients with no apparent underlying cause, in those with some co-morbid conditions, and in those following a clear primary insult. The latter pose a particular challenge to be identified at a stage when the initial insult might still be avoided. In view of the grave consequences, formaldehyde-induced bile duct sclerosis should be such an avoidable case.

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ERCP = endoscopic retrograde cholangiopancreatography

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