CASE REPORT

Secondary sclerosing cholangitis uncovered during endoscopic retrograde cholangiopancreatography in a patient with chronic choledocholithiasis

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Abstract

Untreated biliary cholestasis such as in the case of choledocholithiasis with biliary obstruction can lead to inflammatory strictures, recurrent cholangitis, the formation of more stones and eventually secondary biliary cirrhosis. This can lead to a shortened life expectancy. We report a case of a 61 year old male from Somalia, who presented with recurrent painless jaundice. He had had similar presentations in another country but lacked documentation to show the treatment ensued. Liver function tests (LFTs) at our institution showed evidence of cholestasis. Repeated initial radiological studies failed to show any biliary dilatation and/or obstruction but did reveal evidence of liver cirrhosis with portal hypertension. A liver biopsy at this stage showed bile plugs consistent with a cholestatic picture, as well as evidence of secondary biliary cirrhosis. A magnetic resonance cholangiopancreatography (MRCP) confirmed the presence of biliary dilatation secondary to choledocholithiasis. He underwent an endoscopic retrograde cholangiopancreatography (ERCP), which showed common bile duct stones and an associated biliary stricture, as well as features suggestive of secondary sclerosing cholangitis (SSC) of the intrahepatic ducts. Dilatation and stenting of the stricture were performed, while complete stone clearance was achieved at the second ERCP. LFTs decreased gradually thereafter. Biliary drainage in a patient with cholestasis from a mechanical cause should be the mainstay of treatment. Every effort should be made to prevent the development of chronic cholestasis due to the risk of developing SSC and biliary cirrhosis. Our patient had unfortunately developed chronic choledocholithiasis, with radiological and histological evidence of liver cirrhosis at the time of presentation at our institution.

Key Words

Biliary cirrhosis, Choledocholithiasis, Endoscopic retrograde cholangiopancreatography, Secondary sclerosing cholangitis, Stricture

1 Introduction

Prolonged obstruction of the extrahepatic biliary tree if left untreated, results in significant injury to the cholangiocytes, causing fibrosing inflammatory destruction of the extrahepatic and/or intrahepatic biliary system, also known as secondary sclerosing cholangitis, with subsequent bile stasis, hepatic fibrosis and eventual biliary cirrhosis. This is associated with

significant morbidity and a reduced life expectancy if such cholestasis is left to progress to liver failure. Several causes can result in secondary sclerosing cholangitis, of which the most common is choledocholithiasis.

In cases of biliary obstruction, where there is an underlying mechanical pathology, such as biliary stones or tumours, biliary injury and cholangiopathy can be halted or even reduced if good biliary drainage is achieved, such as in the case of complete stone extraction or stenting of a tumor performed at endoscopic cholangiopancreatography (ERCP). Such drainage should be achieved before irreversible biliary cirrhosis develops.

We hereby report a case of a patient with persistent choledocholithiasis and associated inflammatory biliary stricture formation that resulted in secondary sclerosing cholangitis and eventual biliary cirrhosis.

2 Case presentation

A 61 year old male from Somalia presented to Accident and Emergency Department at Mater Dei Hospital, Malta with a 3 month history of painless jaundice, pruritus, fever, weight loss and nausea. The patient gave a history of undergoing an ERCP one year previously in Cairo but no medical records were available. His current liver function tests (LFTs) were consistent with cholestasis (see Table 1: at presentation). Viral/malaria screen, autoimmune screen, including IgG4 and metabolic screen were all negative. Ca19.9 was elevated at 112U/mL. Stools for Schistosoma ova were negative too. Ultrasound examination showed a coarse liver and a common bile duct (CBD) of 6mm. There was no intrahepatic bile duct dilatation. The pancreatic head was at the upper limit of normal and the spleen was enlarged at 14.8cm, consistent with portal hypertension. He was treated with intravenous antibiotics and made a full recovery, normalizing all liver enzymes and bilirubin at one month after presentation. Five months later, he presented again with another episode of painless jaundice under the general physician. A repeat ultrasound examination showed liver cirrhosis with splenomegaly. Portal flow was diminished but there was no thrombosis. The biliary tree was not dilated and the gallbladder was contracted. The pancreas was also normal. LFTs showed a cholestatic picture though alkaline phosphatase and gamma-glutamyl transpeptidase were not as high as at initial presentation (see Table 1: at 5 months). A repeat liver screen for viral, autoimmune, metabolic causes proved negative again. A liver biopsy was performed at this point given the biochemical evidence of cholestasis but a lack of radiological biliary obstruction. This showed fibrous expansion of the portal tracts with fibrous septa, a marginal ductular proliferation within portal tracts and nodular regeneration. Inflammatory infiltrates were composed of lymphocytes with scattered neutrophils. Cholestasis with bile plugs was noted. The liver biopsy was consistent with obstructive biliary cirrhosis (see Figure 1). Once again, he improved with antibiotics and was referred to the hepatology clinic at this stage.

A third attempt at a liver ultrasound for any evidence of obstruction revealed a dilated CBD of 11mm for the first time. Radiological evidence of liver cirrhosis and portal hypertension was once again reported. A subsequent magnetic resonance cholangiopancreatography (MRCP) confirmed a dilated CBD (13mm), mild intrahepatic duct dilatation and an 11mm stone in the mid-CBD (see Figure 2). He underwent an ERCP, which showed multiple stones in the CBD and a stricture in the proximal part of the common hepatic duct. The stones could not be extracted but the stricture was dilated and stented with a straight plastic stent. He was commenced on ursodeoxycholic acid at this point at a dose of 13mg/kg.

A repeat ERCP four months later showed residual stones in the CBD, as well as the associated inflammatory stricture previously described. The intrahepatic ducts showed pruning and cystic dilatation suggestive of secondary sclerosing cholangitis (SSC) (see Figure 3). The previously placed stent was removed and the sphincterotomy was extended. The stricture was once again dilated and the stones were retrieved using a basket. He also underwent a gastroscopy which showed grade 2 oesophageal varices, which were band ligated on repeat endoscopic sessions. Following ERCP, the liver cholestatic enzymes started to normalize slowly (see Table 1: at 25 months). On the other hand, bilirubin was increasing as a result of liver failure. He was also started on prophylactic ciprofloxacin. At this stage, he expressed interest of permanently moving to another country and was thus lost to further follow-up from our end.

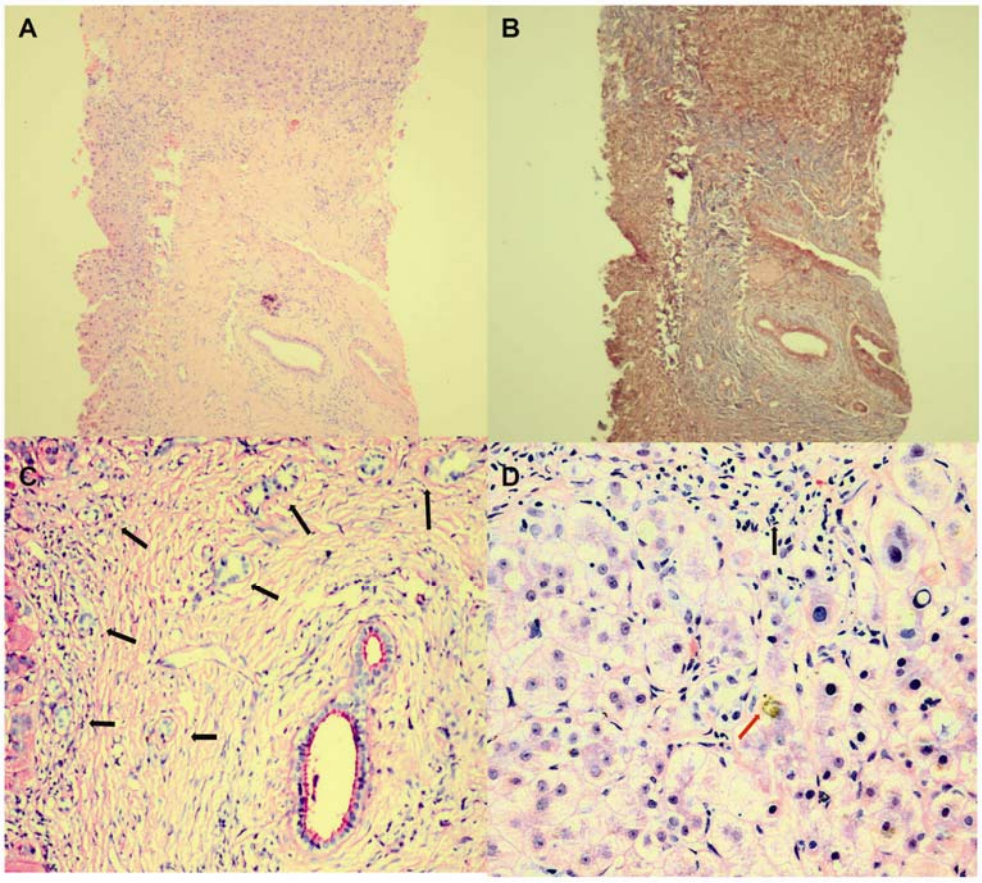

Figure 1. Liver biopsy histology slides highlighting features of cholestasis and secondary biliary cirrhosis. A. Fibrous expansion of the portal tract with fibrous septae emanating from it resulting in a nodular architecture of the liver (H&E stain ×40). B. Masson's trichrome stain highlights the areas of fibrosis (blue) and enhances the nodular architecture of the liver (Masson's trichrome stain ×40). C. Dilatation of the native bile duct with an accompanying ductular proliferation (black arrows) (Periodic acid Schiff stain ×200). D. Bile pigment within the hepatic parenchyma (red arrow) and periportal neutrophils (black arrow) (H&E stain ×400).

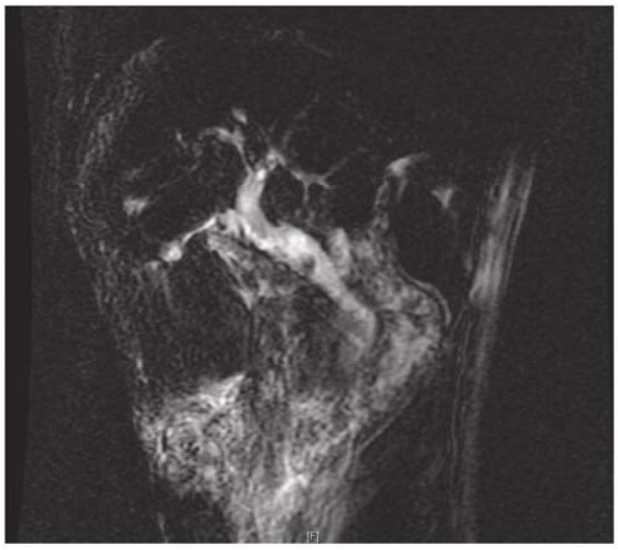

Figure 2. Magnetic resonance cholangiopancreatography showing a dilated common bile duct, as well as strictures and dilatations within the intrahepatic ducts.

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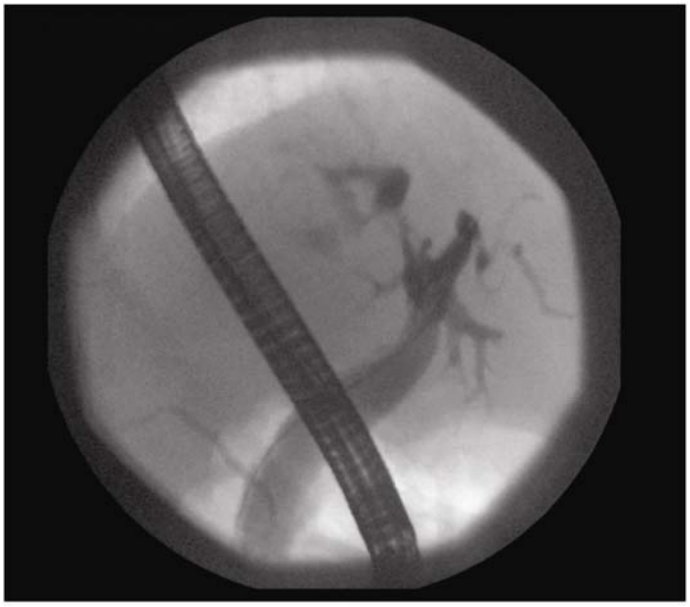

Figure 3. Endoscopic retrograde cholangiopancreatography showing features of secondary sclerosing cholangitis; pruning and cystic dilatation of the intrahepatic ducts.

Table 1. Laboratory results at presentation and during follow up of the named patient.

	At presentation to hospital	**5 months after initial presentation**	**17 months after the initial presentation**	**ERCP**	**21 months after the initial presentation**	**ERCP**	**25 months after the initial presentation**	**Last set of LFTs before moving abroad.**
Bilirubin (1.0 – 17μmol/L)	50	72	51		44		51	60.4
Alkaline phosphatase (40 – 129 u/l)	601	361	441		482		353	279
Alanine transaminase (1.0 – 41 u/l)	67	72	115		94		99	64
Gamma-glutamyl transpeptidase (11.0 – 50 u/l)	805	557	604		638		247	149
Ca 19.9 (0 - 33U/mL)	112		79.8					49.3
Platelets (150 – 450 × 10^9/L)	250	153	140		171		128	94
INR	1.0	0.97	1.0		1.05		1.0	1.13
Albumin (35 – 50 g/l)	35.9	31.9	37		30		30	31.5

3 Discussion

Primary sclerosing cholangitis (PSC) is frequently observed in males, Caucasians and Northern Europeans [1]. The incidence rate is 0.41–1.25 patients/100,000 person-years [2, 3]. The mean age at onset is 42 years [1]. On the contrary, the incidence of secondary sclerosing cholangitis (SSC) is unknown due to the fact that limited data has been published on this

entity, the majority of which consisted of case reports. A study by Gossard et al. identified 10 patients suffering from SSC between 1992 and 2002 [4].

Unlike primary sclerosing cholangitis, secondary sclerosing cholangitis results from a known pathological process or injury. Patients suffering from SSC have been reported to have a shortened life expectancy (72 months transplant-free survival in SSC vs 89 months in PSC) [4]. Occurrences of cholangiocarcinoma and hepatocellular carcinoma, however, were reported in PSC patients but not in SSC patients, possibly suggesting a higher likelihood of malignancies in PSC than in SSC [4].

Several causes of SSC have been identified including common bile duct stones, biliary or blunt abdominal trauma, bile duct neoplasms, Caroli's syndrome, biliary ischaemia in the critically ill patients, intrahepatic artery chemotherapy, recurrent pancreatitis, autoimmune pancreatitis, eosinophilic or mast cell cholangitis/cholangiopathy, hepatic inflammatory pseudotumour, primary immune deficiency, AIDS related cholangiopathy and recurrent pyogenic cholangitis (see Table 2) [5-7].

Table 2. Causes of secondary sclerosing cholangitis

Predominant aetiology	Cause	Pathogenesis
Chronic obstruction	Choledocholithiasis Biliary strictures (e.g. secondary to surgical trauma or chronic pancreatitis) Anastomotic strictures in liver allograft Neoplasms (benign or malignant)	Recurrent supportive changes
Infectious	Parasitic infection (cryptosporidiosis, microsporidiosis) Cytomegalovirus infection	Chronic inflammation
Toxic	Accidental alcohol or formaldehyde instillation in bile ducts.	Direct injury to biliary epithelium
Immunologic	Autoimmune pancreatitis with IgG_4 associated autoimmune sclerosing pancreatitis and cholangitis Eosinophilic cholangitis Mast-cell cholangiopathy	Chronic inflammation
Ischaemic cholangiopathy	Post-tranplantation hepatic artery thrombosis (particularly with a non-heart-beating-donor graft) Hepatic allograft rejection (acute, chronic) Intra-arterial, chemotherapy-related injury Transcatheter arterial embolization therapy Systemic vasculitis Radiation injury	Impairment of arterial blood flow, at the level of the major hepatic artery branch (proximal type) or at the peribiliary vascular plexus (distal type)
Ischaemic-like cholangiopathy	Critically ill patients with acute respiratory distress syndrome	Unknown Ischaemic, toxic and/or genetic predisposition?

SSC is characterized by the induction of proliferative responses, damage to the peribiliary circulation, alterations in epithelial cell transport and secretory function and by the activation of fibrogenic process depending on the initial biliary injury [7]. The long standing existence of choledocholithiasis can result in chronic erosion of the wall of the common bile duct leading to stricture formation and recurrent attacks of cholangitis. This in turn induces further inflammatory stricturing disease with more stone formation and subsequent bile stasis. The long standing existence of such process can lead to biliary cirrhosis. Our patient had two attacks of cholangitis prior to being diagnosed with choledocholithiasis on

MRCP, and stricturing disease on ERCP, however the history of an ERCP in Cairo the year before suggested that the patient had already had a cholestatic pathology at that time. Given the radiological evidence of liver cirrhosis with portal hypertension also suggested that this had been a chronic process. Traveling from one country to the another and the paucity of documentation of the previous treatment carried out in such countries might have contributed to delays in engagement with medical services and resulting in repeated investigations to reach the diagnosis before therapy (biliary drainage in this case) could be carried out.

If biliary obstruction is not longstanding, a liver biopsy would reveal perivenular bilirubinostasis with bile plugging the dilated canaliculi, a variable degree of bile regurgitation into the perisinusoidal space, and phagocytosis of bile by Kupffer cells. Long standing cholestasis would result in periportal cholestatic liver-cell rosettes, which consist of dilated canaliculi surrounded by hepatocytes in a pseudotubular pattern [8]. There is extensive proliferation of smaller bile ductules most commonly occurring at the interface between the septa and the parenchyma. Severe cholestatic features include extensive feathery degeneration and formation of bile lakes. Bile stasis may become less prominent once regenerative nodules have formed. Ascending bacterial infection causes neutrophilic infiltration of bile ducts and an abscess may develop [9].

Ultrasonography will detect gallstones, dilatation of the bile duct or the presence of a hepatic abscess in patients in whom chronic biliary obstruction is the main cause of sclerosing cholangitis. ERCP remains the gold standard for diagnosis of SSC. Findings on ERCP are PSC-like biliary lesions with multifocal strictures and intervening segments of normal or dilated ducts which give the intrahepatic bile ducts a beaded appearance. Small peripheral bile ducts may show poor filling or complete obliteration, giving the biliary tree a pruned appearance. MRCP is less invasive than ERCP but is not as useful for the detection of discrete early lesions [10].

The sensitivity, specificity, and diagnostic accuracy were 86%, 77%, and 83%, respectively, using the MRCP-RARE sequence, and increased further to 93%, 77%, and 88%, respectively, by the inclusion of follow-up MRCP in 52 patients, performed at 6-12-month intervals. MRCP can diagnose PSC but has difficulties in early PSC and in cirrhosis, and in the differentiation of cholangiocarcinoma, Caroli's disease, and secondary sclerosing cholangitis [10]. According to meta-analyses, MRCP shows 86% diagnostic sensitivity and 94 % specificity, demonstrating that it is somewhat inferior in terms of the depiction of the intra/extrahepatic bile duct and a diagnosis of liver cirrhosis and cancer at the early stage [11].

Treatment for patients suffering from primary and secondary biliary cirrhosis is limited. Symptomatology and LFTs can be improved with repeated ERCPs where a sphincterotomy is performed, strictures are dilated and stents are inserted. There should be extraction of biliary casts [12-14].

Ursodeoxycholic acid may improve survival and clinical outcome if given in combination with endoscopic treatment such as ERCP. Biliary tract infections should be treated with antibiotics [15, 16]. Once end-stage liver disease develops, liver transplantation is indicated. Liver transplantation should be appropriately timed before patients develop biliary malignancies as the outcome of patients is poor even after low-grade malignancies [17].

Currently, encountered case reports of SSC in the literature include those secondary to eosinophilic cholangiopathy, ketamine abuse, Behcet’s disease, following severe burns and cholecystectomy amongst others [18-23]. This case report highlights the point that timely biliary drainage in cases with acute cholestasis due to a mechanical cause is paramount before the development of chronic mechanical cholestasis and its subsequent complications, mainly SSC and biliary cirrhosis. Our patient had unfortunately developed chronic choledocholithiasis, with radiological and histological evidence of liver cirrhosis at the time of presentation at our institution.

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References

[1] LaRusso NF, Shneider BL, Black D, Gores GJ, James SP, Doo E, et al. Primary sclerosing cholangitis: summary of a workshop. Hepatology. 2006; 44: 746-64. http://dx.doi.org/10.1002/hep.21337

[2] Bambha K, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United State community. Gastroenterology. 2003; 125: 1364-9. http://dx.doi.org/10.1016/j.gastro.2003.07.011

[3] Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. J Hepatol. 2008; 48: 939-44. http://dx.doi.org/10.1016/j.jhep.2008.02.017

[4] Gossard AA, Angulo P, Lindor KD. Secondary sclerosing cholangitis: a comparison to primary sclerosing cholangitis. Am J Gastroenterol. 2005; 100(6): 1330-3. http://dx.doi.org/10.1111/j.1572-0241.2005.41526.x

[5] Konstantinos N. Lazaridis. Sclerosing Cholangitis Epidemiology and Etiology. Journal of Gastrointestinal Surgery. 2008; 12(3): 417-419. http://dx.doi.org/10.1007/s11605-007-0344-3

[6] Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. Hepatology. 2006 Nov; 44(5): 1063-74. http://dx.doi.org/10.1002/hep.21405

[7] Ruemmele P, Hofstaedter F, Gelbmann CM. Secondary sclerosing cholangitis. Nat Rev Gastroenterol Hepatol. 2009; 6(5): 287-95. http://dx.doi.org/10.1038/nrgastro.2009.46

[8] Burt A D, Portmann B C, Ferrell L D. MacSween's Pathology of the Liver. Chapter 10: Diseases of the Bile Ducts. 5th edn. Edinburgh: Churchill Livingstone/Elsevier; 2007: 517-582.

[9] Kumar V, Abbas A, Fausto N. Robbins and Cotran Pathologic basis of disease 7th Edition, Chapter 18: Liver and Biliary Tract. Elsevier Saunders; 2006: 877-938.

[10] Weber C, Kuhlencordt R, Grotelueschen R, Wedegaertner U, Ang TL, Adam G, Soehendra N, Seitz U. Magnetic resonance cholangio-pancrea-tography in the diagnosis of primary sclerosing cholangitis. Endoscopy. 2008; 40(9): 739-45. http://dx.doi.org/10.1055/s-2008-1077509

[11] Moff SL, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Kalloo AN, et al. Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. Gastrointest Endosc. 2006; 64: 219–23. http://dx.doi.org/10.1016/j.gie.2005.12.034

[12] Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. Hepatology. 1995; 21(3): 661-7.

[13] Wagner S, Gebel M, Meier P, Trautwein C, Bleck J, Nashan B, Manns MP. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. Endoscopy. 1996; 28(7): 546-51. http://dx.doi.org/10.1055/s-2007-1005552

[14] Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc. 2001; 53(3): 308-12.

[15] Nishizawa T, Suzuki H, Takahashi M, Kaneko H, Suzuki M, Hibi T. Effect of ursodeoxycholic acid and endoscopic sphincterotomy in long-term stenting for common bile duct stones. J Gastroenterol Hepatol. 2013; 28(1): 63-7. http://dx.doi.org/10.1111/jgh.12012

[16] Stiehl A, Rudolph G, Sauer P, Benz C, Stremmel W, Walker S, Theilmann L. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. J Hepatol. 1997; 26(3): 560-6. http://dx.doi.org/10.1016/S0168-8278(97)80421-7

[17] Nashan B, Schlitt HJ, Tusch G, Oldhafer KJ, Ringe B, Wagner S, Pichlmayr R. Biliary malignancies in primary sclerosing cholangitis: timing for liver transplantation. Hepatology. 1996; 23(5): 1105-11. http://dx.doi.org/10.1002/hep.510230526

[18] Miura F, Asano T, Amano H, Yoshida M, Toyota N, Wada K, Kato K, Takada T, Fukushima J, Kondo F, Takikawa H. Resected case of eosinophilic cholangiopathy presenting with secondarysclerosing cholangitis. World J Gastroenterol. 2009; 15(11): 1394-7. http://dx.doi.org/10.3748/wjg.15.1394

[19] Turkish A, Luo JJ, Lefkowitch JH. Ketamine abuse, biliary tract disease, and secondary sclerosing cholangitis. Hepatology. 2013; 58(2): 825-7. http://dx.doi.org/10.1002/hep.26459

[20] Al-Benna S, Willert J, Steinau HU, Steinstraesser L. Secondary sclerosing cholangitis, following major burn injury. Burns. 2010; 36(6): 106-10. http://dx.doi.org/10.1016/j.burns.2010.01.015

[21] Ipaktchi R, Knobloch K, Vogt PM. Secondary sclerosing cholangitis following major burn injury-An underestimated issue in burn care? Burns. 2011; 37(2): 355-6. http://dx.doi.org/10.1016/j.burns.2010.06.014

[22] Patrono D, Mazza E, Paraluppi G, Strignano P, David E, Romagnoli R, Salizzoni M.Liver transplantation for"mass-forming" sclerosing cholangitis afterlaparoscopic cholecystectomy. Int J Surg Case Rep. 2013; 4(10): 907-10. http://dx.doi.org/10.1016/j.ijscr.2013.07.021

[23] Ben Slama Trabelsi A, Issaoui D, Ksiaa M, Souguir A, Mama N, Brahem A, Jmaa A, Ajmi S. Sclerosing Cholangitis in Behçet's Disease. Case Rep Med. 2013: 692980.