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Post hepatectomy bile leak and multi-drug-resistant pseudomonas infection treated with acetic acid

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Abstract

A male patient underwent right hepatectomy and portal vein reconstruction for suspected right hepatic duct cholangiocarcinoma. Post operatively, patient developed recurrent episodes of abdominal sepsis alongside a persistent bile leak. After several months of unsuccessful conservative management, with ERCP and PTC failing to localise the source of the bile leak and surgical intervention considered too high risk, the clinical team opted for chemical ablation using 3% acetic acid. This approach aimed to manage both the persistent bile leak from a presumed remnant caudate lobe bile duct and the multi-drug-resistant Pseudomonas infection. The leak eventually resolved 15 months after the hepatectomy.

Background

Bile leak post heatectomy is a relatively common complication with a variable clinical course and many treatment options available. Despite precise surgical technique, patients may develop bile leak due to a variety of reasons such as under-recognised variation in normal biliary anatomy, delayed thermal injury to bile duct and failure of clips/ sutures as well as ischaemic necrosis of part of cut-surface of liver. Bile leakage may lead to intraperitoneal septic complications, liver failure, and ultimately death. A variety of treatment options are available, including conservative approaches such as drain placement, interventional procedures like ERCP and PTC, and surgical management. A few case reports have described the use of less invasive, novel techniques-such as chemical ablation-for the management of non-communicating bile leaks. We present a case of middle aged man, with post hepatectomy bile leak and multi drug resistant pseudomonas infection, who was successfully treated with acetic acid ablation.

Case presentation

A male patient in 40s with a background of well-controlled ulcerative colitis and primary sclerosing cholangitis (PSC) underwent routine surveillance for PSC and was found to have newly deranged liver function tests (LFTs).

This led to the patient undergoing several investigations including endoscopic retrograde cholangiopancreatography (ERCP) and Cholangioscopy. Patient developed severe pancreatitis post-ERCP, requiring stay in Intensive care unit. Investigations for newly deranged LFTs identified a 1.5 cm dominant lesion in the right hepatic duct close to the main and right portal vein junction. Unfortunately, cholangioscopy could not reach the lesion and blind biopsies were inconclusive. Following MDT

discussion, the decision was to offer the patient an operation due to suspected right hepatic duct cholangiocarcinoma. Patient subsequently underwent right hepatectomy. Portal vein was reconstructed due to residual peri portal oedema and proximity of the lesion to right portal vein and main portal vein confluence. Operation was uncomplicated otherwise. No visible bile leak was identified intraoperatively. Drain was placed in right upper quadrant and patient was commenced on heparin infusion and N-acetyl cysteine for peri-operative care for portal vein reconstruction and small for size liver. Fortunately, histology confirmed a benign dominant stricture on background of PSC, and excluded malignant transformation. There was no bile in drain post-operatively and this was removed on day 4. On post-operative day (POD) 10, patient developed wound infection and was commenced on appropriate antibiotics. CT scan showed a new subphrenic collection (Figure 1) and pleural effusion which were both drained. Patient was treated for abdominal sepsis with a variety of antibiotics and antifungal treatments as per culture sensitivity. Prolonged antimicrobial therapy led to the development of resistance to several organisms, including Pseudomonas, necessitating close collaboration with the microbiology team. Although he clinically improved initially, the output from his newly placed abdominal drain changed from purulent to a persistent low-volume bile leak (50–100 mL per day). He was managed with a combination of care in the community and hospital during these recurrent episodes of abdominal sepsis and ongoing issues with bile leak. Abdominal drain was left in situ with intermittent drain exchanges for more than two months post surgery. ERCP was initially contraindicated due to previous ERCP induced pancreatitis. However, due to ongoing recurrent abdominal sepsis and persistence of bile leak, patient underwent ERCP/stent insertion on POD73. However, no obvious bile leak was demonstrated and it was concluded that the source was a peripheral leak, likely at the cut surface of the liver. It was deemed persistent due to potential peripheral bile duct strictures from PSC. Patient had further recurrent episodes of intra-abdominal pseudomonas sepsis alongside ongoing bile leak. He underwent percutaneous cholangiogram, in an attempt to delineate the source of bile leak on POD211. This was complicated by pancreatitis but no obvious site of leak on the left duct cholangiogram, leading to conclusion of an isolated remnant caudate lobe leak. Histogram (Figure 2) as well as percutaneous cavity-scope did not reveal a specific bile leak point. Eventually on POD371 since the right hepatectomy, based on initiative from patient and his partner, and MDT ratification, a decision was made to attempt a trial of ablation with acetic acid (3%) to deal with isolated bile duct leak and persistent multi-resistant pseudomonas infection along with drain exchange, as required (Figure 3). The first session, involved percutaneous nephoscope insertion under sedation. This failed to localise bile leak. Copious irrigation was followed by installation of 27 ml of 3% acetic acid for 15 minutes. Thereafter 12 instillations of 3% acetic acid were carried out every 3 days, with review on a weekly basis demonstrating reducing output, resolving infection and change in colour of drainage from bilious to clear fluid. No side effects were observed. The treatment was successful with gradual abatement of sepsis and bile leak volume leading to removal of drain on POD470. Patient remained asymptomatic without any recurrent symptoms for 3 years post-surgery (Figure 4).

Outcome and follow up: Patient remained asymptomatic without any recurrent symptoms for 3 years post-surgery. However, during the 3rd year of recovery, he developed an incisional hernia which later became obstructed and was successfully repaired. He remains well today.

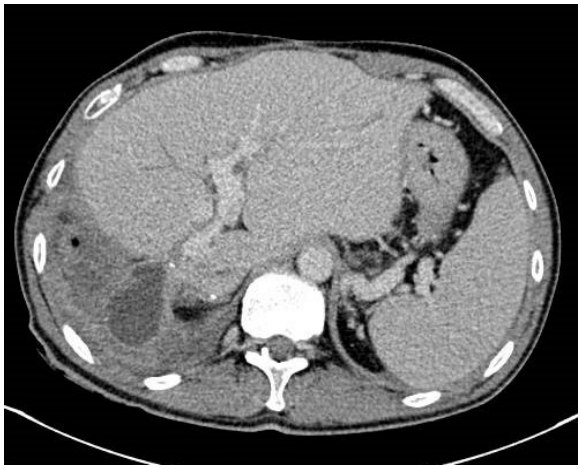

Figure 1: July 2018: Collection along cut surface

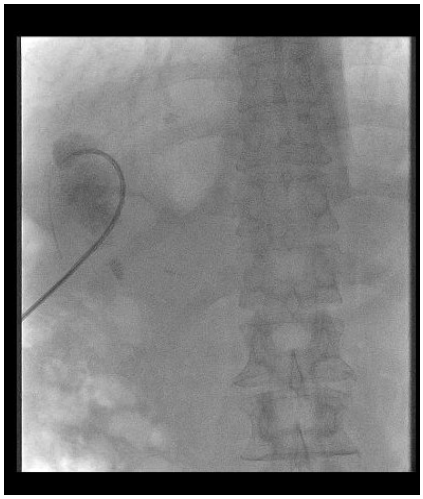

Figure 2: July 2018: Fistulogram showing no opacification of bile ducts.

Figure 3: January 2019: Drain site at time of acetic acid irrigation.

Table 1: Summary of clinical studies in literature reporting outcomes of patients with bile leak.

Author	Year	Journal	Country	N	Bile leak rate	Age	Interventions	Risk factors for bile leak	Length of stay	Mortality related to bile leak
Zimmitti et al [1]	2013	Journal of gastrointestinal surgery	USA	2628	4.80%	57±12.8	NA	Bile duct resection, extended hepatectomy, repeat hepatectomy, en bloc diphragmatic resection, intraoperative transfusion	8(±5.9)	10.30%
Yamashita et al [2]	2001	Annals of surgery	Japan	781	4.60%	NA	Surgical drain, ERCP, Reoperation, ethanol sclerotherapy, balloon catheter occlusion	High risk procedure, intraoperative bleeding, surgical time	NA	NA
Lo et al [3]	1998	Archives of surgery	china	347	8.10%	60±2.5 (SEM)	percutaneous drainage, ERCP, reoperatio	Type of hepatectomy, operation time, blood loss	NA	39%
Cappussotti et al [4]	2006	Archives of surgery	Italy	610	3.60%	63.18	NA	Peripheral cholangiocarcinoma, major hepatectomy, left hepatectomy to segment 1 or segment 5	NA	4.50%
Nagano et al [8]	2003	World journal of surgery	japan	313	5.40%	70.1	reoperation	Hepatectomy with wide surface area, exposure of major glissoninan sheat	NA	NA
Spetzler [9]	2019	Hepatobiliary surgery and nutrition	Germany	501	14%	NA	NA	Chemotherapy within 4 weeks, biliary liver disease, fibrosis/ cirrhosis, major liver resection, biliary anastomosis, ALPPS procedure	NA	7.10%
Sakamoto et al [10]	2016	world journal of surgery	Japan	334	9%	68 (32-87)	Surgical drain, ERCP, Reoperation, ablation, portal vein embolisation	Type of hepatectomy, operation time, blood loss	NA	8.80%
Kyoden et al [11]	2009	Journal of Hepatobiliary pancreatic science	Japan	1269	8.70%	64 (13-90)	ERCP, relaparotomy, Surgical drain, Percutaneous drainage	NA	NA	0%
Vigano et al [14]	2008	The American journal of surgery	Italy	593	5.70%	62.2 (26-78)	Surgical drain, ERCP, PTC	Drain output more than 100ml on pod10	NA	NA
Hoekstra et al [26]	2012	Digestive surgery	Netherlands	381	5%	43±22.1	percutaneous drainage, ERCP, reoperation	Hospital stay, major resection, operation time, relaparotomy	NA	0%
Erdogan et al [27]	2008	Digestive surgery	Netherlands	234	6.80%	59±3	percutaneous drainage, ERCP, reoperation	Male gender, major liver resection, right sided hepatectomy, prolonged operation time, intraoperative blood loss>500ml, red cell transfusion, tumour size, duration of vascular occlusion, surgical irradicality	NA	6%
Nakagawa et al [28]	2016	Journal of HEP	Japan	631	4.80%		NA	Liver metastases, prolonged operation, high risk procedures exposing glissonian sheath, low platelet count, high serum bilirubin POD1	NA	NA

Table 2: Summary of key case reports describing the treatment and outcomes of patients with isolated bile ductleaks following hepatectomy.

Author	Journal	Year	Country	First operation	Isolated bile duct	Treatment method	Outcome
Shimizu et al [20]	World Journal of Gastroenterology	2006	China	Extended posterior segmentectomy including caudate lobe and part of anterior lobe	Anterior bile duct	Ethanol ablation	Resolution
Kyokane et al [19]	Surgery	2002	Japan	Right hepatic lobectomy with en bloc resection of caudate lobe and extra-hepatic bile duct	Posterior branch of the left lateral segmental bile duct	Ethanol ablation	Resolution
Kubo et al [16]	Surgical case reports	2018	Japan	Partial hepatectomy with segments IV + V and cholecystectomy	Segment 5/8	Percutaneous transhepatic portal embolization + Ethanol ablation	Resolution

Kim et al [21]	Korean Journal of hepato-biliary-pancreatic surgery	2012	South Korea	Central lobectomy	Isolated right superior intrahepatic bile duct	Cyanoacrylate glue	Resolution
Park et al [17]	Journal of Vascular and Interventional Radiology	2005	South Korea	Left hemi-hepatectomy	Right posterior segmental bile duct	Acetic acid ablation	Resolution
Kataoka et al [29]	Hepatogastroenterology	2011	Japan	Partial hepatectomy	-	Percutaneous transhepatic ethanol ablation	Resolution
Kamble et al [30]	Annals of clinical case reports	2020	India	Left hepatic resection	Segment 4	Acetic acid ablation	Resolution

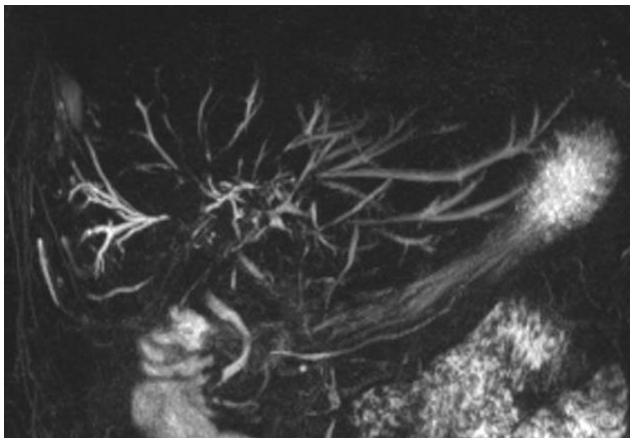

Figure 4: MRCP January 2020: Post bile leak recovery.

Discussion

Bile leak post hepatectomy is a morbid complication.The incidence of bile leak remains high ranging from 2.6% - 33% [1-4]. It occurs in approximately 3.6% to 12% of patients undergoing hepatic resection without biliary reconstruction [5] and in 0.4% to 8% of those undergoing liver resection with biliary reconstruction [6]. According to the International Study Group of Liver Surgery (ISGLS), bile leakage after hepatectomy is defined as drainage of fluid with bilirubin level three times greater than the serum level at postoperative day 3 or the need for interventions owing to bilious collection or biliary peritonitis [7]. It is associated with prolonged hospital stay, readmission, need for invasive interventions and, in severe cases, can lead to sepsis and multi organ failure [1-4,7]. Table 1 summarises key publications describing outcomes of patients with bile leak post hepatectomy. There is no consensus classification of bile leak post hepatobiliary/pancreatic resections [7,8]. Koch et al categorised bile leak into three grades (A-C) according to the type of therapeutic intervention needed for the patient with Grade A requiring no change in management, Grade B needing therapeutic intervention without reoperation, and Grade C necessitating re-operation [7]. Nagano et al classified bile leak post hepatectomy into four types (A-D) depending on their anatomical locations: type A, minor leakage from a cut surface; type B, leakage caused by insufficient closure of the bile duct stump; type C, leakage from the injured bile duct wall at the exposed bile duct or hilar bile duct; and type D, leakage from the distal orifice of the isolated bile duct [8]. The commonest risk factors for bile leak are major hepatectomy, presence of biliary and/or vascular reconstruction, variations to normal anatomy as well as pathologies such as bile duct strictures for example from PSC. Major hepatectomies especially with biliary reconstructions including right, left, central and extended hepatectomies have higher risk of developing bile leak post liver resection [1,2,8-10]. Treatment options for post hepatectomy bile leak includes conservative management with surgical drains allowing spontaneous healing to interventional procedures such as ERCP, PTC and reoperation in some cases. The evidence supporting placement of surgical drains to prevent common complications in liver surgery is still inconclusive despite most surgeons using prophylactic surgical drains after major hepatectomies [11-14]. If the amount of bile leak after 10 days of surgery exceeds 100 ml, then conservative approach is considered to have failed and merits interventional management [14]. Failure of conservative management often leads to patients undergoing interventional procedures which requires a multi-disciplinary approach. Management depends upon the severity and type of leak and includes percutaneous, endoscopic or surgical intervention. In the past, surgery was the main approach to treatment. Surgery is now performed as last resort only in cases with a persistent bile leak refractory to other minimally invasive interventions. Endoscopic treatment, including sphincterotomy with a stent, is now widely accepted as an effective modality to manage biliary leak resulting from classic bile duct injury. However, biliary decompression will not be effective when the leaking ducts do not communicate with the common bile duct [15]. Nagano type D bile leakage is intractable and cannot be treated by simple drainage alone. Patients with Type D/ isolated bile duct leakage need to undergo surgical procedures, such as liver resection or bilio-enteric anastomosis, or non-surgical procedures, such as bile duct ablation, transcatheter arterial embolization (TAE), or percutaneous transhepatic portal embolization (PTPE) of the liver segment that produced the bile leak [16-18]. Several studies have reported the effective use of biliary sclerotherapy/ablation to manage bile leaks from isolated bile ducts, employing agents such as ethanol, acetic acid, or cyanoacrylate (glue). However, there is no definitive consensus to the number of sessions required for each agent. Table 2 summarises key case reports and publications describing the treatment and outcomes of patients with isolated bile duct leaks following hepatectomy. Kyokane et al. were the first to document the safe and successful use of percutaneous ethanol ablation for a postoperative biliary fistula in humans [19]. Similarly, Shimizu et al. treated an obstructed anterior bile duct with ethanol ablation, requiring multiple instillations to achieve effective results [20]. Ethanol exerts its effect by damaging the bile duct epithelium through protein denaturation and cell death, with subsequent infiltration into the liver parenchyma, leading to fibrosis and reduction of bile secretion [19]. Kim et al. described the successful management of a persistent segmental bile duct leak using intrahepatic ablation with N-butyl cyanoacrylate [21]. This agent polymerizes upon contact with tissue, sealing leaks by plugging the fistulous tracts. Park et al. successfully demonstrated the ablation of an isolated bile duct leak post left hemi-hepatectomy with acetic acid, resulting in avoidance of repeated operation and other complications [17]. Another report by Choi et al., reported a successful case of acetic acid sclerotherapy for bile leak from an isolated bile duct after laparoscopic cholecystectomy [15]. Acetic acid functions as a sclerosant and by desiccating proteins,

induces coagulation necrosis. However, a high concentration-approximately 50%-is usually required for effective action [15]. Weak acetic acid (vinegar) has traditionally been used in burn patients to eliminate Pseudomonas colonisation, with several studies demonstrating its effectiveness in promoting the healing of wounds and skin ulcers. Small prospective studies have shown that 3–5% acetic acid successfully eradicates persistent Pseudomonas infections in these cases [22-24]. Its mechanism includes lowering wound pH, enhancing oxygen radical production, improving oxygenation, and possibly increasing macrophage activity while reducing bacterial toxin effects [25]. Treatment typically lasts 7-21 days, with 2-12 applications depending on wound type, particularly higher in diabetic foot ulcers [22,25]. In our case, the objective was to address both the bile leak and persistent Pseudomonas infection. Following multidisciplinary team (MDT) discussions, we proceeded with 3% acetic acid instillations, administered every three days over a total of 12 sessions. Weekly assessments consistently demonstrated a gradual reduction in drain output and resolution of the infection. Eventually, the drain was removed, and the patient remains well to date with no further evidence of bile leak. In conclusion, occasionally treatment of persistent bile leak post-hepatectomy can be challenging and innovative methods along with patient and MDT engagement is vital to success.

Learning points/Take home messages

1. Bile leak post hepatectomy is still a relatively common complication.

2. Multi-disciplinary approach is invaluable in managing persistent bile leaks.

3. Uncommon therapy should be considered in bile leaks refractory to conservative approach before embarking on re-operations.

Patient's perspective: I would like to thank the medical staff involved with my care. I was looked after very well by all of them. Thank you.

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