CASE REPORT

Recurrent ascending cholangitis due to small intestinal bacterial overgrowth, gastrointestinal dysmotility and an afferent loop

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ABSTRACT

Summary We report a complex case involving an extremely rare cause of gastrointestinal dysmotility and an afferent loop, which together predisposed to the development of small intestinal bacterial overgrowth. The bacteria subsequently became multi-resistant. As a further consequence of the dysmotility, repeated bile duct reflux occurred despite the afferent loop being unobstructed. This bile duct reflux produced recurrent sepsis through repeated episodes of ascending cholangitis. Ultimately, the patient was referred to a National Small Intestinal Transplant Centre for consideration for enterectomy and subsequent transplantation. We describe the difficulties encountered in managing this unique case and discuss the underlying aetiology.

BACKGROUND

This case describes a rare presentation of a mimic of 'afferent loop syndrome', a condition in which a surgically formed afferent loop becomes obstructed. In this case, however, the obstruction was not mechanical, but functional due to a co-existent severe dysmotility. The result of this was a severe, recurrent, ascending cholangitis, which proved difficult to treat. This case is particularly relevant now, in the light of the increasing number of afferent loops that are being formed as a result of certain bariatric procedures.¹ Previously, afferent loops were more commonly indicated for the treatment of benign and malignant diseases and, when obstructed, they most commonly presented with jaundice.² In addition, as symptoms of small bowel

dysmotility are often non-specific, diagnoses may not be made prior to the formation of afferent loops. However, as yet, despite increasing awareness of dysmotility, no cases have been reported of its additional relevance in the presence of an afferent loop. Thus, this case, although rare, has several important and potential clinically transferrable aspects.

CASE PRESENTATION

This case revolves around a 39-year-old Caucasian female with a complex past medical and surgical history. Problems began in 1997 following an episode of severe gallstone pancreatitis, which culminated in her requiring surgical interventions. She underwent a cholecystectomy and, subsequently, a pylorus preserving partial pancreatectomy and partial gastrectomy. In 1999, continuous pain led to further surgical reconstruction with an afferent loop, from the biliary and pancreatic drainage, looping up to the stomach. This formed a hepatogastrojejunostomy (figure 1). In 2004, a surgical jejunostomy was created for enteral feeding.

In October 2009, the patient developed bacterial overgrowth as demonstrated by glucose hydrogen and glychocholate breath testing. Rotating antibiotics were commenced.

Despite the use of pancreatic enzymes and augmentation of oral intake by enteral feeding, via the jejunostomy, her nutritional state deteriorated. Oral intake was not aided by the presence of chronic abdominal pain, which was exacerbated by eating and jejunostomy feeding. Pain

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Figure 1 Illustration to demonstrate the patient's anatomy following the operation in 1999 to form a hepatogastrojejunostomy.

persisted in spite of high-dose fentanyl patches, nerve stimulators and coeliac axis blockade. A previous thoraco-lumbar sympathectomy had also failed to help.

In the light of her nutritional deterioration, despite maximal enteral support, parenteral nutrition was commenced in March 2010. Her poor nutritional state at this time was exemplified by her presentation with lower limb bruising, due to night blindness caused by biochemically proven vitamin A deficiency ($0.13 \mu\text{mol/l}$ (ref. $0.99\text{--}3.35 \mu\text{mol/l}$)). Vitamin E ($4.2 \mu\text{mol/l}$ (ref. $9.5\text{--}41.5 \mu\text{mol/l}$)) and selenium ($0.68 \mu\text{mol/l}$ (ref. $0.9\text{--}1.7 \mu\text{mol/l}$)) deficiencies were also identified. Parenteral nutrition was delivered via a tunnelled Hickman line. In October 2010, the jejunostomy tube was removed due to intractable pain.

In addition, further investigation into the nature of the chronic abdominal pain led to a histological review of a small bowel biopsy sample, taken several years earlier. Review by a national expert resulted in the identification of polyglucosan body myopathy (figures 2 and 3). Polyglucosan body myopathy is a rare cause of gastrointestinal dysmotility, which predisposes to bacterial overgrowth.³ Histological evidence of vitamin E deficiency was also identified.

She managed well on parenteral nutrition until August 2010 when she developed sepsis, which was initially presumed to be line-related. She was admitted, cultures were taken and line salvage was attempted with antibiotics, but failed. Thus, she

Figure 2 Electron micrograph image showing electron-dense material with the typical morphology of lipofuscin granules (shown by an arrow), within the cytoplasm of smooth muscle cells.

subsequently underwent line replacement in accordance with unit protocol. However, recurrent episodes of severe sepsis followed, each associated with rises in c-reactive protein (CRP) and liver enzymes. To date, she has been in hospital for over 1 year with recurrent persistent sepsis, due to multiple multi-resistant organisms. Peripheral and central blood cultures, taken over the course of the year, repeatedly demonstrated vancomycin-resistant enterococci (both *faecalis* and *faecium*) and multi-resistant *Candida glabrata* (with

Figure 3 Electron micrograph image showing an ovoid body, with the filamentous ultrastructure of a polyglucosan inclusion body (shown by an arrow), within a myocyte, indenting the nucleus.

associated lung lesions evident on CT) and *Escherichia coli*. Over this time she required long courses of multiple antibiotics and antifungals. Additional therapy included the enteral administrations of the probiotic VSL[#]3 and glutamine into the afferent loop via the jejunostomy feeding tube.

Over the course of the year, extensive investigations were performed in an attempt to determine the infection's source. Line tips were repeatedly culture negative. Other negative investigations included five transthoracic and two transoesophageal echocardiograms, nuclear medicine bone scan, MRI axial skeleton and MRI pelvis, ultrasound abdomen and pelvis, white cell scans (the second being a tomography), CT scans of thorax, abdomen and pelvis, both CT and MRI head and an orthopantomogram. In addition, HIV tests were negative on two different occasions more than 3 months apart, and neutrophil activation tests and immunoglobulin and complement levels were normal.

The only identified source of infection was the gastrointestinal tract. Vancomycin-resistant enterococci were colonised from stool specimens. Endoscopy with aspirates from the duodenal afferent loop (proven under fluoroscopic guidance) showed evidence of the identical micro-organisms, with identical resistances and sensitivities, to those identified through blood cultures. A nasojejunal tube was endoscopically placed in the afferent loop and appropriate antimicrobial agents were administered. This resulted in an almost immediate, but unfortunately temporary (3 weeks), improvement in the sepsis. Repeat endoscopy confirmed displacement of the nasojejunal tube to be associated with the return of the sepsis. This indicated that the return of sepsis was linked to a failure to decolonise the afferent loop. Furthermore, at a subsequent endoscopy contrast was instilled, via the scope, into the afferent loop. This then refluxed up into the bile ducts when she was rolled onto her right-hand side, despite the ducts being 15–20 cm away from the tip of the scope (figure 4). Thus, it was established that the recurrent sepsis was due to recurrent ascending cholangitis on a background of bacterial overgrowth. The latter was predisposed to by dysmotility and post-surgery anatomy, which had generated a redundant loop of small intestine.

OUTCOME AND FOLLOW-UP

As all antimicrobials had failed to eradicate the gut colonisation, surgery was undertaken to refashion the afferent loop, with the hope of limiting the infection and avoiding any further septic episodes. The afferent loop was revised to form a traditional hepatojejunostomy which connected directly onto the small bowel (figure 5). An additional, previously unknown, blind loop of jejunum was found during surgery and was resected. This loop was presumably created for the

Figure 4 Endoscopic contrast study (gastroscope intubating the afferent loop and patient rolling to the right lateral position) showing free reflux of contrast up the biliary tree.

original feeding jejunostomy. Sepsis was not evident for 10 days postoperatively.

Unfortunately, despite this intervention, sepsis returned and persisted, presumably aided by the ongoing dysmotility, in spite of the surgery. Even a period of being 'nil by mouth', in case gut bacterial

Figure 5 Illustration to demonstrate the patient's revised anatomy following the formation of a hepatojejunostomy.

translocation was involved, produced no benefit. In addition, antibiotics not available in the UK, and to which the patient had not previously been exposed, produced little benefit. Following their use, the patient remained symptomatic, with a low-grade pyrexia. Therefore, in the light of unresolved infections, increasing drug resistances and deteriorating line access, our patient has been referred to a National Transplant Centre, for consideration of small intestinal transplantation once infection clear. An initial enterectomy might be required in order to render the patient infection clear before immunosuppression, and thus transplantation, can be considered.

DISCUSSION

In this case report, we report on a patient with an extremely rare cause of small intestinal dysmotility and a post-surgery afferent loop, which together predisposed to small intestinal bacterial colonisation. Despite using rotating antibiotics, these organisms became multi-resistant. Initially, it was hypothesised that the aetiology of the recurrent sepsis was translocation of these multi-resistant organisms through the gastrointestinal wall. However, it was subsequently demonstrated that the underlying aetiology was recurrent bile duct reflux of fluid contaminated by the multi-resistant organisms. Bile duct reflux was predisposed to by both the dysmotility and afferent loop and produced recurrent ascending cholangitis, and thus sepsis. Bile duct reflux was confirmed by contrast on X-ray imaging (figure 4). Infective organisms isolated in blood cultures were confirmed to be exactly the same as those organisms isolated from the gastrointestinal tract, through stool and jejunal aspirate cultures.

Bacterial colonisation of the small intestine is not uncommon, but it is rarely associated with widespread sepsis. Colonisation itself is often a consequence of failure of intestinal clearance of bacteria which may be due to dysmotility or altered anatomy.⁴⁻⁶ The prevalence of bacterial overgrowth varies in association with the predisposing medical disease or surgically modified anatomy, and whether patients studied are symptomatic.

The patient in this case had biopsy-proven polyglucosan body myopathy, an extremely rare cause of dysmotility. Polyglucosan body myopathy is characterised by the presence of polyglucosan inclusion bodies in muscle tissue, visible on light microscopy.⁷⁻⁸ A review found histological evidence of polyglucosan bodies in only 4% of patients who had undergone resection for dysmotility.⁷ Thus, given the rarity of this condition, little is published regarding its associated gastrointestinal manifestations. To the best of our knowledge, there are no published reports of polyglucosan body myopathy being associated with either bacterial overgrowth or ascending cholangitis.

Chronic intestinal dysmotility causes stagnation of small intestinal contents, which predisposes to

bacterial overgrowth.⁵ The prevalence of bacterial overgrowth associated with dysmotility, due to any cause, remains unknown. A prospective capsule endoscopy study in patients with chronic intestinal dysmotility (n=18) reported finding a high frequency of mucosal breaks in 89% of patients. Mucosal breaks were presumed to be due to bacterial overgrowth, but the presence of bacterial colonisation was not proven.⁹ Prior to demonstrating that bile duct reflux, with resultant ascending cholangitis, was the underlying aetiology for the recurrent sepsis, bacterial translocation was hypothesised. Had this been the cause, then the translocation may have been facilitated by mucosal breaks associated with dysmotility.⁹

An additional factor, which favoured translocation as the underlying aetiology, was that the episodes of recurrent sepsis intensified after the initiation of parenteral nutrition. The use of total parenteral nutrition is associated with reduced mucosal immunity. Animal studies with parenteral nutrition show downregulation of both B and T cells within the gastrointestinal mucosal lymphoid tissue compartments, and lower levels of secretory IgA in those given total parenteral nutrition.¹⁰⁻¹¹ A further animal study cultured mesenteric lymph nodes post-total parenteral nutrition administration. This study demonstrated bacteria present in up to 60% of lymph nodes in the parenteral nutrition group in comparison to 0% in the control free-feeding group.¹² This study also confirmed significantly reduced secretory IgA in the parenteral nutrition group. Thus, as our patient had very little enteral intake, it was hypothesised that she would have had reduced gastrointestinal immunity, which would have facilitated translocation of the bacteria colonising the small intestine.

Our patient had also undergone a subtotal gastrectomy with formation of a gastrojejunostomy and an afferent loop, similar to a Billroth II operation. The significance of an afferent loop is that it connects with the lumen at one end, while the other end is blind. Thus, there is no constant luminal stream which predisposes to bacterial colonisation. An uncommon complication of a blind loop is afferent loop syndrome. This occurs when the open end is occluded, with resultant accumulation of biliary and pancreatic secretions and increase in intraluminal pressure. Thus, reflux of secretions in biliary and pancreatic ducts may occur to produce cholangitis or pancreatitis, respectively.¹³⁻¹⁴ Sonographically, an obstructed loop may be evident as a dilated loop lying across the midline.¹⁵ In our case, an ultrasound merely reported slightly dilated loops of bowel on the left of the abdomen, which was thought to represent the known dysmotility. This reflects a functional obstruction, rather than a mechanical one as is described in afferent loop syndrome.

Afferent loops predispose to bacterial colonisation, even in the absence of luminal occlusion or

dysmotility. A study sampling jejunal fluid from the afferent loops of five post-Billroth II patients found evidence of bacterial overgrowth in all.¹⁶ Likewise, a study of complications following types of bariatric surgery involving biliopancreatic diversion showed evidence of bacterial overgrowth in 27% of patients (n=33).¹⁷ An animal study investigating the mechanism behind this showed an extreme loss of motility in the blind loop, in both fed and fasting states.¹⁸ Therefore, in our case, the combination of an afferent loop, with its resultant dysmotility, and the polyglucosan body myopathy-related dysmotility would have further impaired the loop's luminal clearance and would have significantly predisposed to bacterial overgrowth.

Another point of note in our case is that, at presentation, our patient was both vitamin A and E deficient. Vitamins A and E are fat soluble and, unlike vitamin D, are only available from the diet. Fat malabsorption is recognised to occur with bacterial overgrowth due to altered bile salt metabolism.¹⁹ In addition, malabsorption of fat-soluble vitamins has been reported in association with bacterial overgrowth, post-gastric surgery with blind loop formation.²⁰

Enterally delivered glutamine was also used in an attempt to reduce intestinal permeability and thus bacterial translocation which was, at one stage, hypothesised to be the source of the recurrent infection. Animal studies show reduced bacterial translocation in enterally supplemented rats with obstructive jaundice and following abdominal radiation.^{21–22} Benefit was not evident in our case. However, as the recurrent infection was subsequently shown to be due to recurrent cholangitis, benefit would not be anticipated.

In our case, an enterally administered probiotic was trialled, as published studies suggest its benefit in reducing both bacterial overgrowth and translocation. An animal study, involving probiotic supplementation, demonstrated a 43% reduced risk of bacterial translocation in short bowel syndrome.²³ Another study, involving probiotic use by patients for 6 months after Roux-en-Y gastric bypass surgery, demonstrated a statistically significant reduction in bacterial overgrowth at 6 months.²⁴ Unfortunately, in our case, no benefit was seen from probiotic administration.

Bile duct reflux from an afferent loop causing cholangitis has rarely been described. A few case reports describe single episodes of ascending cholangitis, post-Whipple procedure, in the presence of an obstructed afferent loop (afferent loop syndrome).¹³ However, to the best of our knowledge, ours is the only case reporting recurrent ascending cholangitis causing sepsis in the absence of mechanical obstruction of the afferent loop. Given this as the aetiology, rather than bacterial translocation, the question as to why recurrent sepsis occurred only after the patient was established on parenteral nutrition remains

unanswered. One possibility is that previous episodes, prior to tertiary referral, went undiagnosed.

In summary, we describe a complex case involving a rare dysmotility syndrome and a surgically formed afferent loop. Both of these predisposed to bacterial overgrowth and recurrent bile duct reflux of these bacteria to produce recurrent ascending cholangitis and subsequent sepsis. No similar cases have been reported to date. Through the reporting of this case, we endeavour to highlight the possibility of a patient with significant gastrointestinal dysmotility developing recurrent ascending cholangitis despite having a mechanically unobstructed afferent loop.

Key messages

- ▶ Bacterial overgrowth should be considered in the presence of an afferent loop or dysmotility.
- ▶ Obstructed afferent loops predispose to bile duct reflux.
- ▶ Non-obstructed afferent loops, in the presence of dysmotility, may predispose to bile duct reflux.
- ▶ Bacterial overgrowth associated with bile duct reflux may cause recurrent ascending cholangitis.
- ▶ A thorough evaluation of patients with intestinal failure is essential to determine the source of sepsis.

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Competing interests None.

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Authors note This proof is in memory of the patient and co author Ms Wendy Stokes.

REFERENCES

- 1 Cherala SS. Gastric bypass surgeries in New Hampshire, 1996–2007. *Prev Chronic Dis* 2012;9:E72.
- 2 Pannala R, Brandabur JJ, Gan SI, *et al.* Afferent limb syndrome and delayed GI problems after pancreaticoduodenectomy for pancreatic cancer: single-center, 14-year experience. *Gastrointest Endosc* 2011;74:295–302.
- 3 Martin JE, Chowdhury DH, McElwaine S, *et al.* A Novel Phenotype of Glycogen Storage Disease Presenting as Gastrointestinal Neuromuscular Disease. *DDW*, 2010.
- 4 Gabrielli M, Bonazzi P, Scarpellini E, *et al.* Prevalence of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* 2011;26:889–92.
- 5 Marie I, Ducrotté P, Denis P, *et al.* Small intestinal bacterial overgrowth in systemic sclerosis. *Rheumatology (Oxford)* 2009;48:1314–19.
- 6 Lewis HI, Sen A, Cockerell CO, *et al.* Difficulty in walking 10 years after gastric surgery. *Eur J Gastroenterol Hepatol* 2011;23:952–3.
- 7 Knowles CH, Nickols CD, Feakins R, *et al.* A systematic analysis of polyglucosan bodies in the human gastrointestinal tract in health and disease. *Acta Neuropathol* 2003;105:410–13.

- 8 Martin JE, Swash M, Kamm MA, *et al.* Myopathy of internal anal sphincter with polyglucosan inclusions. *J Pathol* 1990;161:221–6.
- 9 Hoog CM, Lindberg G, Sjoqvist U. Findings in patients with chronic intestinal dysmotility investigated by capsule endoscopy. *BMC Gastroenterol* 2007;7:29.
- 10 Li J, Kudsk KA, Gocinski B, *et al.* Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. *J Trauma* 1995;39:44–52.
- 11 Janu R, Li J, Renegar KB, *et al.* Recovery of gut-associated lymphoid tissue and upper respiratory tract immunity after parenteral nutrition. *Ann Surg* 1997;225:707–17.
- 12 Nakasaki H, Mitomi T, Tajima T, *et al.* Gut bacterial translocation during total parenteral nutrition in experimental rats and its countermeasure. *Am J Surg* 1998;175:38–43.
- 13 Spiliotis J, Karnabatidis D, Vaxevanidou A, *et al.* Acute cholangitis due to afferent loop syndrome after a Whipple procedure: a case report. *Cases J* 2009;2:6339.
- 14 Lee MC, Bui JT, Knuttinen MG, *et al.* Enterolith causing afferent loop obstruction: a case report and literature review. *Cardiovasc Intervent Radiol* 2009;32:1091–6.
- 15 Lee DH, Lim JH, Ko YT. Afferent loop syndrome: sonographic findings in seven cases. *AJR Am J Roentgenol* 1991;157:41–3.
- 16 Bardhan PK, Gyr K, Beglinger C, *et al.* Diagnosis of bacterial overgrowth after culturing proximal small-bowel aspirate obtained during routine upper gastrointestinal endoscopy. *Scand J Gastroenterol* 1992;27:253–6.
- 17 Michielson D, Van Hee R, Hendrickx L. Complications of biliopancreatic diversion surgery as proposed by Scopinaro in the treatment of morbid obesity. *Obes Surg* 1996;6:416–20.
- 18 Schippers E, Schumpelick V. Motility disorders in the blind loop after Roux-en-y reconstruction. Electromyography studies in the animal experiment. *Langenbecks Arch Chir* 1994;379:99–104.
- 19 Hasan M, Finucane P. Intestinal malabsorption presenting with night blindness. *Br J Clin Pract* 1993;47:275–6.
- 20 Brin MF, Fetell MR, Green PH, *et al.* Blind loop syndrome, vitamin E malabsorption, and spinocerebellar degeneration. *Neurology* 1985;35:338–42.
- 21 Chun H, Sasaki M, Fujiyama Y, *et al.* Effect of enteral glutamine on intestinal permeability and bacterial translocation after abdominal radiation injury in rats. *J Gastroenterol* 1997;32:189–95.
- 22 Kuru B, Dinc S, Altinok G, *et al.* Effect of different enteral nutrients on bacterial translocation in experimental obstructive jaundice. *Eur Surg Res* 2004;36:45–52.
- 23 Eizaguirre I, Urkia NG, Asensio AB, *et al.* Probiotic supplementation reduces the risk of bacterial translocation in experimental short bowel syndrome. *J Pediatr Surg* 2002;37:699–702.
- 24 Woodard GA, Encarnacion B, Downey JR, *et al.* Probiotics improve outcomes after Roux-en-Y gastric bypass surgery: a prospective randomized trial. *J Gastrointest Surg* 2009;13:1198–204.