Rapidly evolving liver decompensation with some remarkable features 14 years after biliopancreatic derivation: a case report and literature review.

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Abstract

Because of the rising incidence of obesity the use of bariatric surgery is also increasing. For the obese it is the only treatment with a proven long-term benefit on weight, comorbidities including non alcoholic steatohepatitis, and long-term mortality.

There are, however, several reports on hepatic complications after bariatric surgery leading to malabsorption. The risk of liver decompensation or cirrhosis is one of the reasons jejunoileal bypass has been abandoned. Hepatic complications following Roux-en-Y gastric bypass and biliopancreatic derivation (BPD) are also reported but never beyond 2 years of follow-up. There is only one confirmed case of development of cirrhosis following BPD which presented 10 months after surgery.

We present a case of a 39-year-old patient who developed rapidly evolving, and ultimately fatal, liver decompensation in previously unknown cirrhosis, 14 years after BPD. This is the first report of a severe hepatic complication such a long time after a BPD.

Existing literature on hepatic complications after bariatric surgery is discussed as are 2 coincidental findings of pronounced ductular reaction on histology and autoimmune haemolytic anaemia. (Acta gastroenterol. belg., **2010**, 73, **46-51**).

Keywords : Cirrhosis, Hepatic decompensation, Biliopancreatic derivation, Long-term complication, Autoimmune haemolytic anaemia, Ductular reaction.

Introduction

In developed countries, including Belgium, surgical treatment of obesity is being used with increasing frequency over the last decades because of the rising prevalence of obesity (1) which has reached epidemical proportions (2). Obesity is associated with a large number of comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidaemia, vascular disease, obstructive sleep apnea and a number of malignancies (3). Visceral obesity and hyperglycaemia are factors of the metabolic syndrome of which non alcoholic fatty liver disease (NAFLD), or its more severe form non alcoholic steatohepatitis (NASH), is the hepatic complication (4).

Conventional therapy, including diet and exercise often do not lead to sufficient weight loss and weight regain is common (5). At the present there also is no pharmacological therapy with proven long-term efficacy and safety for the treatment of obesity and NASH (6). Bariatric surgery is the only treatment with proven long-term weight control in obese adults (7,8).

Bariatric surgical techniques can be divided into restrictive and malabsorptive procedures. Examples of the former are vertical banded gastroplasty and adjustable gastric banding and of the latter the abandoned jejunoileal bypass (JIB) and biliopancreatic derivation (BPD) with or without duodenal switch (BPD-DS). BPD-DS actually also leads to some restriction of food intake. The Roux-en-Y gastric bypass (RGB) is a combined restrictive and malabsorptive procedure and is considered the gold-standard. It is the most frequently performed technique worldwide (9).

It has clearly been established that bariatric surgery not only causes weight reduction but also produces dramatic improvement or even complete resolution of comorbidities mentioned above. These effects are most apparent after RGB and BPD (7,10). A few, but large, controlled studies show an important reduction of long-term mortality in patients who underwent a purely restrictive procedure or a RGB (11). There are no controlled trials after BPD but available data also indicate a substantial benefit on mortality.

It has also been shown that bariatric surgery can improve liver function and histology (12). Most studies show improvement or no change in histology but in some articles worsening of certain histological features is reported (13-15). There are also several reports of subacute and chronic liver failure after bariatric surgery leading to malabsorption, which has not been described after purely restrictive procedures. One of the main reasons the JIB has been abandoned is the risk of short- and long-term hepatic complications including cirrhosis (16-18). These complications can also develop after the currently used procedures BPD and RGB although the risk is much lower than after JIB (19-25). There is, however, only one confirmed case of development of cirrhosis after BPD published in the literature with a relatively short interval between surgery and diagnosis of cirrhosis of 10 months (19).

We report a case of rapidly evolving liver decompensation in previously unknown cirrhosis 14 years after BPD. Existing literature on hepatic complications after bariatric surgery is discussed as are the coincidental find-

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ings of pronounced ductular reaction on histology and autoimmune haemolytic anaemia.

Case report

A 39-year-old woman was admitted to a secondary hospital because of a short-lasting syncope. There was a one week history of abdominal distention, dark, foul smelling urine and progressive impairment of consciousness. Because the level of consciousness further deteriorated with increasing hyperammonaemia, indicating hepatic encephalopathy, she was transferred to our centre two days later where she was admitted to the intensive care unit.

Because of a clinically diagnosed urinary tract infection she was taking norfloxacin since 5 days which was stopped after transfer. Chronic medication included mebeverine, ferrogluconate, folic acid, vitamin supplements (Supradyn®, Befact forte®), acetylcystein, tiotropium inhalation powder, budesonide/formoterol inhalation powder and occasionally ibuprofen. She had a medical history of a biliopancreatic diversion 14 years before, abdominoplasty, mammoplasty and asthma. Her body weight before bariatric surgery is not known, but it was stable for several years. She only sporadically consumed alcohol and she smoked 20 cigarettes a day. Her family history was positive for type 2 diabetes mellitus in her mother and maternal grandmother but it was negative for hepatological disease.

On admittance she had a Glasgow Coma Scale of 10/15 (E4M4V2) with some forced deviation of head and eyes to the right. Her body temperature was normal and the arterial blood pressure was 128/68 mmHg with a pulse rate of 83 /minute. Her body weight was 80 kg with a BMI of 25.4 kg/m^2. Except for the encephalopathy, physical examination was unremarkable. There were no signs of chronic liver disease and there was no enlargement of the liver or spleen. She was intubated for airway protection and to be able to perform diagnostic investigations.

The results of the most relevant laboratory tests are shown in Table 1. There was a mild anaemia and there was a 10 to 15-fold rise in transaminases, suggesting acute hepatitis. Serologic tests for viral causes of acute hepatitis, syphilis and toxoplasmosis were negative. There were no arguments for toxic hepatitis based on repeated interrogation of the patient and negative toxicological screening of the urine. All biochemically verifiable causes of chronic liver disease were hence excluded. Anti neutrophil cytoplasmic antibodies and anti smooth muscle antibodies were discretely positive in a low titer but this was considered clinically not significant. Other autoantibodies were negative and the total level of γ-globulins was normal, with minimally elevated IgM's, IgA's 1.75 times the upper limit of normal and normal IgG's. Cardiac examinations were normal and there were no arguments for haemodynamic disturbances potentially explaining the rise in transaminases.

Table 1. — **Laboratory results**

Test	*Result*	*Units*	*Normal range*
Hemoglobin	10.7 #	g/dL	12 - 15
MCV	85.6	fL	76 - 96
Leucocytosis	6.0	* 10E9/L	4.3 - 10
Platelets	197 *	10E9/L	140 - 440
CRP	0.08	mg/dL	< 0.5
Electrolytes	normal		
Creatinin	0.58	mg/dL	0.6 - 1.1
ALAT	539 #	U/L	7 - 56
ASAT	606 #	U/L	5 - 40
Bilirubin	2.4 #	mg/dL	0.2 - 1.3
GGT	190 #	U/L	11 - 29
AP	212 #	U/L	36 - 95
Choline esterase	3432 #	U/L	4650 - 10440
INR	1.20		0.90 - 1.20
Ammonia	151 #	µmol/L	1 - 50
AFP	2.6	U/mL	< 5.8
Albumin	3.18 #	g/dL	3.35 - 5.35
Ferritin	29.7	ng/mL	13 - 150
Ceruloplasmin	20	mg/dL	15 - 75
alpha-1-antitrypsin	148	mg/dL	105 - 249
TSH	0.91	µU/mL	0.27 - 4.2
HBV, HCV	negative		
Repeated serology for acute HAV, CMV, EBV, Toxoplasma, syphilis	negative		
ANCA	1/40 #		< 1/20
ASMA	1/40 #		< 1/20
Other autoimmune tests	negative		
γ-globulins	1.23	g/dL	0.53 - 1.52

#: abnormal results
Abbreviations: AFP: alpha-fetoprotein; ALAT: alanine aminotransferase; ANCA: anti-neutrophil cytoplasmic antibodies; AP: alkaline phosphatase; ASAT: aspartate aminotransferase; ASMA: anti smooth muscle antibodies; CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr virus; GGT: gamma-glutamyl transpeptidase; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: International Normalised Ratio; MCV: mean corpuscular volume; TSH: thyroid stimulating hormone.

Examination of spinal fluid was normal. A cranial CT-scan showed no significant abnormalities, nor did a cranial MRI-scan 2 days later.

On abdominal ultrasound the liver was irregular with a heterogeneous parenchyma, suggesting cirrhosis. The common bile duct was slightly dilated but the diameter of the intrahepatic bile ducts was normal. The spleen appeared normal and there was no ascites. Because of the findings on ultrasound a magnetic resonance cholangiopancreatography was performed which confirmed the minimal dilation of the common bile duct but showed no pathological features of the extra- and intrahepatic bile ducts.

On admittance the patient was in Child-Pugh classification B (9 points).

Escherichia coli was cultured in an urinary sample and turned out to be resistant only to norfloxacin. The

urinary tract infection was considered to be the cause of the decompensation of the previously unknown cirrhosis and treatment with ciprofloxacin was initiated.

In an attempt to further elucidate the aetiology of the liver failure, a biopsy was performed. It showed micronodular cirrhosis, severe steatosis, features of acute and chronic inflammation and marked ductular reaction (*Fig. 1a,b,c*). There were no specific features of toxic or auto-immune hepatitis. Under lactulose treatment the neurologic state completely recovered within 2 days after transfer and the patient was transferred to our gastroenterology ward. During the hospitalization there were repetitive episodes of neurological deterioration, mostly without an obvious cause and not always accompanied by hyperammonaemia. Transfer to the intensive care unit was necessary on two occasions.

Additional investigations concerning the cirrhosis showed an elevated transhepatic venous pressure gradient of 13 mmHg with esophageal varices grade 1 for which prophylactic propranolol was initiated and a decreased microsomial function of the hepatocytes on the aminopyrine breath test.

Although absent on admittance, ascites developed in the following weeks and kept increasing despite the use of diuretics, which in turn caused electrolyte disturbances. An oral glucose tolerance test with measurement of insulinaemia was normal.

Due to the recurring encephalopathy she was not able to return home and as stable improvement could not be achieved she was put on the waiting list for liver transplantation. In order to prevent recurrence of hepatic disease after transplantation, reversal of the BPD would be performed as soon as her condition would allow such surgery before or after transplantation.

On admittance the patient had a mild normocytic anaemia, but this worsened during hospitalization because of autoimmune mediated haemolysis with a positive direct antiglobulin test. Treatment with high-dose corticosteroids was necessary.

Ten weeks after admittance to the peripheral hospital she rapidly deteriorated with worsening of encephalopathy, severe coagulation disturbances, rapid increasing bilirubin and acute renal failure. Because of this acute-on-chronic liver failure she was transferred to the intensive care unit where extracorporeal liver support using the Molecular Adsorbents Recirculation System (MARS) was initiated and antibiotics were given because of a positive urine culture (*Escherichia coli* and *Candida albicans*). In spite of these actions she developed a septic shock with multi-organ failure and lactic acidosis. She deceased one day later. Autopsy confirmed the liver cirrhosis with severe steatosis and bile stasis. There were no features indicating auto-immune hepatitis, primary or secondary biliary cirrhosis or primary sclerosing cholangitis. The autopsy further showed a small pulmonary infiltrate, signs of cardiac failure and acute tubular necrosis.

Discussion

This is the first report of a severe hepatic complication many years after a BPD concerning a 39-year old patient who developed rapidly evolving, and ultimately fatal liver decompensation on previously unknown cirrhosis.

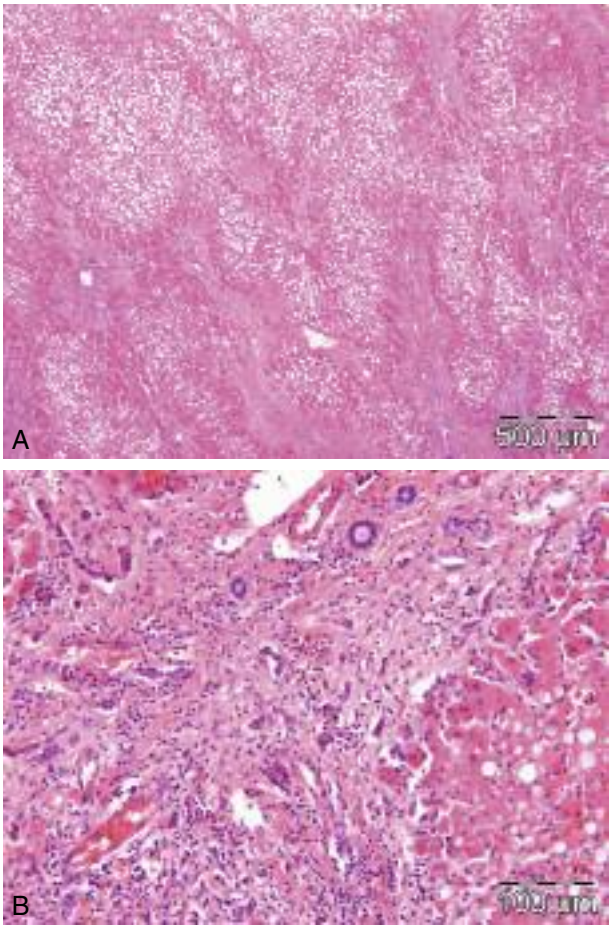

Fig. 1. — Histology of the liver
a. Cirrhosis and severe steatosis (haematoxylin-eosin stain ; ×40) ; b. Marked ductular reaction (haematoxylin-eosin stain ; ×200); c. Marked ductular reaction (cytokeratin 7 stain ; ×100)

The ultimate cause of death, 10 weeks after the diagnosis of cirrhosis, was an acute on chronic liver failure with septic shock, most likely triggered by a urinary tract infection. At that time she was receiving high-dose corticosteroid treatment for an autoimmune haemolytic anaemia. Because there never had been signs of cirrhosis before, it most likely developed after the biliopancreatic derivation which was performed 14 years before. Liver biopsy showed cirrhosis, severe steatosis, acute and chronic inflammation and marked ductular reaction.

As mentioned above, in most studies addressing hepatic pathology after bariatric surgery improvement or no change in liver histology is shown. Only in the articles of Luyckx *et al*. (13), Stratopoulos *et al*. (14) and Kral *et al*. (15) worsening of certain histological features was reported, respectively increase of the prevalence of hepatitis from 14% before surgery to 26% after a mean of 27 months following vertical banded gastroplasty, progression of fibrosis in 8% of the patients after a mean of 18 months following vertical banded gastroplasty and progression of fibrosis in 40% of the patients after a mean of 41 months following BPD. The latter study, which is the largest with 104 patients with repeat biopsies, showed an increase in the degree of fibrosis in patients with mild preoperative fibrosis (grade 0-1) whereas the degree of fibrosis decreased in patients with severe baseline fibrosis (grade 2-5).

There are several reports of subacute and chronic liver failure after bariatric surgery leading to malabsorption. One of the main reasons why the jejunoileal bypass has been abandoned is the risk of hepatic complications: acute liver failure in 3 to 7% and development of cirrhosis in 7 to 10%, 5 to 15 years after surgery (16). There are a number of case reports of liver transplantation for decompensated cirrhosis after JIB (17,18) with a mean of 22 years between JIB and transplantation. If the JIB is not reversed, there is a substantial risk of reoccurrence of fibrosis and cirrhosis (17).

Postulated mechanisms for the development of hepatic disease are protein malnutrition and bacterial overgrowth with production of cytokines which can easily pass the inflamed and damaged enteric mucosa.

Hepatic complications can also develop after the currently used procedures BPD and RGB although the risk is much lower than after JIB and beyond 2 years severe hepatic complications have not been reported. There is one report on hepatic insufficiency after RGB wherein 3 cases of severe hepatic decompensation are described (25). The decompensation presented 7 to 17 months following RGB out of a total of 332 procedures performed in 2.5 years in a single centre. Liver biopsies showed cirrhosis in 2 of them, but preoperatively data are not available. One patient did not survive, one was on the waiting list for liver transplantation when the article was published and the third patient, without cirrhosis, was managed conservatively which included enteral hyperalimentation. Preoperatively all 3 patients were severely obese with BMI's of 49, 61 and 86 kg/m² and they experienced major weight loss, respectively 25, 27 en 51% of their initial weight. They all were malnourished and showed muscle wasting at presentation of the liver decompensation.

BPD and BPD-DS can lead to transient severe liver function disturbances in the first months following surgery. This nearly always improves with hypercaloric and protein rich nutritional support which suggests a possible causative role of protein malnutrition. There are several case reports of liver failure 4 to 18 months after BPD which describe a total of 9 patients (19-24). In 3 of those patients a liver transplantation was performed while the other 6 deceased, some of them on the waiting list for transplantation. One patient died 30 days after transplantation. One of the explanted livers turned out to be cirrhotic while a biopsy before BPD showed no cirrhosis. This is the only confirmed case of development of cirrhosis after BPD published in the literature (19). The interval between the BPD and diagnosis of cirrhosis was 10 months which is much shorter than reported after JIB and also much shorter than in our case. The same authors discuss possible pathophysiological mechanisms for the deterioration of the liver function : bacterial overgrowth with excessive production of toxins, damaging of the mucosa in the excluded short bowel leading to increased permeability for proinflammatory cytokines and bacterial toxins to the portal system, malnutrition due to the intentionally created malabsorption, possibly increased by diarrhea which is partially caused by bacterial overgrowth. They further speculate that bariatric surgery itself could be a cause of acute or subacute hepatic insufficiency, possibly related to postoperative inflammatory and/or hormonal responses. Finally they point out that all 3 patients who developed liver failure in their series had a preoperative BMI $\geq$ 50 kg/m² which is an independent risk factor for bariatric surgery-related mortality.

In our patient the weight before the BPD is not known and there are no data on possible preoperative hepatic disease, especially NASH, so a causative role of the bariatric surgery on the development of cirrhosis cannot be proven although it most likely occurred afterwards given the long interval between the BPD and presentation of hepatic disease. Bacterial overgrowth is postulated as a possible cause of hepatic complications after JIB or BPD as mentioned above. In our patient this cannot be confirmed nor excluded. There was no chronic diarrhea and there were no signs of secondary biliary cirrhosis due to recurrent (subclinical) infections on autopsy but it is not possible to determine the possible role of bacterial toxins, entering the portal circulation to the liver, in the pathogenesis of the liver disease. Nutritional deficiencies have also been implicated in the pathogenesis of bariatric surgery related diseases but our patient was not malnourished and there was no hypoproteinaemia on admittance. Other causes of liver cirrhosis, including excessive alcohol consumption were excluded. The magnetic resonance cholangiopancreatography showed no pathological features of the extra- and intrahepatic bile ducts indicative for primary sclerosing cholangitis or primary

biliary cirrhosis. Anti mitochondrial antibodies were negative. The anti neutrophil cytoplasmic antibodies and anti smooth muscle antibodies were discretely positive but this was considered a secondary phenomenon due to the cirrhosis. There were no other potential signs of autoimmune hepatitis : a normal level of γ-globulins, no characteristic features on biopsy and no improvement of transaminases after the initiation of corticosteroids (for the treatment of the autoimmune haemolytic anaemia).

The cirrhosis presented 14 years after BPD which is much longer than the duration of most follow-up studies. In the largest and longest follow-up study available, however, Scopinaro *et al*. described no patients with newly developed cirrhosis out of a total of 2241 patients who underwent a BPD in the 21 years before (10). Following JIB, cirrhosis developed after 5 to 15 years and transplantation was performed after a mean of 22 years. It is possible that there is underreporting of isolated cases and it is also possible that there will be more new cases in the future because more time passes since larger numbers of BPD are being performed.

As is known from the JIB, reversal of the bariatric surgery is the best long-term treatment and reversal is necessary to prevent recurrence of cirrhosis in the transplanted liver. Our patient was on the waiting list for transplantation and reversal of the BPD would have been performed as soon as her condition would have allowed such surgery.

The cause of the acute hepatitis on presentation cannot be established with certainty. The decompensation of the preexisting cirrhosis can be attributed to the urinary infection but this cannot explain the increase of the level of transaminases by 10-15 times of the upper limit of normal. Alcohol, acute viral infections, toxoplasmosis, syphilis and haemodynamic disturbances all were excluded and there was no suspicion of a toxic cause. The biopsy shows marked steatosis, so an exacerbation of non alcoholic steatohepatitis is the most plausible cause of the rise in transaminases.

We think it might be a specific, rare, subtype of non alcoholic steatohepatitis associated with this type of bariatric surgery and potentially also with the associated factors, especially bacterial overgrowth.

A remarkable finding was the pronounced ductular reaction on liver histology. In our patient it was much more pronounced than is usually seen in other hepatic diseases in which ductular reaction has been described including extrahepatic and intrahepatic cholestatic diseases such as primary biliary cirrhosis and primary sclerosing cholangitis, alcoholic hepatitis, toxic hepatitis, hepatitis C, NASH and also after JIB, particularly in case of long-term parenteral feeding. It is a reaction to cholestasis and hepatocellular damage and contributes to the development of fibrosis. Normally, necrotic and apoptotic hepatocytes are replaced by replication of adjacent hepatocytes. Inhibition of this mechanism by e.g. toxins, steatosis, alcohol or oxidative stress leads to a second form of cellular proliferation : activation of hepatic progenitor cells which develop into hepatocytes, but also into cholangiocytes with formation of bile ductules (26). In hepatitis C and NASH, the extent of the ductular reaction correlates with the severity of the liver disease (26,27).

Our patient developed warm autoimmune haemolytic anaemia (AIHA) for which treatment with corticosteroids was necessary. There were no other autoimmune diseases and she did not receive a blood transfusion before the AIHA. There is an association between AIHA and some liver diseases but to our knowledge AIHA has never been reported after BPD or in cirrhosis after JIB. Case reports predominantly have been published on AIHA with primary biliary cirrhosis and with hepatitis C (28,29). In the latter the relative risk is only higher when the patient is treated with interferon-α (29). AIHA has been described in association with auto-immune hepatitis (30) but as mentioned above we did not have substantial evidence for this diagnosis. One case report has been published of AIHA in a patient with NASH (31).

Conclusion

We report a 39-year old patient who developed rapidly evolving and ultimately fatal liver decompensation in previously unknown cirrhosis 14 years after a biliopancreatic derivation. It is the first time a severe hepatic complication such a long time after a biliopancreatic derivation is published. There were 2 additional remarkable features in this case : histologically there was a marked ductular reaction and the patient developed autoimmune haemolytic anaemia.

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