

### **First intoxication with freshly picked *Amanita phalloides* in winter time in central Europe**

#### **To the Editor,**

On December 5th of 2006 a 72 year old, otherwise healthy man from Asian descent, was admitted to the emergency department of a hospital in central Switzerland with symptoms of acute gastroenteritis. History revealed ingestion of a freshly picked mushroom 24 hours previously. Urine tested positive on  $\alpha$ -amanitin. He was started on therapy with activated charcoal, N-acetylcysteine and silibinin. Due to imminent fulminant hepatic failure, he was transferred to a tertiary centre for assessment of emergency liver transplantation but fortunately, the liver function recovered after five days and he finally could be discharged home on day 7 in stable condition.

To our knowledge, this is the first reported mushroom poisoning with *Amanita phalloides* in central Europe, caused by a freshly picked death cap in the month of December. Naturally death caps grow from May to October [1] in deciduous forests and parks. Accordingly, most cases of intoxication are noted in autumn, although occasionally poisoning with stored mushrooms has been reported in winter months [2]. Our case demonstrates that 'off-season'-intoxication with freshly picked death caps must be considered in patients with otherwise appropriate history of recent mushroom ingestion. It is possible that climate warming leads to more *Amanita phalloides* intoxication in atypical season.

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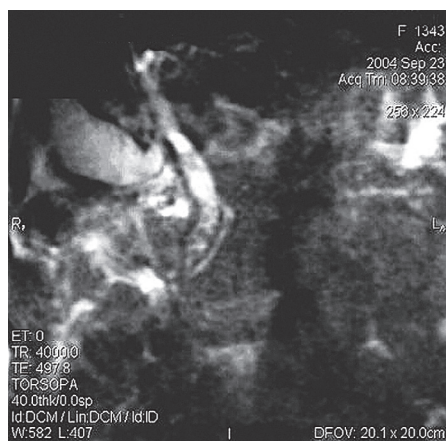
### **Remarkably elevated serum levels of carbohydrate antigen 19-9 in cystic duct and common bile duct lithiasis**

#### **To the Editor,**

During the last few decades, CA19-9 has been demonstrated to be not only a useful marker for epithelial-type gastrointestinal cancers of the pancreas and biliary tract, but also a diagnostic tool in the differentiation of benign and malignant diseases [1]. However, elevations of CA 19-9 without pancreatic or other gastrointestinal malignancies have also been reported in benign cases of pancreatic, biliary, pulmonary and gastrointestinal diseases [2]. Despite these reported facts it is impossible for the clinician not to consider malignancy when he is dealing with an older patient with obstructive jaundice and extremely elevated CA19-9 levels.

An 84-year-old female patient was admitted to our department with fever, right upper quadrant pain and jaundiced sclerae of two days duration. She had also noticed dark urine and discoloured feces during the previous week. Clinical examination revealed a jaundiced patient with Murphy's sign and fever up to 38 °C. History of the patient comprised arterial hypertension, coronary heart disease and an episode of cerebral hemorrhage. Laboratory investigation showed increased white cell count, elevated serum transaminases, bilirubin (6.5mg/dl), alkaline phosphatase (594 UI/ml) and  $\gamma$ -GT (448 UI/ml) levels. Tumor markers routinely monitored for research purposes in jaundiced patients in our department were obtained. A strikingly elevated CA

19-9 level at 32,480 UI/ml (normal values 0-37 UI/ml) was observed, while serum carcinoembryonic antigen (CEA) and alpha-fetoprotein ( $\alpha$ -FP) were within normal limits. Abdominal ultrasonography performed on the first day in the emergency department diagnosed gallbladder and common bile duct (CBD) lithiasis along with hydrops of the gallbladder probably due to stone impaction in the cystic duct. Magnetic resonance cholangiopancreatography (MRCP) performed four days later revealed CBD dilatation, multiple gallbladder and CBD stones but no evidence of a pancreatic or biliary neoplasia (Fig.1). A cholecystectomy and duodenal-choledochal anastomosis were performed five days after admission and the patient recovered completely. Histopathologic examination of the gallbladder and of the CBD was negative for malignancy. CA19-9 levels decreased and reached normal values 20 days later. After two years, the patient had normal CA 19-9 level and biochemical profile.



**Fig.1** MRCP demonstrating multiple stones in the gallbladder, common bile duct and cystic duct.

Serum carbohydrate antigen 19-9, a glycopospholipid of the Lewis blood group is mostly used as a pancreatobiliary tumor marker. Specificity of CA 19-9 for pancreatic cancer, especially when its serum level is  $>1000$  UI/ml, is about 99% (3). However, several benign tract diseases in which serum CA19-9 elevation suggested malignancy were frequently reported, such as liver pseudotumor with CA19-9 levels at 1167.9 UI/ml [4], Mirizzi's syndrome [5] and acute cholangitis with gallbladder and CBD lithiasis [6]. A high level of CA 19-9 was also found in autoimmune biliary diseases such as primary sclerosing cholangitis and autoimmune cholangitis, with normalization of the levels after methylprednisolone [7, 8].

Production and secretion of CA19-9 by malignant cells are considered to be responsible for the high serum CA19-9 level in malignancies. However, in benign biliary tract diseases additional factors are postulated: 1) leakage of condensed CA 19-9 due to biliary tract obstruction from the bile into blood circulation; 2) leakage of CA19-9 from bile duct epithelium where a small amount of this substance is normally present; 3) enhanced production of CA 19-9 in the bile duct epithelium and the gallbladder

mucosa induced by the inflammation and 4) reflux of CA 19-9 from bile duct epithelium into the blood, presumably due to the elevated pressure of the biliary tract.

The high degree of similarity in the clinical picture of benign and malignant biliary diseases makes it difficult to discriminate between these conditions, therefore biochemical data, clinical, serological and radiological findings must be taken into account. Nowadays, the diagnostic accuracy of radiological methods such as CT scan and MRI/MRCP is estimated to be 98% for biliary malignancy, reinforcing the view that assessment of CA19-9 should never be regarded as the gold standard when investigating a patient with biliary tract disease [2].

Summarizing the above evidence, we suggest that caution is required when doctors are debating against or in favour of a biliary malignancy, and when attempting to interpret even an extremely high serum CA19-9 value.

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## Cerebral sinus thrombosis in a patient with ulcerative colitis

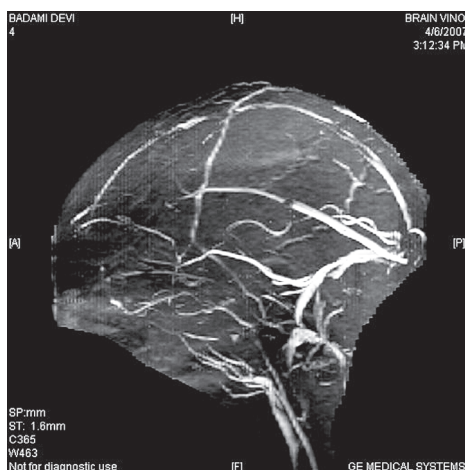
### To the Editor,

Inflammatory bowel disease (IBD) is an idiopathic inflammatory disease of the gastrointestinal tract. There is a well-known risk of thrombosis in patients with IBD. Deep

venous thrombosis and pulmonary emboli are the most common thrombotic complications in IBD, but cerebral vascular involvement is rare [1].

A 55-year-old woman presented with bloody diarrhea (6-8 stools per day) associated with crampy abdominal pain in the left lower abdomen for one month. She also had a history of hemicranial headache associated with photophobia and redness of eyes preceded by earache and decreased hearing. In addition, she had a past history of cholelithiasis for which she had undergone endoscopic stone extraction two years earlier. On examination she was pale, afebrile and hemodynamically stable. Her fundus examination revealed bilateral papillary edema. Neurological examination revealed sensory and motor disturbances. Laboratory data showed normochrome anemia with a hemoglobin of 10.7g/dl, normal total leucocyte and platelet count, elevated ESR (50mm/hr) and C-reactive protein, mild elevation of alanine/aspartate aminotransferase (42/89U/L), serum alkaline phosphatase of 959U/L, normal bilirubin, electrolytes, urea and creatinine levels. Coagulation profile including prothrombin time, partial thromboplastin time, protein C and protein S were normal. Factor V Leiden mutation was absent. Her thyroid stimulating hormone was normal, rheumatoid factor, antinuclear antibody, anticardiolipin antibodies and lupus anticoagulant were negative, carcinoembryonic antigen levels were normal. Abdominal ultrasonography was normal.

Sigmoidoscopy revealed loss of mucosal vascular



**Fig.1** Cerebral MR venography: absence of flow in the superior sagittal sinus

pattern, granularity and friability of the rectum and sigmoid colon mucosa. Rectal biopsy showed an abundant infiltration of neutrophils, lymphocytes and plasma cells, cryptitis, crypt abscesses with mucin depletion. Based on these findings, the patient was diagnosed with moderately active left sided ulcerative colitis. The cerebrospinal fluid examination revealed normal fluid pressure, no cells, proteins 91.1 mg/dl and sugar of 60.9mg/dl. Magnetic resonance venography showed no flow in the superior

sagittal sinus (Fig. 1).

She started therapy with steroid enemas, oral 5-aminosalicylic acid (5-ASA), folic acid, low molecular weight heparin (LMWH) and later switched to warfarin after an overlap period of 5 days to maintain the INR between 2 and 2.5. Her stool frequency decreased to 2-3/day with no blood, her headache, redness of eyes and earache improved. She is still asymptomatic at 6 months of follow-up on 5-ASA 2.4 gm/day and warfarin 4 mg/day.

Extraintestinal manifestations are common in ulcerative colitis, occurring in 25-40% of patients [2]. Cerebral venous thrombosis in association with IBD is rare [3]. The superior sagittal sinus and lateral sinus are commonly involved. The most common symptoms and signs are headache, paresis, seizures, dysphasia and papillary edema.

Bargen and Barker reported extensive thrombosis of blood vessels as a serious complication of ulcerative colitis [4]. The incidence of this complication in clinical studies varies between 1.2 and 7.5%. However, in autopsy studies, a higher incidence of 32-39% has been reported [5]. The cause of hypercoagulability and thromboembolism in ulcerative colitis remains obscure [6]. Thrombocytosis and elevated fibrinogen level, factor V, factor VIII and decreased antithrombin III have been described in the active stage of ulcerative colitis. Deficient platelet aggregation, increased thromboplastin generation and presence of fibrin microclots have been implicated. Coagulation and fibrinolytic cascades are activated in active ulcerative colitis, increasing the risk of thrombosis [7]. In our patient, coagulation studies showed normal values.

Low molecular weight heparin was administered and there were no bleeding complications in this patient. Although cerebral sinus thrombosis is characterized by poor outcome, entailing mortality or important neurological sequelae in 60-80% of cases [8], our patient is asymptomatic at 6 months of follow-up.

In conclusion, cerebral venous thrombosis is a rare complication of ulcerative colitis. Its diagnosis is established by visualizing the thrombus using neuroimaging methods.

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## Extended poststrangulation ischemic jejunal stricture

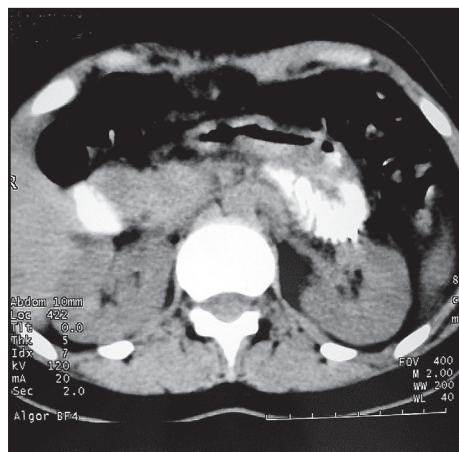
### To the Editor,

Ischemic stricture of the bowel is a rare clinical entity, which can develop as a result of successful surgical resolution of intestinal obstruction, mesenteric vessel pathology and blunt abdominal trauma [1-4].

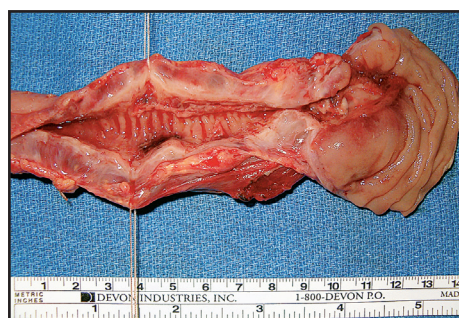
A 26-year-old woman was admitted in our department complaining of colicky pain, abdominal distension and vomiting. Three weeks earlier she had undergone a laparotomy with successful adhesiolysis for strangulated closed-loop obstruction. Barium study of the small bowel demonstrated partial small bowel obstruction caused by a long stricture of the proximal jejunum 5 cm distal to the duodenojejunal flexure (Fig. 1). Abdominal computed tomography (CT) scan revealed a segment of the proximal jejunum with a thickened wall and narrow lumen (Fig. 2). A stenotic 50 cm long jejunal loop, 5 cm from the Treitz ligament was found at laparotomy and resection of the involved segment with primary anastomosis was performed. Macroscopic appearance of the resected specimen showed a thickened wall and narrowed lumen of the resected jejunal loop (Fig. 3). Histological study revealed marked transmural edema and fibrosis, with



**Fig.1** Contrast X-ray demonstrating a long stricture of proximal jejunum.



**Fig.2** Abdominal CT scan revealing a stenotic thickened area in the first loop of the jejunum.



**Fig.3** Resected specimen. A loop of jejunum with fibrotic wall and stenotic lumen.

focal erosion and congestion of the mucosa, which were compatible with ischemia-reperfusion modifications. The postoperative course was uneventful and there was no residual jejunal dysmotility. A 24 month follow up showed no relapse of symptoms.

The main mechanism of the ischemic stenosis is thought to be the infarction resulting from mesenteric vascular damage rather than direct injury to the intestinal wall, reversible mechanical occlusion of the intestinal vessels leading to ischemia-reperfusion injury [5]. From a pathological point of view, stenoses occur due to impaired blood supply resulting in a hemorrhagic infarction of the mucosa, which thus produces ulceration. The serosa remains intact and healing occurs by fibrosis, which results in severe stenosis [5]. This is followed by a relapse of symptoms of small-bowel obstruction. Perforation of the stenotic bowel, although rarely reported [4] represents a serious complication which should be considered in such patients. Ischemic strictures more frequently have been described in the ileum, rarely in the jejunum and extremely rare in the large bowel [1-4]. In most cases, the clinical manifestations of the ischemic stricture occurs from 2 to 6 weeks after damage of the mesenteric blood flow [1, 6]. However, patients with ischemic gut stenosis can present from 5 to 15 months after intestinal or colon ischemia [4]. Small bowel barium infusion (enteroclysis) is considered the most appropriate technique for demonstrating a narrowed intestinal lumen [3]. CT is also a useful investigation in suspected bowel obstruction, as not only does it confirm the presence

of obstruction and mural thickening, but also shows often the cause [7]. In our case, the stenotic ileal loop with its thickened wall was clearly demonstrated on enhanced CT.

To summarize, there still exists a dilemma in determining the bowel viability macroscopically. Since the discoloration disappears during surgery, one may assume that the circulation of the strangulated loop has been restored. However, irreversible transmural ischemia may already have developed. We consider that in a patient presenting with intestinal obstruction symptoms, having a recent history of abdominal trauma or surgery for strangulated obstruction, the possibility of ischemic gut stenosis should be considered and a meticulous differential diagnosis should be made. Once the ischemic bowel stricture has been proven as the cause of intestinal obstruction, laparotomy with resection of the stenotic segment seems to be the most appropriate choice.

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## Prevalence of upper and lower gastrointestinal symptoms in Greek patients with type 2 diabetes mellitus

### To the Editor,

Diabetes mellitus (DM) is often associated with functional disorders of the gastrointestinal tract (GI) due to obesity and neuropathy [1]. Although a few studies have evaluated the relation between DM and gastroesophageal reflux disease (GERD) [1], no study has assessed all GI symptoms concomitantly, i.e. upper (GERD, dyspepsia) and

lower GI (irritable bowel syndrome - IBS) in association with DM.

We evaluated 300 consecutive patients (106 men, 194 women, aged 69±11 years) with a known history of type 2 DM. A questionnaire was completed in order to capture: a) demographic, clinical and laboratory data, including smoking/alcohol habits, educational level, abdominal surgery, chronic or temporary drug use (e.g. NSAIDs, aspirin); b) severity and frequency of upper and lower GI symptoms, and their impact on quality of life during the last 6 months, using validated questionnaires (GSRs and QOLRAD, respectively) [2, 3]; and c) duration, treatment and complications of DM. All data were analyzed using the statistical package SPSS (version 13.0). Chi-square test was used for categorical variables and the Mann-Whitney U test was used for comparison of quantitative variables.

We found that 235 (69%) and 146 (49%) patients reported at least one monthly episode of dyspepsia and GERD during the last 6 months. Diagnosis of both dyspepsia and GERD could be established in 132 (44%) of patients. Hunger pain was the most frequent upper GI symptom (55%), followed by regurgitation (40%) and epigastric pain (39%). Women reported more frequently nausea ( $p=0.021$ ) and regurgitation ( $p=0.04$ ), compared to men. Patients with DM and metabolic syndrome had more frequently upper GI symptoms, compared to those with DM but without metabolic syndrome ( $p=0.002$ ). 150 (50%) patients fulfilled the diagnostic criteria for IBS, whereas 93 (31%) suffered from non-specific lower GI symptoms. Increased bowel gas was the most frequent symptom (62% of the patients reported at least one monthly episode during the last 6 months), followed by hard stools (52%) and bloating (40%). Symptoms of lower GI tract were more frequent in patients with a higher education level ( $p=0.03$ ) and in those with reduced physical activity ( $p=0.021$ ). Duration of DM was not related to frequency of GI symptoms. Professional and social activities were affected in up to 34% of patients with GI symptoms.

In conclusion, we found a high incidence of GI symptoms in patients with type 2 DM. Although there is a caution regarding the applicability of standard questionnaires in patients with DM, as suggested by Carlsson *et al* [4], we were able to evaluate the GI symptoms in patients with DM using the GSRs, which is a relatively simple and validated questionnaire. Similarly to previous studies [1], we found a higher incidence of GI symptoms in patients with DM than in the general adult population, symptoms which have a significant impact on the patients' quality of life. In addition, lower GI symptoms were also evaluated in each patient. Dyspepsia was the most frequently recorded syndrome, and IBS was documented in half of the patients. A significant overlap between upper and lower GI symptoms was recognized. In women, hormonal factors might be responsible for the higher incidence of regurgitation, compared to men [5]. Interestingly, metabolic syndrome had a significant impact on the presence of upper GI symptoms, possibly reflecting the role of obesity and/or other component in dyspepsia and/or GERD. Our study confirmed the impact

of physical activity on normal bowel habits [6].

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## A case of pyloric-type gallbladder adenoma

### To the Editor,

Benign tumors of the gallbladder are very rare. If we do not take into consideration pseudotumors which can occur at this level, such as: inflammatory polyps, cholesterol polyps, adenomyomatosis or hetero ectopias (gastric, pancreatic, hepatic, adrenal), benign tumors represent less than 5% of gallbladder tumors [1]. The vast majority are adenomas. Gallbladder adenomas are rare, being found in 0.1-10% of the cholecystectomies [2]. The tubular pyloric-type adenoma represents one of the rare histopathologic forms of benign epithelial tumor of the gallbladder.

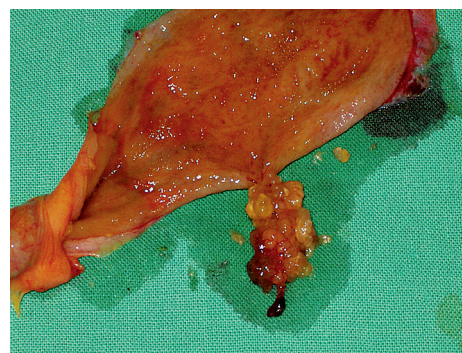
A 77-year old female patient presented to our hospital complaining of several episodes of headaches and vertigo accompanied by nausea and bilious vomiting. She also complained of constrictive retrosternal pain, in relation with moderate physical exertion. Symptoms had a sudden onset about one year ago, when the patient had the first episode of nausea and bilious vomiting followed by vertigo and frontal occipital headaches. This first episode was followed by two more episodes, the last one being extremely severe, forcing the patient to seek for medical help.

The abdominal ultrasonography performed in our hospital revealed a fatty liver, portal vein diameter 9 mm,

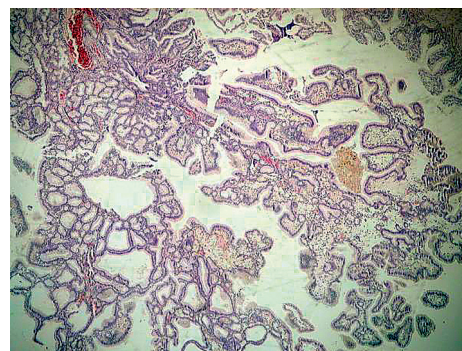
common bile duct 5 mm, a long and hypotonic gallbladder with echogenic images inside it and thickened walls. A 10 mm cyst was detected in the liver parenchyma, close to the gallbladder. The laboratory examinations showed an ESR= 35mm/2h, leucocyte count = 1500/mm<sup>3</sup>. Liver function tests, hematologic examinations, the serum electrolytes and lipid profile within normal limits.

The imaging evaluation suggested the presence of a gallbladder tumor. ECG and cardiovascular investigation allowed the establishing of the diagnosis of non-obstructive hypertrophic cardiomyopathy, exertion angina pectoris, arterial hypertension and left ventricular failure NYHA II. The patient's evolution was favorable under therapy and she was transferred to the surgery department for surgical intervention.

At the level of the diaphragmatic side of the liver, in segment V, a cyst of about 8 mm in diameter with a thin translucent wall was detected. A tumor was detected



**Fig.1** Macroscopic view of the gallbladder tumor after resection.



**Fig.2 a, b** Histopathological aspects of tubular adenoma glands, pyloric-type (H-E a. x 40, b. x 100).

on palpation in the gallbladder. The operation consisted of retrograde cholecystectomy; incision and evacuation of the hepatic cyst; liver biopsy; subhepatic drainage. Macroscopically, the gallbladder had 95 mm in length, elastic walls and dark stasis bile. A papillary tumor of 15/15/10 mm was found in the middle third of the gallbladder, having an implantation basis of 9 mm (Fig. 1). The histopathologic examination revealed a pyloric-type tubular adenoma with several dilated glands, Rokitansky-Aschoff sinuses and moderate inflammatory infiltrate (Fig.2). The post-operative evolution of the patient was favorable and she recovered quickly.

Gallbladder adenomas can be classified according to their histologic architecture into tubular, papillary and mixed. Various types of metaplastic epithelial cells, including pyloric-type gastric cells, can be found in these adenomas [3]. The tumors are accidentally detected during cholecystectomy for gallbladder stones or chronic cholecystitis. They are more rarely diagnosed preoperatively by imaging procedures. Usually they are asymptomatic, except when causing obstruction of the infundibulum or of the cystic duct. In most cases, the symptoms are due to associated gallbladder lithiasis. Chronic inflammatory changes can also be present in the gallbladder in most of the cases, even when gallstones are absent [1].

Microscopically, tubular adenomas contain glandular structures similar to those of the pyloric glands. Displastic changes usually occur in large adenomas.

Unlike gallbladder carcinomas, benign adenomas have a homogeneous sonographic structure, isoechogenic with the hepatic parenchyma. The Doppler examination enables the differential diagnosis of a malignant lesion: the absence of blood flow is frequent in secondary tumor (metastases); a strong vascular signal in the tumor mass or in the gallbladder wall suggests a primary malignant tumor; a decreased blood flow indicates a benign lesion [4]. Endoscopic ultrasonography gives additional details for the differential diagnosis of these tumors. CT and MRI imaging is less useful

to differentiate the polypoid lesions, but can assess parietal invasion in the case of malignant lesions.

Carcinomas developing from adenomas frequently occur in the small intestine and in the colon, and less frequently in the stomach. It is also assumed that gallbladder adenomas might become malignant. The villous adenomas present the highest risk of malignization (25%). Carcinoma foci in situ are present in 9% of the pyloric-type adenomas, and invasive carcinomas in 7% [3, 5]. If a polyp is larger than 10 mm, surgical intervention is mandatory because this polyp is a risk factor for malignant lesions, or it is already a small carcinoma. Cholecystectomy was therefore indicated for our patient. If a polyp is smaller than 10 mm, asymptomatic and lithiasis is not associated, periodical imaging follow-up is required. Even if the polyp is smaller than 10 mm, but it is associated with dyspeptic symptoms or with gallstones, cholecystectomy is usually advised [6].

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