CASE REPORT

Acute lithiasic cholecystitis, pseudoneoplastic form, a cause of conversion for laparoscopic cholecystectomy

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Abstract

Acute lithiasic cholecystitis represents one of the most frequent pathologies of the digestive tract, most often requiring emergency surgical treatment. The prevalence of this condition increases with age and it affects women the most. Laparoscopic cholecystectomy is the preferred surgical treatment, as it diminishes postoperatory pain, it reduces the hospitalization period and medical and social costs, and it also provides a rapid postoperatory recovery. We present the case of an elder female patient, who presented with complex symptoms and signs, suggesting both lithiasic cholecystitis and a gallbladder neoplastic condition. Although there was preferred a laparoscopic cholecystectomy, the presence of an inflammatory process with intense sclerous reaction in the hepatocystic triangle led the conversion of laparoscopic cholecystectomy into an open, classical one. Due to the inflammatory process, the common bile duct (CBD) could not be explored. The subsequent practicing of a cholangiography on the drain tube highlighted the presence of an obstacle in the end zone of the CBD, which could not be removed until the second surgical intervention. The histopahological exams – from frozen sections to immunohistochemistry – had a crucial role in deciding patient's surgical management. The good evolution of the case and the final postoperatory result confirmed that the therapeutic manner chosen for this case was the appropriate one.

Keywords: cholelithiasis, choledocholithiasis, cholecystectomy, conversion to open surgery, laparoscopy.

⊟ Introduction

Acute cholecystitis, characterized by the inflammation of the gallbladder wall, is caused by the presence of biliary stones in approximately 95% of cases, with different causes only in 5% of cases [1].

Biliary lithiasis is quite a frequent condition, generating quite high medical and social costs. In 1998, in the USA, there were spent about 5.8 billion dollars for the diagnosis and treatment of gallbladder conditions [2].

There is estimated that, worldwidely, this condition affects approximately 15–18% of the adult population [3, 4]. Large population studies, using abdominal ultrasound for investigating bile ducts, showed that the prevalence of lithiasic cholecystitis varies according to gender (more frequent in women), age (increases with age), race and geographical area. In the USA, there is estimated that there are about 20.5 million people with gallstones, with about 14.2 million women and 6.3 million men [5].

Apart from the high costs required by this condition, there should be mentioned that biliary lithiasis represents a major risk factor for developing gallbladder cancer [6].

The development of medical imagistics techniques, and especially of abdominal ultrasound, allowed a more precise and accurate diagnosis of biliary lithiasis [7].

Ultrasounds is the most frequently used imagistic method at present for investigating the gallbladder and bile duct, as it is easy to perform, it is cheap, non-invasive and it has a high sensitivity and specificity in lithiasic conditions [8, 9].

Most studies support the idea that the preoperatory exploration of the patient with biliary lithiasis should be a complex and complete one, in order to achieve a complete lesional outcome and to anticipate any possible technical difficulties during surgery. A complete and accurate pre-operatory assessment of patients with biliary lithiasis is very important in establishing the treatment conduct, in order to decrease the risk for intraoperatory incidents and accidents and in order to avoid, as much as possible, the presence of postoperatory complications.

We present a case of cholecystic lithiasis (cholelithiasis) associated with choledochal lithiasis (choledocholithiasis) with special problems of diagnosis and treatment.

⊟ Case presentation

The patient O.S., aged 73 years old, was admitted to the Clinic of General Surgery IV within the Railroads Clinical Hospital of Craiova, Romania, in September 2017, with moderate pain in the right hypochondrium, lack of

appetite, weight loss and physical fatigue. The physical examination showed that the patient presented an old abdominal pathology, of about six years ago, manifested by colic pains in the right hypochondrium, going into the posterior art, accentuated postprandially and accompanied by bile and food vomiting, almost permanent nausea and loss of appetite. All symptoms and signs improved after the administration of antispastic drugs.

The symptoms and signs present at admission started two months before, by moderate pains in the right hypochondrium and loss of appetite, associated with a weight loss of 9 kg in the last four months. At the general practitioner referral, the patient followed an ambulatory treatment with antibiotics and antispastics, which led to the clearance of pain, the patient still presenting loss of appetite, sub-fever (37.3–37.5°C), simultaneously with the scleral sub-jaundice, thus leading to hospitalization.

At admission, the patient presented scleral jaundice, pale skin and mucosa, dehydration, painful abdomen in the right hypochondrium, where the clinical examination highlighted a sub-hepatic sore area. The biological para-clinical investigations highlighted moderate leukocytosis (11 100 leukocytes/mm^3), mild anemia (hemoglobin 10.1 g/dL), slightly increased liver transaminases [glutamic-pyruvic transaminase (GPT) 77 U/L; glutamic-oxalacetic transaminase (GOT) 55 U/L], also slightly high urea (69.71 mg/dL), high total bilirubin (3.4 mg/dL) and high direct bilirubin (2.6 mg/dL). The rest of the biochemical investigations presented normal values.

The abdominal ultrasound highlighted a large-volume gallbladder, infundibularly septated, with diffuse thick walls, especially in the corporeal and fundic regions, up to 12 mm, with no vascular signal, almost entirely inhabited by lithiasic elements with a maximum diameter of 15 mm. The ultrasound could not provide relations about the common bile duct (CBD). The rest of the abdominal organs did not present any imagistic changes.

The upper digestive endoscopy highlighted the presence of a diffuse reflux erosive-hemorrhagic gastritis. The colonoscopy performed up to the cecum highlighted a few dispersed diverticles in the sigmoid colon, requiring no treatment.

There was established the preoperatory diagnosis of acute lithiasic cholecystitis and obstructive jaundice. The patient was scheduled for cholecystectomy using a laparoscopic approach (Operatory Protocol No. 962/ 26.09.2017). The video inspection highlighted the presence of an intense adherent sub-hepatic process, between the great omentum, the inferior margin of the liver, the gallbladder and duodenum. The lysis of adherences was hardly performed, exposing a large volume gallbladder (12/6/4 cm), partially sheltered into the liver (without any demarcation from adjacent hepatic parenchyma), with quite thickened, whitish walls, a filled, endured lumen, thus making impossible its clamping and mobilization. Subsequently, we attempted the exploration of the infundibular area, but the gallbladder was making a common sclerous conjunction with the hepatic pedicle, thus the laparoscopic dissection techniques were dropped, as they were considered too risky. The macroscopic aspect pleaded towards a gallbladder neoplasm, with invasion of the liver and the hepatic pedicle, associated with biliary lithiasis. In order to establish the diagnosis, there was performed a laparoscopic biopsy from the gallbladder

wall, whose histopathological (HP) examination on frozen sections showed the presence of a dense fibrous collagen tissue, with a rich chronic lymphocyte inflammatory infiltrate and ulceration areas.

Under these circumstances, there was decided the conversion of the laparoscopic intervention into an open cholecystectomy, by a right subcostal incision. The manual exploration confirmed the tumoral aspect of the gallbladder, with the invasion of liver parenchyma and the presence of a hard pediculitis, which practically impeded the identification of the main bile duct. There was hardly performed an anterograde cholecystectomy and atypical hepatectomy (in the region of segments IV and V). The cholecystectomy was incomplete, by preserving a portion of the gallbladder infundibular region. On the sectioning, the gallbladder wall was unevenly thickened, sclerous, while the lumen was entirely filled with lithiasic elements (Figure 1).
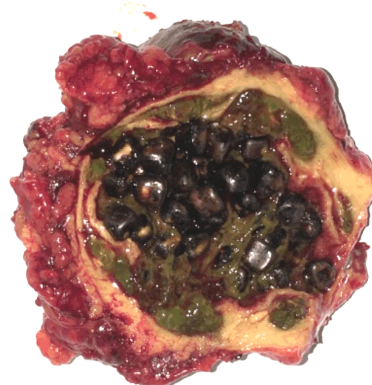
Figure 1 – *The macroscopic aspect of the gallbladder in a transversal sectioning. There could be observed the heterogeneous thickened, sclerous, wall, with a necrotic mucosa and multiple calculi in the lumen.*

For an appropriate diagnosis (taking into consideration the disparity between the intraoperatory macroscopic aspect of the lesions and the laparoscopically harvested biopsy), the surgical specimen was sent for a new examination that reconfirmed the inflammatory aspect of the lesion: acute ulcero-necrotic cholecystitis with marked fibrosis of the wall. Due to the hepatic pedicle sclerosis that did not allow the instrumental exploration of the CBD and the impossibility of performing an intra-operatory cholangiography, we decided and performed transcystic drainage of the CBD.

After surgery, the patient's evolution was a good one, but the external biliary drainage was around 800 mL/ 24 hours. In the ninth day after surgery, the patient was subjected to cholangiography, by the way of the drain tube that showed the presence of an obstacle (possible calculus) in the terminal region of the choledochus.

Fourteen days after the surgery, the patient was transferred to a surgery clinic in Bucharest (Romania) for further investigations and CBD clearance through endoscopic means. Although the computed tomography (CT) scan did not highlight any obstacle in the CBD, but only its dilation in the upper pancreatic region, there was performed an endoscopic intervention, by a large sphincterotomy. Endoscopic retrograde cholangiopancreato-graphy (ERCP) confirmed the presence of a very large choledochal calculus (12–15 mm), located in the upper pancreatic segment of the CBD that could not be extracted.

The patient returned to our Clinic, where she was permanently monitored, and there was decided the temporization of the reintervention in order to reduce the inflammation in the hepatic pedicle. The clinical evolution was a favorable one, the general health state improved, and the biliary drainage decreased significantly (around 300–400 mL/24 hours). After 48 days since the first intervention, there was performed another surgery. During the intervention, the CBD was identified with the thickened walls, dilated by 2 cm. Choledochotomy confirmed the presence of a calculus in the terminal region, which was mobilized into the abdomen during the Benique maneuver, the process being facilitated by the large sphincterotomy and the subsequent reduction of the edema. After that, there was performed a Roux-en-Y hepatico-jejunoanastomosis, protected by a Kehr tube, whose arms were introduced inside the two liver channels. The patient's postoperatory evolution was a favorable one, being discharged after 12 days since the last surgical intervention.

The HP examination of the surgical resection piece continued by its inclusion into paraffin. The sectioning of the biological examination was performed in the Microm HM350 microtome, equipped with a section transfer system on water bath (STS, microM). The HP study was performed on pieces stained with Hematoxylin–Eosin (HE) and the green light trichrome, the Goldner–Szekely (GS) technique. For the differential diagnosis, there was decided the performance of an immunohistochemical (IHC) study to highlight the possible tumor cells and inflammatory reaction in the gallbladder wall. In this regard, the histo-logical cups resulted from the sectioning of the biological material were collected on the poly-L-Lysine covered slides and dried in a thermostat, at 37^0C, for 24 hours, for increasing the section adherence to the port-object slide. Subsequently, the sections followed the classical protocol: deparaffinization, hydration, washing in distilled water. For antigen demasking, the slides were boiled in a sodium citrate solution (pH 6) for 21 minutes in a microwave oven. After boiling and cooling the slides, they were washed in distilled water for 15 minutes. The endogenous peroxidase block was performed by incubating the biological material in 3% oxygenated water for 30 minutes, at room temperature. After that, there followed the non-specific sites block, by using 2% skimmed milk for 30 minutes. Subsequently, the sections were incubated with primary antibodies, for 18 hours (overnight), in a refrigerator at 4^0C. The next day, there was applied the biotinylated secondary antibody for 30 minutes, at room temperature, followed by a 1% phosphate-buffered saline (PBS) washing for 15 minutes and then there was applied Streptavidin–Horseradish peroxidase (HRP) for 30 minutes at room temperature, followed by slides washing in 1% PBS 3×5 minutes. The signal was detected by using 3.3'-Diaminobenzidine (DAB, Dako) and the reaction was stopped in 1% PBS. There followed the Mayer's Hematoxylin contrasting, alcohol dehydration, xylene clarification and slide fixation in a DPX environment (Fluka).

For IHC study, the following antibodies were used: anti-human Ki67 (clone MIB-1, Dako 1:50 dilution), anti-human p53 (clone DO7, Dako, 1:50 dilution), anti-human CD34 (clone QBEnd10, Dako 1:100 dilution), anti-human CD3 (clone F7.2.38, Dako, 1:100 dilution), anti-human CD20cy (clone L26, Dako, 1:100 dilution), anti-human CD68 (clone KP1, Dako, 1:200 dilution), anti-human CD79α (clone JCB117, Dako, 1:50 dilution).

The microscopic study showed a thick gallbladder wall, formed of collagen fibers arranged relatively in order towards the external side of the gallbladder and numerous active fibroblasts (Figure 2), adherent to the peritoneal adipose tissue, while on the internal side, there were predominant the collagen fibers with a disordered arran-gement and extended areas of parietal necrosis (Figure 3). Extended areas of the gallbladder wall were covered with an abundant inflammatory infiltrate rich in lymphocytes, plasmocytes and macrophages, associated with micro-hemorrhages and tissue necroses (Figures 4 and 5). The gallbladder mucosa appeared disorganized, necrotic, with small fragments of epithelium dispersed inside the inflammatory infiltrate (Figure 6).

The IHC examination was negative for the cellular proliferation markers, namely for Ki67 and p53; still, there was observed a positive reaction for the CD34 antibody, thus showing that the remodeling changes of the gallbladder wall were accompanied by a strong reaction of vascular angiogenesis (Figure 7).
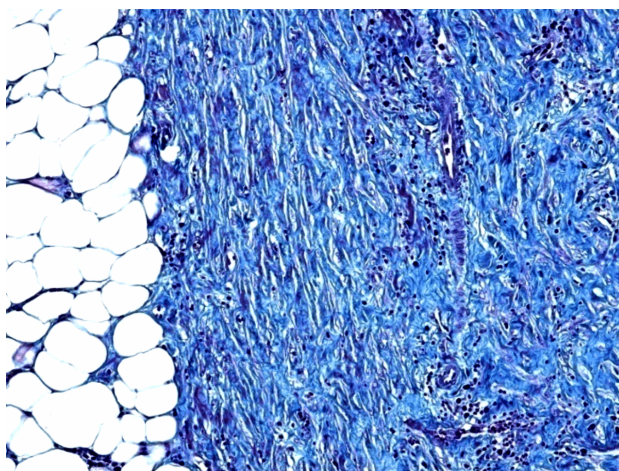

Figure 2 – *Gallbladder wall, external third, where there can be observed a dense, sclerous tissue, made of collagen fibers arranged in order, with numerous reactive fibro-blasts, in contact with the peritoneal adipose tissue. GS trichrome staining, ×100.*
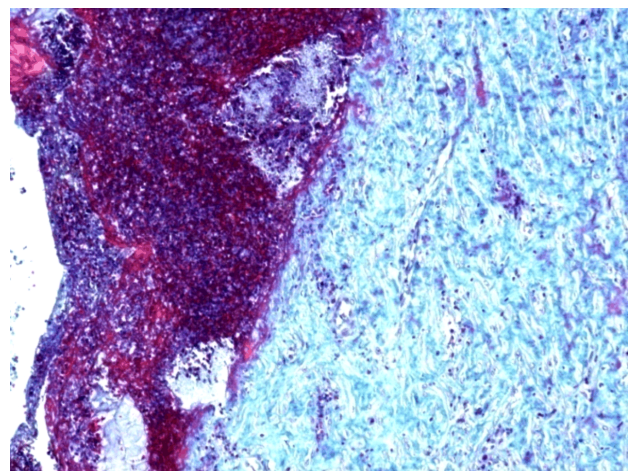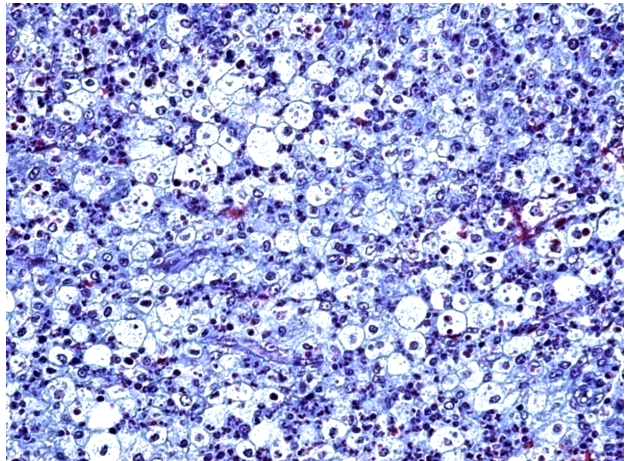

Figure 3 – *Image of the gallbladder wall from the internal third, where there may be observed collagen fibers with a disordered arrangement and extended areas of tissue necrosis. GS trichrome staining, ×100.*
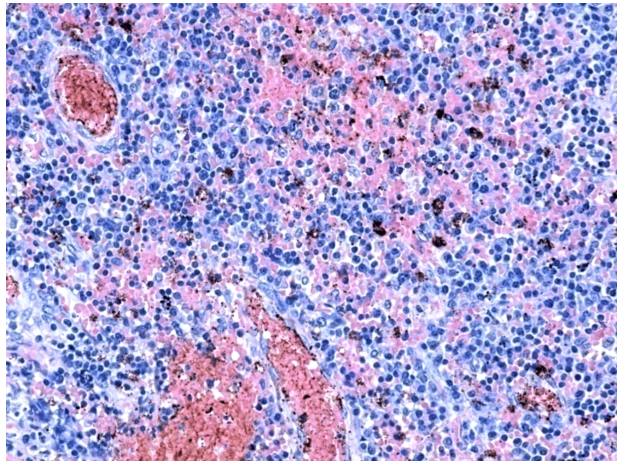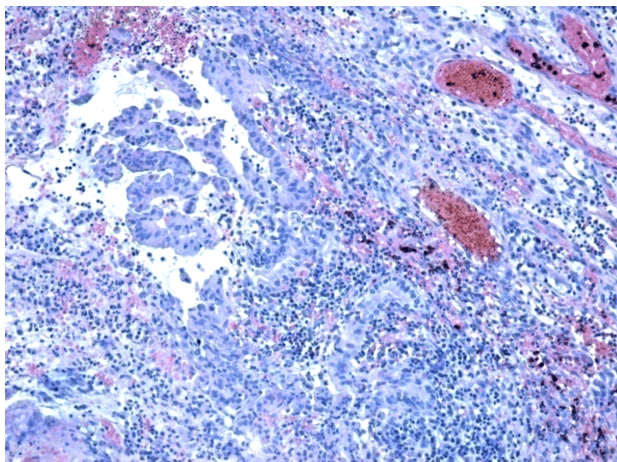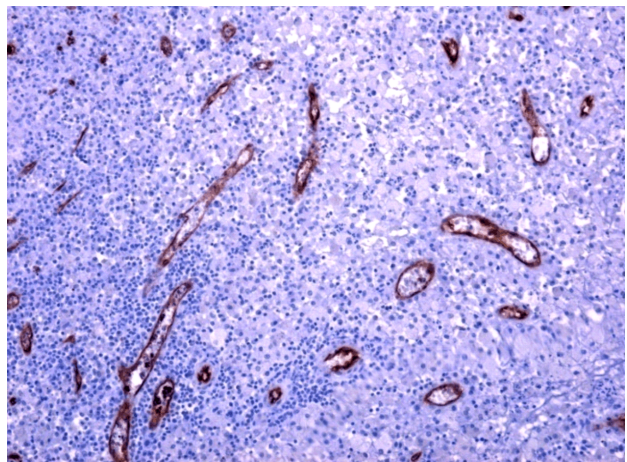
Figure 4 – *Area from the gallbladder wall strongly infiltrated with lymphoplasmocytic cells, vascular congestion and microhemorrhages. HE staining, ×200.*

Figure 5 – *Area from the gallbladder wall strongly infiltrated with foamy macrophage cells. GS trichrome staining, ×200.*



Figure 6 – *Heterogeneous gallbladder mucosa, with a fragmented epithelium, strongly infiltrated with round lymphoplasmocytic cells. HE staining, ×100.*
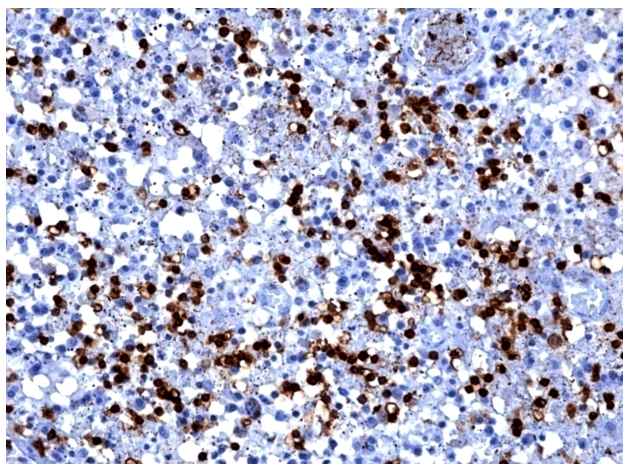

Figure 7 – *Gallbladder wall with a strong inflammatory infiltrate and with numerous angiogenesis vessels. Anti-CD34 antibody immunomarking, ×100.*

IHC study of the inflammatory reaction from the gallbladder wall confirmed the classical HP examination and showed that the inflammatory infiltrate contained numerous T- and B-lymphocytes, plasmocytes and macrophages (Figures 8–11). The distribution of inflammatory cells was completely heterogeneous, being highlighted more or less intense regions of the gallbladder wall populated with different cells of the immune system. Still, of all the immune system cells, the best represented were the macrophages, showing the chronic character of inflammation and the presence of tissue and cell necrosis processes.
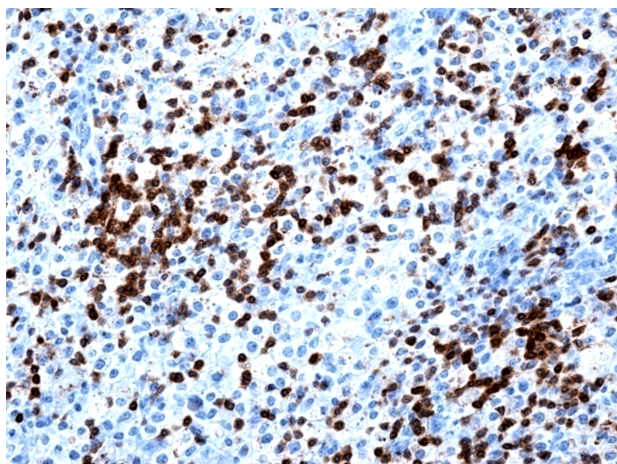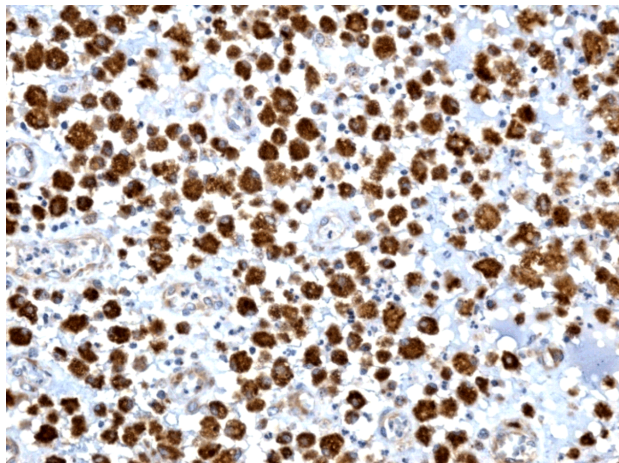

Figure 8 – *Area in the gallbladder wall infiltrated with numerous CD3+ T-lymphocytes. Anti-CD3 antibody immunomarking, ×200.*
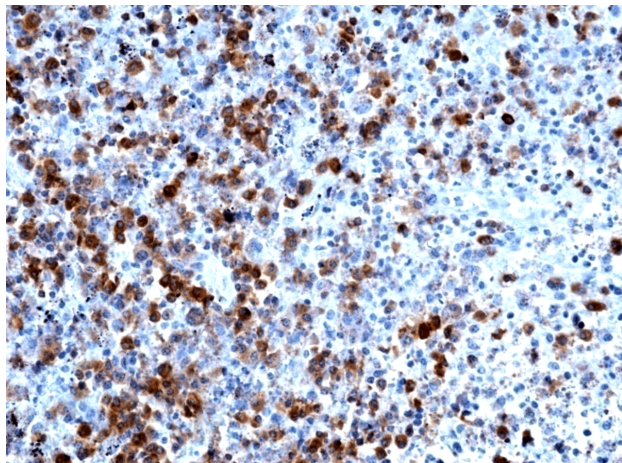

Figure 9 – *CD20+ B-lymphocytes relatively numerous in the inflammatory infiltrate of the gallbladder. Anti-CD20 antibody immunomarking, ×200.*

Figure 10 – *Image of an area of gallbladder wall, strongly infiltrated with CD68+ macrophages. Anti-CD68 antibody immunomarking, ×200.*

Figure 11 – *Microscopic image of strongly infiltrated gallbladder wall with CD79α+ plasmocytes. Anti-CD79α antibody immunomarking, ×200.*

⊟ Discussion

Although gallbladder lithiasis is present in 10–18% of the adult population, only 1–4% of the individuals present clinical symptoms [10], the rest showing no symptoms or signs. Some studies appreciate that 20% of the patients with gallbladder lithiasis have no symptoms at all [11]. Still, acute cholecystitis is one of the most frequent reasons for emergency room presentation, 90–95% of acute cholecystitis having a lithiasic etiology [3].

The clinical signs are non-specific, still they may be suggestive for the diagnosis of acute cholecystitis; abdominal ultrasound is the imagistic investigation that differentiates the diagnosis in over 85% of cases. However, there are cases of cholecystitis where the diagnosis is incorrect or incomplete, especially when there were administered various drugs that mask the disease symptoms and signs.

We presented a case of lithiasic cholecystitis that raises problems of both diagnosis and treatment. Our patient presented old hepatobiliary symptoms and signs, inappropriately investigated, treated in ambulatory with anti-spastics and antibiotics. This situation led to delayed (for 5–6 years) positive diagnosis and accurate treatment. The patient's symptoms at admission, namely pain in the right hypochondrium, loss of appetite, great weight loss and the onset of a progressive jaundice raised the suspicion of biliary lithiasis, but also of CBD or gallbladder cancer. The abdominal ultrasound highlighted the presence of stones in the gallbladder, without identifying the obstacle in the CBD, thus raising the suspicion of a mechanical jaundice with a malignant etiology. Moreover, the laparoscopic aspect was that of a pseudotumor. Only the repeated HP examination doubled with an IHC study clarified the lesion diagnosis and allowed an adequate treatment.

In Romania, as well as in many other countries, biliary lithiasis is quite common, especially in people over 60 years old. Therefore, any hepatobiliary suffering should be investigated both clinically and imagistically, especially in older people. According to some studies, in some geographical areas, biliary lithiasis affects approximately 50% of women and 16% of men over 70 years old [12, 13]. These data make us take into consideration the fact that a lithiasic cholecystitis should be suspected in any abdominal colic situation.

We intended to treat our case by a laparoscopic cholecystectomy, known as the "golden standard" in the benign pathology surgery of gallbladder [14–17]. The advantages of this surgical intervention are multiple ones, namely the diminishing of postoperatory pain, reduction of abdominal scars, rapid postoperatory recovery and reduced hospitalization period and medical and social costs [18–20].

In our patient, the laparoscopic exploration highlighted a pseudotumoral structure that included the gallbladder and the CBD, infiltrating into the liver, with multiple adherences to the surrounding organs. The impossibility of clamping and mobilization of the gallbladder, as well as the impossibility of exploring the infundibular region, together with the tumoral appearance, determined us to abort laparoscopic cholecystectomy and to convert to a classical, open surgical intervention.

Our initial laparoscopic approach was also motivated by the fact that numerous studies showed that laparoscopic cholecystectomy is indicated even in the cases of the elderly, due to the diminishing of postoperatory pain and a faster recovery [21–23]. The decision to converse laparoscopic cholecystectomy into an open one was motivated by the impossibility to approach the hepatic hilum, due to an extended fibrosis in the hepatocystic triangle and the high risk of causing vascular or major biliary tree lesions. This attitude is also supported by some authors that showed the fact that chronic inflammatory processes in the hepatocystic triangle (Callot's triangle) represent a major indication of laparoscopic cholecyst-ectomy conversion [24–27].

The HP examination on frozen sections, which showed that the pseudotumoral formation was an ulcerative-necrotic lithiasic cholecystitis, determined us to perform an incomplete anterograde cholecystectomy (there was preserved a part of the infundibular region of the gallbladder) with an atypical hepatectomy. Due to the intense inflammatory process present in the hepatocystic triangle, the CBD could not be safely investigated laparoscopically or by open approach. The assembly of the transcystic biliary drainage led to an evacuation of large bile quantity in the following days, which a clear improvement of liver functions. The subsequent cholangio-graphy on the drain tube highlighted the presence of an obstacle in the terminal part of the CBD, which could not

be removed unless a second surgical intervention was performed.

We should observe that the recurrent gallbladder inflammatory processes (clinically presented by recurrent colicative pain in the right hypochondrium) led to the formation of a sclerous conjunctive tissue that extended from the gallbladder to the common bile duct and hepatic parenchyma, giving a tumoral appearance.

We should emphasize the fact that in such cases, the HP and IHC examination play a major part in diagnosing the lesion and deciding upon the treatment conduct.

⌂ Conclusions

Acute lithiasic cholecystitis inappropriately treated with antibiotics may lead to miss the optimal surgical moment, while clinically and macroscopically it may acquire the mask of a pseudo-neoplastic syndrome. If the conversion of laparoscopic cholecystectomy usually enhances the surgeon's abilities (as well as corresponding technological equipment), justified by difficult conditions, in the present situation, the conversion had a second absolute indication – the tumoral macroscopic appearance of the gallbladder. The decisive element in clarifying the diagnosis and proper management belongs to the HP and IHC examinations that allowed a successful systematic approach.

Conflict of interests

The authors declare that they have no conflict of interests.

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