CASE REPORT

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Spontaneous cholecystocutaneous fistula as a primary manifestation of gallbladder adenocarcinoma associated with gallbladder lithiasis – case report

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Abstract

Spontaneous cholecystocutaneous fistula (SCF) is a rare complication of neglected calculous biliary disease and also an extremely rare complication of gallbladder neoplasm. This pathology has become even rarer because of prompt diagnosis and expedient surgical intervention for gallstones. So far, there is one published report of a SCF due to gallbladder adenocarcinoma. We present the case of a woman aged 87 years, admitted to the V[th] Department of Surgery, Clinical Municipal Hospital of Cluj-Napoca (Romania) for a tumoral mass located in the epigastrium. In the epigastrium, the patient had three skin orifices of about 1–2 mm each, through which purulent secretion occurred. The abdominal ultrasound highlighted a cholecystocutaneous fistula with the presence of a subcutaneous gallstone. Intraoperatively, we found a cholecystocutaneous fistula, a 1 cm subcutaneous gallstone, gallbladder with thickened walls containing a cylinder-shaped gallstone of 5/3 cm. Fistulectomy, gallstones extraction and cholecystectomy were performed. The histopathological examination highlighted gallbladder adenocarcinoma. In conclusion, SCF can be the first significant manifestation of gallbladder cancer associated with neglected calculous biliary disease.

Keywords: cholecystocutaneous fistula, gallstones, gallbladder adenocarcinoma, immunohistochemistry.

Introduction

Primary cancer of gallbladder is a rare malignant condition, with significant geographical variations regarding incidence and prevalence. The clinical and statistical studies showed that, in the USA, the incidence is 1–2 in 100 000 inhabitants [1, 2], while in other geographical areas (South America, India, Chile), the incidence is a lot higher, reaching even 7.5 in 100 000 men and 23 in 100 000 women [3, 4]. Also, there should be specified that the gallbladder neoplasias are the most frequent cancers localized in the biliary tract, representing 80–95% of all the biliary tract cancers, all over the world [5–8]. Another characteristic of this cancer is its high aggressiveness, being considered the most aggressive form of biliary tract cancer, the survival rate being very low after diagnosis [8]. In advanced stages, the global average rate of survival for the patients with gallbladder cancer is about six months, with a 5% survival rate at five years [1, 9]. The major cause of such a poor prognosis is the early migration of neoplastic cells in the liver or other organs, using lymphatic, perineural, hematogenous pathways, or by direct invasion in the adjacent organs [10, 11].

The early diagnosis of gallbladder cancer is almost impossible, despite the technological progress and the use, on a large scale, of medical imagistic techniques, such as abdominal ultrasounds and computed tomography (CT), as gallbladder tumors remain without symptoms for a long period of time. The clinical symptoms are unspecific and they appear late in stages T3, T4 [12], represented by right hypochondrium pain, nausea, vomiting and, sometimes, mechanical jaundice. Generally, the preoperatory suspicion of gallbladder cancer appears only in 30% of the patients, while the rest of 70% are diagnosed postoperatory, after the histopathological examinations of the gallbladder [13].

We present a case of spontaneous cholecystocutaneous fistula (SCF) with acute calculous cholecystitis masking a gallbladder adenocarcinoma.

Case presentation

A female patient (CV), aged 87 years, was admitted to the Infectious Diseases Hospital of Cluj-Napoca (Romania) for fever (38.2^0C) and a tumoral mass occurring in the epigastrium, with signs of inflammation, appeared one month before the patient came to Hospital. The patient claims no other symptoms prior to this episode.

The patient had a history of essential hypertension treated with triple therapy, hypertensive and ischemic heart disease, mild degenerative aortic stenosis, congestive heart failure class II according to the *New York Heart Association* (NYHA) and diabetes mellitus type 2 under treatment with oral antidiabetic drugs. The case was interpreted as: "cellulitis with abdominal wall fistula by infection with *Escherichia coli* and *Enterococcus faecalis*". She was prescribed supportive treatment, antibiotic, anti-inflammatory, and was referred to our Hospital, after three days, for surgical treatment.

The patient was admitted in Vth Department of Surgery, Clinical Municipal Hospital of Cluj-Napoca (15/09.01.2014), and was operated in the same day. On admission, the patient signed the informed consent form and the consent form for using her medical data in scientific purposes.

The examination performed on admission highlighted excessive adipose tissue on the abdomen, without signs of peritoneal irritation, while at the epigastric level there was palpated a tumoral mass, 5–6 cm diameter, painful, firm consistency, with three fistulous skin orifices, about 1–2 mm each, through which white-yellowish purulent secretion was discharged.

The laboratory tests highlighted leukocytosis (14 200/dL) and hyperglycemia (180 mg/dL).

The abdominal ultrasound highlighted an oblique fistulous tract at epigastric level (Figure 1) through the abdominal wall, containing a few gas bubbles and a gallstone of about 1 cm. The tract continued to the hepatic area and was in contact with the gallbladder fundus. On the fistulous tract, there was a small area of 1 cm diameter that had the aspect of a liquid collection. The gallbladder presented a thick wall with at least one gallstone inside while the liver had fatty appearance. At the time of examination, we could not make other assessments.

Based on ultrasonography and clinical findings, there was established the diagnosis of SCF due to acute suppurative cholecystitis associated with cholelithiasis.

Surgery was performed (80 minutes) and the following were highlighted intraoperative (Figure 2, a and b): a cholecystocutaneous fistula, a subcutaneous migrated 1 cm gallstone and gallbladder with thickened walls, with a 5/3 cm cylinder-shaped gallstone. Because the acute inflammatory process localized in the gallbladder wall and surrounding tissues and the fibrous tissue in the path of fistula, we could not make other intraoperative considerations. Fistulectomy, gallstones extraction, and cholecystectomy were performed. Postoperative evolution was good and the patient was discharged from Hospital seven days after the operation.

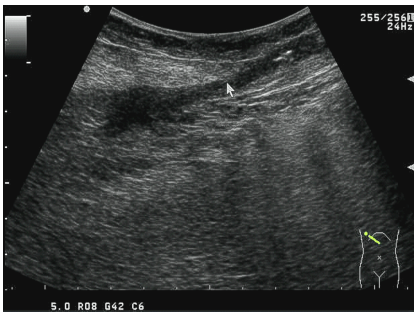

Figure 1 – ***Ultrasound image of the abdominal wall. The presence of a fistula, hypoechogenic tract is observed going deeper from the surface of the skin.***

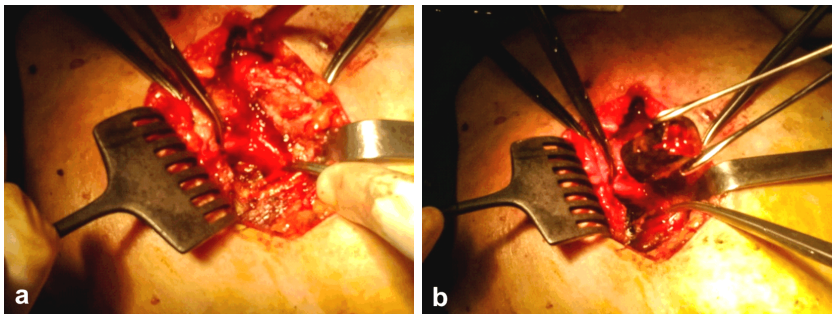

Figure 2 – ***Intraoperative aspect: (a) Cholecystocutaneous fistula with the presence of gallstones; (b) Gallstones extraction.***

The whole piece of surgical exeresis was sent for a histopathological examination. The biological material was fixed in 10% neutral formalin solution and included in paraffin. For the histopathological study, there were used Hematoxylin–Eosin (HE) and Goldner–Szekely (GS) green light trichrome stainings. Due to unusual presentation conditions and the findings on classical histological examination, the pathologist decided to perform also an immunohistochemical study. From the material included in paraffin, there were performed serial sections in the Microm HM350 rotary microtome, equipped with a transfer system of the sections on water bath (STS, microM). The sections were collected on the poly-L-lysine-covered slides and subsequently dried in a thermostat at 37^{0}C for 24 hours. The next day, the sections followed the classical protocol: deparaffinization, hydration, antigen demasking by boiling the cross-sections in pH 6 sodium citrate solution, for 21 minutes in a microwave oven (seven cycles of 3 minutes). After slides cooling, they were washed in tap water and in distilled water for 15 minutes. It followed the endogenous peroxidase blocking by incubating the cross-sections in 3% oxygenated water, for 30 minutes, followed by a wash in distilled water for 10 minutes and a wash in a 1% phosphate-buffered saline (PBS), for 5 minutes. The blocking of non-specific sites was performed using 2% skimmed milk for 30 minutes. The cross-sections were then incubated with primary antibodies, for 18 hours (over night), in a fridge, at 4^{0}C. The next day, there was applied the secondary biotinylated antibody for 30 minutes at room temperature, followed by the wash in 1% PBS (three baths of 5 minutes each), followed by an Streptavidin–Horseradish peroxidase (HRP) apply for 30 minutes at room temperature, followed by the 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 contrasting with Mayer's Hematoxylin, alcohol dehydration, xylene clarification and slides fixation, by using a DPX (Fluka) environment.

The following antibodies were used:

▪ CD20 (monoclonal mouse anti-human CD20cy, clone L26, Dako), 1:50 dilution;
▪ CD3 (monoclonal mouse anti-human CD3, clone F7.2.38, Dako), 1:25 dilution;
▪ PCNA (monoclonal mouse anti-proliferating cell nuclear antigen, clone PC100, Dako), 1:100 dilution;
▪ p53 (monoclonal mouse anti-human, clone DO-7, Dako), 1:50 dilution;
▪ Ki67 (monoclonal mouse anti-human Ki67 antigen, clone MIB-1, Dako), 1:50 dilution;
▪ CD34 (monoclonal mouse anti-human CD34 class II, clone QBEnd 10, Dako), 1:50 dilution;
▪ Mucin 5AC (Sc-71621, 2Q445, mouse, Santa Cruz Biotechnology), 1:200 dilution;
▪ CK 7 (monoclonal mouse anti-human cytokeratin 7, clone OV-TL 12/30, Dako), 1:50 dilution;
▪ CA 19-9 (monoclonal mouse anti-human CA 19-9, clone 1116-NS-19.9, Dako), 1:50 dilution;
▪ CK 5/6 (monoclonal mouse anti-human cytokeratin 5/6, clone D5/16 B4, Dako), 1:50 dilution.

The study of the histopathological material was performed with the Nikon Eclipse 55i microscope, equipped with a 5-megapixel charge-coupled device (CCD) color camera. The images were captured and processed by using the Image ProPlus7 AMS Software (Media Cybernetics, Inc., Buckinghamshire, UK).

The histopathological examination of the cholecyst showed an unevenly thickened wall, with multiple collagen fibers in the submucosa, a parcellary infiltrate of blood and lymphocytes (Figures 3 and 4). In some areas, there were identified lymphoplasmocyte abundant infiltrates (Figure 5), hemorrhagic foci (Figure 6) or areas of parietal necrosis (Figure 7). The gallbladder mucosa was necrotic on almost the entire surface, being replaced by a chronic granulation tissue. Across the entire wall, there were identified tubular structures with various shapes and sizes, with a heterogeneous trajectory that occupied, in some areas, the entire thickness of the gallbladder wall, dislocating and infiltrating the muscular lining of the cholecyst (Figures 8 and 9). The tumoral cells presented numerous atypias, with relatively rare mitoses. The examination of the histopathological samples with high quality microscopic objectives allowed us to highlight the presence of tumor cells in the lymphatic vessels (lymphatic invasion) (Figure 10).

For the support of the positive and differential diagnosis, there were performed various immunohistochemical markings. One of the first markers used for highlighting the malignant characteristic of the tubular structures was antigen CA 19-9 that was intensely positive to all the glandular structures (Figure 11). Also, all the tumor cells were intensely reactive to PCNA (Figure 12).

The evaluation of the tumor cell proliferation was performed by using the Ki67 antibody marking. Overall, the number of glandular tumor cells marked with Ki67 was low (the cellular proliferation index being lower than 5%), except for the small-sized glandular structures, where the cellular proliferation index was up to 25% (Figure 13).

The evaluation of TP53 gene alterations was performed by using the p53 antibody. P53 protein, codified in humans by TP53 gene, is considered to be "the genome guardian", due to its role in preserving the genome stability and preventing genetic mutations. In our case, the immunohistochemical reaction to the anti-p53 antibody was negative (Figure 14).

For evaluating the cytoskeletal filaments of the tumor cells, we used two immunohistochemical markers, namely CK 5/6 and CK 7. The immunohistochemical reaction to CK 5/6 was negative (Figure 15), but it was intensely positive to CK 7 (Figure 16, a and b). CK 7 intensely marked the glandular tumor cells and the isolated tumor cells, being considered the best immunohistochemical marker for micrometastases detection.

The evaluation of immunohistochemical expression of some mucins may provide us with important data regarding the behavior and aggressiveness of tumor cells. In our study, we proposed to evaluate the immunohistochemical expression of Muc5AC marker, which signals the presence of some glycoproteins produced by the tumor cells. As it may be observed (Figure 17), Muc5AC was intensely expressed in most tumor cells. Also, by using the anti-CD34 antibody, we identified a rich network of angiogenesis vessels around the tumor glandular structures (Figure 18).

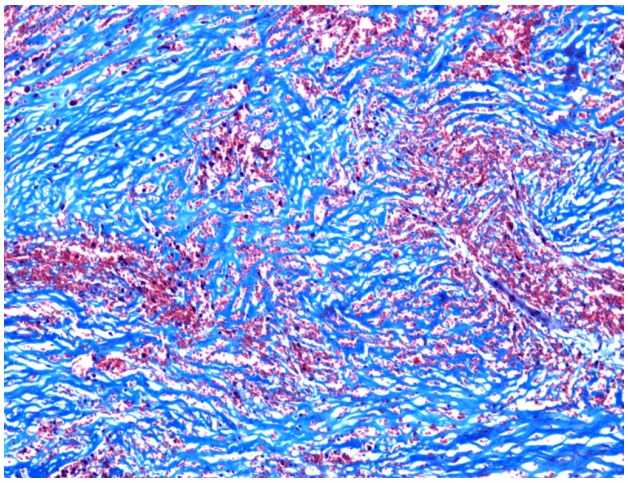

Figure 3 – ***Image of the cholecyst wall where there may be observed the excessive thickness by fibrillary collagen synthesis, with a relatively unordered arrangement, associated with diffuse parietal hemorrhages. GS trichrome staining, ×100.***

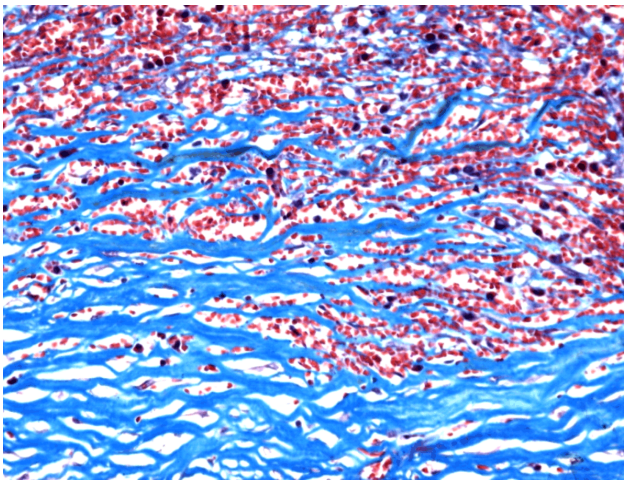

Figure 4 – ***Collagen fibers with a semi-ordered arrangement, infiltrated by hemorrhagic sub fusions (detail from Figure 1). GS trichrome staining, ×200.***

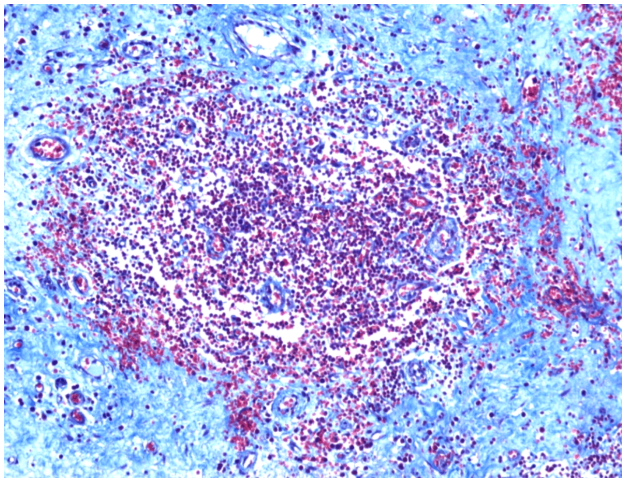

Figure 5 – *Area of cholecyst wall intensely infiltrated with lymphocytes. GS trichrome staining, ×100.*

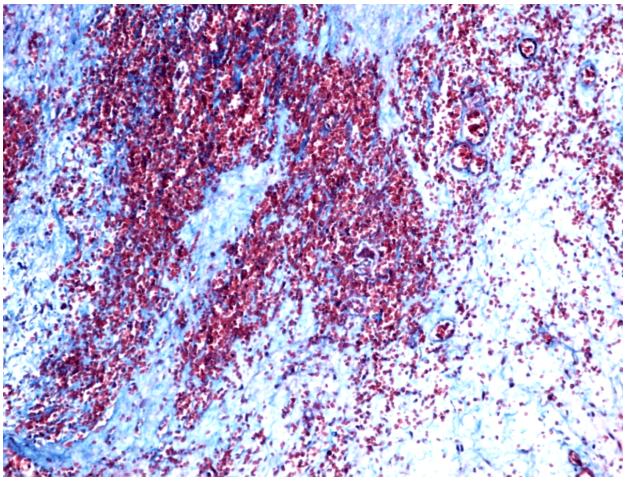

Figure 6 – *Cholecyst wall with multiple hemorrhagic foci. GS trichrome staining, ×100.*

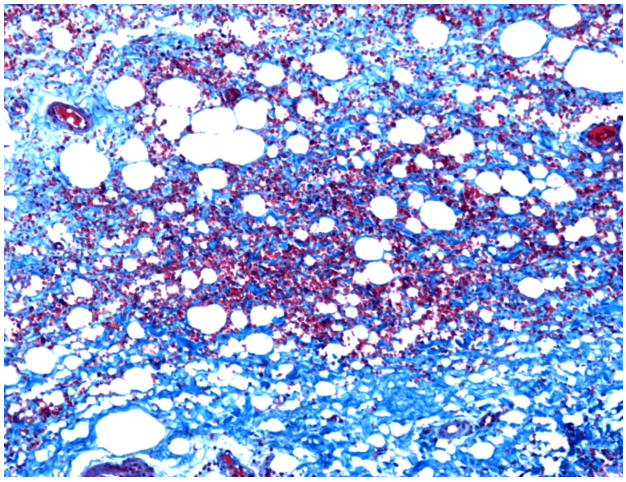

Figure 7 – *Area of cholecyst with hemorrhagic infiltrate and parietal necrosis. GS trichrome staining, ×100.*

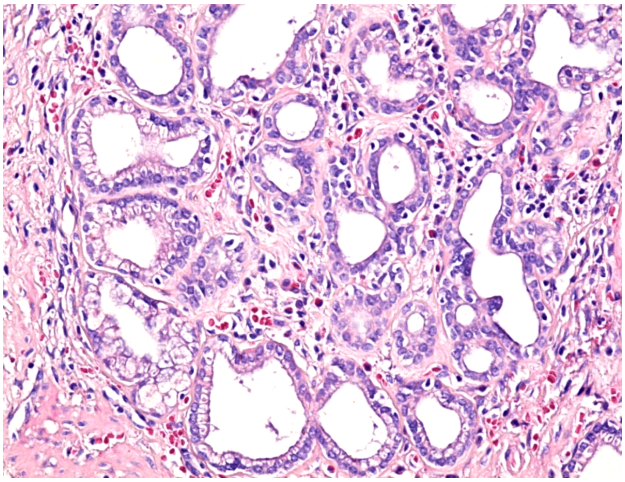

Figure 8 – *Image of cholecyst tubular adenocarcinoma. HE staining, ×200.*

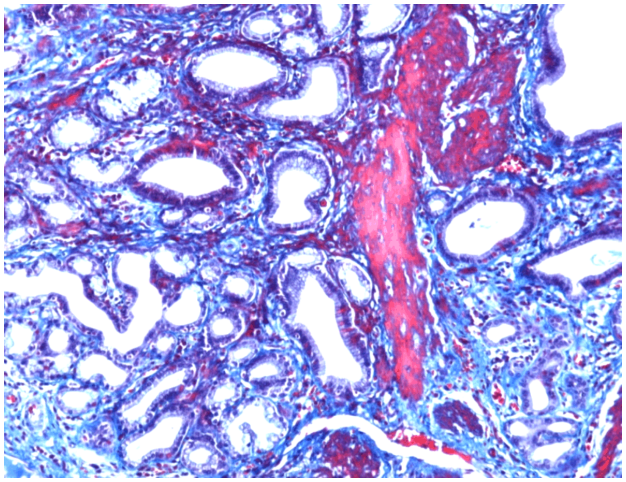

Figure 9 – *Microscopic image of glandular tumor structures, which infiltrate and dislocate the muscular lining of the cholecyst. GS trichrome staining, ×100.*

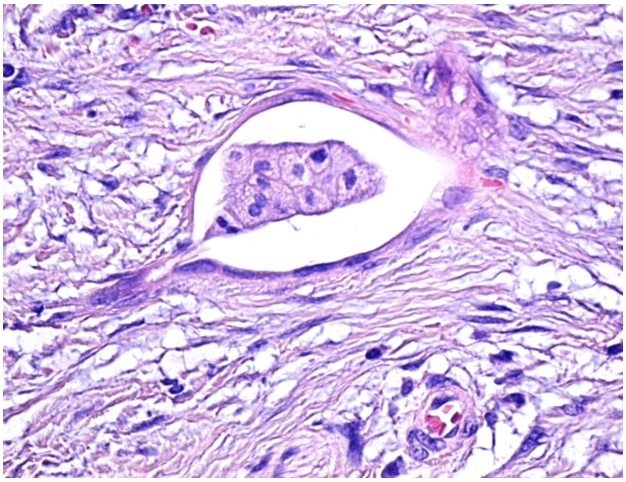

Figure 10 – *Image of tumor cells inside a lymphatic vessel (lymphatic invasion). HE staining, ×400.*

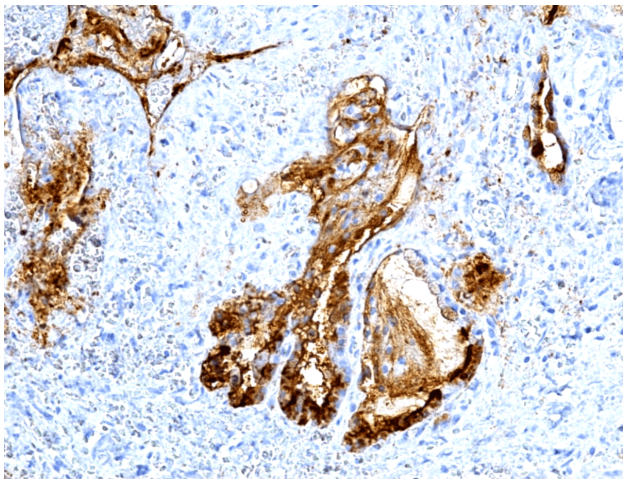

Figure 11 – ***Tumor glands with intense reaction to CA 19-9. Anti-CA 19-9 antibody immunomarking, ×100.***

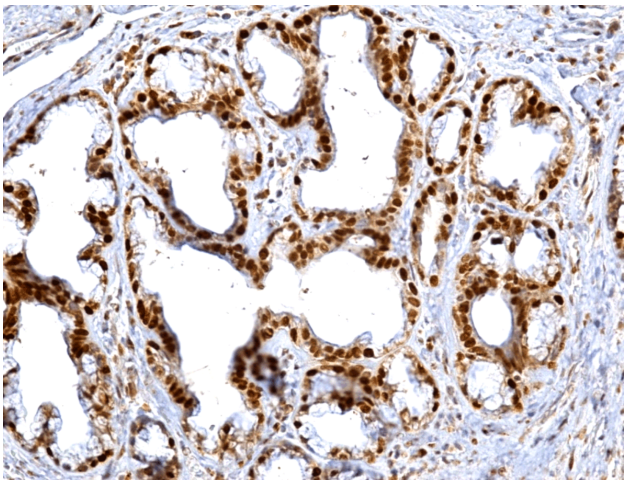

Figure 12 – ***Glandular tumor cells with intense reaction to PCNA. Anti-PCNA antibody immunomarking, ×100.***

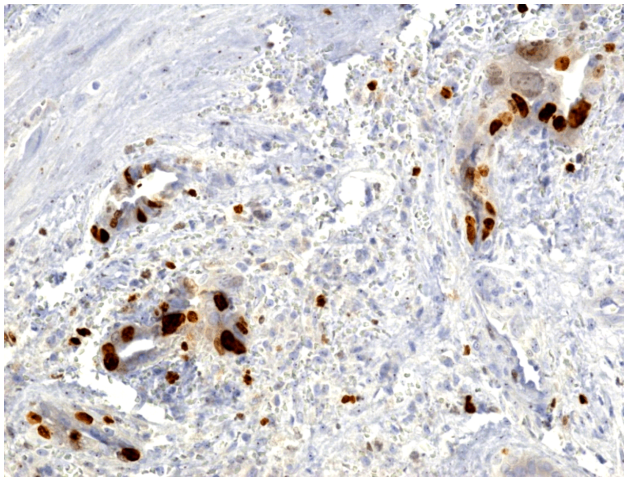

Figure 13 – ***Glandular tumor cells with a moderate positive marking to Ki67. Anti-Ki67 antibody immunomarking, ×200.***

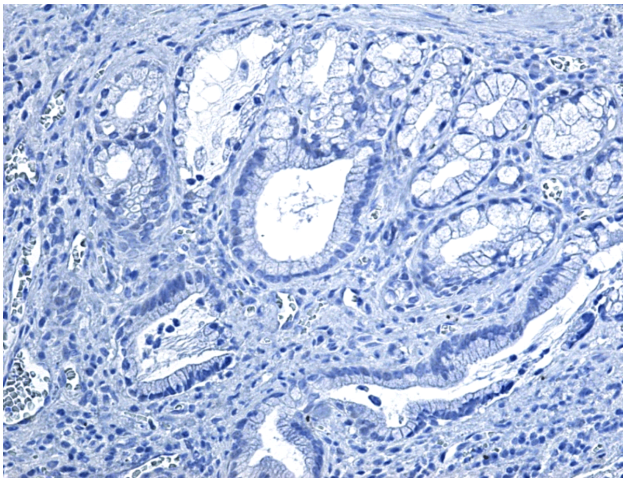

Figure 14 – ***Microscopic image of tumor cells with negative reaction to p53 marker. Anti-p53 antibody immunomarking, ×200.***

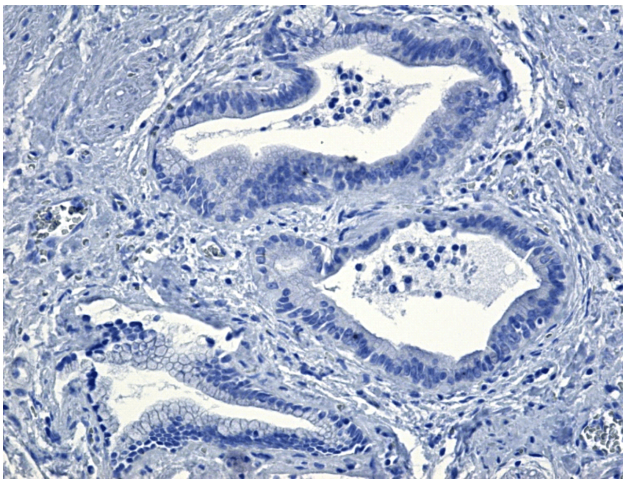

Figure 15 – ***Image of adenocarcinoma with negative reaction to CK 5/6. Anti-CK 5/6 antibody immunomarking, ×200.***

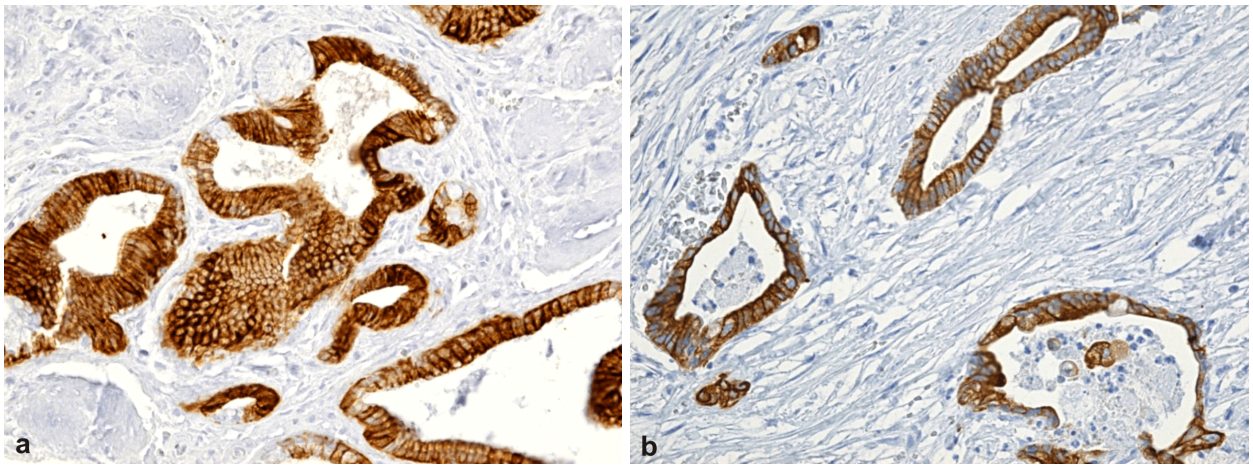

Figure 16 – ***(a) Tumor cells with intense reaction to CK 7; (b) Isolated glands and tumor cells, intensely positive to CK 7. Anti-CK 7 antibody immunomarking, ×200.***

By investigating the peritumoral inflammatory reaction, the immunohistochemical study allowed us to observe that the inflammatory cells were mainly formed of CD3-positive T-lymphocytes (Figure 19) and a lower number of CD20-positive B-lymphocytes (Figure 20). The lymphocyte dissemination in the cholecyst wall structure was completely heterogeneous, most of them being present in the peri-tumoral stroma or in the areas of tissue necrosis.

The pathological examination, correlated with the clinical aspects, allowed us to conclude the diagnosis tubular adenocarcinoma of the gallbladder, pT1bNxMx LoVoRx.

After pathological diagnosis was made, the patient was guided in Department of Oncology for further evaluation and treatment but the patient refuse the treatment proposed by the oncologist.

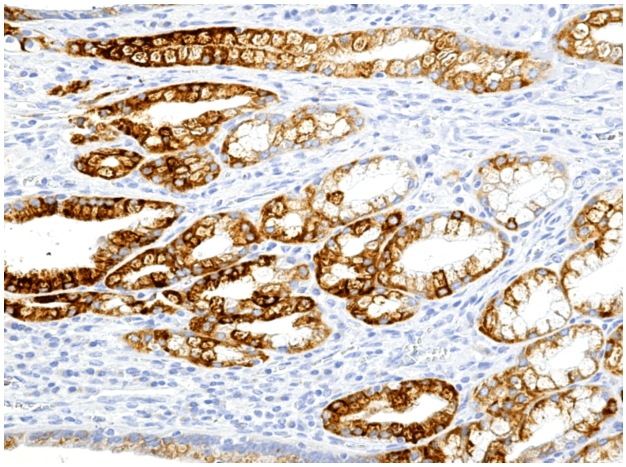

Figure 17 – ***Immunohistochemical image of the tumor glandular structure with intense reaction to Muc5AC. Anti-Muc5AC antibody immunomarking, ×200.***

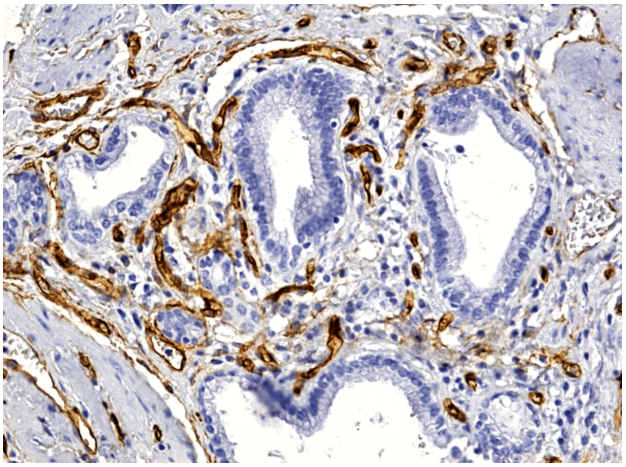

Figure 18 – ***Well-represented angiogenesis vessels around the tumor glandular structures. Anti-CD34 antibody immunomarking, ×200.***

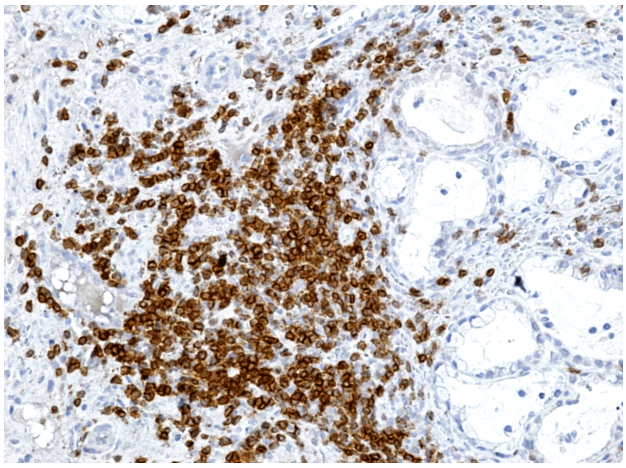

Figure 19 – ***Peritumoral stroma infiltrated with numerous T-lymphocytes. Anti-CD3 antibody immunomarking, ×200.***

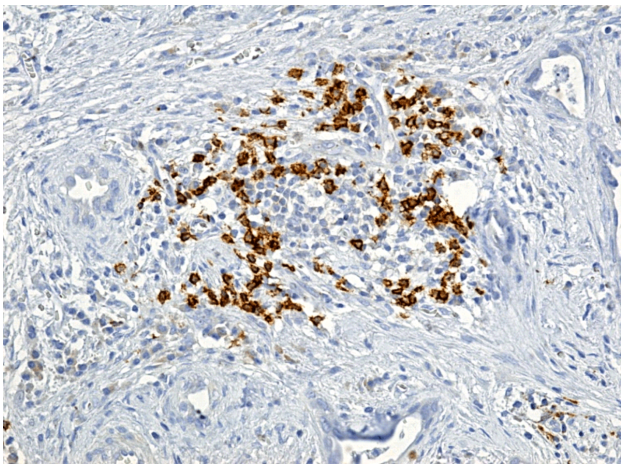

Figure 20 – ***Diffusely disseminated B-lymphocytes in the peritumoral stroma. Anti-CD20 antibody immunomarking, ×200.***

Discussion

Gallbladder cancer is an extremely aggressive malignant condition, with high mortality, because it is difficult to diagnose in early stages. It is a condition affecting mainly women, being about three times more frequent in women than in men [5]. About 70–75% of these conditions are diagnosed belated usually when local complications or distance metastases appear [14], as the specific symptoms lack and the onset is usually insidious. Extremely rare, the gallbladder cancers manifests by cholecystocutaneous fistula.

There were less than 60 reports of SCF in the medical literature over the past half-century, including individual case reports only [15].

Biliary fistulas can be internal or external (cholecystocutaneous fistula). Internal biliary fistula is more common: it can be with the duodenum, stomach, colon, kidney, pleura or bronchus [16–18].

Cholecystocutaneous fistula is an abnormal lined tract connecting the gallbladder and the skin. External biliary fistula is rare, and can be therapeutic, iatrogenic [18], post-traumatic [19], a complication of liver and biliary tract surgery [20], cholangiocarcinoma [21] and SCF.

SCF may occur because of intrahepatic abscess, necrosis or perforation of the gallbladder, or other inflammation of the biliary tree [22]. However, SCF is usually a complication of acute suppurative cholecystitis associated with cholelithiasis [23].

SCF is extremely rare today, but this was a known complication of the biliary tract disease in the past. Thilesus was the first to report a case of SCF in the year 1670. Incidence of SCF has significantly gone down in the last century because of the antibiotics and surgical management of gallstones. Henry & Orr encountered only 36 cases of cholecystocutaneous fistula between 1890 and 1949 [24].

Chronic obstruction due to calculus or tumor mass leads to increased intra-luminal pressure, with secondary decreased blood perfusion and lymphatic drainage, mural necrosis and perforation of the wall. This may lead to generalized peritonitis or abscess formation, with internal or external biliary fistula formation. A localized abscess may penetrate the anterior abdominal wall and may expel the contents outwards [24].

In SCF, the abscess is walled off and penetrates the abdominal wall progressively to expel the contents from the area of least resistance or shortest track [18]. There were reported cases in which the external outlet of the fistula was situated on the scars of previous laparotomies or old surgical scars from surgical drainage [25] (or SCF presenting through an abdominal scar mimicking a post-operative scar [26]. In our case, the anterior abdominal wall was not weakened by a previous laparotomy scar.

Right hypochondrium is the most common site of external opening, but fistula opening may be seen in the left hypochondrium, umbilical region [27, 28], right lumbar region, right iliac fossa and in the gluteal region [29], epigastrium [30] – a location more rarely reported, like in our case.

The main risk factors for gallbladder cancer are cholelithiasis (the risk seems to correlate with stone size [31]), obesity (through association with gallstones, with the increase of endogenous estrogens, or through the ability of fat cells to secrete inflammatory mediators [32], bacterial degradation of bile and chronic infections of the gallbladder, chemicals (pesticides, heavy metals and radiation) [33], hepatobiliary anomalies, porcelain gallbladder, diet [5], medications (oral contraceptives and methyldopa) [33]. Mutations in tumor suppressor genes and oncogenes (P53 and K-ras) have been found [34]. In literature, the most frequent cases of cholecystocutaneous fistula are related to infectious processes of gallbladder but just in one case of SCF, the gallbladder adenocarcinoma diagnosis was made. More likely, in our case gallbladder cancer (appeared as a complication after a long evolution of gallstone biliary disease) was associated with a neglected acute cholecystitis, in a diabetic patient, the infection itself having a major role in the fistulous tract development.

SCF typically presents in the elderly women. Most patients have a history of chronic biliary tract disease, with mild symptoms, but however patients generally do not report a previous distinct episode of acute cholecystitis [30], and this was also our case. History of painless discharge of bilious fluid, stones, or pus may be present. There may be inflammatory and color changes around the chronic sinus opening. A lump may be palpable underneath SCF due to gallbladder herniation or malignancy. The differential diagnosis can be made with infected epidermal cyst, discharging tuberculosis, pyoderma granuloma, chronic osteomyelitis of the ribs and metastatic cancer [18].

Ultrasonography (US) is the initial imaging investigation [23]. However, US cannot always visualize the fistulous tract. Hence, CT is recommended for all cases of unexplained abdominal wall suppuration or cellulitis [35] because specifically CT fistulography not only delineates the fistulous tract accurately, but it also provides sufficient information of the other abdominal organs [27]. In our case, US highlighted the fistulous tract.

Management of SCF includes broad-spectrum antibiotics, drainage of abscess and cholecystectomy with complete excision of the fistulous tract [36]. The patients with SCF are often elderly, with associated co-morbidities, and laparoscopic cholecystectomy may be a good option [37], but not in the case of neoplasm associated with lithiasis.

At the time of the fistula appearance, the disease is obviously in a fairly advanced stage and radical open surgery might be the only option. The intent of treatment is generally palliative and the overall outcome is dismal [22]. Chemotherapy has been used for palliation of unresectable disease associated with symptoms palliation [38].

In our case, the diagnosis of the gallbladder carcinoma was established only postoperatively, therefore the therapeutic act was tailored for complicated acute cholecystitis.

In establishing the diagnosis of gallbladder adenocarcinoma, the histopathological examination played the essential part. The histopathological aspects of tubular structures with varied sizes and shapes, present across all the cholecyst wall thickness reaching the peritoneal serosa, with numerous atypia cells, allowed the diagnosis

of tubular adenocarcinoma. We believe that the morphological and histological changes of the gallbladder wall are the expression of chronic cholecystitis in the presence of lithiasis as main determining factor and only secondary to the development to the adenocarcinoma, for which lithiasis is also a well established risk factor. The immunohistochemical examinations performed by us confirmed gallbladder cancer. Therefore, the positive expression of CA 19-9, Ki67, CK 7 and Muc5AC markers pleaded for the positive diagnosis of tubular adenocarcinoma. The intense positivity of Ki67 and Muc5AC markers is associated with a poor prognosis [39]. It is considered that the high quantity mucin secretion by the gallbladder epithelial cells favors the formation of gallstones, by the aggregation of the mucus and cholesterol immersion and biliary salts. The gallstones generate a chronic local inflammatory response that favors the onset of gallbladder cancer in time [40, 41]. Numerous studies showed that chronic inflammation is inexorably connected to malignant transformation, being a major factor involved in the carcinogenesis process. Chronic inflammation leads to the emergence of genetic mutations, mainly affecting the tumor suppressor genes (especially TP53 gene) or the oncogenes. In our study, the p53 protein expression was negative, which showed that this gene expression was not altered in the case of our patient.

Like other authors [1, 42, 43], we consider that biliary lithiasis is one of the major etiopathogenic factors that intervene in the triggering of biliary carcinogenesis processes, by inducing a chronic inflammatory process in the cholecyst. Our study showed the presence of high quantities of T- and B-lymphocytes, with a heterogeneous distribution in the cholecyst wall.

Moreover, we consider that biliary lithiasis, with minor clinical symptoms or without any clinical signs, diagnosed by imagistic techniques (especially abdominal ultrasound), should be surgically treated (cholecystectomy), due to the possibility of inducing a tumoral process.

Conclusions

SCF was the primary manifestation of biliary lithiasis and gallbladder neoplasm in a previously asymptomatic patient. The diagnosis of SCF due to acute suppurative cholecystitis associated with cholelithiasis was established after clinical examination and ultrasound. Cholecystectomy with excision of the fistula tract is carried out. The pathological examination highlighted tubular adenocarcinoma of the gallbladder, but the patient refuse the treatment further proposed and the follow-up program. SCF should be considered in a patient with chronic sinus on the abdominal wall, especially with a history of gallbladder disease.

Conflict of interests

No conflict of interests to declare.

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