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GALLBLADDER CARCINOMA - A SURPRISINGLY DIAGNOSIS

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ABSTRACT:
GALLBLADDER CARCINOMA IS FAR TO BE AN EXTREMELY RARE DIAGNOSTIC. IT REPRESENTS THE FIFTH LOCATION IN FREQUENCY ORDER FOR DIGESTIVE TRACT MALIGNANCY. IT IS MORE FREQUENT THAN CHOLANGIOCARCINOMA.
WE NOTICED RECENTLY (LAST YEARS) AN INCREASING NUMBER OF GALLBLADDER CARCINOMAS IN OUR CLINIC. MOST OF THEM ARE NOT DIAGNOSED PRE-OPERATIVELY. SOME CASES ARE INTRA-OPERATIVE SURPRISES AND SOME ARE EVEN POST-OPERATIVE SURPRISES FROM HISTOPATHOLOGY LAB.
THE ONCOLOGIC CORRECT SURGICAL TREATMENT ASSUMES A PRE-OPERATIVE DIAGNOSTIC, WHICH, UNFORTUNATELY, IS VERY RARE. SOME SPECIFIC CASES WITH AN ULTRASOUND RESULT SUGGESTING A TUMOR OF THE GALLBLADDER UNDERGO AN ABDOMINAL CT SCAN OR MRI THAT COULD CONFIRM THE DIAGNOSIS. THE MOST COMMON MISMATCH IS ACUTE CHOLECISTITIS.
IN THE LAST FIVE YEARS (2014-2018), WE TREATED IN OUR SURGICAL CLINIC 11 CASES OF GALLBLADDER CARCINOMA.

KEY WORDS: GALLBLADDER CANCER, SURPRISINGLY HISTOPATHOLOGICAL FINDING

INTRODUCTION

The most known predisposing risk factors include cholelithiasis, chronic biliary infections, primary sclerosing cholangitis, and porcelain gallbladder[10]. The exact pathogenesis mechanism remains unclear, although it is supposed that some carcinogens may appear in conditions causing biliary stasis. Another cited mechanisms are malignant degeneration of metaplastic changes after chronic inflammation or mechanical mucosal damages caused by a prolonged lithiasis[11].

In cases of suspected gallbladder disease, ultrasonography is often the first imaging investigation, because of its relatively low cost, widespread availability, non-invasivity and non-iradiating caracteristics[12]. Ultrasound can easily diagnose a big tumor, an advanced stage, but could hard differentiate early lesions from acute cholecistitis with wall thikening.

Approximately 2% of patients with gallbladder carcinoma are diagnosed incidentally at histopathology after cholecystectomy is performed for cholelithiasis, cholecystitis, or biliary dyskinesia[13].

MAIN TEXT

We did a retrospective and descriptive study. We collected the data from patients charts and operatory registry. We studied a 5 years-period, from 1.01.2014 to present and we analysed the

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cases with gallbladder carcinoma confirmed by histopathological exam. There were 11 patients operated in our Clinic, included in our study.

There were 7 women and 4 men, that chimed with literature data, showing a higher incidence in women. The mean age was 67.4 years (73.6 for women and 56,6 for men). The onset of gallbladder carcinoma was more precocious in men. Worldwide gallbladder cancer affects females 2-3 times more commonly than males[14].

All the patients presented at emergency room for abdominal right upper quadrant pain, nausea and vomiting. Every patient included in study had an abdominal ultrasound at the admission time. The admission diagnostics were:

- in 5 cases acute acalculous cholecystitis;
- 4 cases of gallstones with acute cholecystitis;
- 2 cases of gallbladder carcinoma suspicion, but not a confirmed diagnosis. (Chart 1)

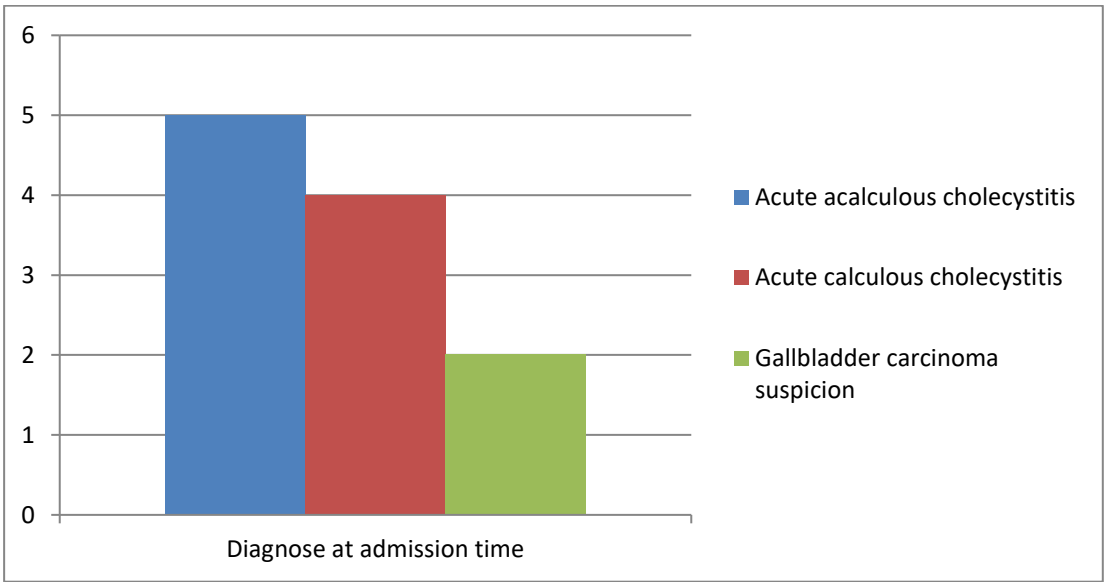

Chart 1. Diagnose at admission time

Wall thickening of the gallbladder was present in all cases at ultrasonography (Figures 1 and 2). The differential diagnosis should also be made with some hepatic affections, in some hepatic or systemic diseases, that could have a quite similar ultrasound findings[15].

[14] Shaffer EA. *Gallbladder cancer: the basics.* Gastroenterol Hepatol (N Y) 2008;4:737–741

[15] Draghici T, Negreanu L, Bratu O, Tincu R, Socea B, Iancu M, Stanescu AM, Diaconu C. *Liver abnormalities in patients with heart failure.* Arch Balk Med Union, 2018, 53(1): 76-81; Paraschiv B, Dediu G, Iancu A, Bratu O, Diaconu C. *Superior vena cava syndrome.* Arch Balk Med Union, 2017, 52(1): 39-43; Diaconescu D, Stoian Pantea A, Socea L, Stanescu AM, Iancu M, Socea B, Pituru S, Bratu O, Diaconu C. *Hepatorenal Syndrome: A Review.* Arch Balk Med Union, 2018, 53(2): 239-245

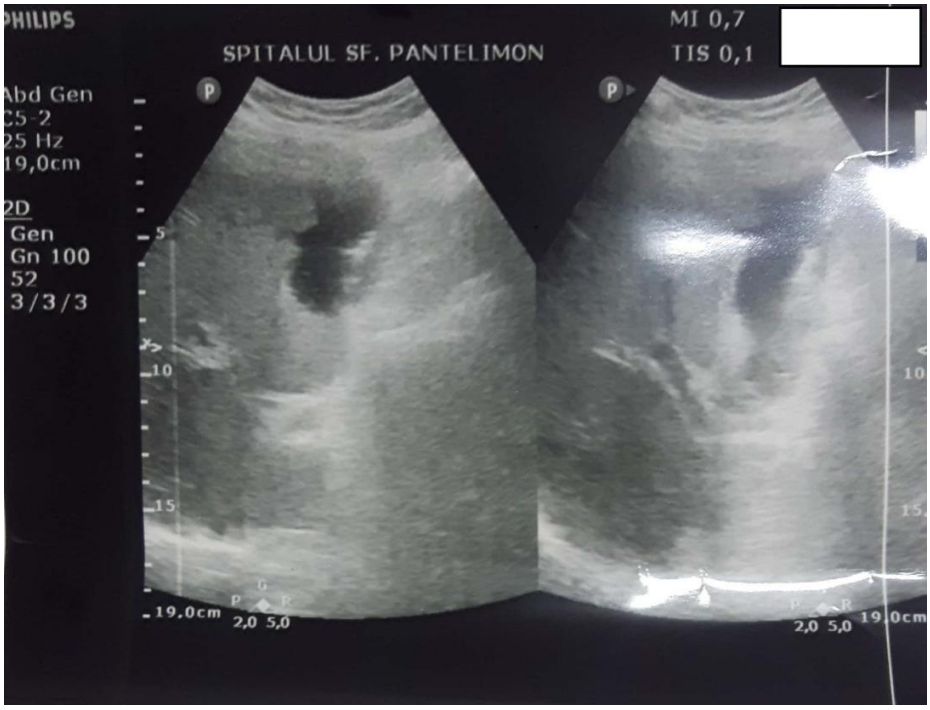

Figure 1

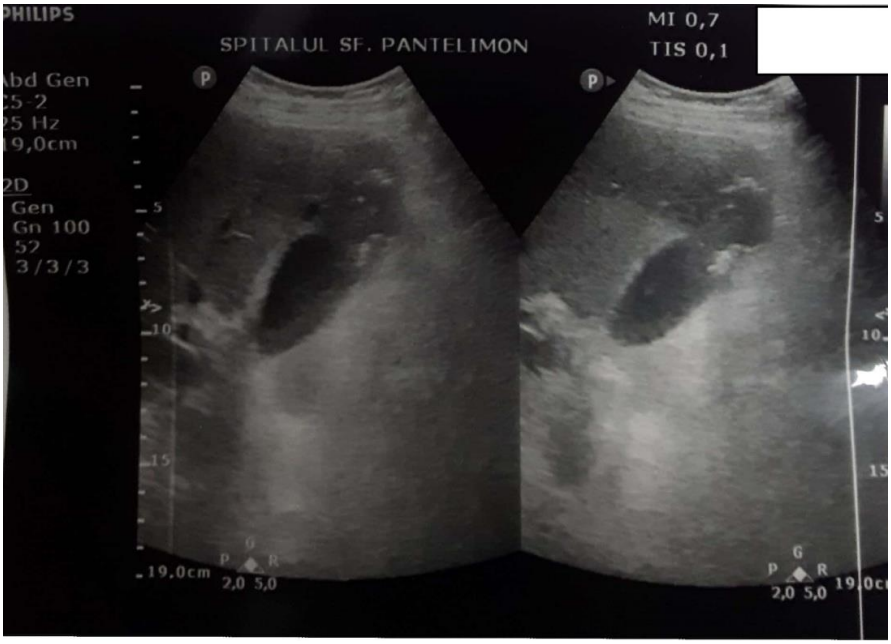

Figure 2

Figures 1 and 2. Asymmetrical and diffuse wall thickening in gallbladder carcinoma

There was a diffuse thickening in 9 cases and asymmetric one in the other 2, diagnosed as suspicion of gallbladder carcinoma. According to literature data, gallbladder carcinoma may

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present as focal or diffuse asymmetric wall thickening in 20– 30% of cases[16]. We had a 100% sensitivity of wall thickening in gallbladder carcinoma, but the specificity of this finding is, obviously, low, being the primary ultrasound description for acute cholecystitis. Gallbladder wall thickening can have mutiple differential diagnosis, including acute and chronic cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis, as well as diffuse hepatic or systemic diseases such as acute hepatitis, portal hypertension, and congestive heart failure[17].

We usually recommend cholecystectomy in acute acalculous cholecystitis, although there is currently no consensus with regard to the use of cholecystectomy or percutaneous cholecystostomy as the therapy of choice for this pathology[18]. But, nonsurgical management may also be a good therapeutic option.

Acute acalculous cholecystitis is traditionally known to occur in critically ill patients and to have a poor prognosis[19]. Diabetes mellitus, malignant disease, abdominal vasculitis (like Takayashu[20]), congestive heart failure, cholesterol embolization, shock, and cardiac arrest have been associated with it. So, whenever we have this diagnosis in young age and otherwise healthy patients, we have to take into account also the diagnosis of gallbladder carcinoma. Acute acalculous cholecystitis at young age may also be a sign of an infectious disease, like leptospirosis[21].

The two patients that showed a suspicion of gallbladder carcinoma on abdominal ultrasound, underwent CT scan, that confirmed the suspicion, but could not certify the diagnosis. Even computer tomography is not pathognomonic for diagnosis. In some cases, the images could be confused with acute cholecystitis (Figures 3 and 4). Thus, the histopathologically exam remains salutary.

[16] Franquet T, Montes M, Ruiz de Azua Y, Jimenez FJ, Cozcolluela R. *Primary gallbladder carcinoma: imaging findings in 50 patients with pathologic correlation.* Gastrointest Radiol 1991; 16:143–148

[17] Corvera CU, Blumgart LH, Akhurst T, et al. *18Ffluorodeoxyglucose positron emission tomography influences management decision in patients with biliary cancer*. J Am Coll Surg 2008; 206:57–65

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[19] Gu MG, Kim TN, Song J, Nam YJ, Lee JY, Park JS. *Risk factors and therapeutic outcomes of acute acalculous cholecystitis.* Digestion. 2014;90(2):75-80. doi: 10.1159/000362444

[20] Socea, Bogdan, Carâp, Alexandru C., Socea, Laura I., Dimitriu, Mihai, Bratu, Ovidiu G., Diaconu, Camelia C., Dumitrescu, Dan, Constantin, Vlad D. *Acute ischemic cholecystitis in Takayasu's syndrome – a rare finding.* Arch Balk Med Union, 2018, 53(2): 293-6

[21] Castelijn DAR, Wattel-Louis GH. *An acute acalculous cholecystitis in a returned travel couple.* PLoS Negl Trop Dis. 2018;12(3):e0006177. Published 2018 Mar 8. doi:10.1371/journal.pntd.0006177

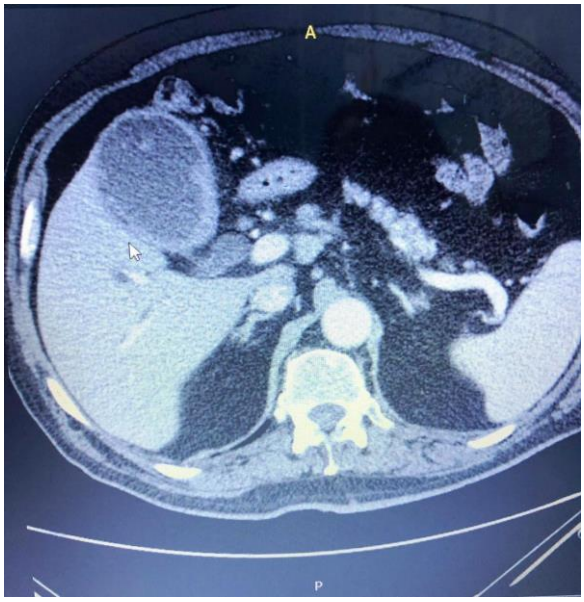

Figure 3

Figure 4

Figures 3 and 4. CT findings in gallbladder cancer could hardly differentiate between acute cholecystitis and carcinoma

In literature, some cases of gallbladder carcinoma associate another locations of cancers, like in Lynch II familial syndromes, with a family predisposition[22].

[22] Hemminki K, Li X. *Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden.* Gut. 2003;52:592–596

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A multidisciplinary discussion with medical oncologists, radiation oncologists, and surgeons is necessary to determine the optimal treatment approach for each patient. Surgical resection offers the best chance for a long-term cure. The prognosis of the disease is poor. The lack of a serosal layer of gallbladder adjacent to the liver thus enabling hepatic invasion and metastatic progression is one of the major cause of its miserable prognosis[23].

Without a confirmed diagnostic of carcinoma, the surgical intervention was only cholecystectomy in all 11 cases (8 laparoscopically and 3 open procedures - 2 first option and one conversion in a difficult case). The outcome seemed to be poor. 3 patients died in the first year and another 5 presented with spread disease (metastatic disease) in the first year of evolution.

The histopathological exam confirmed, in our series, adenocarcinoma of the gallbladder in all cases, alternating with plots of mucosal zones presenting severe and mild dysplasia and carcinoma in situ. Differentiation degree (G) can be seen in Chart 2. 5 of 11 cases presented carcinomatous transformation of Mascagni lymph node. After the confirmation result, all patients underwent oncology consult and adjuvant chemotherapy.

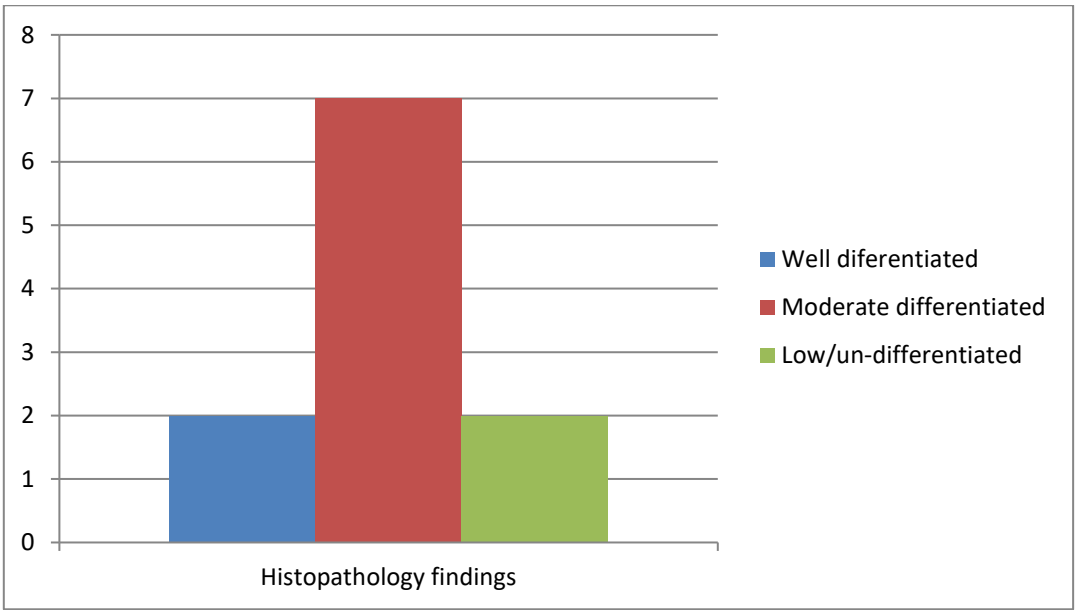

Chart 2. Grades of differentiation on histopathology exams of specimens of adenocarcinomas

Carcinogenesis in gallbladder carcinoma implies passing through a series of transformations before reaching an invasive malignancy. Exposure to carcinogens converts normal gallbladder epithelium to metaplasia, which subsequently forms dysplasia, carcinoma in situ (CIS), and finally proceeding to invasive carcinoma in about 15 years of evolution[24]. Resident gallstones for years in

[23] Hundal R, Shaffer EA. *Gallbladder cancer: epidemiology and outcome.* Clin Epidemiol. 2014;6:99–109
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the gallbladder give rise to chronic cholecystitis, which increases the risk of gallbladder cancer formation. More than 90% of patients with gallbladder carcinoma show also dysplasia and CIS on histopathology specimens[25]. Frequent, there is an unusual asymmetric thickening of the gallbladder wall with infiltration to surrounding structures in gallbladder cancer. Most cases reported in literature as carcinomas of gallbladder are adenocarcinomas (80%-95%). Adenocarconomas can further be papillary, tubular, mucinous, or signet cell type. Some other histopathologically types, which are present in very low frequency include: squamous cell carcinoma (16%), undifferentiated or anaplastic carcinoma (2%-7%), and adeno-squamous carcinoma (1%-4%)[26]. We did not find such rare types in our series. The most frequent location of gallbladder carcinoma is the fundus (60%), followed by the body (30%), and on the third place, the neck region (10%). This is in slight contradiction with the theory of mucosal irritation produced by gallstones, which should be maximal in the neck region. But maximum contact time is in the fundus area, and the product between contact time and firmness of contact is more disadvantageous here.

CONCLUSION

The clinical and radiologic (ultrasound, CT scan) detection of gallbladder carcinoma at a curative stage remains problematic. Gallbladder cancer seems to have a high incidence in our country. Gallbladder cancer is also found in high frequency in Eastern Europe include Poland (14/100000 in Poland), Czech Republic, and Slovakia[27]. It seems to have an unusual geographic distribution worldwide with substantial geographic variation. In a study, it was estimated that 26% of gallbladder cancers are familial, which explains association with another locations like non-polyposis colorectal cancer - Lynch II[28].

Most cases remain surprisingly findings of histopathology results, so, the patients could not achieve a primarily specific surgical intervention. Most of them underwent only cholecystectomy for an acute cholecystitis, which is the most frequent misdiagnosis. Thus, the post-operative outcome is poor, with majority of patients having spread disease at one year after surgery, in spite of complementary adjuvant chemotherapy.

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