Case report **UDC: 616.366-006.5-076**

INTESTINAL TYPE OF VILLOUS ADENOMA OF GALLBLADDER

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Precancerous conditions in the gallbladder are still a matter of interest of numerous investigators, but reliable and definite attitude is not jet available. Particularly, many regenerative/reparative changes during inflammation and cholelithiasis in the gallbladder cannot be classified with certainty as lesions which precede malignant alteration. However, it is considered that metaplastic-dysplastic changes, which appear in mucosa and can lead to malignant neoplasia, are one of the ways of cancer morphogenesis. This way is considered as non-neoplastic way of gallbladder carcinoma development. The other way of cancer genesis goes through precancerous neoplasia, i.e. adenoma.

The aim of this article was to, upon a polyp found in the gallbladder after cholecystectomy in a 70-year-old patient, determine one of the ways of gallbladder carcinoma morphogenesis.

Cholecystectomy was done after ultrasound finding of the gallbladder polyp. Macroscopically and microscopically, it was the intestinal type of villous adenoma with the third degree epithelial dysplasia, which designates that this adenoma has reliable signs for precancerous lesion, and confirms the adenoma-carcinoma sequence theory, already characteristic for large intestine, the opinion the authors agree with. *Acta Medica Medianae 2010;49(3):50-54.*

Key words: *adenomas, carcinomas, gallbladder, precancerous conditions*

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Introduction

It is considered that the gallbladder adenomas are rare polypoid, well-defined, benign neoplasms of mucosa epithelium with malignant potential, and that they can appear in any other parts of the gastrointestinal tract (GIT) (1). Benign lesions range from 0,3% to 0,5% in gallbladders after cholecystectomy due to chronic cholecystitis and calculosis (2,3), while the frequency of villous adenoma in the gallbladder on autopsy series has been only 0,08% (4). However, there are opinions that adenomas are the most frequent neoplasms in the gallbladder (5). The prevalence is higher in females compared to males, appearing from the age of 17 to 73, mostly in the elderly female patients (6,7). Rare do they give symptoms, and sometimes are accidentally detected by ultrasound or in the gallbladder after cholecystectomy (6). It is hard to differentiate them from inflammatory reactions with mucosal hypertrophy and reactivation of the tissue. However, if they appear in the gallbladder neck or its duct, they can give clinical presentation obstruction.

Adenomas can be totally asymptomatic, rarely giving symptoms related to the gallbladder neck, and can be noticed as attached radioluscent defect on cholecystograms. Nowadays, most of them are identified by ultrasound or CT (1). Usually, they are solitary, peduncular or sessile and with the radius smaller than 2cm (8,9), although some of them were up to 4,5cm in size (1); they are rarely multiple (10). They most frequently appear in the corpus, then fundus and neck of the gallbladder (10), but can be found in different dispositions (11,12). As has been noticed, adenomas are usually associated with cholelithiasis and inflammation (8,9,13,14), almost in 80-100% cases, because the presence of calculosis is considered as a factor for development of precancerous lesions of the gallbladder mucosa (13,15-18).

According to macroscopic appearance of their growth, adenomas of gallbladder can be: tubular, papillary or villous and tubulopapilary and look like adenomas of the large intestine (19). According to histological characteristics they can be classified in: pyloric glandular, intestinal and billiary type (6). Tubular adenomas grow from mucosa as violet color firm elevations, until papillary type has cauliflowers appearance. Most of them consist of pyloric type of glands, while others resemble those found in the large intestine, and therefore are considered as the manifestation of metaplastic changes of mucosa (20).

On the other hand, carcinoma of the gallbladder is also rare among white population and accounts for only 3% of all GIT neoplasms (21). However, in Chile, where it is most frequently

found, in Mexico, India and Japan, there is a high incidence of gallbladder carcinoma, which can be up to 15% of all cholecystectomies (22,23).

Aim

The aim of the paper was to, in a broad presentation of etiopathogenesis of polyps and carcioma of gallbladder, and upon our finding, join one of the attitudes if benign adenomas of gallbladder can be premalignant lesions.

Case report

The female patient O.B, 70 years old, felt in the past several weeks intermittent compression pain under the right upper quadrant of the abdomen. After ultrasound finding of a gallbladder polyp, cholecystectomy was performed. Macroscopically, the gallbladder was 8,5x3cm in diameter, with smooth serosa, containing little mucus in the lumen; mucosa was almost all atrophic, except in the vicinity of the neck region were it was impregnated with cholesterin pigment. In the middle part of the corpus of the gallbladder, a nipple-like elevation rises, of whitish color, dimensions 12x8x6mm. After tissue samples were taken from the polyp of the gallbladder, material was processed to paraffin form whose sections were stained with hematoxilin-eosin. Histologically, we noticed chronic phlegmonous cholecystitis in the area of atrophic gallbladder. The polyp was of sessile type, i.e. a large base attached to mucosa, villous with numerous twisted villi (Figure 1), which are covered with dysplastic cells with intestinal phenotype and third degree dysplasia i.e. intraepithelial carcinoma (Figure 2). Polyp cells distributed along the villi, stratified, with irregular nucleocyoplasmatic rate due to nuclei, which are elongated and hyperchromatic; cytoplasm reduced (Figure 3). In mucosa, in the vicinity of adenoma, there were several little tubular-type polyps, with micro papillary architecture and low-grade epithelial dysplasia (Figure 1); in their proximity we noticed a lot of lymphocyte pseudonodules (Figure 4).

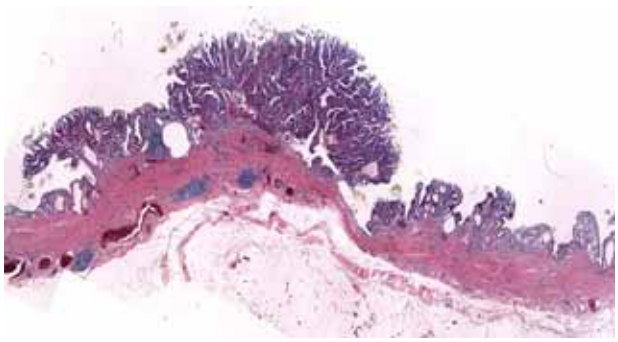

Figure 1. Sessile polyp of cauliflower appearance lies on a broad basis in the gallbladder mucosa, accompanied bya lateral string of micropapillary tubular adenomas. HE,magnification, panoramic view

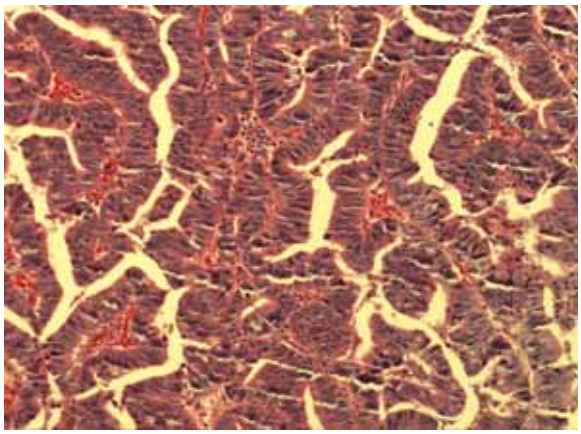

Figure 2. Twisted and branched villi with third-degree epithelial dysplasia. HE, 150x

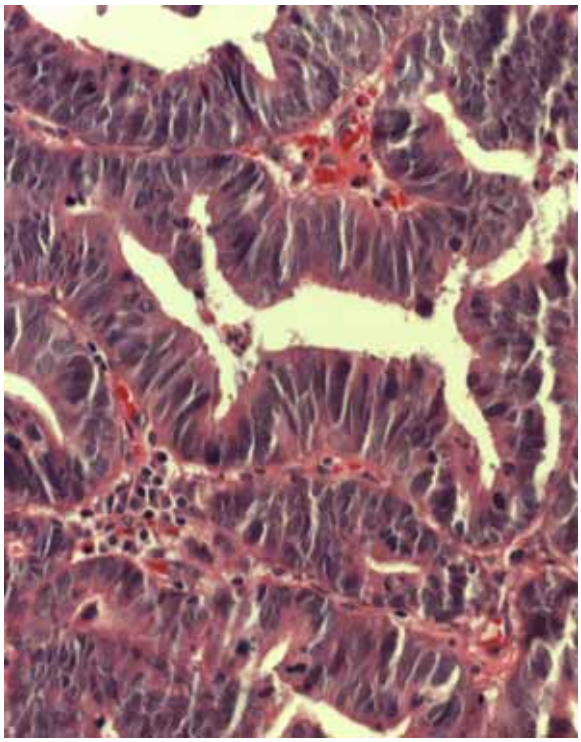

Figure 3. Detail from Figure 2. Villous structures lined with markedly dysplastic cells of hyperchromatic, elongated nuclei reaching the top of the cells HE, 200x

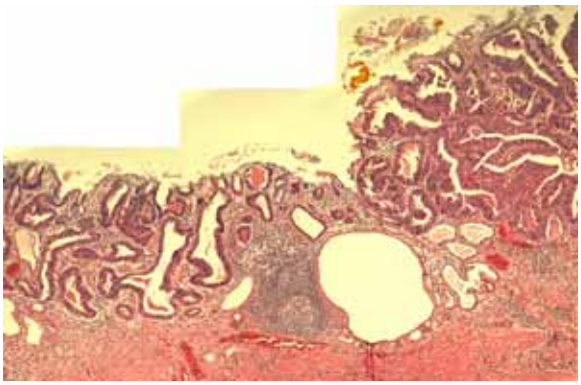

Figure 4. The edge of the polyp covered with micropapillary tubular adenomas of low-degree dysplasia: chronic lymphocyte singular or follicular joining. HE, 100x

Discussion

The presented case report is interesting because of a rare appearance of the gallbladder adenoma; at the same time, it is a motive for considering a possibility that adenoma appearance is a precancerous state. In high percentage of cases, the majority of investigators find cholelythiasis in the gallbladder carcinoma, even up to 100% of cases, which is the reason why calculosis is considered as a sole reason for cancer development (13,15-17).

However, there are opinions and evidences that calculosis is not the only reason for gallbladder carcinoma development. In many hereditary diseases, especially of digestive tract, there has been noticed an increased frequency of gallbladder polyps as well as increased risk for extra intestinal malignancy (24). The existence of synchronous adenocarcinoma of the colon, gallbladder and appendix is very interesting in a female patient 79-year-old, which is very rare but possible in elderly patients. In the gallbladder of this patient, many calculi were found as well as the inflammation. In the colon, at the same time a polyp was found. In the cases presented so far, there have been no genetic predispositions in families of the patients (25). Malt and Ottinger (1973) supposed that the interaction with metil cholantren is very possible (26). Also, some investigators have considered that all three carcinomas are initiated by the same "trigger", and that, as opposed to the widespread opinion, calculosis of the gallbladder does not have the main role in the gallbladder carcinoma development (9,27). Cases of villous adenoma of the gallbladder associated with acromegaly have been noticed, too (1). Also, there is a possibility of adenoma appearance in hamartomatous changes (24). Some investigators think that adenomas, which are rare in the gallbladder, are of tubular type and have potential for development of malignant alteration (15), while others consider polyps and adenomas as benign lesions (28).

There are various hypotheses about the appearance of adenocarcinoma. According to one of them, the sequence is as follows: from epithelial hyperplasia to atypical hyperplasia or dysplasia to carcinoma in situ (in Mexico) and at the end to infiltrative adenocarcinoma of the gallbladder (12), while others believe that dysplasia rises form metaplastic epithelium, especially gastric antral metaplasia as tumor precursor, which is frequently found in chronic inflammation of the gallbladder (11,29). Some of them insist of the following sequence: epithelial regeneration, metaplasia, which can be incomplete and complete, trough dysplasia to carcinoma of the gallbladder (commonest way); there is a close association between high-degree dysplasia and metaplastic epithelium near infiltrative carcinoma (21). Thus, it is considered that there exist two primary morphological ways of cancerogenesis. One of them has already been mentioned: from non-neoplastic states, i.e. de novo carcinomas without adenomas, in which cancer cells rise from clonal expansion of dysplastic cells (30), i.e. the sequence adenoma-carcinoma in the gallbladder do not exist (29,31). Other way of cancerogenesis is from precancerous neoplasia or adenoma i.e. over adenoma-carcinoma sequence (32).

Kramford (1994) think that about 10% of gallbladder adenomas give the picture of carcinoma in situ and that they are very closely connected with developing of carcinoma like these in digestive tract (18). Other authors believe that most of the gallbladder carcinomas rise on pre-existing adenomas because in all carcinomas they found the remnants of adenomas (2,33). Another group of authors, in series of 32 adenomas, found that only two of them made progression to invasive carcinomas (34). Jesurum, Albores-Saaveda (1996) found the foci of carcinoma in situ in approximately 9% of gallbladder adenomas. They believe that prevalence of adenoma is not high in geographic regions where cholelithyasis is endemic, unlike carcinoma which is present in higher percent. These authors noticed that adenomas are less frequent than carcinomas, thus stating that the assertion that here exists the adenoma-carcinoma sequence, like in the large intestine, is quite unattainable (6).

Histological and genetic changes in malignant transformation of gallbladder adenoma have not been clearly defined yet (30,34). Therefore, APC mutation is not present in the gallbladder carcinoma without adenomatous component (32). Kim et al. (2001) consider that genetic changes K-ras, p53 and p16 are important steps in malignant changes of dysplasias (30).

In our case, intestinal type of sessile adenoma, with villous properties, high-degree dysplasia (Ca in situ), and microadenomatous satellites around the main adenoma were found, also reported by other authors (22), contributing to the theory adenoma-carcinoma sequence. However, it is hard to deny that adenomas are not caused by inflammatory process and calculosis, which are often associated with their occurrence. We can accept the possibility of billiary tract intestinalisation occurrence, like small intestine intestinalisation in the large bowel. It is possible that the cause of adenoma and carcinoma development is the same, and that intestinal type of adenomas certainly progress into carcinoma, which can be seen on epithelial high-degree dysplasia in our case. The thesis about adenoma-carcinoma sequence was especially suggested by Kozuka et al. (1982) having examined 1.605 gallbladder carcinomas, noticing the presence of adenomatous fields in carcinomas and malignant fields in the gallbladder adenoma. They postulate that the transformation from adenoma to carcinoma lasts from five to ten years (35). For cancer alteration, undoubtedly important factors, also reported in the large bowel

carcinoma, are: age (over 60), size of adenoma (over 1cm), sessility and villosity.

Conclusion

Adenoma of the gallbladder in the 70-year-old patient, histologically of intestinal type and villous, with third-degree dysplasia, on field of chronic inflammation and cholesterin calculosis is a proof that carcinoma of the gallbladder can be developed from polyp following the principles of adenoma-carcinoma sequence which can be valid here as well as in the case of the large bowel carcinoma.

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VILOZNI ADENOM INTESTINALNOG TIPA ŽUČNE KESE

Bratislav Petrović, Aleksandar Petrović, Vesna Živković, Malina Mitić i Vanja Petrović

Prekancerozna stanja žučne kese i dalje predstavljaju predmet interesovanja istraživača u ovoj oblasti ali pouzdanog i definitivnog stava o njihovoj etiopatogenezi još uvek nema. Naime, mnoge regenerativno-reparativne promene u toku zapaljenja i holelitijaze u žučnoj kesi ne mogu se sa sigurnošću uvrstiti u lezije koje prethode malignoj alteraciji. Međutim, smatra se da bi promene koje se javljaju u sluzokoži, a metaplastično-displastičnog su tipa i mogu dovesti do maligne neoplazije, mogle biti jedan od puteva morfogeneze kancera. Ovaj oblik se smatra neneoplastičnim načinom nastanka kancera žučne kese. Drugi put kancerogeneze bio bi preko prekancerske neoplazije, tj. adenoma.

Cilj rada bio je da se na osnovu patohistoloških karakteristika polipa nađenog u holecistektomisanoj žučnoj kesi žene stare 70 godina, opredelimo za jedan od puteva morfogeneze kancera žučne kese.

Holecistektomija je urađena na osnovu ultrasonografskog nalaza polipa u žučnoj kesi. Makroskopski i mikroskopski je utvrđeno da je reč o viloznom adenomu intestinalnog tipa sa displazijom epitela trećeg stepena, što jasno ukazuje da se radi o adenomu sa pouzdanim znacima prekanceroze. Ovo potvrđuje teoriju adenoma-karcinoma sekvence, karakteristične za debelo crevo koja potvrdu nalazi i u ovom radu. *Acta Medica Medianae 2010;49(3):50-54.*

Ključne reči: *adenom, karcinom, žučna kesa, prekancerozno stanje*