Hyperplasia, metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis – a morphologic study

MANUELA STANCU1, IRINA-DRAGA CĂRUNTU1, SIMONA GIUŞCĂ2, GIOCONDA DOBRESCU1

1) Department of Histology, “Gr. T. Popa” University of Medicine and Pharmacy, Iassy
2) Ist Surgery Clinic, “Sf. Spiridon” University Hospital, Iassy

Abstract
The aim of the study was to analyze the association between chronic cholecystitis, premalignant lesions and gallbladder cancer. The group consisted in 3901 cases of cholecystectomies, diagnosed as acute cholecystitis (250 cases – 6.4%), chronic cholecystitis (3619 cases – 92.8%) and gallbladder carcinoma (32 cases – 0.8%). Chronic cholecystitis associated premalignant lesions as follows: hyperplasia in 124 cases (7.8%), metaplasia in 86 cases (5%) and dysplasia in 10 cases (0.4%). Only in nine cases, the diagnosis of gallbladder carcinoma was formulated presumptively, before surgery; for the other 23 cases this diagnosis was established after the pathologic exam on the cholecystectomy piece. In the areas adjacent to the neoplastic proliferation, premalignant lesions (hyperplasia, metaplasia, dysplasia) were identified in 34.4% cases. The identification of premalignant modifications in the morphologic background of chronic cholecystitis is an argument in favor of the metaplasia–dysplasia–neoplasia sequence and justifies recent recommendations for the performing of colecystectomy.

Keywords: chronic cholecystitis, hyperplasia, metaplasia, dysplasia, gallbladder carcinoma.

Introduction
The diseases of the gallbladder represent one of the most frequent medical situations requiring surgical intervention. Cholelithiasis and chronic cholecystitis affect approximately 10% of the adult population in USA, where approximately 500 000 cholecystectomies are performed every year [1].

Frequently, the chronic cholecystitis presents a large range of associated lesions such as cholesterolosis, muscle hypertrophy, parietal fibrosis, polypoid and adenomatous proliferation of mucous glands, metaplasia, hyperplasia and dysplasia – the last three lesions being unanimously recognized as precursor lesions with cancerous potential. For the carcinoma of the gallbladder, developed on a background of cholelithiasis [2, 3] and chronic cholecystitis [4–8], the early diagnosis is difficult to obtain due to the absence of specific symptoms [9, 10].

Recent studies [6, 11–13] report results obtained on series of cholecystectomies, insisting on the significance of the precursor lesions, as well as on the possibility of accidentally discovering a gallbladder cancer.

Tarcoveanu et al. [13] plead for a more firm and precocious indication of cholecystectomy in cholelithiasis, with consequent results in the diminishing of gallbladder cancer incidence and/or diagnosis in incipient stages.

The aim of our study was to realize a retrospective analysis on the gallbladder pathology diagnosed between 2005 and 2006 in the Pathology Department of “Sf. Spiridon” University Hospital Iassy, focusing on the association between lithiasic and non-lithiasic chronic cholecystitis, malignant precursor lesions and gallbladder cancer.

Material and methods
The study group consisted in 3901 cases of cholecystectomies, performed in the Surgical Clinics of the “Sf. Spiridon” University Hospital Iassy, in a two-year interval (2005 and 2006).

The pathologic exam of the surgical pieces was performed in the Pathologic Department of the hospital. After the macroscopic examination, the fragments were fixed, processed by paraffin embedding and sectioned at 4 microns.

The microscopic specimens were colored with routine (Hematoxylin–Eosin) and special stains (trichrome van Gieson and Alcian blue).

Results
Global characterization of the study group
In the analyzed series, the pathologic exam of the 3901 cases was acute cholecystitis in 250 cases (6.4%), chronic cholecystitis in 3619 cases (92.8%) and gallbladder carcinoma in 32 cases (0.8%).
In the chronic cholecystitis cases, the age classification revealed prevalence in the fifth decade of life (1111 cases – 30.7%) followed by the sixth and fourth decade (740 cases – 20.4% and 652 cases – 18%). The seventh and third decade presented comparable values (440 cases – 12.2% and 439 cases – 12.1%, respectively).

The female sex was predominantly involved (2874 cases – 79.4%) as opposed to the male one (745 cases – 20.6%).

From the point of view of the histologic type, the most predominant were ulcerated chronic cholecystitis (1597 cases – 44.1%), followed by nonspecific cholecystitis (928 cases – 25.6%), erosive cholecystitis (316 cases – 8.7%), sclero-atrophic cholecystitis (264 cases – 7.3%) and polypoid cholecystitis (167 cases – 4.6%). 289 cases (8%) had morphologic features characteristic for associated acute inflammation. In smaller proportions there were also present gangrenous (46 cases – 1.2%), granulomatous (four cases – 0.1%) and ulcero-hemorrhagic (eight cases – 0.2%) forms.

The 32 cases of gallbladder carcinoma with a prevalence of the female sex (26 cases – 81.3%) over the male one (six cases – 18.7%) were present in the sixth and seventh decade of life; there was a case under 20, one case in the fourth decade and six cases in the fifth decade.

From the point of view of the histologic type, well-differentiated carcinoma prevailed (11 cases – 33%), followed by low-differentiated adenocarcinoma (six cases – 19%); moderately differentiated, mucinous and squamous forms were diagnosed in four cases each (13%) and papillary carcinoma in three cases (9%).

**Association between chronic cholecystitis and premalignant lesions**

Chronic cholecystitis associated premalignant lesions as follows: hyperplasia in 124 cases (7.8%), metaplasia in 86 cases (5%) and dysplasia in 10 cases (0.4%). The hyperplastic lesions were of the villous type, presenting papillary mucous folds (Figure 1), covered by simple columnar epithelium with basal nuclei (91 cases – 73.3%) and of the spongious type with coalescent villi organizing a glandular pattern (33 cases – 26.7%).

The metaplastic lesions were predominantly of the pyloric type (72 cases – 83.7% from the total of metaplastic cases), characterized by structures similar to the pyloric glands in the lamina propria (Figure 2), followed by the intestinal type (14 cases – 16.3%), characterized by the presence goblet cells, and enteroctyte-like cells (Figure 3).

The dysplastic lesions, identified in erosive, ulcerated and follicular chronic cholecystitis were of the simple (five cases – 50%), moderate (three cases – 30%) and severe type (two cases – 20%) (Figure 4). Apart from these 10 cases, 17 cases of pyloric metaplasia associated aspects of epithelial dysplasia, involving either an area of the gland (Figure 5) or the entire gland.

**Gallbladder carcinoma**

We must stress the fact that only in nine cases (28.1%) the diagnosis of gallbladder carcinoma was formulated presumptively, before surgery; for the other 23 cases (71.8%) this diagnosis was established after the pathologic exam on the cholecystectomy piece.

In 11 cases (34.4%), in the areas adjacent to the neoplastic proliferation, premalignant lesions were identified: hyperplasia, metaplasia, dysplasia.

Well-differentiated adenocarcinoma was characterized by the presence of glandular or tubular structures (Figure 6), sometimes with acidophilic secretion within the lumen, infiltrating the gallbladder wall. In association there were observed vascular tumoral embolies, perinervous invasion and, in one case, partially rechannelized obliterating arteritis.

The cases with moderately differentiated adenocarcinoma presented, together with glandular structures, nests of tumoral cells and/or isolated tumoral cells. Located in a mucosa with massive ulceration on the surface or necrosis, the tumoral proliferation had a parietal invasive pattern (Figure 7).

A particular aspect was noticed in one case where, at some distance from the tumoral proliferation, there was an area of reepithelization of the ulcerated mucosa, with dysplastic modifications, as well as a giganto-cellular reaction of foreign body type organized on a necrosis background (Figure 8).

In the forms of low-differentiated or undifferentiated adenocarcinoma we identified masses of tumoral cells sometimes with drafts of glandular lumen, sometimes surrounded by a sclero-hyalin stroma. These tumoral masses presented numerous mitoses, atypical and monstrous cells (Figure 9).

Two of these cases presented nodular metastases with massive carcinomatous islands without glandular differentiation.

The mucinous adenocarcinoma cases were characterized by abundant mucus secretion, located within the glandular structures or accumulated in the extraglandular territories (Figures 10 and 11), compressing the carcinomatous masses; in association, there were identified “signet ring” cells (Figure 12).

The numerous tumoral lymphatic embolies justify the unfavorable prognosis, one of the cases developing nodular metastases. Although the primary tumor was mucinous, in the metastatic islands we observed a reduced mucus secretion.

In the cases of squamous cell carcinoma, the carcinomatous islands presented different degrees of keratinization (Figure 13), until the edification of keratin “pearls” (Figure 14). In some tumoral islands, we observed partial necrosis lesions and a polymorph inflammatory reaction.

At some distance from the tumor, on the mucosa surface we noticed areas of squamous metaplasia, with isolated aspects of malignant transformation (Figure 15), the metaplastic mucosa remnants being embedded in the carcinomatous islands. One of the cases associated perineural tumoral invasion, obliterating endarteritis lesions and perinevratitis.
Hyperplasia, metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis – a morphologic study

Figure 1 – Chronic cholecystitis with hyperplastic lesions (H–E, ×10)

Figure 2 – Chronic cholecystitis with pyloric type metaplasia (H–E, ×10)

Figure 3 – Chronic cholecystitis with intestinal type metaplasia (H–E, ×10)

Figure 4 – Chronic cholecystitis with severe dysplasia (H–E, ×10)

Figure 5 – Chronic cholecystitis: cholesterolosis, pyloric type metaplasia; dysplastic lesions in a metaplastic gland (H–E, ×10)
Figure 6 – Well-differentiated adenocarcinoma infiltrating the gallbladder wall (H–E, ×4)

Figure 7 – Moderately differentiated adenocarcinoma associated with ulceration and necrosis of the mucosa (H–E, ×4)

Figure 8 – Low-differentiated adenocarcinoma, gigantocellular reaction (H–E, ×20)

Figure 9 – Low-differentiated adenocarcinoma: atypical mitoses, monstrous cells (H–E, ×20)

Figure 10 – Mucinous adenocarcinoma with extracellular / extraglandular mucus (H–E, ×4)
Hyperplasia, metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis – a morphologic study

Figure 11 – Mucinous adenocarcinoma with mucus secretion in the lumen of the glands (Alcian blue, ×4)

Figure 12 – Mucinous adenocarcinoma: “signet ring” cells (H–E, ×20)

Figure 13 – Moderately differentiated squamous cell carcinoma with important extension in the gallbladder wall (H–E, ×4)

Figure 14 – Moderately differentiated squamous cell carcinoma: tumoral island with keratin “pearls” (H–E, ×20)

Figure 15 – Mucosa with squamous metaplasia and small areas of malignant transformation (H–E, ×20)

Figure 16 – Papillary adenocarcinoma: important proliferation forming villous structures (H–E, ×4)
The papillary adenocarcinomas were characterized by exuberant surface proliferation forming villous structures (Figure 16).

The tumoral cells also infiltrated the gallbladder wall in depth and were accompanied by tumoral lymphatic and blood vessels embolies and perineural invasion.

In one case, at some distance from the tumoral proliferation, the mucosa presented glandular ectasias with areas of pyloric metaplasia associated with intestinal metaplasia.

In the epithelium overlying these areas, with reepithelization aspects, or in some pyloric glands there were isolated lesions of moderate dysplasia.

5 Discussions

The chronic cholecystitis – cholelithiasis – gallbladder carcinoma relationship

Gallbladder carcinoma is on the fifth place as incidence in the gastrointestinal malignant tumors [14, 15]. Due to the occult evolution and the non-specific clinic manifestations, it is rarely diagnosed in its precocious stages. Frequently it is discovered fortuitously, during cholecystectomy performed for a chronic cholecystitis or cholelithiasis [16].

Even though the mechanisms of action have not been completely defined, it is unanimously accepted that these two pathologic conditions have an important role in the gallbladder carcinoma pathogenesis [17–19].

A short review of the literature permitted the comparison of our results with those of other teams/groups with similar preoccupations.

Beginning with the 80’s, numerous studies report the presence of premalignant lesions on cholecystectomy pieces [20], bringing into discussion the metaplasia–dysplasia–neoplasia sequence at the level of the gallbladder epithelium [21–24].

Pyloric metaplasia (of the antral or mucous glands) is the most frequent being identified in 66–84% of cholecystectomies [5, 25–27].

According to the literature [28], the pseudopyloric gland lobules are located in the lamina propria or they can form small nodules of the mucosa or polyps, often associated with hyperplastic lesions of the overlying mucosa. The last aspects were reported in the literature as sessile adenomas or as hyperplastic polyps [26, 29].

Pyloric metaplasia can be associated with intestinal metaplasia, present in 12–52% of the cholecystectomies [24, 25, 30] and/or with dysplasia foci [29].

Although the intestinal metaplasia always comprises goblet cells and less frequently Paneth and endocrine cells (20–50%) there are rarely observed absorbing cells with distinct brush ends [28].

The frequency of dysplasia in the cholecystectomy pieces varies from less than 1% [23, 31] to approximately 30% [21, 25, 27, 32] – 1.4–3.5–9.7% being severe dysplasias, labeled as carcinoma in situ [21, 22, 25, 27, 33, 34].

These differences are due to the population sample investigated and to the criteria used for the diagnosis.

Often the differentiation between a real dysplasia (neoplastic) from atypical epithelial hyperplasia in the case of cholecystitis can be difficult because of inflammation and ulceration [23].

Our results are situated, for the chronic cholecystitis-metaplasia association under the results reported in literature, only 5% from the total of cases presenting metaplastic lesions.

For the chronic cholecystitis-dysplasia association, the 0.4% corresponds to the lower limit reported in literature.

This data particularizing our group may be due to the extremely high incidence of ulcerated (44.1%) and erosive cholecystitis (8.7%) with important destructive lesions of the gallbladder mucosa.

It is possible that the ulcerative and erosive lesions, in their evolution, will have eliminated or hidden a preexistent morphologic background, including metaplasia and dysplasia foci, which cannot be distinguished anymore.

The analysis performed on a series of cholecystectomies (for cholelithiasis or cholecystitis) offer a clear image of the possibility do discover a gallbladder carcinoma most of the times advanced in its evolution. Nevertheless, the development of laparoscopic surgical techniques and the recommendation of cholecystectomy in all cases with a long evolution and general risk factors led to the significant diminish of the number of gallbladder cancer diagnosed in surgery [35].

From 3.5% gallbladder carcinoma in cholecystectomized patients, reported by Black, in 1980 [20], Silecchia et al., in 2002 [11] report 0.35%; this last study [11] included 3900 patients with laparascopic cholecystectomy, identifying 14 cases of carcinoma, from which only six were occult.

Dix FP et al. [12] perform a retrospective analysis on 1308 cholecystectomies between 1995 and 1999; 1249 cases presented lesions of chronic cholecystitis, 18 – acute cholecystitis and 16 gallbladder were extirpated during other interventions. In five cases (0.38%), there were noticed primary carcinoma lesions, the macroscopic aspects upon the opening of the gallbladder being characteristic for a malignant process. In a study on a group of 7695 cholecystectomies performed in eight years (1996–2004), Tarcoveanu E et al. (2005) [13] report 46 carcinomas of the gallbladder, representing 0.6%.

We must stress the fact that 3% of the cases with lithiasis developed cancer and that the diagnosis was established before surgery only in five cases. The results we obtained, respectively 0.8% gallbladder carcinoma intra-surgically diagnosed are in conformity with recent data from the publication mainstream, indicating less than 1% incidence.

High degree metaplastic and dysplastic lesions were identified near the carcinoma territories in 73–92% of cases [21–23, 33, 36].

The dysplastic modifications are almost always developed in the metaplastic mucosa, initially on the surface, then extending in the deep glands [21, 22, 37].
The results of our study do not concur with these reports, premalignant lesions of the hyperplasia, metaplasia or dysplasia type being discovered only in 34.4% of gallbladder carcinomas, in the areas near the neoplastic proliferation.

These differences are caused by the general characteristics of the groups investigated by different researchers.

Conclusions

The identification of premalignant modifications in the morphologic background of chronic cholecystitis is an argument in favor of the metaplasia–dysplasia–neoplastic proliferation. The cholecystectomy allows the discovery of occult carcinomas, resulting in the significant decrease of the number of gallbladder carcinomas diagnosed in advanced stages.

References


**Corresponding author**
Irina-Draga Caruntu, Professor, MD, PhD, Department of Histology, Faculty of Dental Medicine, “Gr. T. Popa” University of Medicine and Pharmacy, 16 University Street, Iassy, Romania; Phone/Fax +40745–638 427, E-mail: dicarunt@mail.dntis.ro

Received: August 30th, 2007

Accepted: October 20th, 2007