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A single-center experience

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Polypoid lesions of the gallbladder in a consecutive series of 2631 patients. A single-center experience.

BACKGROUND: Challenges in the diagnosis of polypoid gallbladder lesion (PLG) is due to the low sensibility (SE) of ultrasound scan (US), and the selection criteria of patients with PLG to be addressed to surgical treatment or follow-up are not yet fully defined.

MATERIALS AND METHODS: Retrospective observational study was conducted on 2631 patients, 1175(44.6%) M, mean age 56 years, 1456(55.4%) F, mean age 46 years, who underwent laparoscopic and open cholecystectomy.

RESULTS: The US diagnosis for PLG was placed in 38/2631(1.4%) patients. On histological examination (HE) the polyps were identified in 68/2631(2.6%) patients and it was associated with biliary lithiasis in 28/2631 (1.1%) cases. From the US and HE comparison, the ultrasound diagnosis was burdened by false positives (8/38; 21%) and false negatives (38/2631;1.45%), with SE 44% (95% c.i.:32.2-55.7). The histological incidence of gall bladder cancer (GBC) was 0.38%(10/2631).

DISCUSSION: US survey underestimated the incidence of PLG compared to the histological finding ($p=0.021$). Female gender has been shown to be a specific risk factor for benign and malignant PLG and non-polypoid mucosal lesions ($p=0.041$). The parietal lesion size <0.5 cm does not exclude the neoplastic nature. Currently the prevention and diagnosis of GBC is based on the early detection and treatment of potentially evolutionary polypoid lesions over a period of about 15 years.

CONCLUSIONS: It is probably that early cholecystectomy in all the patients with PLG of diameter <1 cm, isolated or associated with lithiasis, symptomatic and asymptomatic, can contribute to the reduction of the incidence of GBC.

KEY WORDS: Cholecystectomy, Gallbladder polyps, Gallbladder cancer, Ultrasound scan

Introduction

The polypoid lesions of the gallbladder (PLG), incidentally diagnosed during trans-abdominal ecotomography (US) performed for abdominal pain, or during histolo-

gical examination (HE) after cholecystectomy, affect about 5% of the adult population¹. The prevalence of PLG, assessed by the combination of population studies and surgical studies, is between 0.3 and 12.3%²⁻⁴. The malignant potential varies from 3% to 8%⁵. Currently, the problem is represented by the US differential diagnosis between benign and malignant polyps of diameter <0.5 cm⁶.

In the differential diagnosis between benign and malignant polyps, CT and contrast-enhanced MR appears to be the methods of election, compared to the traditional US and endoscopic US, due to their greater accuracy

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and specificity ⁷. Are considered as predictive criteria of malignancy: patients >50 years of age, female sex, polyps larger than 1 cm in diameter, solitary and symptomatic polyps, polyps associated with biliary lithiasis, rapid growth, sessile type, irregular surface, localization at the bottom of the gallbladder, gallbladder wall thickening greater than 3 mm and adenomyomatosis ^{5,8,9}. In all cases, the instrumental diagnosis of PLG requires histologic confirmation, especially for parietal lesions with a diameter <1cm ^{1,7,10}.

The histopathological survey represents the gold standard for the diagnosis of non-neoplastic polyps (cholesterolosis, inflammatory, fibroepithelial, adenomyomatosis), neoplastic polyps (adenoma, carcinomas, carcinoids), non-polypoid precancerous lesions (low and high-grade dysplasia, muciparous intestinal metaplasia, pyloric gastric metaplasia) and of nodular parietal irregularities of xanthogranulomatous cholecystitis ¹¹. In recent years, attention has been paid to adenomyomatosis and xanthogranulomatous cholecystitis due to assumed increased potential for malignant transformation ^{12,13}.

Adenomyomatosis was classified as one of three variants: widespread (rare form), segmental with high neoplastic risk and localized at low risk ¹⁰. Although no models of carcinogenesis have been identified, the metaplasia-dysplasia-carcinoma sequence ^{13,14} has been hypothesized in the etiopathogenesis of gallbladder neoplasms.

The clinical and US parameters for the selection of patients with PLG to undergo cholecystectomy or follow-up have not been completely defined ⁸. Surgical treatment is currently indicated in case of lesions >1cm in diameter, single, isolated or associated with gallstones, in the presence of a number of polyps >3 and in patients >50 years old ^{15,16}. Laparoscopic cholecystectomy (LC) is considered the elective procedure in the presence of PLG, benign and early-cancers and it is associated with hepatic resection in cases of advanced-cancers ¹¹.

The aim of the study was to evaluate the prevalence of non-neoplastic and neoplastic polyps in patients underwent cholecystectomy, and to evaluate the sensitivity of the US compared to the histological examination (HE) in the identification of PLG.

Patients and Methods

A retrospective observational study was conducted on the medical records of 2631 patients (identified by the ICD-9-CM 51.2 code) underwent election or urgency laparoscopic and open cholecystectomy, in the period between April 2005 - March 2018, at the University hospital "A. Fiorini" of Terracina - Polo Pontino, "Sapienza" University of Rome. All patients underwent US and in all patients with PLG factors such as sex, age, clinical symptomatology, diameter and location of the parietal lesions and the presence of biliary lithiasis, have been taken into account. The histological exami-

nation considered presence and nature of the polyp (non-neoplastic or neoplastic), presence of non-polypoid lesions [low and high-grade dysplasia, intestinal metaplasia (IM), gastric metaplasia (GM)].

STATISTICAL ANALYSIS

The data obtained were compared using chi-square contingency analysis or unidirectional analysis of variance (ANOVA). A p value <0.05 was considered statistically significant. Data processing was performed using statistical software SPSS of IBM statistics version 20.1.1. The study was performed in accordance with the principles of the Helsinki Declaration.

Results

Study population included 2631 patients; 1175 males (44.6%) with median age of 56 years old (range 25 to 95 years), and 1456 females (55.4%) with median age of 46 years (range 17 to 90 years); M/F ratio (4/5). The US showed isolated lithiasis of gallbladder in 2593 patients (98.5 %) of which 1160 male (44.7%) and 1433 female (55.2%). The diagnosis was confirmed at the HE in 2549 patients (96.9% VN) and it was not confirmed in 44 patients (1.7%).

The percentage of patients with PLG diagnosed by US was 1.4% (38/2631); 15 patients were males (39.5%) and 23 were females (60.5%) with median age of 53 years (range 21 to 74 years). The PLG was isolated in 0.4% (10/2631) and associated with lithiasis in 1.1% (28/2631) of patients.

The 38 PLGs identified at the US in 21/38 cases (55.3%) was less than 0.5cm in diameter, associated with lithiasis in 28/38 patients (73.7%).

The 38 PLGs identified at the US were confirmed by HE in 30/38 (79% VP) patients and were not confirmed in 8/38 (21% FP). By comparison with EI, FPs to US were 0.3% (8/2631 patients), not associated with lithiasis. Moreover, from HE the total percentage of FN (incidental PLG) was 1.45%(38/2631).

The US sensibility in the identification of PLG was 44% (95% c.i.: 32.2-55.7).

The HE of VPs PLG patients (68/2631; 2.6%) showed: 2 cases (2.9%) of fibro-epithelial polyps of which one associated with lithiasis, 8 cases (11.8%) of cholesterolosis of which one associated with lithiasis, 35 cases (51.5%) of adenomyomatosis of which 16 associated with lithiasis, 12 cases (17.6%) of xanthogranulomatosis of which one associated with lithiasis, 10 neoplastic cases (14.7%) of which 9 associated with lithiasis and one adenoma (1.5%). The diameter of the PLG was ≤1cm (range 0.2-1cm) in 58.6% of cases and it was >1cm in 41.8% (range 1.1-5 cm).

Compared to the total of 2631 patients, the prevalence

TABLE I – Histological finding of incidental non-polypoid mucosal lesions

HE 2631 pts	n. pts (%) F/Mn. pts median age	Symptomatic biliary lithiasis pts	Associated lesions pts
Low grade dysplasia	23(0.9%) F 15/M 8(64 /64years)	23	Xanthogranulomatous cholecystitis 1 Adenomyomatosis 3 Incidental invasive neoplasm 4
High grade dysplasia	4 (0.1%) F 2/M 2(64/80 years)	4	Low grade dysplasia 2
Muciparous IM Pyloric GM	8 (0.3%) 29 (1.1%)	8 29	High grade dysplasia 4 Low grade dysplasia 23

HE: *histological examination*; IM: *intestinal metaplasia*; GM: *gastric metaplasia*
F: *female*; M: *male*; pts: *patients*

of lithiasis diagnosed by HE was 97% (95% c.i.: 98.1-99) while the prevalence of PLG was 2.6% (95% c.i.: 2.4-3.6).

The percentage of the PLG-lithiasis association described at HE was 1.1% (28/2631) in symptomatic patients. Single and multiple polyps, not associated with calculi, were identified in 40/2631 (1.5%) patients and the HE showed that were included 19 adenomyomatosis, 11 xanthomatosis, 6 cholesterolosis, 2 fibroepithelial, 1 adenoma and 1 adenocarcinoma, all asymptomatic. The most cases were female (34/40; 85%) with median age of 44.5 years (range 21 to 68 years).

Adenomyomatosis were the most common found histological lesions (35/68 patients; 51.5%). In 22 cases they constituted an incidental histological finding (FN) of which 16 cases were associated with lithiasis (16/35; 45.7%) and 6 cases were found in alitiasic gallbladder (6/35; 17%), with diameter <0.5cm in 13 patients (13/35; 37%). Less frequently adenomyomas were associated with xanthogranulomatous cholecystitis (3 cases) and with low-grade dysplasia (2 cases). Adenomyomatosis were more frequently found in the fundus in 22 patients, widespread in 10 patients, in the body-fundus in 2 patients and in the body in 1 patient.

The US diagnosis of xanthogranulomatous cholecystitis was placed in 2/68 patients (2.9%). At HE, the percentage of xanthogranulomatous lesions was 17.6% (12/68). From the comparison between US and HE, the number of FN for xanthomatotic polyps was 10.

The characteristics of incidental non-polypoid mucosal lesions found in HE in symptomatic patients for lithiasis are reported in Table I.

The histological incidence of the neoplastic polyps on the entire sample was 0.38% (10/2631 patients), 3 males and 7 females, with median age of 64 years old, (range 49-80 years).

In 9 cases it was diagnosed an adenocarcinoma, poorly differentiated in 3 patients and a neuroendocrine tumor in

one case. The lesions had a diameter between 0.4 cm and 5 cm, located in the fundus of the gallbladder (7 cases), in the body-fundus (2 cases) and in the body (1 case).

In 3 cases, the neoplasms were identified by US (3/10; 30% VP); the remaining 7 cases were incidental histological findings (7/10; 70% FN), of which 5 with diameter >1cm in the context of a clinical frame of acute lithiasic cholecystitis and 2 with diameter <1cm in a frame of uncomplicated lithiasis.

Discussion

The term PLG identifies the benign and malignant parietal lesions located into the lumen of the gallbladder^{5,17}. The percentage of PLG diagnosed by US varies widely in relation to the type of population studied and the type of study performed. Oscillating ranges are reported in the US from from 0.004 to 13.8% and our data is in line with the literature (1.4%)¹⁻⁴.

Lesions were more frequently associated with lithiasis in symptomatic patients (28/38; 73.7%) and less frequently isolated and asymptomatic (10/38; 26.3% patients). The histological findings of PLG is comparable to literature range (68/2631; 2.6% patients).

From the US and HE comparison, it appeared that the ecotomographic survey underestimated the incidence of PLG compared to the histological finding (38 vs 68 patients) (p value 0.021).

The difference between ecotomographic and histological prevalence was due to 8 patients resulting FP and 38 patients resulting FN from the US and HE comparison⁵. FPs for PLG were a cause of incorrect indication for surgical treatment.

The comparison between US and HE diagnosis confirms the low SE of the ultrasound scan in the identification of the PLG both in the presence and absence of biliary lithiasis.

The adenomyoma, more frequently found histologically, proved to be the most often not identified by US (US 22 patients vs 35 HE patients)¹⁰. The high incidence of FNs (13/35 patients; 37.1%) confirms the low SE of the US in the identification of adenomyoma with a diameter <0.5cm, associated or not with lithiasis. The adenomyomatosis of the fundus and the widespread one have turned out to be the most common forms of histological findings (32/35; 91.5% patients). The segmental histotype, at higher risk of neoplastic transformation, has never been identified^{10,14}. The association of adenomyomatosis-low-grade dysplasia, high-grade dysplasia has not been histologically described, excluding the existence of a correlation between PLG and pre-neoplastic non-polypoid lesions.

Xanthogranulomatous cholecystitis, diagnosed by HE in 12 patients, should always be considered in the US differential diagnosis of protruding parietal lesions. Even in the absence of biliary lithiasis the instrumental diagnosis of this condition was not done in 10 patients. In this study, the histopathological findings of xanthogranulomatous cholecystitis was lower than the literature data¹¹.

Female gender has been shown to be a specific risk factor for benign and malignant PLG and non-polypoid mucosal lesions (p value 0.041).

Low-grade dysplasia has been found in predominantly female patients, all symptomatic for biliary lithiasis. A correlation between sex, lithiasis and potentially evolutionary dysplastic lesion is therefore hypothesized¹⁷. High-grade dysplasia was also found in patients all symptomatic for lithiasis. Similarly, for this lesion a correlation between lithiasis and mucosal lesion can be hypothesized.

It is to be determined the evolutionary potential of Intestinal Metaplasia (IM) and of Gastric Metaplasia (GM) associated with low and high-grade dysplasia.

The histological incidence of the neoplastic polyps (0.38%) was in line with the literature range; 9 adenocarcinomas and 1 incident neuroendocrine tumor, in the absence of specific symptoms^{18,19}.

The histological incidental diagnosis of gall bladder cancer (GBC) in 7/10 (70%) patients confirmed that the traditional US, due to the low SE, was not able to highlight the signs of parietal invasion¹⁵.

Probably in our study there are multiple causes of the non-identification of US malignant wall irregularities: a) the clinical onset in acute lithiasic cholecystitis, obscuring the lesion (5 patients); b) the size <1 cm in the presence of uncomplicated lithiasis (2 patients)²⁰.

The parietal lesion size <0.5cm does not exclude the neoplastic nature. A lesion of a diameter of 0.4cm reported on histopathological examination (FN), proved to be a well differentiated carcinoma pT1b, pNx, pMx. The most favorable stages, 3 cases of pTis, were recorded in patients cholecystectomized early for symptomatic lithiasis with US negative for PLG. In the case of the 3 patients with US diagnosis for neoplastic polyp (VP), in the HE the adenocarcinoma was poorly differentiated (G3) infiltrating the hepatic parenchyma.

Currently the prevention and diagnosis of GBC is based on the early detection and treatment of potentially evolutionary polypoid lesions over a period of about 15 years²¹. Indeed, early detection of stage 1 or 2 carcinoma leads to a 5 year survival at 95-99% and 70% respectively, whereas for a stage 3 or 4 diagnosis the 5-year survival rate is reduced to 5-12 %^{5,22}.

In the absence of certain evidence regarding their malignant potential, the management of PLG is related to the US diameter of the lesions and to the presence or absence of associated lithiasis²². In well-founded cases of doubt, the investigation through US should be integrated with CT, MRI, endoscopic US and, in selected cases, PET-CT^{7,17}.

The major doubts persist on the treatment modalities of polyps in alitiasic cholecystitis, that are not considered at neoplastic risk^{20,23,24}.

On the other hand, surgical treatment is mandatory in symptomatic or asymptomatic patients with PLG with a diameter of >1cm. Moreover, asymptomatic patients with polyps and calculi or only polyps which in the instrumental follow-up show increased lesion size and suspected signs of invasion of the wall, should be addressed to surgical treatment.

Monitoring could be interrupted in cases of reduction or disappearance of the lesion^{25,26}.

An absolute indication for surgical treatment is the imaging compatible with segmental adenomyomatosis, characterized by a high risk of neoplastic degeneration in patients >60 years old²⁷.

Conclusion

The US is confirmed as a method characterized by low sensitivity in the diagnosis of PLG, and in the differential diagnosis between non-neoplastic and neoplastic polyps. However, it is probably that early cholecystectomy for asymptomatic polyps of diameter <1 cm can contribute to the reduction of the incidence of GBC²⁸. However, a more precise assessment of the malignant potential of PLGs requires broader clinical case studies and prolonged follow-ups¹⁴.

Riassunto

INTRODUZIONE: La diagnosi ultrasonografica (US) delle lesioni polipoidi della colecisti (PLG) è difficile per la bassa sensibilità (SE) della metodica. Non sono stati ancora completamente definiti i criteri di selezione dei pazienti con PLG da indirizzare al trattamento chirurgico o al follow-up. L'indagine istopatologica (EI) rappresenta il gold standard per la diagnosi di polipi non-neoplastici (colesterotici, infiammatori, fibroepiteliali, adenomatosi), di polipi neoplastici (carcinomi, carcinoidi), di lesioni precancerose non polipoidi (displasia di

basso ed alto grado, metaplasia intestinale di tipo muciparo, metaplasia gastrica di tipo pilorico) e di irregolarità nodulari parietali della colecistite xanto-granulomatosa. Gli scopi dello studio sono stati quelli di valutare in un campione di pazienti sottoposti a colecistectomia, la prevalenza dei polipi non neoplastici e neoplastici e la sensibilità dell'US tradizionale trans-addominale rispetto all'EI nell'identificazione delle PLG.

MATERIALI E METODI: Studio osservazionale retrospettivo, condotto su un campione di 2631 pazienti, sottoposti a colecistectomia laparoscopica e open, in elezione e in urgenza, identificati mediante il codice ICD-9-CM 51.2, nel periodo Aprile 2005 - Marzo 2018, presso l'ospedale universitario "A. Fiorini" di Terracina - Polo Pontino, "Sapienza" Università di Roma. Tutti i pazienti erano stati sottoposti a US.

RISULTATI: Il campione esaminato era costituito da 1175(44.6%) M, età media 56 anni, range 25-95 anni, 1456(55.4%) F, età media 46anni, range 17-90 anni. La diagnosi US di PLG veniva posta in 38/2631(1.4%) pazienti. All'esame istologico i polipi erano identificati in 68/2631(2.6%) pazienti, associati a litiasi biliare in 28/2631 (1.1%) casi. Dal confronto US e EI la diagnosi ecografica risultava gravata da falsi positivi (FP) (8/38; 21%) e falsi negativi (FN) (38/2631; 1.45%), con SE 44% (95% c.i.:32.2-55.7). L'incidenza istologica di PLG neoplastiche è stata dello 0.38% (10/2631), 3M e 7F, età media 64 anni, (range 49-80 anni). In 3 casi le neoplasie erano state identificate all'US (3/10; 30 % VP); nei restanti 7 casi costituivano reperto istologico incidentale (7/10; 70 % FN), di cui 5 con diametro >1cm nel contesto di un quadro clinico di colecistite acuta litiasica e 2 con diametro <1cm in un quadro di litiasi non complicata.

DISCUSSIONE: L'US tradizionale trans-addominale sotto-stimava l'incidenza delle PLG rispetto all'EI ($p=0.021$) e i FP per PLG isolate sono stati causa di errata indicazione al trattamento chirurgico. Il confronto fra diagnosi US ed EI conferma la bassa SE della metodica ecografica nell'identificazione delle PLG, sia in presenza che in assenza di litiasi biliare. Il sesso femminile si è dimostrato specifico fattore di rischio per PLG benigne e maligne e lesioni mucosali non polipoidi ($p=0.041$). Nel nostro studio, probabilmente, le cause della mancata identificazione US delle irregolarità parietali maligne erano l'oscuramento della lesione dall'esordio clinico della neoplasia in colecistite acuta litiasica (in 5 pazienti) e le dimensioni <1cm in presenza di litiasi non complicata (in 2 pazienti). La dimensione della lesione parietale <0.5cm non escludeva la loro natura neoplastica. Attualmente la prevenzione e la diagnosi di GBC è basata sul precoce riscontro e trattamento delle lesioni polipoidi potenzialmente evolutive nell'arco di circa 15 anni.

CONCLUSIONI: Probabilmente la colecistectomia precoce in tutti i pz con PLG di diametro <1cm, isolate o associate a calcoli, sintomatici e asintomatici, può contribuire alla riduzione dell'incidenza del GBC.

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