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Araştırma

Incidental gallbladder carcinoma and precancerous lesions in laparoscopic cholecystectomy specimens

Laparoskopik kolesistektomi materyallerinde insidental safra kesesi karsinomu ve prekanseröz lezyonlar

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ABSTRACT

Objective: The purpose of our study was to find out the frequency of incidental carcinomas, dysplasias and adenomas of the gallbladder in patients who underwent laparoscopic cholecystectomy.
Methods: We reviewed pathology records of 5063 cholecystectomy specimens Hematoxylin-eosin stained sections of the patients having dysplasia, adenoma, gallbladder carcinoma (GC) were reviewed.
Results: Incidental GC was detected in 6 cases, and 5 of them exhibited accompanying dysplasia. Isolated cases of dysplasia, and adenoma were detected in 13, and 2 cases, respectively. Female-male ratios for dysplasia, and carcinoma were 12: 1, and 4: 2, respectively. Median ages of GC, and dysplasia/adenoma were 65.6, and 56.8 years, respectively. Biliary intraepithelial neoplasia (BillN3) and BillN2 were accompanied with 4, and 1 case with carcinoma. Intestinal metaplasia was noted in 3 carcinoma cases. Isolated cases with BillN3, BillN2, and BillN1without invasive carcinoma were seen in 4, 3, and 6 cases, respectively. Intestinal metaplasia was noted in 2, intestinal+pyloric metaplasia in 1, and pyloric metaplasia in 1 case with BillN.
Conclusion: Incidental GC was found in 0.11% of our cases. Gallbladder stones and advance age seem to be the risk factors for GC. Incidental GC may be predicted in the presence of BillN and metaplastic changes of the gallbladder. Histopathological evaluation is still important for the diagnosis of incidental gallbladder carcinoma and preinvasive lesions. BillN3 is typically associated with invasive carcinoma. Thus, complete sampling should be performed by pathologist when carcinoma is not evident on initial histologic sections.

Keywords: Gallbladder, cancer, dysplasia

ÖZ

Amaç: Laparoskopik kolesistektomi olan hastalarda safra kesesinin insidental karsinom, displazi ve adenom sıklığını saptamayı amaçladık.
Yöntem: 5063 kolesistektomi materyaline ait patoloji raporunu inceledik ve displazi, adenom, safra kesesi karsinomu tanısı olanlara ait Hematoksilen Eozin boyalı kesitleri gözden geçirdik.
Bulgular: İnsidental safra kesesi karsinomu 6 olguda saptanmıştır ve bunların 5'ine displazi eşlik etmektedir. Tek başına displazi 13 olguda, adenom 2 olguda izlenmiştir. Kadın-erkek oranları displazi olguları için 12: 1, karsinom için 4: 2'dir. Ortalama yaş safra kesesi karsinomu olguları için 65,6, displazi/adenom olguları için 56,8'dir. Biliyer intraepitelial neoplazi (BillN3) 4 karsinom olgusuna ve BillN2 1 karsinom olgusuna eşlik etmektedir. İntestinal metaplazi 3 karsinom olgusunda saptandı. İnvaziv karsinom olmaksızın tek başına BillN3 4 olguda, BillN2 3 olguda, BillN1 6 olguda izlenmiştir. İntestinal metaplazi 2 BillN olgusunda, intestinal+pilorik metaplazi 1 olguda ve pilorik metaplazi 1 olguda saptanmıştır.
Sonuç: İnsidental safra kesesi karsinomu %0,11 olarak bulundu. Safra kesesi taşları ve ileri yaş karsinom için risk faktörleri olarak izlendi. İnsidental safra kesesi karsinomu, BillN ve metaplastik değişiklikler varlığında beklenebilir. İnsidental safra kesesi karsinomu ve preinvaziv lezyonların tanısında histopatolojik inceleme hala önem taşımaktadır. BillN3 tipik olarak invaziv karsinomla ilişkili olduğundan, ilk histolojik kesitlerde karsinom olmadığında, patolog tarafından eksize edilen organın ayrıntılı ve tam bir incelenmesi yapılmalıdır.

Anahtar kelimeler: Safra kesesi, kanser, displazi

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INTRODUCTION

Gallbladder carcinoma (GC) is an uncommon malignancy with poor prognosis. The worldwide incidence of GC is 1-2% [1]. The incidence is higher in some countries such as USA, Mexico, Chile, Japan and India [1-3]. GC is often diagnosed incidentally in cholecystectomy specimens histologically examined for acute/chronic cholecystitis and cholelithiasis [3]. The patients with GC are 15-20 years older than patients with gallstones [4].

The most important risk factors for GC are predisposing genetic factors and presence of gallstones. Gallstones are present in >80% of gallbladders with carcinoma [5]. Greater risk has been reported with larger stones [4]. Many other risk factors including obesity, porcelain gallbladder and single, sessile (>10 mm) polyps have been described in the literature [2,4]. Approximately 50% of carcinomas are diagnosed incidentally and usually present at a late stage [6]. Surgical treatment (simple cholecystectomy) is the basic modality for carcinoma patients though other therapeutic approachs for GC depend mainly on tumor stage.

Biliary intraepithelial neoplasia (BillN) is one of the precursor lesions of GC. BillN usually can not be recognized on macroscopic examination. In most cases the gallbladder shows only thickened and indurated wall as a result of chronic inflammation.

Adenomas of gallbladder are small, asymptomatic lesions discovered incidentally in cholecystectomy specimens [3,7]. Histologically they are classified as pyloric, intestinal and biliary adenomas [3,7]. Single adenomas of >1 cm are commonly associated with carcinoma [7]. Intracystic papillary neoplasm of the gallbladder may also be associated with GC [3,7]. It is usually high grade intraepithelial neoplasia characterized by complex papillary structures [3,7].

The purpose of our study was to find out the frequency of incidental carcinomas, dysplasias and adenomas of the gallbladder in patients who underwent laparoscopic cholecystectomy for cholecystitis . and cholelithiasis.

MATERIAL and METHOD

We reviewed pathology records of cholecystectomy specimens obtained between January 2008 and March 2014. Routine preoperative assessment had been performed in all patients, including biochemical assessment of the liver, and abdominal ultrasonography of the hepatobiliary system. Exception criterion was preoperative suspicion of malignancy. Hematoxylin-eosin stained sections of patients having dysplasia, adenoma and carcinoma according to previous reports were reviewed by three pathologists. Tumor staging and diagnosis of dysplasia were based on AJCC seventh edition of TNM and World Health Organization 2010 criteria respectively. Histopathological features of BillN are detailed in Table 1. Clinical and histopathological features were analyzed and results were compared with literature data.

Table 1. Histopathological features of Biliary Intraepithelial Neoplasia.

BillN1	Low grade lesion	Mild cytoarchitectural atypia, enlargement of cells, pseudostratification of nuclei, hyperchromatism	Detected incidentally	No clinical significance
BillN2	İntermediate grade lesion	Mild cytoarchitectural atypia, enlargement of cells, pseudostratification of nuclei, hyperchromatism	Detected incidentally	No clinical significance
BillN3	High grade lesion	Arises in a backround of pyloric and intestinal metaplasia Abrupt transition between dysplasia and normal epithelium	Detected incidentally	Associated with invasive carcinoma

RESULTS

A total of 5063 laparoscopic cholecystectomy specimens of which 3464 having cholelithiasis were reviewed. The histopathologic diagnoses were chronic cholecystitis in 4936, gangrenous cholecystitis in 52, xanthogranulomatous cholecystitis in 30, acute cholecystitis in 20 cases. Incidental GC was detected in 6 cases (0.11%) of which 5 exhibited accompanying dysplasia. Pure dysplasia was detected in 13

(0.25%) cases.

Age distribution and histopathological findings were detailed in Table 2. The female male ratios for cases with dysplasia, and carcinoma were 12:1, and 4:2, respectively. Median ages of cases with GC and dysplasia/adenoma were 65.6 (min:45, max:82 years), and 56.8 (min:30, max:78) years respectively. Tumor differantiation was well in 2, moderate in 4 GC cases. Five of the GC cases exhibited biliary type adenocarcinoma, and 1 case intestinal type adenocarcinoma. Tumor perforated serosa (T3) in 5, and invaded muscular layer (T1b) in 1 case. BillN3, and BillN2 were accompanied by 4, and 1 case of carcinoma . Intestinal metaplasia was noted in 3 carcinoma cases. Pure BillN3, without invasive carcinoma was seen in 4 cases, BillN2 in 3 cases, and BillN1 in 6 cases (Figure 1). Intestinal metaplasia was noted in 2, intestinal + pyloric metaplasia in 1, and pyloric metaplasia in 1

Table 2. Clinical and pathological characteristics of incidental gallbladder carcinoma, dysplasia and adenoma cases.

Case No	Age	Sex	Pathology	pT	Co-Findings
1	49	M	Well differentiatedbiliary type adenocarcinoma	T3	BillN3, Intestinal metaplasia
2	45	F	Well differentiated, biliary type adenocarcinoma	T1b	BillN3
3	79	F	Moderately differentiated, biliary type adenocarcinoma	T3	-
4	82	F	Moderately differentiated, biliary type adenocarcinoma	T3	BillN3, Intestinal metaplasia
5	62	M	Moderately differentiated, intestinal type adenocarcinoma	T3	BillN2, Intestinal metaplasia
6	77	F	Moderately differentiated, biliary type adenocarcinoma	T3	BillN3
7	64	F	BillN 3		Intestinal metaplasia
8	50	F	BillN 1		-
9	43	F	BillN 2		-
10	78	F	BillN 3		Pyloric metaplasia
11	62	F	BillN 1		-
12	71	M	BillN 1		-
13	39	F	BillN 1		-
14	80	F	BillN 3		-
15	61	F	BillN 2		-
16	30	F	BillN 3		Intestinal metaplasia
17	50	F	BillN 1		-
18	58	F	BillN 2		Intestinal+pyloric metaplasia
19	39	F	BillN1		
20	78	M	Tubular Adenoma		-
21	50	M	Tubular Adenoma (pyloric gland type)		BIN 2-3

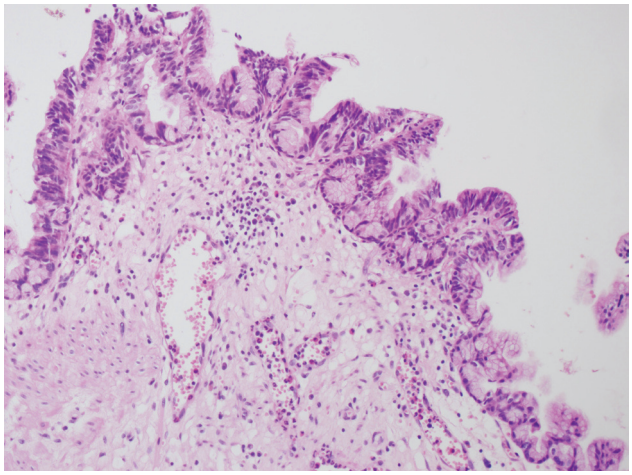

Figure 1. Papillary projections into the lumen showing BillN2 features in the epithelium.

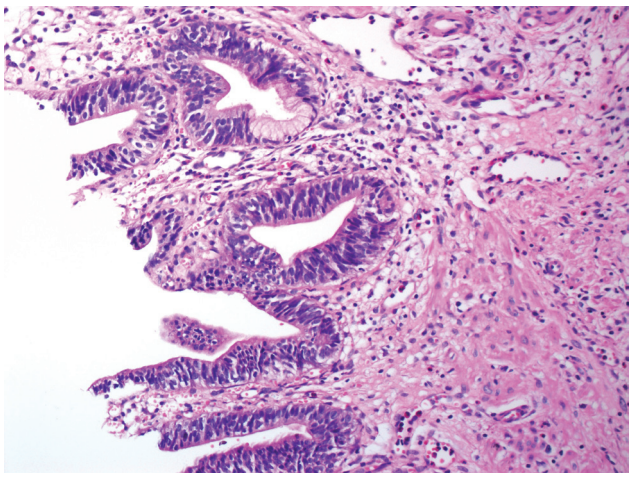

Figure 2. BillN3 features in the epithelium accompanied with metaplastic features.

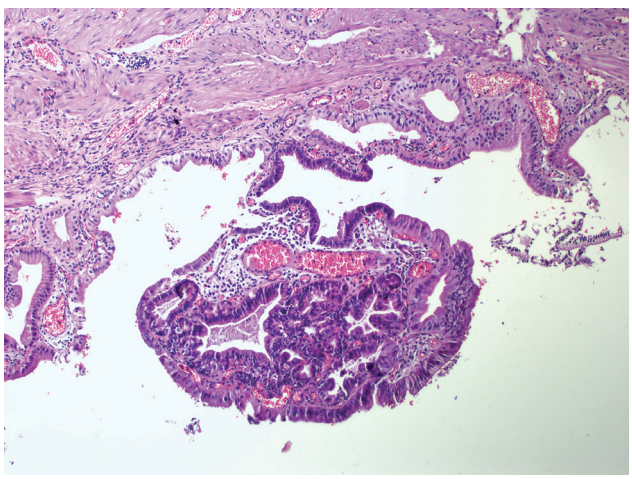

Figure 3. Tubular adenoma showing BillN2-3 features in the epithelium.

BillN case (Figure 2).One case with pyloric type tubular adenoma and and one case with tubular adenoma manifested BillN2-3 features (Figure 3).

The median wall thickness of gallbladder in carcinoma cases was 9 mm. Of the six carcinoma cases five had gallbladder stones. The median tumor diameter was 12.8 mm (min:7, max:20 mm). We noted perineural invasion in case 1 and 6, perineural invasion and necrosis in case 3 and perineural, lymphovascular invasion, necrosis in case 4. Acute cholecystitis accompanied case 4 and xanthogranulomatous and follicular cholecystitis accompanied case 6. In case 1 and 6 gallbladder neck surgical border was positive for tumor. Clinical and histological features of GC cases are detailed in Table 3.

Table 3. Histopathologic characteristics and follow-up data of gallbladder carcinoma cases.

Case No	Wall thickness (mm)	Gallbladder stone	Tumor size (mm)	PNI	LVI	Necrosis	Follow up data
1	10	+	10	+	-	-	Died of gastrointestinal hemorrhage 9 months after diagnosis
2	4	+	7	-	-	-	Alive during 60 months
3	5	+	15	+	-	+	Died of cardiopulmonary arrest 1 month after diagnosis
4	8	+	20	+	+	+	Died at 21th month of diagnosis
5	20	-	15	-	-	-	Died at 9th month of diagnosis
6	7	+	10	+	-	-	Died at 30th month of diagnosis

DISCUSSION

GC is the fifth most common gastrointestinal cancer [4,8]. The prognosis is usually poor and mainly depends on tumor stage. Five-year survival rates have been reported to be less than 5% for advanced stage tumors [9]. The incidence of incidentally diagnosed gallbladder cancer varies between 0.19, and 3.3% [9,10]. Solaini et al. [1] reported the incidence as 0,8% in 864 cholecystectomy materials. Sujata et al. [9] reported 6 (0.9%) incidental GC in 622 laparoscopic cholecystectomy specimen. Genc et al. [8] reported 5 (0.09%) incidental gallbladder carcinoma in 5164 patients and they supposed that the low incidence in Turkish population is related to the avoidance of elective cholecystectomy in advanced stage carcinomas. In our study, the rate of incidental gallbladder cancer was 0.11%. Our rate is a bit lower than that of literature and it may be associated with inadequate sampling of cholecystectomy specimens. Argon et al. [11] studied on macroscopic sampling of cholecystectomy specimens. Their first group included 273 specimens for which one sample was taken from each of the fundus, body and neck regions (classical technique). The second group included 335 specimens for which samples were taken from the neck region and lengthwise from the fundus toward the neck (longitudinal sampling). They found that longitudinal sampling was more effective than classical technique (as we usual do) in detecting precursor lesions. High-grade dysplasia (and carcinoma in situ) is ordinarily associated with invasive carcinoma which suggests that a thorough and complete evaluation of the excised organ should be performed by the pathologist when carcinoma is not evident on initial histologic sections [12].

The female gender and advanced age are demographic risk factors for GC. The male to female ratio was 2:4 in our serial. Median age (65.6) of GC cases was higher than the median age of the remaining patients. Our study confirms the advanced age in incidental GC. Gallbladder carcinoma remains asymptomatic for a long time or presents with nonspesific symptoms like pain, vomiting. In our cancer series five patients were admitted with stomach ache and one patient with jaundice.

BillN is often associated with acute or chronic cholecystitis [13]. Microscopically the normal columnar epithelium of the gallbladder is replaced by aty-

pical cells in flat, papillary, micropapillary, glandular and denuding architecture (13-15). Low/intermediate- grade dysplasia (BillN1 and BillN2) has no clinical significance but high- grade dysplasia (BillN3) is usually associated with invasive carcinoma [13]. BillN3 is often accompanied with pyloric and intestinal metaplasia. Oncocytic, squamous metaplasias, signet ring cell features are also noted infrequently [5,13,16-17]. BillN3 may extend into Rokitansky-Aschoff sinuses. This extension should not be confused with stromal invasion [13,18-22]. BillN may coexist with reactive epithelial changes. Reactive features show a gradual transition with normal epithelium in contrast to the abrupt transition seen in BillN lesions [3,13]. In the present study BillN was accompanied with carcinoma in 5 of 6 gallbladder carcinoma cases and most of them were BillN3. Also metaplastic changes were generally accompanied with BillN and carcinoma cases. Recently Seretis et al. [23] reported that chronic cholecystitis may be a major factor initiating early metaplastic changes which can gradually progress to dysplastic and finally cancerous lesions. This metaplasia-dysplasia-carcinoma sequence is estimated to extend to 10 years [23]. Therefore an early surgical intervention may probably prevent this fateful scenario.

The prognosis for patients with GC depends on the extent of the disease and its histopathological type [24]. The median survival for the incidental GC has been reported to range between 8.1, and 68 months in the literature [8]. In our study, median survival was 21,6 months which was compatible with the literature. Yang et al. [25] in 2012 revealed that curative resection, lymph node metastasis, stage, tumor location, histologic differentiation, intraoperative blood loss, and preoperative jaundice were significant risk factors for survival. The tumour type, stage, surgical margins, grading, vascular invasion, perineurial invasion are prognostic factors [26]. In the present study, one of the stage T1b carcinoma cases with no perineurial and vascular invasion, is stil alive.

The most important clinical feature associated with GC is the presence of gallstones [1]. Symptomatic cholelithiasis for 20 years duration and presence of single gallstone >3 cm are high risk factors [1]. Sujata et al. [9] reported that gallstones are seen in 54-97% of GC cases. In our study, five GC cases (83%) had gallstones and but we could not measure the diameters of the stones. Specific conditions such as porcelain gallbladder and Mirizzi syndrome were not associated with incidental GC and dysplasia in our study similar to Solaini's study performed in 2013 [1].

Also it has been demonstrated that gallbladder wall thickening is an important finding in predicting incidental GC [1]. According to our study median wall thickness of gallbladder in GC group was 9 mm (4-20 mm). Metaplastic changes in gallbladder epithelium are considered to be associated with GC [23]. Seretis et al. reviewed the histopathology reports of 86 cases with chronic cholecystitis to identify the prevalence of gallbladder metaplasia in the course of chronic cholecystitis [23]. The incidence of metaplastic changes was 25.6%. They also found that dysplastic changes were more frequent in gallbladder specimens with concurrent metaplasia [23]. In our study we observed metaplasia in 7 cases (4 intestinal, 2 pyloric and 1 intestinal + pyloric). All the cases showing metaplasia were accompanied with dysplasia as BillN 3 with 5, and BillN 2 with 2 dysplastic cases. While 3 of 6 gallbladder carcinoma cases were associated with intestinal metaplasia.

A review by Lee et al. [27] analyzing the correlations between polypoid lesions and GC showed that polypoid lesions are associated with GC. A recent study analyzing gallbladder adenomas (pyloric, intestinal, foveolar and biliary) in 91 patients indicated that these lesions play a minor role in carcinogenesis of gallbladder [28]. In our study there was two polypoid lesions diagnosed as adenoma and one of them showed BillN3 features.

CONCLUSION

A laparoscopic cholecystectomy that is performed for benign gallbladder disease rarely aids in the diag-

nosis of gallbladder cancer and pre-invasive lesions. In our single- center study the diagnosis of incidental GC was found in 0.11% of the cases. Gallbladder stones and advance age seem to be the risk factors for GC. Incidental GC may be predicted on the presence of BillN and metaplastic changes of the gallbladder. Histopathological evaluation is still important for the diagnosis of incidental gallbladder carcinoma and preinvasive lesions. BillN3 is typically associated with invasive carcinoma. Thus, complete sampling should be performed by pathologist when carcinoma is not evident on initial histologic sections.

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