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Review article

Is there A Standard Strategy for Managing Gall Bladder Polyps?

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Abstract

Gall bladder polyps (GBPs) are a common problem.

Pathology: 70% of GBPs are cholesterol polyps. Adenomas are the next common category. Adenomas can turn into adenocarcinomas. The risk of maliganancy is small but real. Polyps larger than 10 mm and patients older than 50 years are the two main risks for malignancy.

Diagnosis: Most polyps are asymptomatic diagnosed incidentally in the course of investigations for other abdominal conditions. Less than 10% of polyps present symptomatically with indigestion, flatulence, nausea, right upper quadrant pain and discomfort or symptoms of cholecystitis. It is not clear how much of these symptoms can be caused by the actual polyps.

Investigations: Ultrasound is usually the first investigation performed. CT is performed either to investigate other abdominal conditions or to further investigate equivocal ultrasound findings. EUS is a better modality than transabdominal ultrasound but it is not normally used as the first line of imaging.

Management: There is no unified policy to manage GBPs. Laparoscopic cholecystectomy should be offered to patients over 50 years, if polyps are larger than 10 mm, if polyps increase in size during follow up or if the polyps are symptomatic. Management of polyps which fall outside these criteria is debatable. There should be a clear and open discussion between the surgeon and the patient especially if the patients do not quite fulfil the criteria for cholecystectomy.

Keywords: Gall Bladder Polyps; Cholesterol Polyps; Gall Bladder Adenoma

Abbreviations

ASA: American Society of Anesthetists score;

CT: Computed Tomography;

EUS: Endoscopic Ultrasound;

FDG: F-Labelled Deoxy-Glucose;

GBP: Gall Bladder Polyp;

MRI: Magnetic Resonance Imaging;

MSI: Microsatellite Instability;

PCR: Polymerase Chain Reaction;

PET: Positron Emission Tomography;

US: Transabdominal Ultrsound

Introduction

Polypoid lesions of the gall bladder may be defined as elevations of the gall bladder mucosa [1-4]. They are a common problem in clinical practice. More polypoid lesions of the gall bladder are detected with the increasing use of ultrasound and CT in clinical practice. Because of the risk of malignant transformation [4] and the well known dismal prognosis of gall bladder cancer, it is important to establish a management strategy for gall bladder polyps. There is no strong agreement in the literature as to what the natural course and optimal management of the polyps are. Management is rather arbitrary and inconsistent in many hospitals. Not infrequently, decisions are based on individual expert opinion (level IV evidence). This review aims to provide some understanding of the pathology, behaviour and diagnosis of gall bladder polyps (GBP) and discuss the different management options.

Epidemiology and Prevalence

Data are variable in the literature but the prevalence is around an overall figure of about 4-6% with men (7%) being more affected than women (5%) [1,5]. Although fewer reports noted GBPs more frequently in women [6,7], the general view is that GBPs are more common in men, unlike gall stones [5]. There could also be some variation with the ethnic origin of the population studied [5]. GBPs are found in 2 – 12 % of cholecystectomy specimens [8,9].

Obesity particularly visceral obesity has been occasionally associated with GBPs [10,11]. Glucose intolerance is a risk factor for the development of GBPs [5]. Less important demographic factors are lack of physical activity, parity, use of exogenous female hormones, and alcohol consumption [5]. There is no association between GBPs and plasma lipid profile, liver function tests or hepatitis B status [5].

GBPs occur in syndromes associated with intestinal polyps such as Peutz-Jeghers [12] and Gardner's syndromes [5,13] although the association with colorectal polyps other than the above syndromes is not well documented [14].

Pathology

(A) Classification

There is no unified classification for GBPs [4,9]. However, they can be classified as follows [2,8,9,15]:

(A) Pseudotumours (78%): cholesterol polyps, inflammatory polyps, adenomyoma, adenomatous hyperplasia.

(B) True tumours:

1. Benign

(a) Epithelial: adenoma (tubular, papillary, mixed tubulopapillary). The tubular type is most prevalent and consists of pyloric or intestinal type glands.

(b) Mesenchymal (rare): haemangioma, lipoma, leiomyoma, granular cell tumours.

(2) Malignant: Adenocarcinoma and metastatic carcinoma.

(B) Description of the common polyps

Cholesterol polyps constitute around 70% of GBPs [4,14]. Their aetiology is not clear but theories relating to altered hepatic metabolism of cholesterol have been suggested whilst other authors assume they are due to direct deposition of cholesterol from blood [2,15,16]. There is a close relationship between metabolic syndrome and development of cholesterol polyps and patients with cholesterol polyps tend to have high BMI and HbA1c but this is not an invariable association and these relations are inconsistent [15]. Histiocytes (foam cells) gather on the inherent layer of the gall bladder wall, covered with normal epithelium of mucous membrane, thus forming cholesterol polyps [4]. Small sized cholesterol polyps are often multiple lesions without cancerous changes [4]. Cholesterol polyps are almost always less than 10 mm [17]. Cholesterol polyps are observed more frequently in young patients [15].

Gall bladder adenomas are single lesions with a pedicle [4]. Adenomas may coexist with hyperplastic and metaplastic lesions and may show a wide range of morphologic pattern that may further complicate the histological diagnosis [9]. Gall bladder adenoma may develop into carcinoma [4].

60% of the polyps are single and 40% are multiple [15]. Multiplicity is more common in cholesterol polyps compared to true polyps [14] (54% Vs 11% respectively in one study [15]).

Park et al [1] reported 82 (45%) cholesterol polyps, 41 (23%) adenomas and 25 (14%) adenocarcinomas in 180 patients who underwent cholecystectomy for gall bladder polyps.

(C) Risk of malignancy

Among all types of polyps, only adenomatous polyps are associated with cancers as compared with the pseudotumours [6]. In other words, cholesterol polyps have no malignant potential [18], although little is known about the behaviour of rare tumours such as leiomyoma.

The Transformation Process

This process is not clearly explained in the literature. An adenoma to carcinoma pathway similar to colon cancer has been hypothesised although other authors suggest that the pathway is different from that of the colon [1,5]. Metaplasia, dysplasia, carcinoma in situ and invasive carcinoma have been reported in some series but little is known about whether these changes are a part of the course of transformation of polyps into a cancer [5,6,9]. This conclusion was investigated by PCR studies which showed that microsatellite instability (MSI) could be a part of the transformation pathway indicating that inactivation of mismatch gene repair occurs early in the gall bladder carcinogenesis [9]. Most authors believe that gall bladder cancer arises from flat dysplasia and only a few arise in pre-existing polyps [9]. Gall bladder cancer, therefore, could either be an adenocarcinoma with no adenomatous background or an adenocarcinoma in an adenoma background [1]. Most gall bladder cancers arise de novo rather than on top of a pre-existing adenoma [9]. The incidence of malignancy in GBPs is 3 – 8% [9].

Oncogenes p16, p21 and p53 have been implicated in the transformation process [9].

Risk factors for malignancy

Different factors relating to the possible malignant process in GBPs have been studied. These factors are age, size, rate of growth, multiplicity, and shape (sessile or pedunculated). The two most important factors are age and size [1,8]. The risk of malignancy increases with age [1]. There is an increase in the risk of malignancy above the age of 50 [9] although fewer malignant polyps have been reported in patients in their forties and indeed very few have been reported in patients as young as 37 years [1]. No malignant polyps have been reported in patients younger than 30 years [1]. Polyps larger than 10 mm have a significant risk of malignancy [8,19]. Most studies take the 10 mm size as the cut off point for the risk of malignancy although some studies [13,20,21] would take 13 or 15 mm as the cut off point. However, few cases of in situ or invasive cancers have been reported in polyps measuring between 5 and 10 mm [1, 22]. Malignancy in polyps smaller than 5 mm is very rare and indeed, some studies reported that no malignant process virtually exists in polyps smaller than 5 mm [1]. About 50% of polyps show no change in size during follow up [1,2]. Polyps which tend to enlarge are more likely to turn malignant compared to those which do not show change in size [4,19]. Malignant transformation is more likely to happen in single polyps compared to multiple polyps [4,15,19]. Sessile lesions smaller than 10 mm have an increased incidence of malignancy compared with those with a stalk [8,19,23]. In a retrospective study, Kim et al [20] reported that a polyp size ≥15 mm was the strongest predictor for a neoplastic polyp. Furthermore, the hyperechoic foci in a polyp, CT visibility, single or sessile polyps and age older than 50 years would be useful indicators for the differentiation of a neoplastic polyp [20]. Although serum levels of tumour markers like CEA and CA 19-9 increase in gall bladder cancer [8], they are of little value in solving the diagnostic dilemma of the nature of small GBPs.

Relation to gall stones

Between 8 and 21% of GBPs are associated with gall stones [1,8]. As gall stones are a weak independent risk factor for gall bladder cancer [1], it is difficult to draw firm conclusions as to whether gall stones actually increase the risk of malignany in the polyps or whether they are an incidental association. Therefore, it remains speculative whether GBP associated with gall stones are more likely to develop into malignant polyps.

Presentation

Most GBPs are asymptomatic and are found on ultrasound for investigation of nonspecific upper abdominal pain [9,14]. Less than 10% of polyps present symptomatically [15] with indigestion, flatulence, nausea, right upper quadrant pain and discomfort and even symptoms of cholecystitis [15,17,24]. Often the symptoms are nonspecific and vague [8,25]. That said, it is difficult to evaluate the spectrum of the symptoms due to the inadequacy of the studies addressing this issue. Furthermore, it may be rather difficult to understand how relatively small lesions such as the polyps, which are not proved to provoke a significant inflammatory reaction, can logically produce symptoms such as those described above in the gall bladder which is an organ with a spacious lumen. It is generally believed that the polyps as such are asymptomatic and the clinical manifestations are due to gall stones or cholecystitis [7]. Moreover, in symptomatic patients without gall stones, it is uncertain how and to what extent adenomas contribute to the symptoms [7]. It is suggested that the symptoms are due to the prolapse of the polyp into Hartmann's pouch or due to fragments of the polyps obstructing the cystic duct [7] but that would only apply to a minority of polyps.

Imaging

1. Transabdominal ultrsound

Ultrasound (US) is often the first diagnostic tool with a sensitivity of around 90% and specificity of about 94% [4]. Sonographically, GBPs can be defined as immobile echoes protruding from gall bladder wall into the lumen [5]. Cholesterol or inflammatory polyps mostly have a thin pedicle and swinging or floating features. Cholesterol polyps which are normally small (less than 10 mm) are echogenic masses without acoustic shadowing although some cholesterol polyps particularly the large ones (>10 mm) appear partially or completely echogenic on ultrasound [4,18] which could make it difficult to distinguish from adenocarcinoma [26]. The echo density inside cholesterol polyps presents uneven granule shape [4]. Adenoma has

more even echo; however, it is difficult to distinguish early gallbladder carcinoma from adenoma [4,5]. Ultrasound is more reliable in larger polyps as the sensitivity and specificity of US for polyps <1 cm had been reported to be 20% and 95.1%, respectively, whereas the sensitivity and specificity of US for polyps >1 cm was 80% and 99.3%, respectively [24]. Akyurek et al [24] reported better sensitivity, specificity, positive prediction value and negative prediction value for ultrasound in polyps measuring > 1 Cm compared with polyps measuring < 1 Cm.

Gall stones and thick gall bladder wall may obscure GBPs [9] and indeed gall stones may be misinterpreted as polyps on ultrasound. It has been shown [27] that a number of gall bladder showing polyps would turn to show gall stones when ultrasound is repeated at the follow up. In other words, the coexistence of gall stones would decrease the sensitivity of ultrasound in detecting GBPs.

The correlation between ultrasound and histology results has not been clearly defined [5] although in a prospective case-control study Fei et al [28] reported that contrast-enhanced ultrasound may distinguish gallbladder adenoma from cholesterol polyps when the ultrasound findings were compared to pathology reports.

2. CT Scan

CT scan can also be used [15]. In the hospital setting, CT is used to further investigate equivocal ultrasound findings or when polyps are discovered incidentally in patients who have CT for other causes. The preoperative ultrasound and CT measurement of the polyp size is more accurate in true polyps compared to cholesterol polyps when correlated with the size measured on pathological examination [15].

3. MRI [29]

There is an increasing body of evidence to support the use of MRI selectively in gall bladder polyps. Diffusion-weighted MRI may be useful in differentiating between benign and malignant polypoid gall bladder lesions

4. Endoscopic ultrasound

Endoscopic ultrasound (EUS) is better than B-ultrasonogrophy [4,18,24]. As a modality of imaging as the former can provide high resolution images of small lesions with higher ultrasound frequencies (7.5 – 12 MHz vs 3.5 – 5 MHz) [23] but it is not normally used as the first line of imaging. EUS is normally used to further investigate abnormalities found on either ultrasound or CT and is unnecessary in straightforward cases. The accuracy of EUS in identifying neoplastic lesions among polyps is greater for lesions larger than 10 mm compared with lesions smaller than 10 mm (88.9% vs 44.4%, $P < 0.05$) [23,24].

5. PET Scan

The use of positron emission tomography (PET) scanning using F-labelled deoxy-glucose (FDG) has been studied and the authors reported that FDG-PET may become one of the most useful tools for accurate preoperative diagnosis of small GBPs [24]. However, the availability of PET scanning in the standard hospital setting is questionable.

6. CT biliary cystoscopy

CT biliary cystoscopy (endoscopy) has been scarcely described in the literature where the results were superior to conventional CT [30]. However, there is a risk of reaction to the contrast injected in CT biliary cystoscopy and it did not have any convincing advantage over the ultrasound. CT cystoscopy had not been established as a standard modality in clinical practice.

Despite the availability of all these imaging modalities, it may still not be possible to differentiate benign and malignant polypoid lesions by solely depending on imaging studies [8].

Management

Management of GBPs is controversial [3]. There are no randomised clinical trials comparing cholecystectomy versus no cholecystectomy in GBPs [3].

Patients with GBPs greater than 10 mm or those who are symptomatic should have (laparoscopic) cholecystectomy whilst those with polyps less than 10 mm and/or are asymptomatic should have a follow up ultrasound in 6 months [3,4,17,24,31]. Babu et al [32] recommended two scans at six monthly intervals for polyps between 5 and 10 mm with subsequent surveillance tailored to age and growth whilst surveillance may not be needed for GBPs <5 mm. Most authors recommend cholecystectomy in patients older than 50 years [4,9]. Enlargement in the size of the polyp would indicate cholecystectomy [4,32]. Other indications are polyps with single wide base, coexisting gall stones and gall bladders with irregular thickened wall [4,9]. Other authors [4] have added polyps in the gall bladder neck which cause obstruction as an indication for cholecystectomy and although this is theoretically possible, it would only be the case if the polyps are fairly large. The decision is more straightforward in the presence of gall stones as gall stones are normally an indication for cholecystectomy but the real difficulty is when there are no gall stones [7].

Lee et al [33] recommended open cholecystectomy for GBPs larger than 18 mm because of the risk of malignant infiltration. However, it would be controversial whether open cholecystectomy could be justified in the era of laparoscopic surgery on the basis of size alone unless there are suspicious features of malignancy

Different papers have called for the need for randomised trials to address this question [3] However, we think it would be rather impractical to design a randomised trial in this regard. The fact that definitive diagnosis can only be established after cholecystectomy [6] imposes great difficulty in different management aspects including designing a randomised trial. Gurusamy et al. [3] have discussed four problems which may be encountered if a randomised trial was to be designed (blinding, dealing with patients with an increase in the size of polyps or those who develop symptoms during follow up, sample size and the loss of patients follow up). It is; therefore, clear that the most important factors taken into account when making management decisions are the age of the patient and the size of the polyp.

A scheme of management may be suggested as follows [5]:

I. Symptomatic polyps:

Cholecystectomy

II. Asymptomatic polyps

A. Large > 10 mm

Cholecystectomy

B. Small (<10 mm)

1. Age >50 years and/or gall stones

Cholecystectomy

2. Age < 50 years, no gall stones:

Follow up with ultrasound every six months

It is, therefore, recommended that polyps larger that 10 mm warrant cholecystectomy regardless of the presentation [7].

Myers et al [5] added solitary polyp to these indications for cholecystectomy.

In conclusion, (laparoscopic) cholecystectomy would be recommended for:

(a) symptoms

(b) polyps where there is a chance of being malignant as suspected in:

i. polyps larger than 10 mm

ii. polpys which increase in size during follow up

iii. patients above 50 years

(c) associated gall stones

(d) equivocal or suspicious features on scanning.

Discussion

It can be concluded from the above data that most gall bladder polyps do not progress into malignancy [27] but the risk of malignancy is real yet small.

As there are no strict criteria to predict the behaviour of the polyps with confidence and as definitive diagnosis can only be made histologically, there may be a case to have a lower threshold for cholecystectomy in GBPs [22,34]. For example, to offer laparoscopic cholecystectomy for most polyps reserving follow up for those younger than 50 with significant comorbidities (ASA III or worse) and the young who decline surgery if they have polyps less than 10 mm. That means laparoscopic cholecystectomy for polyps of any size (young or otherwise patients) excluding the above mentioned categories, save those with polyps smaller than 5 mm.

The other question arising if follow up policy is adopted is how long and how often the scanning is going to be [33,35], which is another factor in favour of a more proactive policy of cholecystectomy.

Most practitioners, however, would be selective in offering cholecystectomy rather than following this rather generalization plan [35]. That is assuming there are no gall stones or suspicious features. If the latter are found, they should prompt the appropriate surgical management [35].

To solve the dilemma, we believe that there should be a scheme like the one described above, which is based on the commonly accepted practice [35], where the patients who fulfil the criteria for cholecystectomy should be strongly advised to have the operation as the standard way of management. More important than having a scheme, exercising proper clinical judgement integrating all the facts related to any particular patient is most vital in decision making. Furthermore, there should be an open and clear discussion with all the other patients where cholecystectomy should be offered as a preference, being the only way to treat the problem, establish a diagnosis and effectively avoid the risk of malignant transformation.

Conclusions

There is lack of consistency in the literature in most aspects relating to GBPs. However, it is generally agreed that most gall bladder polyps are cholesterol polyps which have no potential to turn malignant. Adenomas of the gall bladder have the potential of malignant transformation. The most important factors related to malignant transformation are age (older than 50 years) and size of the polyp (larger than 10 mm). These are, primarily the two main indications for cholecystectomy in gall bladder polyps. It is not easy to design a randomised trial to address this question and therefore, the management is now based on our best knowledge of behaviour of gall bladder polyps, albeit not based on level I evidence.

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