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Editorial

Gallbladder polyps: benign or malignant and gallbladder cancer

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Gallbladder carcinoma (GBC) is the most common and aggressive type of malignant tumor of the bile ducts; it is highly lethal and has the shortest survival period. In 2018, the International Agency for Research on Cancer (IARC) and the Global Cancer Observatory (GLOBOCAN) estimated that 1.7% of all cancers deaths are attributed to GBC and that 220 000 new cases are diagnosed every year. (1)

GBC occurrence is more common in some regions, and its incidence varies substantially worldwide. Chile reports the highest incidence rates (27/100 000), followed by regions in northern India (21.5/100 000). Specifically, in Chile (South America), in the Mapuche indigenous people of Valdivia, GBC has an incidence of 12.3 per 100 000 inhabitants in men and 27.3 per 100 000 inhabitants in women. (2, 3) Although it rarely occurs in some parts of the world, its occurrence is disproportionately high in some ethnic groups. (1, 3)

GBC affects more women than men because the former tend to develop more vesicular diseases caused by bladder stones. In fact, this type of cancer is one of the few cancers with higher incidence rates in women compared to men (3 to 6 times higher). Moreover, the risk of GBC increases with age, since it has been reported that more than two thirds of people diagnosed with it are older than 65, with an average age of 72 years. (1)

Factors associated with higher GBC occurrence rates include being a woman, geographic location, ethnicity, being obese, family, or personal history of gallbladder stones, and chronic gallbladder inflammation and infection. (1, 2, 4)

70%-90% people with GBC have a history of cholelithiasis; somehow, it should be noted that of most people with cholelithiasis do not develop GBC, with only 0.5%-3% cases resulting in this type of cancer. The exact mechanism through which cholelithiasis results in a carcinoma is not fully understood, and chronic inflammation and damage to the epithelium by irritation is thought to lead to mucosal damage. (1)

Gallbladder stones size contributes to the risk of developing GBC. (4) Specifically, stones >3cm have been associated with a higher risk (9.2 to 10.1 times) compared to with stones <1cm. (1) Persistent inflammation in the gallbladder also seems to contribute to wall calcification, resulting in porcelain gallbladder, which is in turn associated with a high risk of GBC. (1)

Primary sclerosing cholangitis (PSC) is also associated with an increased risk of GBC. (4, 5) Biliary tree anomalies, specifically in the junction of the pancreatic duct with the biliary tract, which are findings with a higher prevalence in Asian population, have also been associated with a higher risk of developing this type of carcinoma. (1)

Inflammation and irritation of the gallbladder can be caused by chronic bacterial infections commonly caused by *Salmonella typhi* or *Helicobacter bilis*. Salmonella carriers are 12 times more at risk of developing GBC. Chronic Salmonella infection is twice as common in women compared to men, while *Helicobacter* has been involved in the formation of cholesterol stones. (1)

Some of the most common findings on ultrasound imaging of the gallbladder are polyps and stones. The presence of polyps in these imaging studies may be discordant with the end diagnosis of the disease since most polyps are benign. One of the goals of some studies on this topic is to compare polypoid lesions of the gallbladder identified in imaging scans with the final diagnosis of GBC after undergoing cholecystectomy. (4, 5)

This issue of the Colombian Journal of Gastroenterology includes a paper on risk factors for malignancy of gallbladder polyps in patients treated at two public hospitals of Peru. (6) To this end, the authors of this retrospective study that includes 9 years of data (2004-2012) reviewed cholecystectomy pathology reports with a confirmed finding and diagnosis of polyps. Out of the total 367 cases included, only 26 (7%) had malignant polyps (adenocarcinoma diagnosis), while polyps were benign in 341 (92.9%). Variables such as malignancy, age, sex, polyp size, number of polyps, presence of stones, gallbladder size, and gallbladder wall thickness were included for analysis. In daily practice, all these factors, besides polyp size, help make clinical decisions, such as defining the pertinence of performing cholecystectomy. (4, 5)

In addition, in said study (6), according to a bivariate analysis, polyp size, gallbladder wall thickness, gallstones, patient age, and gallbladder size were associated with an increased risk of malignant gallbladder polyp. The risk of malignancy increased with polyp size and gallbladder wall thickness. Regarding polyp size, the authors found that polyps >10 mm have an increased risk of malignancy, but they also identified reports of malignancy in polyps <10 mm, establishing a >6 mm diameter cut-off point with adequate sensitivity and specificity. There were not significant differences between sexes or between the presence or absence of stones as risk factors.

This study is very relevant due to its statistical results. Of course, the article relates to the diagnosis of incidental carcinoma (pathology report), where the relevant literature reports that carcinoma is identified in 0.2% to 1.1% of all laparoscopic cholecystectomies. (7)

GBC originates from the gallbladder mucosa. Early development of this carcinoma is usually asymptomatic and has a high probability of metastasis. Therefore, most patients are diagnosed with intermediate or advanced stage GBC, when there is no longer a possibility of providing curative care. (1)

While there is consensus on chronic inflammation as the initial pathogenic event of GBC, the mechanism of tumor progression has not been clearly established yet. Two models have been proposed: transition from metaplasia to dysplasia or from adenoma to dysplasia. (3) The metaplasia-carcinoma sequence model is more widely accepted, because these histological alterations are more frequent compared to adenomatous polyps, which are found in less than 3% of specimens obtained from early carcinomas. (3, 4) This sequence from metaplasia to dysplasia, to cancer *in situ,* and finally to invasive cancer can last about 15 years. (2)

There is also an unusual asymmetric thickening of the gallbladder wall, with infiltration into surrounding structures. Most GBC are adenocarcinomas (80%-95%), which may be papillary, mucinous tubular, or signet ring cells carcinomas. Other rare types of gallbladder tumors are squamous cell carcinomas (16%), anaplastic or undifferentiated carcinomas (2%-7%), and adenosquamous carcinomas (1%-4%). Most tumors are found in the fundus, about 30% in the body, and 10% in the neck. (2)

GBC has one of the shortest survival rates since diagnosis, reflecting its aggressive behavior and late diagnosis. (7) It should be noted that only 1 out of 5 patients can be diagnosed when the disease is still localized in the gallbladder. (1)

GBC may have one of the following three forms of presentation:

1. During the diagnosis of a malignant disease (advanced disease).
2. When the malignancy is detected during a cholecystectomy performed to treat an apparently benign disease.
3. The malignant disease is diagnosed incidentally during the pathological examination of a routine cholecystectomy. (4)

Early GBC is preoperatively suspected through imaging studies in 30%-40% of cases and most of them are detected incidentally during histopathological examination of the gallbladder. (7)

Patients with GBC *in situ* have a survival rate of over 80% at 5 years, which declines to 8% in advanced-stage cancer cases. These figures show the importance of identifying cancerous and precancerous polyps to allow early treatment and prevent metastasis or the development of malignancy. In patients with true gallbladder polyps, laparoscopic cholecystectomy is the standard treatment. (4)

Gallbladder polyps (GP) have an estimated prevalence of 5% in the general population; however, only 5% of them are considered true gallbladder polyps. Most GPs are detected incidentally through radiological imaging or on histological examination after cholecystectomy. (4, 5)

A small number of patients with GPs may be symptomatic and present with symptoms and signs of acute cholecys-

titis secondary to the obstruction of the cystic duct, or to a cholangitis due to polyp fragments that may pass into the bile duct. (5)

Most GPs are classified as pseudopolyps (benign), including cholesterol polyps, focal adenomyosis, hyperplastic polyps, and inflammatory polyps; none of them has a malignant potential, nor require follow-up or intervention. On the other hand, true gallbladder polyps, which include adenomas and adenocarcinomas, require surgical management. Adenomas are benign but must be treated as precancerous since there is evidence of the adenoma-carcinoma sequence in colorectal cancer (CRC). (4) In patients with true gallbladder polyps, laparoscopic cholecystectomy is the best treatment. (5)

Radiological imaging of the gallbladder should be performed with three purposes in mind: to differentiate polyps from stones or folds of the gallbladder mucosa, to differentiate true polyps from pseudopolyps, and to measure the size of polyps accurately, as it is currently the most important factor to determine whether a patient should undergo cholecystectomy or not. (4)

There are risk factors that may help in deciding whether performing a cholecystectomy or not, these include polyp size, the number of polyps, polyp morphology, the presence of stones, age, patient origin (ethnicity), medical history (primary sclerosing cholangitis), and the thickness of the gallbladder wall. (4)

Some studies have shown that malignant polyps tend to be larger than benign polyps. (5, 8) Currently, polyp size in radiological imaging is the most determining factor in the management of gallbladder polyps. Several retrospective studies have found that the risk of malignancy significantly if the size of the polyp is ≥10mm, and the general consensus is that patients with polyps ≥10mm should be treated with cholecystectomy. (3, 4)

The guidelines published by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) support this consensus, but two systematic reviews (4, 9) show that while most malignant polyps have a 10mm size, there is a significant number of cancerous or precancerous polyps below this size threshold. Similar findings were reported in the article published in this issue of the journal. (6)

The main determinant of the risk for GBC is polyp size. (8) However, not all polyps <10mm are benign, which is why it is important to identify risk factors that allow a higher suspicion of malignancy and, this way, performing cholecystectomy in patients with polyps below that size threshold. (4)

Evidence that supports a greater likelihood of malignancy in solitary polyps when compared to multiple polyps is very weak. For example, Bahtt et al. (9) found that the likelihood of malignancy of a solitary polyp <10mm was 4.3%. Based on this result, the probability of malignancy is not high enough to recommend performing cholecystectomy in all solitary polyp cases. Thus, the presence of a single polyp should be considered in combination with other risk factors for malignancy (4) in order to make a better decision in clinical practice regarding the use of cholecystectomy.

In this regard, Kwon et al. (10) report that patients with gallbladder polyps with sessile morphology have an increased risk of malignancy compared to patients with pedunculated polyps (*odds ratio* [OR]: 7.70: 95%confidence interval [CI] 2.48-23.95). In another study (9), the probability of malignancy was 13.9% in sessile polyps <10mm. In addition, if the polyp was solitary and sessile, the probability of malignancy was 24.8% and cholecystectomy was recommended. The ESGAR guideline uses the strength of this evidence to recommend the use of cholecystectomy in all patients with sessile gallbladder polyps with sizes between 6mm and 9mm. (4)

The risk of most cancers increases with age and this is also the case for GBC. Several studies support the age factor, but the risk of malignancy varies significantly between the ages of 50 and 65 years. (4)

In this sense, Bhatt et al. (9) found that in patients older than 50 years with polyps <10mm the probability of malignancy was 20.7% and cholecystectomy was therefore recommended. The ESGE guideline has used this evidence to conclude that if patients are older than 50 years and polyps are between 6mm and 9mm, they should undergo cholecystectomy. (4)

There is little evidence supporting the presence of stones and polyps as a higher risk factor for malignancy. Cholecystectomy is recommended in symptomatic patients due to stones, and the decision is therefore easy to make. However, evidence is not strong enough to suggest cholecystectomy in cases with dual conditions (polyps and stones). (4)

Regarding ethnicity, one study conducted in in 5 391 patients undergoing cholecystectomy (11) reports an increased risk of malignancy (13 times more) in Indian population compared to Caucasian population (*Hazard ratio* [HR] 12.92; 95% CI 3.77-44.29). This is the only study comparing risk of GBC among ethnic groups. The ESGAR believes this article provides sufficient evidence and, consequently, in its guidelines recommends performing cholecystectomy in Indian patients with polyps between 6mm and 9mm. (4)

The presence of all these risk factors, which are included in the paper published in this issue of the journal (6) and addressed in the relevant literature, can help determine in clinical practice whether performing a cholecystectomy or not, as well as decrease the number of true polyps omitted in the <10mm size category.

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