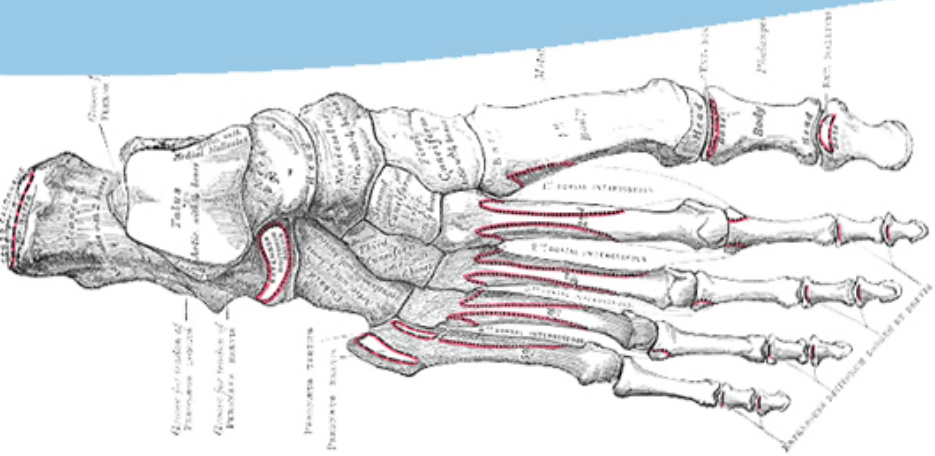

7. Revisión 5

Gallblader carcinomas: from risk factors to targeted therapy

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Abstract:

Objectives: To revise the epidemiology, pathogenesis, diagnosis, treatment and prognosis in gallbladder carcinomas. To revise the role of molecular pathology in this entity and its importance in therapeutic perspectives.

Methods: A revision of all the articles published between 2006-2016 and indexed in PubMed containing the keywords "gallbladder", "cancer", "carcinoma", "diagnosis", "treatment", "perspectives" and/or "targeted therapy " was carried out.

Results: The incidence of gallbladder carcinoma varies greatly depending on the geographical area [considered]. Its natural history is related to chronic inflammation and cholelithiasis is its main risk factor. The diagnosis is usually made at a late stage and, despite the treatment, it shows/has a poor prognosis. Changes in p53 and K-Ras are common. Modulation of inflammation is postulated as a therapeutic alternative.

Conclusions: Gallbladder carcinoma is a neoplasm with an aggressive course. The improvement in its prognosis needs of the control of risk factors and early diagnosis supported by imaging tests. New surgical techniques and the description of new therapeutic targets also offer promising prospects.

Keywords:gallbladder, carcinoma, cancer, pathogenesis, treatment, prospects

Introduction

Gallbladder carcinoma (GBC) is the most common malignant neoplasm of the biliary tract (1). It is also the most aggressive and has the worst survival rates within its group. This is the result of / this is due to the rapid evolution of the tumour, the nonspecific symptomatology that usually accompanies this growth, the lack of screening tests, and the problems with diagnostic imaging. Complete surgical resection is the curative alternative, but it is only feasible in 10% of the cases (2). Surgical morbimortality and bed recurrence rates are high among patients

with early carcinomas susceptible to this type of intervention (3). The objective of this text is to revise the epidemiology, pathogenesis, pathology, treatment and perspectives of GBC.

Material and methods

A revision of the literature on GBC was performed using PubMed. The words "gallbladder", "cancer", "carcinoma", "diagnosis", "treatment", "perspectives" and / or "targeted therapy" were used as keywords. The results were filtered by using only revisions published in the last decade (2006-2016). Secondary references steaming from revisions and original articles indexed in this database were filtered manually. Only relevant studies focused on targeted therapy or perspectives on the disease were included. Clinical cases and communications on infrequent histological variants were not included.

Epidemiology

GBC is the most globally common malignant neoplasm of the biliary tree. It is three times more common in women than men, with a mean age at diagnosis of 72 years. The pathogenesis of GBC has not been clarified, but multiple factors are known to be involved in its development (1) (2). Among them, cholelithiasis seems to be most prominent.

Demographic factors

The incidence of GBC varies according to the geographical area [considered]. Rates for high-risk regions such as Chile (27 / 100,000), India (21,5 / 100,000), Bolivia (15,100,000) or Pakistan (13,8 / 100,000) are much higher than those found in low-risk areas . The United States, Canada, and New Zealand have incidence rates of 0.4-0-8 / 100,000 in men, and 0.6-1.4 / 100,000 in women (1,3,4). Western European countries, including Spain, are considered regions of risk, although with a lower presentation frequency than Asia and the Andean region.

These variations have been attributed to genetic differences and the lifestyle of the population. Diets high in carbohydrates and red meat increase risk (5). The same thing occurring with obesity, which increases the risk of GBC 1.59 times in women, and 1.09 in men (1). The link between being multiparous and GBC is not well understood. It is unknown if it is directly related to carcinogenesis or whether it is secondary to the higher frequency of cholelithiasis in this population group.

Gallblader disease

Cholelithiasis is the disease that shows the highest correlation with the development of GBC. Up to 80% of patients with this neoplasm have lithiasis (3,6). The risk is higher in single-stone lithiasis with a stone greater than 3 cm in diameter. In these cases, a relative risk 10 times higher than the general population has been described (1,2). The composition of the calculus/stone has shown no positive correlation with the development of GBC.

Cholelithiasis stimulates the appearance of chronic inflammatory phenomena that could favour epithelial transformation. Initially, dysplasia would occur on the biliary or metaplastic intestinal / pseudopyloric epithelium. Then/Therefore, the persistence of the damage could promote neoplastic development.

The term "porcelain gallbladder" describes two distinct patterns: diffuse or selective intramural calcification. The patched or selective pattern seems more associated with the occurrence of GBC than the diffuse pattern. Vesicular polyps, especially when they are unique, sessile and larger than 10mm are also a risk factor (2). Abnormalities in the pancreaticobiliary junction and congenital cysts may favour the ascent and remanence of pancreatic secretions in the biliary tract and gallbladder. This stimulates, as in the case of cholelithiasis, chronic inflammatory phenomena that trigger precancerous changes in the mucosa. The same happens with the retention of secretions in primary sclerosing cholangitis.

Other risk factors

Hormone therapy has been linked to GBC (1). This could be related to/could be the result of/could

be due to its prolitogenic role, but also to the direct stimulation of epithelial proliferation and transformation. The association with other drugs and heavy metals has been described, although its contribution to the development of GBC is uncertain. Carriers of Salmonella and Helicobacter (1,6) in the biliary tract have been linked with a higher GBC rate. Bacterial degradation of bile salts is believed to be carcinogenic.

Pathogenesis

Two key pathways have been proposed in GBC development: the dysplasia-carcinoma sequence and the adenoma-carcinoma sequence. In both cases, the transformed epithelium may be that of the gallbladder itself, or intestinal / pseudopyloric metaplastic mucosa. This last point is important considering that up to 80% of GBCs are adenocarcinomas.

In the dysplasia-carcinoma sequence, the initial metabolic frame is chronic inflammation (7-9). When this is associated with biliopancreatic junction abnormalities, it can lead to hyperplasia of the biliary epithelium. Alternatively, when it appears in the cholelithiasis, it normally promotes the appearance of foci of intestinal / pseudopyloric metaplasia. These lesions may progress and stimulate the genesis of dysplastic areas. These premalignant lesions, if the associated factors are maintained and elapsed long enough, may degenerate into carcinomas (7).

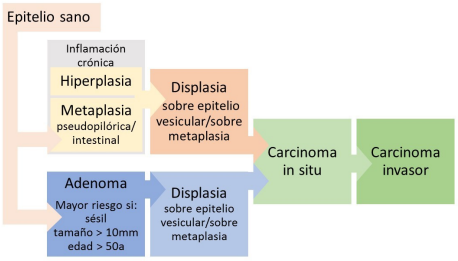

Figure 7.1: Modelo de diseminación y carcinogénesis en la vesícula biliar

During chronic inflammation, multiple cytokines, reactive oxygen species, prostaglandins, growth factors and the like are synthesied in low amounts, but in a sustained manner. This favours the appearance of mutations, epigenetic and/or post-translational modifications in tumour suppressor genes and oncogenes (8,10).

The tumour necrosis factor (TNF) is one of the most prominent mediators. From early stages, it modulates not only macrophagic activity and also stimulates angiogenesis and expression of growth factor receptors, such as EGFR. Chemokines such as CXCL12 have been observed to be increased in GBC. The same applies for MUC5AC, prostaglandins, and COX-2 activity. Therefore, the use of anti-COX2 drugs has been proposed as a modulator of chronic vesicular inflammation and as a possible preventive/adjuvant treatment in GBC (7,8). Sequence changes in p53, tumour suppressor gene (TSG), are present in one-third of the patients with cholelithiasis without GBC. The percentage increases to 52.4% when there is neoplasia. Therefore, the loss of p53 is considered an early change in GBC (7). Changes in the Ras family are less frequent among preneoplastic lesions. However, K-Ras is mutated in 39-59% of GBCs (8).
The loss of heterozygosity (LOH) occurs in several loci in GBC. Early events are considered changes in 5q. LOH at 3p and 9p is associated with progression. Other modifications/changes, described but probably later/at a late stage, occur in 13q and 18q (7).

The methylation of TSG promoters in GBC is a probable but still virtually unexplored event. (11) MiRNAs are molecules whose deregulation can lead to the onset of cancer. In this sense, although not fully studied, high levels of miR-155 have been associated with worse survival rates in GBC (8).

In the adenoma-carcinoma sequence, more uncommon in GBC, the steps are less well-known (7). The polyps with the highest risk of transformation are those already described in previous sections.

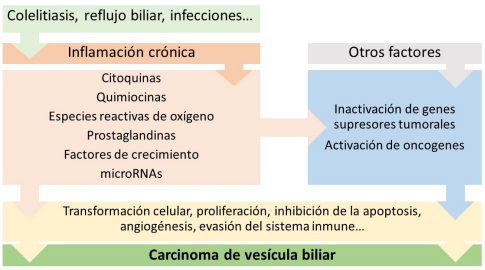

Figure 7.2: Cambios asociados a inflamación crónica y CVB.

Anatomic pathology

A significant fraction of GBCs is diagnosed incidentally after cholecystectomy. The anatomopathological study of the piece is indicated in all cases. In addition, if macroscopic lesions suggestive of BIC are observed during the operation, the intraoperative study is obligatory in order to assess the need to extend the initial surgery.

Macroscopically, between 10-37% of GBCs show features either compatible with chronic cholecystitis or not quite suggestive of a neoplastic formation process. In all other cases, suspicious areas are identified in the surgical specimen. These may be, as in imaging techniques: light occupying masses, polypoid lesions or wall thickenings. Around a 60% of GBCs settle in the fundus of the gallbladder, 30% in the body and 10% in the neck. White nodular lesions are the most commonly associated with intrahepatic invasion (1,2).
More than 80% of GBCs are adenocarcinomas, two-thirds of which are poorly or moderately differentiated. Other much more infrequent but also known histological variants are papillary, mucinous and adenosquamous carcinomas. Other histological types have been described, but their frequency is minimal and, therefore, are not well documented.

Clinical presentation and diagnosis

The symptoms of GBC are often nonspecific, which delays the diagnosis. The most common manifestations are chronic cholecystitis: epigastric pain, dyspepsia, precocious satiety, etc. In some cases, these may be accompanied by the constitutional syndrome. In this situation, hyporexia and weight loss are the most striking signs. Biliary obstruction is related to advanced disease. Digestive haemorrhage and high intestinal obstruction are other possible pictures in the beginning, although their frequency is much lower (2,6).

Two-thirds of treated GBCs are unsuspected carcinomas (2). The remaining third, known or suspected GBC, is diagnosed preoperatively through imaging tests. Among them, the most outstanding are an ultrasound (transabdominal or endoscopic), computed tomography (CT) and magnetic resonance imaging (MRI). Other less used are PET and cholangiography (12). Those patterns more commonly related to GBC are collected/can be observed in image 3 (12,13). The image also shows its frequency of presentation and the problems of differential diagnosis that each of these forms poses/proper of each of these forms.

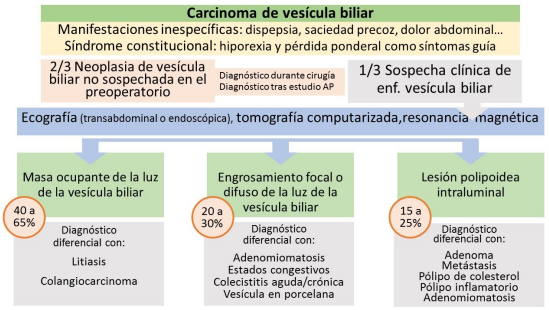

Figure 7.3: Presentación clínica y pruebas de imagen en CVB

Tumor markers

Tumour markers cannot be used as a diagnostic tool in GBC. However, in patients suspected of the disease due to imaging / clinical results, high levels of CEA, CA 19.9 and/or CA 125 may be highly suggestive of the disease (2).

Staging

There are different staging systems in GBC. These include Nevin Staging System, Staging System of the Japanese Society of Biliary Surgery and

TNM Classification of the American Joint Committee on Cancer (AJCC). These are presented in table 2 (1).

Treatment

The GBC treatment may vary according to its spread. Between 0.3 and 3% of all cholecystectomies performed due to cholelithiasis are reported as neoplasia. In this case, which is frequently approached with laparoscopy, up to a 17% of patients recur.

If GBC is suspected or confirmed, an open approach is necessary. The surgical extent will depend on the spreading of the hepatic injury and the existence of adenopathies. Thus, in T1a stage, simple cholecystectomy is curative. In T1b, cholecystectomy may be associated with segmentectomy (IVb and V) and lymphadenectomy. In T2 tumours, this is the appropriate procedure in all cases. T3 GBC needs aggressive surgery. Cholecystectomy plus lymphadenectomy and right hepatectomy may be suggested. If other structures were affected, this technique would be modified according to the circumstances. The T4 carcinomas are not subsidiary of surgical treatment (1, 6). Despite the previous indications, there is no agreement on the initial approach of this neoplasia. Imaging tests and diagnostic laparoscopy may help to evaluate the extent and may determine the technique to choose.

The GBC medical treatment has been little investigated. The therapy may have either the intention of healing or palliating. Three possible scenarios are presented: post-surgery single adjuvant therapy or therapy with radiation; unresectable, not spread disease with or without radiation therapy; and, lastly, palliative chemotherapy in metastatic disease.
In the case of post-surgery adjuvant therapy, a recent meta-analysis shows a possible benefit of chemotherapy for patients with a high risk of metastases. That is, those with a wider tumour extent, especially if accompanied by adenopathies. However, it does not clarify the role of adjuvant therapy for low-risk patients. Among those benefiting from the cytotoxic treatment, there are no preferential instructions. Gemcitabine-cisplatin or fluoropyrimidine are generally applied. In the case of an unresectable disease, previous chemotherapy regimens can be accompanied by radiation therapy. In the scenario of a metastatic disease, palliative chemotherapy /becomes the only alternative. Radiation therapy in GBC has been little evaluated and the results obtained are dissimilar. External radiation therapy might temporarily stop the local-regional spreading. Brachytherapy with Ir-192 might be useful for palliating obstructive symptoms secondary to biliary tract infiltration.

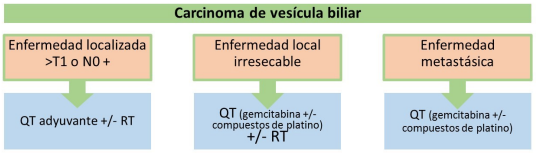

Figure 7.4: Radioterapia y tratamiento sistémico para CVB

Prognosis

The gallbladder cancer prognosis is bleak. Its manifestations are usually unspecific and appear in spread disease. Five-year survival rates after diagnosis reach 5%. Aggressive surgery improves the overall survival, but five-year recurrence rates after complete resection reach 40-60%. Poor prognostic factors for GBC include age, jaundice, palpable mass, T and N stage, the hepatic extent of the disease, squamous cell carcinoma, squamous adenocarcinoma or small cell adenocarcinoma. Tumour markers have been proposed to be included in this list, as well as certain genetic and epigenetic changes. However, the evidence is scarce and needs to be corroborated.

Conclusions

- GBC incidence varies greatly depending on the region [considered]. Some of the risk factors are age, gender, obesity, gallbladder disease, abnormalities of the pan-

creaticobiliary tract and exposure to certain drugs and infectious agents.

- Chronic inflammation is linked to GBC pathogenesis. Maintained synthesis of inflammatory mediators may favour carcinogenesis through TSG inactivation and oncogenes inactivation. Events such as losing of p53 and K-ras mutations are common.
- Clinical findings of GBC are unspecific and, usually, late.
- There are no recommendations for local and systemic treatment of GBC. Surgery and radiation therapy are useful for regional control. In unresectable or metastatic cases, chemotherapy regimens based in gemcitabine are the most employed.
- Adenocarcinoma is the most usual histological variant.
- GBC prognosis is bleak. KRAS, EGFR, BRAF and HER 2 are thought as a therapeutic target.
- Several ongoing clinical trials study the improvement in survival rates when confronting conventional chemotherapy to combined regimens with antiEGFR (cetuximab, erlotinib) /antiBRAF (selumetinib). VEGF has been observed to be overexpressed in biliary tract neoplasias. Thus, employment of angiogenesis inhibitors is also presented as a therapeutical alternative (1)
- Control of chronic inflammation may help to prevent/treat the biliary tract neoplasias. Thus, COX-2 inhibitors may be useful.
- Apart from CEA, Ca-125 and CA 19-9, the utility of markers such as CA242 and CA199 has been proposed for the monitoring and treatment of patients with GBC (14).

TABLA1: Factores de riesgo de CVB

Factores demográficos	Enfermedad de la vesícula biliar	Exposición a	Infecciones
Edad avanzada	Colelitiasis	Metales pesados	Salmonella
Mujer	Vesícula en porcelana	Metildopa	Helicobacter
Obesidad	Pólipos	Isoniacida	
Predisposición genética	Colangitis esclerosante primaria	Estrógenos	
Geográficos	Alteraciones en las vías pancreatobiliares	Tabaco	

TABLA 2: Sistemas de estadiaje en CVB.

TABLA 2. Sistemas de estadiaje en CVB.

Sistemas de estadiaje en CVB				
Sistema de estadiaje de Nevin				
Estadio	**Definición**			
I	El tumor invade mucosa			
II	El tumor invade: mucosa + muscularis			
III	El tumor invade: mucosa + muscularis + subserosa			
IV	El tumor invade: todas las capas de la vesícula + ganglio linfático pericístico			
V	El tumor se extiende al lecho hepático / presenta metástasis			
Sistema de estadiaje de la Sociedad Japonesa de Cirugía Biliar				
Estadio	**I**	**II**	**III**	**IV**
Invasión capsula	Sin invasión capsular	Invasión capsular sospechosa	Marcada invasión capsular	Invasión directa de víscera adyacente

Invasión hepática	Sin invasión hepática	Invasión hepática sospechosa	Marcada invasión hepática perivesicular	Extensa invasión hepática
Invasión de la vía biliar	Sin compromiso de la vía biliar extrahepática	Compromiso sospechoso del conducto biliar común	Marcada afectación de la vía biliar	Daño extenso sobre la vía biliar
Metástasis ganglionares	Sin metástasis ganglionares	Metástasis ganglionares alrededor del conducto hepático común	Metástasis ganglionares alrededor del ligamento hepatoduodenal o área circundante	Metástasis ganglionares regionales
Metástasis hepáticas	Sin metástasis hepáticas	Sin metástasis hepáticas	Sin metástasis hepáticas	Metástasis hepáticas presentes
Diseminación peritoneal	Sin diseminación peritoneal	Sin diseminación peritoneal	Sin diseminación peritoneal	Con diseminación peritoneal

Clasificación TNM de la AJCC

Estadio	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1,T2,T3	N1	M0
IVA	T4	N0,N1	M0
IVB	Cualquier T	Cualquier N	M1
	Cualquier T	N2	M0

T	Tis: Carcinoma in situ T1: a: Tumor que invade la lámina propia. b: Tumor que invade la submucosa T2: Tumor que invade el tejido conjuntivo perimuscular T3: Tumor que perfora la serosa y/o invade el hígado y/o órganos adyacentes (estómago, duodeno, colon, páncreas, vía biliar extrahepática) T4: Tumor que invade la vena porta, la arteria hepática o múltiples órganos
N	N0: no hay metástasis ganglionares loco-regionales N1: Metástasis ganglionares pericísticas o alrededor del pedículo hepático (porta, arteria hepática y conducto hepático común). N2: Metástasis ganglionares periaórticas, pericava, alrededor de la mesentérica superior y/o tronco celiaco.
M	M0: Sin metástasis a distancia M1: Con metástasis a distancia

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