The pleomorphism of gallbladder malignancy

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Learning objectives

Review the different patterns of presentation and dissemination of gallbladder cancer (GBC).

Enhance the role of imaging in staging and definition of resectability status.

Highlight some radiologic features that can be misleading.
Background

Introduction

GBC is an uncommon disease with an estimated incidence of 1.2 to 3 per 100,000 people in the United States and 1.03 per 100,000 in Portugal (1, 2), but is the commonest biliary tract tumor (3). Although some cases are discovered incidentally at histopathology, most patients present clinically with advanced disease. As result, the prognosis for GBC is poor and the curative surgery is limited. Imaging plays a central role in the diagnosis suspicion and in the selection of potential resectable cases by non-invasive staging (4). However, radiologic findings of gallbladder carcinoma are varied and overlap with those of other pathologies, particularly with those of bile duct carcinoma when invasion of the biliary tree is present.

Pathogenesis

The exact pathogenesis of GBC remains unclear, although pooling of carcinogens in conditions causing biliary stasis and malignant degeneration following chronic inflammation are suggested mechanisms (5).

GBC is two to six times more common in woman and the incidence increases with age (6). The most important risk factor for the development of GBC is cholelithiasis (3, 6). Other predisposing risk factors include: primary sclerosing cholangitis, congenital anomalies of the biliary tree, gallbladder polyps, ethnic origin, obesity, porcelain gallbladder, chronic biliary infections (e.g. Salmonella typhi, Opisthorchis viverrini), cigarette smoking, and exposure to certain chemicals (7-15).

Histologically, pancreatobiliary-type adenocarcinomas account for 90% of GBC, ranging from poorly to well differentiated. There are several histologic variants of adenocarcinomas recognized: papillary, intestinal, mucinous, signet-ring cell and clear cell. The remaining epithelial cell types occurring in the gallbladder include adenosquamous carcinoma, squamous cell carcinoma, small cell carcinoma, and undifferentiated carcinoma (16). Less common non-epithelial variants include sarcomas, lymphomas, carcinoid tumors and metastases. The histology and immunoprofile of GBC are similar to that of intra or extrahepatic bile duct carcinoma and pancreatic carcinoma, further confounding the definitive diagnosis (16).

Clinical presentation

Early-stage GBC is typically diagnosed incidentally because of inflammatory symptoms related to coexistent cholelithiasis or cholecystitis (16). Most frequently, patients present with advanced disease, complaining of vague and non-specific symptoms, which may
include abdominal pain, anorexia, weight loss, fever, and a palpable mass in the right upper quadrant or jaundice, if there is associated biliary obstruction (4, 5).

Role of Imaging

The ideal treatment for gallbladder carcinoma is curative surgical resection; therefore, accurate pre-operative evaluation by imaging is essential.

Ultrasonography (US): US is often the first-line investigation in suspected gallbladder disease. It has a relatively high sensitivity for detection of advanced gallbladder malignancy, but it is limited for diagnosis of earlier tumours and unreliable for staging (4, 17, 18).

Computed Tomography (CT): CT is widely used for further characterization and staging of potentially malignant gallbladder lesions, because of its ability to delineate contiguous organ involvement, lymphadenopathy, and distant metastases. In addition, CT is a reliable technique for the evaluation of vascular involvement. Multidetector-CT offers high spatial resolution and is usually performed as a multiphasic study. Multiplanar (MPR) and three-dimensional (3D) volume rendered reconstruction images can be generated which are useful for surgical planning (19-21).

Magnetic Ressonance Imaging (MRI): Although MRI is not typically employed as a primary imaging modality for the gallbladder, it is used widely for further characterization of potentially malignant gallbladder lesions and staging. MRI usually includes T2-weighted (usually fast spin-echo) and T1-weighted (usually gradient-echo in- and out-of-phase) sequences. The so-called all-in-one protocol includes additional highly T2-weighted sequences (MR cholangiography - MRCP) for the study of the biliary tree and dynamic contrast material-enhance fat-suppressed T1-weighted sequences for the vascular assessment and a better delineation of tumoral invasion of the adjacent liver parenchyma (23-24).

Other imaging techniques: 1. PET-CT can be useful in distinguishing benign and malignant diseases but the method lacks specificity in distinguishing primary gallbladder carcinoma from other malignant lesions; 2. ERCP allows evaluation of bile duct invasion with stricture images and is useful in case of palliative stenting of bile duct.
Findings and procedure details

In order to illustrate the variety of imaging findings, we reviewed 33 patients diagnosed with GBC from January 2004 to June 2013 in our institution. Fifteen (45.4%) were considered unresectable based on imaging findings, 12 (36.4%) were considered potentially resectable, although 4 of them (4/12 - 33.3%) showed to be unresectable at surgical exploration, and 6 (18.2%) were discovered incidentally after cholecystectomy for acute cholecystitis.

Imaging findings and diagnosis

At US GBC presents as a heterogeneous, predominantly hypoechoic tumour (25). They are usually hypodense at unenhanced CT, with up to 40% of lesions showing hypervascular foci of enhancement equal to or greater than liver after intravenous contrast administration (26). MRI usually shows hypo to isointense signal characteristics on T1-weighted and moderately hyperintense signal on T2-weighted sequences (24). At CT or MRI, intense irregular enhancement may occur at the periphery of large primary GBC lesions during early arterial phases, which may be retained within fibrous stromal components during later phases, aiding differentiation from central hepatocellular carcinomas, which tend to wash-out contrast (27-28). Intermixed fluid and calcific components may be present.

Gallbladder carcinoma may appear as a mass completely occupying or replacing the gallbladder lumen, focal or diffuse asymmetric gallbladder wall thickening, or an intraluminal polypoid lesion (16).

Mass occupying or replacing the gallbladder lumen

This pattern may be present in 40-65% upon initial detection (17, 29). At US, CT, or MRI, the presence of an obliterative gallbladder mass, often directly invading the surrounding liver parenchyma, is highly suggestive of GBC (4). Sonographically, it appears as a heterogeneous mass with irregular margins in the subhepatic space (Figure 1.1), hence the potential difficulty in locating the gallbladder (1). Heterogeneous echotexture reflects varying degrees of tumour necrosis and/or residual bile (16, 30). Echogenic foci and acoustic shadowing associated with the tumour may be related to co-existing gallstones, gallbladder wall calcification or tumoral calcification (31).

CT demonstrates a hypoattenuating or isoattenuating mass in the gallbladder fossa, featuring heterogeneous enhancement after injection of the contrast medium (Figure 1.2). The tumour may contain low attenuation areas reflecting necrosis, and areas of enhancement reflecting viable tumour (8, 16, 29).
At MRI, these tumours appear as hypo- to isointense signal masses on T1-weighted and moderate hyperintense on T2-weighted sequences (24), with intense enhancement (Figure 1.3).

The differential diagnosis of a mass replacing the gallbladder fossa includes: hepatocellular carcinoma, cholangiocarcinoma, and metastatic disease.

Focal or diffuse asymmetric wall thickening

Wall thickening of the gallbladder secondary to tumor infiltration and inflammatory changes is seen in 20%-30% of cases of gallbladder carcinoma and may be focal (Figure 2-4) or asymmetric diffuse (Figure 5-6) (1, 16, 32). This is the most diagnostically challenging of the three patterns because it mimics the appearance of more common acute and chronic inflammatory conditions of the gallbladder (16). It is therefore particularly important to look for signs of local or metastatic involvement in such cases. Pronounced wall thickening (> 1.0 cm) demonstrated by US or CT, with associated mural irregularity or marked asymmetry with high enhancement during the arterial phase that persists or becomes isodense to the liver during the portal venous phase, should be considered suspicious (1, 20, 28).

Sonographically, the infiltrated gallbladder wall can be either hyperechoic or hypoechoic (1) (Figure 2.1).

In CT, gallbladder carcinoma is characterized by arterial phase enhancement of a thickened inner wall, which remains hyperattenuating or become isodense to the liver parenchyma during the portal venous phase (20) (Figure 2.2, 3, 4, 5a, 6).

On MR, the wall thickening is usually hypo to iso-intense on T1-weighted and moderately hyper-intense on T2-weighted sequences (16) (Figure 5b-c).

Gallbladder wall thickening can have an extensive radiological differential diagnosis including: acute and chronic cholecystitis, xanthogranulomatous cholecystitis, adenomyomatosis, and diffuse hepatic or systemic diseases such as acute hepatitis, portal hypertension, and congestive heart failure (33).

Intraluminal polyp

Gallbladder carcinoma presents as a polypoid lesion in 15-25% of cases (4, 5, 16). Malignant lesions are usually more than 1 cm in diameter and may have a thickened implantation base (4, 16).

These carcinomas tend to expand into the lumen of the gallbladder before invading the wall and seem to be associated with a less invasive, papillary-type carcinoma (29, 32). When an intraluminal mass is first seen along the dependent wall of the gallbladder, it can be mistaken for a nonshadowing stone, sludge or blood clot (1). Movement of the mass
induced by changes in the position of the patient, during examination, may be helpful in the differential diagnosis, once the tumour is fixed.

On ultrasound, large, irregular, fungating masses containing echoes of low intensity are most likely malignant (34) (Figure 7).

The polyp may be hypoattenuating or isoattenuating on CT scans with enhancement (16) (Figure 8.1, 9, 10a-b, 11.1).

At MRI the tumour has the same behaviour as the others previously described, except for the polypoid form (Figure 8.2, 10c-d, 11.2).

The differential diagnosis of an intra-luminal polypoid gallbladder lesion includes adenomatous, hyperplastic and cholesterol polyps, as well as uncommon tumors such as carcinoid or metastases such as melanoma.

**Pre-operative imaging evaluation and staging**

The latest AJCC staging system for GBC (7th edition) defines that GBC is staged according to their depth of invasion into the gallbladder wall and extent of spread to surrounding structures and lymph nodes (25).

T stage describes the relative invasion of tumor through the layers of the gallbladder wall, on the presence or absence of invasion into the liver, hepatic artery, or portal vein, and on the presence or absence of adjacent organ invasion. Tumor confined to the gallbladder is classified as either T1 or T2. Direct invasion of the liver, colon, duodenum, stomach, common bile duct, abdominal wall, and diaphragm, is not considered distant metastases (T3 or T4).

Lymphatic spread is present in over 50% of patients at initial diagnosis. Regional lymph nodes are limited to the hepatic hilum (including nodes along the common bile duct, hepatic artery, portal vein, and cystic duct). Celiac, periduodenal, peripancreatic and superior mesenteric artery nodes involvement is now considered distant metastasis. Accurate pN staging requires that a minimum of three regional lymph nodes are histologically examined.

M stage defines the presence (M1) or absence (M0) of distant metastasis. GBC usually metastasize to the peritoneum and liver and occasionally to the lungs and pleura.

The most common route of dissemination for gallbladder carcinoma to adjacent organs is direct extension, followed by lymphatic and hematageneous extension (1, 16).

Contiguous spread of the tumor is facilitated by the thin gallbladder wall, narrow lamina propria and only a single muscle layer (6). The incidence of liver extension (the organ most frequently involved) at the time of diagnosis, varies from 34% to 89% (32), followed
by involvement of the duodenum (15%), colon (15%) and pancreas (6%) (16). Direct extension to the liver may be seen as a tumour inseparable from the adjacent liver (Figure 1.2.a, 4-6, 8) (16). Infiltrative tumour growth alongside or within the cystic duct is also frequently seen which causes biliary obstruction and dilatation (16) (Figure 1.2.a, 5b, 9c). The tumour can also spread along adjacent vessels (22) (Figure 6c).

The prevalence of lymphatic spread is high in gallbladder carcinoma (50% of patients at diagnosis) (16). Positive lymph nodes are more likely to have an anteroposterior dimension of 10 mm or greater, and ringlike or heterogeneous contrast enhancement at CT (35) (Figure 2a, 12). The masses produced by lymph node metastasis around the distal common bile duct and pancreatic head may mimic a pancreatic head carcinoma (17). The cystic and percholedochal lymph nodes are the primary nodes draining the gallbladder (6, 35). Enlargement of these nodes provides another mechanism for obstruction of the extrahepatic biliary system (29) (Figure 6b). Further lymphatic spread leads to involvement of the posterosuperior pancreaticoduodenal, retroportal, right celiac, hepatic and superior mesenteric nodes (28, 35). The interaortocaval nodes represent the terminal nodes of the regional lymphatic drainage system of gallbladder. Spread to these lymph nodes is regarded as distant metastases (9).

The biliary tree invasion, either by direct extension, by intraductal "seed" or indirectly by compression/invasion from adenopathies, makes the diagnosis of the primary site even more challenging, and the histology in these cases doesn’t help (biliary tree tumour). Moreover, at this stage the tumour is unresectable, irrespective of their source.

Hematogenous metastases are most commonly seen in the liver (Figure 3). Pulmonary, skeletal, cardiac, pancreatic, renal, adrenal and cerebral metastases occur less frequently (16). Hematogenous metastases to the liver and large peritoneal implants (Figure 1.2b), are well depicted by CT and MR imaging. However small hepatic, peritoneal and omental tumour implants can be missed at preoperative imaging, and thorough laparascopic or open exploration should precede aggressive surgery, either at the same or as an earlier operation.
**Fig. 1:** 66-year-old man with right upper abdominal pain and jaundice.

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Fig. 2: 76-year-old woman with jaundice and weight loss.

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Fig. 3: 59-year-old woman with abdominal pain.

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**Fig. 4:** 69-year-old man with abdominal pain and jaundice.

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Fig. 5: 60-year-old woman with abdominal pain, jaundice and systemic symptoms.

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Fig. 6: 83-year-old woman with abdominal pain, jaundice and an abdominal palpable mass in the right hypochondrium.

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Fig. 7: 52-year-old woman with astenia, anorexia and weight loss.

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Fig. 8: 87-year-old, asymptomatic woman.

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Fig. 9: 64-year-old woman with abdominal pain.

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Fig. 10: 64-year-old, with jaundice and anasarca.

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Fig. 11

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Fig. 12: 74-year-old man with abdominal pain and jaundice.

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Conclusion

Although GBC is often detected first by US, MDCT and MRI are more reliable for evaluation of tumor resectability and for monitoring therapy. Understanding the variable appearances of GBC and patterns of disease spread can enhance our diagnostic skills and enable more accurate staging.
References


