6 Clinical Presentation of Gall Bladder Cancer

Vinay K. Kapoor

The National Comprehensive Cancer Network (NCCN 2015) has described four modes of presentation of gall bladder cancer (GBC)

1. Incidental finding at surgery
2. Incidental finding at histopathology
3. Mass on imaging
4. Jaundice

The Author (VKK), however, disagrees with this terminology as GBC detected at surgery is not "incidental".

6.1 Presentations

The Author (Kapoor et al. 1996) had earlier suggested a nomenclature based on the time in clinical presentation at which a diagnosis (or suspicion) of GBC is made.

1. Obvious—(also called overt GBC in some reports) clinically evident, viz. dull continuous non-colicky pain in the right upper abdomen, jaundice, gastric outlet obstruction (GOO), anorexia and weight loss, and palpable GB mass (cf. distended GB of mucocele due to gall stone disease GSD).
2. Suspected—clinical picture (symptoms and signs) is suggestive of benign GSD, i.e., biliary colic, a distended GB (mucocele) may be palpable but a suspicion of GBC is raised on imaging (US/CT) which shows GB wall thickening, mass, or polyp.
3. Unsuspected—preoperative (clinical as well as imaging) diagnosis is benign, i.e., GSD and there is no suspicion of malignancy on imaging but at operation (laparoscopy or laparotomy), the GB is found to be thick walled and/or there is difficulty in dissection of the GB from its bed in the liver or there is a suspicious finding, viz. wall thickening, nodule, polyp, or ulcer (which should then be subjected to frozen section histopathological examination) on gross examination of the GB specimen (Fig. 6.1).
4. Incidental—preoperative and even intraoperative diagnosis is benign, i.e., GSD and there is no suspicion of malignancy even on gross examination of the GB specimen; GBC is found for the first time on histopathological examination of the GB specimen. This, according to the Author (VKK), is true incidental GBC.
5. Missed—either the GB was not sent for histopathological examination (because it looked grossly normal) or an early GBC was missed

Please also see Invited Commentaries on Clinical Presentation of Gall Bladder Cancer by Yuman Fong (pp **–**), Pradeep Ghimire (pp **–**) and Prabin Bikram Thapa (pp **–**)

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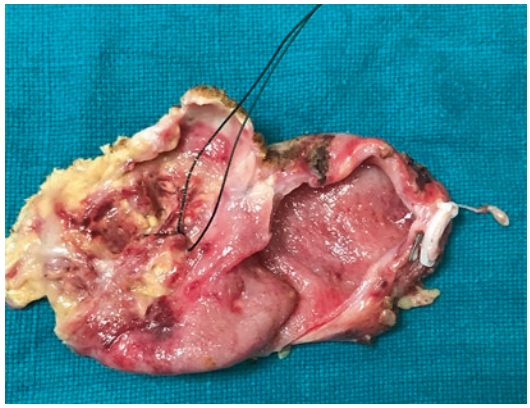

Fig. 6.1 During cholecystectomy for presumed gall stone disease if the specimen reveals a wall thickening, nodule, polyp, or ulcer, it should be called unsuspected (NOT incidental) gall bladder cancer

even by the pathologist on routine histopathological examination of the GB.

Relative proportion of these presentations varies depending on the incidence rates of GBC in the geographical area/ethnic group, the level of index of suspicion of GBC and prevalence and timing of cholecystectomy for GSD. In high GBC incidence areas with a high index of suspicion of GBC and/or low prevalence rates and delayed timing of cholecystectomy for GSD, e.g., India and Japan, obvious/suspected GBC is more common and incidental GBC is less common. At the Tokyo Women's Medical University Japan, only 26 (7%) out of 389 GBCs who underwent surgery between 1969 and 2012 were incidental (Higuchi et al. 2014). On the other hand, 37% of 669 GBC cases in Chile were incidental (Roa et al. 1999). In low GBC incidence areas with a low index of suspicion of GBC and high prevalence rates and early timing of cholecystectomy for GBC, e.g., the USA, obvious/suspected GBC is less common and incidental GBC is more common. Less than one-third of GBCs in the USA are diagnosed preoperatively; majority are diagnosed either at operation or on histopathology. In the USA, 47% of 435 GBCs were incidental (Duffy et al. 2008). In the 10-institution Extrahepatic Biliary Malignancy Consortium in the USA, out of 445 patients with GBC who underwent resection, 266 (60%) were incidental GBC (Ethun et al. 2017). Butte et al. (2011) compared patients with GBC treated in the USA ($n = 130$), Chile ($n = 85$), and Japan ($n = 46$); only 15% of GBCs treated in Japan were incidental (cf. 60% in the USA).

6.2 Symptoms

GBC, in its early stages (i.e., when it is confined to the GB wall), can remain silent (asymptomatic) for a long time. Even when symptomatic, it has no pathognomonic clinical features to enable early diagnosis as symptoms of early GBC are either vague or nonspecific, e.g., dyspepsia or indigestion, or mimic those of GSD, i.e., biliary colic and chronic cholecystitis. Even ultrasonography (US) does not pick up early GBC; these patients undergo cholecystectomy with a preoperative diagnosis of GSD and GBC is suspected either at operation or in the GB specimen on gross examination (unsuspected GBC) or is serendipitously detected after histopathological examination of the grossly normal GB (incidental GBC).

Symptomatic GBC presents with a wide range of symptoms including local, metastatic, and cancer related. Commonest symptom of obvious GBC is pain but patients with GBC may have pain (biliary colic) due to associated GS also; there may be a change in the character of pain from long standing intermittent biliary colic to recent dull continuous diffuse pain (because of local infiltration) in the right upper quadrant or epigastrium of the abdomen. Pain was present in 89% of 385 patients reported by Mishra et al. (2017). Jaundice is seen in about one-fourth to one-third of patients with clinically obvious GBC. Jaundice was seen in 110/424, 26% (Regimbeau et al. 2011), 82/240, 34% (Hawkins et al. 2004), 152/385, 39% (Mishra et al. 2017), and 65/179, 40% (Ethun et al. 2017) patients with GBC. GBC is the commonest cause of malignant jaundice in north India (Sikora et al. 1994). These patients present with yellow eyes (and skin), high colored urine (Fig. 6.2), clay colored stools, and may have associated pruritus.

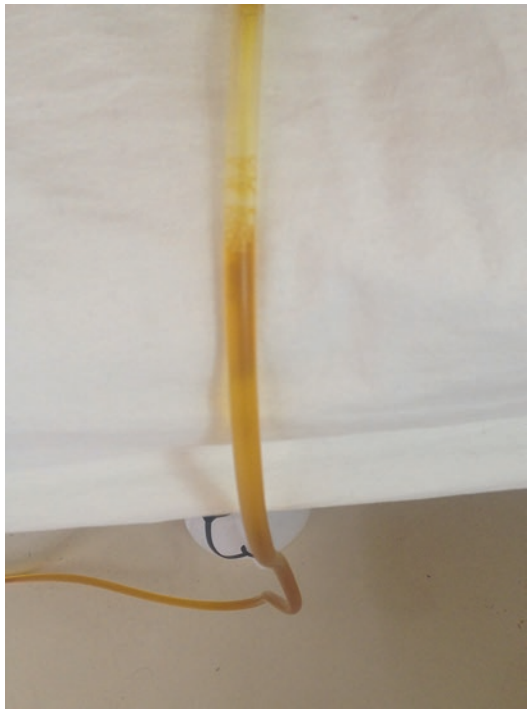

Fig. 6.2 Gall bladder cancer patients with biliary obstruction have jaundice and pass high colored urine

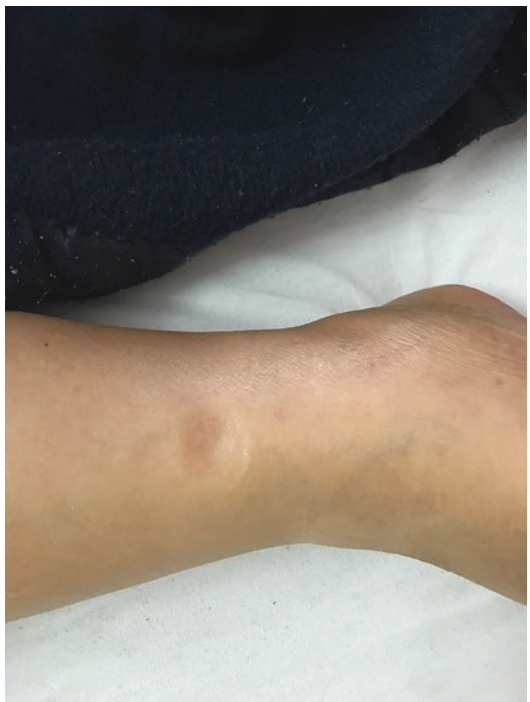

Fig. 6.3 Patients with advanced/metastatic gall bladder cancer may be malnourished and have bilateral pitting pedal edema

Cholangitis, i.e., high-grade fever with chills and rigors, though not as common in complete malignant biliary obstruction of GBC as in incomplete biliary obstruction due to benign causes, e.g., CBD stones, may supervene in patients with GBC and jaundice. Jaundice is caused by direct infiltration of the CBD by GBC neck or by compression of the common bile duct (CBD) by enlarged metastatic lymph nodes (LNs) in the hepatoduodenal ligament (HDL). Jaundice in GBC is usually associated with pain but may rarely present as painless progressive jaundice and thus mimic periampullary carcinoma and cholangiocarcinoma. Anorexia and weight loss, and generalized weakness, malaise, and lethargy are frequently present in patients with GBC and usually indicate advanced disease. Loss of appetite (60%) and loss of weight (63%) were very common in 385 patients with GBC seen at a tertiary level hospital in north India from 2003 to 2014 (Mishra et al. 2017). Symptomatic (obvious) GBC is usually in advanced stage as the symptoms are a result of infiltration of adjacent organs.

Metastatic symptoms include

1. Liver—no specific symptoms other than anorexia and weight loss; rarely, a large metastasis near the hepatic hilum can cause biliary obstruction and jaundice (it must, however, be noted that the common mechanism of causation of jaundice in GBC is infiltration of the common bile duct by a GBC neck)
2. Lungs—persistent cough, chest pain, shortness of breath, hemoptysis
3. Bones—bone pain, fracture (spontaneous or after trivial trauma)
4. Brain—persistent headache and vomiting, convulsions.

6.3 Signs

Patients with advanced GBC may be malnourished with loss of body fat and pedal edema (Fig. 6.3); they may even be cachectic. Jaundice (icterus) may be present (Fig. 6.4) and pruritic scratch marks (Fig. 6.5) are frequently present in patients with jaundice. A firm to hard non-tender

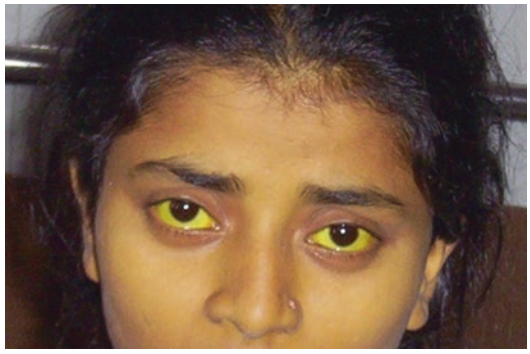

Fig. 6.4 Jaundice (icterus) is present in as many as one-fourth to one-third of patients with clinically obvious gall bladder cancer

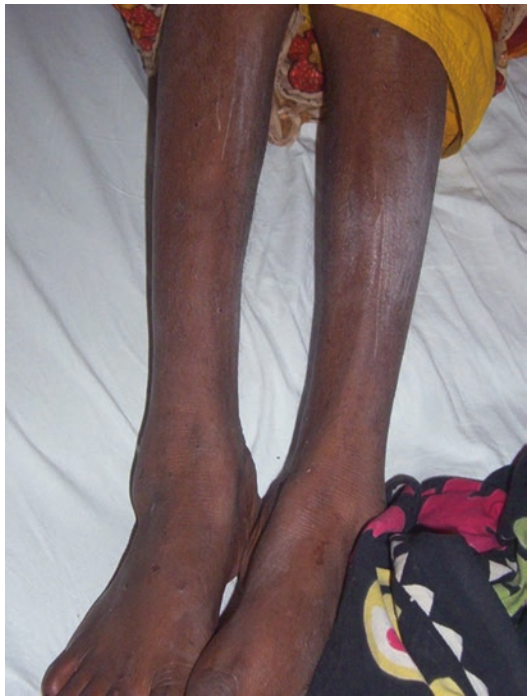

Fig. 6.5 Patients with obstructive jaundice also have pruritus—scratch marks can be seen on examination

GB lump (Fig. 6.6) (cf. distended GB of mucocele) is palpable in a large number of cases. Hepatomegaly, which may be hard nodular (metastases) or firm diffuse (cholestasis due to biliary obstruction), may be present. Ascites which may be metastatic (peritoneal dissemination) or nutritional (when it is associated with pedal edema) should be looked for. Pelvic (recto-

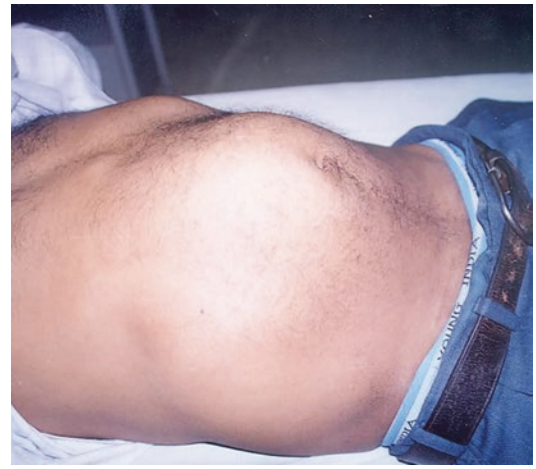

Fig. 6.6 Advanced GBC presents as a firm to hard non-tender palpable GB lump

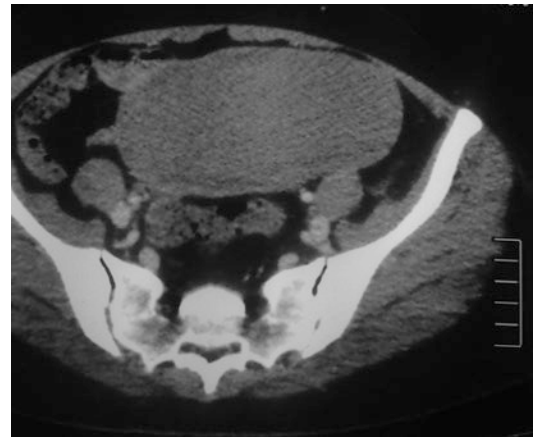

Fig. 6.7 A large ovarian deposit from gall bladder cancer may be palpable on per vaginal (PV) or per rectal (PR) examination

vesical and recto-uterine pouch) or ovarian (Fig. 6.7) metastatic deposits may be palpable on per rectal (PR) or per vaginal (PV) examination.

Most patients in whom a preoperative diagnosis of GBC is made either clinically or on imaging (US, CT, or MRI) have advanced, i.e., either locally advanced or metastatic disease.

The statement "*In malignancy of the GB, when a diagnosis can be made without exploration, no operation should be performed, as much as it only shortens the patient's life.*" made by Alfred Blalock a century ago in 1924 is not far from truth even today.

6.4 Unusual Clinical Presentations

Like any other disease, GBC has several unusual and atypical clinical presentations, which make the diagnosis difficult (Haribhakti et al. 1997). They should be kept in mind to have a suspicion of GBC, especially in high GBC incidence areas/populations. Locally advanced GBC can infiltrate (the first part of) the duodenum or (the antro-pyloric region of) the stomach and cause mechanical gastric outlet obstruction (GOO) (Fig. 6.8) causing early satiety, post-prandial fullness, nausea, and frank (non-bilious) vomiting. GOO was present in 8% of 385 patients with GBC reported by Mishra et al. (2017). Some patients may have symptoms suggestive of GOO but without mechanical gastro-duodenal obstruction—this is malignant gastroparesis (similar to the one seen in locally advanced pancreatic cancer). We showed delayed gastric emptying on radioisotope scintigraphy in a significant proportion of patients with GBC (Singh et al. 1998). While mechanical GOO will respond to gastro-jejunostomy (GJ) or antro-duodenal stenting, malignant gastroparesis may not. GBC may result in intestinal obstruction—colonic (due to direct infiltration of the hepatic flexure or proximal transverse colon) and small bowel (due to a large peritoneal deposit). GBC may also cause gastro-intestinal (GI) bleed due to direct infiltration of the duodenum/stomach (upper GI bleed) or colon (lower GI bleed). A tumor in the GB neck or the cystic duct may result in a mucocele (distended palpable GB) (Fig. 6.9) thus mimicking GSD. This is an exception to the usual clinical scenario where a distended palpable GB in malignant obstructive jaundice suggests a lower biliary obstruction due to a pancreatic head or periampullary cancer. Patients with GBC may present with acute cholecystitis and empyema due to obstruction of the cystic duct. In fact, the incidence of incidental GBC is higher in patients with acute cholecystitis than in those with chronic cholecystitis. Clinical diagnosis of empyema in an elderly (>60 years) patient should raise the suspicion of GBC (Lohsiriwat et al. 2009). Perforated GBC presenting as a sinus/fistula has been reported. A large GB mass can undergo central necrosis and look like a liver abscess on imaging (Fig. 6.10); fever of tumor necrosis may also be present further confusing the clinical diagnosis. Unusual sites of metastases, e.g., umbilical nodule (Fig. 6.11), left supra-clavicular (Fig. 6.12), axillary (Fig. 6.13), or inguinal LN and scalp nodule

Fig. 6.8 Patients with advanced gall bladder cancer can have gastric outlet obstruction due to infiltration of the first part of the duodenum

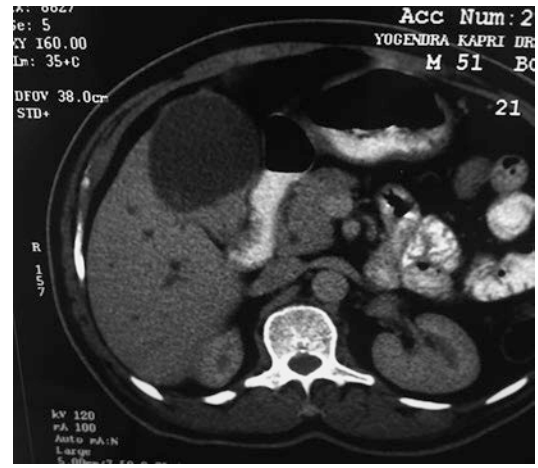

Fig. 6.9 Patients with GBC at neck can have a firm distended GB—mucocele

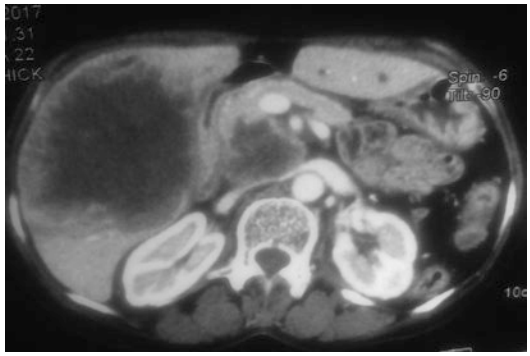

Fig. 6.10 A large gall bladder cancer can undergo central necrosis and look like a liver abscess; fever of tumor necrosis may also be present

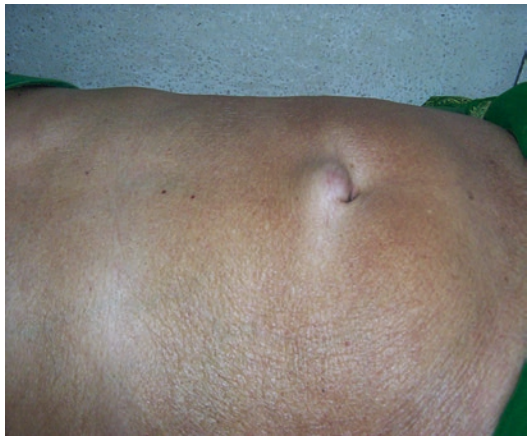

Fig. 6.11 An unusual but easily detectable site of metastasis from gall bladder cancer is the umbilicus (hard palpable nodule)

have been reported. Patients with incidental GBC may present with scar (following open cholecystectomy) or port-site (following laparoscopic cholecystectomy) metastasis, especially if long time has elapsed since the index cholecystectomy. Post-cholecystectomy jaundice is usually benign, either due to retained CBD stones or because of a bile duct injury and benign biliary stricture; it may rarely be malignant due to recurrence of a missed GBC (Fig. 6.14). An uneventful postoperative course, i.e., no bile leak after cholecystectomy, GB not sent for histopathological examination, high (hilar) biliary obstruction and the presence of a mass on imaging should suggest the possibility that the post-cholecystectomy

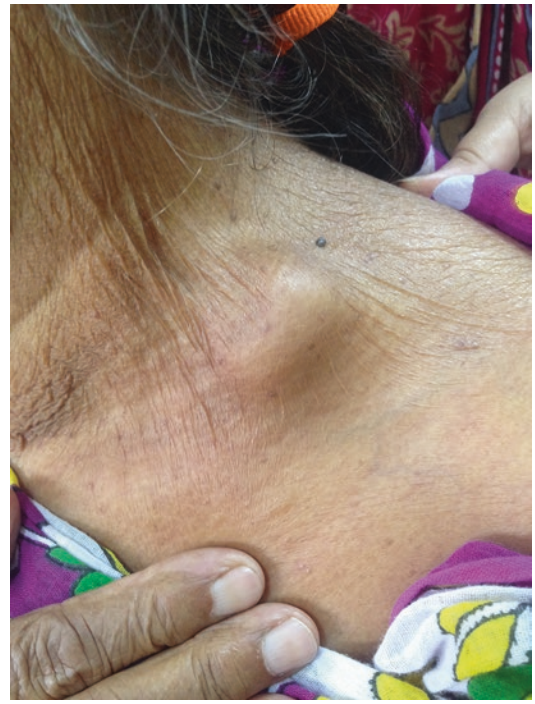

Fig. 6.12 Gall bladder cancer may spread to the left supraclavicular lymph nodes which are easily palpable and can be subjected to fine needle aspiration cytology (FNAC)

jaundice is not benign but malignant (Sharma et al. 2008). Recurrent/missed GBC may present as scar site (after open cholecystectomy)/port-site (after laparoscopic cholecystectomy) metastases in the form of hard non-tender nodules.

6.5 Differential Diagnosis

Differential diagnosis of GBC may include

1. Gall stone disease as symptoms of early GBC may be same as that of GSD.
2. GB perforation (on the hepatic side) due to complications of GS may look like a GBC on imaging (US, CT, or MRI) (Fig. 6.15). At the same time, patients with a clinical diagnosis of acute cholecystitis or empyema are more likely to turn out to have an incidental GBC.
3. Clinical picture of GBC patients with jaundice may resemble that of patients with CBD stones and Mirizzi syndrome (Fig. 6.16)—

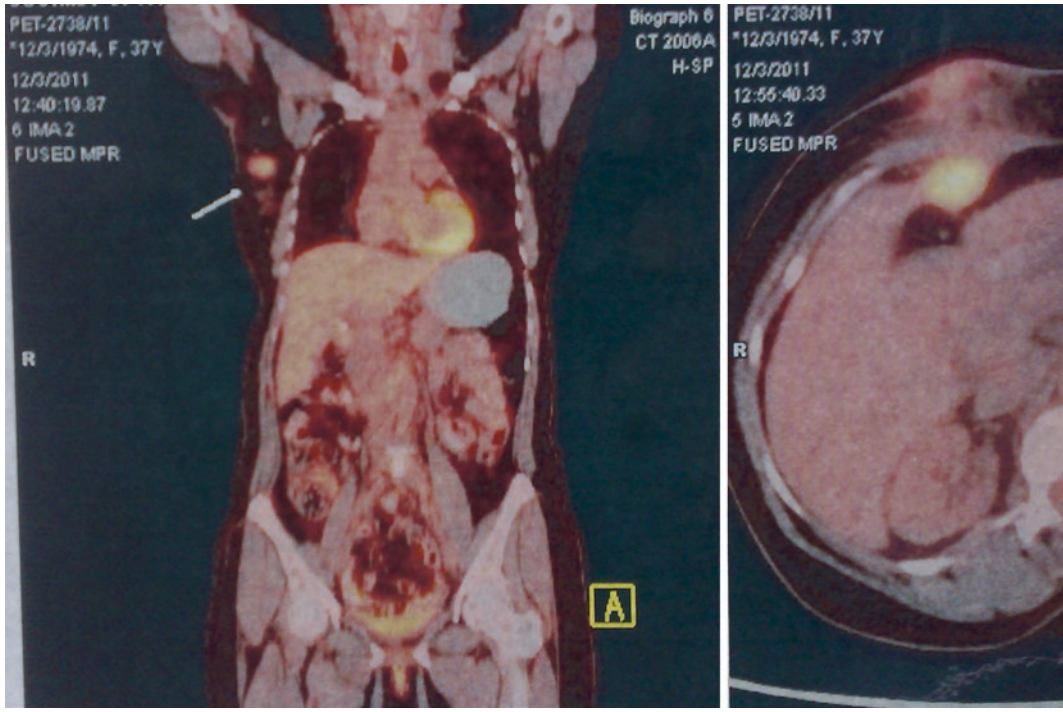

Fig. 6.13 PET scan shows FDG avid lesions in the right axilla and the GB. (Image courtesy Dr. Amit Javed GB Pant Hospital New Delhi)

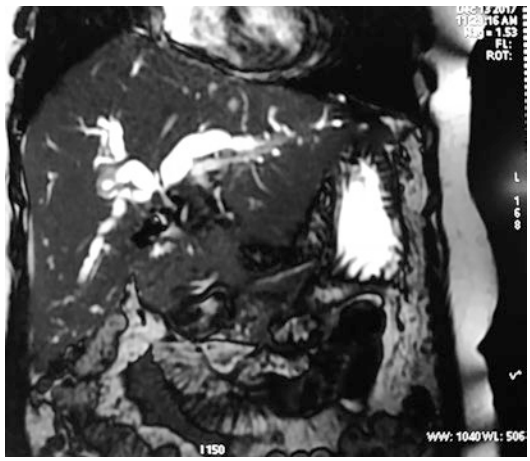

Fig. 6.14 Post-cholecystectomy jaundice may be due to recurrence of a gall bladder cancer which was missed at cholecystectomy because the gall bladder was not sent for histopathological examination

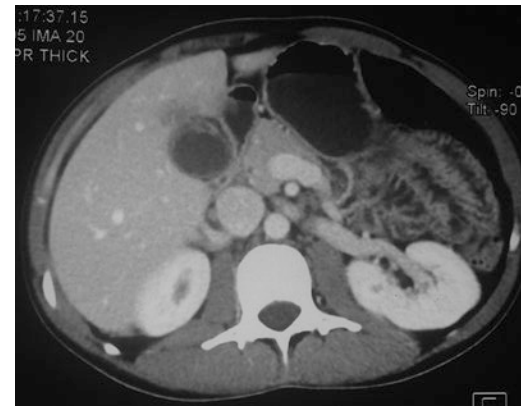

Fig. 6.15 Gall bladder perforation into the liver parenchyma and the resulting abscess may look like a gall bladder cancer infiltrating the liver on imaging

there is a higher chance of finding incidental GBC in these scenarios. Jaundice due to associated CBD stones in a patient with GBC is a favorable scenario where the CBD stones can be cleared endoscopically and then the GBC can be treated on its own merits.

4. In a patient presenting with obstructive jaundice, which on clinical grounds appears to be malignant, if the US shows a high (Fig. 6.17) or mid (Fig. 6.18) CBD (cf. low

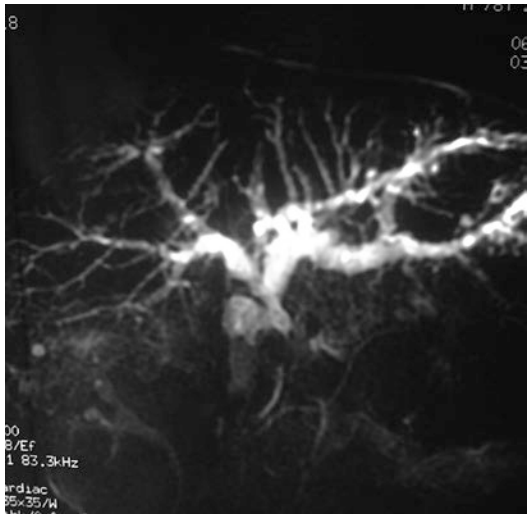

Fig. 6.16 Mirizzi syndrome may look like gall bladder cancer with common bile duct infiltration

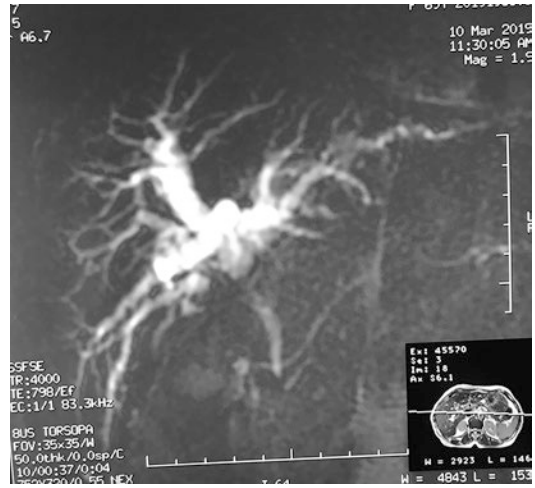

Fig. 6.18 Gall bladder cancer can infiltrate the common bile duct (CBD) and look like a mid CBD cholangiocarcinoma

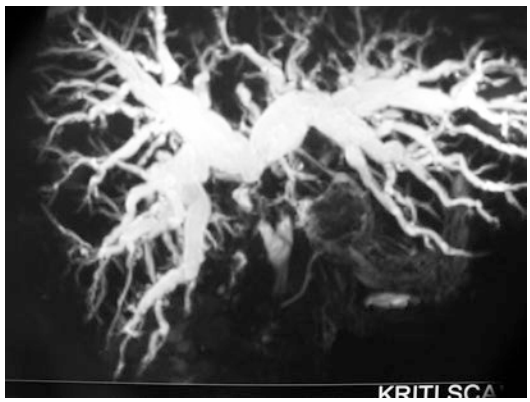

Fig. 6.17 Gall bladder cancer can infiltrate into the common hepatic duct (CHD) or the biliary ductal confluence and look like a hilar (high) cholangiocarcinoma

block in pancreatic and periampullary cancers) block, it could be GBC neck or cholangiocarcinoma (hilar and mid CBD) and differentiation between them is not easy (Kapoor 2015). The presence of pain (either biliary colic due to associated GS or dull diffuse continuous ache of liver infiltration) suggests GBC as cholangiocarcinoma is usually painless, but cholangiocarcinoma may also be associated with GS which cause pain and and a small GBC neck may be painless. The presence of a mass on imaging (US, CT, MRI) is more in favor of a GBC than cholangiocarcinoma. On cholangiogram, selective involvement of the right anterior sectoral pedicle (which lies in the GB bed) suggests GBC whereas involvement of the left hepatic duct (and segment IV duct) indicates hilar cholangiocarcinoma. Similarly, involvement of the left hepatic artery and/or the left portal vein suggests cholangiocarcinoma. Uncommonly, a patient with GBC may have lower CBD obstruction due to enlarged periduodenal/peripancreatic LNs which may look like pancreatic or periampullary carcinoma.

5. Post-cholecystectomy jaundice, especially if the GB was not sent for histopathological examination, may be because of a missed (rather than CBD stones or biliary stricture which are more common).
6. GBC presenting as thick-walled GB (TWGB) on imaging (US or CT) (Fig. 6.19) or at operation may finally (fortunately) turn out to be benign, e.g., chronic cholecystitis (CC) or xantho-granulomatous cholecystitis (XGC) on histopathological examination—most reports of extended cholecystectomy with a presumed diagnosis of GBC include a significant proportion of patients in whom the final histology is benign, i.e., CC or XGC.
7. A GB fossa mass on imaging which looks like GBC may be a hepatocellular carcinoma

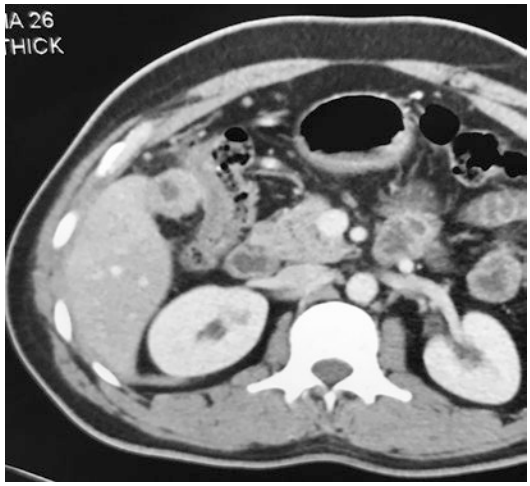

Fig. 6.19 A thick-walled gall bladder (TWGB) on US or CT is usually benign but may turn out to be gall bladder cancer

(HCC) or a metastasis (from another primary).

8. Rare entities, e.g., hepatobiliary tuberculosis (Haque et al. 2019), IgG4-related sclerosing cholecystitis (Ichinokawa et al. 2019; Jearth et al. 2020).

A high index of suspicion is required, especially in geographical areas and ethnic groups with high incidence rates of GBC, for the clinical diagnosis of GBC. In geographical areas and ethnic groups with low incidence rates of GBC, it should be considered as a possible differential diagnosis when dealing with above-mentioned conditions/situations.

Early GBC is difficult to diagnose; clinically obvious GBC is usually advanced and is difficult to treat.

Invited Commentary on Clinical Presentation of Gall Bladder Cancer

Yuman Fong

In this chapter on clinical presentation of gallbladder cancer (GBC), Professor Kapoor summarizes the recommendations of the National Comprehensive Cancer Network (NCCN) for classifying GBC into (1) incidental finding at surgery, (2) incidental finding at histopathology, (3) mass on imaging, and (4) jaundice. Professor Kapoor then recommends an alternative classification system as (1) obvious clinical symptoms and signs, (2) suspected, (3) unsuspected, (4) incidental, and (5) missed GBC.

A much simpler way of classifying GBC is as to when the mass is noted. Gallbladder cancers are masses that can be recognized as cancer prior to surgery (radiologic diagnosis), at the time of surgery (surgical diagnosis), or after surgery (pathologic diagnosis).

Pathologically diagnosed: For those patients with pathologically diagnosed GBC, it is very important to ask the pathologist to report (1) whether the gross specimen was intact or ruptured, i.e., bile spill occurred during cholecystectomy, (2) whether the tumor was on the liver side or the peritoneal side of the specimen, (3) the deep margin status, (4) the cystic duct margin status, and (5) the cancer status of the Calot's (cystic) lymph node, if available. The data is very clear that patients with intact specimens, negative margins, and carcinoma in situ or T1a GBC do not need additional surgery. All other patients including those with T1b GBC deserve further radiologic staging. If resectable localized disease is found, additional resection is warranted.

Surgically diagnosed: The cases of GBC diagnosed in the operating room can either be (1) disseminated disease, (2) advanced localized disease (liver invasion or nodal dissemination of cancer), or (3) gallbladder-confined disease resectable by cholecystectomy.

For disseminated disease, biopsy of peritoneal or non-contiguous liver tumor proves unresectable disease, and obtaining sufficient sample for molecular analysis (BRAF mutational status, microsatellite instability MSI, and mutational burden) helps drive trials and the treatment of disseminated disease.

For disease found at surgery that has advanced local extension to liver or lymph nodes, most surgeons will biopsy the liver tumor (through normal liver parenchyma in order to minimize spillage of tumor) or sample a lymph node and stop. Most will return later after obtaining full informed consent for more extensive resection, and possibly after neoadjuvant chemotherapy.

For those found to have gallbladder-confined disease which is highly suspected to be gallbladder cancer (intraoperative sonographically confirmed mass or clear mass on the external portion of the gallbladder), operative conduct should be modified. (1) Consideration should be given to avoiding of grabbing the gallbladder to avoid spillage of gallbladder contents. (2) The cystic plate (serosa of the gallbladder) on the liver side of the gallbladder should be removed. Taking off the cystic plate gets rid of all the lymphatics in the gallbladder and avoids the plane of T1 and T2 gallbladder cancers. (3) Immediate documentation of the cystic duct margin status reduces the need for a second operative procedure (to excise the CBD). (4) Cystic duct node or suspicious nodes should be sent for frozen section evaluation. These steps provide a strong possibility for immediate resection of early gallbladder cancer and minimize the need for second operations.

Radiologically diagnosed: Radiologically diagnosed GBC comes in four forms: (1) advanced disseminated disease, (2) advanced local disease including jaundiced patients, (3) resectable obvious masses, and (4) small masses including gallbladder polyps.

The first two radiologic presentations constitute non-surgical disease. In particular, the reason that the NCCN segregates out jaundice as a symptom in that most patients with GBC as the cause of their jaundice are incurable (Hawkins et al. 2004). When patients are found to have advanced disease, biopsy of a deposit to prove stage IV disease allows for appropriate systemic cancer therapy or palliative therapies.

Obvious resectable masses demand further imaging for cancer staging. FDG-PET is recommended for these patients to document local and regional disease to define the extent of surgical resection or to document distant disease to rule out resection (Ramos-Font et al. 2014). Patients with stage III GBC should have resections at high volume centers for HPB surgery.

For those with small luminal masses including polyps, one should follow the surgical process as outlined above for intraoperatively discovered small masses to avoid cancer spillage, and to ensure the highest cure rate in as few operative procedures as possible.

Discovering GBC and performing the right operation for potential cure requires vigilance when examining preoperative scans. The rate of diagnosing GBC is related to the vigilance, with as high a rate as >90% preoperative diagnosis in Japan (Higuchi et al. 2014), versus >60% in Chile (Roa et al. 1999), and only approximately 40% in the USA (Ethun et al. 2017; Butte et al. 2011).

Invited Commentary on Clinical Presentation of Gall Bladder Cancer

Pradeep Ghimire

Gallbladder carcinoma (GBC) is known to show an unusual geographic distribution worldwide, with quite a substantial geographic variation noted. In Asia, the northern Indian population and southern Pakistani population from Karachi appear to be the highest of affected, showing a rate of 21.5 and 13.8 per 100,000 population, respectively.

With the pre-operative diagnosis occurring in less than 20% of afflicted patients; in spite of the recent advancement and the availability of various diagnostic approaches and modalities, the preoperative diagnosis of GBC is still regarded as an exception, rather than the diagnosis being a rule. Most of the cases of GBC are diagnosed during or after surgery performed for stones or benign biliary diseases. Lack of timely diagnosis and subsequent poor prognosis at the time of discovery can be considered a major problem in the treatment of GBC, with poor outcomes encountered.

GBC is more commonly encountered in the females; however, the mortality rate appears to be higher in the males. The etiology of GBC has been attributed to the presence of cholelithiasis, various genetic and environmental causes, infection of the gallbladder, porcelain gallbladder, Mirizzi syndrome, gallbladder polyps, choledochal cyst, and biliary reflux. A positive family history of gallbladder calculi, chemical exposure (including wood dust and coal dust), tobacco consumption, longer interval between meals, higher concentration of secondary bile acids, and excessive intake

of fried food are also associated risk factors. Interestingly, patients residing in the Gangetic belt have also shown an increased risk in the development of GBC, probably due to exposure to high cadmium, chromium, and lead particles. Consumption of fruits on a regular basis has been associated with protective effect against GBC.

GBC is widely considered as the fifth most common cancer of the digestive tract and the most common malignancy of the biliary tract. Among the fatal carcinomas afflicting the Nepalese population, GBC is regarded as a relatively common entity. According to the American Institute for Cancer Research, of the top 20 countries with the highest rates of GBC in 2018, Nepal had the sixth highest rate of 6.7 per 100,000 population for both the sexes, the fifth highest rate of 6.0 per 100,000 population for males and the third highest rate of 7.3 per 100,000 population for females. In a study conducted by our team at Fishtail Hospital and Research Center, Pokhara, Nepal, the incidence of GBC in cases of routine cholecystectomy among 783 patients operated over 11 years was found to be 1.28% (Ghimire et al. 2011). As also recommended in the study, it is a standard practice to perform routine histopathological examinations for all cholecystectomy specimens. Various studies, including the working report of the Royal College of Pathologists have recommended for this routine standard practice, as it helps in detection of a large number of cases of occult (incidental) GBC. Also, given that primary GBCs are known for their late presentation and hence poor survival rates; occult GBC diagnosed incidentally on histopathological examination of post-cholecystectomy specimen are usually detected at earlier stages and thus have better prognosis.

Invited Commentary on Clinical Presentation of Gall Bladder Cancer

Prabin Bikram Thapa

Gallbladder cancer (GBC) is notorious for being asymptomatic in early stages of the disease. While there are many clinical scenarios in which GBC can be detected by the clinician, as enumerated by the Author (VKK), their presentation can be characterized into the following categories:

1. Asymptomatic
2. Symptoms pertaining to gallstone disease
3. Symptoms of locally advanced disease
4. Symptoms of metastatic disease

Up to 90% of cases of GBC are associated with gallstone disease, and in most instances they mimic symptoms of cholelithiasis such as right upper quadrant pain (Grobmyer et al. 2004). However, they are more often than not characterized by constant pain rather than the typical colicky type of pain seen in biliary colic. Elderly patients with above-mentioned features who are from high-incidence areas should be suspected of having GBC, particularly when the symptoms are associated with anorexia, weight loss, and jaundice.

Locally advanced disease may clinically manifest as obstructive jaundice, usually from the direct invasion of the biliary tree. Invasion of the tumor into the gastro-duodenum may also result in gastric outlet obstruction (Sharma et al. 2010).

Palpable gall bladder, hepatomegaly, ascites, weight loss, and anorexia usually are tell-tale signs of advanced disease. Metastatic disease may also manifest as jaundice due to the involvement of the hepatoduodenal ligament or as a periumbilical nodule or left supraclavicular lymphadenopathy. Rarely, GBC may present with paraneoplastic syndromes (due to ectopic hormone secretion) such as Cushing syndrome, hypercalcemia, acanthosis nigricans, bullous pemphigoid, dermatomyositis, and the Leser-Trélat sign, i.e., explosive onset of multiple seborrheic keratoses (many pigmented skin lesions) (Uribe-Uribe et al. 2009).

Given the myriad nature of presentations of GBC, a high degree of clinical suspicion is warranted for the timely detection and appropriate treatment of the disease.

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