Pathology of Hepatobiliary and Pancreatic Cancer

2

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2.1 Introduction

The prevalence of gastrointestinal (GI) cancers shows a marked geographical variation. These differences can be attributed to many factors including lifestyle, genetics and infection. Globally, colorectum, stomach and liver are the third, fourth and fifth most commonly diagnosed cancers in males, colorectum being the second most common in females [1].

2.2 Gall Bladder

Gall bladder cancer is uncommon in many European countries and the USA and commoner in some countries in Latin America and Asia. The highest incidence occurs in women from Delhi (India) (around 21/100,000) followed by South Karachi, Pakistan and Quito, Ecuador [2].

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The risk factors for gall bladder cancers have not been clearly identified. However, gall stones are found in more than 80% of the patients with carcinoma and a causal relationship is suggested [3].

Adenoma of the gall bladder is uncommon, but they are the most common benign neoplasms. Adults are affected with a female preponderance. They can measure from 0.5 to 2 cm in diameter and can be sessile or pedunculated. They are usually detected incidentally or while investigating for calculous or acalculous chronic cholecystitis. They are benign lesions and cholecystectomy is curative.

The overall pathogenesis of adenocarcinoma of the gall bladder is thought to result from dysplasia to carcinoma. Metaplasia (gastric, pyloric type and intestinal) are not thought to be premalignant per se. Mutation in the TP53 gene is a common event, and immunohistochemistry (IHC) overexpression of P53 correlates with point mutation.

Grossly, gall bladder carcinomas usually result in localised thickening rather than diffuse thickening. They are mostly located in the body and the fundus (90%) and about 10% are in the neck.

Precursor lesions of adenocarcinomas are termed as biliary intraepithelial neoplasia (low-grade Bil IN 1, 2) and high-grade (Bil IN 3) as in bile ducts [4, 5].

The commonest histological type of cancers of the gall bladder is adenocarcinoma, which accounts for 75–85% of all carcinomas (Fig. 2.1). They can show papillary, tubular architecture and show a variety of cell types such as intestinal,

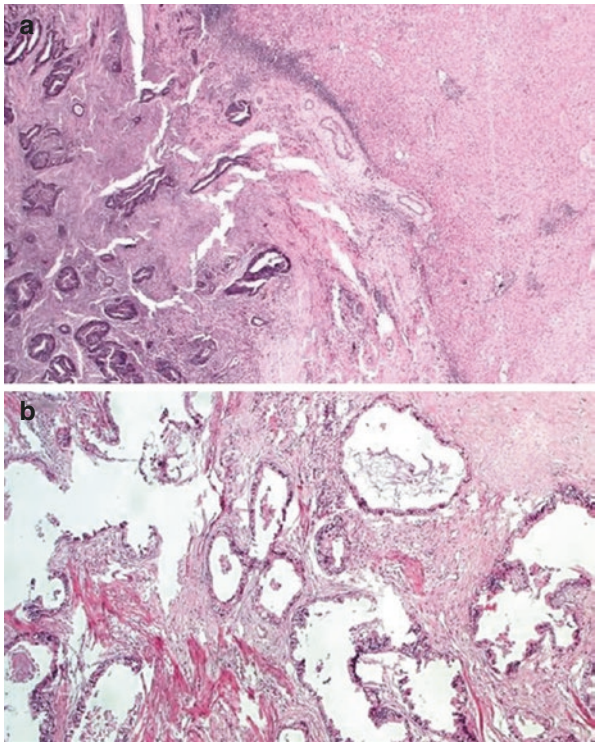

Fig. 2.1 Moderately differentiated adenocarcinoma of the gall bladder. (**a**) Tumour invades the gall bladder adventitia and is close to liver parenchyma (low power). (**b**) High-power view of adenocarcinoma

mucinous, clear cell type. Squamous differentiation is commonly seen and can be variable.

Squamous carcinoma, small-cell neuroendocrine carcinoma and undifferentiated carcinoma are some of the uncommon types of carcinomas, each forming upto 3% [4, 6]. Histologically, squamous differentiation in the adenocarcinoma of the gall bladder is common. Hence, diagnosis of a primary squamous carcinoma of the gall bladder is made after extensive sampling and after excluding gland formation as well as any other secondary tumour.

Undifferentiated carcinoma lacks gland formation and can have spindle cells, giant cells and pleomorphic cells. They are very aggressive tumours which frequently metastasize.

The prognosis depends on the stage of the disease.

Nonneoplasic lesion of the gall bladder includes inflammatory polyp, adenomyoma and cholesterol polyps.

Liver cancer is much more common in men than in women. In men, it is the second leading cause of cancer death worldwide and in fewer developing countries [1].

Liver cancer rates are the highest in East and Southeast Asia and Northern and Western Africa. Most primary liver cancers (70–90%) are hepatocellular carcinomas (HCC) (Fig. 2.2). Chronic liver disease and cirrhosis remain the most important risk factors for development of HCC of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide [7]. Several histological patterns are identified such as clear cell type, adenomatoid, small cell type, etc. Fibro lamellar HCC is a special variant which is seen in young adults and occurs in the liver that are normal. No risk factors are identified for this variant.

Other type of cancers includes cholangiocarcinoma, hepatoblastoma (in younger age) and angiosarcoma.

Cholangiocarcinomas (CC) can have similar histological and immunohistochemical (IHC) profile to that of gall bladder and pancreatic adenocarcinomas. The distinction of cholangiocarcinoma from HCC on a needle-core biopsy can be tricky.

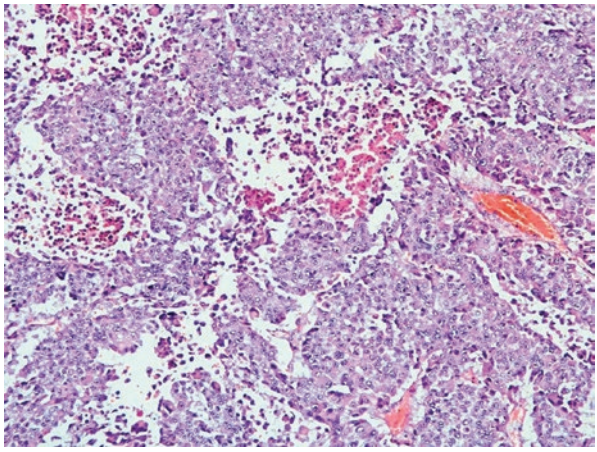

Fig. 2.2 Hepatocellular carcinoma. Histology shows hepatoid tumour cells having rather sheeted appearance and foci of necrosis. No portal triads are seen

HCC are generally immunopositive for Heppar-1 and glypican 3, whereas CC are positive for CK7, CK20 and CK19 and are negative for Heppar-1 and glypican 3. But often, histopathologist looks at clues such as tumour markers (raised alfa feto protein levels versus raised serum Ca19.9/CEA levels) and contrast enhancement in arterial phase on CT scan. Combined hepatocellular and cholangiocarcinoma (CHC) is a recognised entity and accounts for 0.4–14.2% of primary liver cancers. They have overlapping histological features of both HCC and CC [8].

Hepatoblastoma is the most common malignant liver tumour in children and comprises approximately 1% of all paediatric cancers. Nearly 90% of cases occur in the age group of 6 months to 5 years. It is seen typically as a large single mass, occurs in normal livers and almost always shows a marked rise in serum alfa feto protein levels [4]. Histologically, they are of epithelial and mixed epithelial and mesenchymal type and can show cartilage/osteoid, which may give diagnostic clues in imaging. Extramedullary haematopoiesis is often seen in these tumours.

Hepatocellular adenoma is seen mostly in young women during reproductive age and is uncommon in males. They are often solitary and occur in livers that are normal. Long-term use of oral contraceptive pills (OC pills) and use of anabolic steroids are risk factors. Other risk factors include diabetes, glycogen storage diseases types I and IV, tyrosinemia and galactosemia [4]. Hepatic adenoma shows proliferation of hepatocytes with minimal atypia, but with lack of portal zones. The reticulin framework is often maintained. Immunohistochemistry is not helpful in the diagnosis.

Bile duct adenoma is a localised benign ductular proliferation of bile ducts. They are subcapsular in location, smaller than 2 cm in size, and are usually single. They are often sent for frozen section examination to exclude metastatic adenocarcinoma. This can be a difficult diagnosis. Round outline and lack of atypia can point towards this diagnosis.

2.3 Pancreatic Carcinoma

Pancreatic carcinoma is one of the most lethal of all solid malignancies despite therapeutic and research advances. Five-year survival is less than 5% [9].

The incidence rates and mortality rates of pancreatic cancers are generally higher in the USA, Europe, Australia and Japan and lower in India, Africa and parts of Middle East. In India, the age adjusted incidence rate is 1.1/100,000 [10]. More than 95% of pancreatic cancers arise in exocrine portion, whereas about 5% arise in the endocrine portion of the pancreas. The majority are ductal-type adenocarcinomas (Fig. 2.3).

Pancreatic cancer cells, cancer stem cells and tumour microenvironment are the three most crucial components. Pancreatic cancer stem cells (which can comprise of 1–5%) of the total cancer cell population are resistant to chemotherapy. Additionally, the poorly vascularised characteristic pancreatic stroma plays an important role in progression and invasion. Pancreatic stellate cells (also called as myofibroblasts) are a key cellular element in the stroma [11].

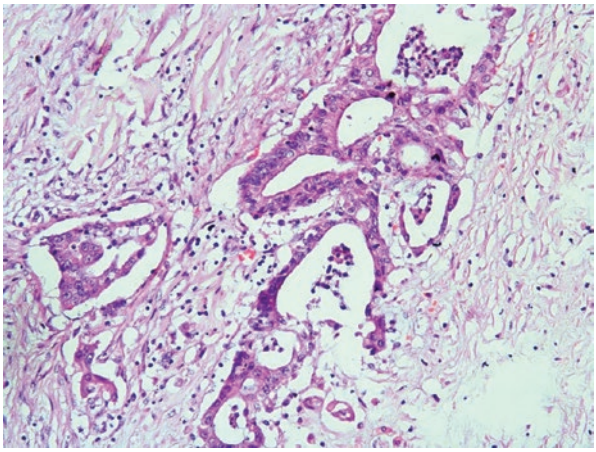

Fig. 2.3 Ductal-type pancreatic adenocarcinoma. Neoplastic glands are irregularly situated in the stroma showing a myxoid and fibrous response

Epidemiological studies looking for aetiology of pancreatic cancers are inconclusive. However, a twofold increase in risk for tobacco smokers is observed than nonsmokers [12].

It is now well established that in the pancreas, similar to colorectal carcinoma, noninvasive precursor lesions of the conventional ductal carcinoma exist. They are termed as pancreatic intraepithelial neoplasia (Pan In). They have been identified from studies of the resected specimens and autopsy studies [13]. The same genes are mutated in Pan Ins as in invasive pancreatic ductal carcinoma.

Pan Ins are microscopic lesions (less than 0.5 cm) and arise in the smaller ducts. They are divided into Pan In1,2 (low grade) and Pan In 3 (high grade). These show increasing degree of nuclear crowding, pseudostratification and hyperchromasia (grade 3 being most severe).

Pan In needs to be distinguished from intraductal pancreatic mucinous neoplasm (IPMN). The latter is the larger mass-forming lesions and can be diagnosed on imaging.

The variants of pancreatic carcinoma include colloid carcinoma (pools of mucin in which atypical mucinous epithelial cells are seen). They almost always arise on the background of intestinal type of IPMN and exhibit intestinal differentiation evident by CDX-2 (transcription factor regulating intestinal programming) and MUC2 (goblet cell type of intestinal mucin). They have a significantly better prognosis than conventional ductal adenocarcinomas [4].

Medullary carcinoma is a distinct subtype of pancreatic carcinoma characterised by poor differentiation, syncytial growth pattern, pushing borders and Crohn's-like lymphoid infiltrate. Most of these tumours are MSI (microsatellite instability) high tumours. IHC can play a role in identifying this subtype, as MSI high tumours have a better prognosis and predict poor response to 5FU-based chemotherapy.

Other pancreatic carcinoma types are undifferentiated carcinoma and acinar carcinoma.

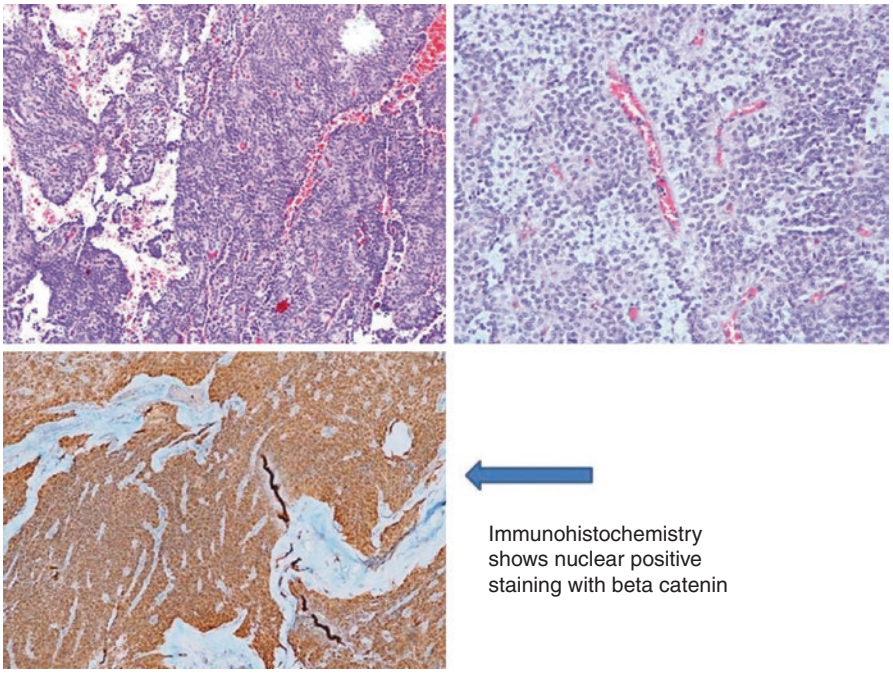

Fig. 2.4 Solid pseudopapillary tumour of the pancreas (SPEN). Histology shows pseudopapillae lined by relatively uniform cells. Immunohistochemistry shows nuclear beta catenin positivity

Mucinous cystic neoplasm is a cystic tumour lined by mucinous epithelium and ovarian-type stroma. They arise in premenopausal women (female to male ratio 201:1) but can be seen in males as well. They involve pancreatic tail more often than the head. The epithelium shows increasing grades of dysplasia.

Solid pseudopapillary tumour of the pancreas (SPEN) is a distinct neoplasm seen in younger females. It is a slow growing tumour and has a favourable prognosis. Surgery is curative (Fig. 2.4).

Key Points

Gall Bladder

- The overall pathogenesis of adenocarcinoma of the gall bladder is thought to result from dysplasia to carcinoma.
- In general, gall bladder carcinomas usually result from localised thickening rather than diffuse thickening. They are mostly located in the body and the fundus (90%) and about 10% are in the neck.

- The commonest histological type of cancers of the gall bladder is adenocarcinoma, which accounts for 75–85% of all carcinomas.
- Squamous carcinoma, small-cell neuroendocrine carcinoma and undifferentiated carcinoma are some of the uncommon types.

Liver Cancer

- Most primary liver cancers (70–90%) are hepatocellular carcinomas (HCC). Several histological patterns are identified such as clear cell type, adenomatoid, small cell type, etc.
- Fibro lamellar HCC is a special variant which is seen in young adults and occurs in the liver that is normal.
- Cholangiocarcinomas (CC) can have similar histological and immunohistochemical (IHC) profile to that of gall bladder and pancreatic adenocarcinomas.
- Combined hepatocellular and cholangiocarcinoma (CHC) is a recognised entity and accounts for 0.4–14.2% of primary liver cancers.

Pancreatic Carcinoma

- The majority are ductal-type adenocarcinomas.
- It is now well established that in the pancreas, similar to colorectal carcinoma, noninvasive precursor lesions of the conventional ductal carcinoma exist.
- Medullary carcinoma is a distinct subtype of pancreatic carcinoma.
- Mucinous cystic neoplasm is a cystic tumour lined by mucinous epithelium and ovarian-type stroma.
- Solid pseudopapillary tumour of the pancreas (SPEN) is a distinct neoplasm seen in younger females. It is a slow growing tumour and has a favourable prognosis.

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