Section: Pathology

Original Research Article

CLINICOPATHOLOGICAL ANALYSIS OF HEPATOBILIARY MALIGNANCIES IN A TERTIARY CARE HOSPITAL – A RETROSPECTIVE STUDY

Meenakumari Gopalakrishnan[1], Jeyanthi Gnanamuthu[2], K.Rani[3], R.Manaswini[4], Ashwin Ilango[5]

[1]Professor, Department of Pathology, Govt Theni Medical College, Theni, Tamil Nadu, India
[2]Associate Professor, Department of Pathology, Madurai Medical College, Madurai, Tamil Nadu, India.
[3]Professor, Department of Pathology, Madurai Medical College, Madurai, Tamil Nadu, India
[4]Department of Pathology, Madurai Medical College, Madurai, Tamil Nadu, India
[5]MBBS, Madurai, Tamil Nadu, India.

Received : 05/01/2024
Received in revised form : 15/03/2024
Accepted : 30/03/2024

Keywords:
Hepatocellular carcinoma, Cholangiocarcinoma , Hepatoblastoma.

Corresponding Author:
Dr. Meenakumari Gopalakrishnan,
Email: meenakumariilango1971@gmail.com

DOI: 10.47009/jamp.2024.6.2.228

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (2); 1138-1145

Abstract

Background: Hepatobiliary malignancy is a vast , challenging and diverse entity. It is the third leading cause of cancer related death worldwide . It comprises of primary and metastatic tumours and varies in paediatric and adult population. Distinguishing between them is important because of its different prognostic and therapeutic implications. Aim: The aim of this study is to analyse the various histopathological features of hepatobiliary malignancies and its clinical correlation along with the review of the literature. **Materials and Methods:** This is a retrospective study of 36 cases of hepatobiliary malignancies reported at our department during a period of 3 years from January 2020 to December 2022. The clinical data of those cases were retrieved from the medical records. Both biopsies and hepatectomy specimens are included in this study. Specimens fixed in 10% formalin were processed, cut into 5 microns sections and stained with hematoxylin and eosin. Immunohistochemical studies were performed wherever necessary. Histopathological features of these various tumors were analysed and clinically correlated. **Finding and Conclusion:** Hepatobiliary Malignancies accounted for 0.8% of the total number of malignant cases received at our centre. There was a male preponderance with a peak incidence in 50 to 60 age group. Secondaries were more common than Primary malignancies. Most cases of secondaries had colorectal primary malignancy. Among the primary hepatobiliary malignancies ,Hepatocellular carcinoma was most common followed by Cholangiocarcinoma. Hepatoblastoma was the common tumour observed in paediatric population. Uncommon cases of intraductal hepatocellular carcinoma without parenchymal involvement and Primary hepatic lymphomas were encountered. Better understanding of pathological diagnosis and appropriate standardized multimodal therapies goes a long way in the patient care.

INTRODUCTION

Hepatobiliary malignancy is a vast, challenging and diverse entity. It is the third leading cause of cancer related death worldwide and fifth most common cancer in men and ninth in women.[1] It comprises of primary and metastatic tumours and varies in paediatric and adult population. Distinguishing between them is important because of its different prognostic and therapeutic implications.

Primary hepatobiliary malignancies include Hepatocellular carcinomas, Hepatoblastoma, Mesenchymal tumors, Hematopoietic malignancies, Cholangiocarcinomas, carcinomas of extrahepatic bileducts and gallbladder. The unique architectural composition of liver renders it as one of the most common sites of metastases. Among the various primary tumours, Gastrointestinal tract, breast and prostate malignancies commonly metastasize to liver.[2]

The aim of this study is to analyse the various histopathological features of hepatobiliary malignancies and its clinical correlation along with the review of the literature.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

MATERIALS AND METHODS

This is a retrospective study of 36 cases of hepatobiliary malignancies reported at our department during a period of 3 years from January 2020 to December 2022. The clinical data of those cases were retrieved from the medical records. Both biopsies and hepatectomy specimens are included in this study. In hepatectomy specimens, macroscopic features of tumours including size, focality and other features were noted. Specimens fixed in 10% formalin were processed, cut into 5 microns sections and stained with hematoxylin and eosin. Immunohistochemical studies were performed wherever necessary. Histopathological features of these various tumours were analysed and clinically correlated.

RESULTS

Among the total number of 4629 malignant tumours received at our centre from January 2020 to December 2023, 36 were Hepatobiliary malignancies accounting for 0.8 %.

Among the 36 cases,19 were males (53%) and 17 were females. (47%) with the male female ratio being 1.1:1. Peak incidence occurred in 50 to 60 age group. [Figure 1,Table 1] Abdominal pain was the most common presenting symptom.

Secondaries were more common than Primary malignancies. (30%) Among the Primary hepatobiliary malignancies, Hepatocellular carcinoma was the most common (28%) followed by Cholangiocarcinoma (25%) and Hepatoblastoma (11%). Primary Lymphoma of liver (one case) and carcinoma of gallbladder (one case) were the other tumours encountered. [Figure 2]

In the present study incidence of hepatic metastases was higher (11 cases). Higher incidence was observed in 50 to 60 age group with a female preponderance. Abdominal pain was the common symptom. Of the 11 cases, 5 were metastases from colorectal malignancies, 3 were from carcinoma breast, 2 from carcinoma pancreas and one was metastatic deposits of neuroendocrine carcinoma.

In this study, hepatocellular carcinomas accounted for 28% of hepatobiliary malignancies. (10 cases). Mean age of occurrence was 57 years. Among the 10 cases of Hepatocellular carcinomas, 8 were males with a male female ratio of 4:1. Abdominal pain, jaundice and fever were the common clinical symptoms. Clinical signs included hepatomegaly and ascites. Right lobe of liver was most commonly involved with the tumour size being more than 10 cm. Associated fatty change was observed in one case and cirrhosis in one case. Among the 10 cases, 6 were well differentiated (grade 1) and the remaining grade 2.

One case showed a rare presentation of intraductal hepatocellular carcinoma without parenchymal involvement. Clinically diagnosed as hilar cholangiocarcinoma type 3A/ tumour infiltrating into right anterior sectoral duct and Right hepatectomy with caudate excision was done. Hepatectomy (18 x 14 x 9 cm) with caudate lobe (6 x3 x2 cm) was received. Cutsurface revealed multiple dilated ducts in the hilar region larger measuring 1 x 0.5 x 0.5 cm. The ducts were filled with grey white tumour. [Figure 3] Surrounding liver parenchyma was greenish yellow with no tumour involvement. On Histopathological examination the dilated intrahepatic bile ducts ducts showed tumour cells arranged in sheets with intervening vascular spaces. The tumour cells had round nuclei with clear cytoplasm. [Figure 4,5]. Surrounding hepatic parenchyma showed cholestasis and bile ductular proliferation with no evidence of tumour involvement. On immunohistochemical studies the tumour cells showed positivity for HepPar 1, Glypican and negative for Cytokeratin 7, 19 and 20. [Figure 6,7]. Diagnosis of Intraductal Clear cell variant of Hepatocellular Carcinoma without parenchymal tumour was made.

Next common tumour in the present study was Cholangiocarcinomas forming 25% (9 cases). Mean age of occurrence was 54 with a female preponderance (56%). No associated risk factors were found in all the cases. Jaundice was the most common clinical presentation. Tumour markers were available for only for few patients and showed no correlation with tumour stage.

Among the 9 cases of Cholangiocarcinomas, 6 were intrahepatic (66.7%) and 3 were extrahepatic (33.3%). All the intrahepatic cholangiocarcinomas were large duct type. Out of the 6 cases, 5 showed periductal infiltrative growth pattern and one mass/periductal growth pattern. 4 cases were well differentiated and 2 were moderately differentiated adenocarcinomas. Perineural invasion was observed in 4/6 cases and lymphovascular invasion in 3/6 cases. [Table 2]

Among the 3 cases of extrahepatic cholangiocarcinoma, 2 cases were well differentiated and one was moderately differentiated adenocarcinoma. 2 cases showed perineural, lymphovascular invasion and regional lymphnodal involvement. Intraepithelial neoplasia of bileduct with invasion into the surrounding wall of bileduct and adjacent gall bladder was observed in one case.

In the present study out of the 36 cases, 4 cases were hepatoblastoma (11%).All the 4 cases were male children less than 5 years old . Right lobe was involved in 3 of the 4 cases and left lobe in one case. On histopathological examination all the four cases were of Epithelial type exhibiting mixed patterns of fetal and embryonal. [Figure 8,9]

One case of Primary Hepatic NonHodgkin lymphoma was reported in the present study. 49 year old male patient presented with the complaints of abdominal pain, loss of weight and appetite. Liver function was altered. Alphafetal protein levels, Complete hemogram and bonemarrow examination were normal. Computed tomography scan of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

abdomen revealed a hypodense mass in the right lobe of liver. Right hepatectomy was done. Macroscopy revealed a solitary greyish white firm mass measuring 19 x 15 x 8 cm confined to liver. [Figure 10]. Histopathological examination showed a wellcircumscribed tumour composed of tumour cells with round nuclei and scanty cytoplasm arranged in sheets. [Figure 11]. On immunohistochemical studies the tumour cells showed diffuse positivity for CD 45, CD 20 and negative for cytokeratin 7 and for HepPar1. [Figure 12]. As patient had no other tumour involvement elsewhere diagnosis of Primary Nonhodgkin Lymphoma was made.

In the present study only one case of carcinoma gallbladder was encountered. 68 year old female diagnosed as carcinoma gallbladder and extended cholecystectomy with extrahepatic bileduct excision was performed. Macroscopic examination revealed a 4x4 x3 cm greyish white mass in the fundus of gallbladder associated with a yellowish gallstone of size 2cm in diameter. On histopathological examination it was reported as Adenocarcinoma – Intestinal type grade 1 stage pT1bpN0.

Table 1

			Age						Sex Distribution	
S. No	Tumours	No. of Cases	0-5	20-30	30-40	40-50	50-60	60-70	Males	Females
1	Metastatic Tumours	11	-	1	-	3	5	2	2	9
2	Hepatocellular carcinoma	10	-	-	-1	2	2	5	8	2
3	Cholangio carcinoma Intrahepatic	6	-	-	-	3	2	1	2	4
4	Cholangio carcinoma extrahepatic	3	-	-	-	1	1	1	2	1
5	Hepatoblastoma	4	4	-	-	-	-	-	4	-
6	NHL	1	-	-	-	1	-	-	1	-
7	Carcinoma of Gall bladder	1	-	-	-	-	-	1	-	1

Table 2

S. No		Type	Growth Pattern	Adenocarcinoma Grade	Angio Invasion	Perineural Invasion	Lymph node Involvement
1	690/20	Intrahepatic – Large duct type	Periductal Infiltrating	II	Absent	Present	Absent
2	1407/20	Intrahepatic – Large duct type	Mixed growth pattern (mass formed periductal infiltrating)	I	Present	Absent	Absent
3	1805/20	Intrahepatic – Large duct type	Periductal Infiltrating	I	Absent	Present	Absent
4	2233/21	Intrahepatic – Large duct type	Periductal Infiltrating	I	Absent	Absent	Absent
5	384/22	Intrahepatic – Large duct type	Periductal Infiltrating	I	Present	Present	Absent
6	1584/22	Intrahepatic – Large duct type	Periductal Infiltrating	II	Present	Present	Absent
7	1699/20	Extrahepatic		II	Present	Present	Present
8	3613/22	Extrahepatic		I	Present	Present	Present
9	3446/22	Extrahepatic		I	Absent	Absent	Absent

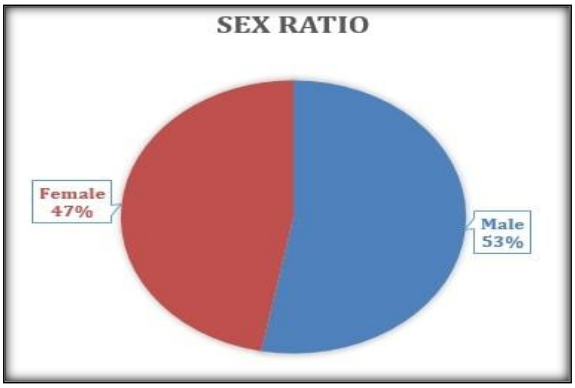

Figure 1

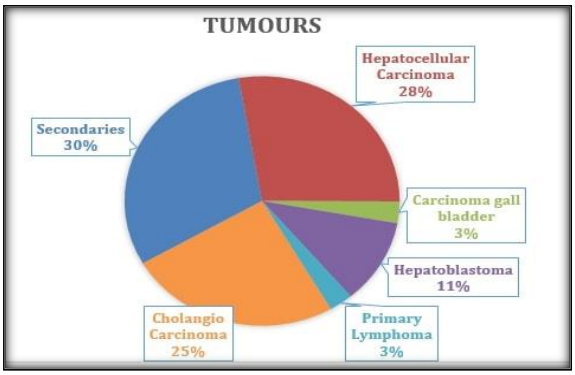

Figure 2

Figure 3: dilated ducts showing greyish white growth without parenchymal involvement

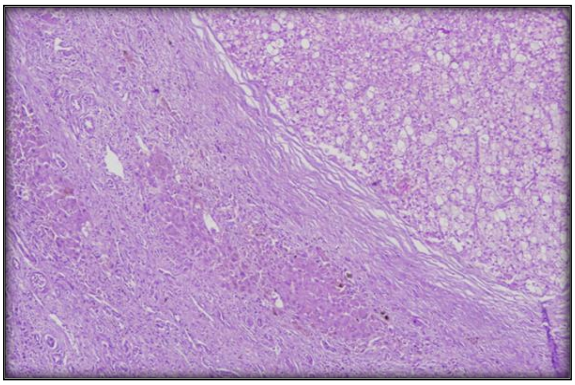

Figure 4: 10x H&E-Tumor cells with clear cytoplasm seen within duct

ISSN (O): 2687-5365; ISSN (P): 2753-6556

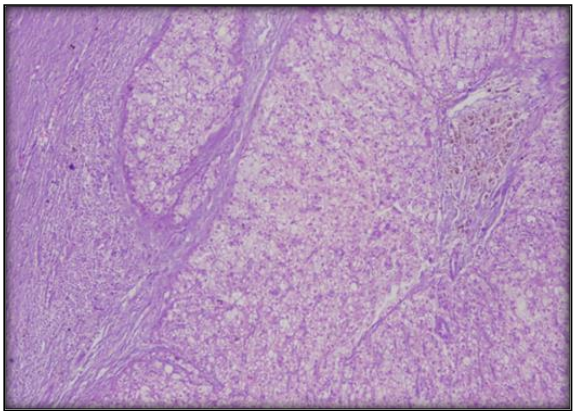

Figure 5: 10x H&E - Tumor cells with clear cytoplasm

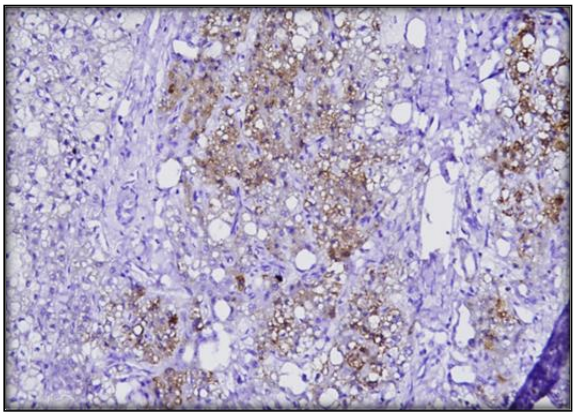

Figure 6: Tumor cells positive for HepPar 1 -10x

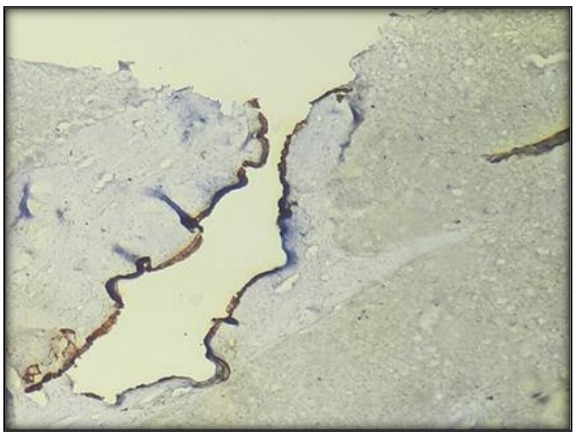

Figure 7: Tumor cells negative for CK7 while duct lining cells are positive -10x

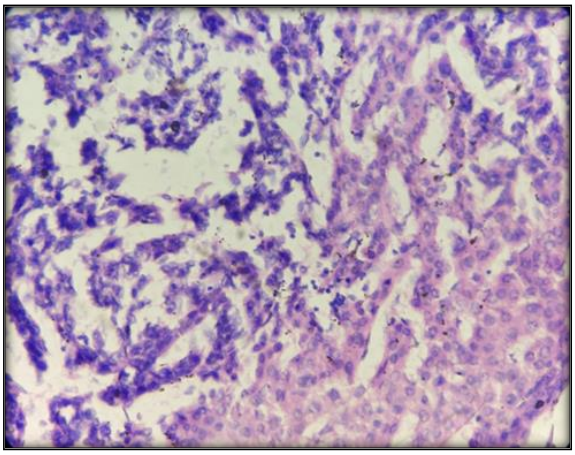

Figure 8: 10x - H&E -Hepatoblastoma - Fetal and Embryonal area

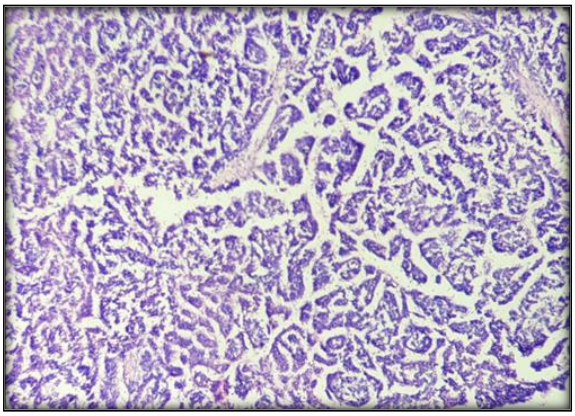

Figure 9: 10x H&E Hepatoblastoma - Fetal áreas

Figure 10: solitary greyish white mass

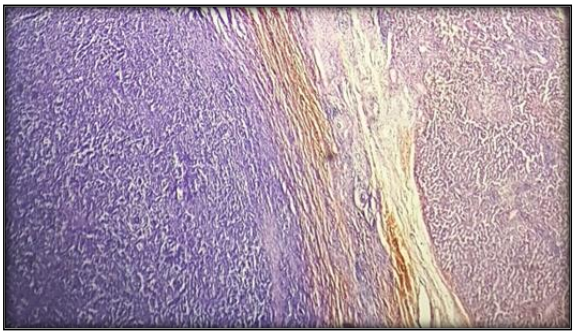

Figure 11: 10x H&E - tumor cells with round nuclei and scant cytoplasm

ISSN (O): 2687-5365; ISSN (P): 2753-6556

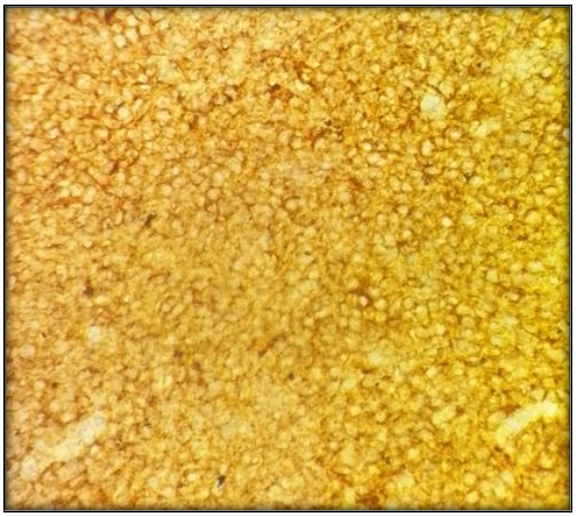

Figure 12: tumor cells positive for CD20-10x

DISCUSSION

Cancer has become a global health problem accounting for about 1 in 7 deaths.[1] Among various cancers, hepatobiliary malignancy is the 5th most common cancer in men and 9th in women worldwide.[1] Liver malignancies may be either Primary or Secondary and distinguishing between them is important.

In the present study Secondaries were more common than Primary hepatic malignancy similar to Ragini Thapa and Pushpalatha Pai study.[3] Liver is a most common site of metastases due to its unique architecture and dual blood supply.[2] Metastases to noncirrhotic liver is more common than to cirrhotic liver. Depending on the disease burden the patient may present with various symptoms like abdominal pain, ascites and jaundice. In our study abdominal pain was the commonest symptom.

Tumours which commonly metastasize to liver include GI malignancies, carcinomas of prostate, breast, neuroendocrine tumors and sarcomas.[2,3] The common primary site varies with age at diagnosis. In younger women with hepatic metastasis breast is the common primary site and in younger men colorectal malignancy is the common primary.[2] With increasing age carcinomas from many heterogenous sites may metastasize to liver. In the present study colorectal malignancy was the most common primary accounting for 5 out of the 11 cases followed by carcinomas of breast and pancreas.

Hepatocellular carcinoma is the most common Primary liver malignancy,[3] and is the sixth most common cancer in the world. In this study there was a male preponderance with a mean age of occurrence of 57 years comparable with Faten Limaiem study.[4] Most common risk factors associated with the development of Hepatocellular carcinoma are HBV and HCV infection, cirrhosis, alcohol consumption, obesity, diabetes mellitus, non-alcoholic fatty liver disease and inherited liver diseases.[4,5] The incidence varies in different countries depending on the prevalence of chronic liver diseases and chronic viral hepatitis.[4] In the present study one patient had associated steatosis and another had associated cirrhosis. Most patients presented with clinical signs and symptoms of abdominal pain, fever, jaundice hepatomegaly and ascites as observed in other studies.[5]

Elevated serum Alpha fetal protein is found in 70 to 80% of cases. Larger tumours, poorly differentiated tumors and advanced stage are associated with higher levels. In the present study, 80% percent of the cases had increased AFP levels comparable with other studies.[4]

On macroscopic examination Hepatocellular carcinomas may present as a single mass, multiple nodular masses or as diffuse liver involvement resembling cirrhosis. In our series most tumours presented as a large nodular mass as in other studies.[5] Most tumours are soft and necrotic due to lack of abundant stroma except scirrous and fibrolamellar variant. Large tumours tend to invade hepatic or portal vein which was not observed in our study.

On histological examination Hepatocellular carcinoma show loss of normal architecture with reduced or loss of reticulin framework. They show increased arterialization and loss of portal tracts. Hepatocellular carcinomas exhibits four principal growth patterns including trabecular, solid, pseudoglandular and macrotrabecular. Mixed patterns can also occur. In the present study mixed pattern composed of trabecular,solid and pseudoglandular pattern was observed in 9 out of the 10 cases.

Histological variants of Hepatocellular carcinoma includes scirrhous, Fibrolamellar, Steatohepatic, Lymphocyte rich, neutrophil rich, macrotrabecular, clear cell and chromophobe representing distinct molecular and clinicopathological entities. Fibrolamellar carcinoma occurs at a median age of 25 with no associated liver disease. Macrotrabecular pattern where the trabeculae are more than 10 cells thick are associated with high serum Alpha fetoprotein and worse prognosis. Clear cell and Lymphocyte rich subtypes have a better prognosis.

In this study, one case of Intraductal Hepatocellular Carcinoma (Clear cell variant) without Parenchymal tumour was reported which is very rare and only reported in case reports(24,25) . Clear cytoplasm is due to accumulation of glycogen. This variant should be distinguished from metastatic deposits of renal cell carcinoma. Immunohistochemical studies plays an important role as this variant is positive for markers of HCC and negative for renal markers as in our case. Histologically they are graded as well, moderate and poorly differentiated tumours. In the present study 6/10 cases were well differentiated. Tumour grading is essential as it predicts patient survival and disease free survival after resection(23).

Hence accurate diagnosis, grading and staging are essential for planning optimal treatment and determining prognosis.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Cholangiocarcinoma is the second most common type of Primary liver malignancy and accounts for 3% of all gastrointestinal malignancies.[9] Increasing incidence could be attributed to the increased prevalence of risk factors and improved cancer recognition and treatment. In our study, the mean age at presentation was 54 whereas it was 62 in Priya Nairet al study.[10] Male female ratio was 0.79:1 in the present study whereas male preponderance was seen in other studies.[10]

Cholangiocarcinoma arise from different location within biliary tree and can be intrahepatic or extrahepatic. Intrahepatic cholangiocarcinoma arise in the liver proximal to right and left hepatic ducts. It can be classified into large duct type and small duct type and have different molecular and morphological charecterestics. Large duct type of intrahepatic cholangiocarcinoma are often located closer to liver hilum and show periductal infiltrating or periductal infiltrating and mass forming pattern. Associated risk factors include Primary sclerosing cholangitis, hepatolithiasis and liver fluke infection. They may evolve from precursor lesions like biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile ducts.[26] Small duct type of cholangiocarcinoma occur in the peripheral liver parenchyma and show a mass forming pattern. Risk factors include non biliary cirrhosis and chronic viral hepatitis. No precursor lesions have been described though a few cases have been associated with biliary adenofibroma.[27] In the present study all were large duct type with most showing periductal infiltrative pattern. No associated risk factors were seen in all the cases.

Cholangiocarcinomas tends to be asymptomatic in early stages. Large duct type may present with cholestasis. In the present study jaundice was the most common clinical presentation similar to other studies(10).

Intrahepatic cholangiocarcinomas are adenocarcinomas with variable desmoplastic reaction. They are graded as well, moderate and poorly differentiated. Perineural and lymphatic invasion are frequent in the large duct type. In this study, 4 cases were well differentiated and 2 were moderately differentiated adenocarcinomas. Perineural invasion was observed in 4/6 cases and lymphovascular invasion in 3/6 cases.

Intrahepatic cholangiocarcinomas are aggressive tumours with poor survival rate. Small duct type has a higher postoperative survival rate than large duct type.[28]

Extrahepatic cholangiocarcinoma arise in the extrahepatic hepatic or common bile duct. They present in the sixth or seventh decade. No female predilection have been noted probably due to lack of association with gall stones.

They usually present early with obstructive jaundice. They may have abdominal pain, weight loss and fever with chills if cholangitis develops. In the present study all the three cases presented with jaundice.

Risk factors include primary sclerosing cholangitis, cholelithiasis, Caroli disease, various metabolic conditions, type 1 diabetes, chronic pancreatitis and gout. In this study no associated risk factors were observed.

Precursor lesions associated with extrahepatic cholangiocarcinomas are Biliary intraepithelial neoplasia and intraductal papillary neoplasm of bile ducts. In this study biliary intraepithelial neoplasia was seen in one case.

Macroscopically they appear as sclerosing, nodular or papillary lesions and microscopically most are pancreaticobiliary type of adenocarcinomas. In the present study out of the 3 cases of extrahepatic cholangiocarcinoma, 2 cases were well differentiated and one was moderately differentiated adenocarcinoma. 2 cases showed perineural, lymphovascular invasion and regional lymphnodal involvement.

Prognosis depend on the stage of presentation and resectability of the tumour.[29] Poor differentiation, perineural and vascular invasion are associated with poor prognosis.[30]

Hepatoblastoma is a rare malignant liver tumour which occurs in infants and children less than 5 years. It accounts for 79% of all paediatric liver tumors.[11] In our study 3 out of 4 cases occurred in the age group of 0-5 years similar to other studies.[11] Male preponderance was noted and right lobe was involved in 3 out of 4 cases. Marked elevation of serum AFP is observed in 90% of cases and plays an important role in monitoring chemotherapy induced regression and recurrence. Decreased AFP levels are seen associated with aggressive course and small cell undifferentiated subtype. Alphafetal protein was elevated in all the 4 cases in the present study.

Macroscopically Hepatoblastomas appear as single or multiple nodules. On cutsurface the appearance depends on the components of the tumour and the presence of haemorrhage and necrosis. In the present study, all the cases presented as a welldelineated single mass. Histologically Hepatoblastomas are classified as Epithelial and Mixed Epithelial and mesenchymal types. Epithelial type may exhibit fetal, embryonal, small cell undifferentiated (SCUD), cholangioblastic, macrotrabecular and mixed patterns. Fetal pattern includes well differentiated (fetal pattern with low mitotic activity)and crowded fetal (mitotically active). In the present study all the four case were of Epithelial type exhibiting mixed patterns of fetal and embryonal.

Accurate diagnosis of histological type is essential for predicting prognosis and deciding the treatment modalities. Pure well differentiated fetal hepatoblastoma has a favourable prognosis and they do not require chemotherapy. Whereas presence of even a small foci of SCUD component leads to an unfavourable prognosis.

One case of Primary Hepatic Lymphoma (PHL) was reported in the present study. PHLs are very rare tumours constituting 0.4% of extranodal lymphomas.[31] Though a definite pathogenesis is

ISSN (O): 2687-5365; ISSN (P): 2753-6556

unclear it has been associated with viral etiology like HCV, HIV, HBV, Epstein Barr virus, liver cirrhosis, Primary biliary cirrhosis and autoimmune diseases.[32] Most demonstate B cell phenotype as in our case. With the latest treatment modalities prognosis have drastically changed in recent times. Hence recognition of this uncommon tumour is necessary for appropriate treatment.

Carcinoma of gall bladder is the most common cancer of the biliary tract and the fifth most common neoplasm of the digestive tract.[21] In the present study it accounted for 2.8%. Geographical variation in the incidence of gallbladder cancer has been observed. This may be attributed to the prevalence of risk factors. Cholelithiasis and chronic salmonella infections are important predisposing factors others being porcelain gallbladder, polyps, chronic cholecystitis, congenital biliary cyst and abnormal pancreatobiliary duct junction.[3] These tumours are often not suspected clinically as they present with symptoms similar to benign diseases of gallbladder like right upperquadrant pain, jaundice, nausea and vomiting. 70% of the cases are diagnosed as postoperative incidental findings.[21] Mean age of occurrence is 65 years and are more common in women.[22] Most cancers orginate in fundus of gallbladder, associated with gallstones. Histologically they display features typical of pancreaticobiliary adenocarcinomas. Nonspecific late symptoms and close proximity to other organs leads to late diagnosis and poor prognosis.[8]

CONCLUSION

In the present study, Hepatobiliary malignancies showed a predisposition to male sex with a peak incidence in the 50 to 60 age group. Secondaries were more common than primary malignancies. Among the primary malignancies, hepatocellular carcinomas were more common followed by cholangiocarcinomas consistent with other studies. Uncommon cases of intraductal hepatocellular carcinoma without parenchymal involvement and Primary hepatic lymphomas were encountered. Better understanding of pathological diagnosis and appropriate standardized multimodal therapies goes a long way in the patient care.

REFERENCES

1. Namita Sharma, Guresh Kumar,Puja Sahai et.al.Epidemiologic Study of patients registered in Oncology unit at a tertiary care centre in India.Indian J Med Paediatr Oncol 2020;41:358-67.
2. Samantha R Horn,Kelsey C Stoltzfus, Eric J Lehrer et.al.Epidemiology of liver metastases.CancerEpidemiology .Volume 67, August 2020,101760.
3. Ragini Thapa and K.Pushpalatha Pai.Histopathological study of hepatobiliary malignancies and its correlation with clinical features.IJBAR.2014;05(09).
4. Faten Limaiem,Marwa Bouhamed,Ghada Sahraoui et.al.Hepatocellular carcinoma:a clinicopathological study of 64 cases.Pan African Medical Journal.2017;27:41.
5. Lencioni R.Loco –regional treatment of hepatocellular carcinoma.Hepatology.2010; 52(2):762-73.
6. Sarin SK, Thakur V, Guptan RC, et al.: Profile of hepatocellular carcinoma in India: An insight into the possible etiologic associations. J Gastroenterol Hepatol .2001;16:666-673.
7. Kumar A, Acharya SK, Singh SP, et al.: 2019 Update of Indian National Association for Study of the Liver Consensus on Prevention, Diagnosis, And Management of Hepatocellular Carcinoma in India: The Puri II recommendations. J Clin Exp Hepatol .2020;10:43-80.
8. Ghassan Kabbach, Hussein A Assi,George Bolotin et.al.Hepatobiliary Tumors:Update on Diagnosis and Management.J Clin Transl Hepatol .2015,Sep 28;3(3):169-181.
9. Overview of the surveillance,Epidemiology and results database:evolution,data variables and quality assurance.Curr Probl.Cancer,2012.
10. L Hendriks et.al. Single organ metastatic disease and local disease status, prognostic factors for overall survival in stage IV non-small cell lung cancr:results from a population based study.Eur.J.Cancer.2015..
11. Yang J D ,Roberts L R.Hepatocellular carcinoma:a global view.Nat Rev Gastroenterol Hepatol.2010;(8:448-58.
12. Aravalli R N,Steer C J, Cressman E N.Molecular mechanisms of hepatocellular carcinoma.Hepatology.2008;48 (6):2047-63.
13. El-Serag H B,Rudolph K L.Hepatocellular carcinoma:Epidemiology and molecular carcinogenesis.Gastroenterology.2007;132(7):2557-76.
14. Global Burden of Disease Cancer Collaboration. The Global Burden of Cancer 2013.JAMA Oncol.2015;1(4):505-27.
15. Priya Nair,Harshavardhan Rao B,Anoop K.Koshy et.al. Cholangiocarcinoma in South India:unprecedented, unanticipated and underreported.Int J Community Med Public Health 2021 Aug;8(8):3854-3863.
16. Esakki Muthuvel,Vimala Chander and Chitra Srinivasan.A Clinicopathological Study of Paediatric Liver Tumours in a Tertiary Care Hospital.J Clin Diagn Res .2017 Mar;11(3):EC50-EC53.
17. Freeman C.BergJW,Cutler SJ .Occurence and prognosis of extranodal lymphomas.Cancer:1972;29:252-60.
18. Ata AA,Kamel IA.Primary reticulum cell sarcoma of the liver.A case report.J Egypt Med Assoc.1965;48:514-21.
19. Santos ES,Raez LE,Salvatierra J,Morgensztern D et.al.Primary Non-Hodgkins lymphoma: Case report and review of literature.Am J Gastroenterol.2003;98:2789-93.
20. Bauduer F,Marty F, Gemain MC et.al.Primary NonHodgkins lymphoma of then liver in a patient with hepatitis B,C,HIV infections.Am J Hematol.1997:54;265.
21. Varshney S, Butturini G,Gupta R.Incidental carcinoma of the gallbladder.Eur J Surg Oncol.2002;28:4-10.
22. Albores –Saavedra J.,Henson D.E, and Klimstra D.S.Tumors of the gallbladder,extrahepatic bile ducts and vaterian system,Atlas of Tumor Pathology.Armed Forces Institute of Pathology: Silver Spring, Maryland;2015.
23. Zhou L,Rui J,Wang SB,et.al.Outcomes and prognostic factors of cirrhotic patients with hepatocellular carcinoma after radical major hepatectomy.World J Surg.2007 Sep;31(9):1782-7.
24. Philips CA, Paramaguru R, Mahadevan P, Augustine P. Isolated intraductal variant of hepatocellular carcinoma. BMJ Case Rep. 2017;2017.
25. Ramakrishna B, Shah GJ, Vyas F. Intraductal hepatocellular carcinoma without parenchymal tumor: A case report. J Gastrointest Canc. 2012;43(Suppl 1):S77–9.
26. Aishima S,Oda Y.Pathogenesis and classification of intrahepatic cholangiocarcinoma:different characters of perihilar large duct type versus peripheal small duct type.J Hepatobiliary Pancreat.Sci.2015Feb:22(2):94-100.
27. Bhalla A,Mann SA,Chen S,et.al.Histopathological evidence of neoplastic progression of von Meyenburg complex to intrahepatic cholangiocarcinoma.Hum Pathol.2017 Sep:67:217 -4.
28. Liau JY,Tsai JH,Yuan RH,et.al.Morphological subclassification of intrahepatic

ISSN (O): 2687-5365; ISSN (P): 2753-6556

cholangiocarcinoma:etiological,clinicopathological and molecular features.Mod Pathol.2014 Aug;27(8):1163-73.
29. Hong SM, Pawlik TM,Cho H,et.al Depth of tumor invasion better predicts prognosis than the current American Joint Committee on Cancer T classification for distal bile duct carcinoma.Surgery.2009 Aug;146(2):250-7. .
30. Roa I,Ibacache G,Munoz S,et.al.Gallbladder cancer in Chile:pathological charecterestics of survival and prognostic factors: analysis of 1366 cases.Am J Clin Pathol.2014 May;141(5):675 -82.
31. El Fattah MA.Non-Hodgkin lymphoma of the liver: a US population based analysis.J Clin Transl Hepatol.2017 Jun 28;5(2):83-91.
32. Kikuma K,Watanabe J,Oshiro Y,et.al.Etiological factors in primary hepatic Bcell lymphoma.Virchows Arch.2012 April ;460(4):379-87

ISSN (O): 2687-5365; ISSN (P): 2753-6556