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Pediatric Hepatopathology: A Case Series With Review Of Literature

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Abstract

Background : Liver histopathology is of significance in paediatric health care as it serves the dual purpose of being an excellent diagnostic tool while also aiding the assessment of the severity of the lesions identified [(1)]

Objective: To study the clinicopathological features and analyse the histological presentation of certain interesting liver pathologies in paediatric patients.

Materials And Methods: A retrospective and prospective observational study of liver specimens of children sent to our Department over a span of 48 months. Of 34 cases received, 04 cases were selected .

Results: We report four interesting liver case reports ; A) Concomintant presence of glycogen storage disorder and hepatoblastoma, B) Metastasis of neuroendocrine tumour to the liver, C) Embryonal sarcoma in the liver, D) Biliary atresia splenic malformation syndrome.

Conclusion:The pediatric liver can present with a spectrum of pathologies both neoplastic and non neoplastic which can prove to be diagnostically challenging.Certain metabolic diseases may increase the risk of development of pediatric hepatic neoplasms. Ancillary techniques like Immunohistochemistry can prove to be a game changer in diagnosis of rare metastasis to the liver.

Keywords: Histopathology, Hepatomegaly, Immunohistochemistry, Liver , Metabolic diseases, Pediatric

Introduction

Liver disorders occupy a noteworthy proportion amongst the etiologies for childhood morbitites and mortalities whose timely reporting can abet the further management and overall prognosis of the condition.

The etiology of the disease can be assessed using biopsy in children presenting with signs and symptoms such as jaundice, hepatomegaly, pain in abdomen, ascites , clay coloured stools etc which are suggestive of underlying liver disease. Thus, histopathology is of significance in paediatric health care as it serves the dual purpose of being an excellent diagnostic tool while also aiding the assessment of the severity of the histopathological lesions identified [(1)]

The histologic interpretation of hepatic pathology in neonates and young children requires knowledge of the varied lesions and diseases that are of diagnostic importance in this age group.

The spectrum of pediatric liver diseases, especially those with genetic and metabolic etiologies, show variation according to geographical locations. This urges studies on various characteristics of pediatric liver diseases in different countries and communities [(2)]. Many of the inherited metabolic diseases of the liver are expressed in infancy. Glycogen storage disorders which occur due to inborn errors of carbohydrate metabolism due to genetic mutations demonstrate remarkable phenotypic, biochemical, and clinical heterogeneity[(3)].

The causes of hepatocellular neoplasms include infections, metabolic disorders that are constitutional and heritable, and from environmental exposure or from certain medications. Hepatoblastoma most commonly occurs as a single large mass compressing the surrounding parenchyma, which is otherwise normal. Development of hepatoblastoma along with the presence of co existing metabolic lesions such as glycogen storage disorder are not reported frequently in literature yet. Hepatoblastoma is the most common primary pediatric liver tumor, typically diagnosed within the first 3 years of life, and the incidence appears to be slowly increasing [(4)]

Sarcomas primary in the liver are exceptional. Their differential diagnosis includes metastases from sarcomas of other sites, and sarcomatoid liver cell carcinomas[(5)]. In infants and children, there have been isolated reports of embryonal rhabdomyosarcoma and rhabdoid tumor[(6)] . Undifferentiated (embryonal) sarcoma, is a rare hepatic mesenchymal tumor also known as malignant mesenchymoma, occurs predominantly in children but has also been seen in adults [(6)].

Two clinical patterns of Biliary atresia have been described: a perinatal or acquired form, which accounts for approximately 80% of affected infants, and an embryonic form, which is often associated with congenital anomalies such as midline symmetric liver, intestinal malrotation, situs inversus, asplenia and polysplenia. This embryonic form is defined as Biliary atresia associated with splenic malformation syndrome (heterotaxy) or BASM [(5)].

In this case series we report four case reports of the above mentioned interesting pediatric liver pathologies.

Materials And Methods:

A retrospective and prospective observational study was carried out on all liver biopsies and liver resection specimens sent to our department for histopatholgical examination from may 2016 till may 2020. Out of 34 patients whose samples were received, 04 were selected for this study. For retrospective evaluation slides and requisition forms was collected from the Pathology department. The required history and clinical, radiological details and laboratory investigations were collected from the medical records department .

Histopathological specimens was processed as per the standard methods. The tissue obtained from the biopsy was kept in 10% neutral buffered formalin. After processing, paraffin blocks were made and the the sections were cut at 4 to5 micron thickness and stained with haematoxylin and eosin and other necessary special stains where indicated.The sections were studied to form a histopathological report.

In this study we aimed to assess the clinicopathological features and analyse the histological presentation of certain interesting liver pathologies in paediatric patients.

Results:

Our study included 04 patients which were as follows ; A) Concomintant presence of glycogen storage disorder and hepatoblastoma, B) Metastasis of neuroendocrine tumour to the liver, C) Embryonal sarcoma in the liver, D) Biliary atresia splenic malformation syndrome.

<u>CASE 1: Concomitant presence of glycogen storage disorder and Hepatoblastoma in a single patient.</u>

A 10 month old male infant presented with progressive abdominal distention along with history of reduced oral intake and excessive irritability since last 3 days. On examination, he had hepatomegaly, the spleen was not palpable and there was no lymphadenopathy

Serum aspartate transaminase was 78 IU/ml.

Computed tomography done outside was suggestive of a liver lesion measuring 3x3 centimetres. Biopsy was immediately fixed in 10% formalin and sent for histopathological examination.

Gross examination: Specimen consisted of 3 grey white cores of tissue , largest measuring 1.5 cm

Microscopy findings: Biopsy studied showed effaced hepatic architecture. Individual hepatocytes were large, polygonal with centrally placed round nuclei and compact nuclei. Cytoplasm appeared clear in most cells with eosinophilic granules within.

Portal areas showed mild lymphocytic infiltration Sinusoids were compressed.(Picture 1)

No evidence of malignancy in the material studied.

PAS Stain was positive (Picture 2)

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Impression : Suggestive of glycogen storage disorder.

4 months later, right lobectomy of the same patient was received.

Gross Examination: Specimen consisted of right lobe of liver measuring 11x5.2x3.2 cm. External surface showed bare area measuring 4.5x4.2 cm. Capsular surface of the liver showed a reddish brown raised area. Cut surface showed a well circumscribed univocal mass confined to the liver measuring 5x 4.7x 3.8 cm showing greenish to tan coloured nodules of varying size separated by thin fibrous septa. Tumour is 0.2 cm from the resection margin.

Microscopy findings: Hepatoblastoma, epithelial type, fetal pattern.(Picture 3)

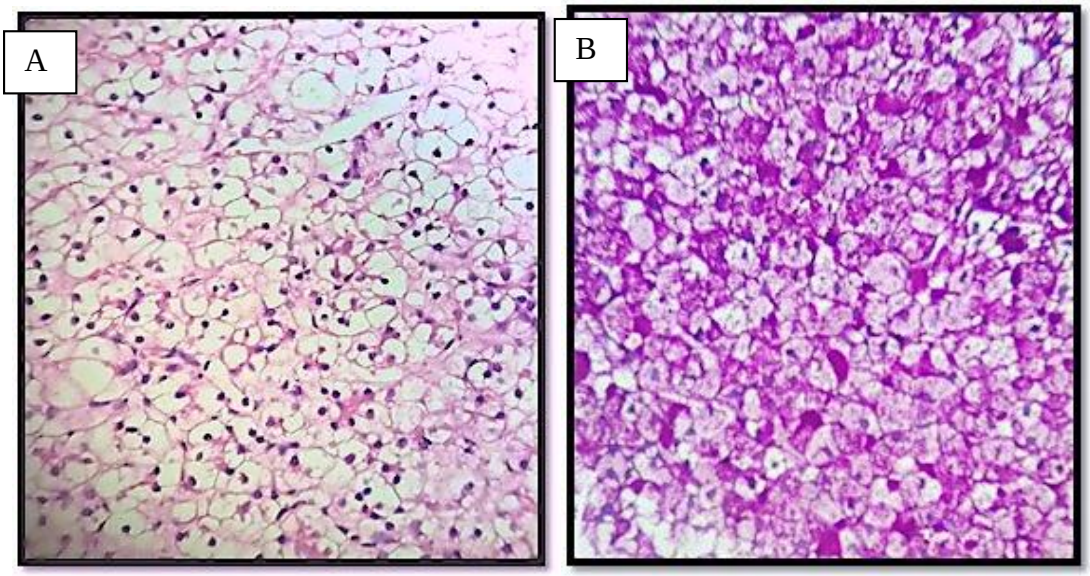
Mitosis: 3-4/10 High power field (HPF)

Margins: Surgical resection margin was involved by tumour

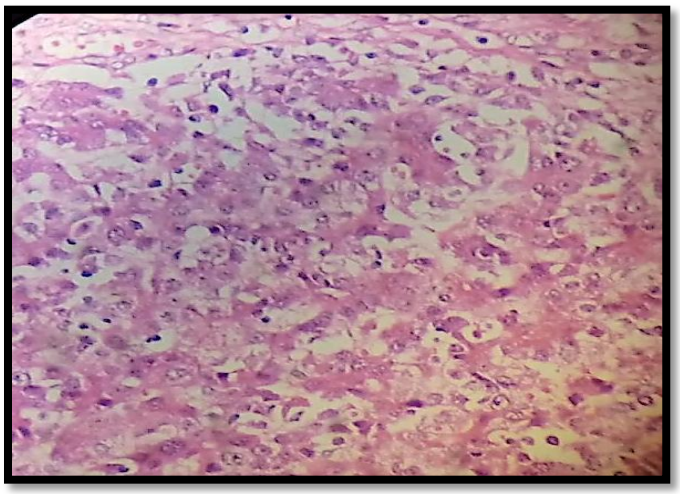
Capsule was not involved by tumour.

Adjacent liver parenchyma showed features of glycogen storage disease received in earlier biopsy

PICTURE 1 & 2: GLYCOGEN STORAGE DISORDERS (H&E, PAS 400x)



PICTURE 3: HEPATOBLASTOMA (H &E 400x)



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CASE 2 : Metastasis to liver from neuroendocrine tumour

14 year old female presented with complains of fever with abdominal distention. Computed tomography (CT) showed hepatomegaly with multiple poorly enhancing lesions , most likely to be neoplastic in etiology. Subsequent biopsy was sent for histopathology.

Gross Examination: Specimen consisted of 2 pearly white linear cores each measuring 0.4 cm.

Microscopy findings: Tumour was seen in organoid and glandular pattern. The individual tumour cells were round to oval with eosinophilic granular cytoplasm. Many vascular channels were seen separating the tumour cell clusters. At places mesenchymal pattern of tumour was noted

Immunohistochemistry (IHC) panel:

Synaptophysin and Chromogranin A: Strongly positive (Picture 6 & 7)

Ki 67 proliferative index : 18 % (Grade II) (Picture 9)

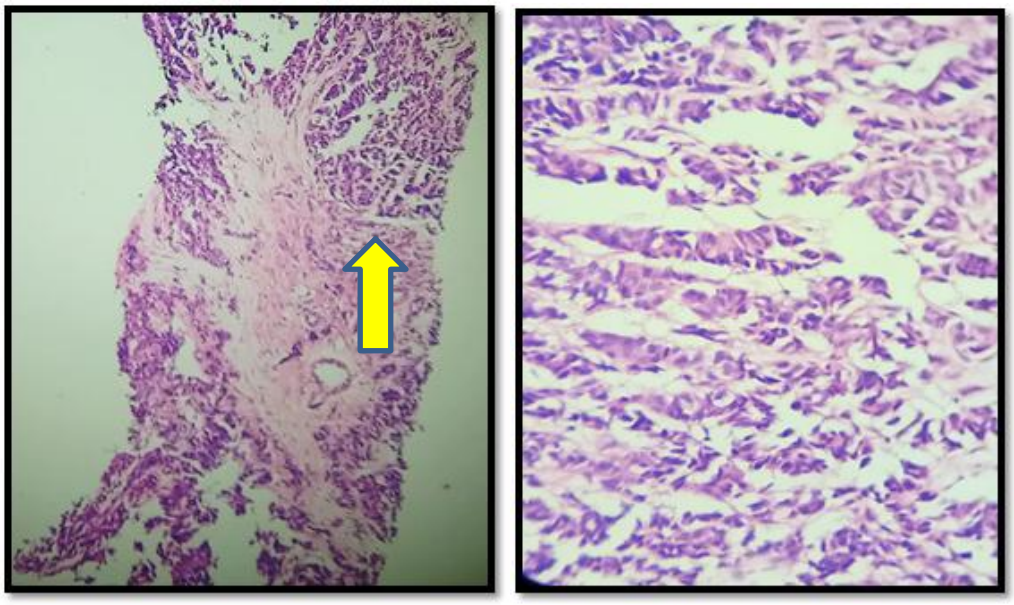
Vimentin, Hep Par 1: Negative (Picture 8)

Cytokeratin CK7,CK20: Negative

Thus, Negative markers ruled out hepatic primary and confirmed neuroendocrine origin.

Impression : Metastatic deposits from neuroendocrine carcinoma.

PICTURE 4 & 5: METASTASIS FROM NET (H&E 100x and 400x)



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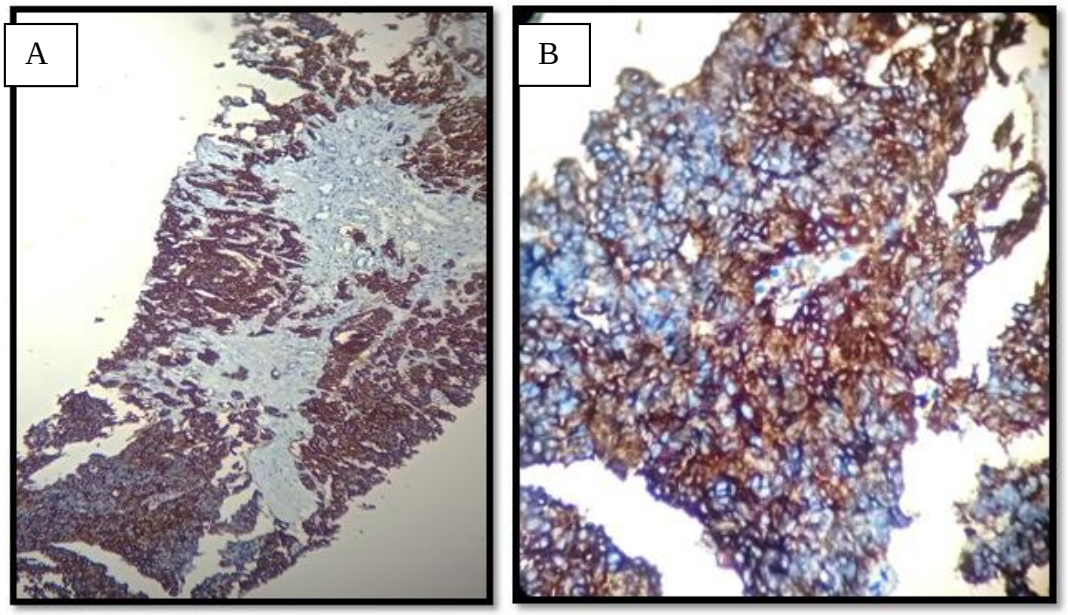
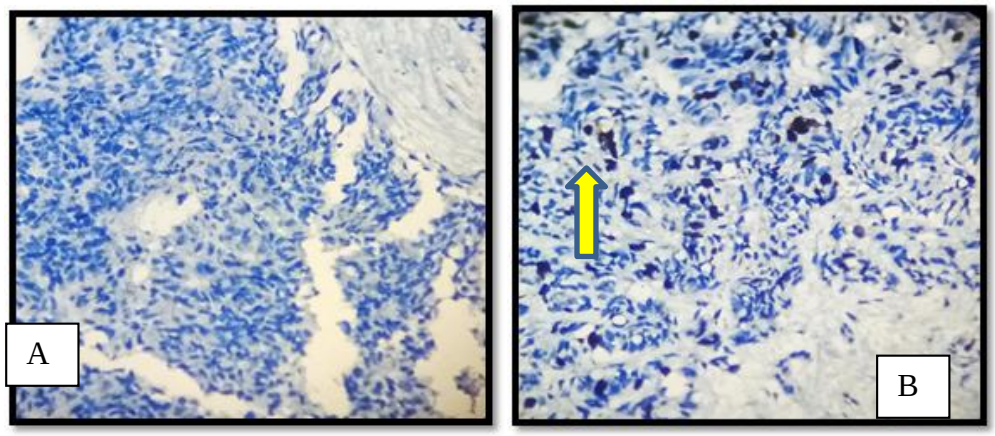
PICTURE 6 & 7 : METASTASIS FROM NET (IHC) (100x and 400x)



PICTURE 8 & 9: METASTASIS FROM NET (IHC) (400x)



CASE 3: EMBRYONAL SARCOMA

7 year old male presented with complains of right hypochondriac pain and weight loss since 6 months. PET scan was suggestive of lesion in right lober of liver. Right lobectomy specimen was sent for histopathological examination.

Gross Examination:Specimen consisted of right lobe of liver measuring 17x14x7.5 cm and weighing 890 grams. External capsular surface had a wrinkled appearance along with a raw area measuring 12x10x7 cm. Cut surface showed many yellowish myxoid areas. The tumour reached upto the resection margin.(Picture 10)

Microscopy findings: Tumour was seen along with normal liver parenchyma. Tumour cells were composed of spindle shaped and stellate cells dispersed singly in the myxoid stroma which showed extensive necrosis. Many acinar structures suggestive of bile ducts were seen within the tumour. Many hemosiderin laden macrophages were seen.

Impression: Undifferentiated embryonal sarcoma of the liver (UESL)

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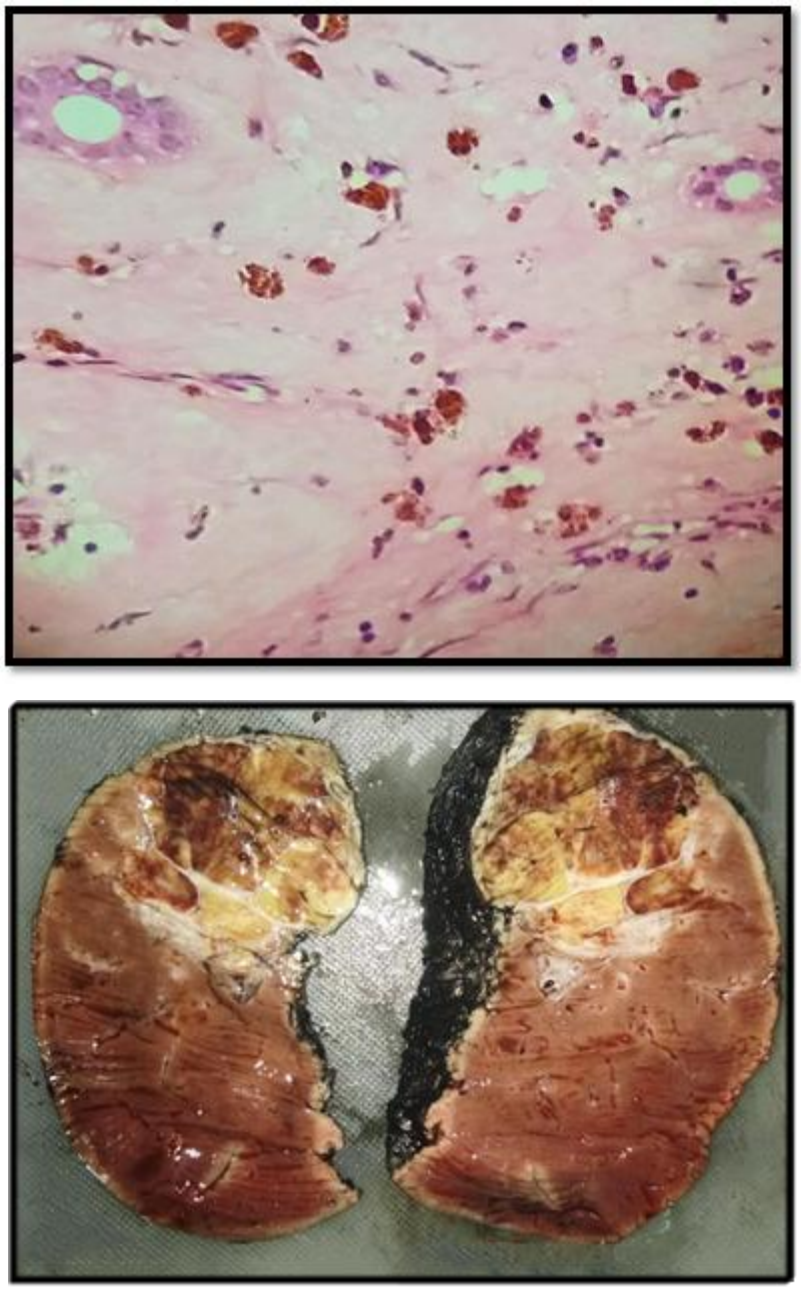
PICTURE 10 :UESL



CASE 4: Biliary atresia splenic malformation (BASM) syndrome

An 1 month 18 day old female presented with obstructive jaundice, icterus since the first week of life. General physical examination revealed a vitally stable infant. Abdominal examination revealed hepatomegaly. Her laboratory investigations showed conjugated hyperbilirubinemia (total bilirubin 8.49 mg/dl, and direct bilirubin 6.62 mg/dl), S.SGOT 490, SGPT 192, S. Alkaline phosphatase 437. Coagulation profile was deranged with Prothrombin time 17.7, aPTT 48.9 fibrinogen levels 323. On radiological examination, the presence of polysplenia with situs invertus of the liver was revealed.

Subsequent biopsy was sent for histopathology.

Gross Examination: Specimen consisted of multiple pearly white linear cores of tissue each measuring 0.8 to 1 cm.

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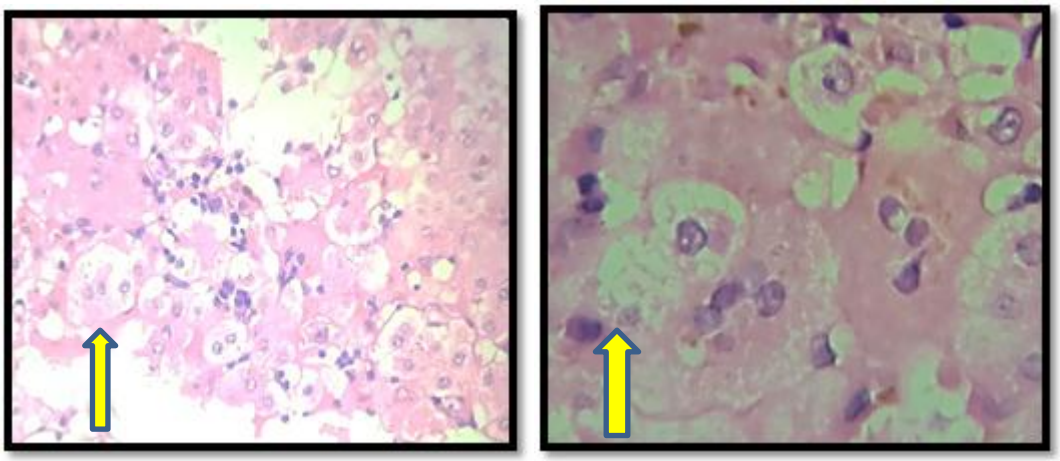
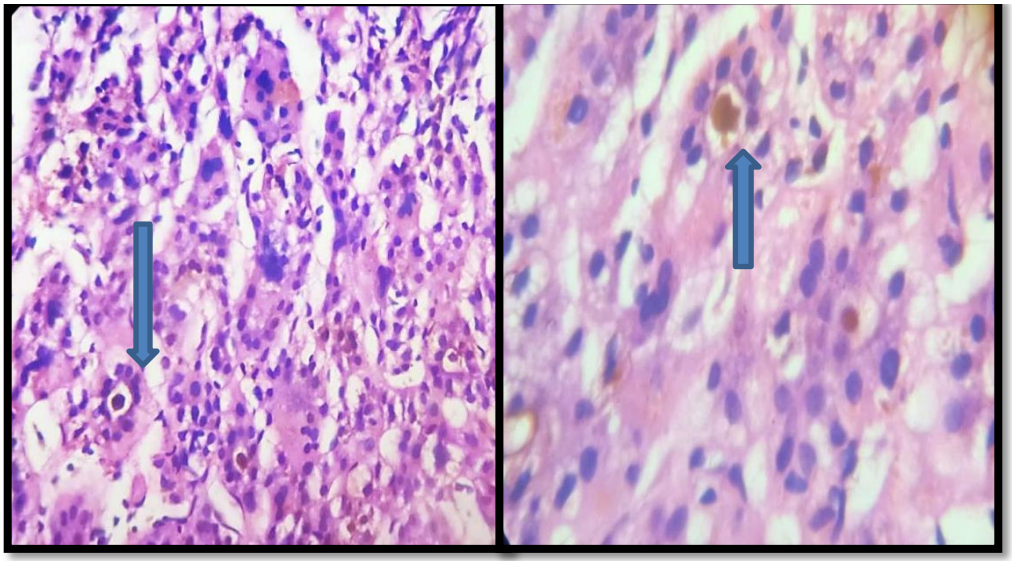
Microscopy findings: Biopsy showed preserved hepatic architecture. Hepatocytes showed ballooning degeneration with intracellular cholestasis. Sinusoids were dilated. Bile duct proliferation was noted. Periportal chronic inflammatory infiltrate was noted. Numerous bile plugs were seen. Foci of extra medullary hematopoiesis was noted

Impression: Neonatal cholestasis with Extra hepatic biliary atresia (EHBA)

PICTURE 11 & 12: DEGENERATION OF HEPATOCYTES (H& E 100x and 400x)



PICTURE 13 &14: BILE PLUGS (INTRACANALICULAR) (H& E 100x and 400x)



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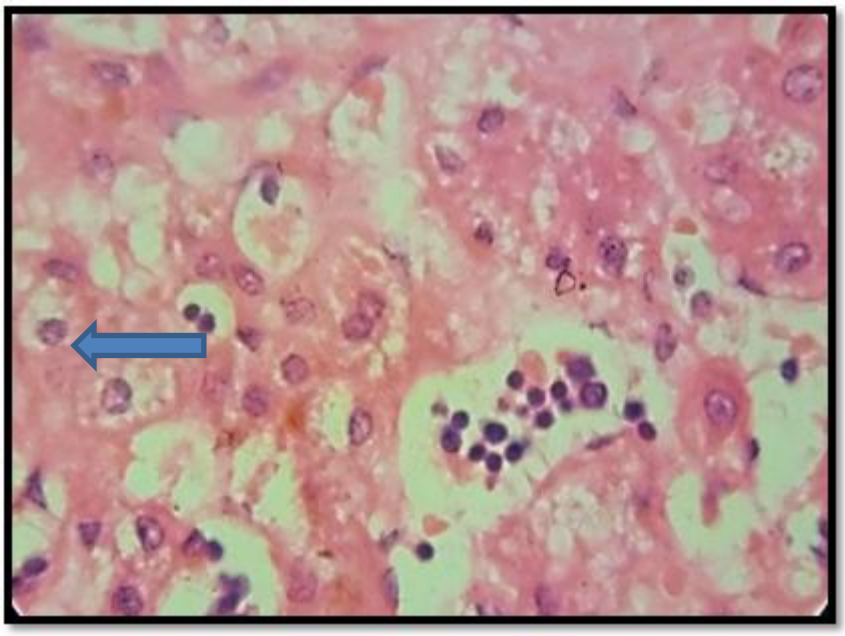
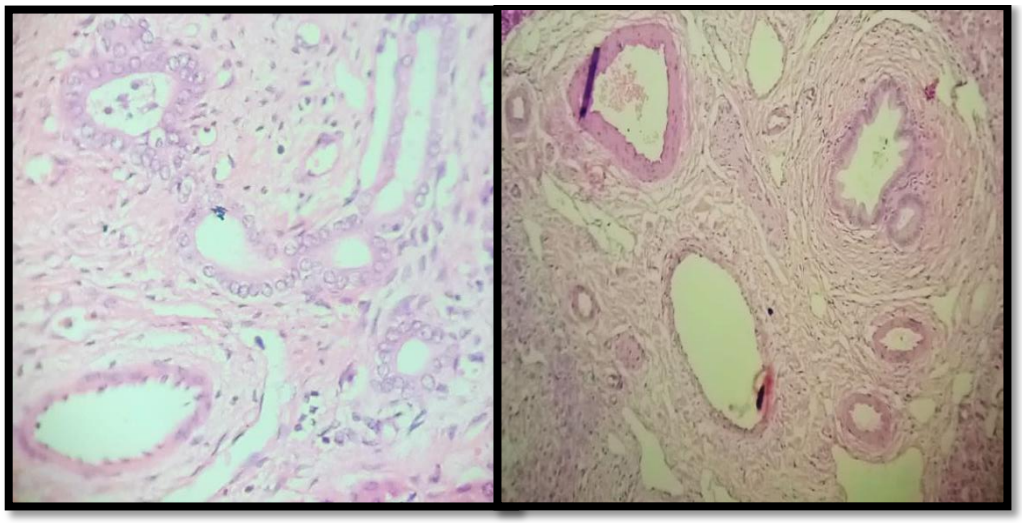
PICTURE 15: CHOLESTASIS (H&E 400x)



PICTURE 16 &17 : EHBA with BILE DUCT PROLIFERATION (H& E 100x and 400x)



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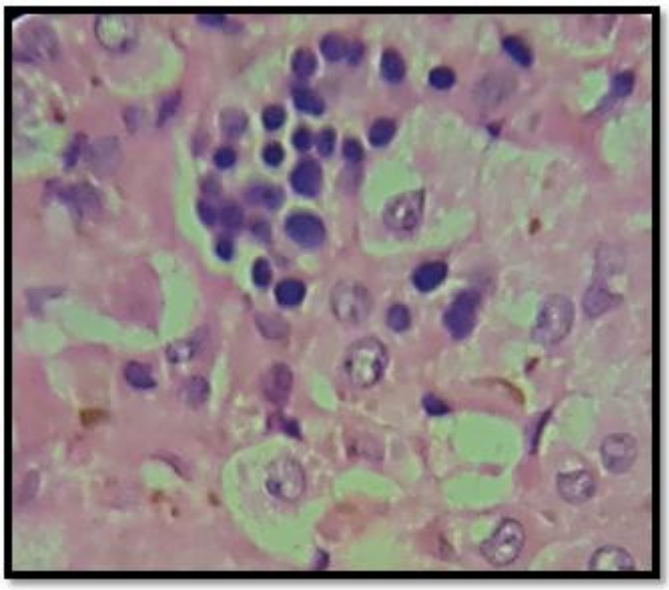
PICTURE 18 : EXTRAMEDULLARY HEMATOPOIESIS (H& E 400x)



Discussion:

Concomintant presence of glycogen storage disorder (GSD) with Hepatoblastoma as described in Case 1 (Picture 1-3) is a rare occurance according to literature. Hepatoblastoma may be associated with other conditions like Familial Adenomatous Polyposis (FAP) and Beckwith-Wiedman Syndrome , however GSD is uncommonly associated [(7)]. GSD are incompletely understood. They are characterized by defective breakdown of liver glycogen to glucose due to deficiency of glucose-6-phosphorylase enzyme. Previous studies have attempted postulating that metabolic disorder of GSD can be an accomplice in the development of hepatoblastoma and hepatocellular carcinoma by the proposed mechanisms either in isolation or combination , these are: 1) glucagon/insulin imbalance; 2) cellular glycogen overload; and 3) proto-oncogene activation [(8)]. Genetic and molecular studies have documented recurrent chromosomal abnormalities and aberrant activation of developmental and oncogenic signaling pathways in hepatoblastomas [(9)]. Alternatively, the "toxic-metabolite" model of pathogenesis proposed that metabolic disorders initially present with characteristic histologic and ultra-structural patterns on liver biopsy but chronic injury over months or years may lead to cirrhosis or hepatic neoplasia [(10)]. There are very few studies which have attempted describing the association between hepatoblastoma and GSD and apparently none reported from the Indian subcontinent [(7,11)].

The study done by Shirazi N[(7)] et al (2016) is in agreement, it reported a case of rare case of hepatoblastoma with co-existent GSD in an infant male . Another study by Ito [(11)] et al (1987) reported a case of GSD and hepatoblastoma was in siblings thus showing an association between the two pathologies. However the mechanism couldn't be elucidated in either of the two studies.

Case 2 is that of metastasis from neuroendocrine carcinoma (Picture4-9) Neuroendocrine tumour (NET) are infrequently seen in the pediatric population with an incidence rate of 2.8 per million[(12)]. Overall, appendiceal NET (carcinoids) are the most common subtype and is rarely associated with metastatic disease in children. Extra-appendiceal carcinoid tumors and neuroendocrine carcinomas are more poorly characterized and have a greater chance for metastatic spread compared with carcinoids arising in the appendix[(13)]. Broaddus [(13)] et al published 5 of 13 cases that were initially diagnosed in the liver, with no other primary sites identified. They concluded that it is not known if these tumors represent true primary hepatic neoplasms or metastases from asymptomatic, occult pancreatic, gastrointestinal, or pulmonary primary tumors.

Case 3 is that of embryonal sarcoma (Picture 10). Undifferentiated embryonal sarcoma of the liver (UESL) is an extremely rare hepatic mesenchymal tumor that was first reported and classified by Stocker et al in 1978 [(14)]. The incidence of the disease

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has no significant gender difference. In addition, 90% of patients are aged 6–10 years, and the disease accounts for about 5–8% of hepatic tumors in children. The tumor is mainly localized or found in the hepatic right lobe (59%), while it rarely develops in the hepatic left lobe (22%) or the bilateral lobe (20%). UESL typically has a diameter of 10–25 cm with a solitary clear boundary[15].

Generally, a definite diagnosis of UESL is difficult to be determined preoperatively; the diagnosis relies on postoperative pathological analysis and immunohistochemical results. UESL ought to be differentiated from other more common hepatic primaries such as hepatoblastoma, embryonal rhabdomyosarcoma, hepatic mesenchymal hamartoma and hepatic echinococcosis.

Case 4 is that of Biliary atresia splenic malformation (BASM) syndrome (Picture 11-18), described as a splenic malformation (polysplenia or asplenia) that occurs in conjunction with at least another significant malformation usually within the spectrum of laterality disorders. A study done by Davenport M et al (2006) [16] had 10% of cases of Biliary atresia related to BASM syndrome, they noted that the pathogenesis responsible for this syndrome may occur during the period of embryogenesis and these cases may present with an earlier onset of symtoms compared to non syndromic cases of BA. They also concluded that BASM infants were more likely to be female (P = .04). These findings were in concordance with our case.

In a retrospective multicenter study of 289 infants participating in the Childhood Liver Disease Research and Education Network (ChiLDREN), 242 (84 %) had isolated Biliary atresia without any major malformation, 17 (6 %) had a major malformation with no laterality defect, and 30 (10 %) had syndromic laterality defect [17] . Infants with BASM tend to get clinical treatment earlier than those without symptoms, although it is uncertain if this is due an earlier onset of biliary obstruction and jaundice or whether the underling abnormalities prompt earlier evaluation.

Conclusion:

The pediatric liver can present with a spectrum of pathologies both neoplastic and non neoplastic which can prove to be diagnostically challenging . Certain metabolic diseases may increase the risk of development of pediatric hepatic neoplasms, however further studies are needed to consolidate the pathogenesis of the association of Hepatoblastoma with Glycogen Storage Diseases and to further define their risk of malignant transformation.

Ancillary techniques like Immunohistochemistry can prove to be a game changer in diagnosis of rare metastasis to the liver as well as rare primaries from the liver such UESL.

List of Abbreviations:

BASM : Biliary Atresia Splenic Malformation

CT: Computed tomography

EHBA: Extra hepatic biliary atresia

Glycogen storage disorder: GSD

H&E: Hematoxylin and Eosin

NET: Neuroendocrine tumour

PAS: Periodic Acid Schiff

UESL: Undifferentiated Embryonal Sarcoma of the liver

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