Pediatric Liver Tumors

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Background

- Liver is the third-most-common site for intra-abdominal malignancy in children, following adrenal neuroblastoma and wilms tumor
- 1.3% of all pediatric tumours
- Malignant or benign

Table 1 Pediatric liver tumors consensus classification

- *Epithelial tumors*
  - Hepatocellular[a]
    - Benign and tumor-like conditions
      - Hepatocellular adenoma (adenomatosis)
      - Focal nodular hyperplasia
      - Macroregenerative Nodule
    - Premalignant lesions
      - Dysplastic nodules
    - Malignant
      - Hepatoblastoma
        - Epithelial variants
          - Pure fetal with low mitotic activity
          - Fetal, mitotically active
          - Pleomorphic, poorly differentiated
          - Embryonal
          - Small-cell undifferentiated
            - INI1-negative
            - INI1-positive
          - Epithelial mixed (any/all above)
          - Cholangioblastic
          - Epithelial macrotrabecular pattern
        - Mixed epithelial and mesenchymal
          - Without teratoid features
          - With teratoid features
        - Hepatocellular carcinoma
          - Classic HCC
          - Fibrolamellar HCC
        - Hepatocellular neoplasm NOS[b]
  - Biliary
    - Benign
      - Bile duct adenoma/hamartoma, other
    - Malignant
      - Cholangiocarcinoma
      - Combined (hepatocellular cholangioca)
- *Mesenchymal tumors*
  - Benign
    - Vascular tumors
      - Infantile hemangioma
    - Mesenchymal hamartoma
    - Pecomas
  - Malignant
    - Embryonal sarcoma
    - Rhabdomyosarcoma
    - Vascular tumors
      - Epithelioid hemangioendothelioma
      - Angiosarcoma
- *Other malignancies*
  - Tumors of uncertain origin
    - Malignant rhabdoid tumor
      - INI1 − (documented *INI1* mut)
      - INI1 +
    - Nested epithelial stromal tumor
  - Other
    - Germ cell tumors
      - Teratoma
      - Yolk sac tumor
    - DSRCT
    - pPNET
  - Metastatic (and secondary)
    - Solid tumors (NB, Wilms, other)
    - Acute myeloid leukemia (M7)

Hepatoblastoma

- Most common pediatric primary liver tumor (90% of tumors in<= 5yo)
- Incidence increasing the last 30y
- Sporadic or associated with genetic abnormalities, malformation and syndromes
- Believed to arise from hepatocellular precursors that often recapitulate stages of liver development
- Molecular abnormalities: Wnt (CTNNB1 mutations), SHH, Notch, PI3K/AKT
- Over the past 3 decades, overall survival has improved from 30% to 80% following innovative advances in chemotherapy and surgical techniques

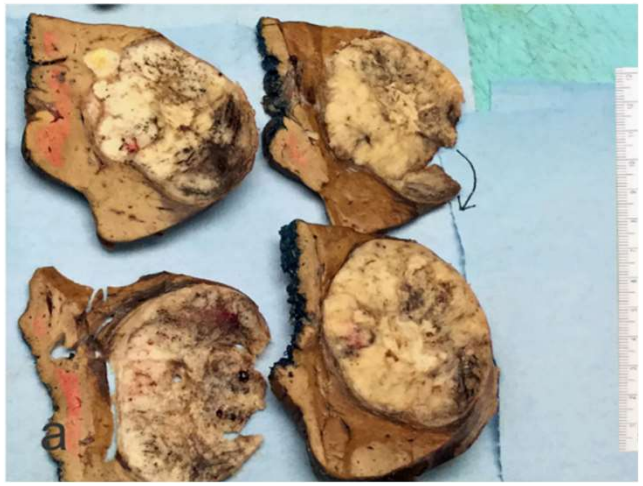
Very rare tumours

No consensus classification ->International Pediatric Liver tumors Consensus Classification (2011) -> WHO (2019)

Diagnosis challenging -> importance of systematic central review

Macroscopical features:

- large, solitary mass (80%)
- localized to the right lobe (60%).
- Over one half cases extension into the vena cava



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Hepatoblastoma subtypes

Epithelial type

Fetal subtype

- *Low mitotic activity (well-differentiated)*
- *Mitotically active (crowded fetal)*
- *Pleomorphic*

Embrional subtype

Small cell undifferentiated

- *SMARCB1 (INI1)-negative*
- *SMARCB1 (INI1)-positive*

Cholangioblastic subtype

Macrotrabecular subtype

Mixed epithelial

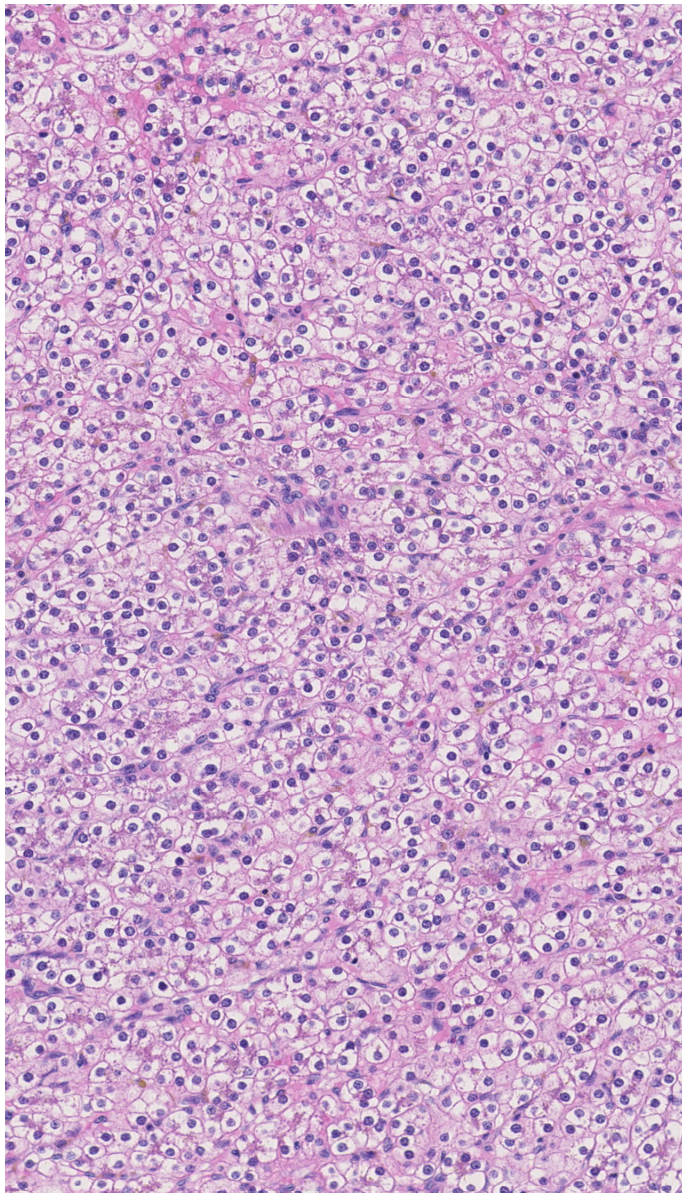
Mixed epithelial and mesenchymal type

Without teratoid features

With teratoid features

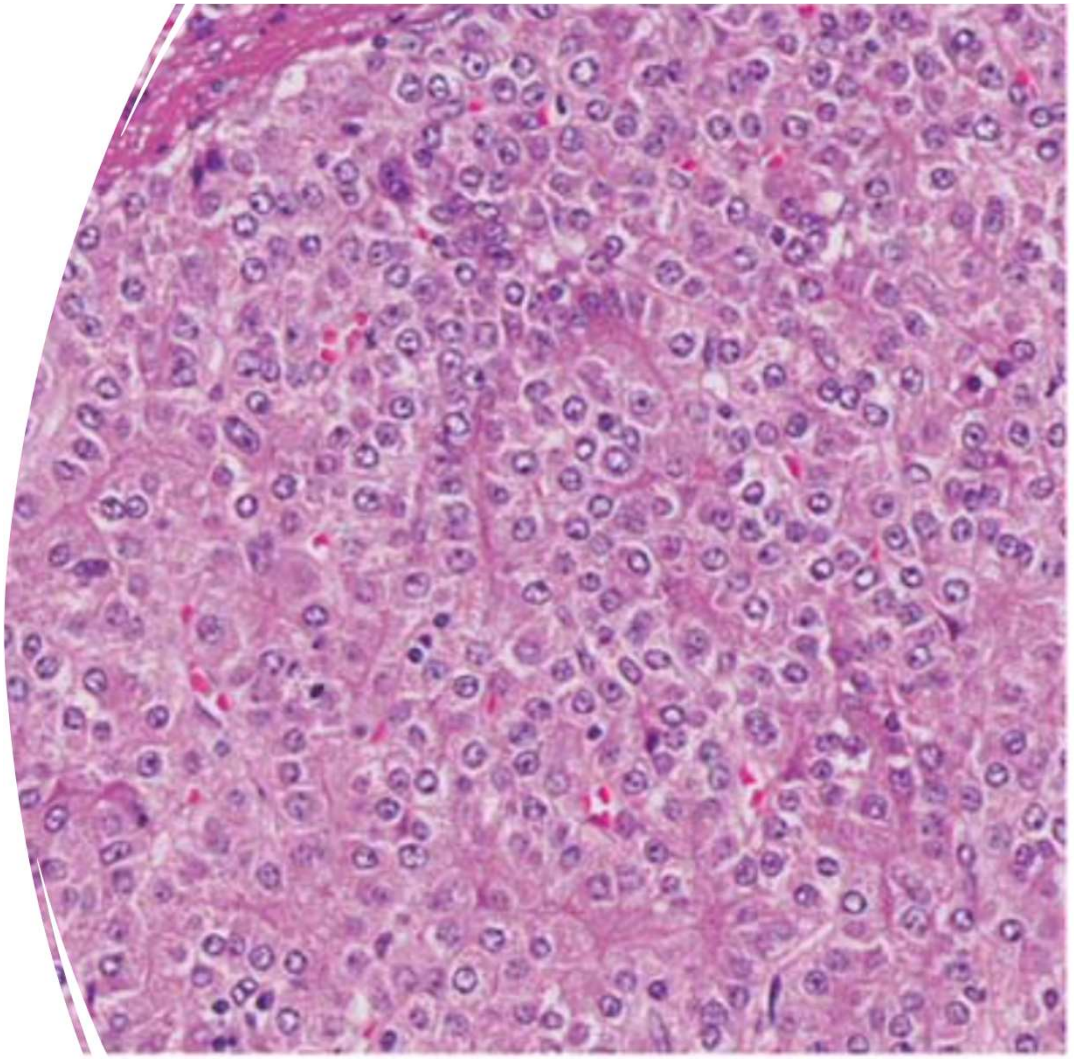
Well differentiated fetal hepatoblastoma (or pure fetal hepatoblastoma with low mitotic activity)

- Cells of 10-20μ in 1/2cell thickness trabeculae or sheets
- Ressemblance to fetal hepatocytes and could contain glycogen or lipids
- Extramedullary hematopoiesis common
- Minimal mitotic activity (<2 10HPF)
- Better outcome, especially if pure
- If pure surgical treatment alone
- Post chemotherapy changes may mimic mixed hepatoblastoma

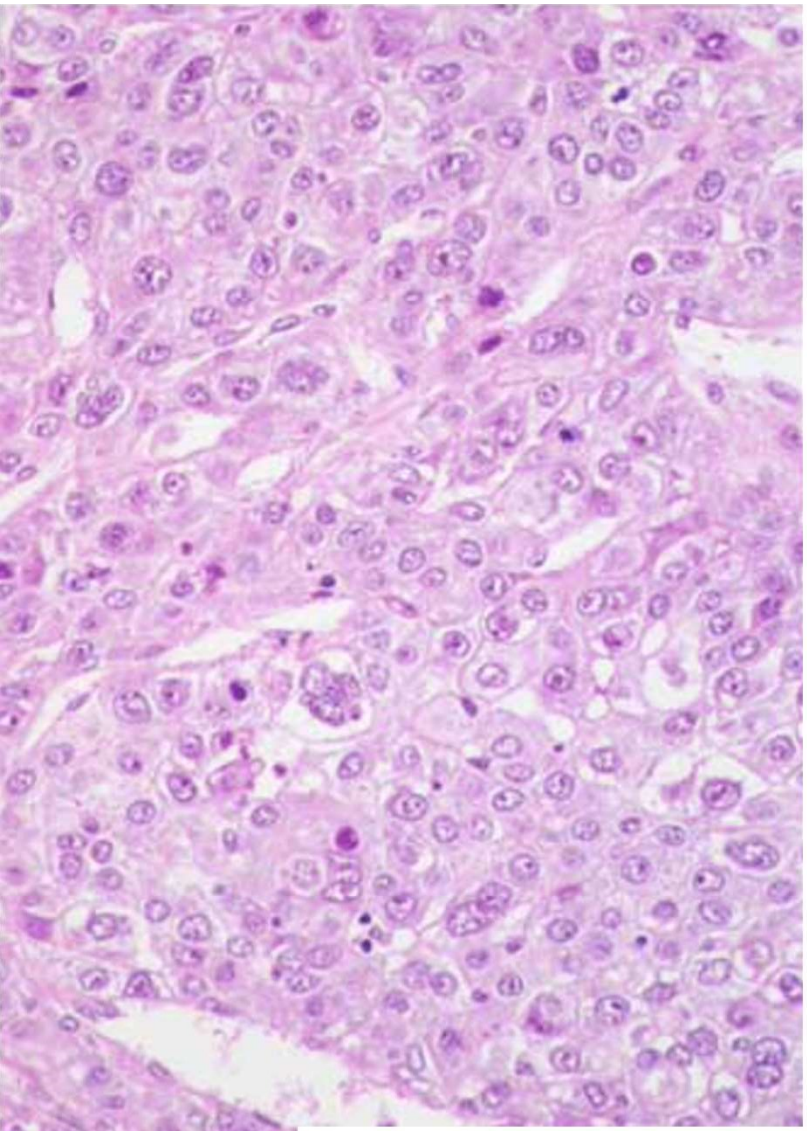


Crowded fetal hepatoblastoma (or mitotically active fetal)

- More amphophilic cytoplasm and higher nuclear/cytoplasmic ratio
- >2 mitosis 10HPF
- Need chemotherapy
- Rarely unique pattern (often adjacent to embrional area)
- Glypican 3 usefull (well-differentiated fetal finely granular nuclear positivity)



MODERN PATHOLOGY (2014) 27, 472–491



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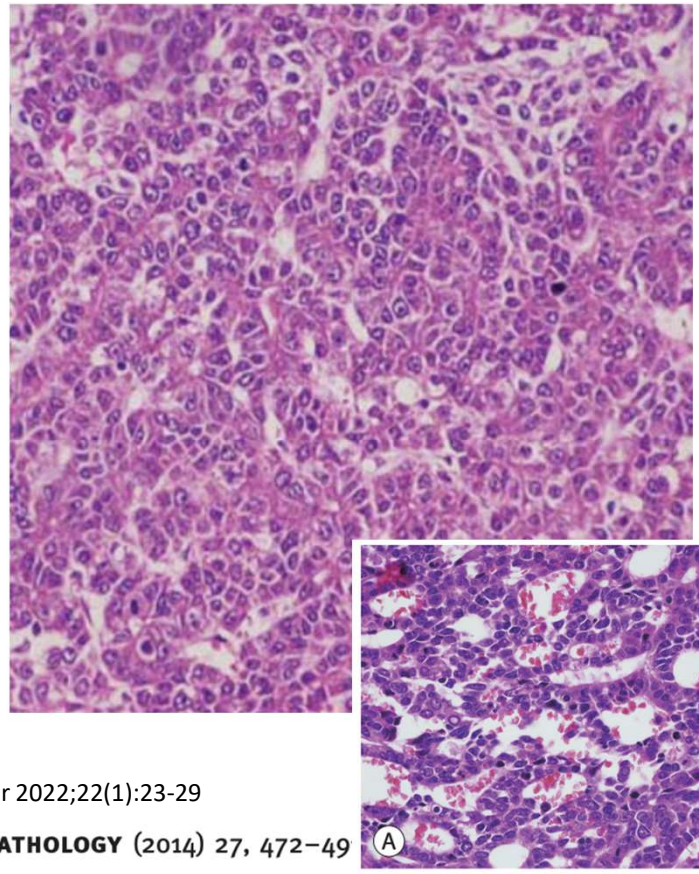
Pleomorphic component

- More often seen post-chemotherapy
- Pleomorphic pattern, irregular shape and conspicuous nucleoli
- Pleomophic cells, anaplasia or atypical mitosis rare
- DD: heptocellular carcinoma

Embrional subtype

- Most common pattern
- Resembles to liver at 6-8 weeks
- Cells of 10-15µ , scant cytoplasm, angulated nuclei, high N/C
- Organized in sheets or tubulo-acinar formations
- Mitotic activity higher than in fetal type
- Extramedullary hematopoiesis rare



J Liver Cancer 2022;22(1):23-29

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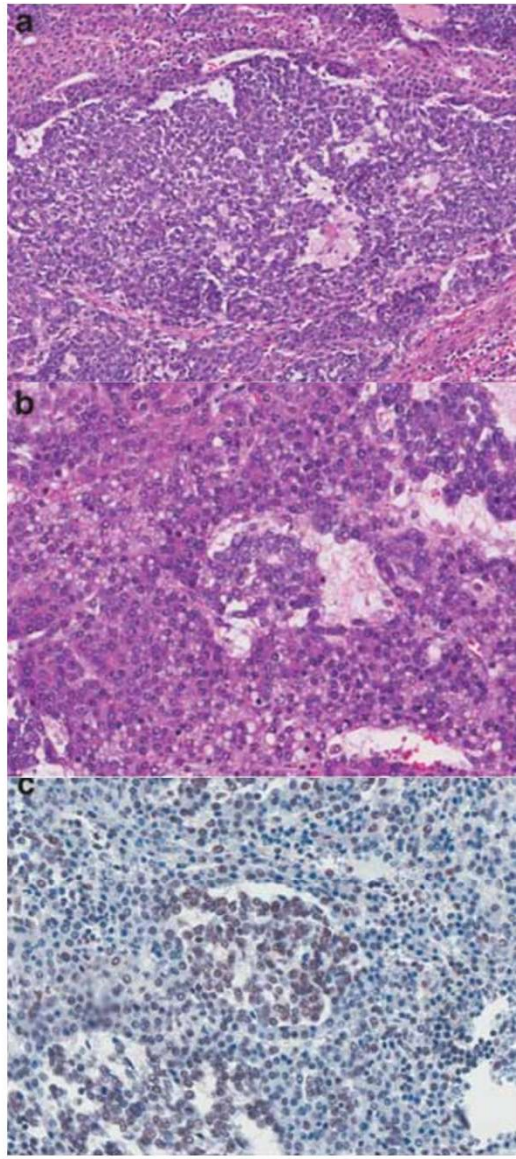
Small cell undifferentiated hepatoblastoma

- Undifferentiated small cells (slightly larger than lymphocytes, low mitotic activity, diffuse/organoid pattern
- Originally reported as 'anaplastic type'
- <5%hepatoblastomas, frequently mixed
- Clinically: low or normal serum level of AFP, more agressive, worse survival
- It could be easly missed (inadequate sampling, misinterpretation)
- Immunohistochemistry : variable expression of CK, CK8 and 18, and vimentin, and do not express alpha-feto protein or glypican.



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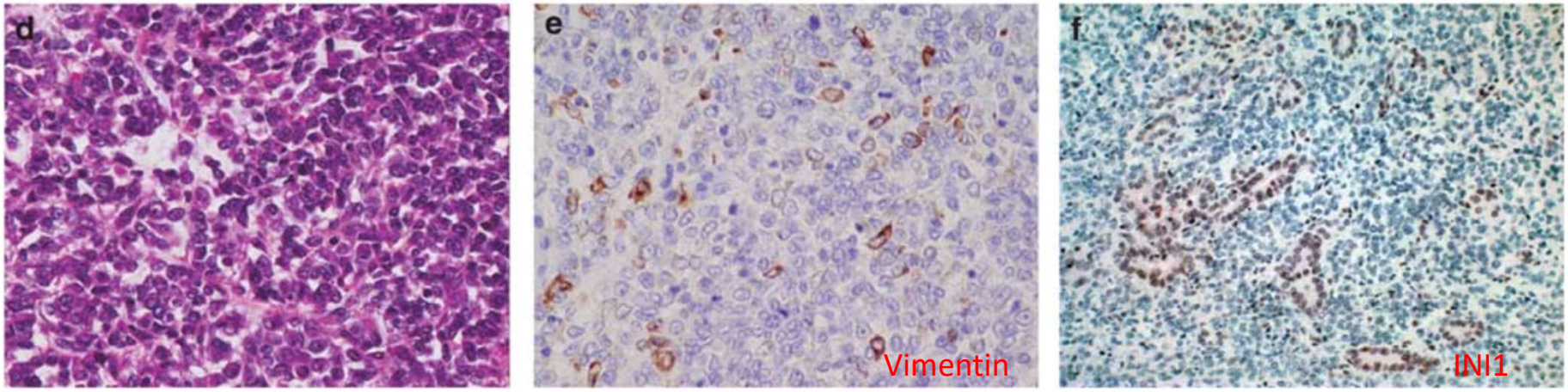
- INI1-negative cases similar features of rhabdoid tumors
- INI1-negative small cell undifferentiated hepatoblastoma likely represents hepatic rhabdoid tumors
- Important do identify this variant (benefit from CT for rhabdoid tumors)
- INI1-positive small cell undifferentiated hepatoblastoma better prognosis than INI1-negative

- Recommandation for small cel undifferentiated pattern -> estimation of %



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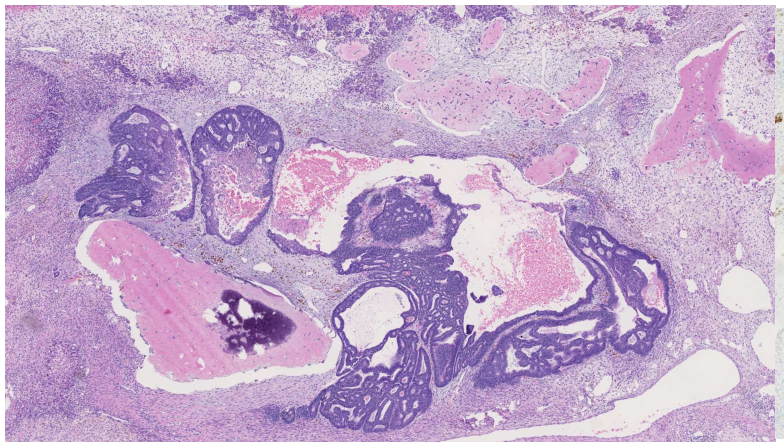
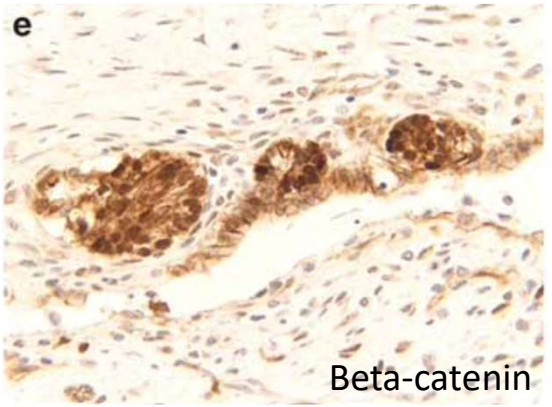
Cholangioblastic hepatoblastoma

- Neoplastic cells differentiate as cholangiocytes and form small ducts
- Expression of cholangiocyte lineage markers
- Need to be differentiated from tubular or acinar structures found in embryonal hepatoblastoma, which are typically small with less cytoplasm, more mitotically active, and express glypican 3
- Beta catenin staining usefull to differentaite this component from benign ductal proliferation especially after chemotherapy
- DD: ductal plate tumors, pediatric intrahepatic cholangio-carcinoma





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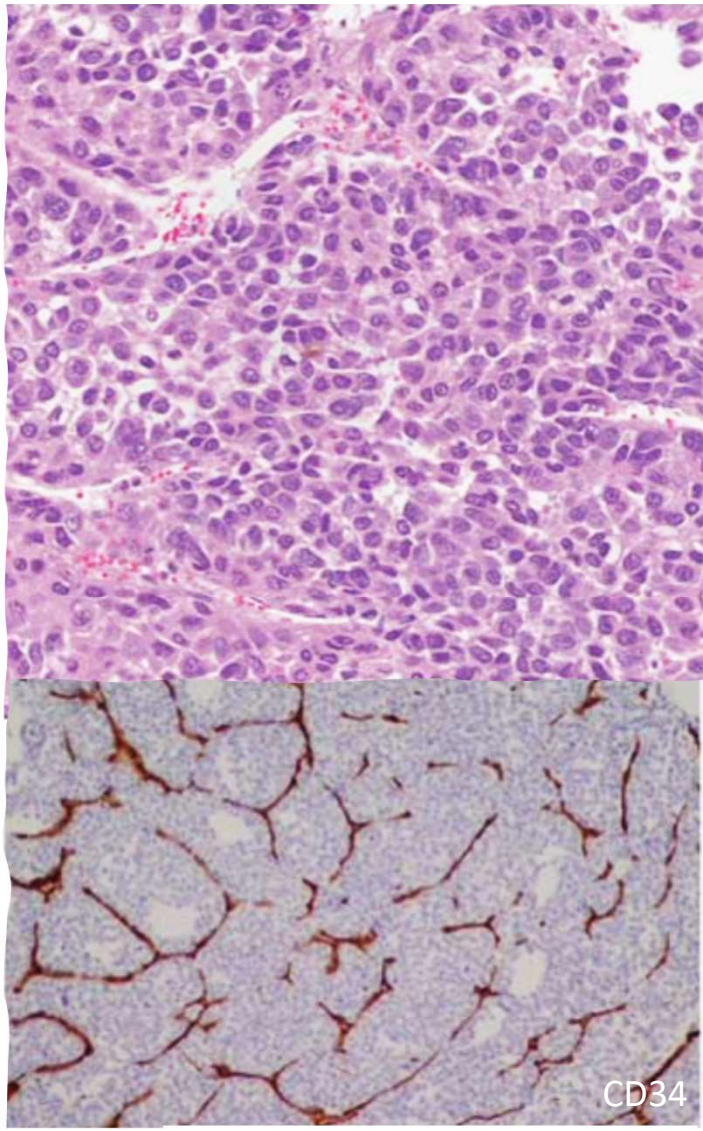
Macrotrabecular subtype

- <5% cases
- Similar to HCC (>=5 cell thick)
- In general mixed to other epithelial patterns
- Prognostic relevance of this pattern is still unknown



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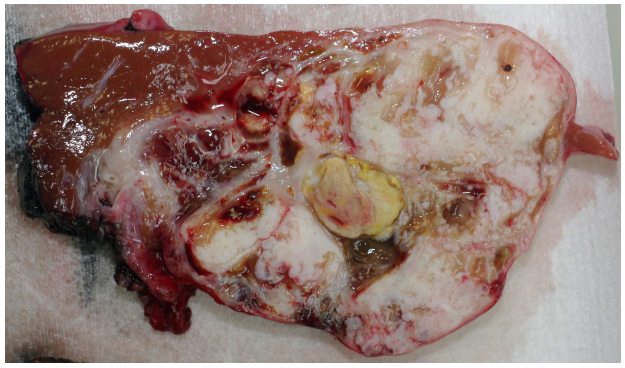
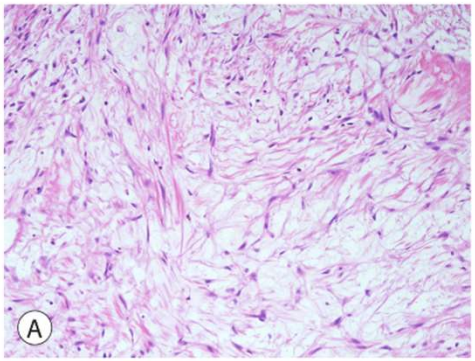
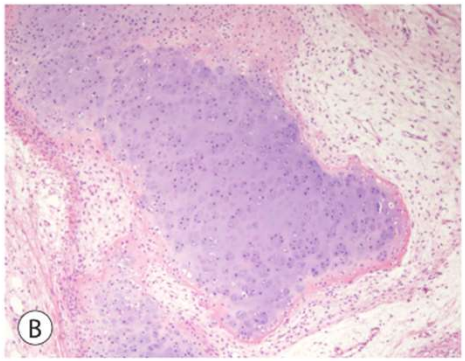
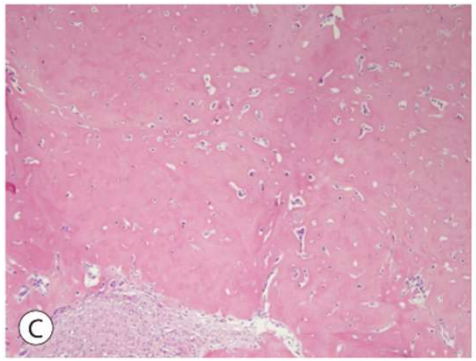
Mixed epithelial and mesenchymal type without teratoid features

- 20-30% hepatoblastomas
- Comprises stromal derivatives with mature and immature fibrous tissue, osteoid or osteoidlike tissue, and hyaline cartilage
- The mesenchymal component is integral part of tumors and distinct from chemotherapy-induced or metaplastic changes









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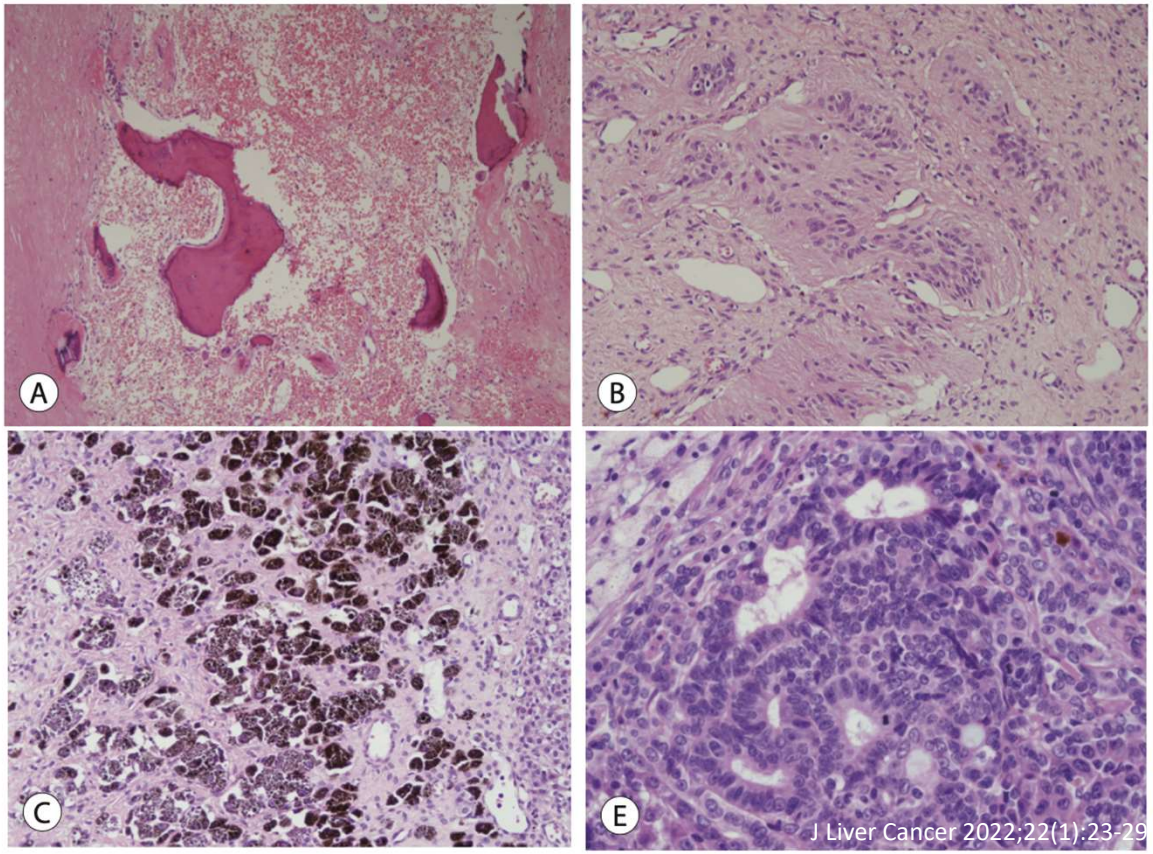
Mixed epithelial and mesenchymal type with teratoid features

- A small percentage of mixed epithelial and mesenchymal hepatoblastoma may exhibit stromal derivatives with teratoid features (neural or neuroectoderamal differentiation, mature brain, primitive neuroepithelial components, melanin, and retinal pigment, squamous epithelium, mucinous glands, striated muscle, cartilage, and bone)

- Prognostic significance still uncertain



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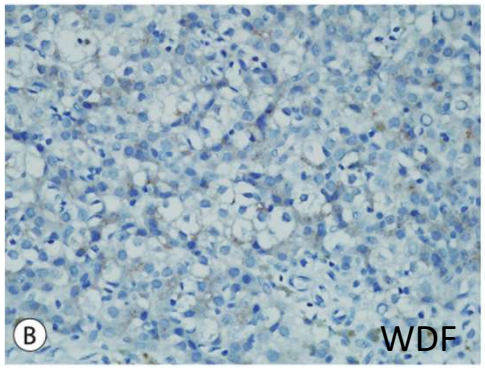
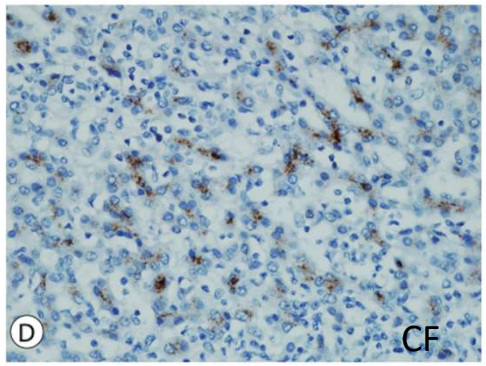
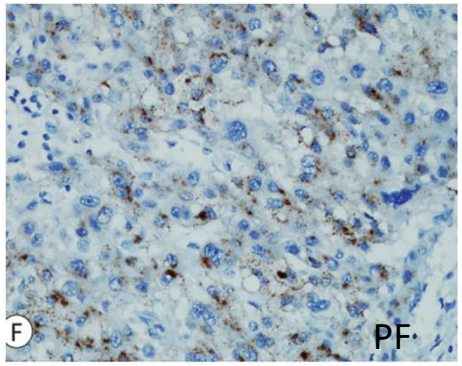
Immunohistochemistry for the diagnosis of hepatoblastoma

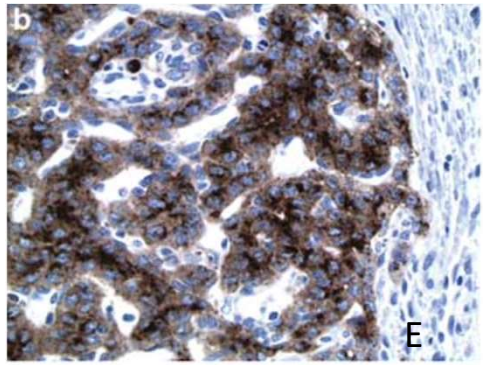
	Glypican 3	β-catenin	Glutamine synthetase	Hep par-1	Cyclin D1	CK7	CK19	Vimentin	INI1
Fetal, WD	Finely granular	Variably +/+++ nuclear or membranous	+++	+++	−	−	−	−	+++
Fetal, crowded	+++ coarse	+/+++	+++	+++	+/++	−	−	−	+++
Fetal, pleomorphic	++ coarse	+/+++	Variable	Variable	+/+++	−	−	−	+++
Embryonal	+++ coarse/rare −	+/+++ nuclear, can be −	Variable, can be −	Usually −	+/+++	−	−	−	+++
Small-cell undifferentiated	−, rare + cell	+++ nuclear	−	−	+/++	−/+	+/++ variable	+/++	− in pure SCUD
Cholangioblastic	−	Variable/+ nuclear	−	−	−	+++	+++	Usually −	+++

WD, well-differentiated; SCUD, small-cell undifferentiated.





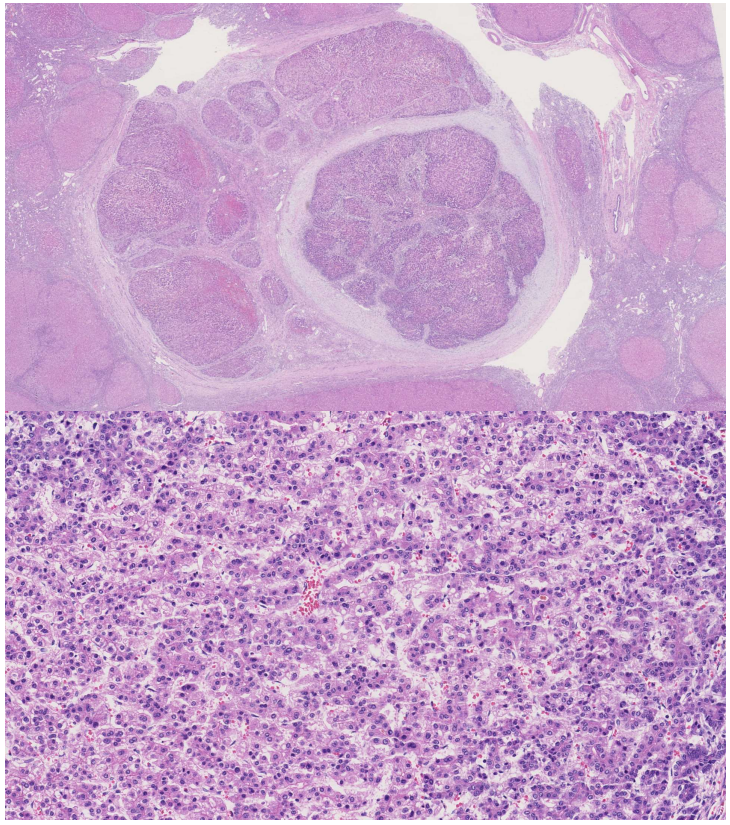




J Liver Cancer 2022;22(1):23-29

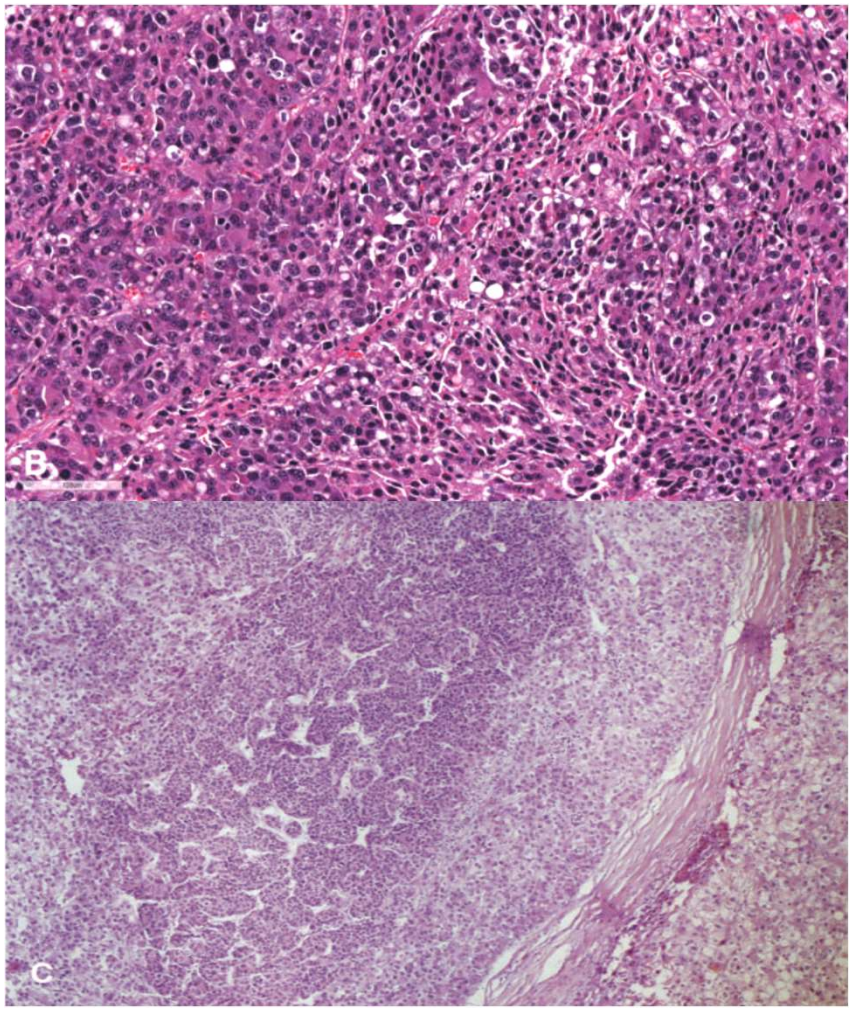
Hepatocellular carcinoma

- HCC represents 20% of all malignant liver tumors diagnosed in children
- large, unresectable lesions, typically in an older children/adolescent population
- Two groups:
  - One associated with underlying metabolic and/or genetic diseases
  - The second group arises in livers without underlying chronic disease.
- Fibrolamellar hepatocellular carcinoma is a distincts entity



Hepatocellular Neoplasm NOS

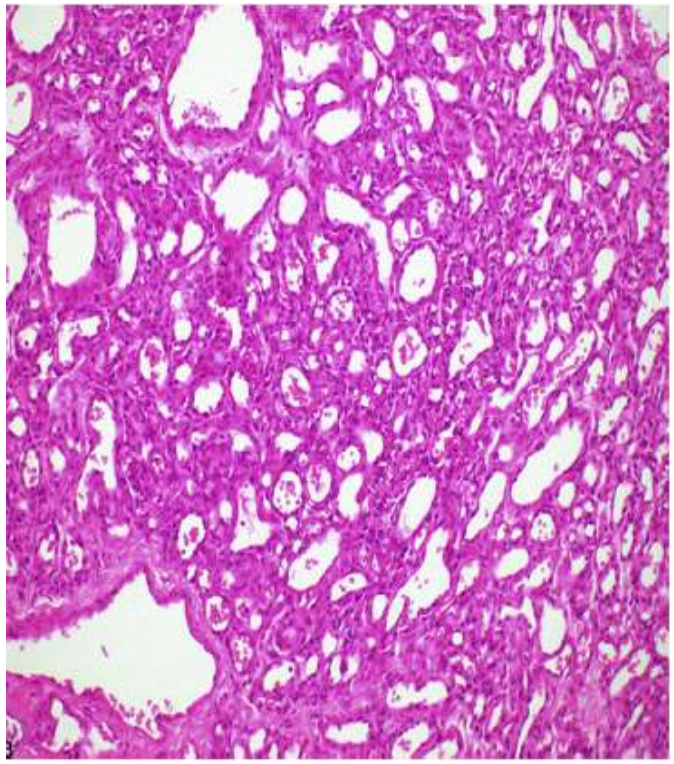
- Hybrid features, making their classification difficult
- Previously defined as ‘‘transitional cell liver tumors’’ -> highly aggressive tumors with overlapping features of both HB and HCC (different zones or intermediate features)
- Older children usually over the age of 8 years, and are associated with very high levels of AFP
- Background of normal liver with no predisposing liver disease
- b-cat is usually negative or only focally positive (nuclear) in HCC compared to the heterogeneous pattern seen in HCN-NOS
- Treated as high risk hepatoblastomas



Ranganathan et al., Pediatric and developmental pathology 2019

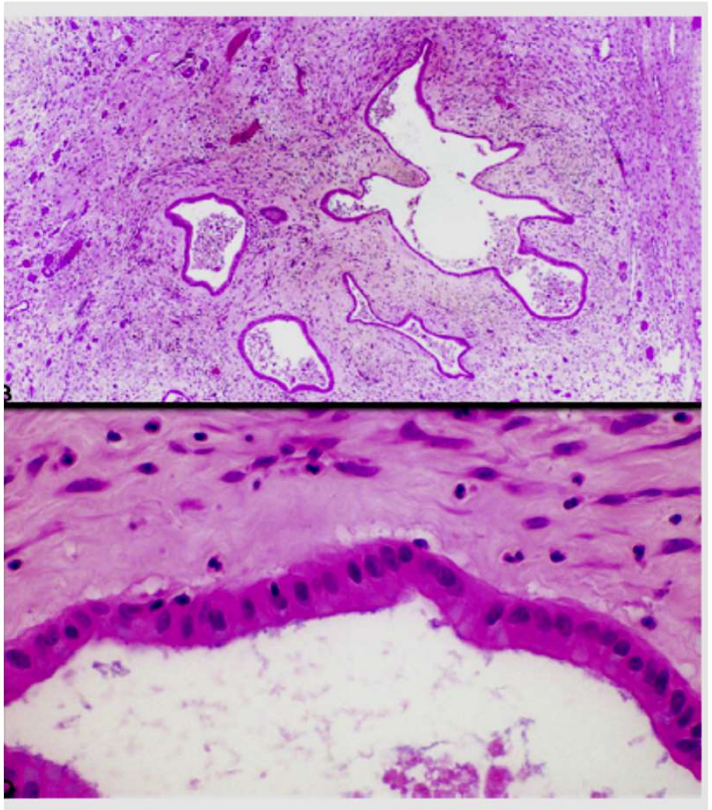
Infantile haemangioma (formerly termed infantile haemangioendothelioma)

- Second most common liver tumour
- Well-defined proliferation of numerous small, capillary-like vascular channels that are particularly prominent at the periphery
- Lesion is commonly surrounded by small amounts of compact or loose fibrous stroma
- Lesion surrounded by compact or loose fibrous stroma
- Entrapment of hepatocytes, small bile ducts peripherally, extramedullary haematopoiesis could be observed
- CD31, CD34, factor VIII, GLUT1 are positive.
- GLUT1 helps to distinguish this entity from other non-neoplastic vascular lesions

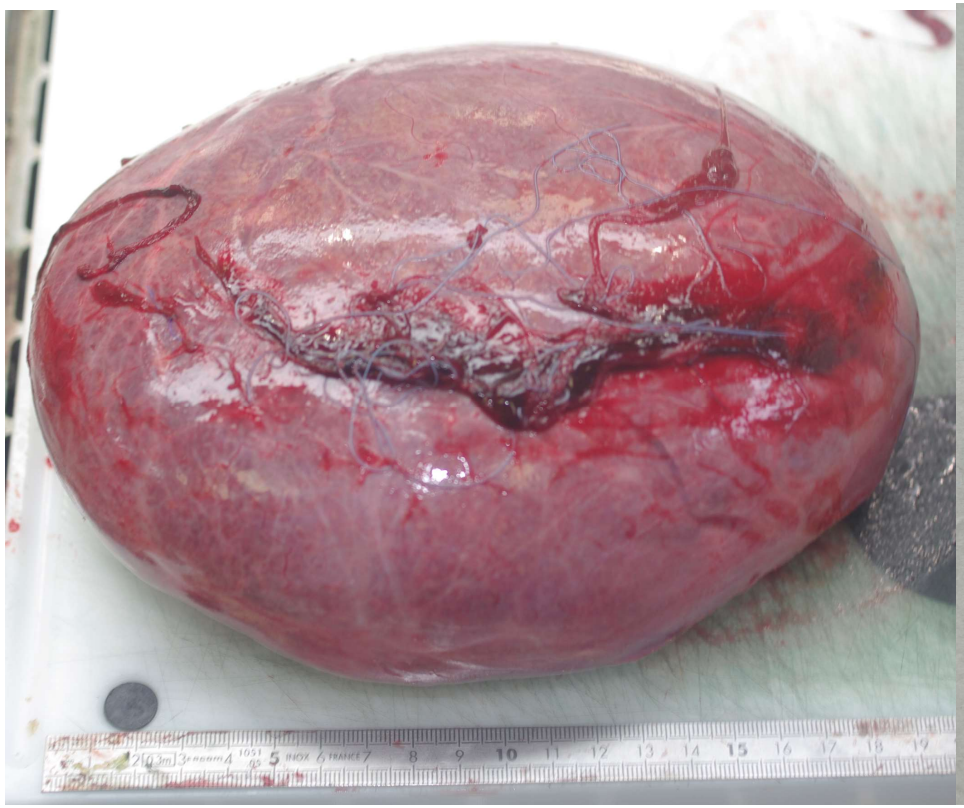


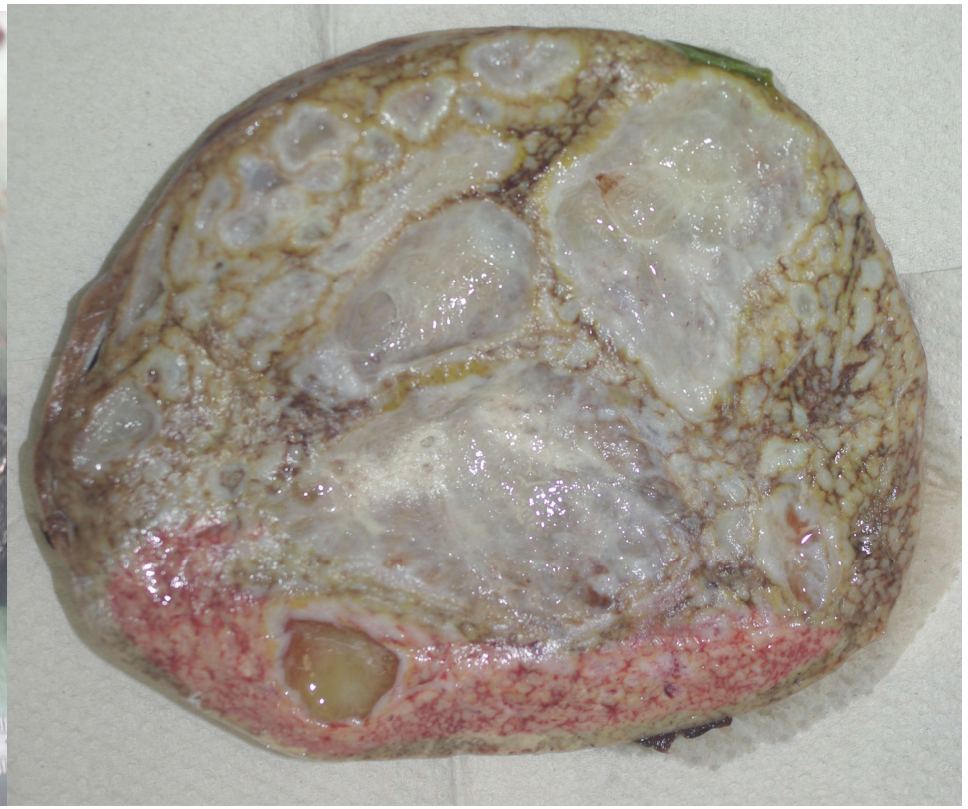
Mesenchymal hamartoma

- Benign tumor of the liver
- Third most common hepatic tumour of childhood
- Male predominance
- Multicystic loose connective tissue accompanied by a ductal component with ductal plate malformation changes
- Cytogenetic features: androgenetic-biparental mosaicism (ABM) and chromosomal involving cr19, translocations of the MALAT1 gene at chromosome 11q13 (sporadic lesions)
- About 75% occur in the right lobe of the liver



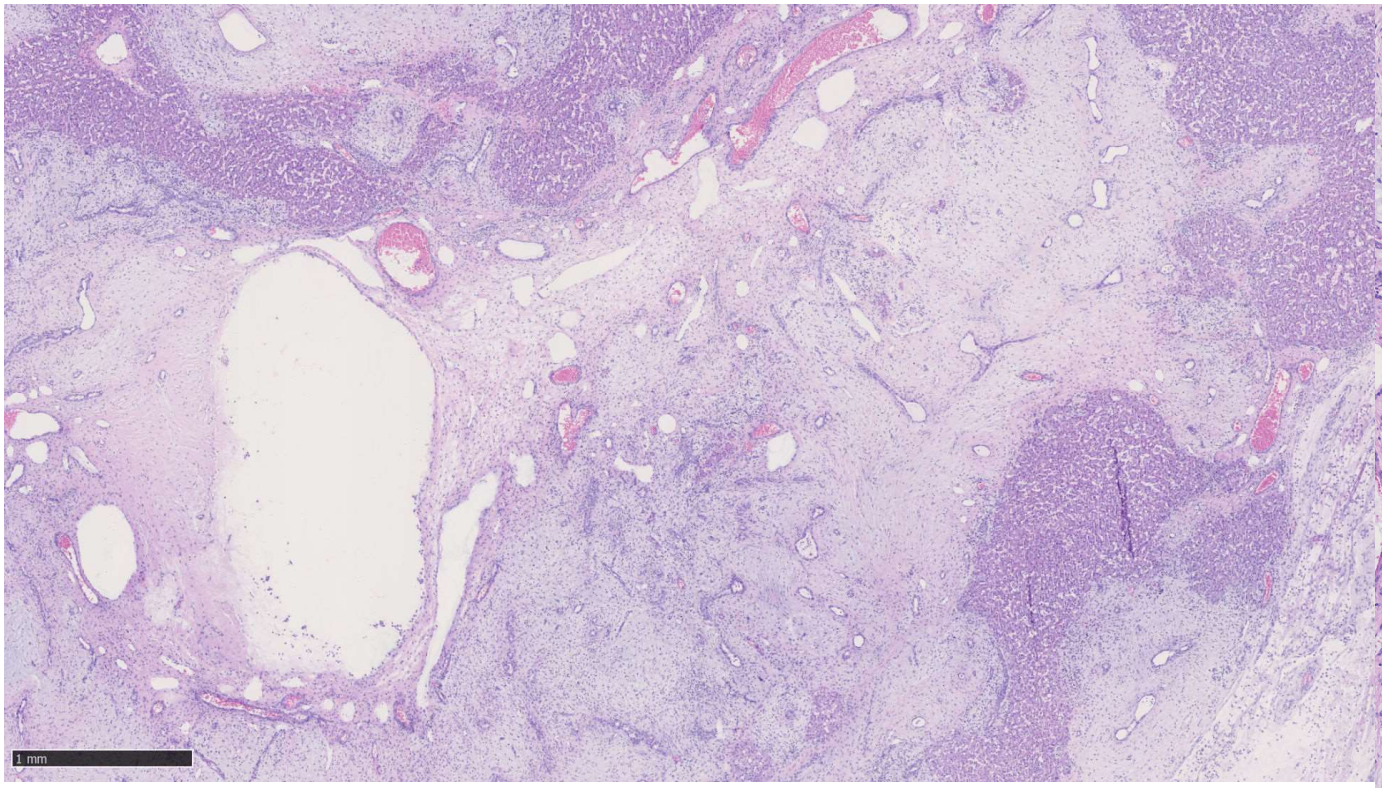
Pathology (2022), 54(2), March

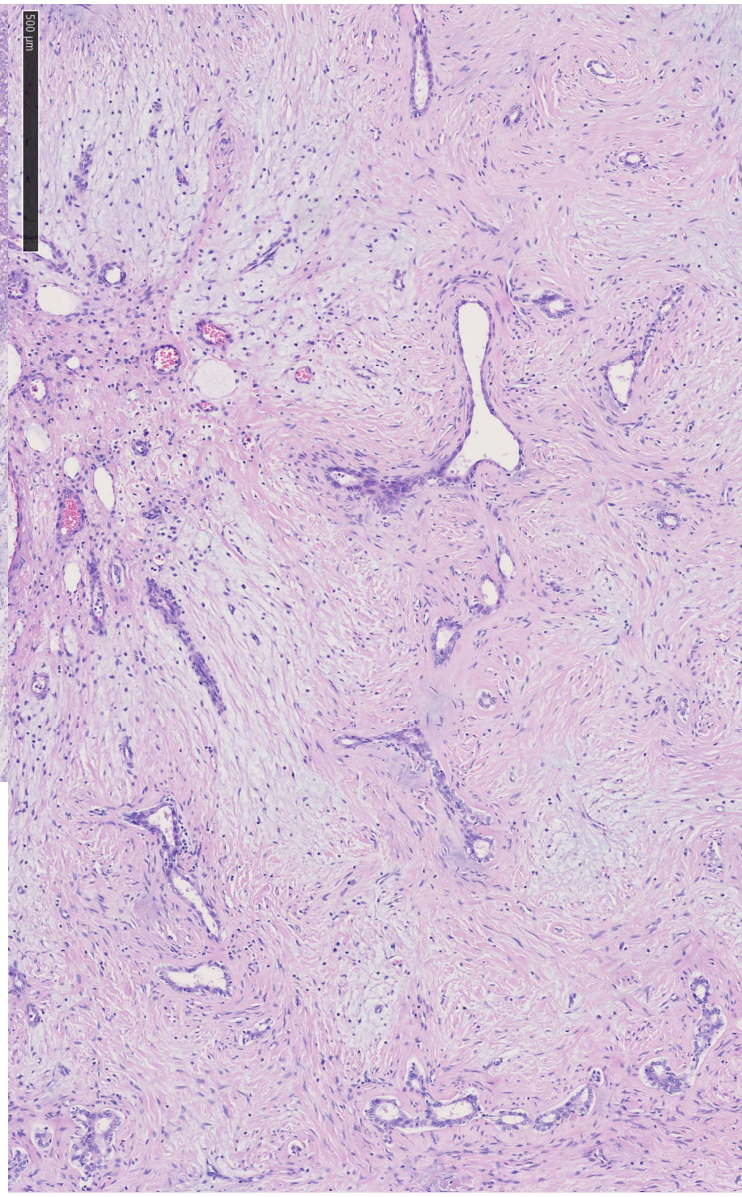




- Expanding, well-delineated and unencapsulated masses. Multiple cystic spaces lacking communication with bile ducts are noted in 85% of cases.

- Cysts often range in size from a few millimeters to 15 cm and contain yellow fluid or gelatinous material.



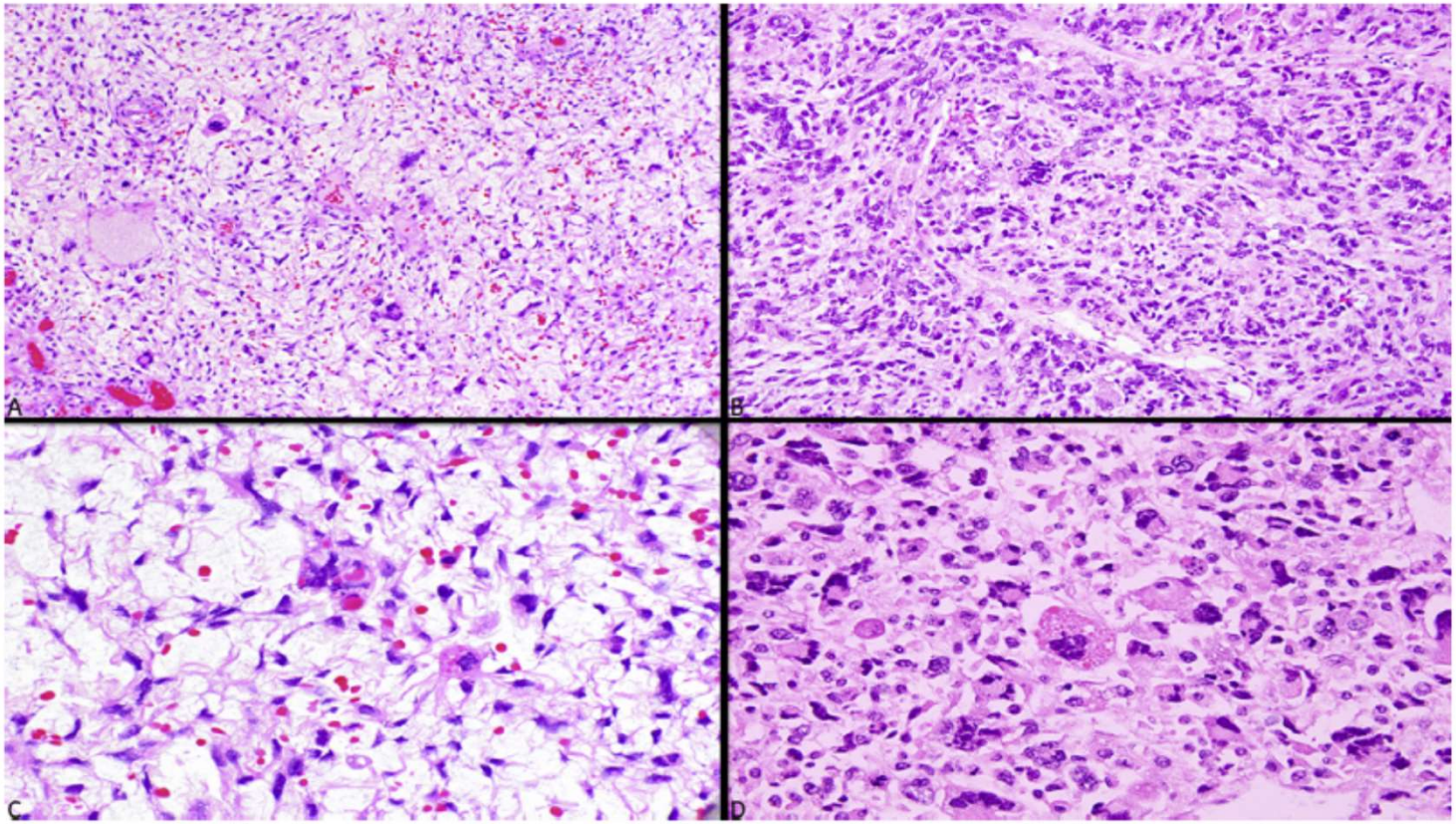


- Histology: loose connective tissue and epithelial bile ducts arranged in lobulated islands.
- Foci of extramedullary haematopoiesis are observed in 85% of cases.
- In biopsy: differential diagnosis

Undifferentiated embryonal sarcoma

- The most common malignant mesenchymal neoplasm of the liver
- Rare tumor (children between the ages of 5–15)
- Clinically: abdominal distention, pain, fever and weight loss.
- Grossly: well-circumscribed, unencapsulated, large sized (10–30 cm), heterogenous surface, with alternating solid, fleshy and mucoid areas and foci of cystic degeneration, necrosis, and haemorrhage

- Composed of heterogenous undifferentiated mesenchymal cells

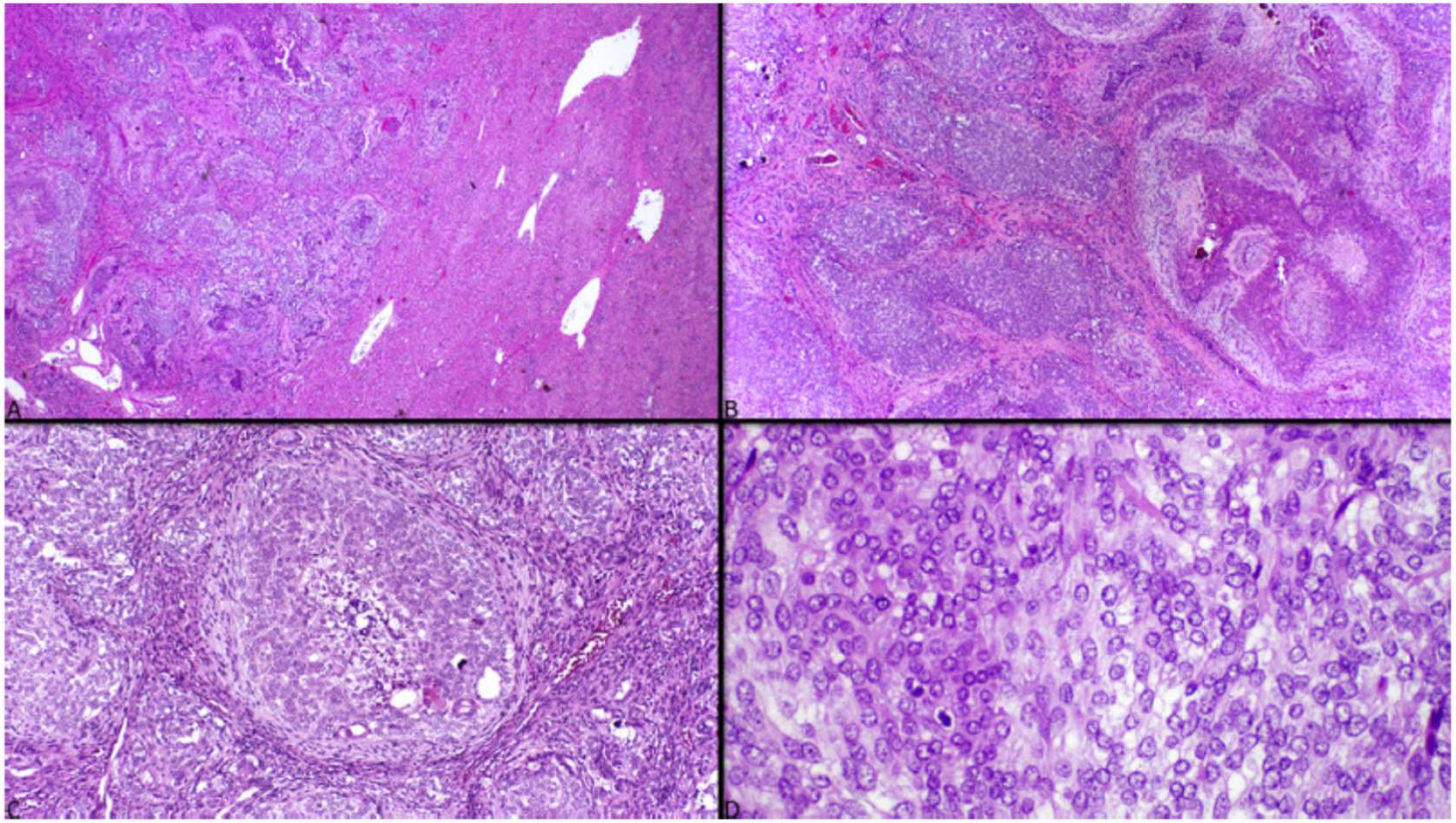


- Histology: spindled, stellate, and pleomorphic giant cells loosely arranged in a myxoid stroma, mitotic activity is brisk
- Peripheral entrapment of bile ducts and extramedullary haematopoiesis are also present
- No specific immunophenotype (PAS+ cytoplasmic hyaline bodies in giant cells)
- Cytogenetic: complex karyotype with a balanced translocation, t(11; 19) (q13; q13.4).

Pathology (2022), 54(2), March

Calcifying nested stromal-epithelial tumour (CNSET)

- Rare, low grade neoplasm of uncertain lineage
- Nested architecture surrounded by a cellular myofibroblastic stroma and psammomatous calcifications
- In general sporadic but association with Beckwith-Wiedemann syndrome is described

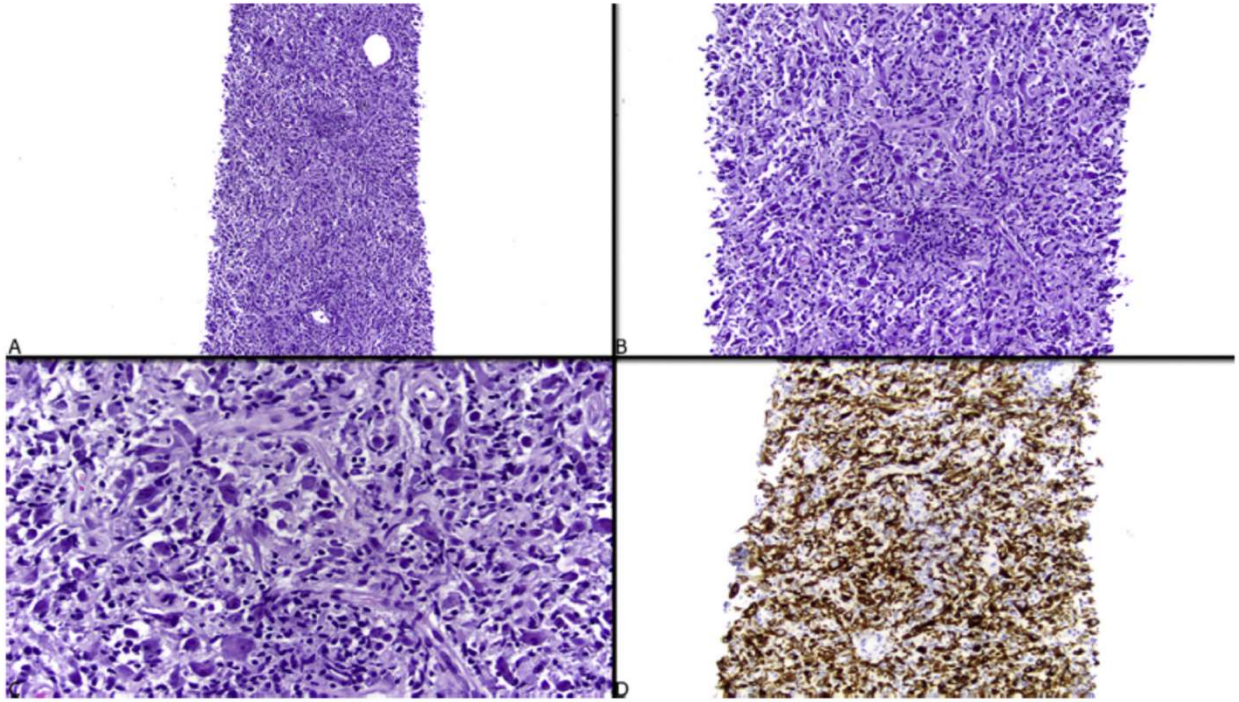


- Histology: ovoid nests of spindle to epithelioid cells cuffed by cellular stroma
- Immunohistochemistry: CK, WT-1, beta-catenin (desmin, chromogranin and synaptophysin -)

Pathology (2022), 54(2), March

Inflammatory myofibroblastic tumour

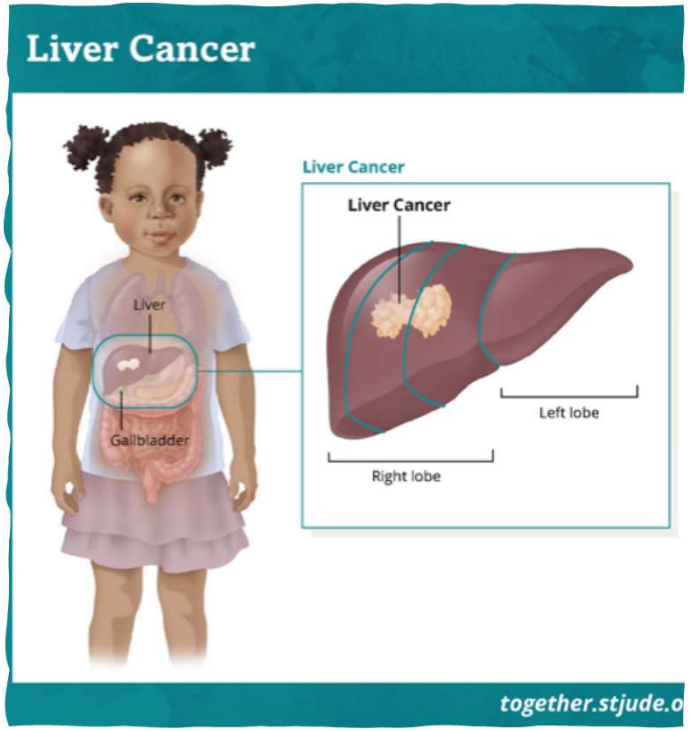
- Fibroblastic/myofibroblastic lineage with intermediate biological potential
- and a prominent
- Inflammatory infiltrate, mainly of lymphocytes and plasma cells.
- children and young adults broad age range
- clinically present with abdominal pain and fever
- Laboratory: anaemia, leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinaemia (half patients)
- Macroscopic examination: 3-12 cm mass with white to yellow firm cut surface.



- Histology: fascicles of uniform, plump spindle in a myxoid or collagenous matrix containing inflammatory infiltrate dominated by lymphocytes and plasma cells with fewer eosinophils and neutrophils
- Low mitotic activity, necrosis absent.
- Immunohistochemistry: SMA +, desmin +half, Ck + in 20-30%, ALK (60%).
- KIT, DOG-1, CD34, S100, SOX and EMA -
- ALK – cases higher risk of metastasis

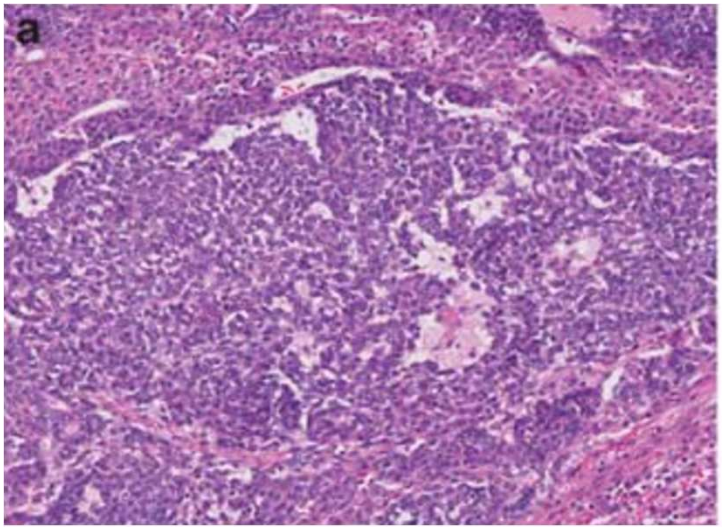
Pathology (March 2022) **54**(2), pp. 225–235

Conclusion



- Pediatric liver tumor are rare lesions
- Diagnosis is challenging -> ask for a second opinion or send to a central reviewer
- Diagnosis in general in a biopsy
- Macroscopical evaluation and sampling is important
- Don’t misinterprete changes due to chemotherapy


Thank you for
your
attention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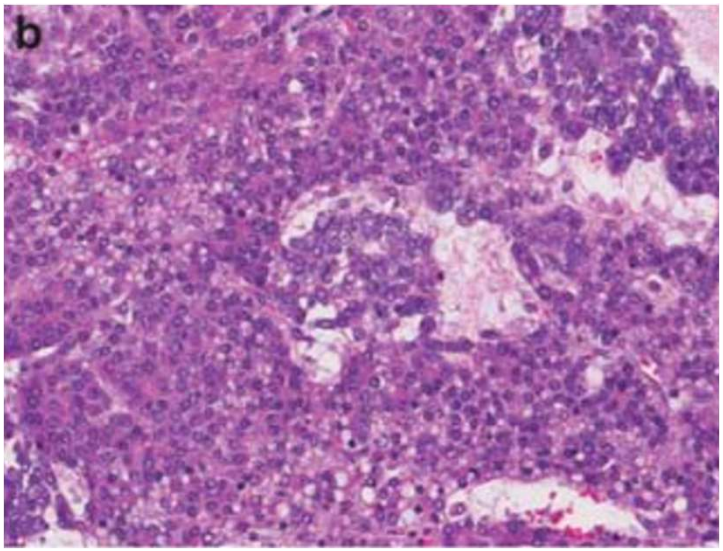
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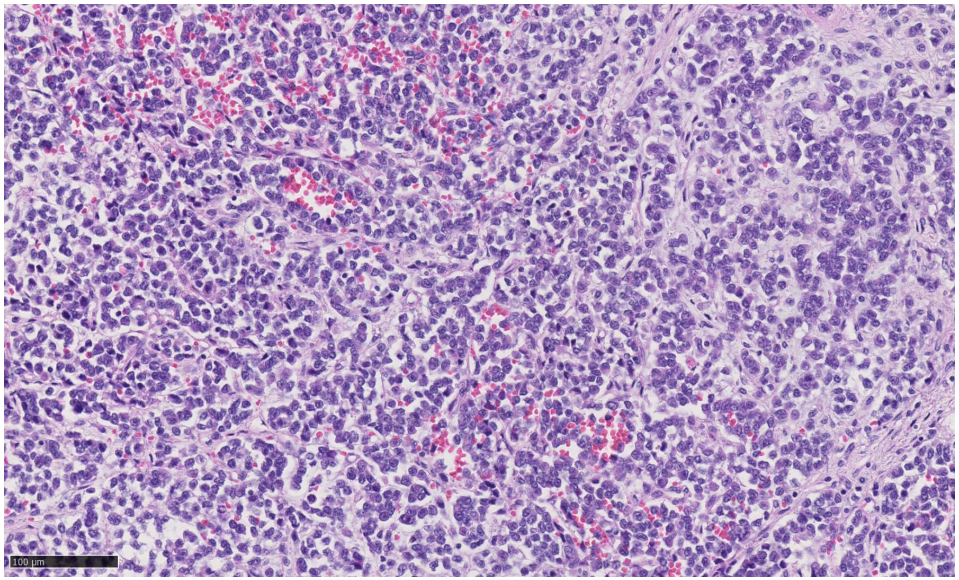
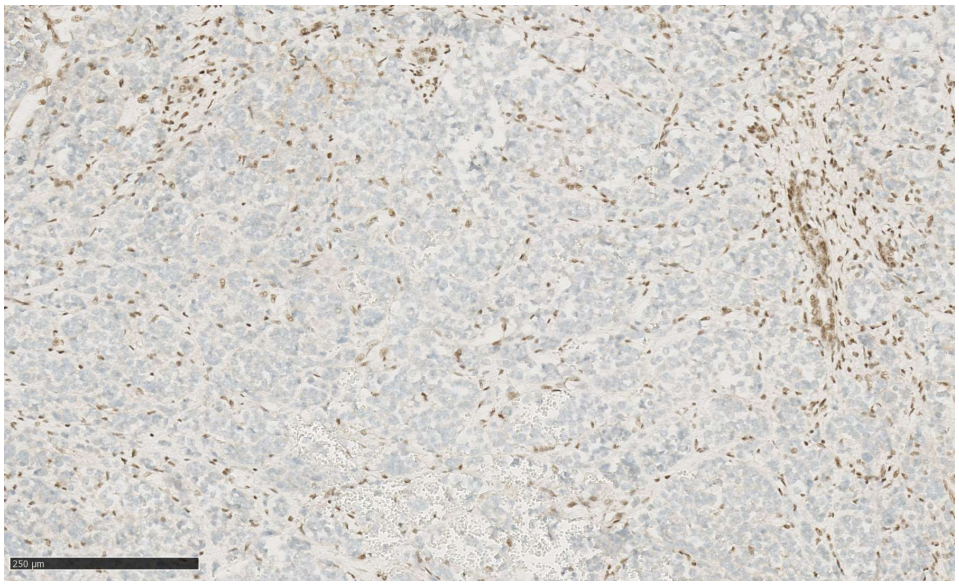

100 µm


250 µm