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Review

New insights in gastrointestinal "pediatric" neoplasms in adult patients: pancreatoblastoma, hepatoblastoma and embryonal sarcoma of the liver. A practical approach by GIPPI-GIPAD Groups

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Summary

Pediatric solid neoplasms are rare and very different from those observed in adults. The majority of them are referred to as embryonal because they arise as a result of alterations in the processes of organogenesis or normal growth and are characterized by proliferation of primitive cells, reproducing the corresponding tissue at various stages of embryonic development. This review will focus on embryonal gastrointestinal pediatric neoplasms in adult patients, including pancreatoblastoma, hepatoblastoma, and embryonal sarcoma of the liver. Although they are classically considered pediatric neoplasms, they may (rarely) occur in adult patients. Hepatoblastoma represents the most frequent liver neoplasm in the pediatric population, followed by hepatocellular carcinoma and embryonal sarcoma of the liver; while pancreatoblastoma is the most common malignant pancreatic tumor in childhood. Both in children and adults, the mainstay of treatment is complete surgical resection, either up front or following neoadjuvant chemotherapy. Unresectable and/or metastatic neoplasms may be amenable to complete delayed surgery after neoadjuvant chemotherapy. However, these neoplasms display a more aggressive behavior and overall poorer prognosis in adults than in children, probably because they are diagnosed in later stages of diseases.

Key words: hepatic embryonal sarcoma, hepatoblastoma, pancreatoblastoma, pediatric tumors, gastro-intestinal tumors

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Introduction

Pediatric neoplasms represent an important diagnostic challenge for pathologists, even in specialized institutions, both for their rarity and for their peculiarity when compared to adult neoplasms. The majority of them are referred to as embryonal because they arise as a result of alterations in the process of organogenesis or normal growth and are characterized by a proliferation of primitive cells, reproducing the corresponding tissue at various stages of embryonic development. Considering these peculiarities, these tumors are the borderland between embryology and pathology, as defined by Willis in 1950. This review will focus on embryonal gastrointestinal pediatric neoplasms in adults, which comprise pancreatoblastoma, hepatoblastoma and embryonal

sarcoma of the liver. Although they are classically considered pediatric neoplasms, they may (rarely) occur in adult patients with an overall poorer prognosis than in children. The pathologist plays a crucial role in the initial diagnosis with important implications in patient management and therapeutic choice. Moreover, the introduction of pediatric therapeutic collaborative protocols has achieved the correct identification of histologic subtypes through systematic central histopathological review, and to collect frozen material for the integration of new biological parameters for future tailored treatments.

Pancreatoblastoma

Pancreatoblastoma (PB) is a malignant epithelial neoplasm characterized by solid architecture, acinar differentiation and the presence of squamoid nests. This neoplasm is typical of young patients (median age at diagnosis: 4-5 years) and represents almost 25% of all pancreatic lesions during childhood [1-5]. However, PB can also be diagnosed in adults (second age peak: 40 years old), although in this age range it is considered a very rare malignancy, representing < 1% of all pancreatic tumors [1-3]. No sex predominance is established. The etiology of this entity is unknown and the vast majority of cases are sporadic. However, emerging clinical data suggest an association between PB and two different genetic syndromes, namely Beckwith-Wiedemann syndrome [1,6,7] and familial adenomatous polyposis (FAP) [8].

Clinical features

The most common signs/symptoms of PB include abdominal pain, nausea, vomiting, weight loss and diarrhea; a palpable mass can be found in pediatric patients. Notably, a non-negligible proportion of cases is incidentally discovered.

Rarely, PB can secrete various hormones provoking the corresponding symptoms. In the pediatric population, elevated serum levels of alpha-fetoprotein (AFP) are a common finding, which can be used as a biomarker for follow-up after surgical resection. This occurrence, however, is uncommon in adults [9,10]. A small fraction of patients may present with a concomitant para-neoplastic Cushing syndrome, due to an inappropriate secretion of ACTH [1,11-13].

Macroscopic features

PBs are usually large masses, with diameters ranging from 1.5 to 20 cm (mean 10 cm) [14]. They are usually well circumscribed or incapsulated, solid, neoplasms. PBs can occur in the head, the body or the tail of the pancreas without showing any specific anatomical predilection. The cut surface has tan to yellowish color and consists of various lobules separated by fibrous bands forming nests of different sizes. Some PBs can present hemorrhagic changes and/or cystic degeneration, which are more often associated with genetic syndromes [15].

Microscopic features and cytology

Histologically, the tumor is composed of highly cellular lobules separated by fibrous bands and admixed with unequally distributed squamous nests (Fig. 1) [1,2]. The number, cellularity and width of the fibrous bands on the tumor sample can vary, also depending on the patient's age. In adult patients for example, PBs are similar to those of childhood, but stromal bands are usually less abundant and less cellular [1]. PBs can exhibit solid, acinar and/or trabecular growth patterns. The neoplastic elements are monomorphic and roundish-to-polygonal, with small nuclei including an evident nucleolus; mild to modest nuclear atypia is generally observed. The histological hallmark of PBs, which is a necessary element to differentiate them from acinar cell carcinomas, is represented by squamous nests (Fig. 1) [1,2]. Even though squamoid nests, can be easily documented in histological sections, as pale and round areas, sometimes with a whorled aspect, their identification in cytological samples may be challenging. Interestingly, Reid and colleagues [16] distinguished two different subtypes of cells composing squamoid nests of PBs on cytological samples. The first subtype is represented by well defined, large and ovoid cells with clear cytoplasm, without significant atypia. The second subgroup is composed of ill-defined, loosely cohesive cells that may present nuclear clearing due to the accumulation of biotin [17]. Although squamoid nests are a crucial key for PB diagnosis, their distribution is uneven throughout the neoplasm and between different PBs. This indicates that, in case of pancreatic tumors with acinar differentiation, an accurate and exhaustive tumor sampling should be performed in order to document the presence of squamoid nests, which can be focal. Lastly, calcifications are sometimes present.

Immunohistochemical and molecular features

The predominant acinar component of PB at immunohistochemistry (IHC) shows a diffuse and strong pos-

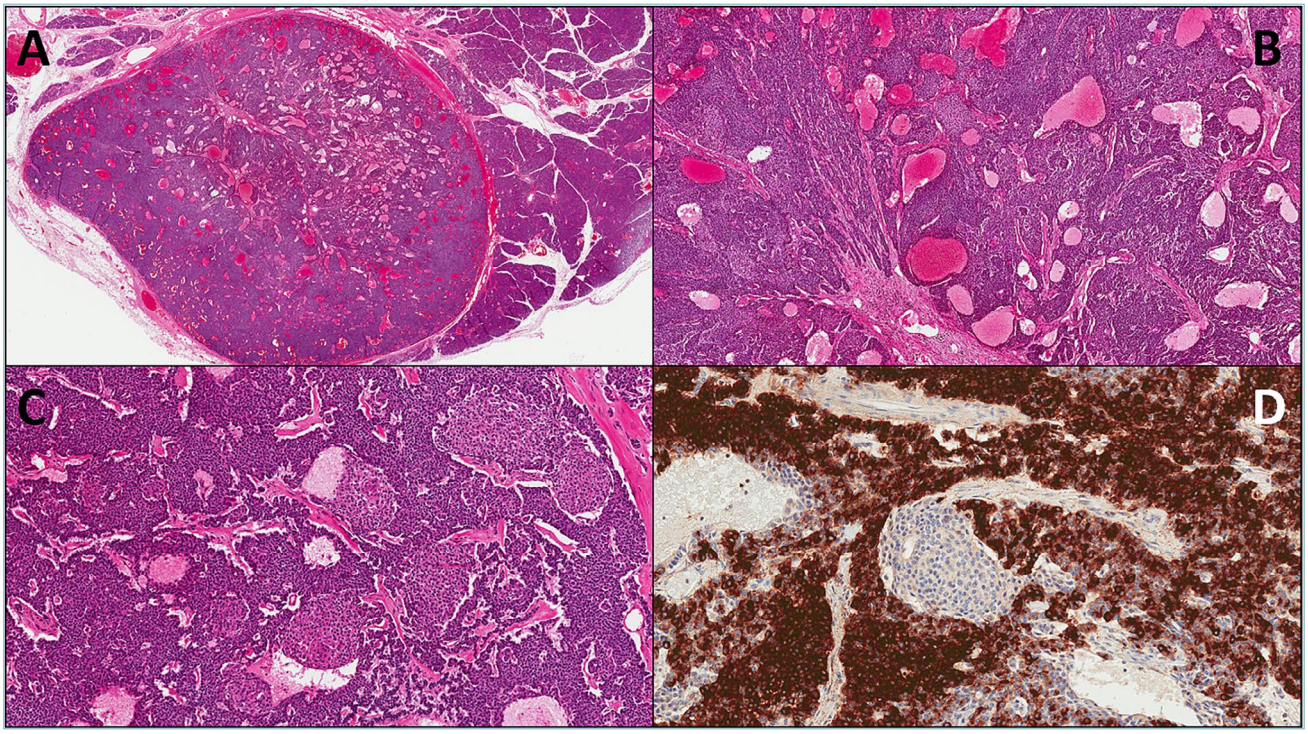

Figure 1. Figure summarizing the most important microscopic features of pancreatoblastoma. (A) Pancreatoblastomas are usually well-circumscribed neoplasms (hematoxylin-eosin, magnification: 2X); (B) the stromal component may be well represented (hematoxylin-eosin, magnification: 4X); (C) the classic histological appearance is of a hypercellular neoplasm with pale and roundish areas representing the so-called squamoid nests (hematoxylin-eosin, magnification: 10X); (D) detail at a higher magnification, with immunostaining for Bcl-10: this marker shows a very strong positivity in pancreatoblastomas, except for squamoid nests, which are negative (magnification: 20X).

itivity for Bcl-10 and trypsin, while squamoid nests remain negative (Fig. 1). Squamous nests, on the other hand, may express immunostaining for β-catenin (aberrant nuclear accumulation), CD200 and EMA[1,2,18]. PBs can also show positive staining for chromogranin and synaptophysin, but, if present, positivity is usually focal or very focal. IHC may be required to exclude a neuroendocrine tumor, but in this kind of differential diagnosis the morphology is usually sufficient [1,5]. Diagnostic criteria for the most important differential diagnosis of PBs are summarized in Table I.

The molecular profile of PB has not been completely deciphered. One of the most common genetic alterations in PB is represented by the loss of the short arm of chromosome 11 (loss of 11p), also seen in patients with Beckwith-Wiedemann syndrome [6]. This alteration leads to the dysregulation of IGF2[16]. A genetic hallmark of PB is represented by the presence of recurrent upregulation of the WNT pathway [1,8,18-21]; this can depend on activating *CTNNB1* mutations but also due to inactivating *APC* mutations, the latter present in FAP syndrome [22]. Of note, no cases of PBs with microsatellite instability high-tumor mutational burden have been so far reported.

Prognosis

In adults, PB may be successfully treated, in the case of limited extension, by radical resection; unfortunately, they can present with a significant degree of local invasion and distant metastasis in up to 1/3 of patients at the time of diagnosis. The most common site of distant metastases is represented by the liver. The overall survival rate of PB patients is 50%, which increases to up to 2/3 of patients in patients with surgically resected tumors [1,2,21]. Differently from adults, children display a more favorable prognosis. One possible reason is that children are diagnosed in earlier stages, with small tumor masses and without local or distant metastasis [1,2,21]. Computed tomography and magnetic resonance are of help in radiological diagnosis; such analyses are recommended also for the follow-up after resection, integrating radiologic data with AFP dosage [23,24].

Table I. Most important features helpful in the main differential diagnosis of pancreatoblastoma.

Tumor type/ subtype	Most common architectural patterns	Squamoid nests	Necrosis	Stroma	Evident nucleoli	Acinar cell IHC markers expression	Neuroendocrine marker expression	Most important IHC markers for diagnosis
Pancreatoblastoma	Acinar, trabecular, solid	Yes	Possible	Fibrous, often hypercellular	Yes	Yes	No or focal	Bcl10, trypsin; EMA (SN)
Acinar cell carcinoma	Acinar, glandular, trabecular, solid	No	Frequent	Fibrous, occasional	Yes	Yes	No or focal	Bcl10, trypsin
Pancreatic NET	Nesting, trabecular, glandular, solid	No	Very rare	Highly vascular, hyalinized	No (salt-pepper chromatin)	No	Yes, diffuse and strong	Chromogranin, Synaptophysin, Ki67 for grading

Abbreviations: IHC: immunohistochemical; SN: squamoid nests, NET: neuroendocrine tumors.

Hepatoblastoma

Hepatoblastoma (HB) is a malignant hepatic embryonal tumor arising from a hepatocyte precursor cell that recapitulates the various stages of liver development, consisting of a combination of either epithelial or epithelial and mesenchymal elements. HB is the most frequent liver tumor in children, accounting for 1% of all pediatric malignancies, with a worldwide estimated incidence of 1-1.5 cases per million children [25,26]. A rising incidence of HB has been reported, probably related to a higher number of premature birth and low-birth-weight survivors [26,27]. The majority of HBs are sporadic, but a subset can occur in the context of several congenital abnormalities and constitutional genetic syndromes, such as Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, trisomy 18 (Edward syndrome), Sotos syndrome and familial adenomatous polyposis coli [28-31].

Clinical features

HB mostly affects infants and young children between 6 months and 5 years (80-90%), with a median age of 18 months [32,33], but cases have also been reported in neonates, adolescents and (rarely) adults up to the age of 80 years [34]. There is a slight male predominance [32]. HB usually presents as an enlarging solitary mass in 80-85% of cases, involving the right lobe (55-60%), the left lobe (15-20%), or both lobes in the remaining cases. Multifocal masses at presentation do occur, and metastases at diagnosis are present in 5% of cases, usually to the lungs. The most common presentation symptoms are abdominal pain, anorexia, weight loss, nausea, and vomiting; jaundice is present in less than 5%. Liver enzymes are generally normal; thrombocytosis with platelet counts above 450,000/μL is frequent. Alpha-fetoprotein (AFP) is highly elevated (in the thousands and even millions ng/mL), and is useful for monitoring recurrence of disease and chemotherapy response. Imaging studies are necessary for PRETEXT (PRE-Treatment EXTent of tumor) staging of the tumor, and are important for disease assessment and treatment selection. Enhanced computerized tomography (CT) and magnetic resonance imaging (MRI) are recommended for this purpose [35,36]. HB presents as well-delineated hypodense (rarely isodense) mass on CT. Foci of calcification, ossification, and hemorrhage may be present. By MRI, most tumors are T2 hyperintense, T1 hypointense, and hypointense with gadolinium in the epatobiliary phase.

Macroscopic features

HB is usually a single, well-delineated and lobulated mass, within a normal liver, with a variegated cut surface, and an irregular thin pseudocapsule. Post-therapy tumors usually show cystic change, necrosis, hemorrhage, and a more accentuated pseudocapsule (Fig. 2). Gross examination is crucial either in upfront surgery (primary resection) or in post-chemotherapy surgery. A mapping liver tumor resection specimens with a complete sampling of at least 1 cross-section of tumor (similar to Wilms tumor or osteosarcoma) is recommended, in order to assess the percent of

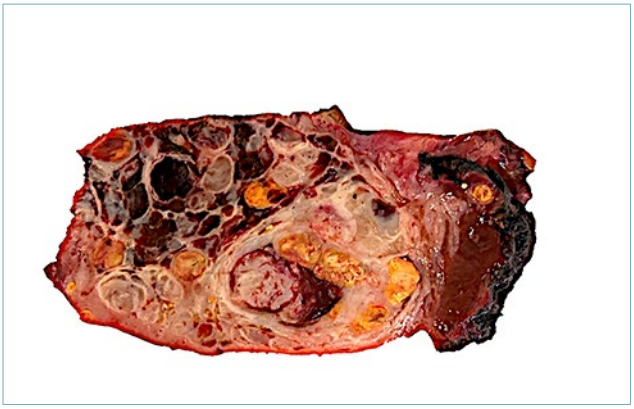

Figure 2. Gross resection of post-therapy tumor. The cut surface shows cystic change, necrosis, and hemorrhage.

post-chemotherapy necrosis and the morphology of the residual tumor. Accurate sampling also permits identification of worrisome/significant areas, which require further sampling. Additional sections from normal parenchyma should be performed [37].

Microscopic and immunohistochemical features

According to the International Pediatric Liver Tumor Consensus Classification (PLTCC), HB is histologically classified on the basis of the components present as either epithelial HB or mixed HB when both epithelial and mesenchymal components are present [38,39].

Epithelial HB

Well-Differentiated Fetal (WDF) HB (or pure fetal HB with low mitotic activity) (Fig. 3) is composed of thin plates, cords or nests of uniformly small-medium, polygonal cells with a well-defined outline and abundant eosinophilic to clear vacuolated cytoplasm, resulting in a characteristic dark-and-clear cell pattern. The nuclei are central and round, without nucleoli. Mitoses are rare (< 2/10 HPF); necrosis and pleomorphism are absent. Extramedullary hematopoiesis is typical. Immunohistochemically, the neoplastic cells show strong cytoplasmic positivity for glutamine synthetase (GS); weak, but diffuse staining of glypican 3 (GPC3) in a fine stippled pericanalicular cytoplasmic pattern; and membranous, even cytoplasmic, with rare, never strong diffuse, nuclear positivity for β-catenin. WDF HB cannot be diagnosed on biopsies or postchemotherapy specimens, but only on primary resection specimens. According to the Pediatric Hepatic International Tumor Trial (PHITT) protocol, the diagnosis

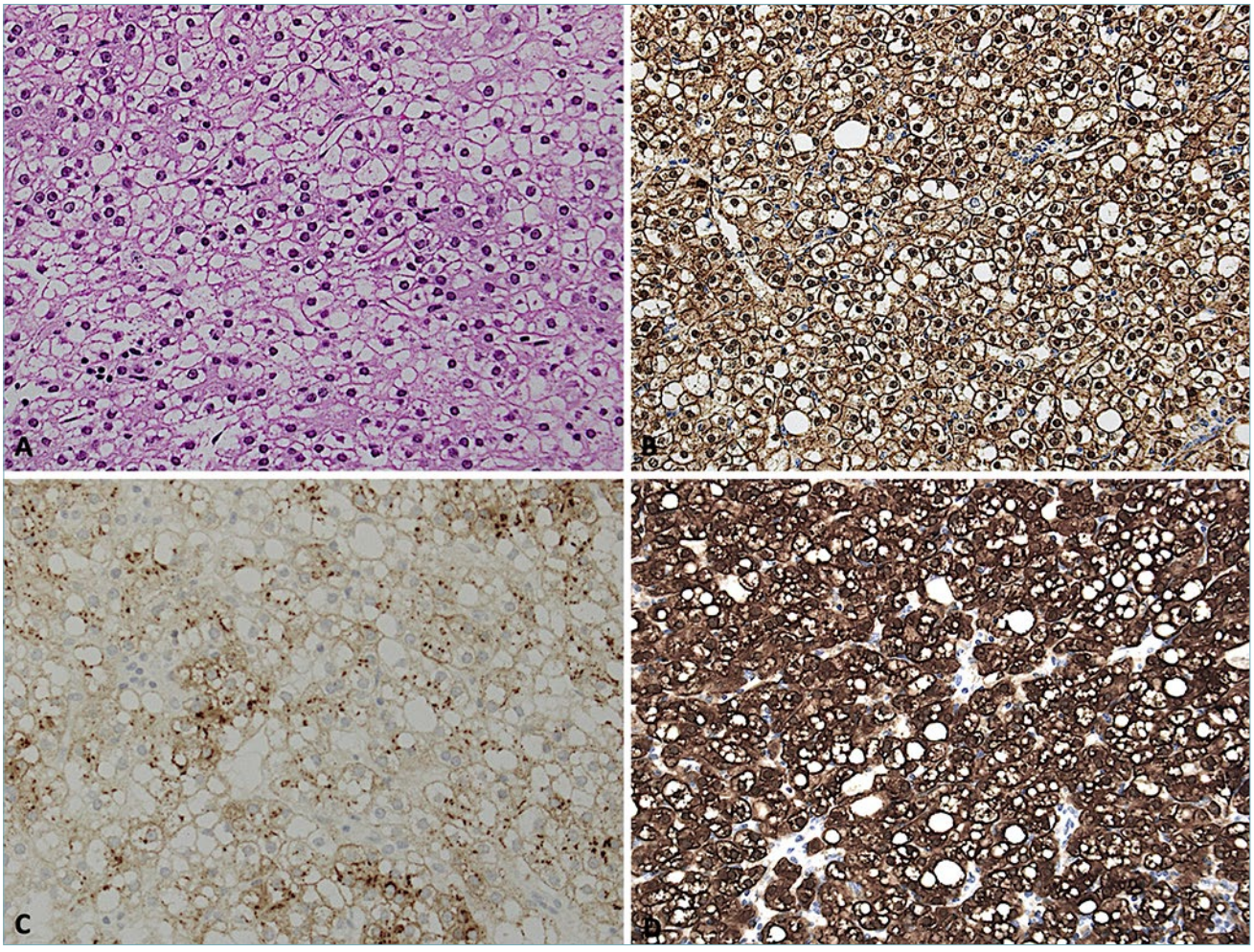

Figure 3. Well differentiated fetal hepatoblastoma. (A) Uniform small-medium and polygonal cells with well-defined outline and characteristic dark-and-clear cell pattern. (B) Cytoplasmic and membranous β-catenin staining with weak positive and negative nuclei. (C) Cytoplasmic GPC3 staining in a fine stippled pattern. (D) Strong cytoplasmic GS staining.

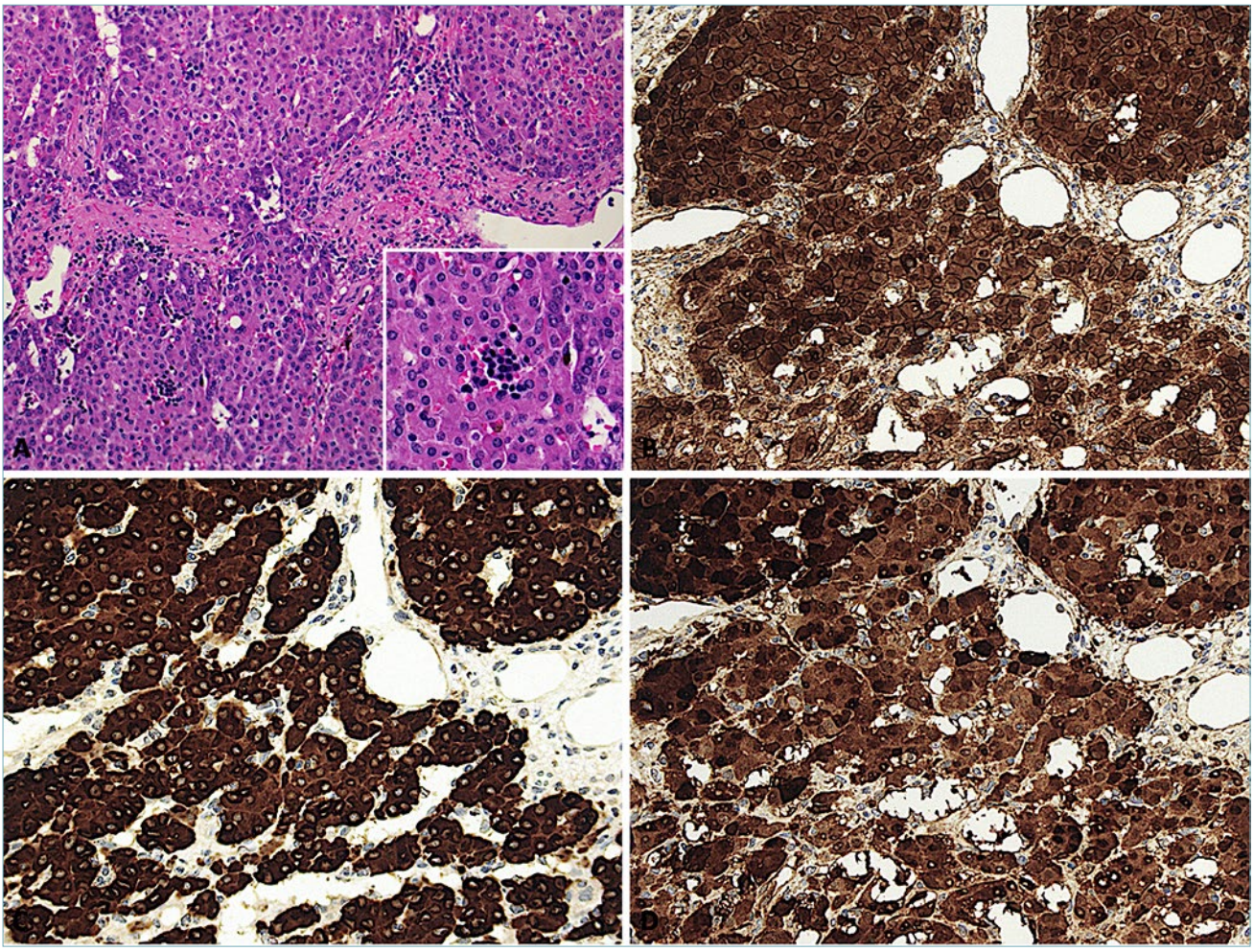

Figure 4. Crowded fetal hepatoblastoma. (A) The neoplastic cells show slightly increased N/C, round nuclei with frequent nucleoli and dense eosinophilic cytoplasm; extramedullary hematopoiesis is frequent (inset). (B) Strong nuclear β-catenin staining. (C) Diffuse and coarse cytoplasmic GPC3 staining. (D) Diffuse and strong cytoplasmic GS staining.

of pure fetal HB identifies the group of very-low-risk patients, treated with upfront surgery only, without the need for further therapy if completely resected [40].

Crowded fetal (CF) HB (also known mitotically active fetal HB) (Fig. 4) is a fetal HB with closely packed ("crowded") cells and mitotic activity ≥ 2/10 HPF. The neoplastic cells show higher nuclear-cytoplasmic (N/C) ratio, round nuclei with frequent nucleoli and a dense eosinophilic cytoplasm due to minor cytoplasmic glycogen storage. Extramedullary hematopoiesis is frequent. Nuclear pleomorphism and atypical mitoses are absent (and should suggest a pleomorphic fetal HB when seen). Immunohistochemically, the neoplastic cells show diffuse and strong cytoplasmic positivity for GS, and a diffuse and coarse cytoplasmic staining of GPC3. Many nuclei are positive for b-catenin. These tumors will require chemotherapy.

Embryonal HB (Fig. 5) recapitulates the embryonic stage of liver developmental and is composed of poorly cohesive cells with scant and poorly outlined cytoplasm, high N/C, and a large, angulated to oval nucleus with a prominent nucleolus. Mitoses are frequent and necrosis may be seen. The neoplastic cells are arranged in solid sheets or plates of variable thickness, incomplete/complete tubulo-glandular structures and rosette-like configurations. The vascular network is well developed encompassing a fine capillary network and large vascular channels. Extramedullary hematopoiesis is very rarely observed. Immunohistochemically, the neoplastic cells show uniform nuclear β-catenin positivity, variable GS staining from patchy single cell positivity to negativity, and variable GPC3 from absent to strong, coarse, diffuse cytoplasmic staining. Embryonal HB almost always occurs in

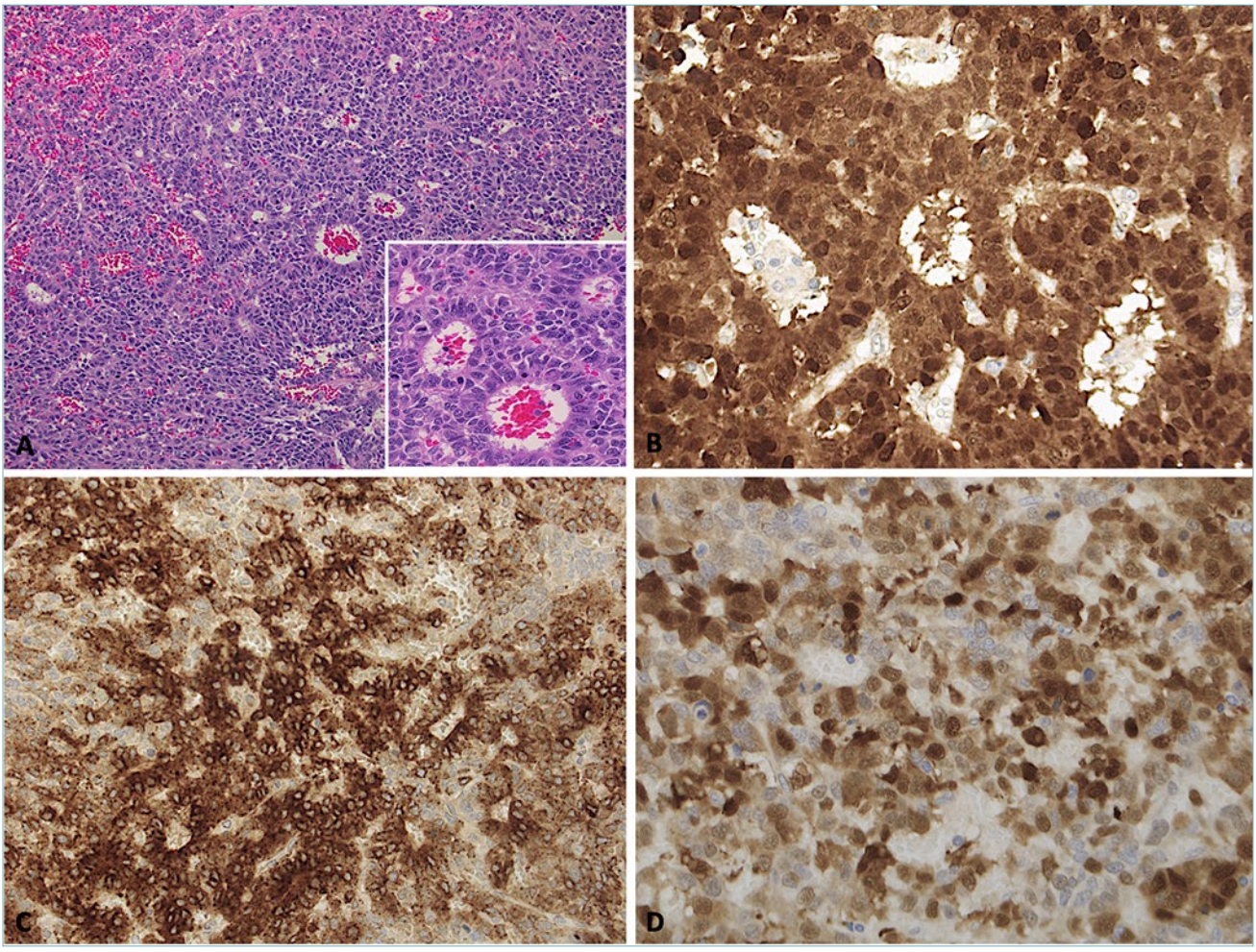

Figure 5. Embryonal hepatoblastoma. (A) The neoplastic cells are densely arranged in solid sheets/plates, incomplete/complete tubulo-glandular structures, and rosette-like configurations, and show scant cytoplasm, high N/C, angulated/oval nucleus and numerous mitoses (inset). (B) Uniform nuclear β-catenin staining. (C) Strong, coarse, granular GPC3 staining. (D) Variable GS staining.

combination, often intermixed without demarcation, with a fetal component. A zonation is observed with embryonal cells in the centre, surrounded by CF cells, rimmed by varying proportion of WDF cells.

Small cell undifferentiated HB (*SCU HB*) was originally termed "anaplastic" and described as a lesion having small cells resembling those of neuroblastoma. Subsequently, the term "anaplasia" had been replaced by "small-cell undifferentiated (SCU)", based on the evidence of small undifferentiated round and spindle cells. However, the definition of SCU HB in recent years has dramatically changed. In fact, this entity in the past was uniformly assigned a worse prognosis both in cases with diffuse and in cases with minimal small cell morphology. Subsequently, the evidence of integrase interactor *1* (INI-1) loss of expression in tumors with a diffuse SCU morphology, has contributed in their reclassification as as hepatic rhabdoid tumors. HBs with a minimal SCU component show sheets and nests of small round to ovoid cells with scant cytoplasm, relatively fine nuclear chromatin with variable mitoses, intimately intermixed with embryonal HB areas. INI-1 is usually preserved. Whether a small component of SCU, usually less than 5% of tumor, with INI-1 preserved, in an otherwise typical epithelial HB is associated with an aggressive clinical behavior, remains object of debate.

Macrotrabecular (MT) HB (Fig. 6A) is a provisional category, representing a growth pattern rather than a histotype. Its morphologic overlap with pediatric hepatocellular carcinoma (HCC) and hepatocellular neoplasm NOS (HCN-NOS) (see below) may be a di-

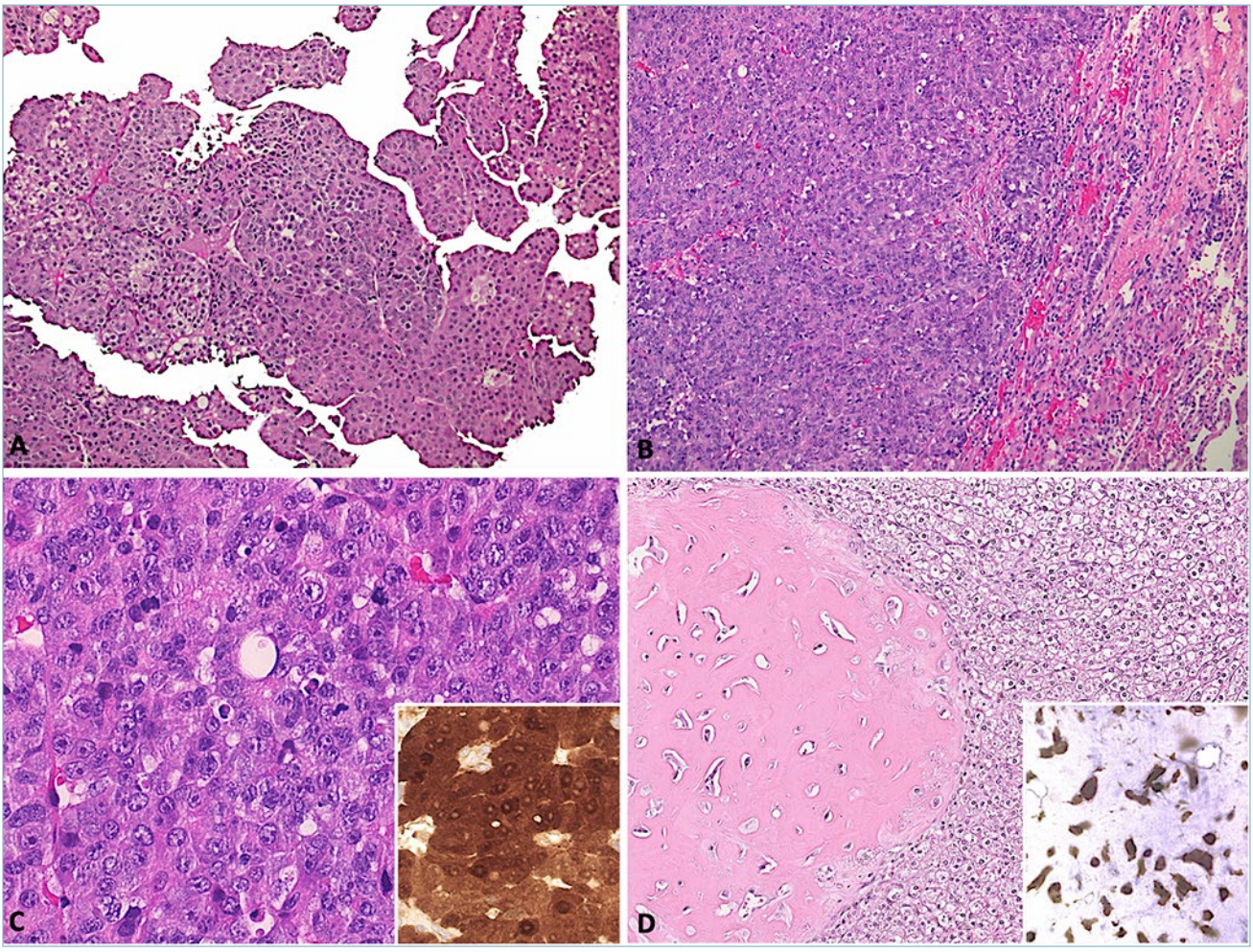

Figure 6. Variants of hepatoblastoma. (A) Macrotrabecular pattern with fetal morphology and focal pleomorphism. (B-C) Post-chemotherapy lung metastasis of same patient showed in A. The neoplasm is more pleomorphic, with abnormal mitoses, conspicuous nucleoli, and strong nuclear β-catenin staining (inset C). (D) Mixed HB with osteoid showing strong nuclear β-catenin staining (inset).

agnostic challenge, especially on biopsy. MT pattern could be found pure (rarely) or in combination with other patterns, and is characterized by trabeculae greater than 5 cells and less than 10-20 cells in thickness. The cells within these macrotrabeculae show crowded fetal or embryonal morphology, reproducing the immunophenotype of these components, with strong nuclear β-catenin staining. The presence of trabeculae less than 10-20 cells in thickness, the coexistence of otherwise typical areas of HB, and the strong nuclear β-catenin staining help in distinguishing this pattern from pediatric HCC. At present, there is no evidence of a prognostic significance of macrotrabecular pattern.

Pleomorphic epithelial HB is an uncommon pattern of HB, more often seen in post-chemotherapy resection specimens and in metastases following chemotherapy. Nuclear features are more pleomorphic when compared with WDF or CF HB, with irregular shape, abnormal mitoses, and large, conspicuous nucleoli. When these pleomorphic cells assume a macrotrabecular growth pattern, the tumor may simulate HCC or may overlap with HCN-NOS (Fig. 6B, C). Strong nuclear β-catenin, strong GS, and variable GPC3 staining help in distinguishing pleomorphic MT HB from pediatric HCC. Immunostains are less useful in the distinction from HCN-NOS.

Cholangioblastic HB exhibits prominent cholangioblastic features and forms small ducts. The cells tend to be cuboidal rather than columnar, and the nuclei are usually round with coarse chromatin. This variant needs to

be differentiated from acinar structures in areas of fetal HB and from ductular reaction at the periphery of the tumor, especially after chemotherapy. The choloangioblastic component shows nuclear β-catenin positivity unlike ductular reaction, and GS and GPC3 negativity unlike the acinar structures of fetal HB.

Mixed HB

Mixed HB is characterized by a complex mixture of epithelial and mesenchymal elements. The neoplastic mesenchymal elements are integral part of the tumor, showing nuclear β-catenin positivity, and do not represent the result of the chemotherapy or a "metaplastic" change (Fig. 6D). The mesenchymal elements most often consist of mature/immature fibrous tissue, osteoid, and cartilage. A small percentage of mixed HBs displays teratoid features *(i.e. teratoid HB or HB with heterologous elements)* characterized by a mixture of heterologous elements, such as endoderm, neural elements, and neuroectodermal derivates.

Hepatocellular neoplasm - NOS

Hepatocellular neoplasm - NOS (HCN-NOS) is a new provisional category, previously designated as "transitional cell liver tumors" (TCLT) by Prokurat [41], including hybrid lesions with overlapping HB and HCC features. HCN-NOS are highly aggressive and typically occur in older children (over the age of 8 years) with high or very high serum AFP levels, and an overall unfavourable outcome. The neoplasm may show macrotrabecular growth pattern and HCC-like features, especially in post-therapy specimens. At the molecular level, HCN-NOS carry β-catenin (*CTNNB1*) mutations as well as other mutations seen in HCC, such as TERT promoter mutations [42,43].

Molecular features

HBs are neoplasms with relatively stable genomes, with a limited number of structural and numerical abnormalities [44,45]. The vast majority (up to 90%) of HBs harbor activation of the canonical Wnt-signaling pathway, through somatic mutations of *CTNNB1* in over 80%, or more rarely, other Wnt-signaling genes; germline alterations, including *APC* mutations [44-49] may also be observed. *NFE2L2* (also known as *NRF2*) is the second most mutated gene, found in 5-10% of HB, and followed by mutations in *TERT* promoter, both associated with poor prognosis. Other pathways involved in HB pathogenesis include Notch, Sonic Hedgehog, PI3K/AKT, EGFR and Hippo pathway (YAP) [42,46,50-53]. Integrated genomic studies reported 3 distinct risk-stratifying molecular HB subtypes associated with low, intermediate, and high risk [42,53]. High risk tumors are characterized by high *NFE2L2* activity; high LIN28B, HMGA2, SALL4, and AFP expression; low let-7 expression; and HNF1A activity; and high coordinated expression of oncofetal proteins and stem cell markers [49,51]. Moreover, HB epigenomic profiling revealed genome-wide dysregulation of RNA editing in HB demonstrating additional epigenomic clusters, including an aggressive subtype characterized by progenitor-like phenotype, methylation features, strong 14q32 locus expression, and *CTNNB1* and *NFE2L2* mutations [54].

Prognosis

Tumor stage

The PRETEXT system is used for staging and risk stratification for HB. The PRETEXT system comprises the PRETEXT group, and the annotation factors. The PRETEXT groups (PRETEXT I, II, III, or IV) reflect hepatic parenchymal tumor involvement; while the annotation factors describe the extension of tumor beyond the hepatic parenchyma and include hepatic venous/inferior vena cava involvement (V), portal venous involvement (P), extrahepatic disease (E), multifocality (F), tumor rupture (R), and metastatic disease (M). CHIC (Children's Hepatic International Collaboration) has created a new risk-stratified staging system in children with HB, the Children's Hepatic International Collaboration - Hepatoblastoma Stratification (CHIC-HS) [40]. This system was established with risk factors including PRETEXT groups, metastatic disease, age at diagnosis (< 3 years, 3-7 years, and ≥ 8 years), AFP concentration (≤ 100 μg/L and 101-1000 μg/L), PRETEXT annotation factors, and tumor resectbility at diagnosis. The primary and most important factor for risk stratification is the PRETEXT group, followed by metastatic disease. All patients with metastatic disease were defined as high risk. Age ≥ 8 years in PRETEXT I/II/III group and age ≥ 3 years in PRETEXT IV group were high-risk factor. Younger patients with AFP level ≤ 100 ng/mL are stratified as high-risk group.

Embryonal sarcoma of the liver

Embryonal sarcoma of the liver (ESL), also known as "*undifferentiated embryonal sarcoma*", is a malignant mesenchymal neoplasm of the liver. The terms "*embryonal and undifferentiated*" refer to the fact that the tumor is histologically composed of mesenchymal cells with no evidence of differentiation [1,55,56]. ESL,

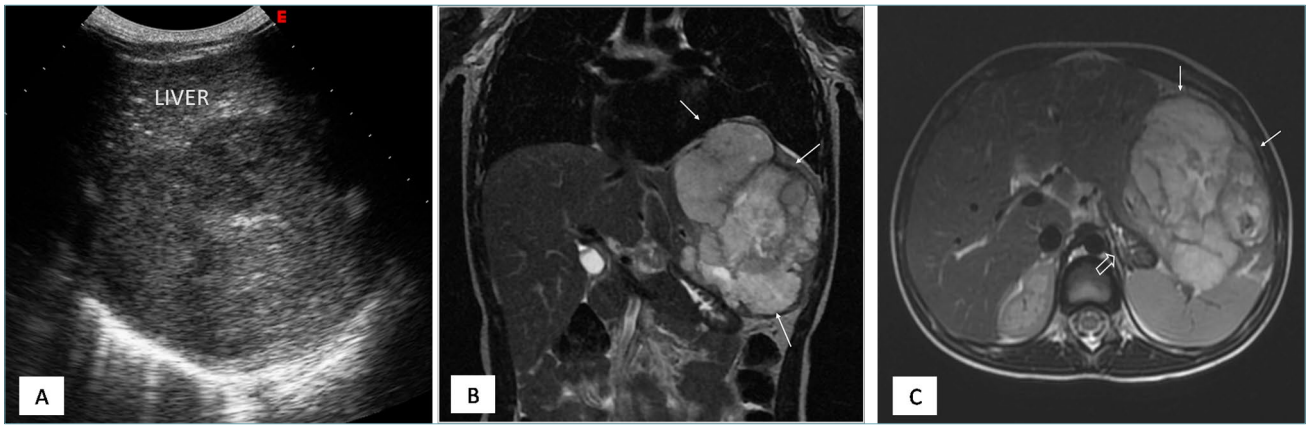

Figure 7. Ultrasound examination of ESL showing a solid hyperechoic tumor, with hypoechoic/anechoic, cystic portions (A). ESL typically presents on coronal and axial MRI as hyperintense on T2 and hypointense on T1 mass with distinct borders (B, C).

first described by Stocker and Ishak in 1978 [57], typically occurs in children with an age ranging from 5 to 20 years, with a peak of incidence between 6 and 10 years [1,54-60]. It accounts approximately for 6-13% of all hepatic pediatric malignancies, representing the third most frequent malignant tumor of the liver after hepatoblastoma and hepatocellular carcinoma in this age group [1,54-60]. Although ESL is classically considered a pediatric neoplasm, some cases have also been reported in adult patients with a predilection for women [58,61,62]. The etiology of ESL is largely unknown; based on the evidence that some cases of ESL may contain areas with mesenchymal hamartoma (MH)-like histology and/or share with this benign tumor the same chromosome translocation t(11;19) (q13;q13.4), a molecular continuum between these two entities has been suggested[63,64].

Clinical features

Most patients present with a palpable mass associated with abdominal distension, pain, fever, anorexia, vomiting, irregular alvus, respiratory distress and weight loss [1,54-60,65]. Hemoperitoneum due to the rupture of the liver is a rare complication [1,54-60]. Although there are no specific laboratory findings, leukocytosis and increased serum alkaline phosphatase are frequently found [55,56]; liver neoplastic serum markers are usually normal. On ultrasonography, ESL usually presents as large solid-cystic mass (Fig. 7A) [55,56,66,67]. If the cystic component is prominent, the tumor may be misinterpreted as a benign neoplasm, causing diagnostic and therapeutic delays for the patient [55,56,66,67]. Computed tomography usually reveals a single, predominantly hypodense, cystic mass, with internal septations [66,67]. Magnetic resonance imaging, showing a T2-hyperintense and T1-hypointense mass (Fig. 7B, C), is also useful for planning the surgical approach, due to its high accuracy in the detection of vascular invasion, biliary obstruction and hilar lymphadenopathy [55,56,66,67]. The diagnosis is histologically-based on liver needle/wedge biopsy.

Macroscopic features

ESL occurs more frequently in the right hepatic lobe [55,56]. On gross examination, the tumor presents as a single, large-sized, well-demarcated and unencapsulated lesion, measuring 10-30 cm in its greatest diameter (Fig. 8A) [55,56]. The well-defined margins of the mass are due to the presence of a fibrous pseudocapsule resulting from the adjacent compressed liver parenchyma [55,56]. The cut surface shows a solid mass, gray-whitish in color, with alternating myxoid and cystic areas (Fig. 8B) [55]. Necrotic and hemorrhagic areas are commonly seen [56].

Histopathologic features

Histologically, ESL is predominantly composed of variably-sized spindle, oval to stellate cells, compactly or loosely set in a variably fibro-myxoid stroma (Fig. 9A-D) [1,54,55,66]. The most striking feature of ELS is the presence of pleomorphic, often multinucleated, cells with hyperchromatic nuclei (Fig. 9D) [1,54,55,68]. In the more collagenized areas, neoplastic cells adopt a spindled morphology and are arranged in a fascicular or storiform growth pattern [1,54,55,68]. Notably, neoplastic cells exhibit eosinophilic granular cytoplasm, inconspicuous nucleoli and indistinct cell borders. The presence of multiple, PAS-positive, diastase-resistant, eosinophilic, cytoplasmic and extracellular hyaline globules is a characteristic finding of ESL (Fig. 9C) [1,54,55,68]. Mitotic activity is usually high and atypical mitoses and

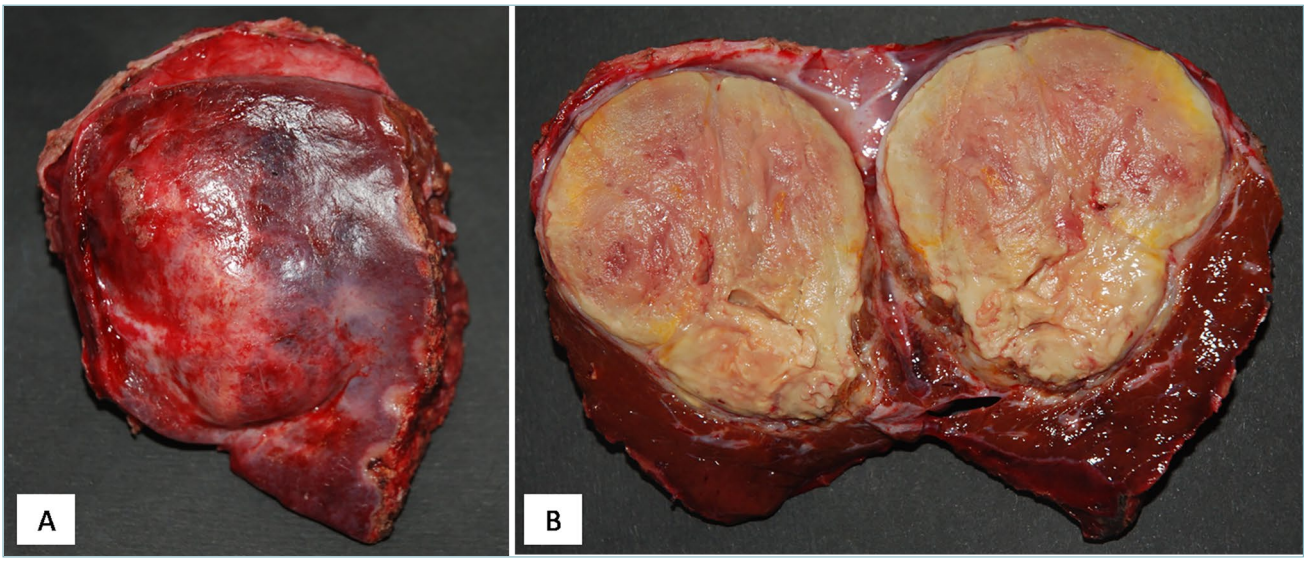

Figure 8. Gross examination of partial hepatectomy after neoadjuvant chemotherapy showing a large-sized and oval-shaped mass with well-demarcated margins (A). On cut surface, the tumor is yellow to whitish in color and often exhibits alternating solid and cystic areas. Necrosis and extensive fibrosis, due to the effects of the neoadjuvant chemotherapy are seen (B).

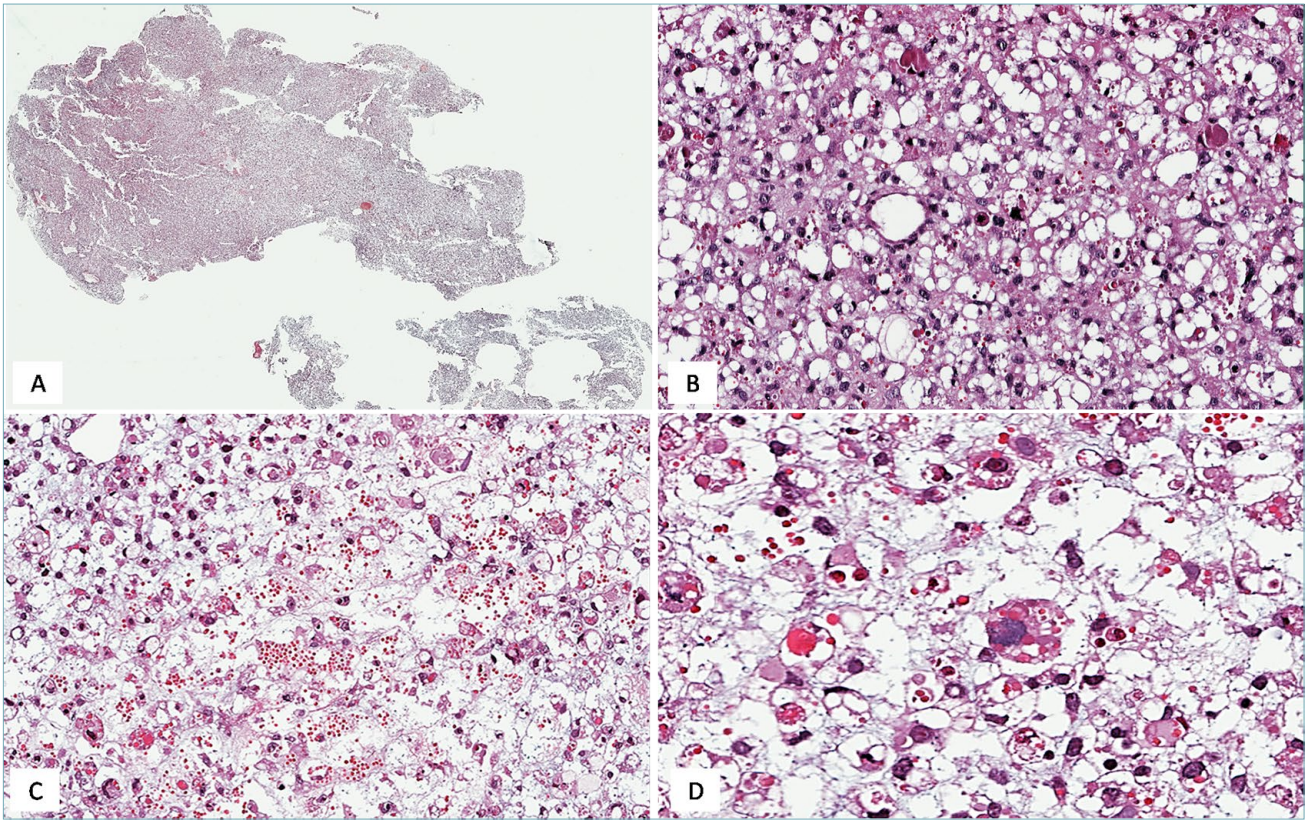

Figure 9. Wedge biopsy showing a moderately cellular tumor completely replacing liver parenchyma (H&E; original magnification 25x) (A). Higher magnification showing mitotically-active, rounded- and stellate-shaped neoplastic cells with ill-defined borders, set in a fibrous stroma; apoptotic bodies are also seen. (H&E; original magnification 200x) (B). ESL may also exhibit myxoid areas; notice the typical eosinophilic intra- and extra-cellular hyaline globules (H&E; original magnification 200x) (C). The detection of highly pleomorphic neoplastic cells is an additional characteristic feature (H&E; original magnification 400x) (D).

apoptotic bodies are often seen (Fig. 9B). Intratumoral necrosis and hemorrhage are common. Clusters of entrapped hepatocytes and biliary ducts may be found at the periphery of the tumor, as well as foci of extramedullary hematopoiesis [1,55,56]. Uncommon morphological features include tumor areas with MH-like [1,55,56,68] or rhabdoid morphology [69].

Immunohistochemical and molecular features

ESL exhibits a non-specific immunophenotyped [1,55,56]. Neoplastic cells are diffusely stained with vimentin, α-1-antitrypsin and α-1-antichymotrypsin, and focally with glypican-3, α-smooth muscle actin, muscle-specific actin, desmin, CD34, S-100, calponin, cytokeratins, CD68, BCL-2, CD10 and p53 [68]. A dot-like immunopositivity for cytokeratins and membrane staining with CD56 has been also described[70]. Neoplastic cells are consistently negative for EMA, myogenin, Myo-D1, α-FP and Hep Par-1 [1,55,56]. Ki-67 proliferation index is usually high, ranging from 30% to 95%. Hyaline bodies are usually stained with vimentin, α-1-antitrypsin and α-1-antichymotrypsin. The variable co-expression of histiocytic, muscle and epithelial markers suggests a tumor origin from primitive stem cells [55,56]. As ESL may exhibit focal or dot-like positivity for cytokeratins AE1/AE3 and CAM5.2, a misdiagnosis of carcinoma may be rendered. As the half of cases of ESL share the expression of glypican-3 with hepatocellular carcinoma and hepatoblastoma, the use of this immunomarker should be avoided in the differential diagnosis [55,56].

The differential diagnosis of ESL in the pediatric age mainly includes embryonal rhabdomyosarcoma, hepatoblastoma and MH; in adult patients, ESL should be distinguished from sarcomatoid hepatocellular carcinoma, malignant melanoma and metastatic gastro-intestinal stromal tumor [55,56]. The most relevant criteria for the differential diagnosis are summarized in Table II. The genetic landscape of ELS is still largely unknown. Comparative genomic hybridization data suggested a potential role for chromosomal instability in the pathogenesis of this tumor, showing that copy number alterations are frequently found [59,71,72]. In addition, gains in chromosomes 1q, 5p, 6q and losses in chromosome 14, 9p and 11p. are recurrent molecular events of this tumor [59,71,72]. As mentioned above, some cases of ESL share with MH the same chromosome translocation t(11;19) (q13;q13.4), suggesting a molecular continuum between these two lesions [63,64]. Mutations in the DNA-binding domain of the *TP53* gene have also been reported [71,73].

Prognosis

Although ESL is a malignant tumor with an aggressive biological behavior characterized by metastatic spread to the lungs and peritoneum. The prognosis of patients treated with surgical resection (partial hepatectomy) and adjuvant chemotherapy is generally favorable (5-year overall survival > 70%) [1,55,56,74-77]. Tu-

Table II. Main differential diagnoses of embryonal sarcoma of the liver.

Tumor type/subtype	Age of presentation	Histopathologic features	Immunohistochemical features
Embrional sarcoma of the liver	6-10 years	Sheets of pleomorphic spindle, oval to stellate cells set in a fibro-myxoid stroma High mitotic activity Atypical mitoses Hyaline globules	Not specific Vimentin, CD68, CD56, BCL2, CD10, a-1-antitrypsin, cytokeratins and Glypican-3
Mesenchymal hamartoma	< 2 years	Myxomatous stroma with branching bile ducts and entrapped hepatocytes arranged into a lobular architecture	Not useful
Hepatoblastoma	Mean age: 19 months	Different subtypes resembling the different stages of liver development	β-catenin (nuclear and membranous staining) Glypican-3 and glutamine synthetase
Embryonal rhabdomyosarcoma of the biliary tract	< 5 years	Small round blue cell tumor	Desmin, Myogenin and Myo-D1
Sarcomatoid hepatocellular carcinoma	Adults	Thickened trabeculae with pleomorphic spindle cells Mallory hyaline bodies	Hep Par-1, Glypican-3, a-FP, arginase, CD10 (canalicular) and pCEA (canalicular)
Metastatic gastro-intestinal stromal tumor	Adults	Spindle cells with eosinophilic cytoplasm	CD117 (c-kit), DOG-1 and CD34
Malignant melanoma	Adults	Highly pleomorphic spindle and/or epithelioid neoplastic cells Melanin pigment High mitotic activity	S100, Melan-A, HMB-45 and SOX-10

mor size > 15 cm and extrahepatic dissemination at the diagnosis are negative prognostic indicators [74-77]. Neoadjuvant chemotherapy followed by surgery is reserved to the patients with unresectable tumors, while liver transplantation is a possibility for patients who are resistant to neoadjuvant chemotherapy [74-77].

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