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PRIMARY AND METASTATIC MALIGNANT TUMORS OF THE LIVER

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ABSTRACT
The liver represents the most common localization of primary and metastatic hepatic tumors. This paper aims to review hepatic premalignant lesions and the histopathological classification of malignant tumors of the liver, describing the main growth patterns, citoarchitectural features and immunohistochemical profile of epithelial and mesenchymal hepatic tumors. Clinical aspects, differential diagnosis criteria and developmental-prognostic behavior are discussed.
Key words: hepatic tumors, hepatocellular carcinoma, immunohistochemisty, Hep Par-1, α-fetoprotein.

Hepatic localization of malignant neoplasms, both secondary and primary is common, metastases in the liver being more frequently found than primary malignant tumors.

A. PRIMARY EPITHELIAL TUMORS

1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), a common neoplasm worldwide with an incidence of one million new cases per year, is more frequently found in Asia and Central Africa, with a decreased frequency in North America and Europe. The most important risk factors are viral infections with B and C viruses, hemochromatosis, cirrhosis, alcoholic liver disease, as well as a variety of drugs and toxins (Anthony P.P., 2002); HCC is rarely associated with metabolic disorders or other liver diseases.

The viral DNA of hepatitis B integrated into the host genome is considered to be decisive in initiating liver carcinogenesis. Repeated and persistent infection followed by inflammation and regeneration triggers a cascade of events in the process of carcinogenesis (De Souza A., 1997). HCV infection is also associated with a high incidence of HCC. HCV is an RNA virus with a different replication than that of HBV; it is not integrated into the host genome, the mechanism of hepatocarcinogenesis being probably different.

Clinical features

Clinical manifestations of HCC are varied and nonspecific, including abdominal pain, weight loss, and with progression of the disease, hepatomegaly, jaundice and signs of obstruction of the bile ducts. Abnormal but nonspecific liver tests often reflect a liver disease. Although not entirely specific, high serum values of α-fetoprotein (AFP) indicate the appearance of HCC. Even if imaging techniques can show early lesions, HCCs ≤ 1.5 cm often remain undetected. Large tumors have a poor prognosis, while the fibrolamellar variant of HCC may have a somewhat better prognosis (Stuart K.E., 1996).

HCC can be solitary or multinodular, in the latter case the multicentric origin of the tumor versus intrahepatic metastases being discussed. About 90% of HCCs are developed in a liver with underlying hepatic cirrhosis (especially in areas with a higher incidence), these neoplasms being also found in noncirrhotic liver.

HCC has a predilection for intravascular dissemination, most frequently for the portal vein system. Hepatic veins can also be involved, with obstruction of venous out-flow (Budd-Chiari syndrome). The tumor can extend towards the inferior vena cava, the right atrium, associating even esophageal and gastric varices (Anthony P.P., 2002). Invasion of bile ducts can determin hemobilia or symptoms related with obstruction of large bile ducts. Invasion of adjacent organs, such as stomach and duodenum, can also be possible. Rarely, HCC can go through a spontaneous regression.

Histopathological classification

Although numerous criteria of classification have been proposed, the revised WHO classification (Table 1) is widely accepted, emphasizing the importance of architectural and cytologic features (International Working Party, 1995).

TABLE 1. ***Hepatic primary epithelial tumors (revised WHO classification)***

1. Hepatocellular carcinoma
2. Hepatoblastoma
3. Cholangiocarcinoma
4. Mixed hepatocholangiocarcinoma
5. Hepatobiliary cystadenocarcinoma

The histopathological classification shows several *architectural patterns*:

- *The trabecular or sinusoidal pattern* (Fig. 1) is the most common pattern, made up of thickened liver trabeculae, sometimes as thick as 15-20

cells separated by sinusoids that maintain the endothelial lining cells (Ishak K.G., 1994). The endothelial cells cand be identified using IHC markers such as factor VIII, CD31 and CD34 (Fig. 11). Solid areas, necrosis foci and Kupffer cells in reduced numbers can be present.

- *Acinar or pseudoglandular pattern* – with glandlike structures formed by hepatocytes that contain fibrin, bile, and even histiocytes. The bile that can be seen in the cytoplasm of tumor cells is pathognomonic, being observed more frequently in the acinar variant. Many HCCs can have a mixed pattern, with both trabecular and acinar areas (Fig. 2).
- *The solid, compact, or pelioid pattern* (Fig. 3, 4) – made up of hepatocyte trabeculae of several cells thick, often compressed, giving the impression of a solid neoplasm. Sometimes large pseudovascular spaces full with blood, similar to those of peliosis hepatis can be observed. The rupture of these tumors can cause hemoperitoneum.

Histologic variants of HCC (Table 2)

Many well-differentiated HCCs can be formed by hepatocytes with a quite normal aspect and minimal cytologic atypia: polygonal shaped cells with eosinophilic finely granular cytoplasm, with round but atypical, enlarged and hyperchromatic nuclei, irregular nuclear contour chromatin. Nuclei of dysplastic cells often show cytologic atypia (prominent eosinophilic nucleoli) more expressed than in the nuclei of well-differentiated HCC.

TABLE 2. *Histologic variants of hepatocellular carcinoma*

1. HCC the classic type
2. Sclerosing HCC
3. Clear cell HCC
4. Spindle cell (sarcomatoid) HCC
5. Pleomorphic HCC (anaplastic, giant cell)
6. Fibrolamellar HCC

a) Hepatocellular carcinoma the classic type can be made up of cells similar to nonneoplastic hepatocytes, arranged in trabeculae of several cells thick, with a slightly basophilic cytoplasm and variable degrees of nuclear pleomorphism. Tumor cells can contain a variety of intracytoplasmic inclusions: Mallory-like material, fibrinogen, albumin, pale bodies, megamitochondria, intranuclear eosinophilic pseudoinclusions (representing intranuclear focal invaginations of the cytoplasm). The presence of mucin (unusual in HCC) should suggest a cholangiocarcinoma or a metastatic adenocarcinoma. In spite of the association between HCC and HBV infection, viral antigens are rarely demonstrated in tumor cells (Subramony C., 1993).

The differential diagnosis of classic HCC is made with macroregenerative nodules (MRNs), hepatocellular adenoma (HA), cholangiocarcinoma (CC) and hepatoblastoma.

Distinguishing between HCC and MRNs with liver cell dysplasia can be difficult. In well-differentiated HCC, liver cells can have an aspect similar to benign hepatocytes, while dysnplastic hepatocytes often show marked cytologic atypia. Both lesions can have a similar architectural pattern, but hepatocyte trabeculae are usually thicker in HCC. On hepatic biopsy the differential diagnosis can be extremely difficult, sections colored with silver impregnation that emphasize attenuation or even disappearance of the reticulin network in the majority of HCC being needed.

Similar diagnostic difficulties can also be found in differentiation between HCC and HA. While the majority of HCC develop on underlying cirrhosis, HA appears in the absence of cirrhosis, like a tumor with solid architecture (sometimes with focal acinar patter) and keeping the reticulin network, but without significant cytologic atypia.

Differentiation between acinar HCC and CC can also be difficult, especially on hepatic biopsies (Lau S., 2002). The presence of intracytoplasmic mucin pleads for a CC, while intracytoplasmic bile suggests a HCC. Desmoplasia is more evident in CC, but is not always helpful, being also found in sclerosing HCC.

b) Sclerosing hepatocellular carcinoma

The sclerosing variant of HCC shows a trabecular, acinar, or mixed (trabecular-acinar) architectural pattern, with malignant hepatocytes embedded in fibrous, abundant, relatively dense, hypocellular stroma (Fig. 5). The tumor, seen more frequently in elderly patients, is often associated with hypercalcemia (Anthony P.P., 2002).

Differentiation between the sclerosing variant of fibrolamellar HCC, cholangiocarcinoma and metastatic adenocarcinoma can be difficult. Large, polygonal hepatocytes, with eosinophilic cytoplasm and the presence of a large number of pale intracitoplasmic bodies, disposed in a fibrous stroma of lamellar aspect, as well as a higher incidence in younger patients plead for fibrolamellar HCC.

Metastatic adenocarcinomas (arising in the pancreas and biliary tree) can also have a significant desmoplastic stroma, but not as abundant as in sclerosing HCC. Immunohistochemical reactions can be useful for a correct diagnosis.

c) Clear cell hepatocellular carcinoma (Fig. 6) is made up of tumor cells with clear cytoplasm, abundant in glycogen, alternating with tumor cells resembling nonneoplastic hepatocytes. Often, the tumor can be associated with hypoglycemia and can have a somewhat better prognosis. It is difficult to differentiate this tumor from a hepatic metastasis of clear cell renal carcinoma,

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but the association of cirrhosis as well as the negative immunoreaction for vimentin (characteristic of renal carcinomas) and the presence of bile in tumor cells favor a primary hepatic tumor (Craig J.R., 1989).

d) Spindle cell (sarcomatoid) hepatocellular carcinoma

The sarcomatoid variant (spindle cell) of HCC is a rare tumor consisting of spindle cells arranged in fascicles or in an organoid pattern, often presenting multinucleated giant cells (Haratake J., 1991). Differentiation from true sarcomas (leiomyosarcomas and fibrosarcomas) can be difficult, positive expression for vimentin suggesting a mesenchymal tumor.

e) Pleomorphic (anaplastic, giant cell) hepatocellular carcinoma (Fig. 7) is the most rare variant of HCC, composed of tumor cells with bizarre nuclear features and aspects of multinucleation, arranged in solid sheets (Hood D.L., 1990).

f) Fibrolamellar hepatocellular carcinoma – a tumor with incompletly known pathogenesis and a generally better prognosis, is more frequently found in younger adults (affecting both sexes equally), being developped in the absence of cirrhosis (LeBrun D.P., 1991).

It is composed of tumor cells with abundant eosinophilic granular cytoplasm (oncocytic type) arranged in sheets separated by a pale, paucicellular, fibrous stroma of lamellar aspect, offering a characteristic microscopic appearance to the tumor. Tumor cells can contain bile, pale bodies (immunoreactive for fibrinogen), eosinophilic intracytoplasmic globules (composed of C reactive protein, fibrinogen and α_1-antitrypsin), copper and copper-binding protein (present in most cases).

Histologic grading of hepatocellular carcinoma has not proven useful in appreciating the prognosis. Edmondson and Steiner proposed four grades of HCC. Most HCCs are grade II and III; well-differentiated HCC (grade I) may be difficult to distinguish from hepatocellular adenomas or macroregenerative nodules with dysplasia and grade IV tumors are hardly distinguished from undifferentiated adenocarcinomas with other primary localization.

Immunohistochemistry

Specific and reliable immunohistochemical markers for HCC are not known.

Hepatic α-fetoprotein (AFP) can be demonstrable in 10%-50% of HCCs (Fig. 10). While hepatocytes (benign and malignant) show strong immunoreactivity for low molecular weight keratins (CAM 5.2, CK8) but not for high molecular weight keratins (CK7, CK19), cholangiocarcinoma can be positive for both types of markers (Ma C.K., 1993).

α1-antitrypsin (α_1-AT), α_1-antichemotripsin (α_1-ACT), polyclonal carcinoembrionic antigen (that reacts with biliary canaliculae) and Hep Par-1 (Fig. 9) can be useful in establishing the diagnosis of HCC (Ljubimova J.Y., 1997).

HCCs with neuroendocrine differentiation are immunoreactive for neuroendocrine markers such as chromogranin and synaptophysin (Subramony C., 1993); tumor cells can also be positive for estrogen and progesterone receptors, as well as for human chorionic gonadotropin.

Proliferation markers, such as proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1) (Fig. 12), may be useful in assessing the proliferation rate of tumor cells, but are not useful in establishing the diagnosis (Ojanguren I., 1993).

Flow cytometry and morphometric studies led to contradictory results. *Image analysis* can be useful in differentiating between dysplasia, well-differentiated and poorly differentiated HCCs, *electron microscopy* being rarely used in routine practice (An C., 1997).

Molecular biology studies showed significant differences in the expression of various oncogenes in nonneoplastic liver and HCC, including hepatocyte growth factor (HGF) and its receptors, c-met and c-myc. HGF RNA is not expressed in normal or cirrhotic liver tissue, but it is present in HA and HCC. C-met was also elevated in HA and HCC, as compared to normal liver, and the expression of HGF and c-met was associated with higher expression of c-myc protooncogene. The role of a stem cell in regeneration and carcinogenesis is still obscure. Computer-assisted imaging system can be useful in differentiating hepatocellular large cell dysplasia from HCC (Ljubimova J.Y., 1997).

2. Premalignant lesions

Liver cell dysplasia

Liver cell dysplasia was described for the first time 20 years ago in cirrhotic nodules under the form of atypical hepatocytes, being considered a preneoplstic lesion and defined as large cell and small cell dysplasia. Because the significance and premalignant potential of these lesions remain controversial, it was recommended to replace the term of dysplasia with large cell and small cell change (Wanless I., 1995).

Large cell change is characterized by large hepatocytes with enlarged hyperchromatic nuclei and prominent nucleoli, with aspects of multinucleation, but with normal nucleus to cytoplasm ratio and often with intranuclear inclusions. Although large cell change was predominantly associated with HCC, it is frequently found in cirrhotic liver (after a chronic infection with HBV or HCV), being considered a premalignant process. As compared to HCC, large cell change is characterized by a normal nucleus to cytoplasm ratio, the absence of mitoses, low proliferation rate and the absence of p53 mutations. A recent study states that the predictive value of large cell change for HCC is <20%; but it can represent a regenerative or degenerative phenomenon, or it reflects a response to prolonged liver cholestasis (Natarajan S., 1997).

Small cell change (more rarely found) is characterized by hepatocytes smaller than the normal ones, with increased nucleus to cytoplasm ratio and nuclear hyperchromasia, high proliferative activity and overexpression of p53 protein. When it appears in small foci it can be associated with HCC, more frequently than large cell change. Diffuse or poorly defined areas of small cell change, without nodular configuration, can represent a regenerative process or they can appear in chronic biliary lesions, probably not being neoplastic (Su Q., 1997).

The term of dysplasia is used to describe a population of cells with abnormal histologic features caused by supposed genetic alterations, but without any sure criteria of malignancy (Wanless I., 1995).

Because the genetic alterations are not established, the diagnosis and classification of dysplasia is based upon the topography and morphologic features of abnormal cell nests: the nests with dysplastic hepatocytes of <1mm in diameter are named dysplastic foci, and the ones over 1 mm- dysplastic nodules, that are classified on the basis of cytological features in low and high grade dysplastic nodules.

Displastic foci can be seen in chronic hepatitis with HBV and HCV, in α_1-antitripsin deficit and tyrosinemia (Ishak K.G., 2001). These foci have distinct but irregular margins and are made up of usually uniform cells that are different from the surrounding hepatocytes by the spectrum of nuclear atypia (variable from minimum to severe), cytoplasmic stain and the content of fats or glycogen.

It is considered that ***low grade displastic nodules (DN)*** from cirrhotic liver represent a clone proliferation of hepatocytes, with clinical and pathological features similar to macroregenerative nodules (MRN). Low grade DNs are made up of a more uniform population of hepatocytes, without specific morphologic features. In the absence of clone studies, the terms of MRN and low grade DN are used to describe the nodules without cytological or architectural features of high grade dysplasia.

High grade displastic nodules (DN), also known as borderline nodules, type II MRN, atypical MRNs and atypical adenomatous hyperplasia can appear almost always in a cirrhotic liver. Serum AFP is normal or in the limits found in chronic hepatic disease or cirrhosis. In the case of these lesions considered premalignant processes, surgical excision is recommended (Ferrell L., 1994).

Macroscopically, high grade DNs have an aspect similar to MRNs and low grade DNs, but with an irregular, poorly circumscribed outline.

Microscopically, dysplastic changes can be present uniformly in the nodule or as foci. Usually the nodule is recognized through the areas with small cell change with increased nucleus to cytoplasm ratio and nuclear density (estimated number of hepatocyte nuclei/microscopic field), as compared to normal liver (Ferrell L., 1993). Large cell change is rarely a feature of high grade DN, but when it is present, the focus consists of an area with atypical cells and not under the form of dispersed nuclei in the nodule.

Other features commonly found in high grade DN include: focal hepatocyte trabeculae 3 cells thick, zonal reduction of the reticulin network, slight dilatation of sinusoids and sometimes areas with acinar (pseudoglandular) architecture, Mallory bodies, steatosis, clear cell changes, basophilic cytoplasm, bile, the presence of portal spaces and the absence of iron deposits (these being common in low grade DN or in MRN).

Differentiation between high grade DN and HCC is based on the presence of trabeculae ≥3 cells thick, moderate mitotic activity, nuclear density twice higher than normal, the collapse of reticulin network, numerous arteries and the absence of portal spaces – features that confirm the diagnosis of HCC.

3. Hepatoblastoma

Hepatoblastoma is a primary hepatic tumor that affects especially male children under the age of 3 years old and appears rarely in adults. The tumor was associated with congenital anomalies such as Down syndrome, Beckwith-Wiedemann syndrome, nephroblastoma, the absence of right adrenal gland, fetal hydrops, Meckel diverticulum and umbilical hernia, familial cases being rarely described. Clinic, it presents as an abdominal tumor mass with rapid growth, invading surrounding tissues and organs, being associated with high serum AFP values (Koneru B., 1991).

Histopathologically, the tumor comprises irregular tumor nodules (with epithelial and mesenchym al components) separated by thin fibrous strands, resembling a cirrhotic liver.

- *Epithelial* hepatoblastoma is made up of elongated or spindle *embryonal* cells, arranged in cords or forming rosette-like structures and *fetal* cells that resemble fetal hepatocytes arranged in two or three-cell-thick cords; the fetal cells contain variable amounts of glycogen and neutral fat; extramedullary hematopoiesis foci can be observed. Some hepatoblastomas (with macrotrabecular growth pattern) are similar to HCC and have a poorer prognosis (Wakely P.E., 1990).
- *Mixed epithelial-mesenchymal* hepatoblastoma has, in addition to the epithelial component, mesenchymal tissue composed of fibroblasts, collagen fibers and osteoid formation, sometimes these tumors being described as *teratoid* hepatoblastomas.
- *Anaplastic* hepatoblastoma is composed of small, undifferentiated cells with reduced cytoplasm and hyperchromatic nuclei, having a worse prognosis than that of other types (Goldstein R.M., 1993).
- Combined hepatoblastomas and Yolk sac tumor have also been described (Cross S.S., 1992).

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Immunohistochemically, hepatoblastoma shows positive expression for high and low molecular weight keratins, CAM 5.2 and AE 1/3, for AFP, S-100 protein and vimentin (especially hepatoblastomas with embryonal spindle cells).

Hepatoblastomas with neuroendocrine differentiation that are positive for chromogranin and neuron-specific enolase (NSE), as well as tumors that secrete human chorionic gonadotropin (demonstrable on tissue sections), or hepatoblastomas that contain melanin have been described (Ruck P., 1993).

The prognosis is not favorable, sometimes patients present with distant metatatses (in lungs, brain, or bone marrow) when diagnosed. After liver transplantation, survival is generally better in hepatoblastoma than in HCC (Koneru B., 1991). Hepatoblastomas with fetal pattern can respond to therapy.

4. Cholangiocarcinoma

Cholangiocarcinoma (CC) is an adenocarcinoma with origin in bile ducts with intrahepatic (peripheral), hilar (Klatskin tumor), or extrahepatic localization. Usually, it is a solitary tumor that develops in the absence of cirrhosis, in patients with ages between 50-70 years, affecting both sexes equally. Factors associated with CC include primary sclerosing cholangitis, parasite infestation (oriental), congenital biliary cysts (including Caroli disease and choledochal cyst) and exposure to thorium dioxide (Thorotrast) (Ruiz J., 1992).

Peripheral CC – the most common form, it affects small intrahepatic bile ducts; clinic symptoms manifest late, when the tumor has unresectable significant dimensions.

The *hilar* variant of CC associates incipient clinic manifestations, patients presenting jaundice and symptoms of bile duct obstruction.

Extrahepatic CC can have its origin between the hepatic duct and ampulla of Vater. The hilar and extrahepatic variants affect predominantly men in the sixth and seventh decades of life.

Histopathologically, CC is a tumor with glandular architecture (and sometimes papillary or solid), with marked desmoplastic stromal reaction. The tumor is composed of columnar or cuboidal cells with mildly basophilic cytoplasm (with or without intracytoplsmic mucin), round or ovoid nuclei and indistinct nucleoli.

CCs are tumors with variable degrees of differentiation: the poorly differentiated and usually the papillary variant presents a signet ring component; tumors with focal squamous differentiation were also described (with features of mucoepidermoid or adenosquamous carcinoma).

The tumor infiltrates portal spaces and invades periportal sinusoids, it leads to metastases in regional lymph nodes (already present at the time of diagnosis) and distant metastases in lungs and peritoneal surface.

CC may be impossible to distinguish from adenocarcinoma originating from pancreas or the extrahepatic biliary tree, and sometimes from HCC with acinar architecture. Positive IHC reactions for epithelial membrane antigen (EMA), high molecular weight keratins, CEA, blood group antigens, tissue polypeptide antigens and carbohydrate antigen CA 19-9 support the diagnosis of cholangiocarcinoma (Lau S., 2002).

5. Mixed cholangiohepatocellular carcinoma

Mixed cholangiohepatocellular carcinoma is a rare tumor that associates histological features of HCC and CC and elevated serum AFP values. The diagnosis needs immunohistochemical and electronic microscopy investigations.

6. Hepatoid tumor

Hepatoid tumors represent a separate group of malignant HCC-like neoplasias that produce AFP. This kind of tumors was described in the ovary, stomach, gallbladder, pancreas, lung, kidney and endometrium (Gardiner G.W., 1992).

7. Hepatobiliary mucinous cystadenocarcinoma

Hepatobiliary mucinous cystadenocarcinoma with mesenchymal stroma (similar to ovarian tumor) is a rare malignant tumor that occurs almost exclusively in women. It develops in the setting of congenital hepatic fibrosis, choledochal cyst or of a pre-existing hepatobiliary cystadenoma. It can also arise from ectopic rests of duct epithelium or gallbladder.

Histopathologically, it is a multilocular cystic tumor with cystic cavities lined with columnar or simple cuboidal epithelium, with or without mucin secretion, separated by a distinctive mesenchymal stroma composed of spindle cells (resembling ovarian stroma or fetal mesenchyme).

The tumor expresses hormonal receptors for estrogen and progesterone. It is a less aggressive tumor and the hepatic resection in incipient stages can be curative. The differential diagnosis is made with CC and CC with hepatic cysts (Weihing R.R., 1997).

B. NON-EPITHELIAL PRIMARY MALIGNANT TUMORS

1. Angiosarcoma

Angiosarcoma is the most common primary malignant mesenchymal neoplasm of the liver that appears more frequently in males, in parallel with increasing age. Long-term exposure to vinyl chloride, thorium dioxide, arsenic and steroids are known risk factors; associations with alcoholic cirrhosis and hemochromatosis were also described (Rojter S.E., 1995).

On hepatic biopsy, the diagnosis can be difficult and differentiation from epithelioid hemangioendothelioma almost impossible. While angiosarcoma has an

unfavorable prognosis, hemangioendothelioma can be treated by transplantation. Four distinct growth patterns were described: diffuse micronodular, diffuse multinodular, massive and mixed, as well as several histopathological patterns often combined:

- The *sinusoidal or cavernous* pattern is made up of sinusoid-like or dilated vascular spaces lined by enlarged malignant spindle epithelial cells, with irregular hyperchromatic nuclei and often with bizarre nuclear features. Tumor cells are positive for endothelial markers: factor VIII, Ulex Europeaus, CD31, and CD34.
- Tumors with *solid* pattern of growth are composed of spindle cells without obvious vascular spaces, the differential diagnosis being problematic; less differentiated tumors show weak immunoreactivity for specific endothelial markers.

The differential diagnosis is made with other sarcomas, especially on biopsy material.

TABLE 3. *Non-epithelial primary malignant tumors of the liver*

1. Angiosarcoma
2. Epithelioid hemangioendothelioma
3. Kaposi sarcoma
4. Lymphomas
5. Histiocytosis X
6. Other

2. Epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a relatively rare malignant vascular tumor, generally with intermediate or low malignancy grade, females being affected twice as often as males, anytime between the second and the seventh decade of life. Usually it is a slow growing tumor, patients accusing abdominal pain, malaise, weight loss, jaundice and sometimes Budd-Chiari syndrome. The tumor is multinodular, often with confluent nodules, giving the impression of one massive nodule.

Histopathologically, two patterns are recognized and described:

- A *dendritic* pattern with stellate and spindle cells included in a dense and myxoid fibrous stroma, with vacuolation of tumor cells (representing lumens of primitive vessels), sometimes presenting a glandular appearance. IHC, tumor cells are positive for factor VIII, Ulex, CD31, and CD34, ultrastructurally presenting endothelial differentiation, tight junctions, pinocytotic vesicles and Weibel-Palade bodies in approximately 30% of cases.
- The *epithelioid* pattern is composed of large atypical cells with abundant cytoplasm, arranged in solid areas and surrounded by inflammatory infiltrate with lymphocytes, polymorphonuclear and eosinophilic leukocytes. EHE has a propensity for vascular dissemination, often mimicking venoocclusive disease.

The differential diagnosis includes other vascular tumors (angiosarcoma, Kaposi sarcoma, bacillary angiomatosis), as well as non-neoplastic lesions (venoocclusive disease).

3. Kaposi Sarcoma

Kaposi sarcoma is a neoplastic proliferation of endothelial cells, most likely of lymphatic origin, appearing as hemorrhagic, well defined hepatic. Patients with hepatic Kaposi sarcoma are almost always seropositive for HIV, being in an advanced stage of AIDS, with multiple lesions in several regions of the body.

Histopathologically, it is made up of spindle tumor cells, often with intracytoplasmic inclusions (probably representing phagocytosed erythrocytes), with a relatively normal aspect of the nuclei, without significant cytologic atypia or an expressed mitotic activity. In addition, vascular spaces without endothelial lining, containing extravasated red blood cells, hemosiderin-laden macrophages and lymphocytes can be observed. IHC stains for endothelial markers (factor VIII, CD31 and CD34) are rarely positive.

The differential diagnosis is made with angiosarcoma.

Bacillary angiomatosis occurs similar to Kaposi sarcoma, in patients with AIDS and is caused by *Bartonella quintana/henselae*, which can be demonstrated ultrastucturally with Warthin-Starry stain or by polymerase chain reaction (Leboit P.E., 1989)

C. LYMPHOPROLIFERATIVE LESIONS OF THE LIVER

The liver can be secondarily involved in leukemias and lymphomas (Hodgkin and non-Hodgkin) (Marcelin A.G., 2004).

Involvement of the liver in *leukemia* shows a diffuse pattern with infiltration of the sinusoids with leukemic cells, excepting lymphocytic chronic and lymfoblastic acute leukemia that involve often portal spaces, similar to the infiltration pattern from lymphomas. Leukemia with hairy cells can be associated with formation of lesions such as hepatic peliosis, with dilated sinusoids surrounded by tumor cells.

Liver involvement in *Hodgkin lymphoma* appears like nodular masses in portal spaces. Although the certitude of diagnosis is given by Steinberg-Reed cells, the presence of cell infiltrate composed of lymphocytes, plasma cells, eosinophilic cells and numerous atypic cells is enough to establish the diagnosis of Hodgkin lymphoma, if this was confirmed in another primary localization. Occasionally, epithelioid granulomas can be observed in the parenchyma or portal spaces, but their

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presence without other features previously described is insufficient for the diagnosis. Rarely, intrahepatic cholestasis can be observed, occasionally associated with biliary duct loss.

Non-Hodgkin lymphoma involves the liver in the context of disseminated disease, with formation of nodular masses in portal spaces. In some lymphomas sinusoid infiltration with tumor cells can be observed, aspects similar with those of leukemia. The liver is involved especially in periferic lymphomas with T cells (in about 50%) of patients. Also, epithelioid granulomas and intrahepatic cholestasis can be noted, similar to Hodgkin lymphoma (Scheimberg I., 1995).

Primary hepatic lymphomas are rare (0,4% of extranodal lymphomas), presenting as single or multiple masses, rarely with diffuse infiltration of the liver. The majority are diffuse lymphomas with type B big cells, sometimes can be Burkitt lymphomas and low grade lymphomas with B cells, MALT type. Associations with AIDS, hepatitis B and C, autoimmune disease, primary biliary cirrhosis and antisupressive therapy were described (Page R.D., 2001).

Hepatosplenic lymphoma with T cells with origin in gamma delta citotoxic T lymphocytes involves the liver with sinusoid and portal space infiltration, the spleen and bone marrow being affected at the same time. These tumors are very aggressive, with a mean survival of 1 year (Santos E.S., 2003).

D. THE LIVER IN HISTIOCYTOSIS X

Histiocytosis X is a term used to define the spectrum of three diseases: Hand-Schüller-Christian, Letterer-Siwe and eosinophilic granuloma of the bone. Rarely, patients show clinical manifestations similar to sclerosing cholangitis, with jaundice and portal hypertension.

Hepatic biopsy shows: (1) cellular infiltrate composed of many eosinophilic leukocytes and S-100-positive Langerhans-type cells (containing Birbeck granules), present in portal spaces, with a tendency to intralobular extension and (2) interlobular bile ducts with epithelial changes similar to those of primary sclerosing cholangitis and small bile duct proliferation (Pirovino M., 1988).

E. OTHER RARE MALIGNANT TUMORS

Other rare malignant hepatic tumors include: (1) primary malignant neuroendocrine tumors (gastrinoma and hepatic apudoma) described rarely in the liver and in the biliary tree; (2) ectopic hepatic cell carcinoma from the abdominal cavity; (3) primary hepatic malignant melanoma, also undifferentiated sarcoma (embryonal, mesenchymal), choriocarcinoma, endodermal sinus tumor, adrenal or pancreatic rest tumor, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, osteosarcoma, liposarcoma, malignant schwannoma, hemangiopericytoma, malignant fibrous histiocytoma and squamous cell carcinoma (Alonso J.F., 1992).

F. METASTATIC TUMORS

The liver represents a common, special site for numerous metastatic neoplastic processes and almost any tumor can give metastases in the liver (Fig. 8). Hepatic biopsies are often performed to determine if a hepatic tumor mass is primary or secondary. Fine-needle aspiration of the liver is generally not useful in the diagnosis of liver diseases, but being necessary in tumor diagnosis. Immunohistochemical studies are also useful (Kondo Y., 1991).

G. CHANGES ASSOCIATED WITH MASS LESIONS

In hepatic parenchyma adjacent to a neoplastic or non-neoplastic lesion (mass) typical changes can be highlighted, such as: bile duct proliferation with periductal inflammatory infiltrate with polimorphonuclear leukocytes, dilated sinusoids and cholestasis.

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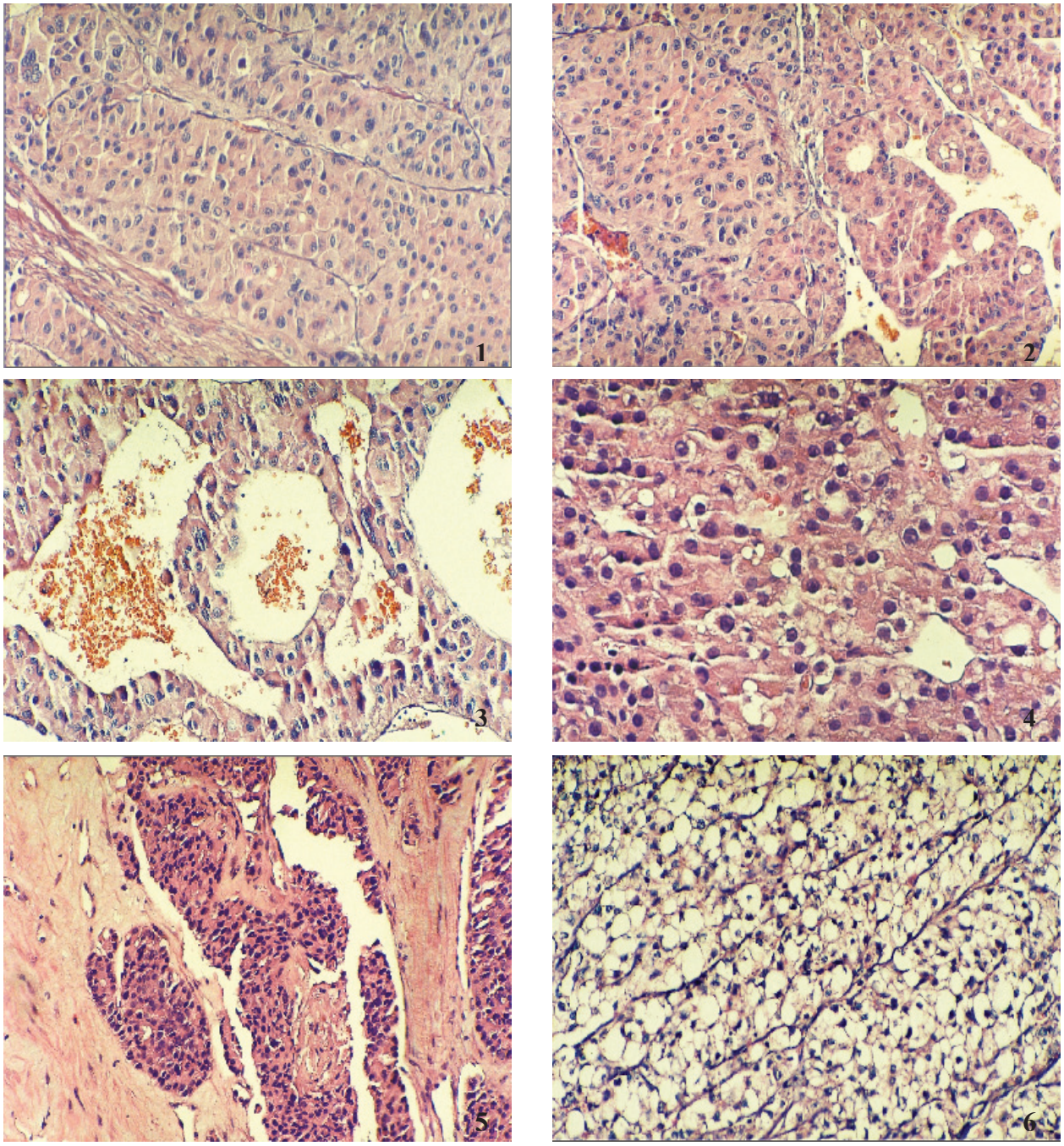
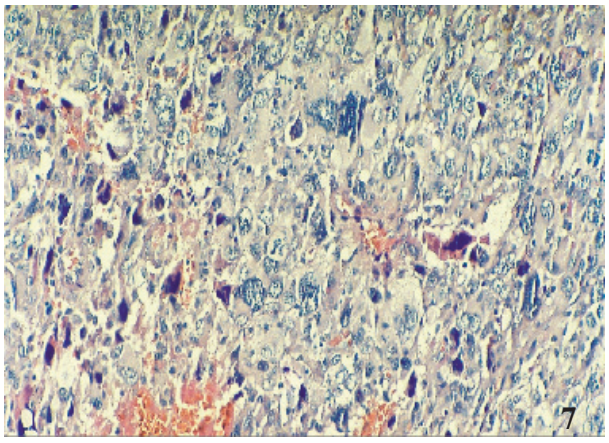
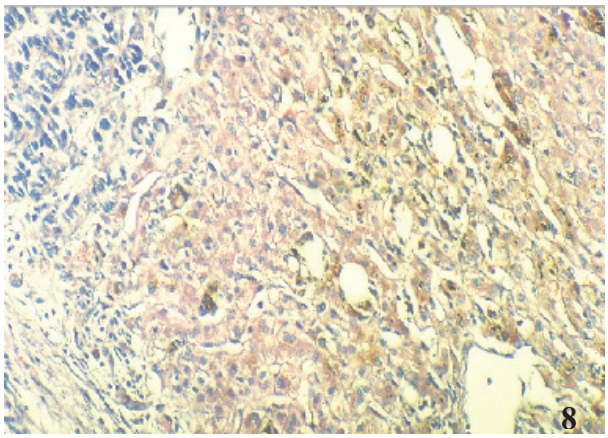
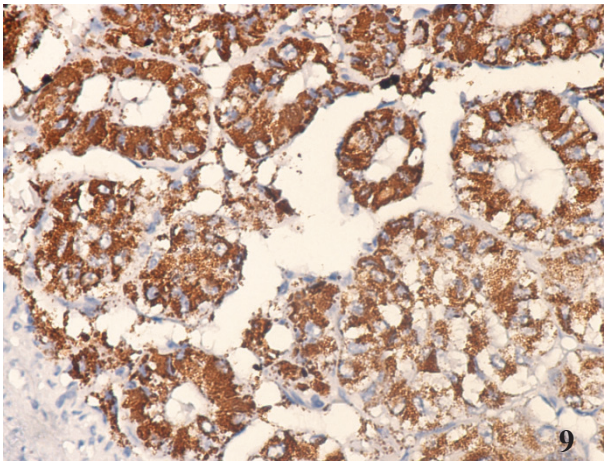
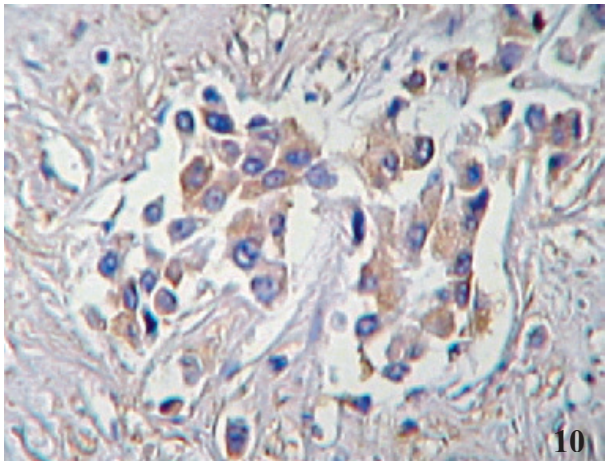


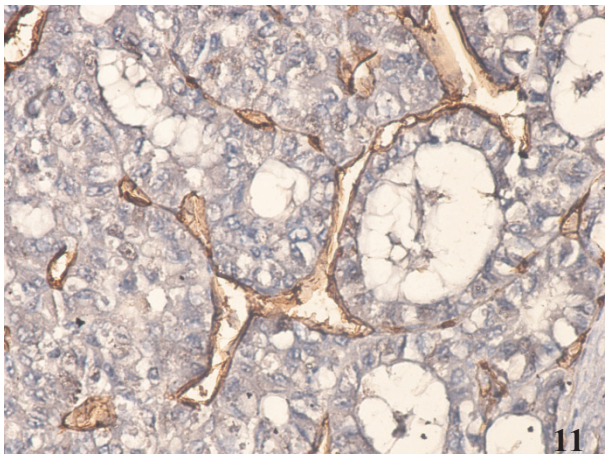
Fig. 1. HCC with trabecular pattern. HE; **Fig. 2.** HCC with mixed pattern (trabecular and acinar). HE; **Fig. 3.** HCC with peliosis-type pseudovascular spaces. HE; **Fig. 4.** HCC with solid, compact pattern. HE; **Fig. 5.** HCC sclerosing type. HE; **Fig. 6.** HCC clear cell type. HE











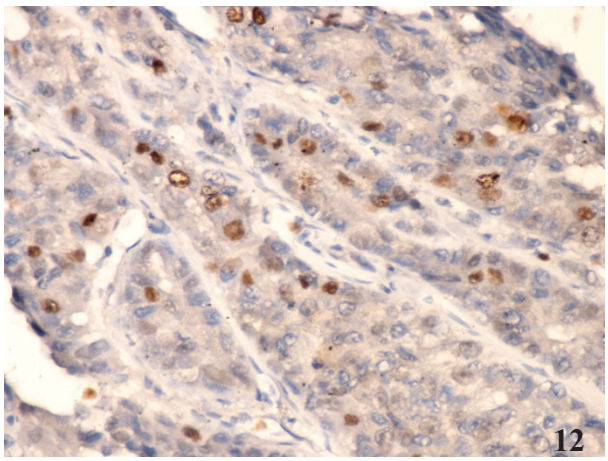


Fig. 7. Anaplastic HCC. HE; **Fig. 8.** Hepatic metastasis of a lung carcinoma with small cells. HE ; **Fig. 9.** Hep Par-1 in acinar HCC. EnVision; **Fig. 10.** HCC positive for α-fetoprotein. Peroxidase LSAB ; **Fig. 11.** CD34 expression in acinar HCC. Peroxidase LSAB ; **Fig. 12.** Ki-67 in trabecular HCC. Peroxidase LSAB.