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Focal lesions in the liver - differential diagnosis

In recent years the number of patients with US-detected focal lesions has been increasing. This is not only due to higher incidence of hepatic structural changes but also higher availability of good quality ultrasonography. However, the ultrasound examiner often cannot assess explicitly the detected focus without clinical data. To obtain a full picture, the data concerning medical history, physical examination, laboratory tests and characteristic radiological features of an individual change are needed.

The aim of the study was to collect clinical, radiological and histopathological data typical of various focal lesions in order to distinguish those which are clinically important and to determine proper further management.

The whole diagnostic process requires strict cooperation among physicians of different specialties: gastroenterologists, radiologists, histopathologists and surgeons. The correctness of diagnosis often depends on the quality of this cooperation and data sharing.

The notion of focal lesion is a radiological term. It denotes the presence of abnormal hepatic structure detected at US. Such changes are mostly detected incidentally; in some situations, however, examinations are intended to search for focal lesions. A great difficulty is the fact that small focal lesions, even malignant ones, are asymptomatic. On the other hand, symptoms frequently depend not only on the lesion nature but also its size and location. Moreover, the number of lesions is not significantly important as the majority may occur as a single lesion or multiple lesions. The clinical classification of focal lesions is presented in Table 1 (1).

Table 1. Classification of focal lesions

Benign epithelial tumours	Hepatocellular adenoma Bile duct adenoma Biliary cystadenoma
Benign non-epithelial tumours	Hemangioma Lipoma Angiomyolipoma Hamartoma
Malignant epithelial tumours	Metastases Hepatocellular carcinoma Cholangiocellular carcinoma Hepatoblastoma Biliary cystadenocarcinoma
Malignant non-epithelial tumours	Metastases Lymphomas Hemangioendothelioma
Other	Cysts Abscesses (pyogenic, amoebic) Focal nodular hyperplasia Focal fatty infiltration

The following diagnostic methods are used to diagnose, locate and evaluate the nature of the focal lesion (2, 4): 1) ultrasonography (USG), 2) computed tomography (CT) with two- and three-phase techniques, 3) vascular examinations, 4) hepatic scintigraphy, 5) hepatic biopsy, 6) endoscopic retrograde cholangiopancreatography. The most common foci observed in the liver are benign lesions. Two of them – adenoma and focal nodular hyperplasia occur as single lesions in the majority of cases (about 80%).

ADENOMA

It originates from the hepatic cells and its incidence is nine times higher in women than in men. The risk factors of adenoma include oral contraceptives and anabolic steroids. The US examination visualizes it as a big, well-separated from the remaining parenchyma and highly vascularized tumour. A hypoechogenic ring is likely to be present around the focus. At CT, adenoma is a hypodense tumour whose internal structure is often irregular (haemorrhages, necrotic foci). Contrast enhancement is observed in the arterial phase, which rapidly disappears. This tumour is commonly asymptomatic, although some patients have a slight pain. In 1/3 of cases the tumour may rupture and start to bleed; in extremely rare cases the tumour is likely to undergo a malignant change (1, 4, 6).

FOCAL NODULAR HYPERPLASIA

It occurs as a hard nodule within the unchanged hepatic parenchyma, is well-delineated from the surrounding structures and non-encapsulated. At CT the tumour's absorption index is smaller than that of the surrounding parenchyma, after iv contrast administration a short enhancement period is observed. In the central part a connective tissue, star-shaped scar can be found. This kind of lesion is detected in about 3% of the population, two times more often in young and middle-aged women, and it is associated with oral contraception. The main symptoms are abdominal pains which occur in 1/3 of patients. In the majority of cases, focal nodular hyperplasia does not require treatment unless it results in compression symptoms due to its large size. Biopsy with histopathological evaluation is a very useful means of diagnosing this lesion (1, 8).

HEMANGIOMA

The most frequent focal lesion in the liver is hemangioma; according to various sources, it accounts for 1.5–7% of cases in adult population. This lesion is a benign tumour of mesenchymal origin. At US it is visible as a well-delineated, round hyperechogenic focus. CT reveals a hypodense lesion, which after contrast administration undergoes enhancement progressing from the periphery to the central part of hemangioma within 30–60s. The lesion is five times more frequent in women, and occurs seven times more often as a single change. Generally, hemangiomas are clinically asymptomatic, however some may result in thrombocytopenia. In adults they do not undergo malignant change and rarely induce haemorrhages. In pregnancy and hormonal therapy their sizes may increase. When hemangioma is suspected, biopsy is contraindicated as it may cause bleeding (5, 6).

HEPATIC CYSTS

Hepatic cysts are almost as common as hemangiomas and account for about 5% of cases in the population. At US cysts are visible as round, smooth-walled, echonegative fluid reservoirs with typical acoustic enhancement outside the cyst. Calcifications are likely to be present in the cyst's wall. At CT cysts are hypodense foci with the X-ray absorption index similar to that of water. After iv contrast administration, enhancement is not observed. Cysts may be single or multiple; they are 10 times more frequent in women, usually at the age of 50–60. Small cysts are asymptomatic, big and multiple cysts may cause pain or/and symptoms of cholestasis. Occasionally they may be complicated by rupture, haemorrhage to the cysts, portal hypertension. The hepatic lesions are often accompanied by cystic changes in other organs, e.g. kidneys. A special form of cysts is

a parasitic cyst. In Poland the most common types of echinococcus cysts are: *Echinococcus granulosus* and *Echinococcus multilocularis*. The former is visualized at US as a thick-walled, unilocular cyst, often containing parasites and characteristic hooks. The latter forms numerous small cysts which may involve both hepatic lobes and lead to failure. The parasitic infection is confirmed by serological examinations. Fine-needle biopsy is not recommended due to possible spread of the infection (8, 10).

FOCAL FATTY INFILTRATION

The development of such lesions is often associated with alcohol abuse, diabetes, chemo- and hormone therapy. The steatosis foci are most frequently found in the region of the falciform ligament, around portal branches or in the caudate lobe. The US reveals a hyperechogenic focus with sharp contours, CT shows a hypodense area characterized by poor enhancement after contrast administration, round or diffuse. Patients with steatosis foci are clinically asymptomatic (4, 8).

HEPATIC ABSCESSSES

Hepatic infectious lesions are less common than benign foci. The infectious factors which are likely to cause them include: *Escherichia coli*, *Klebsiella*, *Enterococcus*, *Staphylococcus aureus*, *Streptococcus*, *Bacteroides*. Parasitic abscesses are caused by *Entamoeba histolytica*. The routes of microorganism penetration to the liver are varied. Most often they pass from the biliary tract, in fewer cases from the inflammatory foci in the abdominal cavity: appendicitis, diverticulitis or perforation of intestines. Bacteria may reach the liver by blood or due to injuries. Abscesses as one of few focal lesions cause clinical symptoms: fever, chills, nausea, vomiting. Additionally, they may induce pain in the right epigastrium, lack of appetite, weakness and jaundice. The US examination reveals a round or oval area, in the phase of infiltration – the tissue focus with decreased echogenicity, in the phase of disintegration – the fluid reservoir with acoustic enhancement and numerous, often irregular internal reflections surrounded by a clear sheath. CT visualizes a hypodense focus (of a bigger absorption index than that in cysts), the abscess capsule is markedly enhanced by contrast. An important element of diagnosis is blood culture, which is positive in about 50% of cases. Moreover, it is necessary to determine the level of bilirubin, activities of ALAT, AspAT, FZ and GGTP and inflammatory indices: CPR and leucocytosis. The “golden standard” is the culture of abscess contents (9,10).

From the clinical point of view important hepatic lesions are primary malignant neoplasms. Similarly to benign lesions, they may be clinically asymptomatic for a long time. Their occurrence is often associated with big sizes of tumours.

HEPATOCELLULAR CARCINOMA

Family doctors and clinicians should be familiar with risk factors of its development and precancerous conditions. These include: chronic hepatitis B and C, cirrhosis of the liver of any etiology, haemochromatosis, alfa 1-antitrypsin deficiency, anabolic steroids and aflatoxin poisoning. An early diagnosis of this carcinoma may be difficult due to lack of clinical symptoms when tumour is small. When it is big, the following symptoms are present: weight loss, lack of appetite, pain in the right epigastrium, jaundice, nausea, vomiting, fever, anaemia, general weakness. Symptoms often overlap the existing pathology of the liver, particularly cirrhosis.

The following macroscopic forms of hepatocellular carcinoma are distinguished – three categories according to the Eggel’s classification: nodular (2/3) – the liver studded with small nodules, big tumour (almost 1/3) – one big tumour, sometimes with satellite nodules, diffuse form.

The US image largely depends on the presence of adipose and fibrous tissue, bleedings and necrotic areas. The Doppler examination visualizes rich vascularization of the tumour. Pre-contrast CT shows a mass of a lower density than that of normal hepatic parenchyma. The two-phase technique discloses clear, transient contrast enhancement in the arterial phase and heterogenous structure with smooth or heterogenous contours in the venous phase. A typical accompanying symptom

is portal vein thrombosis. Searching for hepatocellular carcinoma, HbsAg, a-HCV, AIAt, AspAt, FZ, GGTP and alfa-fetoprotein should be determined. The diagnosis should be confirmed by biopsy (1, 2, 3, 6, 10).

CHOLANGIOCELLULAR CARCINOMA

The risk factors of this carcinoma include: sclerosing cholangitis, Caroli's syndrome and other hereditary anomalies of the biliary tract, ulcerative inflammation of the large intestine and parasitic infections (liver fluke). Clinical symptoms develop slightly earlier than in hepatocellular carcinoma and include: jaundice, stomach ache, nausea, vomiting, lack of appetite, weight loss.

Neither US nor CT are conclusive of the diagnosis. Among the imaging examinations used, endoscopic retrograde cholangiopancreatography is most informative. Biopsy is often impossible due to difficult location of the tumour.

Laboratory tests are likely to show increased levels of bilirubin, FZ, GGTP, occasionally – of transaminases. The determinations of CEA, CA 19-9 are of low diagnostic value (1, 4, 6, 7).

METASTASES TO THE LIVER

Undoubtedly, the most common hepatic lesions of malignant nature are neoplastic metastases. In different geographical regions the proportions between primary and metastatic cancers are varied. For example, in USA they are 1:47, while in Japan – 1:2.6. This is explained by higher incidence of HBV and HCV infections on the Asian continent.

The liver is a kind of filter thanks to its vascularization from the portal vein. Therefore, the primary focus is mostly located in the digestive tract: the large intestine, pancreas, stomach, gall bladder as well as mammary glands, endocrine glands and lungs.

At US, four basic sonographic patterns of metastases are distinguished: hyperechogenic focus, hypoechogenic focus, cystic lesion and diffuse lesions. The CT scans may also vary: multiple hypo-, hyper- or isodense foci; enhancement depends on vascularization. Despite the fact that their presence is related to marked progression of the neoplastic process, metastases may not cause any complaints. In the majority of cases, however, they induce: pains in the right epigastrium, jaundice and weakness. Physical examination is likely to demonstrate the hepatomegaly with hard and irregular borders. Generally, no characteristic changes are observed in laboratory tests. In cases where the primary focus is unknown, the first aim of diagnosis is to search for it, most often within the digestive tract. If, despite comprehensive diagnosis, the focus remains unknown biopsy of the hepatic lesion is recommended (1, 4, 6, 8, 10).

The above-considered issues allow us to draw the following conclusions:

1. The combined knowledge of clinicians, histopathologists and radiologists enables us to distinguish the foci which, due to their nature, are subjected only to observation. These include: hemangiomas, cysts, adenomas, focal nodular hyperplasia and focal fatty infiltration.
2. The lesions such as abscesses, primary neoplasms and metastases should be consulted with a surgeon who is to decide about possible surgical intervention.
3. Accurate surveillance should involve the patients with high risk of malignant lesions. This group includes the patients: with cirrhosis of the liver, irrespective of its etiology, with HBV and HCV infections, after resections of neoplastic lesions, with ulcerative colitis, with congenital anomalies of the biliary tract, women taking oral contraceptives.

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SUMMARY

In recent years the number of patients with US-detected focal lesions has been increasing. Despite better ultrasound diagnostics, the radiological image is not enough to establish correct diagnosis, therefore the knowledge of clinical symptoms, radiological and histopathological features of focal lesions is essential. The aim of the study is to sort out the data in order to distinguish clinically important features and provide proper further management. Benign lesions, e.g. hemangiomas, cysts, adenomas, focal nodular hyperplasia and focal fatty infiltration are US followed up, while abscesses, primary neoplasms and metastases should be consulted with oncologists-surgeons, who decide about the need of surgical intervention. Special surveillance should be provided for patients at high risk of malignant lesions.

Zmiany ogniskowe w wątrobie – diagnostyka różnicowa

W ostatnich latach wzrasta liczba pacjentów ze stwierdzanymi w badaniu ultrasonograficznym (USG) zmianami ogniskowymi. Jednak mimo coraz lepszej diagnostyki USG sam obraz radiologiczny nie wystarczy do postawienia właściwego rozpoznania. Stąd konieczna jest znajomość objawów klinicznych, cech radiologicznych i histopatologicznych poszczególnych zmian ogniskowych. Celem pracy jest uporządkowanie danych, tak by wyodrębnić te o istotnym znaczeniu klinicznym i właściwie pokierować dalszym losem pacjenta. Zmiany łagodne, takie jak naczyniaki, torbiele, gruczolaki, ogniskowy rozrost guzkowy i ogniskowe stłuszczenie wątroby, podlegają dalszej obserwacji ultrasonograficznej, natomiast zmiany takie, jak ropnie, pierwotne nowotwory i przerzuty, powinny być skonsultowane ze specjalistą chirurgiem, który podejmuje decyzję o ewentualnej interwencji operacyjnej. Szczególnym nadzorem powinni być objęci ci chorzy, u których występuje duże ryzyko wystąpienia zmian złośliwych.